12th World Congress of Microcirculation

Beijing,China
20-24,Sep
2023

Program & Abstracts

Organizer | Chinese Society of Microcirculation
International Liaison Committee for Microcirculation

President of Congress | Professor Jing-Yan Han

Co-President of Congress | Professor Qi-Min Zhan, Professor Nai-Feng Liu

https://12thwcm.tri-think.cn

12th World Congress of Microcirculation (12thWCM)

Program & Abstracts

September 20-24, 2023
Guoce International Convention and Exhibition Center, Beijing, China

President, 12th WCM
Jing-Yan Han
Tenured Professor and Chairman of Department of Integration of Chinese and Western Medicine, Peking University Health Science Center, Beijing, China
Director of Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China
Vice President of Chinese Society of Microcirculation

Co-President, 12th WCM
Qi-Min Zhan
Academician of Chinese Academy of Engineering
Professor of Peking University Health Science Center
Vice President and Secretary General of Chinese Society of Microcirculation

Nai-Feng Liu
Professor of Cardiology, School of Medicine, Southeast University
President of Chinese Society of Microcirculation

Organizer
Chinese Society of Microcirculation
International Liaison Committee for Microcirculation

WELCOME MESSAGE

Dear Colleagues and Friends,

As the President of the Congress, and on behalf of the Co-Presidents, Core Scientific Committee, International Scientific Committee, and Local Organizing Committee, I warmly welcome you to attend the 12th World Congress of Microcirculation (12thWCM), which is held from September 20th to 24th, 2023, in Beijing.

The 12th WCM, authorized by the International Liaison Committee for Microcirculation (ILCM) and approved by the China Association for Science and Technology, is co-organized by the Chinese Society of Microcirculation and ILCM. Over 750 scholars from all around the world, including the United States, Canada, the United Kingdom, France, Germany, Italy, Hungary, Switzerland, Sweden, Netherlands, Russia, Croatia, Japan, Australia, Thailand, Indonesia, Nigeria, China and Hong Kong Special Administrative Region of China, will participate in this conference in person or virtually.

Recommended by the ILCM, Core Scientific Committee, International Scientific Committee, Local Organizing Committee, and microcirculation societies of the United States, Europe, Japan, Australia/New Zealand and China, and voted by ILCM and Core Scientific Committee, *Professor Stefanie Dimmeler* (Germany), *Professor Britta Engelhardt* (Switzerland), *Professor Kesheng Dai* (China), *Professor Sarah Yuan* (USA) and *Professor Michael Hickey* (Australia) will deliver keynote lectures in the congress.

Furthermore, *Professor Luis A. Martinez-Lemus*, winner of the Zweifach Award of the American Microcirculation Society, *Professor Makoto Matsumoto*, winner of the Nishimaru-Tsuchiya International Award of the Japanese Society for Microcirculation, and *Academician Qi-Min Zhan*, winner of the TaiShan Award of the Chinese Society of Microcirculation, will deliver award lectures in the congress.

Professor Donald Welsh (Canada), *Professor Xunbin Wei* (China), *Dr. Paul Fraser* (United Kingdom), *Professor Amanda Jo LeBlanc* (USA), *Professor Gilles Pagès* (France), *Professor Giovanni E. Mann* (United Kingdom), *Professor Geert Schmid-Schonbein* (USA), *Professor Yoshikazu Tsuzuki* (Japan) and *Associate Professor Congying Wu* (China) will deliver plenary lectures.

164 scholars and young scientists will give a talk in 41 symposia organized by the microcirculation societies of the United States, Europe, Japan, Australia/New Zealand and China. Additionally, 28 young scientists will give a talk in 7 young symposia organized by the microcirculation societies of the United States, Europe, Australia/New Zealand, Japan, and China.

The congress will also organize 3 lunch lectures. 66 speakers will give a talk in 13 satellite symposia organized by the 13 specialized committees of the Chinese Society of Microcirculation; 66 speakers selected from abstract submission will give a talk in 11 free oral communications. There are also 180 poster presentations.

The congress will select Young Investigator Award form speakers who attend the conference in person and are aged 35 years old or under in the symposia, young symposia, and free oral communications. Travel Award will be selected from poster presenters who attend the conference in person.

The congress will gather scholars and young scientists from various disciplines, including microcirculation, basic and clinical science, pharmaceutical research, integrative medicine and emerging technologies, and will focus on microcirculatory disturbance of critical diseases, chronic diseases and newly emerged infectious diseases, and exchange new ideas, methodologies and advancements in microcirculation research, and provide a platform for the communications and collaborations between basic and clinical science, medicine and pharmacy, and microcirculation and multiple disciplines.

We would like to thank the ILCM and the national microcirculation societies for their support to the congress.

We would like to thank the Core Scientific Committee, International Scientific Committee, and Local Organizing Committee of the congress for their participation and support to the congress.

We also would like to thank the scholars, young scientists and relevant enterprises for their participation in the congress.

The weather of Beijing is pleasant and comfortable in September, and we cordially invite you to join the congress. The active participation of participants is the key to the success of the conference. You can enjoy the beautiful autumn scenery and Chinese food, experience the 800-year history of Beijing as the capital city, while conducting academic exchanges.

Looking forward to seeing you in Beijing in September!

President

Jing-Yan Han

Tenured Professor and Chairman of Department of Integration of Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing, China

Director of Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China.

Vice President of Chinese Society of Microcirculation

Co-President

Qi-Min Zhan

Academician of Chinese Academy of Engineering

Professor of Peking University Health Science Center

Vice President and Secretary General of Chinese Society of Microcirculation

Co-President

Nai-Feng Liu

Professor of Cardiology, School of Medicine, Southeast University

President of Chinese Society of Microcirculation

ORGANIZATION-CSM

Council of Chinese Society of Microcirculation (CSM)

Position	Name	Institution	City
Honorary President	Rui-Juan Xiu	Chinese Academy of Medical Sciences	Beijing
President	Nai-Feng Liu	Southeast University	Nanjing
Vice President and Secretary General	Qi-Min Zhan	Peking University	Beijing
Vice President	Jing-Yan Han	Peking University	Beijing
	Qiao-Bing Huang	Southern Medical University	Guangzhou
	Zi-Lin Sun	Southeast University	Nanjing
	Hua Zhang	Chinese Academy of Medical Sciences	Beijing
	Jian Zhang	Chinese Academy of Medical Sciences,	Beijing
Deputy Secretary General	Yue-Hong Zheng	Peking Union Medical Colleage Hospital	Beijing
	Bao-Liang Sun	Taishan Medical School	Tai'an
Council Member	Gang Jin	Chinese Academy of Sciences	Beijing
	Hai-Bin Gong	Xuzhou Institute of Cardiovascular Disease	Xuzhou
	Qing-Fu Zhang	Hebei Medical University	Shijiazhuang
	Si-Feng Chen	Fudan University	Shanghai
	Li Yang	Chongqing University	Chongqing
	Jun Yang	Yuhuangding Hospital	Yantai
	Xue-Long Jin	Tianjin Medical University	Tianjin
	Zhi-Cheng Jin	Fuwai Hospital	Beijing
	Fang-Tian Dong	Peking Union Medical Colleage Hospital	Beijing
	Ai-Ling Li	Chinese Academy of Medical Sciences	Beijing
	Jian-Qun Han	Chinese Academy of Medical Sciences	Beijing
	Yan-Feng Li	Peking Union Medical Colleage Hospital	Beijing
	Shuang-Yi Fan	Chinese PLA 307 Hospital	Beijing
	Hua-Qiu Zhang	Tongji Hospital	Wuhan
	Guang-Wei Wei	Shandong University	Jinan
	Ke-Sheng Dai	Suzhou University	Suzhou
	Bo-Jun Zhao	Shandong Provincial Hospital	Ji'nan
	Yu-Zhen Li	Chinese PLA General Hospital	Beijing
	Dan Meng	Fudan University	Shanghai
	Hui Yuan	Taishan Medical School	Tai'an
	Guo-Long Cai	Zhejiang Hospital	Hangzhou
	Hong Jiang	Sichuan University	Chengdu
	Wei-Xing Wang	Wuhan University	Wuhan
	Jian-Bo Wu	Southwest Medical University	Luzhou
	Yan-Ling Wang	Capital Medical University	Beijing
	Wang-De Zhang	Capital Medical University	Beijing
	Tian-Ran Dai	Beijing Aerospace General Hospital	Beijing
	Jun Zhou	Land Force General Hospital	Beijing

ORGANIZATION-CSM

Professional Committee	Chair	City
Peripheral Vascular Disease	Yue-Hong Zheng	Beijing
Neurodegenerative Disease	Yan-Feng Li	Beijing
Ocular Microcirculation	Fang-Tian Dong	Beijing
Diabetes and Microcirculation	Zi-Lin Sun	Nanjing
Shock	Qing-Fu Zhang	Shijiazhuang
Blood Therapy	Shuang-Yi Fan	Beijing
Phlegm-Stasis	Dong Han	Beijing
Cerebral Vascular Disease	Xue-Long Jin	Tianjin
Hemorheology	Xiang Wang	Chongqing
Neuroprotection and Recovery	Bao-Liang Sun	Tai'an
Information and Technology	Jian Zhang	Beijing
Tumor	Guang-Wei Wei	Ji'nan
Translational Medicine	Zhi-Liang Li	Shenzhen
TCM and Microcirculation	Jiang-Yi Yu	Nanjing
Bone Microcirculation	Wei Sun	Beijing
Liver Microcirculation	Xin-Ting Sang	Beijing
Pharmaceutical Research	Feng Han	Nanjing
Grass-roots Chronic Disease Management	Zi-Lin Sun	Nanjing

INTERNATIONAL LIAISON COMMITTEE FOR MICROCIRCULATION (ILCM)

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Gerald A. Meininger
United States

ILCM Vice Chair

Cor de Wit
Germany

Asia-Pacific Community

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Australia
Society: ANZMS

Tim Murphy
Australia
Society: ANZMS

Jing-Yan Han
China
Society: CSM

Qiao-Bing Huang
Guangzhou, China
Society: CSM

Hidekazu Suzuki
Tokyo, Japan
Society: JMS

Patumraj Suthilik
Bangkok, Thailand
Society: TMS

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United States
Society: MCS

Shayn Pierce-Cottler
United States
Society: MCS

Michael A. Hill
United States
Society: MCS

Amanda Jo LeBlanc
United States
Society: MCS

Walter Lee Murfee
United States
Society: MCS

Europe

Nicola J. Brown
United Kingdom
Society: BMS/ESM

Angela Shore
United Kingdom
Society: BMS/ESM

Akos Koller
Hungary
Society: ESM

Ed T. van Bavel
Netherlands
Society: DMS

Markus Sperandio
Germany
Society: GMS

Immediate Past President of the World Congress

Donald Welsh
Canada
Society: MCS

President of the Current World Congress

Jing-Yan Han
China
Society: CSM

Past Chair of ILCM

Axel Pries
Germany
Society: GMS

ABOUT WORLD CONGRESS OF MICROCIRCULATION (WCM)

List of World Congress of Microcirculation

	Year	President	City
1st WCM	1975	Professor John Grayson	Toronto, Canada
2nd WCM	1979	Professor Benjamin W. Zweifach	La Jolla, United States
3rd WCM	1984	Professor Terence J. Ryan	Oxford, United Kingdom
4th WCM	1987	Professor Masaharu Tsuchiya	Tokyo, Japan
5th WCM	1991	Professor Patrick Harris	Louisville, United States
6th WCM	1996	Professor Konrad Messer	Munich, Germany
7th WCM	2001	Professor Michael Perry	Sydney, Australia
8th WCM	2007	Professor Julian Lombard	Milwaukee, United States
9th WCM	2010	Professor Eric Vicaut	Paris, France
10th WCM	2015	Professor Makoto Suematsu	Kyoto, Japan
11th WCM	2018	Professor Donald Welsh	Vancouver, Canada
12th WCM	**2023**	**Professor Jing-Yan Han**	**Beijing, China**

CORE SCIENTIFIC COMMITTEE

North & South America


Gerald A. Meininger
United States


Geert Schmid-Schoenbein
United States


Michael A. Hill
United States


Shayn Peirce-Cottler
United States


Walter Núñez Durán
United States


Walter Lee Murfee
United States


Jerome W. Breslin
United States


Donald Welsh
Canada


Eliete Bouskela
Brazil

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Akos Koller
Hungary


Nicola J. Brown
United Kingdom


Geraldine Clough
United Kingdom


Daniel Henrion
Angers, France


Gilles Pages
France


Henning Morawietz
Germany


Cor de Wit
Germany


Beat Imhof
Switzerland


Benedetta Bussolati
Italy


Boy Houben
Netherlands

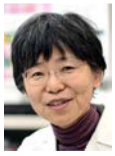
Asia-Pacific


Jing-Yan Han
China


Qiao-Bing Huang
China


Hidekazu Suzuki
Japan


Makoto Suematsu
Japan


Mayumi Kajimura
Japan


Patumraj Suthilik
Thailand


Georges E. R. Grau
Australia


Timothy Murphy
Australia

INTERNATIONAL SCIENTIFIC COMMITTEE

Asia-Pacific	The Americans	Europe	
Qi-Min Zhan China	Brant Isakson United States	Angela Shore United Kingdom	Cor de Wit Germany
Nai-Feng Liu China	William Jackson United States	Neena Kalia United Kingdom	Axel Radlach Pries Germany
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Michael Hickey Australia	Luis A. Martinez-Lemus United States	Daniel Henrion France	Carlota Saldanha Portugal
Marianne Tare Australia	Andy P.Braun Canada	Ulrich Pohl Germany	Alexei Muravjev Russia
	Eliete Bouskela Brazil	Markus Sperandio Germany	Irina Tikhomirova Russia

LOCAL ORGANIZING COMMITTEE

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Rui-Juan Xiu, Beijing	Shuang-Yi Fan, Beijing	Bao-Xue Yang, Beijing
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Dong-Ye Li, Xuzhou	Dong Han, Beijing	Yi-Long Wang, Beijing
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Cheng-Xing Shen, Shanghai	Zhi-Liang Li, Shenzhen	Jian-Xun Liu, Beijing
Gang Jin, Beijing	Jiang-Yi Yu, Nanjing	Da-Zhuo Shi, Beijing
Hai-Bin Gong, Xuzhou	Wei Sun, Beijing	Ming Xu, Beijing
Qing-Fu Zhang, Shijiazhuang	Xin-Ting Shang, Beijing	Ping Li, Beijing
Si-Feng Chen, Shanghai	You-Yi Zhang, Beijing	Shi-Jun Wang, Ji'nan
Li Yang, Chongqing	Xiu-Hua Liu, Beijing	Yan Lei, Beijing
Jun Yang, Yantai	Chun-Yu Niu, Shijiazhuang	Jian-Gang Shen, Hongkong
Zhi-Cheng Jing, Beijing	Zhi-Gang Zhao, Zhangjiakou	Xue-Long Jin, Tianjin
Fang-Tian Dong, Beijing	Ai-Ling Li, Beijing	

Academic Team		
Nai-Feng Liu	Jing-Yan Han	Qiao-Bing Huang
Zi-Lin Sun	Jian Zhang	Gang-Min Ning
Bao-Liang Sun	Jian-Bo Wu	Jing Li
Feng Han	Dan Meng	Xiao-Hua Guo
Jing Wu	Cheng-Xing Shen	Jian Liu
Xin-Sheng Ding	Lei-Ting Pan	Jing Zhao
Xing-Shun Xu	Hua-Yu Yang	Sheng-Han Song
Qing Xia	Min Zha	Bo-Jun Zhao
Yong-Gang Lv	Xin Li	Ming-Ming Liu
Bing Wang	Sen Liu	Wen-Tao Liu
Shan-Hu Qiu		
Conference Secretary		
Jian Liu		

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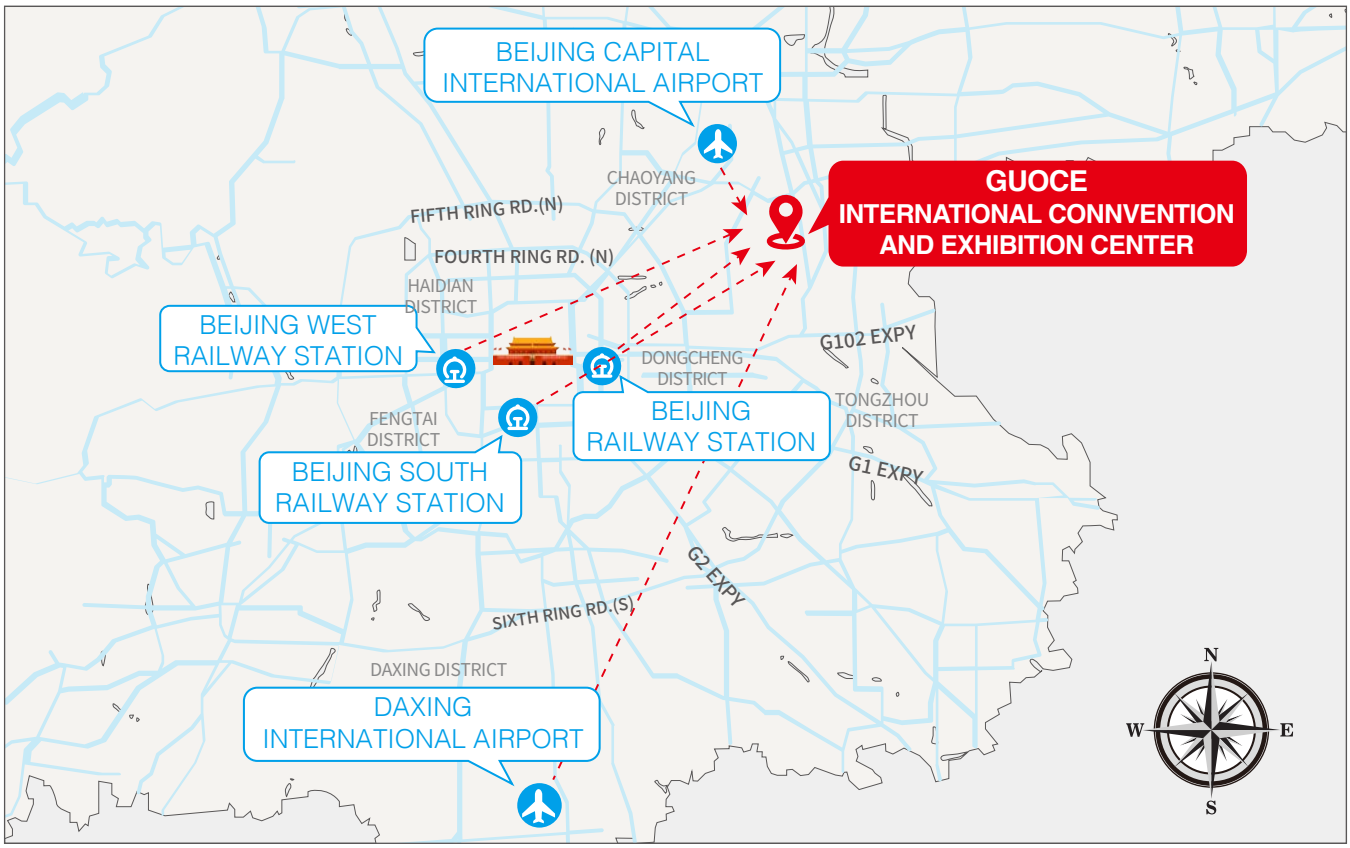

BEIJING CAPITAL INTERNATIONAL AIRPORT

Terminal 1/2	Taxi: 9 km	20mins	~RMB 30
Terminal 3*	Taxi: 5 km	15mins	~RMB 25

*The conference will arrange shuttle bus for attendees

- Terminal 3 Exit > Guoce Hotel | 09:00-17:00 (every 30 mins) | 20th September
- Guoce Hotel > Terminal 3 | 11:00-17:00 (every 30 mins) | 24th September

DAXING INTERNATIONAL AIRPORT

Taxi: 80 km | 100mins | ~RMB 270

You can also take the subway to Beijing Capital International Airport T3 and then by taxi or shuttle bus to Guoce Hotel

BEIJING RAILWAY STATION

Taxi: 33 km | 60mins | ~RMB 110

You can also take the subway to Beijing Capital International Airport T3 and then by taxi or shuttle bus to Guoce Hotel

BEIJING WEST RAILWAY STATION

Taxi: 45 km | 90mins | ~RMB 150

You can also take the subway to Beijing Capital International Airport T3 and then by taxi or shuttle bus to Guoce Hotel

BEIJING SOUTH RAILWAY STATION

Taxi: 40 km | 70mins | ~RMB 140

You can also take the subway to Beijing Capital International Airport T3 and then by taxi or shuttle bus to Guoce Hotel

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Escalator Vertical elevator Tiolet

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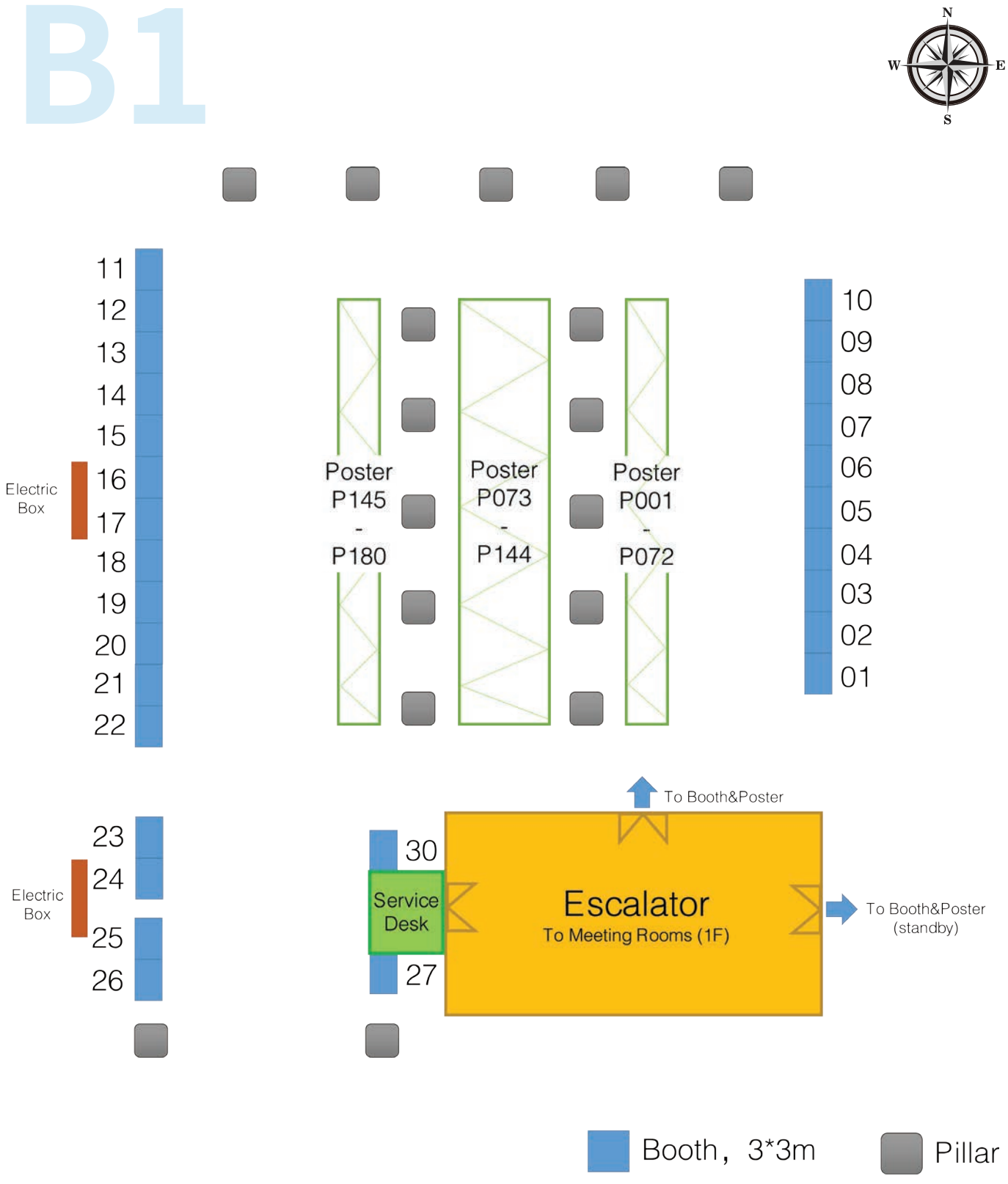
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To Booth&Poster (standby)
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Pillar

NOTICE FOR ATTENDEES

1. **Date**

   September 20 (Wednesday) - 24 (Sunday), 2023

2. **Venue**

   Guoce International Convention and Exhibition Center (GICEC)
   Address: No.6, Huihai South Road, Airport Economic Core District, Shunyi District, Beijing

3. **Registration***

   - September 19 (Tuesday): 1:30 - 18:00
   - September 20 (Wednesday) - September 23 (Saturday): 8:00 - 17:00
   - September 24 (Sunday): 8:00-11:00

   **Registration Counter at the Lobby, First Floor of GICEC*

4. **Conference fee**

	Onsite Attendance	**Online Attendance (60% of Onsite)**
Early registration *(Updated Deadline:30 April, 2023)*	Scholar *(over 35 years old)* 500 USD or 3500 RMB	300 USD or 2100 RMB
	Young Scientist *(35 years old or under)* 280 USD or 1960 RMB	168 USD or 1176 RMB
Late registration *(1 May to 30 August, 2023)*	Scholar *(over 35 years old)* 580 USD or 4060 RMB	348 USD or 2436 RMB
	Young Scientist *(35 years old or under)* 300 USD or 2100 RMB	180 USD or 1260 RMB
Accompanying family members	100 USD or 700RMB	
One day ticket	143 USD or 1000 RMB	
Half day ticket	86 USD or 600 RMB	
Welcome reception ticket	50 USD or 350 RMB	
Banquet ticket	50 USD or 350 RMB	
Buffet dinner ticket	23 USD or 158 RMB	

Early and late onsite attendance registration fee: Including access to all conference sessions, conference badge or presentation certificate, chair certificate, conference program book, conference bag, note book and pen, drinking water, poster board, lunch box and dinner during the conference.

Online attendance registration fee: Including online access to all conference sessions, conference badge or presentation certificate, chair certificate, conference program book, conference bag.

Accompanying family members' registration fee: Including the welcome reception on September 20th and the banquet on September 23rd, excluding the access to conference session.

One day ticket: Including 1-day conference badge, conference program book, conference bag, note book and pen, drinking water, and one lunch box on the day of attendance.

Half day ticket: Including half-day conference badge, conference program book, conference bag, note book and pen, and drinking water.

Welcome reception ticket: meal ticket for the welcome reception on September 20th.

Banquet ticket: meal ticket for the banquet on September 23rd.

Buffet Dinner: meal tickets for buffet dinner on September 21st or 22nd

Cancel of registration: 80% of the registration fee will be refunded if registration canceled before June 30th, 2023, and none will be refunded after.

5. Hotel (at your own expense)

Guoce International Convention and Exhibition Center
(No.6, Huihai South Road, Airport Economic Core District, Shunyi District, Beijing)

Contacts: Weiqian Sun; Phone: 86-10-5090-7999, 86-13718867069.

Reservation made before August 30 will receive the special price.

» Rooms:

» Double room in Main building (Regular price 2688 RMB, special price for the conference 600 RMB/night or 87.3 USD) (breakfast included);

- Twin room in Main building (Regular price 2688 RMB/night, special price for the conference 650 RMB/night or 94.575 USD) (breakfast included);
- Double room in Business building (Regular price 1088 RMB, special price for the conference 450 RMB/night or 65.475 USD) (breakfast included);
- Twin room in Business building (Regular price 1888 RMB, special price for the conference 550 RMB/night or 80.025USD) (breakfast included);

» Please log into *https://12thwcm.tri-think.cn* and **click on the "Hotel" tab**.

» For payments in Chinese Yuan (RMB), kindly scan the QR code provided and input your reservation details to complete the payment using the WeChat payment system.

- If paying in US Dollars (USD), please click on
- *https://www.guoceicec.com/index.php/default/category/43.html* and enter your reservation information. Invoices can be collected at the hotel reception during the conference.

6. Transport:

A. Beijing Capital International Airport T1 or T2 to Guoce Hotel
   » By taxi: about RMB 30
B. Beijing Capital International Airport T3 to Guoce Hotel
   » By taxi: about RMB 25
C. Beijing South/North/East/West Railway Station to Guoce Hotel
   » By subway to Beijing Capital International Airport T3
   » By taxi to Guoce Hotel.
D. Beijing DaXing International Airport T1 or T2 to Guoce Hotel
   » By subway to Beijing Capital International Airport T3
   » By taxi to Guoce Hotel.
E. The conference will arrange shuttle bus for attendees
   » Airport T3 Exit > Guoce Hotel | 09:00-17:00 (every 30 mins) | 20th September.
   » Guoce Hotel > Airport T3 | 11:00-17:00 (every 30 mins) | 24th September.

7. For Online Attendees

This conference adopts a hybrid format with both onsite and online participation.
Please log in using your email and password to access the daily schedules of various venues and abstracts of every session on our website, and choose the dates and sessions that you are interested.

» Before the conference begins, you will receive the Zoom IDs and passwords for each session.
» Please note that these passwords are for registered participants only.
» To ensure the smooth running of Zoom meetings, kindly mute your audio and disable your video upon entering the Zoom session.
» After the presentation is over and during the Q&A time, you can unmute your audio and enable your video following the chair's instructions for asking questions.

IMPORTANT EVENTS FOR ATTENDEES

- **Opening Ceremony**
  September 20 (Wednesday) | 16:40-17:30 | Guorui Hall (1F, GICEC)
- **Opening Reception***
  September 20 (Wednesday) | 17:30 - 19:30 | Landiao Restaurant (3F, GICEC)
  **with meal tickets*
- **Banquet***
  September 23 (Saturday) | 17:40-20:00 | Guoce Hall (2F, GICEC)
  **with meal tickets*
- **Closing Ceremony**
  September 24 (Sunday) | 11:40-12:20 | Guorui Hall (1F, GICEC)
- **Breakfast***
  Time: From 6:30
  Venue: Grand Cafe (1F, GICEC)
  **with room card*
- **Lunch***
  September 21th - 23rd (Thursday - Saturday) | 12:20-12:50 | East Exhibition Hall (1F, GICEC)
  **with meal tickets*
- **Buffet Dinner***
  September 21 (Thursday) | 19:10-20:30 | East Exhibition Hall (1F, GICEC)
  September 22 (Friday) | 17:30-20:30 | East Exhibition Hall (1F, GICEC)
  **with meal tickets*

NOTICE FOR SPEAKERS

The conference language is English.

- **Keynote Lectures:** 43 minutes' presentation | no discussion
- **Award Lectures:** 43 minutes' presentation | no discussion
- **Plenary Lectures:** 24 minutes' presentation | 4 minutes' discussion
- **Lunch lectures:** 38 minutes' presentation | no discussion
- **Symposiums:**
  A. with 2 Senior Speakers and 2 Young Speakers:
  » Senior Speakers: 19 minutes' presentation | 4 minutes' discussion
  » Young Speakers: 14 minutes' presentation | 4 minutes' discussion

  B. with 3 Senior Speakers and 1 Young Researcher Talk
  » Senior Speakers: 18 minutes' presentation | 4 minutes' discussion
  » Young Speakers: 14 minutes' presentation | 4 minute's discussion

  C. with 4 Senior Speakers
  » Senior Speakers: 17 minutes' presentation | 4 minutes' discussion
- **Satellite Symposiums:** 17 minutes' presentation | 4 minutes' discussion
- **Young Symposiums:** 17 minutes' presentation | 4 minutes' discussion
- **Free oral communications:** 9 minutes' presentation | 4 minutes' discussion

Collect and preview PowerPoint in Room 8

» Speakers scheduled in the Morning should submit their USB drives containing the PowerPoint files to the staff in Room 8 by 17:00 one day before their presentation.
» Afternoon speakers should submit their USB drives by 12:00 on the same day of their presentation

For Keynote Lectures, Award Lectures, Plenary Lectures, Lunch lectures, Symposiums, Young Symposiums, and Free oral communications

» Speakers should take their seats at the "Next Speaker's Seat" on the left side of the front row of the lecture hall at least 10 minutes before the start of your presentation.
» As this conference combines both in-person and online formats, speakers are advised to stand in front of their computers and speak into the microphone during the presentation and Q&A session.
» Please note that the conference computers only support mirrored display mode and do not support extended display mode, so please do not read from a script

For online speakers

» Please log in using your email and password to access the daily schedules of various venues and abstracts of every session on our website.
» Before the conference begins, you will receive the Zoom IDs and passwords for each venue.
» Please note that these passwords are for your use only
» Please enter the Zoom meeting 10 minutes before the start of the session in which you join.
» After the chair introduces you and your presentation topic, you can begin your presentation by sharing your screen and showing your PowerPoint slides.
» Once your presentation is over, please stop screen sharing and engage in the discussion led by the chair

If you are delivering your presentation in a pre-recorded format

- » Please submit the video to the conference organizers within the specified timeframe
- » Please enter the Zoom meeting 10 minutes before the start of the session in which you join
- » After the playback of your pre-recorded presentation, please participate in the discussion under the guidance of the chair

Each poster presenter will be provided with a poster board

- » Please prepare your poster with dimensions of 90 cm in width and 120 cm in height
- » Posters should be affixed to the designated boards according to their assigned poster numbers in the poster area on the basement 1st floor of the Guoce International Convention and Exhibition Center before 21:00 on September 20th
- » Poster sessions will take place between 13:30 and 15:00 from September 21st to 23rd
- » On September 21st, presenters with odd poster numbers should stand by their posters
- » On September 22nd, presenters with even poster numbers should stand by their posters
- » On September 23rd, all poster presenters should stand by their posters
- » All posters should be removed by 17:00 on September 23rd

NOTICE FOR CHAIRS

- Chairs are kindly requested to take their seats at the “Next Chair’s Seat” on the right side of the front row of the lecture hall 10 minutes before the start of your session.

- **Chairs of Keynote Lectures** can take 2 minutes to introduce the speaker. No discussion section. After the lecture, chairs present the speaker with a certificate and take a photograph. Please strictly comply with the time.

- **For Award Lectures**, chairs can take 2 minutes to introduce the speaker. No discussion section. After the lecture, chairs present the speaker with a certificate and prize money, and take a photograph. Please strictly comply with the time.

- **For Plenary Lectures**, chairs can take 1 minute to introduce the speaker and organize 4 minutes’ discussion at the end of the presentation. After the lecture, chairs present the speaker with a certificate and take a photograph. Please strictly comply with the time.

- **For Lunch lectures**, can take 1 minutes to introduce the speaker. No discussion section. After the lecture, chairs present the speaker with a certificate and take a photograph. Please strictly comply with the time.

- **For Symposiums, Satellite Symposiums, and Young Symposiums**, chairs only need to introduce the speaker’s name, affiliation and topic, and organize a discussion at the end of the presentation. After the presentation, chairs present the speaker with a certificate. Please strictly comply with the time.

- **For Free oral communications**, chairs only need to introduce the speaker’s name, affiliation and topic, and organize a discussion at the end of the presentation. After the presentation, chairs present the speaker with a certificate. Please strictly comply with the time.

- Poster sessions do not have chairs.
  - » Winners of the Travel Award (Outstanding Poster Award) will be selected by experts of the review committee onsite.
  - » The names, affiliations, and poster numbers of the winners should be submitted to the Outstanding Poster Award Committee in Room 8 by 17:00 on September 23rd.

- **For online chairs**, please log in using your email and password to access the daily schedules and abstracts of related sessions on our website in advance. Before the conference begins, you will receive the Zoom IDs and passwords for each venue. Please note that these passwords are for your use only. Please enter the Zoom meeting 10 minutes before the start of the session you chair. Once the previous session is over, and the venue broadcaster announces the start of the session you chair, you may begin to chair your session online.

AWARDS

- **Zweifach Award**

  Selected by the American Microcirculation Society, the awardee will deliver the lecture on September 22nd from 11:30 to 12:20. The American Microcirculation Society will award the certificate and prize money.

- **The Nishimaru-Tsuchiya International Award**

  Selected by the Japanese Society for Microcirculation, the awardee will deliver the lecture on September 23rd from 16:40 to 17:30. The Japanese Society for Microcirculation will award the certificate and prize money.

- **TaiShan Award**

  Selected by the Chinese Society of Microcirculation, the awardee will deliver the lecture on September 21st from 11:30 to 12:20. The Chinese Society of Microcirculation will award the certificate, medal, and prize money.

- **The Young Investigator Award**

  Selected from speakers who attend the conference in person and are aged 35 years old or under in the symposiums, young symposiums, and free oral communications by some Core Scientific Committee members and some members of the Local Organizing Committee, and will be awarded during the closing ceremony of the conference on September 24th.

- **The Travel Award (Outstanding Poster Award)**

  Selected from poster presenters who attend the conference in person by some Core Scientific Committee members and some members of the Local Organizing Committee, and will be awarded during the closing ceremony of the conference on September 24th.

SCIENTIFIC PROGRAM

SCHEDULE

	20 (Wed)	21 (Thu)	22 (Fri)	23 (Sat)	24 (Sun)
8:30-10:00 (Beijing) 20:30-22:00 (Boston, -1 day) 17:30-19:00 (California, -1 day) 00:30-2:00 (Greenwich) 10:30-12:00 (Sydney) 9:30-11:00 (Tokyo)		Symposium 1-3 Young Symposium 1 Free oral communication 1-2 Satellite Symposium 3	Symposium 15-19 Free oral communication 7 Satellite Symposium 6	Symposium 27-30 Free oral communication 11 Satellite Symposium 9 Plenary Lecture 1-3	Symposium 39-41 Young Symposium 7 Satellite Symposium 12- 13 Plenary Lecture 7-9
10:00-11:30 (Beijing) 22:00-23:30 (Boston, -1 day) 19:00-20:30 (California, -1 day) 2:00-3:30 (Greenwich) 12:00-13:30 (Sydney) 11:00-12:30 (Tokyo)		Symposium 4-6 Free oral communication 3-4 Satellite Symposium 4	Symposium 20-22 Young Symposium 3 Free oral communication 8-9 Satellite Symposium 7	Symposium 31-34 Young Symposium 5 Satellite Symposium 10	Keynote Lecture 4 Keynote Lecture 5
11:30-12:20 (Beijing) 23:30-00:20 (Boston, -1 day) 20:30-21:20 (California, -1 day) 3:30-4:20 (Greenwich) 13:30-14:20 (Sydney) 12:30-13:20 (Tokyo)		Award Lecture CSM	Zweifach Award	Keynote Lecture 3	Closing Ceremony
12:20-12:50(Beijing)	Lunch				
12:50-13:30 (Beijing) 00:50-1:30 (Boston) 21:50-22:30 (California, -1 day) 4:50-5:30 (Greenwich) 14:50-15:30 (Sydney) 13:50-14:30 (Tokyo)	Registration	Lunch Lecture 1	Lunch Lecture 2	Lunch Lecture 3	
13:30-15:00 (Beijing) 1:30-3:00 (Boston) 22:30-0:00 (California, -1 day) 5:30-7:00 (Greenwich) 15:30-17:00 (Sydney) 14:30-16:00 (Tokyo)	Satellite Symposium 1	Poster	Poster	Poster	
15:00-16:30 (Beijing) 3:00-4:30 (Boston) 0:00-1:30 (California) 7:00-8:30 (Greenwich) 17:00-18:30 (Sydney) 16:00-17:30 (Tokyo)	Satellite Symposium 2	Symposium 7-9 Young Symposium 2 Free oral communication 5-6 Satellite Symposium 5	Symposium 23-26 Young Symposium 4 Free oral communication 10 Satellite Symposium 8	Symposium 35-38 Young Symposium 6 Satellite Symposium 11 Plenary 4-6	
16:40-17:30 (Beijing) 4:40-5:30 (Boston) 1:40-2:30 (California) 8:40-9:30 (Greenwich) 18:40-19:30 (Sydney) 17:40-18:30 (Tokyo)	Opening Ceremony	Keynote Lecture 1	Keynote Lecture 2	The Nishimaru-Tsuchiya International Award	
17:40-19:10 (Beijing) 5:40-7:10 (Boston) 2:40-4:20 (California) 9:40-11:20 (Greenwich) 19:40-21:20 (Sydney) 18:40-20:20 (Tokyo)	Welcome Reception	Symposium 10-14	Buffet Dinner	Banquet	
19:10-20-00 (Beijing)		Buffet Dinner			

20 SEP (WED)

	Lobby, 1/F	Banquet Hall, 3/F	Guorui Hall
12:20-13:30 (Beijing)			
13:30-15:00 (Beijing) 1:30-3:00 (Boston) 22:30-0:00 (California, -1 day) 5:30-7:00 (Greenwich) 15:30-17:00 (Sydney) 14:30-16:00 (Tokyo)	**Registration**		**Satellite Symposium 1** Traditional Chinese Medicine and Microcirculation
15:00-16:30 (Beijing) 3:00-4:30 (Boston) 0:00-1:30 (California) 7:00-8:30 (Greenwich) 17:00-18:30 (Sydney) 16:00-17:30 (Tokyo)			**Satellite Symposium 2** From Microcirculation and Vascular Biology to Drug Target
16:40-17:30 (Beijing) 4:40-5:30 (Boston) 1:40-2:30 (California) 8:40-9:30 (Greenwich) 18:40-19:30 (Sydney) 17:40-18:30 (Tokyo)			**Opening Ceremony**
17:40-20:00 (Beijing)		**Welcome Reception**	

21 SEP (THU)

	Room 1	Room 2	Room 4	Room 5	Room 6	Room 7	Guorui Hall
8:30-10:00 (Beijing) 20:30-22:00 (Boston, -1 day) 17:30-19:00 (California, -1 day) 00:30-2:00 (Greenwich) 10:30-12:00 (Sydney) 9:30-11:00 (Tokyo)	**Symposium 1** KCa Channels as Regulators of Vascular Function	**Symposium 2** Ion Channels in Pulmonary Microcirculation in Health and Disease	**Symposium 3** Endothelial Glycocalyx in Health and Disease	**Free Oral Communication 1** Cancer and Microcirculation	**Young Symposium 1** JSM young investigator symposium	**Free Oral Communication 2** Cardiac Microcirculation	**Satellite Symposium 3** Microvascular Network Modeling and Visualization
10:00-11:30 (Beijing) 22:00-23:30 (Boston, -1 day) 19:00-20:30 (California, -1 day) 2:00-3:30 (Greenwich) 12:00-13:30 (Sydney) 11:00-12:30 (Tokyo)	**Symposium 4** Anti-Cancer Treatments and Endothelial Dysfunction: Mechanisms and Clinical Implications	**Symposium 5** Capillary Sensing	**Symposium 6** Novel Mechanisms of Regulation of Endothelial Cell Function	**Free Oral Communication 3** Cerebral Microvascular Injury and Microcirculation	**Free Oral Communication 4** Kidney and Lung Microcirculation		**Satellite Symposium 4** Hemoglobin-Based Oxygen Carrier and Microcirculation
11:30-12:20 (Beijing) 23:30-00:20 (Boston, -1 day) 20:30-21:20 (California, -1 day) 3:30-4:20 (Greenwich) 13:30-14:20 (Sydney) 12:30-13:20 (Tokyo)							**Award Lecture CSM**
12:20-12:50(Beijing)	**Lunch**						
12:50-13:30 (Beijing) 00:50-1:30 (Boston) 21:50-22:30 (California, -1 day) 4:50-5:30 (Greenwich) 14:50-15:30 (Sydney) 13:50-14:30 (Tokyo)							**Lunch Lecture 1**
13:30-15:00 (Beijing) 1:30-3:00 (Boston) 22:30-0:00 (California, -1 day) 5:30-7:00 (Greenwich) 15:30-17:00 (Sydney) 14:30-16:00 (Tokyo)	**Poster**						
15:00-16:30 (Beijing) 3:00-4:30 (Boston) 0:00-1:30 (California) 7:00-8:30 (Greenwich) 17:00-18:30 (Sydney) 16:00-17:30 (Tokyo)	**Symposium 7** Hemodynamic Characterization of the Coronary Microvasculature	**Symposium 8** Microcirculation in Gastrointestinal Cancer and Inflammation	**Symposium 9** Mitochondria/ Endoplasmic Reticulum and Microcirculation	**Young Symposium 2** Exploring the Molecular Events of Cerebrovascular Injury	**Free Oral Communication 5** Endoplasmic Reticulum, Mitochondria and Cell Death	**Free Oral Communication 6** Pericyte	**Satellite Symposium 5** Living Complex Fluid and Microcirculation
16:40-17:30 (Beijing) 4:40-5:30 (Boston) 1:40-2:30 (California) 8:40-9:30 (Greenwich) 18:40-19:30 (Sydney) 17:40-18:30 (Tokyo)							**Keynote Lecture 1** Noncoding RNAs in Vascular Health and Diseases
17:40-19:10 (Beijing) 5:40-7:10 (Boston) 2:40-4:20 (California) 9:40-11:20 (Greenwich) 19:40-21:20 (Sydney) 18:40-20:20 (Tokyo)	**Symposium 10** Myeloid Cell Interactions in the Tumor Microvasculature	**Symposium 11** Glial Regulation of Cerebral Blood Flow Responses	**Symposium 12** Molecules Going with the Flow: Physiology and Disease	**Symposium 13** Atherosclerosis, Sex and Microcirculation: The Influence of Hemodynamics	**Symposium 14** Aquaporins		
19:10-20-00 (Beijing)	Buffet Dinner						

22 SEP (FRI)

	Room 1	Room 2	Room 4	Room 5	Room 6	Room 7	Guorui Hall
8:30-10:00 (Beijing) 20:30-22:00 (Boston, -1 day) 17:30-19:00 (California, -1 day) 00:30-2:00 (Greenwich) 10:30-12:00 (Sydney) 9:30-11:00 (Tokyo)	**Symposium 15** Metabolism and Vascular Disease	**Symposium 16** MCS Presidents' Perspectives for Future Discoveries	**Symposium 17** Leukocyte Recruitment in Microvascular Inflammation	**Symposium 18** "Image-Based"Vascular Systems Biology and Emerging Technologies	**Free Oral Communication 7** Inflammation	**Symposium 19** The Cerebral Microcirculation as a Novel Target to Treat Dementia	**Satellite Symposium 6** Microcirculation and Ocular Diseases
10:00-11:30 (Beijing) 22:00-23:30 (Boston, -1 day) 19:00-20:30 (California, -1 day) 2:00-3:30 (Greenwich) 12:00-13:30 (Sydney) 11:00-12:30 (Tokyo)	**Free Oral Communication 8** Stroke	**Symposium 20** Infection and the Microcirculation: Lessons From COVID-19	**Symposium 21** Microcirculation in Diabetes	**Symposium 22** Cerebrovascular Diseases and BBB Permeability: Molecular Targets and Therapeutic Strategies	**Young Symposium 3** Young Symposium of Diabeto-Mircrocirculation	**Free Oral Communication 9** Shock	**Satellite Symposium 7** Microcirculation and Hemorheology in Shock
11:30-12:20 (Beijing) 23:30-00:20 (Boston, -1 day) 20:30-21:20 (California, -1 day) 3:30-4:20 (Greenwich) 13:30-14:20 (Sydney) 12:30-13:20 (Tokyo)							**Zweifach Award**
12:20-12:50(Beijing)	**Lunch**						
12:50-13:30 (Beijing) 00:50-1:30 (Boston) 21:50-22:30 (California, -1 day) 4:50-5:30 (Greenwich) 14:50-15:30 (Sydney) 13:50-14:30 (Tokyo)							**Lunch Lecture 2**
13:30-15:00 (Beijing) 1:30-3:00 (Boston) 22:30-0:00 (California, -1 day) 5:30-7:00 (Greenwich) 15:30-17:00 (Sydney) 14:30-16:00 (Tokyo)	**Poster**						
15:00-16:30 (Beijing) 3:00-4:30 (Boston) 0:00-1:30 (California) 7:00-8:30 (Greenwich) 17:00-18:30 (Sydney) 16:00-17:30 (Tokyo)	**Symposium 23** Microcirculation From Bench to Bedside: Translational Newest Findings	**Symposium 24** Cross-talk Between Microcirculation and Microrheology of Blood Cells	**Symposium 25** The Advantage of Traditional Chinese Medicine in Treating COVID-19	**Symposium 26** Vascular Redox Signaling and Oxidative Stress	**Young Symposium 4** A Window into the Microcirculation - Using Imaging to Unravel Physiological Mechanisms	**Free Oral Communication 10** New Methods and New Techniques	**Satellite Symposium 8** Endovascular Intervention of Peripheral Vascular Microcirculation Dysfunction Diseases
16:40-17:30 (Beijing) 4:40-5:30 (Boston) 1:40-2:30 (California) 8:40-9:30 (Greenwich) 18:40-19:30 (Sydney) 17:40-18:30 (Tokyo)							**Keynote Lecture 2** Brain Endothelium and Neuro-Inflammation
17:40-20:00 (Beijing)	Buffet Dinner						

23 SEP (SAT)

	Room 1	Room 2	Room 4	Room 5	Room 6	Room 7	Guorui Hall
8:30-10:00 (Beijing) 20:30-22:00 (Boston, -1 day) 17:30-19:00 (California, -1 day) 00:30-2:00 (Greenwich) 10:30-12:00 (Sydney) 9:30-11:00 (Tokyo)	**Symposium 27** Lymphatic Functions in Cardiovascular Disease	**Symposium 28** Novel Functions of Pericytes in the Microcirculation	**Symposium 29** Vascular Adaption in Aging, Obesity, and Metabolic Syndrome	**Symposium 30** Microcirculation, Stem Cells and Tissue Repair	**Free Oral Communication 11** Vascular Hyperpermeability	**Satellite Symposium 9** Diabetes and Microcirculation	**Plenary Lecture 1-3**
10:00-11:30 (Beijing) 22:00-23:30 (Boston, -1 day) 19:00-20:30 (California, -1 day) 2:00-3:30 (Greenwich) 12:00-13:30 (Sydney) 11:00-12:30 (Tokyo)	**Symposium 31** Cerebral Microvascular Injury and Pharmacological Intervention	**Symposium 32** Adaptations in Pregnancy in Health and Disease	**Symposium 33** Microcirculation and Cardiovascular Diseases	**Symposium 34** Novel Treatment Targets for Brain Disorders	**Young Symposium 5** Microcirculation Disturbance of Cardiovascular and Cerebrovascular Diseases and Drug Intervention		**Satellite Symposium 10** Advanced Technologies and Translational Medicine in Tumor Microcirculation
11:30-12:20 (Beijing) 23:30-00:20 (Boston, -1 day) 20:30-21:20 (California, -1 day) 3:30-4:20 (Greenwich) 13:30-14:20 (Sydney) 12:30-13:20 (Tokyo)							**Keynote Lecture 3** The regulation of platelet lifespan and its clinical implications
12:20-12:50(Beijing)	**Lunch**						
12:50-13:30 (Beijing) 00:50-1:30 (Boston) 21:50-22:30 (California, -1 day) 4:50-5:30 (Greenwich) 14:50-15:30 (Sydney) 13:50-14:30 (Tokyo)							**Lunch Lecture 3**
13:30-15:00 (Beijing) 1:30-3:00 (Boston) 22:30-0:00 (California, -1 day) 5:30-7:00 (Greenwich) 15:30-17:00 (Sydney) 14:30-16:00 (Tokyo)	**Poster**						
15:00-16:30 (Beijing) 3:00-4:30 (Boston) 0:00-1:30 (California) 7:00-8:30 (Greenwich) 17:00-18:30 (Sydney) 16:00-17:30 (Tokyo)	**Symposium 35** Vascular and Intravascular Components of Microcirculation in Norm and Disease	**Symposium 36** Integrated Traditional Chinese and Western Medicine for Cerebrovascular Disease	**Symposium 37** The Impact of Microvascular Aging on Brain Neural Functions: Experimental and Theoretical Approaches	**Symposium 38** Micro- and Macro-Circulatory Dysfunction in Disease	**Young Symposium 6** ESM/MCS/ANZMS Young Investigator Symposium	**Satellite Symposium 11** Myocardial Perfusion: From Pericardial Vessel to Microcirculation	**Plenary Lecture 4-6**
16:40-17:30 (Beijing) 4:40-5:30 (Boston) 1:40-2:30 (California) 8:40-9:30 (Greenwich) 18:40-19:30 (Sydney) 17:40-18:30 (Tokyo)							**The Nishimaru-Tsuchiya International Award** Imaging Metabolomics: Making the Invisible Visible without Labeling
17:40-20:00 (Beijing)	**Banquet**						

24 Sep (SUN)

	Room 1	Room 2	Room 4	Room 5	Room 6	Room 7	Guorui Hall
8:30-10:00 (Beijing) 20:30-22:00 (Boston, -1 day) 17:30-19:00 (California, -1 day) 00:30-2:00 (Greenwich) 10:30-12:00 (Sydney) 9:30-11:00 (Tokyo)	**Symposium 39** Emerging Mechanisms Underlying Vascular Contributions to Cognitive Impairment and Dementia. (Small Vessels Big Problems)	**Symposium 40** China-Japan Joint Symposium of Qi-Blood	**Symposium 41** The Vascular Endothelium in Human Gastroenterology and Hepatology Diseases	**Young Symposium 7** Selected From Abstract Submission	**Satellite Symposium 12** Microcirculation and Osteonecrosis	**Satellite Symposium 13** Microcirculation and Translational Medicine	**Plenary Lecture 7-9**
10:00-10:50 (Beijing) 22:00-22:50 (Boston, -1 day) 19:00-19:50 (California, -1 day) 2:00-2:50 (Greenwich) 12:00-12:50 (Sydney) 11:00-11:50 (Tokyo)							**Keynote Lecture 4** Targeting microvascular hyperpermeability to improve organ function
10:50-11:40 (Beijing) 22:50-23:40 (Boston, -1 day) 19:50-20:40 (California, -1 day) 2:50-3:40 (Greenwich) 12:50-13:40 (Sydney) 11:50-12:40 (Tokyo)							**Keynote Lecture 5** The glomerular microvasculature – where inflammatory leukocyte recruitment doesn't follow the rules
11:40-12:20 (Beijing) 23:40-24:20 (Boston, -1 day) 20:40-21:20 (California, -1 day) 3:40-4:20 (Greenwich) 13:40-14:20 (Sydney) 12:40-13:20 (Tokyo)							**Closing Ceremony**

GUORUI HALL

13:30-15:00 **Satellite Symposium 1: Traditional Chinese Medicine and Microcirculation**
Supported by Specialty Committee of Qi-Blood of World Federation of Chinese Medicine Societies and Professional Committee of Microcirculation of Chinese Association of Integrative Medicine

Chair: Ke-Wu Zeng, *Peking University, China*

Co-Chair: Jian Liu, *Peking University, China*

S01-1 **The ameliorative effect of salvianolic acid A, one main water-soluble component of salvia miltiorrhiza, on Lipopolysaccharide-Induced Leukocyte Recruitment and Oxidative Stress in Mesenteric Venules in Rats**

Chunshui Pan

Peking University Health Science Center, China

S01-2 **MALT1/NF-κB Study on the regulatory mechanism of microglia-mediated neuroinflammation after cerebral ischemia and the intervention effect of Dengzhanshengmai Formula**

Jingjing Zhang

Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China

S01-3 **Compound Danshen Dripping Pill inhibits vascular calcification in ApoE-deficient mice as well as VSMCs and ECs**

Yunhui Hu

Tasly International Gene Network Drug Innovation Center Co., Ltd, China

S01-4 **Advanced technologies for cellular targets identification of neuroprotective agents**

Ke-Wu Zeng

Peking University, China

15:00-16:30 **Satellite Symposium 2: From Microcirculation and Vascular Biology to Drug Target**
Supported by Professional Committee on Pharmaceutical Research of CSM

Chair: Feng Han, *Nanjing Medical University, China*

Co-Chair: Kohji Fukunaga, *Tohoku University, Sendai, Japan*

S02-1 **Fatty acid-binding proteins 3 and 5 mediate the mitochondrial damage in brain ischemia**

Kohji Fukunaga

Tohoku University, Japan

S02-2 **The role of endothelial Sema3G on vascular remodeling and spine formation**

Ying-Mei Lu

Nanjing Medical University, China

S02-3 **Analysis Platform for disease-oriented drug discovery by drug repurposing**

Katsuhisa Horimoto

SOCIUM Inc. Japan

S02-4 **Tissue optical clearing for vascular structure and function imaging**

Dan Zhu

Huazhong University of Science and Technology, China

16:40-17:30 **Opening Ceremony**

17:40-20:00 **Welcome Reception** (Banquet Hall, 3/F)

ROOM 1

08:30-10:00 **Symposium 1: KCa Channels as Regulators of Vascular Function**
Organized by MCS and Supported by 12th WCM

Chair: Andrew Braun, *University of Calgary, Canada*
Co-Chair: Michael Hill, *University of Missouri, USA*

001-SS1 **Vascular control by ion channel trafficking**
Jonathan Jaggar
University of Tennessee Health Science Center, United States

001-SS2 **Endothelial KCa channels as therapeutic targets in Type 2 Diabetes**
Andrew Braun
University of Calgary, Canada

001-SS3 **Role of Na+/K+ ATPase in Pulmonary Hypertension**
Jin-Song Bian
Southern University of Science and Technology, China

001-YS1 **The Functions of Vascular KCa Channels in Aging**
Erik Behringer
Loma Linda University, United States

10:00-11:30 **Symposium 4: Anti-Cancer Treatments and Endothelial Dysfunction: Mechanisms and Clinical Implications**
Organized by MCS and Supported by 12th WCM

Chair: Andreas Beyer, *Medical College of Wisconsin, United States*
Co-Chair: Karima Ait-Aissa, *Lincoln Memorial University, United States*

004-SS1 **Accelerated vascular aging induced by common chemotherapeutic agents: Understanding underlying mechanisms to inform future therapeutics strategies**
Zachary Clayton
University of Colorado, US

004-SS2 **iPSC Models Uncovering Statin's Epigenetic Role in Vascular Health Protection**
Chun Liu
Stanford University, United States

004-SS3 **Moesin and its Phosphorylation in VE-cadherin Expression and Distribution in Endothelial Adherens Junctions**
Qiaobing Huang
Southern Medical University, China

004-YS1 **Anti-cancer therapies induce human microvascular endothelial toxicity through direct and secondary signaling mechanisms**
Janée Terwoord
Rocky Vista University, US

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 7: Hemodynamic Characterization of the Coronary Microvasculature**
Organized by ESM/12th WCM and Supported by 12th WCM

Chair: Chunshui Pan, *Peking University Health Science Center, China*

007-SS1 **Mechanosensors and Their Significance in Vascular Diseases**
Jing Zhou
Peking University Health Science Center, China

007-SS2 **Multiparametric evaluation of coronary microvascular dysfunction in heart transplantation patients**

Annagrazia Cecere

University of Padova, Italy

007-YS1 **Rb1 attenuates cardiac microvascular hyperpermeability and hemorrhage after ischemia and reperfusion injury through restoration of microvascular endothelial cell junction and basement membrane**

Xinmei Huo

Peking University Health Science Center, China

007-YS2 **Spinning disk confocal intravital imaging revealed platelet and neutrophil dynamics in microvascular obstruction following ischemia-reperfusion injury and their synergistic interventions**

Zeng-Rong Chen

Fuwai Hospital, Chinese Academy of Medical Sciences, China

17:40-19:10 **Symposium 10: Myeloid Cell Interactions in the Tumor Microvasculature**

Supported by Sonderforschungsbereich SFB 914 of Deutsche Forschungsgemeinschaft (DFG)

Chair: Christoph Reichel, *Ludwig-Maximilians-Universität München, Germany*

Co-Chair: Sven Brandau, *University of Essen, Germany*

010-SS1 **Neutrophil trafficking in malignant tumors**

Sven Brandau

University of Essen, Germany

010-SS2 **Galectins in cancer-associated inflammation and thrombosis**

Elmina Bach

Ludwig-Maximilians-University of Munich, Germany

010-SS3 **Platelet functions in cancer**

Monika Haemmerle

University of Halle, Germany

010-SS4 **Platelets misguide immune cell responses in cancer**

Bernd Uhl

Ludwig-Maximilians-University of Munich, Germany

010-YS1 **A transcriptomic pan-cancer signature for survival prognostication and prediction of immunotherapy response based on endothelial senescence**

Zhen-Quan Wu

Ludwig-Maximilians-University of Munich, Germany

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 2

08:30-10:00 **Symposium 2: Ion Channels in Pulmonary Microcirculation in Health and Disease**
Organized by MCS and Supported by 12th WCM

Chair: Swapnil Sonkusare, *University of Virginia School of Medicine, United States*

Co-Chair: Nikki Jernigan, *University of New Mexico, United States*

002-SS1 **Endothelial Piezo1 channels in pulmonary hypertension**
Jason Yuan
University of California at San Diego, United States

002-SS2 **Acid-sensing ion channels in pulmonary hypertension**
Nikki Jernigan
University of New Mexico, United States

002-SS3 **Critical role of mechanosensitive ion channel Piezo1 in endothelial biology**
Jing Li
Guangzhou University of Chinese Medicine, China

002-YS1 **Impaired Endothelial Piezo1-Pannexin1-TRPV4 Channel Signaling Reduces Flow-Induced Dilation of Resistance Pulmonary Arteries in Pulmonary Hypertension**
Zdravka Daneva
University of Virginia , United States

10:00-11:30 **Symposium 5: Capillary Sensing**
Organized by MCS and Supported by 12th WCM

Chair: Hibi Toshifumi, *Kitasato University, Japan*

005-SS1 **Electro-metabolic signaling via capillaries regulates blood flow in heart**
W. Jonathan Lederer
University of Maryland, United States

005-SS2 **Cell-cell crosstalk in limb ischemia microenvironment**
Juan Feng
Peking University Health Science Center, China

005-SS3 **Spatiotemporal manipulation of capillary network flow**
Kazuto Masamoto
University of Electro-Communications, Japan

005-YS1 **Piezo1 Is a Mechanosensor Channel in Central Nervous System Capillaries**
Osama Harraz
University of Vermont, USA

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 8: Microcirculation in Gastrointestinal Cancer and Inflammation**
Organized by JSM and Supported by 12th WCM

Chair: Toshio Watanabe, *Osaka City University Graduate School of Medicine, Japan*

Co-Chair: Yuji Naito, *Kyoto Prefectural University of Medicine, Japan*

008-SS1 **Movement of Innate lymphoid Cells from Intestinal Mucosa to mesenteric lymph node through lymph collecting ducts in rats**
Ryota Hokari
National Defense Medical College, Japan

008-SS2 **The role of heme oxygenase-1 in intestinal ischemia/reperfusion injury in mice**
Tomohisa Takagi
Kyoto Prefectural University of Medicine, Japan

008-SS3 **Inflammation and microvascular sensitivity to flow and insulin**
Luis A. Martinez-Lemus
University of Missouri-Columbia, United States

008-YS1 **Current status of magnifying endoscopy for digestive neoplasms according to microvessel findings**
Osamu Dohi
Kyoto Prefectural University of Medicine, Japan

17:40-19:10 **Symposium 11: Glial Regulation of Cerebral Blood Flow Responses**
Organized by ESM and Supported by 12th WCM

Chair: Eszter Farkas, *University of Szeged, Hungary*
Co-Chair: Anusha Mishra, *Oregon Health and Science University, United States*

011-SS1 **Astrocyte regulation of the microvasculature in health and disease**
Anusha Mishra
Oregon Health and Science University, United States

011-YS1 **Reduced microvascular reactivity after stroke: the role of reactive astrocytes**
Ákos Menyhárt
University of Szeged, Hungary

011-YS2 **A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation**
Xiao-Yuan Yang
Morsani College of Medicine, University of South Florida, United States

011-SS2 **Microglia influence cerebral blood flow via direct and indirect purinergic actions**
Ádám Dénes
Institute of Experimental Medicine, Hungary

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 4

08:30-10:00 **Symposium 3: Endothelial Glycocalyx in Health and Disease**
Organized by MCS and Supported by 12th WCM

Chair: Qiaobing Huang, *Southern Medical University, China*
Co-Chair: Bingmei Fu, *The City College of the City University of New York, USA*

003-SS1 **The impact of intravenous fluid resuscitation on sepsis-associated glycocalyx dysfunction**
Eric P Schmidt
Denver Health Medical Center, University of Colorado Denver, Aurora, CO, USA

003-SS2 **Determining the structure, function and compositional relationship in capillary walls**
Kenton Arkill
University of Nottingham, U.K

003-SS3 **Endothelial glycocalyx degradation and microvascular hyperpermeability**
Jerome Breslin
University of South Florida, USA

003-YS1 **Restoration of Glycocalyx by sphingosine 1-phosphate**
Ye Zeng
Sichuan University, China

10:00-11:30 **Symposium 6: Novel Mechanisms of Regulation of Endothelial Cell Function**
Organized by ANZMS and Supported by 12th WCM

Chair: Michael Hickey, *Monash University, Australia*
Co-Chair: Giovanni E. Mann, *King's College London, United Kingdom*

006-SS1 **Regulation of blood brain barrier function in Alzheimer's Disease**
Kaka Ting
University of Sydney, Australia

006-SS2 **Nedd4 controls lymphatic endothelial cell sprouting and adhesion by regulating sphingosine 1-phosphate receptor activity**
Genevieve Secker
University of South Australia, Australia

006-SS3 **New regulators of Vegfc-driven lymphangiogenesis and vascular proliferation**
Kazuhide Okuda
Peter MacCallum Cancer Institute, Australia

006-YS1 **Mechanisms of Capillary Signaling to Arterioles to Regulate Oxygen Delivery**
Paulina Kowalewska
Robarts Research Institute, Western University, Canada

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 9: Mitochondria / Endoplasmic Reticulum and Microcirculation**
Supported by 12th WCM

Chair: Yu-Zhen Li, *Chinese PLA General Hospital, China*

009-SS1 **Coronary microcirculation: novel mechanisms and therapeutic targeting**
Miao Wang
Fuwai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences

009-SS2 **Cardiac mitochondria elongate as a physiological adaptation towards necroptosis**
Sang-Bing Ong
The Chinese University of Hong Kong (CUHK), Hong Kong SAR, China

009-YS1 **QiShenYiQi Pills improves retinal microvascular exudation in type 2 diabetic mice through restoration of energy metabolism**
Jian Liu
Peking University, China

009-YS2 **Role of mitochondrial quality control in cardiac microvascular ischemia/reperfusion injury**
Hao Zhou
PLA General Hospital, China

17:40-19:10 **Symposium 12: Molecules Going with the Flow: Physiology and Disease**
Organized by ESM and Supported by 12th WCM

Chair: Akos Koller, *New York Medical College, USA*
Co-Chair: Ines Drenjancevic, *University of Osijek, Osijek, Croatia*

012-SS1 **Flow-induced release of multifunction molecules from the endothelium: from fish to humans**
Akos Koller
New York Medical College, USA

012-SS2 **The Pathogenic Role of Cytokine-like Protein FAM3D in Vascular Injury**
Yi Fu
Peking University Health Science Center, China

012-SS3 **Permissive role of angiotensin II in the mediation of flow-induced responses**
Ines Drenjancevic
University of Osijek, Osijek, Croatia

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 5

08:30-10:00 Free Oral Communication 1: Cancer and Microcirculation

Chair: Qing Xia, *Peking University, China*

Co-Chair: Ryota Hokari, *National Defense Medical College, Japan*

F01-1 **Arid5b competes with STAU2 regulating BAI1 mRNA stability to regulate breast tumor angiogenesis**

Wenbao Lu

Institute of Microcirculation, China

F01-2 **AAV-delivery of engineered tRNA-enzyme pairs to overcome nonsense mutation in vivo**

Zhetao Zheng

Peking University, China

F01-3 **New Treatment Strategies of Glioblastoma: Targeted Regulation of Blood–Brain Barrier for Enhanced Therapeutic Efficiency of Hypoxia-Modifier Nanoparticles and Immune Checkpoint Blockade Antibodies**

zhouyue wu

Nanjing Medical University, China

F01-4 **Sodium Pentobarbital Suppresses Breast Cancer Cell Growth Partly via Normalizing Microcirculatory Hemodynamics and Oxygenation in Tumors**

Qin Wang

Institute of Microcirculation, China

F01-5 **Abrupt disruption of tumor microcirculation to block tumor growth by an innovative anti-CD39 monoclonal antibody**

huishan sun

Peking Union Medical College Hospital, China

F01-6 **Construction of an efficient gene prognosis signature in pancreatic cancer based on microvascular angiogenesis feature**

Shixiang Guo

Chongqing General Hospital, China

10:00-11:30 Free Oral Communication 3: Cerebral Microvascular Injury and Microcirculation

Chair: Yu-Min Luo, *Xuanwu Hospital Capital Medical University, China*

Co-Chair: Anqi Zhang, *Capital Medical University, China*

F03-1 **Erythropoietin-derived peptide ARA290 mediates brain tissue protection through the β-common receptor in mice with cerebral ischemic stroke**

Rongliang Wang

Cerebrovascular Disease Research, China

F03-2 **Knock down of lncRNA H19 attenuates cerebral ischemia/reperfusion injury by regulating IMP2**

Liyuan Zhong

Xuanwu Hospital of Capital Medical University, China

F03-3 **Electroacupuncture improves post-stroke central pain in rats by regulating miR-21-5p/Smad7 pathway**

Guihua Tian

Dongzhimen Hospital, China

F03-4 **Association of microvascular complications with reduced neuronal activity and cognitive impairment in type 2 diabetes mellitus: a resting-state fMRI study**

Jiaqing Shao

Nanjing University, China

F03-5 **Differential impact of factor XII, factor XI and prekallikrein deficiency on thrombosis in mice**
Lejia Hu
FUWAI Hospital, China

F03-6 **Panax notoginseng saponins promotes angiogenesis after cerebral ischemia-reperfusion injury**
Haiyan Xiao
Peking Union Medical College, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Young Symposium 2: Exploring the Molecular Events of Cerebrovascular Injury**
Supported by International Joint Laboratory for Drug Target of Critical Illnesses of Jiangsu Province, China

Chair: Feng Han, *Nanjing Medical University, China*

Y02-1 **In situ Imaging of Toxic Metabolites Mediating Neurovascular Injuries**
Xin Li
Zhejiang University, China

Y02-2 **Effect of acupuncture on boosting microvascular repair in neurodegenerative disease**
Rongrong Tao
Guangzhou University of Chinese Medicine, China

Y02-3 **Endothelial Cdk5 Deficit Leads to the Development of Spontaneous Epilepsy Through CXCL1/CXCR2-Mediated Reactive Astrogliosis**
Xiu-Xiu Liu
Nanjing Medical University, China

Y02-4 **Uncovering the Role of Fatty Acid-Binding Proteins in Mitochondrial Dysfunction: A Potential Therapy for Dementia and Cerebrovascular Injury**
Ichiro Kawahata
Ichiro Kawahata, Tohoku University, Japan

17:40-19:10 **Symposium 13: Atherosclerosis, Sex and Microcirculation: The Influence of Hemodynamics**
Oraganized by ESM and Supported by 12th WCM

Chair: Elena Osto, *University of Zurich and University Hospital Zurich, Switzerland*

Co-Chair: Francesco Tona, *University Hospital Padova, Italy*

013-SS1 **Microvascular endothelial dysfunction in skin is associated with higher risk of heart failure with preserved ejection fraction in women with type 2 diabetes: the Hoorn Diabetes Care System Cohort**
Elisa Dal Canto
University Medical Center Utrecht, Utrecht, the Netherlands

013-SS2 **Metabolism and vascular function**
Lemin Zheng
Peking University Health Science Center, China

013-YS1 **Sex-related differences in hemodynamics and atherosclerosis**
Jolanda Wentzel
Erasmus MC, Rotterdam, the Netherlands

013-YS2 **Deletion of BACH1 Attenuates Atherosclerosis by Reducing Endothelial Inflammation**
Dan Meng
Fudan University, China

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 6

08:30-10:00 **Young Symposium 1: JSM Young Investigator Symposium**

Supported by Japanese Society for Microcirculation

Chair: Hidekazu Suzuki, *Tokai University Scool of Medicine, Japan*

Co-Chair: Yoshikazu Tsuzuki, *Department of Gastroenterology, Saitama Medical University, Japan*

Y01-1 **Possible association of Proprotein Convertase Subtilisin/Kexin Type 9 expression and inflammation after cerebral reperfusion injury**

Atsushi Mizuma

Tokai University School of Medicine, Japan

Y01-2 **The smallest unit of capillary activity in the somatosensory cortex of awake mouse**

Hiroki Suzuki

The University of Electro-Communications, Japan

Y01-3 **Endoscopic hemostasis and transarterial embolization in patients with GI bleeding - Microcirculatory study and measures to improve the visibility of the bleeding blood vessels**

Masaya Sano

Tokai University School of Medicine, Japan

Y01-4 **Role of Prostaglandin E2 related pathways in gastric adenocarcinoma**

Yuji Nadatani

Osaka city university, Japan

10:00-11:30 **Free Oral Communication 4: Kidney and Lung Microcirculation**

Chair: Xin Li, *Zhejiang University, China*

Co-Chair: Wen-Tao Liu, *National Center for Nanoscience and Technology, China*

F04-1 **D-Ribose Induces Podocyte NLRP3 Inflammasome Activation and Glomerular Injury via AGEs/RAGE Pathway**

Jinni Hong

Guangdong provincial hospital, China

F04-2 **The Protective Effects of a Pure Chinese Medicinal Preparation from Eucommia Ulmoides and Pinoresinol Diglucoside on Renal and Intestinal Wall Microcirculatory Blood Perfusion and Vasomotion in Spontaneously Hypertensive Rats**

Jianqun Han

Peking Union Medical College, China

F04-3 **SHR Improves the Prediction of Contrast-Induced Nephropathy in NSTE-ACS Patients Undergoing PCI: A Retrospective Cohort Study**

Mingkang Li

Zhongda Hospital, China

F04-4 **Value of contrast-enhanced ultrasound in evaluating foot microcirculation in diabetes**

Da Zhang

Air Force Medical Center, China

F04-5 **Network Pharmacology and Experimental Assessment to Explore the Effects of Shenzhuo Formula against Diabetes Kidney Disease Podocyte Apoptosis**

lili Zhang

Guang'anmen Hospital, China

F04-6 **Inhibition of Endothelial-to-Mesenchymal Transition and Capillary Injury With TFA Alleviates Renal Fibrosis in Diabetic Kidney Disease**

Yi-Gang Wan

Nanjing Drum Tower Hospital, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Free Oral Communication 5: Endoplasmic Reticulum, Mitochondria and Cell Death**

Chair: Kazuto Masamoto, *University of Electro-Communications, Japan*

Co-Chair: Katrin Schröder, *Goethe-University Frankfurt, Faculty of Medicine, Germany*

F05-1 **Vascular endothelial cell-specific arginase 2 is involved in vasculopathies through regulating mitochondrial dynamics in diabetes**

Feng Guo

Shandong University of Traditional Chinese Medicine, China

F05-2 **TFEB nitration alleviating autophagy is involved in vascular endothelial cell senescence in hyperhomocysteinemia**

Wenjing Yan

Capital Medical University, China

F05-3 **Serpina3c derived from peripheral adipocytes alleviates atherosclerosis by inhibiting perivascular adipose tissue inflammation**

Yu Jiang

Zhongda Hospital, China

F05-4 **Semaglutide alleviates endothelial cell injury induced by high glucose and fat through regulating mitochondrial energy balance**

Jun Song

Shanghai East Hospital, China

F05-5 **The mechanism of HDAC4 regulating mitophagy of fibroblasts on wound healing of diabetic foot ulcers**

Changlong Bi

The Eighth Affiliated Hospital of Sun Yat-sen University, China

F05-6 **The crude polysaccharide of Fructus Ligustri Lucidi relieved renal fibrosis of UUO mice and I/R mice by alleviating kidney mitochondrial injury**

Jiali Zhang

Shanghai University of Traditional Chinese Medicine, China

17:40-19:10 **Symposium 14: Aquaporins**

Supported by 12th WCM

Chair: Baoxue Yang, *Peking University, China*

Co-Chair: Masato Yasui, *Keio University School of Medicine, Japan*

014-SS2 **Soluble (pro) renin receptor as a new regulator of collecting duct water reabsorption**

Tianxin Yang

University of Utah, USA

014-SS2 **Pathological roles of aquaporin-4 in neurodegenerative disorders**

Masato Yasui

Keio University School of Medicine, Japan

014-YS1 **Physiological roles of aquaporin-3 as glycerol channel**

Yi Ying

Peking University, China

014-YS2 **KLF5-mediated aquaporin 3 activated autophagy to facilitate cisplatin resistance of gastric cancer**

Yong Chen

The Second People's Hospital of Huai'an, China

ROOM 7

08:30-10:00 **Free Oral Communication 2: Cardiac Microcirculation**

Chair: Miao Wang, *Fuwai Hospital, China*

Co-Chair: Yan Zhu, *Tianjin University of Traditional Chinese Medicine, China*

F02-1 **Pulsatile Flow Promotes Microcirculatory Perfusion and Maintains the Endothelial Integrity during Extracorporeal Membrane Oxygenation**

Guanhua Li

Sun Yat-sen Memorial Hospital, China

F02-2 **Cardiac-Specific BACH1 Ablation Attenuates Pathological Cardiac Hypertrophy by Inhibiting the Ang II Type 1 Receptor Expression and the Ca2+/CaMKII Pathway**

Xiangxiang Wei

Fudan University, China

F02-3 **YiQiFuMai injection inhibits pulmonary interstitial edema after myocardial infarction by protecting the cellular junctions via energy metabolism and ZEB1/PARD3/TBC1D2b pathway**

Ting-Ting Xie

Peking University Health Science Center, China

F02-4 **Evaluation of the drug-drug interaction potential of neoadjuvant chemotherapy using a physiologically-based pharmacokinetic modelling approach**

Tongtong li

Nanjing Medical University, China

F02-5 **Clinical study of antibiotic loaded bone cement in treatment of 104 patients with moderate to severe diabetic foot infection**

Chenbing Zhao

Henan Provincial People's Hospital, China

F02-6 **Physiologically-Based Pharmacokinetic (PBPK) Modeling of midazolam injection in neonates**

Tangping Zhao

Nanjing Medical University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Free Oral Communication 6: Pericyte**

Chair: Guiling Zhao, *University of Maryland School of Medicine, USA*

Co-Chair: Sheng-Han Song, *Beijing Chaoyang Hospital, China*

F06-1 **HDAC1 regulates peripheral neuropathy to affect diabetic foot wound healing**

Aixia Zhai

The Eighth Affiliated Hospital of Sun Yat-sen University, China

F06-2 **Glycation of fibronectin inhibits PDGF-BB signaling activation by uncoupling PDGF receptor-β-α5β1 integrin cross-talk**

Liqun Wang

Southwest Medical University, China

F06-3 **Single-cell profilling of pericytes in adult mouse and identifying cell-type specific molecular change in Alzheimer's disease**

Xiaochen Yuan

Peking Union Medical College, China

F06-4 **High glucose mediates diabetic peripheral neuropathy by inducing Schwann cell apoptosis through the Dgkh/PKC-α signaling pathway**

Linhui Zuo

Xiangya Hospital of Centeral South University, China

F06-5 **Endothelial TFEB signaling-mediated autophagic disturbance initiates microglial activation and cognitive dysfunction**

Yaping Lu

Nanjing Medical University, China

F06-6 **Epitranscriptomic mechanisms of N6-methyladenosine methylation regulating mammalian hypertension development by determined spontaneously hypertensive rats pericytes**

Qingbin Wu

Peking Union Medical College, China

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

GUORUI HALL

08:30-10:00 **Satellite Symposium 3: Microvascular Network Modeling and Visualization**
Supported by Professional Committee on Information and Technology of CSM

Chair: Yang Li, *Biomedical Engineering College of Chongqing University, China*

Co-Chair: Gangmin Ning, *Zhejiang University, China*

S03-1 **Recent Advances in Tumor Microcirculation Visualization and Its Applications in Cancer Research**
Meng Yang
AntiCancer PDOX, LLC

S03-2 **Modelling Microcirculation System – From Structure to Function**
Gangmin Ning
Zhejiang University, China

S03-3 **Quantitative microvascular angiography and blood flowmetry by optical speckle imaging**
Pengcheng Li
Huazhong University of Science and Technology, China

S03-4 **Pulsatile Hemodynamics in the Microvascular Networks – Insights from Computational Approaches**
Qing Pan
Zhejiang University of Technology, China

10:00-11:30 **Satellite Symposium 4: Hemoglobin-Based Oxygen Carrier and Microcirculation**
Supported by Professional Committee on Information and Technology of CSM

Chair: Jiaxin Liu, *Chinese Academy of Medical Sciences & Peking Union Medical College, China*

Co-Chair: Baoliang Sun, *Shandong First Medical University, China*

S04-1 **Polymerized human hemoglobin enhanced tumor oxygenation: A novel strategy for cancer therapy**
Jiaxin Liu
Chinese Academy of Medical Sciences & Peking Union Medical College, China

S04-2 **Study on the role of active ingredient of earthworm in improving microcirculation disorders**
Sun Jianbo
China Pharmaceutical University, China

S04-3 **Improvement of microcirculatory perfusion by hemoglobin-based oxygen carriers after experimental cerebral ischemia**
Baoliang Sun
Shandong First Medical University, China

S04-4 **Effects of compound anisodine on functional status of microvascular vasomotion in rats**
Jian Zhang
Institute of Microcirculation, Chinese Academy of Medical Sciences, China

11:30-12:20 **TaiShan Award Lecture**

Chair: Ruijuan Xiu, *Institute of Microcirculation, Chinese Academy of Medical Sciences, China*

Naifeng Liu, *School of Medicine, Southeast University, China*

AL-01 **Tumor suppressor-associated cell cycle regulators in the malignant development of tumors**
Qimin Zhan
Peking University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

12:50-13:30 **Lunch Lecture 1**

Chair: Qiaobing Huang,*Southern Medical University, China*

LL-01 **Efficacy and Safety of Angoing Niuhuang Pill as an Adjunct Therapy for thrombolytic treatment for ischemic stroke**

Jiangang Shen

Shool of Chinese Medicine, State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong SAR, China

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Satellite Symposium 5: Living Complex Fluid and Microcirculation**

Supported by Professional Committee on Phlegm-Stasis of CSM

Chair: Dong Han, *National Center for Nanoscience and Technology, China*

Co-Chair: John Gore, *Vanderbilt University Institute of Imaging Science, USA*

S05-1 **Magnetic resonance imaging on structure of living interstitium and fluid behaviour within**

Xiaohan Zhou

National Center for Nanoscience and Technology, China

S05-2 **Randomized controlled trial of Kuanxiong aerosol to improve coronary microcirculation disorder during PCI**

Hongxu Liu

Beijing Hospital of Traditional Chinese Medicine, China

S05-3 **Hypersensitive MR Angiography based on Nanoprobe for Diagnosis of Cardiac-cerebral Vascular Diseases**

Yi Hou

University of Chemical Technology, China

S05-4 **Functional MRI of White Matter**

John Gore

Vanderbilt University Medical Center, America

16:40-17:30 **Keynote Lecture 1**

Chair: Henning Morawietz, *University of Technology Dresden,Germany*

KL-01 **Noncoding RNAs in Vascular Health and Diseases**

Stefanie Dimmeler

Institute for Cardiovascular Regeneration, Goethe University, Germany

19:10-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

B1/F

Cardiac Microcirculation

P001: **Incremental prognostic value of dynamic lactate in critically ill patients with acute myocardial infarction**
Yuanyuan Zhao, Hongjian Dong, Genshan Ma, Lijuan Chen

P003: **Risk stratification and predictive value of serum sodium fluctuation for adverse prognosis in acute coronary syndrome patients**
Xiangwei Bo, Lijuan Chen

P005: **Trimetazidine alleviated cardiac dysfunction and fibrosis after myocardial infarction in rats**
Leilei Tang, Yang Liu, Jiawen Yu, Lingdi Zhang, Mengling Ye, Guojun Jiang

P007: **3, 4-dihydroxyl-phenyl lactic acid attenuated ischemia/reperfusion induced cardiac microvascular endothelial dysfunction through regulating Syndecan-4**
Li Yan, Chun-Shui Pan, Quan Li, Xin-Mei Huo, Yu-Ying Liu, Xin Chang, Ping Huang, Kai Sun, Jing-Yan Han

P009: **Dynamic Assessments of Coronary Flow Reserve After Myocardial Ischemia Reperfusion in mice**
Ziyu Guo, Ao Wang, Yanxiang Gao, Enmin Xie, Zixiang Ye, Yike Li, Xuecheng Zhao, Nan Shen, Jingang Zheng

P011: **Diagnostic value of magnetocardiography in stable coronary artery disease patients with microvascular dysfunction**
Bo Wang, Yawei Xu, Hailing Li

Traditional Chinese Medicine and Microcirculation

P013: **Unraveling the molecular mechanisms of Qing-Xin-Jie-Yu Formula against coronary heart disease, based on bioinformatics and network pharmacology with molecular docking and dynamic simulation**
Zhuyu Yuan, Yi Guo, Li Chen, Xiaoang Liu, Hua Qu, Dazhuo Shi

P015: **Gushe Tongluo Formula on glomerular filtration rate in patients with chronic renal failure**
GuanYi Ye

P017: **The research of microcirculation evaluation of rats with Qi deficiency and blood stasis**
Hao Guo, Tingting Hao, Xiaoshan Cui, Jianxun Liu

P019: **Sanpian decoction ameliorates cerebral ischemia-reperfusion injury by regulating SIRT1/ERK/HIF-1α pathway through in silico analysis and experimental validation**
Tong Yang , Xiaolu Liu ,, Yue Zhou , Lipeng Du , Yang Fu , Yanan Luo , Wenli Zhang , Zhitao Feng , Jinwen Ge , Zhigang Mei ,

Thrombosis and Thrombolysis

P021: **YangXueQingNao Wan attenuated blood-brain barrier disruption after tissue plasminogen activator thrombolysis in mice**
Shuqi Yao, Yang Ye, Quan Li, Xiaoyi Wang, Li Yan, Xinmei Huo, Chunshui Pan, Jingyan Han

P023: **QiShenYiQi Pills ameliorates aspirin and clopidogrel induced stomach hemorrhage in rats**
Ru-Yu Zhan, An-Qing Li, Huan Li, Gulinigaer Anwaier, Li Yan, Chun-Shui Pan, Kai Sun, Xin Chang, Chuan-She Wang, Jing-Yu Fan, Xin-Mei Huo, Jian Liu, Jing-Yan Han

P027: **Epidermal growth factor receptor (EGFR) dependent on insulin signaling pathway regulates hepatic insulin resistance through insulin activation**
Tian Li

Diabetes and Microcirculation

P029: **Time in range, especially overnight timein range, is associated with sudomotordysfunction in patients with type 1 diabetes**
Zhou-qin Feng, Jiaqing Shao, Ping Gu

P031: **Difference analysis in artery plaque above or below the knee in patients with diabetic foot ulcer and periptery artery disease by proteomics**
Jun Xu, Tiantian Li, Hong Jiang, Yanming Li, Baixi Zhuang, Miao Yang, Bai Chang

P033: **Renal fat fraction and its influencing factors in patients with type 2 diabetes mellitus**
Mingming Li, Hong Sun

P035: **Pathogenic bacteria distribution and drug sensitivity of diabetic foot ulcer complicated with necrotizing fasciitis of lower extremity**
Huifeng Zhang, Yantao Li

P037: **Acarbose attenuates endothelial progenitor cell dysfunction in streptozotocin-induced diabetic mice**
Jia-Wen Yu, Guo-Jun Jiang, Lei-Lei Tang, Ling-Di Zhang, Jian-Jun Zhu

P039: **The association of circulating chemerin level with mild cognitive impairment in patients with type 2 diabetes mellitus, a cross-sectional study based on resting-state fMRI analysis**
Xinyi Yang, Wei Wang, Yuting Yang, Bingjie Yang, Bin Lu, Xiaoyan Hui, Ping Gu, Jiaqing Shao

P041: **Newly established LC-MS/MS method for measurement of plasma BH4 as a predictive biomarker for kidney injury in diabetes**
Chunxia Deng, Shuo Wang, Zhili Niu, Yahong Ye, Ling Gao

Stroke

P043: **uPAR and cFn: candidates for assisting in guiding whether thrombolysis or not in acute ischemic stroke**
Yilin Wang, Yuyou Huang, Ziping Han, Zhenhong Yang, Yumin Luo

P045: **Total Salvianolic Acid Injection Attenuates Blood-Brain Barrier Disruption and Hemorrhagic Transformation in Ischemic Stroke Mice with Delayed RhPro-UK Treatment**
Xiao-Yi Wang, Quan Li, Chun-Shui Pan, Li Yan, Jing-Yu Fan, Zhi-Zhong Ma, Jing-Yan Han

P047: **The Mechanism of Mitophagy Regulated by USP30 in Activation of NLRP3 Inflammasome after Subarachnoid Hemorrhage**
Yang Liu

P049: **Effect of glucocorticoid in the treatment of inflammatory response in cerebral venous thrombosis**
Xue Li, Shuyuan Hu, Yiwei Zhang, Jiangang Duan, Haiping Zhao

P051: **LC-MS/MS metabolomic profiling of the protective butylphthalide effect in cerebral ischemia/reperfusion mice**

Yangmin Zheng, Fangfang Zhao, Yue Hu, Feng Yan, Yue Tian, Rongliang Wang, Yuyou Huang, Liyuan Zhong, Yumin Luo, Qingfeng Ma

P053: **Naotaifang formula attenuates ferroptosis and necroptosis following cerebral ischemia/reperfusion injury via regulating HSP90-GCN2-ATF4 signaling pathway**
Yue Zhou, Tong Yang, Xiangyu Chen, Qi Liang, Runying Tian, Jiarui Zhang, Xiangyuan Wang, Zhigang Mei, Jinwen Ge

P055: **Astragaloside IV combined with ligustrazine alleviated cerebral ischemia reperfusion injury by regulating mitochondrial dynamics via the Drp1 SUMO/deSUMOylation**
Xiangyu Chen, Gangying Fu, Tong Yang, Yue Zhou, Feiyue Sun, Jing Zhou, Runying Tian, Zhigang Mei

P057: **Role of bone marrow-derived mesenchymal stem cells on hemorrhagic shock-induced lung injury in rats**
Wendi Wang, Ziye Meng, Zhen-Ao Zhao

Hypertension and Microcirculation

P059: **Toll-like receptor4 contributes to impaired pancreatic microvascular vasomotion in spontaneously hypertensive rat via mediating endothelial dysfunction**
Ailing Li, Mingming Liu, Xiaoyan Zhang, Bing Wang, Xueting Liu, Yuan Li, Bingwei Li, Qin Wang, Wenbao Lu, Hongwei Li, Jianqun Han, Ruijuan Xiu

Dementia and Microcirculation

P061: **Study on the mechanism of Coptis chinensis Franch. and its main active components in treating Alzheimer's disease based on SCFAs using Orbitrap Fusion Lumos Tribrid MS**
Qi Wang

Cerebral Microcirculation

Atherosclerosis

P065: **Serpina3c alleviates atherosclerosis via inhibiting sphingomyelin secretion from adipose tissue**
Jiaqi Guo, Zhenjun Ji, Yu Jiang, Ya Wu, Genshan Ma, Yuyu Yao

Arterial Stiffness

P067: **Hyperlipidaemia initiates vascular calcification via mitochondrial stress-triggered VEC senescence-dependent osteoblastic differentiation in VSMCs and macrophage formation in monocytes**
Zhengdong Chen , Naifeng Liu

Inflammation

P069: **Roukou Wuwei Pills ameliorate depression through attenuating neuroinflammation**
Yan-Chen Liu, Ke-Wu Zeng, Jing-Yan Han

Cancer and Microcirculation

P071: **AIMP2: promising biomarker for therapeutic target and prognosis of Breast Cancer**
Heda Zhang

P073: **Fatty acids reshape the fitness and functionality of tumor-resident CD8+ T cells by maintaining ITM2A expression**
Maoxiao Feng

P075: **Autophagy inhibition by chloroquine enhances the anti-tumor effects of bazedoxifene in colon cancer, in vitro and in vivo**
San-hong Li

P077: **Biomarkers and Prognostic Factors of PD-1/PD-L1 Inhibitor-Based Therapy in Patients with Advanced Hepatocellular Carcinoma**
Zhang Nan, Yang Xu, Piao Mingjian, Xun Ziyu, Wang Yunchao, Ning Cong, Zhang Xinmu, Zhang Longhao, Wang Yanyu, Wang Shanshan, Zhao Haitao

Endothelial Cells

P081: **Glycyrrhizic acid induces endothelium-dependent relaxation in rat mesenteric artery via PI3K/Akt/eNOS pathway**
Ding-Zhou Weng, Hui-Yu Chen, Chun-Shui Pan, Kai Sun, Jing-Yan Han, Jian Liu

P083: **DDX24 is essential for placental development and uterine spiral artery remodeling in mice**
Yan Liang, Jie Liu, Zexiao Wei, Shengnan Wang, Li Wang#

Pericytes

P085: **The moleoule mechanism of ASK1 on pericytes damage induced by cerebral ischemia and reperfusion**
Wendi Wang, Ying Wang

P087: **Inhibition of Pericyte-Myofibroblast Transition and Platelet-Derived Growth Factor Receptors Activation With Fucoidan Ameliorates Renal Congestive Fibrosis**
Si-Yu Cha, Yu Wang, Yi-Gang Wan

Neutrophils

P089: **Analysis of epidemiological characteristics and risk factors of 86 chronic wound patients**
Chenyang Ge , Xuegang Zhao , Qingfu Zhang

Pulmonary Microcirculation

P091: **Hypoxia-induced lactation modification of TG2 to promote pulmonary vascular remodeling in hypoxic pulmonary hypertension**
Linqing Li , Minhao Zhang , Qi Xue , Zhanneng Yang , Dong Wang , Gaoliang Yan , Yong Qiao , Changchun Tang

P093: **Clinical and genetic features of pulmonary sclerosing pneumocytoma: a clinical study of 58 Chinese patients**
Di Wu, Jun Chen

P095: **Influence of different thoracoscopic operations on pulmonary function tests and analysis of related factors**
Di Wu, Jun Chen

P097: **Apatinib added when NSCLC patients get slow progression with EGFR-TKI: a prospective, single-arm study**
Minghui Liu, Jun Chen

P099: **Chinese patent medicine Zilongjin tablet combined with chemotherapy in the treatment of postoperative adenocarcinoma of lung**
HUA YU

Macrophages

P101: **Anti-colorectal Cancer Activity of Bilobalide in Patient-derived Colorectal Cancer Organoids and AOM/DSS Mouse Model**

Heng Zhang, Deqiang Wang

Stem Cells

P103: **The homing and neuroprotective effects of hair follicle stem cells after cerebral ischemia-reperfusion**
Hao Tang, Fu Jin

Mitochondria

P105: **The protective effect and mechanism of rhein on cardiomyocyte injury in diabetic cardiomyopathy**
Tiantian Wang, Wei Wang, Cuihua Yang, Bin Lu, Jiaqing Shao

Extracellular Vesicles

P107: **Adipocyte-derived exosomal miR-22-3p modulated by circadian rhythm disruption regulates insulin sensitivity in skeletal muscle cells**
Haohao Zhang, Xiaoning Zhang, Hengru Guo, Bo Qiao, Wanting Li

Intestinal Microcirculation

P109: **Gut microbiota regulates blood pressure by modulating the synthesis of pentosidine in individuals with high-salt diet-induced hypertension**
Tianhao Liu, Hong Wei, Liguo Chen

miRNA

P111: **MicroRNA-221-3p inhibits the inflammatory response of keratinocytes by regulating the DYRK1A/STAT3 signaling pathway to promote wound healing in diabetes**
Keyan Hu, Lei Liu, Songtao Tang, Qiu Zhang

Noncoding RNAs

P113: **Screening and biological function validation of circRNA associated with matestasis of hepatocellular carcinoma**
Sheng Su, Zhiqiang Hu

Oxidative Stress

P115: **Changes in pancreatic structure and function in rats with high-voltage electrical burns and intervention effect of N-acetylcysteine**
Meixiu Li

Renal Microcirculation

P117: **Role of SGLT2 inhibitor on diabetic renal tubular lipid accumulation**
Hong Sun

P119: **Shenzhuo Formula improves microcirculation in the treatment of diabetic kidney disease by regulating lipid metabolism**
Yu Wei, Lili Zhang, Linhua Zhao

P121: **Convolutional neural networks for the detection of diabetic nephropathy and membranous nephropathy from retinal fundus images**
Yu-Qi Wang, Li-Qiang Wang, Yi-Fei Huang

Angiognesis

P123: **CD44 impairs vascular basement membrane integrity in pathological angiogenesis**
Xiaoxia Huang, Jiaqing Hu, Zhuanhua Liu, Xing Zhou, Maomao Sun, Yiwei Lin, Zexi Zhao, Xiaohua Guo, Qiaobing Huang

Ferroptosis

P125: **M6A Demethylase FTO Affecting the Biological Behavior of Papillary Thyroid Carcinoma by Regulating Ferroptosis**
Feihong Ji

P127: **SCD-1 down-regulation mediates hepatocyte ferroptosis and leads to septic liver injury**
Zhuanhua Liu, Qin Zhang, Jiayi Wei, Xiaoxia Huang, Xing Zhou, Maomao Sun, Junrui Zhu, Xiaohua Guo, Qiaobing Huang

Vascular Barrier

P129: **Mechanism Research of Electroacupuncture for Neuropathic Pain after Sciatic Nerve Injury Based on Blood Nerve / Spinal Cord Barrier**
Xianfei XIE, Ke HE, Xinyi LI, Junyi LONG, Guihua TIAN

Lymphatic Vesse

P131: **Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases**
Baoliang Sun, Ying Wang, Jingyi Sun, Mingfeng Yang, Hui Yuan, Robert A Colvin

P133: **Role of mitophagy in estrogen-induced improvement of lymphatic contractility in hemorrhagic shock**
Sen-Lu Zhang, Hong Chang, Yi-Ming Li, Hai-Ning Zheng, Zhen-Ao Zhao, Hui-Bo Du, Hong Zhang, Chun-Yu Niu, Zi-Gang Zhao

Hepatic Microcirculation

P135: **Targeting PTP1B to investigate the amelioration of hepatic lipid accumulation and microcirculation dysfunction in mice**
Jiang Li, Xiaolin Zhang, Jinying Tian, Juan Li, Xuechen Li, Song Wu, Yuying Liu, Dongting Chen, Jingyan Han, Fei Ye

P137: **Nitrative NCOA4 promotes liver injury induced by homocysteine**
Wenjing Yan

P139: **Prognostic efficacy and prognostic factors of TACE combined with TKI and ICIs in the treatment of unresectable hepatocellular carcinoma: a retrospective study**
Faji Yang, Qingqiang Ni, Shizhe Zhang, Xie Song, Hengjun Gao

Fibrosis

P143: **3,4-dihydroxyl-phenyl lactic acid ameliorates cardiac fibrosis and cardiac hypertrophy induced by pressure overload**
Fan-Kai Chen, Gulinigaer Anwaier, Chun-Shui Pan, An-Qing Li, Li Yan, Kai Sun, Jing-Yan Han, Jian Liu

New Concepts and Technology

P145: **Clinical outcomes of retrievable inferior vena cava filters for venous thromboembolic diseases**
Peng JIANG

P147: **Diverse Effect of Virtual Reality Visual Perceptual Plastic**

Training in Glaucoma Patients of Different Age and Different Severity
Yan Lu, Mengyu Zhao

P149: **The effect of microcirculation on prediction of delayed extubation**
Yan-Jie Zhang, Feng-Mei Guo, Jing-Yuan Xu

Ocular Fundus Microcirculation

P151: **Alteration of intestinal microbiota is associated with diabetic retinopathy and its severity: samples collected from southeast coast Chinese**
Qihan Zhu, Chaoyin Lu, Jian Pan, Jianzhong Ye, Xuemei Gu

P153: **Retinal fluid is associated with cytokines of aqueous humor in the intraocular microvascular inflammation**
Siyuan Song, Kai Jin, Shuai Wang, Ce Yang, Jingxin Zhou, Zhiqing Chen, Juan Ye

P155: **Effectiveness of aflibercept in the treatment of neovascular age-related macular degeneration of eyes and related prognostic factors influencing the drug efficacy**
Ling Yuan, Zhijuan Hua, Wenchang Yang, Dongli Li, Lu Shen, Yuxiang Zheng, Qiying Zhang, Yixin Cui, Boyong Zhang

Bone Microcirculation

P157: **Effect and Mechanism of Kunling Wan to Improve Osteoporosis and Fat Accumulation in Ovariectomized Female Mice**
Xiaoqing Lu, Yuxin Jin, Jingyan Han, Yin Li

Ischemia and Reperfusion Injury

P159: **The effects of different solutions on oxygen carrying/releasing capacity, ATP and acidity/basicity of stored red blood cells (SRBCs)**
Ming Sheng

P161: **Naotaifang Formula ameliorates cerebral ischemia-reperfusion injury by attenuating ferroptosis and m6A demethylases via FTO/ALKBH5/GPX4 signaling pathway**
Tong Yang, Yue Zhou, Xiangyu Chen, Qi Liang, Runying Tian, Jiarui Zhang, Xiangyuan Wang, Zhigang Mei, Jinwen Ge

L-Cardiac Microcirculation

P163: **Extracellular vesicle-derived circCEBPZOS attenuates postmyocardial infarction remodeling by promoting angiogenesis via the miR-1178-3p/ PDPK1 axis**
Mao Shuai

L-Diabetes and Microcirculation

P165: **The effect of novel dimeric peptide GX1 mediated by TGM2 on antiangiogenic activity to diabetic retinopathy**
Xiaoli Hui, Lu Wang, Yingying Luo, Wei Cui, Kaichun Wu

P167: **Association of first-phase insulin secretion with diabetic vascular complications in type 2 diabetes**
Zhenlin Li, Ying Chen, Changlong Bi, Aixia Zhai, Kaming Yang, Wanwen Lao, Xinyi Kong, Shitong Zhang, Jiaxin Li, Jianhua Zhong, Chaiying Ke, Yiqi Lin, Yang Liu, Yuetong Li

P169: **Sex differences in the glycocalyx integrity of the sublingual microvessels in individuals with type 2 diabetes: impact of body fat and LDL-cholesterol**
Andrew Forbes Brown, Kim Gooding, Mawson David, Aizawa Kuni, Ball Claire, Govier Alina, Balma Silvia, Watkins Darcy, Barnes Anna, Kirkwood John, Gilchrist Mark, Angela Shore

L-Stroke

P171: **Novel function of NMMHC IIA identified by Ruscogenin in blood brain barrier**
Yujie Dai, Shuaishuai GONG, Fang Li, Yuanyuan Zhang, Junping Kou

L-Cerebral Microcirculation

P173: **Both acute kidney injury and chronic kidney disease sensitize cerebral vasoconstriction through fibroblast growth factor 2 signaling pathway**
Liang Zhao, Chunxiang Xu, Xingyu Qiu, Gensheng Zhang, Jianhua Mao, Enyin Lai

L-Noncoding RNAs

P175: **Hypoxia-induced circPLOD2a/b promote migration and invasion of GBM cells via suppressing XIRP1 through binding to HuR**
Aixin Yu, Yiqi Wang, Chao Duan, Wendai Bao, Zhiqiang Dong

L-Lymphatic Vessel

P177: **12th World Congress of Microcirculation**
Oxana Semyachkina-Glushkovskaya, Fedosov Ivan, Kurths Jürgen

L-Stem Cells

P179: **Photomodulation promotes the differentiation of adipose-derived stem cells towards endothelial progenitor cells**
Yuqian He, Zhang Tao, Ma Xiaoyu, Lei Jiaojiao, Wu Jianbo

ROOM 1

08:30-10:00 **Symposium 15: Metabolism and Vascular Disease**

Supported by 12th WCM

Chair: Weizhen Zhang, *School of Basic Medicine, Peking University, China*

Co-Chair: Zijian Li, *Peking University Third Hospital, China*

015-SS1 **Adaptor protein HIP-55-mediated signalosome protects against ferroptosis in myocardial infarction**

Zijian Li

Peking University Third Hospital, China

015-SS2 **Role of GPCRs in hepatic triglyceride and cholesterol metabolism**

Weizhen Zhang

School of Basic Medicine, Peking University, China

015-SS3 **Effect And Mechanism Of Silibinin To Improve Non-Alcoholic Fatty Liver Disease**

Yin Li

School of Basic Medical Sciences, Peking University, China

015-SS4 **Single base-edited stem cell derived endothelial cells for modelling arteriovenous malformation**

Kai Wang

Peking University, China

10:00-11:30 **Free Oral Communication 8: Stroke**

Chair: Quan Li, *Peking University Health Science Center, China*

Co-Chair: Juan Feng, *Peking University Health Science Center, China*

F08-1 **Effects of Drag-Reducing Polymers on Microcirculation and Tissue Oxygenation in Rats with Traumatic Brain Injury of Varying Severity: Gender and Dosage Differences**

Denis Bragin

Lovelace Biomedical Research Institute, USA

F08-2 **Menaquinone-4 attenuates early brain injury after subarachnoid hemorrhage by inhibiting neuronal iron death through upregulation of DHODH**

Jiatong Zhang

Nanjing University, China

F08-3 **A cold case of thrombolysis: Cold recombinant tissue plasminogen activator confers enhanced neuroprotection in experimental stroke**

Yuyou Huang

Xuanwu Hospital of Capital Medical University, China

F08-4 **Administration of intramuscular AAV-BDNF and intranasal AAV-TrkB promotes neurological recovery via enhancing corticospinal synaptic connections in stroke rats**

Jing Wang

Shandong First Medical University, China

F08-5 **Antagonism of histamine H3 receptor promotes angiogenesis following focal cerebral ischemia**

Lei Jiang

Zhejiang University, China

F08-6 **C/EBPβ predict the infection followed by acute ischemic stroke onset within a week**

Zhenhong Yang

Xuanwu Hospital, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 23: Microcirculation From Bench to Bedside: Translational Newest Findings**
Organzied by ESM and Supported by 12th WCM

Chair: Elena Osto, *University of Zurich and University Hospital Zurich, Switzerland*

Co-Chair: Nicola J Brown, *University of Sheffield, Sheffield, United Kingdom*

023-SS1 **Sex in microcirculation: concepts from cardiovascular research**
Elena Osto
University of Zurich and University Hospital Zurich, Zurich, Switzerland

023-SS2 **Coronary microvascular dysfunction in immunometabolic disorders**
Francesco Tona
University Hospital Padova, Italy

023-YS1 **The sublingual glycocalyx and perfused boundary region in health**
Andrew Forbes Brown
University Of Exeter Medical School, UK

023-YS2 **Vascular age is not only atherosclerosis, it is also arteriosclerosis**
Rosa Maria Bruno
Université de Paris, Paris, France

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 2

08:30-10:00 **Symposium 16: MCS Presidents' Perspectives for Future Discoveries**
Organized by MCS and Supported by 12th WCM

Chair: Jerome Breslin, *University of South Florida, USA*

Co-Chair: Gerald Meininger, *University of Missouri, USA*

016-SS1 **Innovative Views of early RBC interactions in forming rouleaux and in dispersing rouleaux**
Mary Frame
Stony Brook University, USA

016-SS2 **Innovative Views for Watching Cell Dynamics During Microvascular Growth**
Walter L. Murfee
University of Florida, USA

016-SS3 **In Silico Views of Angiogenesis During Tissue Fibrosis**
Shayn Peirce-Cottler
University of Virginia, USA

10:00-11:30 **Symposium 20: Infection and the Microcirculation: Lessons From COVID-19**
Supported by 12th WCM

Chair: Michael Hill, *University of Missouri, USA*

Co-Chair: Hongquan Zhang, *Peking University, China*

020-SS1 **Ruscogenin improves sepsis-induced lung injury**
Junping Kou
China Pharmaceutical University, China

020-SS2 **Protein-based Inhibition of SARS-CoV-2 Binding to ACE2**
Fong Lam
Baylor College of Medicine, USA

020-SS3 **Induction of alarmin S100A8/A9 mediates activation of aberrant neutrophils in the pathogenesis of COVID-19**
Fu-Ping You
Peking University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 24: Cross-Talk Between Microcirculation and Microrheology of Blood Cells in Arterial Hypertension and Diabetes Mellitus**
Organized by ESM and Supported by 12th WCM

Chair: Andrei E. Lugovtsov, *Lomonosov Moscow State University, Russia*

Co-Chair: Xuejun Li, *Peking University, Peking, China*

024-SS1 **Microcirculatory and hemorheologic alterations in diabetes mellitus measured in vitro and in vivo by different optical techniques**
Andrei E. Lugovtsov
Lomonosov Moscow State University, Russia

024-SS2 **Effect of Traditional-Chinese-medicine-based blood-regulating therapy on abnormal vascular function in psoriasis**
Ping Li
Beijing Institute of Traditional Chinese Medicine, China

024-SS3 **Transcription factor FOXO1 and diabetic complication**
Lu Tie
Peking University, China

024-YS1 **Microhemorheological and microcirculatory profile of hypertensive patients**
Petr Ermolinskiy
Lomonosov Moscow State University, Moscow, Russia

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 4

08:30-10:00 **Symposium 17: Leukocyte Recruitment in Microvascular Inflammation**
Organized by MCS and Supported by 12th WCM

Chair: Zhichao Fan, *UConn Health, USA*

Co-Chair: Xunbin Wei, *Peking University Health Science Center, China*

017-SS1 **Contributions of leukocyte beta2 integrins in myocardial ischemia-reperfusion injury**
Zhichao Fan
UConn Health, USA

017-SS2 **Regulation of immune cell trafficking by adhesion signaling**
Jianfeng Chen
Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, China

017-YS1 **Fishing for microRNAs and their targets that regulate neutrophil migration**
Qing Deng
Purdue University, USA

017-YS2 **CD34+ Cell-derived Fibroblast–Macrophage Crosstalk Drives Limb Ischemia Recovery through the OSM–ANGPTL Signaling Axis**
Yuwei Song
Peking University, China

10:00-11:30 **Symposium 21: Microcirculation in Diabetes**
Supported by 12th WCM

Chair: Zilin Sun, *Southeast Universit, China*

Co-Chair: Eliete Bouskela, *Rio de Janeiro State University, Brazil*

021-SS1 **Microvascular Insulin Resistance and Diabetes**
Zhenqi Liu
University of Virginia Health System, USA

021-SS2 **AI-based screening of diabetic retinopathy**
Zilin Sun
Southeast University, China

021-SS3 **Redox regulation of endothelial dysfunction in diabetes**
Alex Chen
Shanghai Jiaotong University Affiliated Xinhua Hospital, China

021-YS1 **TRPC6 mediated podocyte foot process effacement in early diabetic kidney injury**
Bingchen Liu
The Second Affiliated Hospital of Zhejiang University School of Medicine, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 25: The Advantage of Traditional Chinese Medicine in Treating COVID-19**
Supported by 12th WCM

Chair: Wei-Dong Zhang, *Shanghai University of Traditional Chinese Medicine, China*

025-SS1 **Deciphering the covalent SARS-CoV-2 3CLpro inhibitors from herbal medicines via integrating chemoproteomic and biochemical approaches**
Guang-Bo Ge
Shanghai University of Traditional Chinese Medicine, China

025-SS2 **Further understanding of anti-SARS-CoV2 by using TCM: attach equal importance to antiviral and anti-inflammatory therapies**

Zi-Feng Yang

Guangzhou Institute of Respiratory Health, China

025-YS1 **Qing-Fei-Pai-Du-Tang, a Chinese medicine formula, attenuates lipopolysaccharide-induced pulmonary microcirculatory disturbances in rats**

Kai Sun

Peking University Health Science Center, China

025-YS2 **Understanding the mechanism of Qing-Fei-Pai-Du decoction in coronavirus-induced pneumonia based on omics approaches**

Houkai Li

Shanghai University of Traditional Chinese Medicine, China

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 5

08:30-10:00 **Symposium 18: "Image-Based" Vascular Systems Biology and Emerging Technologies**
Organized by MCS and Supported by 12th WCM

Chair: Arvind Pathak, *The Johns Hopkins University School of Medicine, USA*

Co-Chair: Fong Lam, *Baylor College of Medicine, USA*

018-SS1 **Image-based Vascular Systems Biology: A New Frontier Beckons**
Arvind Pathak
The Johns Hopkins University School of Medicine, USA

018-SS2 **Image-based Patient-Specific Characterization of Cancer Hemodynamics**
Thomas Yankeelov
University of Texas Austin, USA

018-YS1 **VascuViz: A Multimodality and Multiscale Imaging and Visualization Pipeline for Vascular Systems Biology**
Akanksha Bhargava
The Johns Hopkins University School of Medicine, USA

018-YS2 **A bioengineered 3D platform to dissect cell-cell interactions in tumour angiogenesis**
Laura Bray
Queensland University of Technology, Australia

10:00-11:30 **Symposium 22: Cerebrovascular Diseases and BBB Permeability: Molecular Targets and Therapeutic Strategies**
Supported by 12th WCM

Chair: Jian-Gang Shen, *University of Hong Kong, Hong Kong SAR, China*

022-SS1 **Cerebral tissue oxygenation and blood brain barrier damage in ischemic stroke**
Ke-Jian Liu
University of New Mexico, USA

022-SS2 **Acute Alteration of Brain Microvasculatures following Hypoxic-Ischemic Brain Injury Model**
Hong-Shuo Sun
University of Toronto, Canada

022-SS3 **Ion channels as therapeutics targets in the cerebral microcirculation**
William F. Jackson
Pharmacology & Toxicology, Michigan State University, USA

022-SS4 **Regulatory role of caveolin-1 in the proliferation and differentiation of neural stem cells in post-ischemic brain**
Yue Li
University of Macau, Macao Special Administrative Region, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 26: Vascular Redox Signaling and Oxidative Stress**
Organized by TU Dresden German Society for Microcirculation and Vascular Biology and Supported by 12th WCM

Chair: Henning Morawietz, *TU Dresden, Faculty of Medicine, Germany*

Co-Chair: Katrin Schröder, *Goethe-University Frankfurt, Faculty of Medicine, Germany*

026-SS1 **Vascular redox signaling and oxidative stress**
Katrin Schröder
Goethe-University Frankfurt, Faculty of Medicine, Germany

026-SS2 **Cross-talk between oxidized LDL, oxidative stress and renin-angiotensin-aldosterone system: Impact on microcirculation and atherosclerosis**

Henning Morawietz

TU Dresden, Faculty of Medicine, Germany

026-YS1 **HIF-2α mediates regulation of Endothelium-derived semaphorin 3G expression via Nrp2/PlexinD1 pathway under hypoxia**

Yi Shi

Nanjing Medical University, Nanjing Medical University, China

026-YS2 **Inhibition of endothelial nitrosative stress attenuates cisplatin-induced neurotoxicity in the arcuate nucleus**

Sun Meiling

Nanjing Medical University, China

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 6

08:30-10:00 **Free Oral Communication 7: Inflammation**

Chair: Gilles Pagès, *University Côte d'Azur, France*

Co-Chair: Yoshikazu Tsuzuki, *Department of Gastroenterology, Saitama Medical University, Japan*

F07-1 **Cathepsin B inhibition ameliorates leukocyte-endothelial adhesion in the BTBR mouse model of autism**

Quan-Xin Zhang

Nanjing Medical Universtiy, China

F07-2 **The role and mechanism of exosomal miR-486-3p after subarachnoid hemorrhage**

Bin Sheng

Nanjing Drum Tower Hospital, China

F07-3 **Association of microglia- and neutrophil-derived inflammatory factors with neurological injury in severe CVT**

Shuyuan Hu

Xuanwu Hospital, China

F07-4 **Xuebijing injection inhibited NETs formation to improve pulmonary microcirculation in septic mice**

Ting Shang

Tianjin university of traditional Chinese medicine, China

F07-5 **Beinaglutide alleviates weight and reduces adipocyte differentiation by inhibiting JNK signaling**

Zhanjun Guo

Xiangya Hospital of Central South University, China

F07-6 **Therapeutic mechanism of classical formula Zhishi Xiebai Guizhi Decoction against Pulmonary hypertension in rats**

Li Yao

College of Pharmacy, Harbin Medical University, China

10:00-11:30 **Young Symposium 3: Young Symposium of Diabeto-Mircrocirculation**

Supported by 12th WCM

Chair: Liming Chen, *Metabolic Diseases Hospital of Tianjin Medical University, China*

Co-Chair: Yanbing Li, *The First Affiliated Hospital of Sun Yat-sen University, China*

Y03-1 **Advanced glycation end products induce endothelial hyperpermeability via β-catenin phosphorylation and subsequent upregulation of ADAM10**

Xiaohua Guo

School of Basic Medical Science, Southern Medical University, China

Y03-2 **Early intensive insulin therapy in patients with type 2 diabetes: transforming current understanding to real-world clinical benefits**

Liehua Liu

The First Affiliated Hospital of Sun Yat-sen University, China

Y03-3 **Direct Activation of the Angiotensin II Type-2 Receptors Enhances Muscle Microvascular Perfusion, Oxygenation and Insulin Delivery in Male Rats**

Fei Yan

Qilu Hospital of Shandong University, China

Y03-4 **Clinical characteristics and mechamism of carbapenem resistant Acinetobacter baumannii in diabetic foot**

Jun Xu

Metabolic Diseases Hospital of Tianjin Medical University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Young Symposium 4: A Window into the Microcirculation - Using Imaging to Unravel Physiological Mechanisms**

Organized by the British Microcirculation and Vascular Biology Society and Supported by 12th WCM

Chair: Georgiana Neag, *University of Birmingham, United Kingdom*

Chair: Juma El-Awaisi, *University of Birmingham, United Kingdom*

Y04-1 **Getting to the Heart of the Matter: Intravital Imaging of the coronary microcirculation in the injured and aged beating heart**

Juma El-Awaisi

University of Birmingham, United Kingdom

Y04-2 **Imaging inflammation and tissue damage in ex vivo human liver tissue using multiphoton microscopy**

Scott Davies

University of Birmingham, United Kingdom

Y04-3 **Multi-scaled molecular imaging modalities reveal contributions of the bone matrix in the sexual dimorphism of the skeletal vasculature**

Aikta Sharma

University of Southampton, United Kingdom

Y04-4 **Structural and functional studies of erythrocyte membrane-skeleton by super-resolution microscopy and microfluidics**

Leiting Pan

Nankai University, China

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

ROOM 7

08:30-10:00 **Symposium 19: The Cerebral Microcirculation as a Novel Target to Treat Dementia**
Supported by American Physiological Society, Cardiovascular Section

Chair: William Jackson, *Michigan State University, USA*

019-SS1 **TRPV4 and hypertension associated cognitive impairment**
Anne Dorrance
Michigan State University, USA

019-SS2 **YangxueQingnao Wan ameliorates hippocampal neuron injury by regulating cerebral arteriole constriction and cerebral microvascular hyperpermeability**
Yingqian Jiao
Peking University Health Science Center, China

019-YS1 **BKca nitrosylation is associated with micro- and neurovascular dysfunction in a mouse model of Alzheimer's Disease**
Paulo Pires
University of Arizona, USA

019-YS2 **Influence of Hypertension with Multiple Risk Factors on Brain Tissue Pathomorphology and Cognitive Impairment-Related Biomarkers**
Surui Chang
Xiyuan Hospital, China Academy of Chinese Medical Sciences, China

10:00-11:30 **Free Oral Communication 9: Shock**

Chair: Yugeesh Lankadeva, *University of Melbourne, Australia*
Co-Chair: Kai Sun, *Peking University Health Science Center, China*

F09-1 **Mechanisms underlying regional vascular hypo-responsiveness in sepsis**
Marianne Tare
Monash University, Australia

F09-2 **STING-regulated macrophage ferroptosis exacerbates sepsis via its interaction with NCOA4**
Qinjie Liu
Zhong Da Hospital, China

F09-3 **Spinning disk confocal imaging of immune-induced microvascular hyperpermeability**
Zekun Peng
FUWAI Hospital, China

F09-4 **Alteration of N6-methyladenosine-tagged circular RNA in the rats' hippocampus with PTSD triggered by high-voltage electrical burn**
Xuegang Zhao
The First Hospital of Hebei Medical University, China

F09-5 **Transcriptome analysis of parabiotic tissues in high-voltage electrical burns**
Jiawen Hao
The First Hospital of Hebei Medical University, China

F09-6 **A case of residual gangrene of the feet caused by sepsis and literature review**
Jie Gao
Tianjin Medical University General Hospital, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Free Oral Communication 10: New Methods and New Techniques**

Chair: Marianne Tare, *Monash University, Australia*

Co-Chair: Bing Wang, *Institute of Microcirculation, Chinese Academy of Medical Sciences, China*

F10-1 **Design and application of probes targeting different molecules of nitrosative stress during cerebral ischemia**

Zhengmao Li

Nanjing medical university, China

F10-2 **Profile as an interpretable ECG based algorithm to analyze and predict mental stress induced myocardial ischemia**

Dantong Li

Guangdong provincial people's hospital, China

F10-3 **A three-dimensional microcirculation culture system was established to simulate and analyze the bone marrow hematopoietic niche**

Runjin Liu

Chongqing University, China

F10-4 **Recapitulating influenza virus infection and facilitating antiviral and neuroprotective screening in tractable brain organoids**

Liangzhen Dong

Peking University, China

F10-5 **The glymphatic system delivery enhances the transduction efficiency of AAV1 to brain endothelial cells in adult mice**

Jia-Wen Cheng

Nanjing Medical University, China

F10-6 **Exploring the Magnetocardiographic Characteristics of Myocardial Infarction with Non-obstructive Coronary Artery Disease**

Yijing Guo

Shanghai Jiao Tong University, China

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

GUORUI HALL

08:30-10:00 **Satellite Symposium 6: Microcirculation and Ocular Diseases**
Supportedt by Professional Committee on Ocular Microcirculation of CSM

Chair: Hua Zhang, *Chinese Academy of Medical Sciences and Peking Union Medical College, China*

Co-Chair: Gang-Ming Zou, *University of Hawaii, USA*

S06-1 **Retinoschisis with multiple abnormal blood vessels in high myopia**
Weihong Yu
Peking Union Medical College Hospital, China

S06-2 **Deep learning for identification of choroidal microcirculation activity in age-related macular degeneration**
Kai Jin
The Second Affiliated Hospital, School of Medicine, Zhejiang University, China

S06-3 **Natural-Language Diagnostic Report Generation by Multi-Modal AI for Macular Diseases**
Xufeng Zhao
Peking Union Medical College Hospital, China

S06-4 **The therapeutic application of autologous ozonized blood transfusion (AOBT) in diabetic vascular ldisease through improvement of microcirculation**
Gang-Ming Zou
University of Hawaii, America

10:00-11:30 **Satellite Symposium 7: Microcirculation and Hemorheology in Shock**
Supported by Professional Committee on Shock and Hemorheology of CSM

Chair: Fulong Liao, *China Academy of Traditional Chinese Sciences, China*

Co-Chair: Xiang Wang, *Chongqing University, China*

S07-1 **Oxidative stress mediates hippocampal neuronal apoptosis through ROS/JNK/P53 pathway in rats with PTSD triggered by high-voltage electrical burn**
Ying Lv
The First Hospital of Hebei Medical University, China

S07-2 **Luseogliflozin, a SGLT2 inhibitor, does not affect glucose uptake kinetics in renal proximal tubules of live mice**
Anqi Zhang
Capital Medical University, China

S07-3 **Surface-anchored framework for generating RhD-epitope stealth red blood cells**
Ben Wang
Zhejiang University, China

S07-4 **Biomechanical Risk Stratification for Cardiovascular Diseases**
Zhiyong Li
Ningbo University, China

11:30-12:20 **Zweifach Award**

Chair: Amanda Jo LeBlanc, *University of Louisvill, USA*

AL-02 **A journey in arteriolar remodeling: from the extracellular matrix to the cytoskeleton**
Luis A. Martinez-Lemus
Department of Medical Pharmacology and Physiology, University of Missouri-Columbia, USA

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

12:50-13:30 **Lunch Lecture 2**

Chair: Miao Wang, *Fuwai Hospital, Chinese Academy of Medical Sciences, China*

LL-02 **Mechanisms of Qi Tonifying and Blood Activating Compound Chinese Medicine in Improving Myocardial Microcirculation Dysfunction, Myocardial Injury, and Myocardial Fibrosis Induced by Ischemia-Reperfusion**

Jian Liu

Peking University, China

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Satellite Symposium 8: Endovascular Intervention of Peripheral Vascular Microcirculation Dysfunction Diseases**

Supported by Professional Committee on Peripheral Vascular Disease of CSM

Chair: Yuehong Zheng, *Peking Union Medical College Hospital, China*

S08-1 **Current strategy for femoropopliteal artery in-stent restenosis**

Yang Zhang

Beijing Chao-Yang Hospital, Capital Medical University, China

S08-2 **Study on the diagnostic value of interleukins in deep vein thrombosis**

Yongkang Dang

Chifeng Hospital, China

S08-3 **Quality-of-life endpoints are associated with coronary microvascular resistance in patients with hypertrophic cardiomyopathy**

Jie Ma

Fuwai Hospital, China

S08-4 **Endovascular treatment of long CTO lesions in femoropopliteral artery**

Shenghan Song

Beijing Chao-Yang Hospital, China

16:40-17:30 **Keynote Lecture 2**

Chair: Georges Grau, *The University of Sydney, Australia*

KL-02 **Brain endothelium and neuro-inflammation**

Britta Engelhardt

Kocher Institute, University of Bern, Switzerland

17:40-20:00 **Buffet Dinner** (East Exhibition Hall, 1/F)

B1/F

Cardiac Microcirculation

P002: **Changes in myocardial SOD, MDA, and MPO in rats with high-voltage electrical burns and the effect of NAC intervention**
Wenfei Yang

P004: **Qishen Yiqi Dropping Dills can Improve Cardiac Function in Rats with Heart Failure by Regulating Metabolism and Inhibiting Inflammation**
Liu Yang, Xueqi Lv, Qifeng Liu, Congcong Guo, Yue Xu, Haowen Zhu, Xiangju Jin, Yinghong Wang

P006: **QiShenYiQi Pills® Protects Myocardial Fibrosis Caused by in Stent Restenosis in Miniature Pigs**
Lu-Lu Yan, Xiao-Hong Wei, Qiu-Ping Shi, Chun-Shui Pan, Kai-Yin Li, Bin Zhang, Xin-Gang Wang, Bo Zheng, Ming-Xia Wang, Li Yan, Ping Huang, Jian Liu, Jing-Yu Fan, Huan Li, Chuan-She Wang, Ming Chen, Jing-Yan Han

P010: **Ginsenoside Rb1 ameliorates isoproterenol-induced cardiac fibrosis in mice**
Bing-yuan Zhao, An-qing Li, Fan-kai Chen, Ding-zhou Weng, Chun-shui Pan, Kai Sun, Li Yan, Jing-yan Han, Jian Liu

P012: **Reconstruction of Postinfarcted Cardiac Functions Through Injection of Tanshinone IIA@ Reactive Oxygen Species-Sensitive Microspheres Encapsulated in a Thermoreversible Hydrogel**
Ling Yu

Traditional Chinese Medicine and Microcirculation

P014: **The effect of microbiota mediated Pyroptosis pathway on Diabetic Nephropathy and the intervention mechanism of Jiangtang Decoction**
Hong Jinni, Fu Tingting, Du Yu, Bu Junmin, Liu Weizhen, Yu Miao, Lin Yanshan, Min Cunyun

P016: **Discovery of Acupuncture Points to Meridians**
Zhenzhan Chang, Yuankai Hong, Lixin Huang

P018: **Pharmacological manipulation of Ezh2 with Salvianolic acid B results in tumor vascular normalization and synergizes with cisplatin and T cell-mediated immunotherapy**
Cheng Qian, Aiyun Wang, Yang Zhao, Yin Lu

P020: **Paeoniflorin attenuates limb ischemia by promoting angiogenesis through ERα/ROCK-2 pathway**
Sinan Zhu, Yuxin Bai, Qianyi Wang, Wei Sun, Zhirui Fang, Lu Chen, Hong Wang

Hemorrhage

P022: **the difference of Hb redox forms in cerebral spinal fluid between perimesencephalic SAH and aneurysmal SAH**
Qi Zhu

Obesity and Microcirculation

P024: **Arcuate nucleus Kir2.1 protein involved in melanocortin-4 receptor trafficking and control of energy balance**
Haohao Zhang, Hengru Guo, Xiaoning Zhang, Bo Qiao, Wanting Li

P026: **Kallistatin Improves High-fat-induced Insulin Resistance via Epididymal Adipose Tissue-derived Exosomes**
Ziwei Yang

Diabetes and Microcirculation

P028: **Time in range, assessed with continuous glucose monitoring, is associated with brachial-ankle pulse wave velocity in type 2 diabetes: A retrospective single-center analysis**
Hui Zhou, Jiaqing Shao, Ping Gu

P030: **How does diabetic peripheral neuropathy (DPN) impact patients' burden of illness and the economy? A retrospective study in Beijing, China**
Qi Pan, Sijia Fei, Jingyi Luo, Lina Zhang, Huan Chen, Weihao Wang, Fei Xiao, Lixin Guo

P032: **Bilateral gastrocnemius diabetic myonecrosis: Atypical involvement of a rare complication**
Qiming Meng, Zehao Liu

P034: **Mechanism of methylglyoxal damage on microvascular endothelial cell based on metabolomics and possible intervention strategy**
Songtao Tang, Yan Liu, Qiong Hu, Zhenzhen Chen, Lei Liu, Qiu Zhang

P036: **Liraglutide Improves the Integrated Pancreatic Microcirculation in Type 2 Diabetes Mellitus Mice: Evidence from the Common Microcirculatory Framework**
Yuan Li, Bing Wang, Sunjing Fu, Mengting Xu, Bingwei Li, Xueting Liu, Xiaoyan Zhang, Qin Wang, Ailing Li, Mingming Liu

P038: **Glycine supplement protects against the damage of integrated pancreatic microcirculation in streptozotocin-induced type 1 diabetic mice**
Wang Bing, Zhang Xu, Song Xiaohong, Liu Xueting, Li Bingwei, Fu Sunjing, Xu Mengting, Li Yuan, Wang Qin, Zhang Xiaoyan, Li Ailing, Liu Mingming

P040: **TIR**
Bin Lu

Stroke

P042: **The CCA repair during reperfusion in MCAO filament model could not replace the ECA cross-sectional MCAO filament model in mice**
Yue Hu, Zhenhong Yang, Yumin Luo

P044: **Effect of intracranial venous system on blood-brain barrier permeability in rats with cerebral ischemia/reperfusion injury and improvement of Ginsenoside Rb1 and Emodin combinative interventionon**
Guo qing Zheng, Xi le Zhang

P046: **Prognostic effect of silybin on patients with liver injury after subarachnoid hemorrhage**
Yue Cui

P048: **Effect of DNA methylation level on the prognosis of patients with subarachnoid hemorrhage**
Peng-fei Ding, Chun-hua Hang, Wei Li

P050: **The alteration profiles of N6-methyladenosine modification of neutrophilic RNA in ischemic stroke**
Junfen Fan, Liyuan Zhong, Feng Yan, Haiping Zhao, Ziping Han, Rongliang Wang, Zhen Tao, Yangmin Zheng, Qingfeng Ma, Yumin Luo

P052: **AnGong NiuHuang (AGNH) pill alleviates neuro-inflammation in ischemic stroke rat by inhibiting Tyrobp/**

Syk and Tlr2/Myd88
Hongjun Yang, Jingjing Zhang, Liangliang Tian

P054: **Astragaloside IV and ligustrazine alleviated cerebral ischemia reperfusion injury by regulating mitochondrial dynamics via the Drp1 SUMO/deSUMOylation**
Xiangyu Chen, Gangying Fu, Tong Yang, Yue Zhou, Feiyue Sun, Jing Zhou, Runying Tian

P056: **Stellate Ganglion Block Reverses PHSML-induced Vascular Hypo-reactivity through Inhibiting Autophagy-mediated Phenotypic Transformation in VSMCs**
Cai-Juan Li, Hui-Bo Du, Zhen-Ao Zhao, Qi Sun, Yi-Ming Li, Si-Jie Chen, Nan Zhang, Chun-Yu Niu, Zi-Gang Zhao

Hypertension and Microcirculation

P058: **To observe the effect of Shexiang Baoxin Pill on coronary microvascular dysfunction in refractory hypertensive patients of young and middle-aged adults with semi-quantitative index of SPECT myocardial perfusion imaging**
Yao Qi, Haibin Gong

Dementia and Microcirculation

P060: **W1302, a novel drug discovery with new mechanisms for treatment of vascular dementia based on ultrastructure imaging method**
Didi Li, Weiping Wang, Shaofeng Xu, Ling Wang, Jiang Li, Xiaoliang Wang

Cerebral Microcirculation

P062: **Qingkailing improves the no-reflow phenomenon of cerebral ischemia-reperfusion in mice by inhibition of RhoA/ROCK pathway in pericytes**
Shuang Zhang, Chang-xiang Li, Jia Wang, Yi Shen, Qing-guo Wang, Fa-feng Cheng, Jing-yan Han

Atherosclerosis

P066: **Serum Metrnl levels are positively associated with high-density lipoprotein cholesterol in patients with type 2 diabetes mellitus**
Chenxia Zhou, Yan Tian, Jun Song

Inflammation

P068: **Relationship between fibrinogen to albumin ratio and type 2 diabetic retinopathy**
Xiaoyi Chen

P070: **Association between the Neutrophil to High-density Lipoprotein Cholesterol Ratio and Peripheral Artery Disease: Findings from National Health and Nutrition Examination Survey (1999-2004)**
Qiaodan Lu, Yufen Ma, Lianglin Wu, Jiawei Zhou, Liyun Zhu, Ranxun An, Yuehong Zheng, Lei Wang

Cancer and Microcirculation

P072: **Integrative analysis of transcriptomic and genomic data reveals the correlation between PANoptosis-related genes and tumor immune microenvironment in glioma**
WenDai Bao, Fengzeng Sun, Zhiqiang Dong

P074: **NIR-Triggered and ROS-Boosted Nanoplatform for Enhanced Chemo/ PDT/PTT Synergistic Therapy of Sorafenib in Hepatocellular Carcinoma**
Chonggao Wang

P076: **Triphenyl Phosphate, a common flame retardant however an vicious gastric cancer accelerant**
Liu Hongda, Zhang Xu, Zhang Qun, Xu Zekuan

P078: **Synthetic Lethal and Resistance Interactions with BET Bromodomain Inhibitors in Triple-Negative Breast Cancer**
Shaokun Shu

Endothelial Cells

P080: **Characteristics of inflammatory and normal endothelial exosomes on endothelial function and the development of hypertension**
Bingwei Li, Qiuju Zhang, Rui Yang, Yuhong He, Honggang Zhang

P082: **Tumor cell-released autophagosomes (TRAPs) promote lung metastasis through inducing PD-L1 high expression of pulmonary vascular endothelial cells (PVECs) in breast cancer**
Xuru Wang

Vascular Smooth Muscle Cells

P084: **Effects of male BPA exposure on offspring placental blood vessels and fetal development**
Yuming Cao, Li Wang

Pericytes

P086: **Combined with Putative Endothelial Progenitor Cells, TFA Reduces Renal Interstitial Fibrosis in Diabetic Kidney Disease by Diminishing Pericyte-Myofibroblast Transition and Capillary Injury**
Yu Wang, Yi-Gang Wan

P088: **Combined With Bone Marrow-Derived Mesenchymal Stem Cells, Fucoidan Attenuates Renal Fibrosis in Diabetic Kidney Disease by Inhibiting Pericyte-Myofibroblast Transition and Capillary Injury**
Ya-Jing Li, Yu Wang, Yi-Gang Wan

Neutrophils

P090: **Tumor cell-released autophagosomes (TRAPs) promote neutrophil extracellular traps formation**
Xiaohe Zhou

Pulmonary Microcirculation

P092: **The Therapeutic Effects of Novel Mettl3 Inhibitor STM2457 in Experimental Pulmonary Hypertension**
Du Qiang

P094: **NAD+ metabolism affects the tumor microenvironment and the cytotoxicity of CD8+T cells**
Guangsheng Zhu

P096: **GSDME-dependent pyroptosis affects the prognosis and response to immunotherapy in lung adenocarcinoma**
Peijun Cao, Guangsheng Zhu, Jun Chen

P098: **Exploratory study on prognostic markers of nonsmall cell lung cancer based on ctDNA and high-throughput sequencing**
HUA YU

Platelets

P102: **Buyang Huanwu decoction ameliorates myocardial injury and attenuates platelet activation and clot retraction by regulating the Rap1 signaling pathway**
Jiaming Gao

Mitochondria

P104: **Acacetin inhibits mitochondrial impairment in mesenteric arterioles to protect against vascular dysfunction in hypertension**
Yuan Li, Ying Ma, Qingya Dang, Chuting Han, Liju Yang, Chang Che, Min Zhang, Jun Cheng, Yan Yang, Pengyun Li

P106: **The Effect and Molecular Mechanism of Slibinin on Improving Non-alcoholic Fatty Liver Induced by PM2.5**
Dexin Li

Extracellular Vesicles

P108: **Tumor cell-released autophagosomes (TRAPs) remodel the breast tumor microenvironment by inducing the formation of inflammatory cancer-associated fibroblasts (CAFs)**
Chengdong Wu

miRNA

P110: **Resveratrol alleviates NLRP3 inflammasome activation via miR-217 mediated SIRT1/NOX4-XBP1s axis in naturally aging thoracic aorta and senescent endothelial cells induced by H2O2**
Yunxia Lu, Qiongqiong Cao, Fangmei Yu, Yueming Long, Heng Zhou, Li Gui

Noncoding RNAs

P112: **Tumor-associated macrophages induced circTAM in promoting glycolysis and tumor growth of hepatocellular carcinoma via USP22/HIF-1α**
Songyang Yu, Zhiqiang Hu, Xiaowu Huang

Aquaporin

P114: **The polar distribution of AQP4 is altered by trifluoperazine in rats after intraparenchymal hemorrhage**
Gang Wu, Yiwen Xu, Yuanxia Bao, Zhengli Jiang, Xiaoping Jin

Oxidative Stress

P116: **The preventive and therapeutic effects of Qishen Yiqi Drop Pill (QSYQ) and its main components on statin induced rhabdomyolysis syndrome and potential mechanism**
Jingxin Zhang, Yin Li

Renal Microcirculation

P118: **Lysosomal regulation of extracellular vesicle excretion during D-ribose induced NLRP3 inflflammasome activation in diabetic nephropathy**
Jinni Hong, Tingting Fu, Yu Du, Weiwei Li, Pinlan Li, Cunyun Min

P120: **Quantitive proteomic analysis based on iTRAG mass spectrum method reveals the effect of methylglyoxal and carnosine on proximal tubule epithelial cells**
Lei Liu, Juan Xu, Shiqi Zhang, Yadi Cao, Bing Shen, Yonggui Wu, Qiu Zhang

Angiognesis

P124: **Angiogenic pattern and influencing hemodynamic factors in the developing vitelline vascular network: a computational study**
Qing Pan, Shuo Wang, Peilun Li, Huanghui Shen, Wenjie Huang, Fei Lu, Luping Fang, Gangmin Ning

Ferroptosis

P126: **Mechanisms of Nrf2 Regulation of Iron Overload and Ferroptosis in Subarachnoid Hemorrhage**
Simmn Zhi

Vascular Permeability

P128: **Spinning disk confocal imaging of immune induced microvascular hyperpermeability**
Zekun Peng, Zengrong Chen, Huihui Li, Miao Wang

Vascular Barrier

P130: **Paternal bisphenol A exposure induces fetal placental vascular dysplasia and fetal growth restriction in offspring**
Yuming Cao, Shengnan Wang, Zexiao Wei, Li Wang#

Lymphatic Vesse

P132: **Role of intestinal flora remodeling in stellate ganglion block reducing PHSML-mediated lung injury**
Si-Jie Chen, Hui-Bo Du, Zhen-Ao Zhao, Yu-Ping Zhang, Zi-gang Zhao, Chun-YU Niu

P134: **Stellate ganglion blockage alleviates exosomes payload in post-hemorrhagic shock mesenteric lymph-mediated acute lung injury through autophagy inhibition**
Hong Zhang, Ze-Hua Fan, Hui-Bo Du, Zhen-Ao Zhao, Zi-Gang Zhao, Chun-Yu Niu

Hepatic Microcirculation

P136: **Mechanism of Wnt/β-catenin signaling pathway promoting immune evasion in hepatocellular carcinoma**
Yamei Huang

P138: **Clinical and genetic characteristics of Chinese patients with hepatic hereditary hemorrhagic telangiectasia**
Zhaochen Liu, Shanglei Ning, Yuxin Chen

P140: **Mechanism of improvement of non-alcoholic fatty liver disease by silibinin in db/db mice**
Yu-xin Jin, Xiao-qing Lu, Jing-xin Zhang, De-xin Li, Jing-yan Han, Yin Li

P142: **Risk assessment and preoperative prediction of microvascular invasion in hepatocellular carcinoma**
Jian Li, Xin Su, Xiao Xu, Ang Liu, Changchun Zhao, Xiangyong Hao

COVID-19

P144: **Endothelial dysfunction in long-COVID depression: The hub of the abnormal neurovascular-immunity cell communication network**
Yi-Xuan Zhang, Ying-Mei Lu, Feng Han

New Concepts and Technology

P146: **Quantitative and Noninvasive Detection of SAH-related MiRNA in Cerebrospinal Fluids in Vivo Using SERS Sensor Based on Acupuncture-based Technology**

Jingyi Sun, Yanan Song, Mengyue Wang, Peng Zhao, Feng Gao, Junqi Li, Mingfeng Yang, Hui Yuan, Baoliang Sun, Ying Wang

P148: **Binocular visual perceptual function in patients with glaucoma in comparison with normal controls**
Mengdan Fang, Chunyuan Zhou, Yan Lu, Hang Chu, Li Yan

P150: **Exploring the global perfusion characteristics of microcirculation based on local vascular information by mathematical model**
Peilun Li, Qing Pan, Molei Yan, Guolong Cai, Gangmin Ning

Ocular Fundus Microcirculation

P152: **Investigation into the AMD fundus microcirculation features by deep learning model**
Lei Sun, Siyuan Song, Yichong Wang, Kai Jin, Juan Ye, Jiquan Liu, Gangmin Ning

P154: **Serum Disease-Specific IgG Fc Glycosylation as potential biomarkers for Nonproliferative Diabetic Retinopathy Using Mass Spectrometry**
Yixin Zhang, Zhizhen Lai, Zhonghao Yuan, Bin Qu, Yan Li, Wenyun Yan, Bing Li, Weihong Yu, Shanjun Cai, Hua Zhang

P156: **Efficacy and Safety of Intravitreal Injection of Conbercept for Moderate to Severe Nonproliferative Diabetic Retinopathy**
Lu Shen, Yuxiang Zheng, Ling Yuan

Ischemia and Reperfusion Injury

P158: **Co-expression network between placenta tissues and trophoblast organoids highlights ARRDC3 as a diagnostic biomarker supporting the response to hypoxic microenvironment in preeclampsia**
Jinfeng Xu, Shiting Peng, Shengnan Wang, Li Wang

P160: **Naotaifang formula alleviates cerebral ischemia/ reperfusion injury via attenuating ferroptosis and necroptosis**
Yue Zhou, Tong Yang, Xiangyu Chen, Qi Liang, Runying Tian, Jiarui Zhang, Xiangyuan Wang, Jinwen Ge, Zhigang Mei

L-Cardiac Microcirculation

P162: **Correlation Analysis of Tongue Diagnosis and Cardiovascular and Renal Functions in Chronic Heart Failure Patients**
Yeuk Lan Alice Leung, Jiangang Shen

P164: **Exacerbated post-infarct pathological myocardial remodelling in diabetes is associated with impaired autophagy and aggravated NLRP3 inflammasome activation**
MAO Shuai

L-Diabetes and Microcirculation

P166: **Advanced multifunctional hydrogels for diabetic foot ulcer healing: active substances and biological functions**
Yuetong Li, Yuxin Leng, Yang Liu, Jianhua Zhong, Jiaxin Li, Shitong Zhang, Zhenlin Li, Kaming Yang, Xinyi Kong, Wanwen Lao, Changlong Bi, Aixia Zhai

P168: **Liraglutide Accelerates Ischemia-Induced Angiogenesis in a Murine Diabetic Model**
Yu Ma, Yu-xin Zhu, Yi Li, Li-qun Wang, Mao Luo, Jian-bo Wu, Rong Li

P170: **DETECTION OF LOWER LIMBS VASCULAR STENOSES IN PATIENTS WITH DIABETES MELLITUS BY PERFUSION ASSESSMENT USING INCOHERENT OPTICAL FLUCTUATION FLOWMETRY**
Alexey Glazkov, Polina Glazkova, Dmitry Kulikov, Yulia Kovaleva, Alina Babenko, Roman Larkov, Timur Britvin, Dmitry Rogatkin

L-Shock

P172: **The Role of TIPE2 in Dendritic Cell Maturation Dysfunction Induced by Post-Hemorrhagic Shock Mesenteric lymph**
Zhao Wang, Hu Jiang, Jia-Li Zhou, Hui-Bo Du, Hong Zhang, Yu-ying Rong, Shi-Ying Yang, Zi-gang Zhao, Chun-yu Niu, Li-Na Jiang

L-Ferroptosis

P174: **A Ferroptosis-Related Long Noncoding RNA Signature Predicts the Prognosis of Colorectal Cancer Patients**
Xiaofei Zhi, Sijun Chen

L-Aging and Microcirculation

P176: **EFFECT Of OLIGOPEPTIDE TO MICROCIRCULATION AS A NUTRITION FOR ANTI AGING & REGENERATION**
Hani Surjati Oey

L-Monocytes

P178: **Calciprotein particles cause pro-inflammatory response in systemic circulation**
Daria Shishkova, Vera Matveeva, Victoria Markova, Yulia Dyleva, Anton Kutikhin

L-Stem Cells

Yuqian He, Zhang Tao, Ma Xiaoyu, Lei Jiaojiao, Wu Jianbo

P180: **TC14012 inhibited tumor cell-induced endothelial necroptosis**
Huifeng Hao, Yanna Jiao, Dong Xue, Shuyan Han, Pingping Li

ROOM 1

08:30-10:00 **Symposium 27: Lymphatic Functions in Cardiovascular Disease**
Organized by MCS and Supported by 12th WCM

Chair: Joseph Rutkowski, *Texas A&M University College of Medicine, USA*

Co-Chair: Rachelle (Shelly) Crescenzi, *Vanderbilt University Medical Center, USA*

027-SS1 **Renal Lymphatic Roles in Blood Pressure Regulation**
Brett Mitchell
Texas A&M University College of Medicine, USA

027-SS2 **Extracellular vesicles and lymphatic function in chronic inflammatory conditions**
Catherine Martel
Université de Montréal, Canada

027-YS1 **Enteral Treatment with a Mitochondrially-targeted Antioxidant Preserves Pulmonary Lymphatic Function in an Ovine Model of Congenital Heart Disease with Increased Pulmonary Blood Flow**
Sanjeev Datar
UC San Francisco, USA

027-YS2 **Estrogen activates its receptors to improve lymphatic contractility through suppression of endoplasmic reticulum stress induced by hemorrhagic shock**
Jia-Yi Zhai
Hebei North University, China

10:00-11:30 **Symposium 31: Cerebral Microvascular Injury and Pharmacological Intervention**
Supported by 12th WCM

Chair: Xiao-Liang Wang, *Institute of Materia Madica, Chinese Academy of Medical Sciences and Peking Union Medical College, China*

Co-Chair: Luis A. Martinez-Lemus, *University of Missouri-Columbia, USA*

031-SS1 **Cerebral micro-blood vessels were changed in neuronal degenerative diseases**
Xiao-Liang Wang
Institute of Materia Madica, Chinese Academy of Medical Sciences and Peking Union Medical College, China

031-SS2 **Pharmacological target of neurovascular unit in cerebrovascular disease**
Feng Han
Nanjing Medical University, China

031-SS3 **Mineralocorticoid Receptor Antagonists as Therapeutic Strategies for Vascular Cognitive Impairment**
Anne Dorrance
Department of Pharmacology and Toxicology, Michigan State University, USA

031-YS1 **Ameliorative Effects of YangXueQingNao Wan, a compound Chinese Medicine, on Cerebral Microcirculation Disturbance in Diabetic Mice**
Yi Zhang
Peking University Health Science Center, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 35: Vascular and Intravascular Components of Microcirculation in Norm and Disease**
Organzied by ESM and Supported by 12th WCM

Chair: Richard Siow, *King's College London, UK*

Co-Chair: Wei Kong, *Peking University, Beijing, China*

035-SS1 **Vascular aging in health and disease: consequences for Nrf2 redox signalling**

Richard Siow

King's College London, UK

035-SS2 **Structural and functional state of various parts of skin microcirculation at an early stage of hypertension in working-age men**

Andrei Korolev

Federal State Institution "National Medical Research Center for Therapy and Preventive Medicine" of the Ministry of Healthcare of the Russian Federation, Russia

035-SS3 **Extracellular matrix regulation of vascular homeostasis and disease**

Wei Kong

Peking University, Beijing, China

035-SS4 **The new formula for cell supply in tissues with the help of blood circulation is a fact. Let's talk about the consequences of this Law and Order in the Theory of Microcirculation**

Jordan M. Petrow

University of Rostock, Germany

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 2

08:30-10:00 **Symposium 28: Novel Functions of Pericytes in the Microcirculation**
Organized by MCS and Supported by 12th WCM

Chair: Guiling Zhao, *University of Maryland School of Medicine, USA*
Co-Chair: Albert Gonzalez, *University of Nevada, Reno, USA*

028-SS1 **Pericyte in heart microcirculation**
Guiling Zhao
University of Maryland School of Medicine, USA

028-SS2 **Brain capillary pericytes as metabolic sentinels in the control of brain blood flow**
Thomas Longden
University of Maryland School of Medicine, USA

028-SS3 **The Pericyte Microenvironment in Health and Disease**
John Chappell
Virginia Polytechnic Institute and State University, USA

028-YS1 **Intraluminal pressure elevates intracellular calcium and constricts central nervous system pericytes**
Nicholas Klug
University of Vermont, USA

10:00-11:30 **Symposium 32: Adaptations in Pregnancy in Health and Disease**
Organized by ANZMS and Supported by 12th WCM

Chair: Shaun Sandow, *Universities of the Sunshine Coast / and Queensland, Australia*
Co-Chair: Marianne Tare, *Monash University, Australia*

032-SS1 **Preeclampsia and the maternal brain**
Marilyn Cipolla
University of Vermont, USA

032-SS2 **Microvascular significance in the newborn; an evolving paradigm**
Yvonne Eiby
University of Queensland, Australia

032-SS3 **Uterine vascular RAGE in gestational diabetes**
Tim Murphy
University of New South Wales, Australia

032-YS1 **Cholesterol depletion alters human myometrial artery compliance in normal pregnancy, but not preeclampsia**
Nathan Luque
University of New South Wales, Australia

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 36: Integrated Traditional Chinese and Western Medicine for Cerebrovascular Disease**
Supported by 12th WCM

Chair: Feng Han, *Nanjing Medical University, China*
Co-Chair: Huai-Lian Guo, *China*

036-SS1 **Microcirculatory Disturbance in Dementia**
Yoshiaki Itoh
Osaka City University Graduate School of Medicine, Japan

036-SS2 **Reactive nitrogen species are critical therapeutic targets for reducing delayed thrombolysis-mediated hemorrhage transformation and improving therapeutic outcome in ischemic stroke**

Jian-Gang Shen

University of Hong Kong, Hong Kong SAR, China

036-SS3 **Cognitive impairments and blood-brain barrier damage in a mouse model of chronic cerebral hypoperfusion**

Huai-Lian Guo

China

036-YS1 **YiQiFuMai Lyophilized Injection Attenuates Blood-Brain Barrier Disruption and Hemorrhagic Transformation and Improves Neurological Outcome in Ischemic Stroke mice with Delayed t-PA Treatment**

Quan Li

Peking University Health Science Center, China

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 4

08:30-10:00 **Symposium 29: Vascular Adaption in Aging, Obesity, and Metabolic Syndrome**
Organized by MCS and Supported by 12th WCM

Chair: Walter L. Murfee, *University of Florida, USA*

Co-Chair: Pingnian He, *Pennsylvania State University, College of Medicine, USA*

029-SS1 **Potential Role of Neurovascular Senescence in Cognitive Decline**
Anna Csiszar
University of Oklahoma Health Science Center, USA

029-SS2 **High fat diet provokes distinct responses in male and female adipose endothelial cells**
Tara Haas
York University, USA

029-SS3 **Increased circulating microparticles contribute to severe infection and adverse outcomes of COVID-19 patients with diabetes**
Pingnian He
Pennsylvania State University, College of Medicine, USA

029-YS1 **Obesity as a Premature Aging Phenotype – Implications for Skeletal Muscle Function**
Joshua Butcher
College of Veterinary Medicine, Oklahoma State University, USA

10:00-11:30 **Symposium 33: Microcirculation and Cardiovascular Diseases**
Supported by 12th WCM

Chair: Bao-Feng Yang, *Harbin Medical University, China*

Co-Chair: Mariappan Muthuchamy, *Texas A&M University, USA*

033-SS1 **Regulatory role of non-coding RNAs on microcirculation in myocardial infarction**
Yong Zhang
Harbin Medical University, China

033-SS2 **The role and mechanism of non-coding RNAs in cardiac remodeling**
Hai-Hai Liang
Harbin Medical University, China

033-YS1 **Cardiotonic Pills, a traditional Chinese medicine, ameliorates isoproterenol-induced cardiac injury and fibrosis via regulating myocardial metabolism**
Xiao-Hong Wei
Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China

033-YS2 **The Effect and Mechanism of QishenYiQi and its Effective Ingredients on Pressure Overload-induced Myocardial Fibrosis**
Gulinigaer Anwaier
School of Basic Medical Sciences, Peking University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 37: The Impact of Microvascular Aging on Brain Neural Functions: Experimental and Theoretical Approaches**
Organized by JSM and Supported by 12th WCM

Chair: Kazuto Masamoto, *University of Electro-Communications, Japan*

Co-Chair: Makoto Suematsu, *Keio University School of Medicine, Japan*

037-SS1 **Neurogenic control of brain vasculature**
Harumi Kanashiki
Tokyo Metropolitan Institute of Gerontology, Japan

037-YS1 **Multiphysics modeling of cellular and tissue-scale oxygen distribution in cerebral cortex**
Satoshi Ii
Tokyo Metropolitan University, Japan

037-YS2 **Perfusion changes in response to microvascular disturbances across scales and brain areas**
Franca Schmid
University of Bern, Switzerland

037-YS3 **Therapeutic Effect and Mechanisms of AnGongNiuHuang Wan in Ameliorating LPS-Induced Cerebral Microvascular Injury and Edema**
Bo-Tong Liu
Peking University, China

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 5

08:30-10:00 **Symposium 30: Microcirculation, Stem Cells and Tissue Repair**
Organized by MCS and Supported by 12th WCM

Chair: Jianbo Wu, *Southwest Medical University, China*

Co-Chair: Michael Hill, *University of Missouri, USA*

030-SS1 **Critical role of mitochondrial integrity in the vascular endothlium in development of cardiac dysfunction**
Andreas Beyer
Medical College of Wisconsin, USA

030-SS2 **Microvascular Regeneration Following Skeletal Muscle Injury**
Steve Segal
University of Missouri, USA

030-SS3 **Improving vasculoprotective effects of MSCs in coronary microvessels – benefits of 3D culture, sub-populations and heparin**
Neena Kalia
College of Medical and Dental Sciences, University of Birmginham, UK

030-SS4 **Regulation of Photomodulation in Angiogenesis**
Jianbo Wu
Southwest Medical University, China

10:00-11:30 **Symposium 34: Novel Treatment Targets for Brain Disorders**
Organized by JSM and Supported by 12th WCM

Chair: Yoshiaki Itoh, *Osaka City University Graduate School of Medicine, Japan*

Co-Chair: Takato Abe, *Tokai University School of Medicine, Japan*

034-SS1 **Neurovascular unit and Stroke: metabolic response of astroglia**
Shinichi Takahashi
Saitama Medical University International Medical Center, Japan

034-SS2 **Neurovascular unit in multiple sclerosis: New gateway to disease modification?**
Jin Nakahara
Keio University School of Medicine, Japan

034-YS1 **Alzheimer's Disease and Glymphatic System**
Itsuki Hasegawa
Osaka City University Graduate School of Medicine, Japan

034-YS2 **Post-Sepsis Microcirculatory Dysfunction Alleviation by Drag-Reducing Polymers**
Denis Bragin
Lovelace Biomedical Research Institute, USA

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Symposium 38: Micro- and Macro-Circulatory Dysfunction in Disease**
Organized by ANZMS and Supported by 12th WCM

Chair: Marianne Tare, *Monash University, Australia*

Co-Chair: Georges Grau, *The University of Sydney, Australia*

038-SS1 **Effect of stroke beyond the brain**
Connie Wong
Monash University, Australia

038-SS2 **Novel therapeutics for pulmonary arterial hypertension**
Kristen Bubb
Monash University, Australia

038-SS3 **Importance of extracellular vesicles in microvascular pathologies**
Georges Grau
The University of Sydney, Australia

038-YS1 **Bench-to-bedside translation of mega-dose sodium ascorbate to reverse sepsis-induced brain and kidney micro-circulatory dysfunction**
Yugeesh Lankadeva
University of Melbourne, Australia

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 6

08:30-10:00 **Free Oral Communication 11: Vascular Hyperpermeability**

Chair: Kristen Bubb, *Monash University, Australia*

Co-Chair: Xiao-Hua Guo, *outhern Medical University, China*

F11-1 **Endothelium-derived Cdk5 deficit aggravates air pollution-induced peripheral vasoconstriction through AT1R upregulation**

Chen Xiang

Nanjing Medical University, China

F11-2 **Water molecular using a Near-infrared spectroscope applied to discriminate the early-stage hyperglycemia and the effect of YanXueQingNao (YXQN)**

Yasuhiro Kato

Keio University, Japan

F11-3 **An ex vivo method may evaluate vasoactivity induced by Hemoglobin-Based Oxygen Carriers in resistance vessels**

Hang Yu

Academy of Military Science of the Chinese People's Liberation Army, China

F11-4 **Effects of sulforaphane on MGO-induced inflammatory response and pyroptosis in Human Umbilical Vein Endothelial Cells**

Mao Luo

Southwest Medical University, China

F11-5 **Quantitative Assessment of OCT and OCTA Parameters in Diabetic Retinopathy With or Without Macular Edema: Single-center Cross-sectional Analysis**

Bojun Zhao

Shandong Provincial Hospital, China

F11-6 **Is the microvascular responsiveness to the locally delivered glucagon-like peptide-1 analogue, liraglutide, impaired in individuals with type 2 diabetes and retinopathy?**

Kim Gooding

University of Exeter Medical School, United Kingdom

10:00-11:30 **Young Symposium 5: Microcirculation Disturbance of Cardiovascular and Cerebrovascular Diseases and Drug Intervention**

Supported by Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences, China

Chair: Gui-Bo Sun, *Chinese Academy of Medical Sciences & Peking Union Medical College, China*

Co-Chair: Meng Qin, *Beijing University of Chemical Technology, China*

Y05-1 **Subclinical myocardial aging: Physiological and Translational Perspective on Aging-related cardiovascular disease**

Heng Ma

Fourth Military Medical University, China

Y05-2 **Nanotechnology for the Diagnosis and Therapy of Ischemic Microvascular Diseases**

Meng Qin

Beijing University of Chemical Technology, China

Y05-3 **Calenduloside E Ameliorates Myocardial Ischemia-Reperfusion Injury through Regulation of AMPK and Mitochondrial OPA1**

Min Wang

Chinese Academy of Medical Sciences & Peking Union Medical College, China

Y05-4 **Microglial NFAT5 aggravates neuroinflammation via regulating NLRP6 in experimental model of ischemia stroke**

Gan Hui

Chongqing Medical University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Young Symposium 6: ESM/MCS/ANZMS Young Investigator Symposium**

Supported by ASM/MCS/ANZMS

Chair: William Jackson*, Michigan State University, USA*

Co-Chair: Henning Morawietz*, University of Technology Dresden,Germany*

Y06-1 **Role of Plasmacytoid Dendritic Cells in the Development of Macro- and Microvascular Dysfunction in Type 2 Diabetic Mice**

Kiran Alluri

Physiological Science / EVMS, USA

Y06-2 **STIM1 disruption in regulatory T cells protects against renovascular hypertension-induced vascular endothelial dysfunction**

Balaji Srinivas

Physiological Science / EVMS, USA

Y06-3 **Choriocapillaris perfusion correlates with retinal capillary perfusion in all three retinal vascular plexuses in type 2 diabetes**

Natalia Rolinska

University of Exeter Medical School, UK

Y06-4 **QSYQ and its core blood component combination ameliorate diabetic peripheral arterial disease by simultaneously regulating T cell-mediated angiogenic and inflammatory processes**

Li Peng

Tianjin University of Traditional Chinese Medicine, China

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 7

08:30-11:30 **Satellite Symposium 9: Diabetes and Microcirculation**
Supported by Professional Committee on Diabetes and Microcirculation of CSM

FIRST SESSION

Chair: Yuxiu Li, *Peking Union Medical College Hospital, China*

Co-Chair: Donald Welsh, *University of Western Ontario, Canada*

S9-1 **Diabetes and gastroparesis**
Chris Rayner
University of Adelaide, Australia

S9-2 **New target for prevention and treatment of diabetic retinopathy**
Liming Chen
Tianjin Medical University Metabolic Diseases Hospital, China

S9-3 **Kallikrein kinin system and diabetic microvascular complications**
Zhaoyun Zhang
Huashan Hospital, Fudan University, China

S9-4 **Mitochondrial oxidative stress and diabetic nephropathy**
Yi Zheng
the Second Affiliated Hospital of Army Medical University, China

SECOND SESSION

Chair: Jiaqing Shao, *TJinling Hospital, School of Medicine, Nanjing University, China*

S9-5 **Postprandial hypotension – prevalence, pathophysiology and approaches to treatment**
Karen Jones
The University of Adelaide, Australia

S9-6 **Type 2 diabetes and Alzheimer's disease in China**
Yan Bi
Nanjing University, China

S9-7 **Lactic acid: metabolic waste or signaling molecules?**
Xiaoyan Hui
The Chinese University of Hong Kong, China

S9-8 **The Adipokine Tetranectin Inhibits Insulin Secretion from β Cells in Diabetes**
Jingjing Zhang
Second Xiangya Hospital of Central South University, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

13:30-15:00 **Poster** (Poster Area, B1/F)

08:30-11:30 **Satellite Symposium 11: Myocardial Perfusion: From Pericardial Vessel to Microcirculation**
Supported by China Magnetocardiogram Cooperation Group

FIRST SESSION

Chair: Chengxing Shen, *Shanghai Sixth People's Hospital, China*

Co-Chair: Yundai Chen, *PLA General Hospital, China*

S11-1 **Noninvasive detection of myocardial ischemia: Diagnostic value of magnetocardiography for coronary artery disease**
Yixian Lin
Hong Kong Canossa Hospital, Hongkong, China

S011-2 **Non-Invasive Magnetocardiography for the Early Diagnosis of Coronary Microcirculation Dysfunction**

Jian Ma

hanghai Sixth Peple's hospital, China

S011-3 **Magnetocardiography Based Detection of Acute Myocardial Infarction with Single-vessel Disease**

Yijing Guo

Shanghai Sixth Peple's hospital, China

S011-4 **On-Site Computed Tomography-Derived Fractional Flow Reserve to guide management of patients With stable coronary artery disease using a machine learning: The TARGET Randomized Trial**

Yundai Chen

PLA General Hospital, China

SECOND SESSION

Chair: Chengxing Shen, *Shanghai Sixth People's Hospital, China*

Co-Chair: Yundai Chen, *PLA General Hospital, China*

S011-5 **The Clinical Research and Application of FFR in STEMI Complicated with Multi-vessel Disease**

Chengxing Shen

Shanghai Sixth People's Hospital, China

S011-6 **Clinical Research and Application of FFR Combined with Intravascular Imaging**

Jian Liu

Peking University People's Hospital, China

S011-7 **Application of FFR in the Stent Optimization and Prediction of Long-term Outcomes Post PCI**

Yafeng Zhou

The First Affiliated Hospital of Soochow University, China

S011-8 **Brachial and central hypertension in relation to coronary stenosis in patients with coronary angiography**

Yu Chen

Shanghai Sixth Peple's Hospital, China

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

GUORUI HALL

08:30-10:00 **Plenary Lecture 1-3**

Chair: Michael Hickey, *Monash University, Australia*

Plenary Lecture 1

PL-01 **Functional Bias in the Cerebral Circulation: Reimagining Electro- and Pharmaco- Mechanical Coupling in Blood Flow Control**

Donald Welsh

Institution: Robarts Research Institute, University of Western Ontario, Canada

Plenary Lecture 2

PL-02 **Non-invasive monitoring of circulating melanoma cells by in vivo flow cytometry**

Xunbin Wei

Peking University Health Science Center, China

Plenary Lecture 3

PL-03 **Possible role for Endothelial Derived Hyperpolarization in Coronary Microvascular Dysfunction**

Paul Fraser

Vascular Biology & Inflammation,School of Cardiovascular Metabolic Medicine & Sciences, BHF Centre for Research Excellence, King's College London,UK

10:00-11:30 **Satellite Symposium 10: Advanced Technologies and Translational Medicine in Tumor Microcirculation**

Supported by Professional Committee on Tumor of CSM

Chair: Qing Xia, *Peking University, China*

Co-Chair: Chuan-Hui Han, *Peking University, China*

S10-1 **STAT1 lactylation induced by Helicobacter pylori activates GNB4 expression to promote gastric carcinogenesis**

Duanrui Liu

Shandong Provincial Hospital Affiliated to Shandong First Medical University, China

S10-2 **Intrinsic and microenvironmental factors promotes temozolomide resistance of glioblastoma**

Zhiqiang Dong

Huazhong Agricultural University, China

S10-3 **Lymphangiogenesis-related gene model in microcirculation for predicting prognosis and immune microenvironment of pancreatic cancer**

Huaizhi Wang

Chongqing General Hospital, China

S10-4 **Apply CRISPRomics in Cancer Target discovery**

Shaokun Shu

Peking University, China

11:30-12:20 **Keynote Lecture 3**

Chair: Jing-Yan Han, *Peking University, China*

KL-03 **The regulation of platelet lifespan and its clinical implications**

Kesheng Dai

Department of Thrombosis and Hemostasis, Jiangsu Institute of Hematology, China

12:20-12:50 **Lunch** (East Exhibition Hall, 1/F)

12:50-13:30 **Lunch Lecture 3**

Chair: Zhizhong Ma, *Peking University, China*

LL-03 **The Effect and Mechanism of YangXueQingNaoWan Attenuating Blood Brain Barrier Disruption after Thrombolysis with Tissue Plasminogen Activator in Ischemia Stroke**

Ying-Qian Jiao

Peking University, China

13:30-15:00 **Poster** (Poster Area, B1/F)

15:00-16:30 **Plenary Lecture 4-6**

Chair: Paul Fraser, *King's College London, UK*

Plenary Lecture 4

PL-04 **Mitochondrial influence in the aging coronary microcirculation**

Amanda Jo LeBlanc

Department of Cardiovascular and Thoracic Surgery Cardiovascular Innovation Institute, University of Louisvill, USA

Plenary Lecture 5

PL-05 **From the discovery of mechanisms of resistance to conventional therapies to the establishment of innovative treatments for metastatic kidney cancers**

Gilles Pages

University Côte d'Azur, France

Plenary Lecture 6

PL-06 **Transcriptional activation of NRF2 antioxidant genes in endothelial cells under physiological oxygen levels: implications for improved clinical translation**

Giovanni E Mann

School of Cardiovascular and Metabolic Medicine & Sciences, Faculty of Life Sciences & Medicine & King's College London,UK

16:40-17:30 **The Nishimaru-Tsuchiya International Award**

Chair: Hidekazu Suzuki, *Tokai University School of Medicine, Japan*

AL-03 **Imaging metabolomics: making the invisible visible without labeling**

Makoto Suematsu

Department of Biochemistry of Keio University School of Medicine

17:40-20:00 **Banquet** (Guoce Hall, 2F, GICEC)

ROOM 1

08:30-10:00 **Symposium 39: Emerging Mechanisms Underlying Vascular Contributions to Cognitive Impairment and Dementia. (Small Vessels Big Problems)**

Supported by 12th WCM

Chair: Richard Roman, *University of Mississippi Medical Center, USA*

039-SS1 **Cerebral microcirculatory dysfunction and age-related cognitive impairments**

Zoltan Ungvari

University of Oklahoma Medical Center, USA

039-SS2 **Enhanced Cerebral Hemodynamics and Cognitive Function Via Knockout of Dual-Specificity Protein Phosphatase 5**

Fan Fan

Medical College of Georgia, Augusta University, USA

039-SS3 **Diminished pericyte remodeling in the aged mouse brain causes prolonged disruptions to capillary flow**

Andy Shih

Seattle Children's Research Institute, USA

039-SS4 **Capillary perfusion and mitochondria deficits in age-related neurodegeneration**

Kevin Lin

Louisiana State University Health Sciences Center, USA

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

ROOM 2

08:30-10:00 **Symposium 40: China-Japan Joint Symposium of Qi-Blood**

Supported by 12th WCM

Chair: Jing-Yan Han, *School of Basic Medical Sciences, Peking University, China*

Co-Chair: Hidekazu Suzuki, *Tokai University School of Medicine, Japan*

040-SS1 **Imaging metabolomics to decipher cancer metabolic systems in human cancer**

Makoto Suematsu

Keio University School of Medicine, Japan

040-SS2 **Herbal Medicine and Gastrointestinal Diseases**

Hidekazu Suzuki

Tokai University School of Medicine, Japan

040-SS3 **Tonifying Qi with QiShenYiQi Prevents Microvascular Hyperpermeability Induced by Ischemia-Reperfusion**

Yang Ye

Peking University, China

040-SS4 **Phase-specific mechanism of Qi-benefiting- and blood-activating-components of QishenYiqi for the synergistic protection of ischemic stroke**

Yan Zhu

Tianjin University of Traditional Chinese Medicine, China

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

ROOM 4

08:30-10:00 **Symposium 41: The Vascular Endothelium in Human Gastroenterology and Hepatology Diseases**

Supported by 12th WCM

Chair: Fanyin Meng, *Indiana University School of Medicine, USA*

041-SS1 **Role of the vascular endothelium in irritable bowel syndrome**

Nicholas Verne

University of Tennessee Health Science Center, USA

041-SS2 **Hepatocyte ADK Promotes Steatotic Liver Disease and Increases Angiogenesis**

Chaodong Wu

Texas A&M University, USA

041-SS3 **Vascular Endothelial Growth Factor Signaling and Angiogenesis in Post-Infectious Irritable Bowel Syndrome**

Qiqi Zhou

University of Tennessee Health Science Center, USA

041-SS4 **Aging associated endothelial dysfunction in chronic liver diseases**

Fanyin Meng

Indiana University School of Medicine, USA

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

SUN 24 SEP

ROOM 5

08:30-10:00 **Young Symposium 7:Selected from Abstract Submission**

Supported by 12th WCM

Chair: Jing Wu, *Xiangya Hospital of Centeral South University, China*

Co-Chair: Jian Liu, *Peking University, China*

Y07-1 **GPR124 facilitates pericyte polarization and migration by regulating the formation of filopodia during ischemic injury**

Li-Shan Lin

Nanjing Medical University, China

Y07-2 **Pericyte-derived SENP1 restore neurovascular function after brain Ischemia**

Xingfeng Mao

Nanjing Medical University, China

Y07-3 **The association of circulating chemerin levels with mild cognitive impairment in patients with type 2 diabetes mellitus, a cross-sectional study based on resting-state fMRI analysis**

Xinyi Yang

Medical school of Nanjing University, China

Y07-4 **Myocardial Mitochondrial Antiviral Signaling Protein Promotes Heart Ischemia-reperfusion Injury via the TAK1/TRAF6 Axis**

Desheng Hu

Wuhan Union Hospital, China

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

ROOM 6

08:30-10:00 **Satellite Symposium 12: Microcirculation and Osteonecrosis**
Supported by Professional Committee on Bone Microcirculation of CSM

Chair: Wei Sun, *China-Japan Friendship School of Clinical Medicine, China*

Co-Chair: Jike Lu, *Beijing United Family Hospital (BJU), China*

S12-1 **Marrow adipogenic lineage precursors (MALPs) facilitate bone marrow recovery after chemotherapy**
Jiankang Fang
University of Pennsylvania, America

S12-2 **Magnesium-based Orthopaedic Implants Induced Osteogenesis and Angiogenesis through Upregulation of Neuropeptides**
Ling Qin
The Chinese University of Hong Kong, China

S12-3 **Advancements in the Application of Platelet-Rich Plasma (PRP) for Musculoskeletal Disorders**
Jike Lu
Beijing United Family Hospital, China

S12-4 **Autocrine Activity of Extracellular Vesicles Induced by Icariin and Its Effectiveness in Glucocorticoid-Induced Injury of Bone Microvascular Endothelial Cells**
Fuqiang Gao
China Japan Friendship Hospital, China

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

ROOM 7

08:30-10:00 **Satellite Symposium 13: Microcirculation and Translational Medicine**
Supported by Professional Committee on Translational Medicine of CSM

Chair: Jun Chen, *Tianjin Medical University General Hospital, China*

Co-Chair: Changlin Zhang, *The Second Affiliated Hospital of Dalian Medical University, China*

S13-1 **Development of high-performance MRI contrast agent for tumor diagnosis and therapy**
Zhenghuan Zhao
Chongqing Medical University, China

S13-2 **The Interplay between Phase Separation and Enhancer Mechanisms in Disease Progression**
Zhijie “Jason” Liu
University of Texas Health Science Center at San Antonio, America

S13-3 **Identification and validation of autoantibodies against tumor-associated antigens as potential serological biomarkers in osteosarcoma: SERPA combined with protein microarray**
Jitian Li
Henan Luoyang Orthopedic Hospital, China

S13-4 **Effects of bivalirudin on coronary blood flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention**
Dan Jiang
Second Hospital of Dalian Medical University, China

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

GUORUI HALL

08:30-10:00 **Plenary Lecture 7-9**

Chair: Jian-Yuan Luo, *Peking University, China*

Plenary Lecture 7

PL-07 **Microvascular Dysfunctions and Organ Failure by Autodigestion**

Geert Schmid-Schonbein

Gene Ley Department of Bioengineering, University of California San Diego

Plenary Lecture 8

PL-08 **Mucosal microcirculation in inflammatory bowel disease**

Yoshikazu Tsuzuki

Department of Gastroenterology, Saitama Medical University, Japan

Plenary Lecture 9

PL-09 **Mechanical instability generated by Myosin 19 contributes to mitochondria cristae architecture and functions**

Congying Wu

Institute of Systems Biomedicine, School of Basic Medical Sciences, Peking University Health Science Center,China

10:00-10:50 **Keynote Lecture 4**

Chair: William Jackson, *Michigan State University, USA*

KL-04 **Targeting microvascular hyperpermeability to improve organ function**

Sarah Yuan

University of South Florida School of Medicine, USA

10:50-11:40 **Keynote Lecture 5**

Chair: Yugeesh Lankadeva, *University of Melbourne, Australia*

KL-05 **The glomerular microvasculature –where inflammatory leukocyte recruitment doesn't follow the rules**

Michael Hickey

Monash Centre for Inflammatory Diseases, Monash University, Australia

11:40-12:20 **Closing Ceremony** (GUORUI HALL)

ORAL SESSIONS ABSTRACTS

KEYNOTE LECTURE 1

Thursday | 16:40-17:30 | Guorui Hall

Chair: Henning Morawietz, University of Technology Dresden,Germany

Speaker: Stefanie Dimmeler

Dr.Stefanie Dimmeler is born on 18.07.1967 in Ravensburg, Germany. Dr. Dimmeler received her undergraduate, graduate, and Ph.D. degree from the University of Konstanz in Konstanz (Germany) and then completed a fellowship in Experimental Surgery at the University of Cologne and in Molecular Cardiology at the University of Frankfurt (Germany). She is Professor of Experimental Medicine (since 2001) and Director of the Institute of Cardiovascular Regeneration, Center for Molecular Medicine at the University of Frankfurt since 2008.

In the last years, she has been invited as a speaker in more than 300 national and international meetings and seminars and has presented various keynote lectures. She also received several awards and is among the top 3 female Scientists in Germany. She is also spokesperson of the "Cardiopulmonary Institute" (CPI) which is funded by the Excellence Strategy Program of the German Research Foundation and spokesperson of the German Center for Cardiovascular Research (DZHK). She also received three Advanced Investigator Grants by the European Research Community (ERC).

Her group elucidates the basic mechanisms underlying cardiovascular disease and vessel growth with the aim to develop new cellular and pharmacological therapies for improving the treatment of cardiovascular disease. Ongoing research focuses on epigenetic mechanisms that control cardiovascular repair, specifically non-coding RNAs.

KL-01

Noncoding RNAs in Vascular Health and Diseases

Stefanie Dimmeler

Non-coding RNAs gained increasing attention as key regulators of vascular function. Particularly microRNAs, which bind to mRNAs thereby blocking translation or inducing degradation, are well known to exhibit various activities and control endothelial, smooth muscle and inflammatory cell functions. For example, targeting of miR-92a by antimiR-92a improved endothelial cell functions and improved the recovery after myocardial infarction formation (Bonauer et al, Science 2009, Hinkel et al Circulation 2013). These inhibitors were successfully tested in Phase I clinical studies (Abplanalp et al, 2020) and may now be further developed as therapies for the treatment of cardiovascular disease. The second class of non-coding RNAs, the long non-coding RNAs (lncRNAs), is more complex and these RNAs exhibit various functions. For example, lncRNAs control gene expression by affecting transcription factors and epigenetic control processes, or can posttranscriptionally control splicing. Some lncRNAs such as MALAT1 have been shown to regulate endothelial cell proliferation and atherosclerotic lesion formation (Michalik et al, Circ Res 2014, Cremer et al, Circulation 2019). We also recently showed the functional relevance of a novel class of non-coding RNAs, namely circular RNAs (Boeckel et al, Circ Res 2015; Zhou et al MedComm 2020). Deletion of the circRNA cZfp292 impaired flow-induced responses in endothelial cells (Heumüller et al, Circ Res 2022). This lecture will provide examples of microRNAs, lncRNAs and circRNAs, which regulate vessel functions.

KEYNOTE LECTURE 2

Friday | 16:40-17:30 | Guorui Hall

Chair: Georges Grau, The University of Sydney, Australia

Speaker: Britta Engelhardt

Since 2003 Britta Engelhardt is Professor for Immunobiology and the Director of the Theodor Kocher Institute at the University of Bern in Switzerland. After studying Human Biology at the Philipps-University, Marburg in Germany she pursued her PhD thesis with Prof. Hartmut Wekerle at the Max-Planck Research Group for Multiple Sclerosis in W√ºrzburg, Germany and the Max-Planck Institute für Psychiatry in Munich, Germany and obtained a PhD (Dr. rer. physiol.) in January 1991. After a post-doctoral fellowship in the laboratory of Eugene C. Butcher at Stanford University, California, she set up her own research group at the Max-Planck Institute for Physiological and Clinical Research, Bad Nauheim, Germany in the department of Werner Risau in 1993. In 1998 she obtained the Venia Legendi for Immunology and Cell Biology from the Medical Faculty of the Philipps University Marburg, Germany. From 1999 to 2003 she headed her independent research group at the same institute and the Max-Planck Institute for Vascular Cell Biology in M√ºnster, Germany.

Britta Engelhardt is a renowned expert in brain barriers research. Her work is dedicated to understanding the role of the brain barriers in maintaining central nervous system (CNS) immune privilege. Using advanced in vitro and in vivo live cell imaging approaches her laboratory has significantly contributed to the current understanding of the anatomical routes and molecular mechanisms used by immune cells to enter the CNS during immune surveillance and neuroinflammation in the context of multiple sclerosis and ischemic stroke. She has published over 250 manuscripts that are highly cited. She is an opinion leader in her field as shown by her regular presentations as invited and keynote speaker at international meetings.

Britta Engelhardt has served the scientific community by coordinating several national (Singergia UnmetMS, ProDocCellMigration) and international collaborative networks (JUSTBRIN, BtRAIN) dedicated to brain barriers research and neuroinflammation. Together with Peter Vajkoczy she has received the Herman-Rein-Prize for their pioneering in vivo imaging of T cell migration across cervical spinal cord microvessels. For her continuous contributions on the central nervous system microcirculation, she has obtained the prestigious Malpighi Award of the European Society for Microcirculation (ESM) in 2023. She was elected Vice-Chair and Chair of the Gordon Research Conference Barriers of the CNS in 2016 and 2018, respectively. She is the president of the Swiss Society for Microcirculation and Vascular Research (SSMVR), the Co-President of the Medico Scientific Advisory Board of the Swiss MS Society and the Vice-President/President Elect of the International Brain Barriers Society.

KL-02

Brain endothelium and neuro-inflammation

Britta Engelhardt

To maintain central nervous system (CNS) homeostatis the microvascular endothelial cells of CNS microvessels tightly regulate the movement of ions and molecules between the blood and the CNS. The unique properties of these microvascular endothelial cells are termed blood-brain barrier (BBB) and extend to regulating immune cell trafficking into the immune privileged CNS during health and disease. BBB breakdown and increased immune cell infiltration into the CNS are early hallmarks of multiple sclerosis (MS). In general, extravasation of circulating immune cells is a multi-step process regulated by the sequential interaction of adhesion and signalling molecules between the endothelial cells and the immune cells. Accounting for the unique barrier properties of CNS microvessels, immune cell migration across the BBB is distinct and characterized by several adaptations. I will describe our current knowledge on the mechanisms that regulate CD4 versus CD8 T cell trafficking across the BBB in neuroinflammation, with a focus on the current state-of-the-art in vitro and in vivo imaging observations.

KEYNOTE LECTURE 3

Saturday | 11:30-12:20 | Guorui Hall

Chair: Jing-Yan Han, Peking University, China

Speaker: Kesheng Dai

Professor Kesheng Dai received his medical doctor degree in Hematology from Soochow University in 2002 and performed postdoctoral training at the University of Illinois at Chicago. In 2005, Dr. Dai was recruited as a Distinguished Professor at Beihang University (Beijing, China). In 2011, he relocated to Soochow University (Suzhou, China), where he served as a Distinguished Professor and the Vice Director of the Cyrus Tang Medical Institute, Jiangsu Institute of Hematology, Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, National Clinical Medicine Research Center in Hematological Diseases and State Key Laboratory of Radiation Medicine and Protection. Dr. Dai also served key roles in many (inter) national scientific organizations, including as a member of the International Academy of Astronautics, the Chairman of the Committee of Microcirculation within the Chinese Association of Physiopathology, the Deputy Director of the Group of Vascular Biology within the Chinese Association of Pathophysiology, and the Chairman of the Committee of Thrombosis and Hemostasis within the Chinese Association of Integrative Medicine.

Dr. Dai's research focus on regulatory mechanisms and clinical implications of platelet apoptosis and lifespan, signaling and regulatory mechanisms of a platelet adhesion receptor glycoprotein Ib-IX complex, and the signaling cascades leading to the activation of the platelet integrin alpha IIb/beta 3, and their applications in therapy and diagnosis of thrombotic and hemorrhagic diseases.

He has achieved many outstanding accomplishments and contributions in this field, including more than 70 peer-reviewed scientific papers, many of which on premium journals including PNAS, J Clin Invest, Blood, and Circ Res. His scientific discoveries include the following topics

1.The regulatory role of GPIb-IX in platelet adhesion and thrombus formation.
2.The regulatory mechanisms of platelet apoptosis and lifespan and their clinical implications.
3.Effect of gravity on platelet function.

KL-03

The regulation of platelet lifespan and its clinical implications

Kesheng Dai

Platelets are the central regulator for keeping the vital balance between thrombosis and hemorrhage in the circulation. Platelet apoptosis is the main reason for platelet clearance which plays a critical role in controlling the lifespan and number of circulating platelets. However, the mechanism for the regulation of the lifespan of circulating platelets and its physiological and pathophysiological importance still remain unclear.

Our research team has been studying the mechanism of regulation of the lifespan of circulating platelets for more than ten years. We found that von Willebrand factor binding to platelet glycoprotein (GP) IbŒ± and pathologic shear stresses can induce platelet apoptosis. Various drugs can induce platelet apoptosis, which is the main reason for drug-induced thrombocytopenia. We found that platelet apoptosis provoked by various pathological stimuli results in thrombocytopenia in many common diseases, such as infection, diabetes, and immune thrombocytopenia (ITP). We investigated the mechanism of various pathophysiological factor-induced platelet apoptosis, and found that trace amounts of thrombin generated in the circulation reduced PKA activity in platelets. PKA inhibition resulted in dephosphorylation of the proapoptotic protein Bad at Ser155, resulting in sequestration of prosurvival protein BCL-XL in mitochondria and subsequent apoptosis. In vivo experiment results showed that platelet lifespan was extended in PKA- and Bad-knockout mice, leading to a modest elevation of peripheral platelets. Bad deficiency is protective against PKA inhibitor-induced platelet apoptosis in vitro and platelet clearance in vivo, further demonstrating that PKA regulates platelet lifespan via Bad-mediated platelet apoptosis. PKA activation protected platelets from apoptosis induced by pathological stimuli and elevated peripheral platelet levels in a murine model of ITP, suggesting that PKA regulates platelet apoptosis by changing the phosphorylation of platelet proapoptotic protein Bad. We demonstrate that anti-GPIbŒ± antibody binding to platelets activates Akt, which elicits platelet apoptosis through phosphodiesterase (PDE3A)-mediated PKA inhibition, and the platelets were mainly removed by macrophages in the liver, which is an essential cause of refractory ITP. Based on this finding, we selected the PKA activator aminophylline, which was proved to markedly decreased autoantibodies-induced platelet apoptotic events in vitro and elevated peripheral platelet levels in a murine model of ITP. Clinical trials evaluating the efficacy of aminophylline as a therapeutic were identified for some refractory ITPs patients. Furthermore, our study identified the essential role of GPIbŒ± in platelet activation and apoptosis. Deletion of GPIbŒ± inhibited integrin Œ±IIbŒ≤3 activation and granule secretion, reduced arterial thrombus formation, extended tail bleeding time, and prolonged lifespans of circulating platelets. We demonstrated that GPIbŒ± through competitive binding of 14-3-3Œð regulates PKCŒ± and PKCŒ±-mediated integrin activation, secretion, and apoptosis. We further discovered that GPIbŒ±-dependent platelet activation was essential for tumor metastasis. The regulatory function of GPIbŒ± plays a crucial role in the occurrence and regulation of major diseases such as thrombosis and tumor metastasis. These findings indicate that platelet GPIbŒ± plays a key role in the regulation of platelet function and apoptosis, which contributes to the regulation of the occurrence of thrombosis, cancer metastasis and other major diseases.

In conclusion, our study reveals the regulatory mechanism of platelet lifespan under different pathological and physiological conditions, uncovers the pathophysiological mechanism of platelet number-related diseases, and provides novel targets and strategies for the treatment of platelet-related diseases.

KEYNOTE LECTURE 4

Sunday | 10:00-10:50 | Guorui Hall

Chair: William Jackson, Michigan State University, USA

Speaker: Sarah Yuan

Dr. Sarah Yuan is a Professor of Pharmacology and Physiology at the University of South Florida. Her laboratory investigates the molecular mechanisms of microcirculatory dysfunction, focusing on leukocyte/endothelial cell-cell/matrix interactions and their effects to cause vascular barrier leakage during trauma, infection, sepsis, atherosclerosis, and peripheral vascular diseases. Her group is internationally recognized for their expertise in studying microvascular permeability, as well as developing innovative experimental approaches that incorporate intravital microscopy, molecular imaging, proteomics, and nanotechnology into a comprehensive analysis of barrier structure and function. Their work has led to the identification of novel molecular pathways in the endothelial hyperpermeability response, including the NO-PKC and MLCK signaling cascades, ADAM-catalyzed glycocalyx shedding, and palmitoylation-mediated posttranslational regulation of junction barrier property. Currently, her lab is carrying out research projects on the gut-lung-brain axis of microvascular inflammatory response, aiming to decipher its underlying molecular mechanisms and translate them into organ pathophysiology with potential diagnostic and therapeutic implications.

KL-04

Targeting microvascular hyperpermeability to improve organ function

Sarah Yuan

The vascular endothelium forms a semi-permeable barrier that controls blood-tissue exchange. Barrier breakdown leads to aberrant transport of circulating components into the vessel wall and surrounding tissues. This process critically contributes to the pathogenesis of inflammatory injury associated with trauma, infection, sepsis, atherosclerosis, diabetes, ischemia-reperfusion, and peripheral vascular diseases. We study the cellular and molecular mechanisms of microvascular barrier dysfunction at multiple levels: within the blood circulation, we characterize circulating factors, including extracellular vesicles, neutrophil extracellular traps, and glycocalyx shedding products that are capable of targeting endothelial barrier to cause leakage; at the blood-endothelium interface, we identify cell surface receptors, transmembrane molecules, and intracellular signals that interact with circulating factors and transduce their hyperpermeability effects; and down to the endothelial barrier structure, we elucidate key molecular mechanisms controlling barrier property, focusing on cell-cell junctions, cytoskeleton, glycocalyx matrix, and focal adhesions. This lecture describes our recent findings related to these areas, including a disintegrin metalloprotease-catalyzed glycocalyx shedding, and leukocyte/endothelium-derived extracellular vesicles/traps, in mediating microvascular hyperpermeability at organ/tissue levels involving the gut, lung, and brain.

KEYNOTE LECTURE 5

Sunday | 10:50-11:40 | Guorui Hall

Chair: Yugeesh Lankadeva, University of Melbourne, Australia

Speaker: Michael Hickey

Professor Michael Hickey is Director of the Centre for Inflammatory Diseases and Professor (Research) in the Monash University Department of Medicine at Monash Medical Centre, in Melbourne, Australia. He received his PhD from the University of Melbourne in 1996, and subsequently undertook a postdoctoral fellowship at the University of Calgary in Canada, in the laboratory of Dr. Paul Kubes, where he developed expertise in intravital microscopy and the investigation of the mechanisms of leukocyte recruitment. Michael returned to Australia in 2000, and joined the Centre for Inflammatory Diseases at Monash in 2001. He was appointed Deputy Centre Director in 2014 and Centre Director in 2019. His expertise lies in the analysis of the actions of immune cell subsets during inflammatory responses. Michael's laboratory uses various forms of advanced in vivo imaging, including multiphoton microscopy, to image a wide range of tissues during the inflammatory response. In recent years, Michael's lab has used these approaches to investigate the mechanisms of neutrophil and monocyte recruitment and behaviour in the inflamed kidney in conditions such as glomerulonephritis and acute kidney injury, and the actions of regulatory T cells in skin during contact hypersensitivity responses. His work has been published in journals such as Nature Medicine, Nature Communications, Proc. Natl. Acad. Sci. USA and the Journal of Immunology.

KL-05

The glomerular microvasculature -where inflammatory leukocyte recruitment doesn't follow the rules

Michael Hickey

The glomerular microvasculature can be the target of leukocyte-mediated inflammation, known as glomerulonephritis, with the potential to impair glomerular and renal function. In progressive forms of immune-mediated glomerulonephritis, this inflammatory response can lead to severe damage, fibrosis and necrosis of glomeruli. In these forms of glomerulonephritis, various leukocyte subsets including T cells, inflammatory monocytes and neutrophils, are recruited to the glomerulus where they promote glomerular inflammation and injury. Our research has used intravital microscopy to investigate the mechanisms of neutrophil and monocyte recruitment to the glomerulus in models of glomerulonephritis, revealing that leukocyte recruitment to the glomerular capillaries does not follow the normal cascade of leukocyte-endothelial cell interactions established via studies of postcapillary venules. In glomerular capillaries, circulating neutrophils and monocytes undergo immediate arrest and are subsequently retained within the capillary lumen, where some of these cells can undergo extensive intravascular migration, before detaching and returning to the bloodstream. The major effect of acute glomerular inflammation is to increase the duration of neutrophil and monocyte retention within the vascular lumen. While retained within the vascular lumen, neutrophils and monocytes promote glomerular injury without undergoing transmigration. Monocytes can also assume other roles in this intravascular location, such as presenting intraglomerular antigens to effector T cells within the glomerular microvasculature, as a mechanism of initiation of T cell-mediated glomerulonephritis. This presentation will summarise these findings and highlight future research directions in understanding leukocyte function in the glomerulus.

TAISHAN AWARD LECTURE

Thursday | 11:30-12:20 | Guorui Hall

Chair: Ruijuan Xiu, Institute of Microcirculation, Chinese Academy of Medical Sciences, China
Naifeng Liu, School of Medicine, Southeast University, China

Speaker: Qimin Zhan

ZHAN Qimin, MD, is currently an Academician of the Chinese Academy of Engineering, the endowed Boya Professor of Peking University (PKU), the Director for PKU International Cancer Institute, the Director for PKU Health Data Science Institute, and the Director for the laboratory of Molecular Oncology. Dr. Zhan was the Chairman of the National Advisory Board for 863 High-Tech Plan in the field of biomedical sciences and the Chief Scientist of the 973 National Fundamental Program. He is currently serving as the Vice Chairman for the Chinese Association of Microcirculation and the Vice Chairman of the Chinese Doctor Association.

Dr. Zhan obtained his medical degrees from the Suzhou Medical College (1982), and the Graduate School of Peking Union Medical College (1987). He did is postdoctoral training in the University of California San Fransisco, the Southwestern Medical Center of UT at Dallas and the National Cancer Center of NIH in USA (1989-1995). After finishing the postdoc training, he worked as a tenure-tracked assistant professor and the tenured associate professor in Pittsburgh University Cancer Institute (1997-2003).

Dr. Zhan's research interest is focused on the molecular pathways involved in the control of cell cycle and the signaling pathways involved in the regulation of the maintenance of genomic stability, tumor angiogenesis and tumor metastasis. He made the first demonstration in defining the molecular function of tumor suppressor p53 in the control of cell cycle checkpoint and characterizing the Gadd45 as the first p53-downstreaam gene, which is mainly involved in the G2/M growth arrest and regulating tumor angiogenesis through its interaction with Stat 3 pathway. His group also firstly demonstrated the genomic profiles of Esophageal Squamous Cell Carcinoma (ESCC), which provided the novel insights of ESCC carcinogenesis and identified the biomarkers for clinical treatment of ESCC. In the recent years, Dr. Zhan has paid great attention to the cancer translational study, including molecular diagnosis and personalized therapy. His research has successfully attracted multiple grants from different national funding agencies. Dr. Zhan's has published more than 270 peer-reviewed SCI papers. Many of his publications are in the prestigious journals of the biomedical field, including Nature, Cell, Journal of Clinical Investigation, EMBO, Nat Communication, American J of Human Genetics, Cancer Research, Molecular Cancer and Oncogene. To date, these papers have been cited more than 20,400 times.

AL-01

Tumor suppressor-associated cell cycle regulators in the malignant development of tumors

Qimin Zhan

Tumor suppressors including p53 and BRCA1 have been implicated in the control of cell cycle progression and tumorigenesis. P53 has been demonstrated to play critical roles in the cell cycle checkpoint, probably through its downstream genes. Over the last decades, we have identified the first p53-regulated gene Gadd45 and showed that Gadd45 plays role in cell cycle G2/M growth arrest through its interaction with Cdc2. Later on, we demonstrated that Gadd45 plays an important role in suppression of tumor angiogenesis. Gadd45 deletion significantly increases microvessel density in tumors and stimulates an angiogenic response in a chicken embryo chorioallantoic membrane assay. Disruption of endogenous Gadd45 promotes tube formation and migration of endothelial cells. We also show that Gadd45a deletion increases phosphorylation of STAT3 at Ser-727 and, in turn, elevates the STAT3 transcriptional activity. This process substantially induces both expression and secretion of VEGFa, a STAT3 responsive gene, and promotes tumor angiogenesis. Interestingly, Gadd45 is able to physically associate with mammalian target of rapamycin (mTOR), a kinase that mediates Ser-727 phosphorylation of STAT3. The interaction of Gadd45a with mTOR suppresses STAT3 phosphorylation at Ser-727 and leads to down-regulation of VEGFa.

Recently, we firstly demonstrated the landscape for genomic alterations of human Esophageal Squamous Cell Carcinoma (ESCC), which is one of the most aggressive cancers and is the sixth leading cause of cancer death worldwide. We identified a group of the frequent-mutated genes in ESCC, such as P53, RB, CDKN2A, PIK3CA, NOTCH1, NFE2L2, ADAM29 and FAM135B. We also analyzed the copy number variations and genomic structure variation as well. Interestingly, most of important cell cycle regulators were mutated or amplified during the molecular oncogenesis of ESCC. Furthermore, we found that MicroRNA 548 was localized at an amplified genomic region, and played an important role in ESCC tumorigenesis and metastasis. Most recently, we employed approaches of multi-omic analyses in molecular classification and molecular typing of ESCC, and demonstrated that clinical ESCC could be divided into 4 groups, which might be greatly contribute to the development of novel clinical approaches.

ZWEIFACH AWARD LECTURE

Friday | 11:30-12:20 | Guorui Hall

Chair: Amanda Jo LeBlanc, University of Louisvill, USA

Speaker: Luis A. Martinez-Lemus

EDUCATION

Postdoctoral Texas A&M University (2004).

Ph.D. Texas A&M University (1998).

M.S. Auburn University (1994).

D.V.M. Universidad Nacional Autonoma de M√©xico (1991).

PROFESSIONAL EXPERIENCE (after postdoctoral fellowship)

- Director: Center for Precision Medicine, University of Missouri-Columbia, Columbia, Missouri. (November 2020-Present)
- James O. Davis Distinguished Professor of Cardiovascular Research: University of Missouri- Columbia, Columbia, Missouri. (December 2019-Present)
- Dalton Cardiovascular Research Center Investigator: University of Missouri-Columbia, Columbia, Missouri. (November 2005-December 2021)
- Faculty Research Lead, Cardiovascular and Metabolic Disorders: NextGen Precision Health Initiative, University of Missouri-Columbia, Columbia, Missouri. (December 2020-June 2021)
- Assistant to Full Professor: Department of Medical Pharmacology and Physiology, University of Missouri-Columbia, Columbia, Missouri. (2005-Present)

HONORS AND AWARDS (after Ph.D.)

- Appointed as the James O. Davis Distinguished Professorship of Cardiovascular Research in Medical Pharmacology and Physiology at the University of Missouri School of Medicine. (December 2019).
- Honored as Fellow of the American Physiological Society (Cardiovascular Section). (April 2014).
- Trainee travel award: Awarded travel expenses by the National Heart, Lung and Blood Institute, National Institutes of Health (NHLBI, NIH) to attend the XIIIth International Vascular Biology Meeting in Toronto, Canada. (July 2004).
- Research Career Enhancement Award: Selected by the American Physiological Society as a recipient of one of the 2002 Research Career Enhancement awards (July 2002).
- Professor Luis A. Martinez-Lemus has published 105 articles in SCI journals, including Hypertension and Cardiovascular Research.

AL-02

A journey in arteriolar remodeling: from the extracellular matrix to the cytoskeleton

Luis A. Martinez-Lemus

Structural remodeling of the microcirculation, in particular that of the arteriolar network has been the focus of numerous studies due to its pathophysiological implications in peripheral vascular resistance and end-organ damage. At the initial stages of my career in vascular research, seminal work by numerous distinguished microcirculation investigators had established a clear association between various structural changes in arterioles with cardiovascular disease conditions such as hypertension. A specific question being asked at that time was how resistance vessels in hypertension reduce their passive structural diameter while maintaining the same amount of wall material (i.e., conserving the same cross-sectional area of the wall). In other words, what are the mechanisms by which arterioles undergo inward eutrophic remodeling in hypertension? While visiting the laboratories of Drs. Ulrich Pohl and Steffen S. Bolz as a postdoctoral fellow under the mentorship of Dr. Gerald A. Meininger, we discovered that some vascular smooth muscle cells within the wall of isolated arterioles change their positions when exposed for several hours to a vasoconstrictor agonist. This led us to hypothesize that dynamic changes in the vascular extracellular matrix and smooth muscle cytoskeletal structures need to occur for arteries and arterioles to remodel in association with different conditions including obesity, type 2 diabetes, hypertension, and aging. Throughout my independent scientific career, my research has been focused on testing that hypothesis and finding therapeutic approaches to intervene in the vascular remodeling process and ameliorate its detrimental cardiovascular effects. My laboratory in collaboration with other investigators such as Drs. Michael A. Hill, James Sowers, Camila Manrique, and Jaume Padilla discovered that the activity of multiple enzymes including matrix metalloproteinases, tissue transglutaminase, LIM kinase, and cofilin participate in modulating the production, degradation, and structural organization of the extracellular matrix and cytoskeletal structures. We further focused on the role that actin polymerization plays in arterial stiffening and discovered that reducing the formation of actin stress fibers and promoting their depolymerization represents a potential therapeutic avenue to prevent arteriolar inward remodeling and reduce arterial stiffness in multiple cardiovascular disease conditions. We have intervened at levels that include ligation of cellular receptors by the extracellular matrix and humoral agonist as well as intracellular promotors and inhibitors of actin dynamics. My ultimate hope is that these discoveries lead to clinical approaches able to reduce cardiovascular disease incidence and mortality.

NISHIMARU-TSUCHIYA AWARD LECTURE

Saturday | 16:40-17:30 | Guorui Hall

Chair: Hidekazu Suzuki, Tokai University School of Medicine, Japan

Speaker: Makoto Suematsu

Makoto Suematsu MD, PhD is Director, Central Institute for Experimental Animals (CIEA) and PI of WPI-Bio2Q Research Centre and Professor Emeritus of Keio University.

After graduation from Keio University School of Medicine, he was supervised by the late Professor Tsuchiya from 1983. He was Professor and Chair, Department of Biochemistry at the school of Medicine. From 2007-2015, he was Dean of the School of Medicine. In 2015, under governmental initiatives, he used to be the founding President of Japan Agency for Medical Research and Development (AMED). He was the last President of Japanese Society for Microcirculation, and President of 10th World Congress for Microcirculation in Kyoto in 2015. His speciality is Gas Biology, which deciphers molecular mechanisms for gas-mediated biological responses. Imaging metabolomics and gold-nanoparticle-based SERS imaging device are developed to improve diagnosis of human solid cancers.

AL-03

Visualization of reactive oxygen and sulfur species by imaging metabolomics: A challenge for making invisible metabolites visible

Makoto Suematsu

In 1980-90', an era before bioimaging sciences, the late Professor Masaharu Tsuchiya and I translated an ultrasensitive photon-counting camera, Japan's invention for astronomy, to visualize reactive oxygen species (ROS) in vitro and in vivo.1,2 Leukocyte-endothelial interactions turned out to cause ROS at the sites of adhesion, and the ROS burst was diminished by blocking the leukocyte adhesion.3 After the discovery of roles of nitric oxide in the endothelium for cancelling ROS,4 in the mesenteric microcirculation, researchers asked whether parenchymal cells in organ microcirculation may also serve as a source of ROS and contribute to tissue injury. Fluorescence probes allowed us to visualize ROS that were synthesized through incomplete oxygen consumption in mitochondria and cytoplasm, and researchers enabled to track spatiotemporal relationship between ROS burst and cell death.5,6 Our group discovered roles of carbon monoxide (CO) in dilating sinusoids of liver or constricting pre-capillary arterioles in neurovascular units, while CO was difficult to be visualized.7,8 While researchers focused specific molecules of interests, mass spectroscopy (MS) emerged as multi-omics technology and was translated into imaging MS that enables to snapshot hundreds of metabolites at once in frozen tissue sections.9,10 Direct visualization of metabolites in tissues allowed us to discover high glutathione in solid cancers or GABA in B-lymphocytes.7,11 However, use of high-energy laser for molecular ionization in imaging MS hampers detection of redox metabolites that are readily oxidized artificially. We overcame many technical difficulties to visualize many reactive sulfur species using infrared laser-scanning large-area surface-enhanced Raman spectroscopy (SERS) equipped with gold-nanoparticle-based two-dimensional SERS substrate.12,13,14 The method showed that polysulfides at 480cm-1, but neither glutathione (300cm-1) nor hypotaurine (978cm-1), occur in stroma of invasive breast cancer and clear cell ovarian carcinoma, and serve as a marker of invasiveness, chemoresistance and overall survival after the surgery. History to visualize small metabolites in organ microcirculation is superimposable to history of merging pathology, physiology and biochemistry.

PLENARY LECTURE 1

Saturday | 08:30-09:00 | Guorui Hall

Speaker: Donald Welsh

Dr. Donald Welsh is a Professor of Physiology & Pharmacology and the Rorabeck Chair of Neuroscience & Vascular Biology at the University of Western Ontario. He has published 90 peer reviewed manuscripts on the various aspect of arterial tone development, particularly in skeletal muscle and brain. Of note is his work on role on L-type and T-type Ca2+ channels in tone development and the mechanistic foundation of intercellular electrical conduction in resistance arteries. Dr. Welsh recently completed the authoritative summary of the latter topic for Physiological Reviews. Today, Dr. Welsh will be departing somewhat from his comfort zone as he rationalizes why vascular smooth muscle is encoded with two general contractile mechanisms, that being electrical and non-electrical, and how each plays a role in shaping how much and where blood flow is delivered.

PL-01

Functional Bias in the Cerebral Circulation: Reimagining Electro- and Pharmaco- Mechanical Coupling in Blood Flow Control

Donald Welsh

Constrictor agonists working through G-protein coupled receptors set arterial tone and blood flow through processes tied to (electromechanical) and independent of (pharmacomechanical) membrane potential (Vm). Electromechanical coupling is classically defined as modulation of myosin light chain kinase through changes in Vm, driving Ca2+ influx via voltage-gated Ca2+ channels. In contrast, pharmacomechanical coupling is defined by the regulation of myosin light chain phosphatase and the actin stress fibres through key signaling pathways. While constrictors engage both processes, why two general mechanisms are needed to accomplish one straightforward task remains unresolved. We argue, herein, that agonist-induced vasomotor responses are mechanistically variable and “bias” toward electro- or pharmaco- mechanical coupling, dependent on agent presentation and the intrinsic properties of receptors and tissue. This functional bias enables resistance vessels to generate unique vasomotor signatures which are key to optimizing how much and where blood flow is delivered in a complex network. This intriguing concept, developed and experimentally validated in the cerebral circulation, will be used to reexamine the mechanistic foundation of vasospasm/transient ischemic attack and to propose new therapeutic targets.

PLENARY LECTURE 2

Saturday | 09:00-09:30 | Guorui Hall

Speaker: Xunbin Wei

Dr. Wei received his bachelor in physics from University of Science and Technology of China, Hefei. He received his PhD from Department of Physiology and Biophysics, University of California, Irvine. Dr. Wei completed his post-doc training at Children's Hospital, Harvard Medical School. From 2006-2010, he is a professor in Fudan University, China. From 2006-2010, he was a professor and chair in Deparment of Biomedical Instrumentation, School of Biomedical Engineering, Shanghai Jiao Tong University, China. Currently, he is currently a professor at Department of Biomedical Engineering, Peking University. Dr. Wei is an SPIE Fellow, and recipient of Chinese Outstanding Young Scholar Award. He has published more than 100 peer-reviewed papers, including in Nature and PNAS. His research interests include cancer detection by optical means, optical manipulation of cells, and light treatment of Alzheimer disease.

PL-02

Non-invasive monitoring of circulating melanoma cells by in vivo flow cytometry

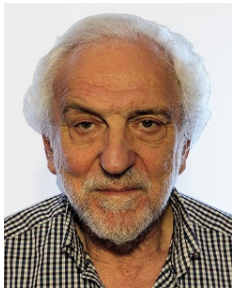
Xunbin Wei

Malignant melanoma, developing from melanocytes, is a kind of high metastatic tumor. Circulating melanoma cells, as a marker for metastasis development, are found in blood or lymphatic system at the early stage. Thus, quantitative detection of circulating melanoma cells has great significance to diagnose carcinoma and monitor tumor metastasis. In contrast to in vitro detection methods and in vivo fluorescence-based flow cytometry (IVFC), the in vivo photoacoustic flow cytometry (PAFC) utilizes melanoma cells' predominant optical absorption in the near-infrared range over other absorbers to receive the photoacoustic (PA) signals without fluorescent dye labeling in a non-invasive way. The sensitivity of the PAFC system was demonstrated by in vitro and in vivo experiments. PAFC provides a new tool for in vivo, label-free, and noninvasive detection of circulating tumor cells (CTCs) and has practical use and strong clinical prospects.

PLENARY LECTURE 3

Saturday | 09:30-10:00 | Guorui Hall

Speaker: Paul Fraser



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Dr Fraser gained his BSc in Psychology & Physiology from the University of Edinburgh, MSc and PhD in Physiology from University College London. He was appointed to King's College London in 1979 and has remained there since. His research for many years was concerned with measuring the regulation of permeability of blood-brain barrier vessels in single venular capillaries. This led to an understanding of the role of free radical generation in the disruption of the barrier following stroke and reperfusion injury. He has collaborated with Prof GE Mann to investigate dietary activation of NRF2 targeted antioxidant enzymes to prevent the disruption, hence preventing neuroinflammation. His research has also shown that glycated albumin, as found in diabetic patients, directly increases retinal vascular leakage, via NOX2 activation. He has established with Dr PI Aaronson the role of hydrogen peroxide in endothelial-derived hyperpolarization, not as a transmissible factor, but as a potentiator of endothelial Ca2+ release from stores, which has led to the current interest in coronary microvascular dysfunction.

PL-03

Possible role for Endothelial Derived Hyperpolarization in Coronary Microvascular Dysfunction

Paul Fraser

Chest pain is often examined by coronary angiography, but about 40% of female patients, have no discernible narrowing of the epicardial arteries. This was called Coronary Syndrome X, and is now thought to be due to a failure of the small arteries to dilate, hence coronary microvascular dysfunction (CMD). I will present some reasons for thinking that this is due to altered endothelial action, and endothelial derived hyperpolarization (EDH) in particular.

Previously, we have shown that endothelial Ca2+ release from stores is potentiated by cytochrome P450 derived H2O2, which is key to IKca and SKca channel (also known as SK channels) opening that underlies endothelial hyperpolarization (Chidgey et al., Free Radic Biol Med. 2016:97 274-284) This hyperpolarization will increase Ca2+ entry to the cells and hence the possibility of calcium overload. Channel endocytosis and recycling avoids this (Balut et al., ChemMedChem 2012:7:1741-55). These channels, however, must be functional to avoid vasospasm (Mauban & Weir Am J Physiol Heart Circ Physiol. 2004:287:H608-16 and Garland et al., Sci Signal:2017 10(406)). Hence it is possible that in CMD these channels do not function properly, which could be due to disruption of proper channel cycling. There is clinical evidence to support this hypothesis. Coronary arterioles from diabetic patients dilated less to endothelial agonists than matched non-diabetics, and the specific IKca and SKca currents were much lower, without there being a significant immunoreactive reduction in these channels (Liu et al J Am Heart Assoc. 2015;4:e002062).

Pre-clinical experiments have indicated that ROS plays a role in disrupting the cycling of these channels. Porcine coronary arteries treated with homocysteine, dilate less well and have reduced SK channel currents when activated with NS309. The total expression is unchanged, but the SK channels on the endothelial surface is much reduced (Wang et al., Atherosclerosis 2015;242:191-8). Our own work showed that mice that had been born to and reared by dams on an obesogenic diet, but placed on a normal diet post-weaning had completely lost the EDH component of acetylcholine which was associated with a loss of the IKca channel from the endothelial surface (Stead et al., J Hypertension 2016 34:452-63). These animals had raised plasma glucose levels, which would be expected to raise mitochondrial ROS generation. We have carried out some experiments to test this idea using endothelial cell cultures. These which showed that just a brief exposure to H2O2 resulted in a decrease in the surface expression of IKca, without affecting the total, which indicates that oxygen stress is sufficient to disrupt the EDH response.

PLENARY LECTURE 4

Saturday | 15:00-15:30 | Guorui Hall

Speaker: Amanda Jo LeBlanc

Dr. Amanda Jo LeBlanc has an extensive research background in cardiovascular physiology, focusing most exclusively on myocardial perfusion and reactivity in models of both aging and sex-specific cardiology. Her training focused on the structural and functional microvascular alterations that occur in the heart with advancing age and sex differences. Upon starting her own laboratory within the Cardiovascular Innovation Institute (CII) at the University of Louisville, she focused on translational research in cardiac physiology. Her current line of investigation is centered on regenerative medicine in aging-induced cardiovascular complications. Dr. Leblanc's lab is developing cell-based therapies designed to improve the function of the microcirculation and is involved in advancing this adipose-derived tissue engineering technology to the preclinical phase.

Since joining the faculty at the University of Louisville in 2012, Dr. LeBlanc has achieved national funding from the National Institutes of Health, the American Heart Association, and the Department of Defense. She currently serves on the International Liaison Committee for Microcirculation and is an Associate Editor for the American Journal of Physiology - Heart and Circulatory Physiology. Dr. LeBlanc serves as Chairperson of numerous NIH special emphasis panels and AHA study sections.

PL-04

Mitochondrial influence in the aging coronary microcirculation

Amanda Jo LeBlanc

In aging post-menopausal women, Coronary Microvascular Disease (CMD) leads to hyperconstricted tone, reduced perfusion and chronic micro-ischemia with angina. This is in line with our previous data that show that aged female rats exhibit dilatory dysfunction similar to males, but show hyperconstriction to agonists in opposition to what was observed in males as they age. We have shown an age-related increase in coronary microvascular ROS alongside increased prooxidant gene and protein expression associated with blunted vasodilation. Adipose Stromal Vascular Fraction (SVF) is a heterogenous cell population that reduces vascular ROS to improve vasodilation. Oxidative stress with aging may be mediated by mitochondrial dysfunction, including fission/fusion imbalance. This presentation will describe our efforts in reversing age-related coronary microvascular dysfunction in aging females via SVF therapy and our most recent use of a mitochondrial-targeted diet to alter fission/fusion relationship.

PLENARY LECTURE 5

Saturday | 15:30-16:00 | Guorui Hall

Speaker: Gilles Pages

After a PhD in molecular biology, Dr. Gilles Pages obtained a permanent Assistant Professor position at the University of Nice, France in 1990. In 2008, he transitioned to a permanent position as a Director of Research at INSERM, allowing him to focus on a translational research program dedicated to treating patients. Since the year 2000, he has dedicated his research to studying the mechanism of angiogenesis. His focus has been on understanding the mechanism of resistance to anti-angiogenic drugs (AAD). He obtained several grants from National cancer agencies and European agencies, collaborating with national researchers and clinicians from various cancer centers across France, such as Nice, Lyon, Rennes, and Paris. The primary focus of his program was on renal cancer, which is highly vascularized, and anti-angiogenic drugs are the standard of care for this particular type of cancer. Throughout this research program, he established collaborations with international partners from the USA, Europe, Japan, and China. Currently, he is part of a H2020 program that has brought together European teams working in this field.

Through the investigations into these mechanisms, his team and he have identified several prognostic and predictive markers of resistance to AAD, as well as potential therapeutic targets. he has published 200 original articles and review that he is cited more the 15000 times, with H index of 62. Since the inception of this project, his ultimate goal has been to introduce new treatments into clinical practice, either to enhance the quality of life for patients or to achieve the elusive goal of a cure. To expedite this process, he has created two startups with a stronger commitment to this ultimate goal was the most viable option. The products from the first startup are expected to enter clinical trials in 2024, with the products from the second startup following in 2025. His expertise in angiogenesis has also led to the repurposing of certain drugs originally used in the clinic for kidney cancer, now being explored for the treatment of pediatric medulloblastoma. This demonstrates the versatility and impact of angiogenesis research in different therapeutic areas. In summary, his overarching objective is to improve the lives of patients by leveraging his expertise in angiogenesis research and translating scientific discoveries into practical clinical solutions.

PL-05

From the discovery of mechanisms of resistance to conventional therapies to the establishment of innovative treatments for metastatic kidney cancers

Gilles Pages

Metastatic renal cell carcinoma (RCC) stands as a prime model for pioneering therapeutic advancements, with 15+ agents securing approval for combatting these cancers over the past decade. Despite this fervent activity, none of these treatments have managed to definitively eradicate these tumors.

In the realm of innovative therapies, the late 2000s witnessed the emergence of anti-angiogenic therapies (AAT), marked by the advent of the first anti-VEGFA monoclonal antibodies and the generation of multityrosine kinase inhibitors. These interventions marked have enhanced disease-free survival among patients who previously faced life expectancies of mere months. Although these therapies secured approval based on their impact on disease-free survival, they failed to extend overall patient survival. The fervent development targeting VEGFA or its receptors and PDGF receptors led to intense competition, resulting in the endorsement of drugs for first, second, and third-line use. Collectively, these steps culminated in improved overall patient survival without achieving curative outcomes.

A more recent breakthrough involved the validation of immune checkpoint inhibitors (ICI), ushering in a revolutionary era in RCC treatment. These therapies exhibit efficacy in a subset of patients, yielding prolonged survival periods. Despite this, the current standard of care,Äîcombining AAT and ICI,Äîstill falls short of achieving curative intent.

Over the past 15 years, we gradually unveil the mechanisms underpinning resistance to AAT. The initial mechanism involves the sequestration of the standard-of-care drug sunitinib/Sutent within lysosomes, consequently prompting the expression of ABC transporters on the tumor cell surface. This phenomenon also triggers an incomplete autophagy process coupled with alterations in the tumor cell secretome.

Another discovery entails the observation that prolonged exposure of tumor cells to anti-VEGFA therapy, such as bevacizumab/Avastin, leads to diminished expression of the tyrosine phosphatase receptor Kappa (PTPRk), culminating in the activation of several tyrosine kinase receptors, most notably EGFR. This activation subsequently fuels the proliferation of adapted tumor cells.

Continuous exposure to AAT further results in a shift within the tumor cell secretome, marked by elevated expression of alternative angiogenic factors from the interleukin 8 family (ELR+CXCL cytokines), along with a relative of VEGFA, VEGFC. These alternative proangiogenic/prolymphangiogenic factors incite autocrine proliferation of tumor cells via the CXCR2 receptor, in tandem with VEGFC co-receptors neuropilin 1 and 2 (NRP1/2). These factors contribute to the formation of blood vessels independent of the VEGFA pathway, alongside an alternate lymphatic network that fuels metastatic spread, all within an immunotolerant context.

Given the translational orientation of our research, we have showcased that the factors implicated in resistance mechanisms function as prognostic indicators and predictive markers for treatment resistance.

With a resolute focus on promptly translating our findings into concrete clinical applications, we have not only secured multiple patents but have also taken proactive measures by founding two startups to harness their potential.

The overarching mission is to craft innovative treatments targeted against the CXCR2 receptor or VEGFC, along with its co-receptors NRPs. Ultimately, our aspiration is to overcome the limitations inherent in current treatments and, at long last, achieve complete remissions among patients grappling with metastatic RCC.

PLENARY LECTURE 6

Saturday | 16:00-16:30 | Guorui Hall

Speaker: Giovanni E. Mann

Professor of Vascular Physiology

King's British Heart Foundation Centre of Research Excellence

School of Cardiovascular and Metabolic Medicine & Sciences

Faculty of Life Sciences & Medicine

King's College London

150 Stamford Street, London SE1 9NH, U.K

Email: giovanni.mann@kcl.ac.uk

University Education

1974-1977	PhD Physiology, Department of Physiology, University College London, U.K.
1973-1974	MSc Physiology, Department of Physiology, University College London, U.K.
1969-1973	BSc (Hons. 2.1) Zoology, Department of Biological Sciences, George Washington University, Wash. D.C., USA

Appointments/Awards

2022-2024	President of Society for Free Radical Research International (SFRRI)
2022-2026	ECMage External Advisory Group for BBSRC/MRC Interdisciplinary Initiative ‚ÄòAgeing across the life course'
2022-2026	Advisory Board Doctoral Programme in Experimental Biomedicine and Biology, Univ. Coimbra, Portugal
2018	Elected Fellow of The Physiological Society
2018-2023	Scientific Advisor for Society for Free Radical Research Europe Executive
2018-	International Lead, School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, UK
2017	Society for Free Radical Research Europe ‚ÄòLifetime Achievement Award', Berlin, Germany
2017	Oxygen Club California ‚ÄòLifetime Achievement Award', Berlin, Germany
2016	FEBS Plenary Lecture, Portuguese Biochemical Society, Guimar.es, Portugal
2014	European Society for Free Radical Research Annual Lecture, Paris, France
2013-2017	President (2015-2017) and President-Elect (2013-2015) Society for Free Radical Research - Europe
2013	President and Chair of 27th European Society for Microcirculation Conference, Birmingham, UK
2013	PhD Supervisor Excellence Award, School of Medicine, King's College London, UK
2012	Chair, 16th Society for Free Radical Research International Conference, London, UK
2012	British Microcirculation Society PromoCell Basic Science Award Lecture, Oxford, UK
2012	Oxygen Club of California ‚ÄòLifeTime Membership Award', Alba, Italy
2011-2019	General Secretary, Society for Free Radical Research International
2011-2013	International Union of Physiological Sciences (IUPS 2013) Scientific Programme Committee
2011	Physiological Society Inaugural International Prize Lecturer, Beijing and Shanghai, China
2011	International Advisor to Asian Microcirculation Society
2018-	Chair, King's-KC Wong Fellowship Awards Committee
2018-	International Committee, Faculty of Life Sciences & Medicine
2018-2024	International Lead, School of Cardiovascular & Metabolic Medicine & Sciences, Faculty Life Sciences & Medicine
1999-2014	Head of Postgraduate Research Studies - School of Biomedical & Health Sciences

Membership of Learned Societies

The Physiological Society, U.K.
British Microcirculation Society
European Society for Microcirculation
European Society for Cardiovascular Research
Microcirculatory Society USA
Royal Society for Biology
Society for Free Radical Research International
Society for Redox Biology & Medicine
Society for Free Radical Research Europe

Administrative Experience at King's College London

2018-	Chair, King's-KC Wong Fellowship Awards Committee
2018-	International Committee, Faculty of Life Sciences & Medicine
2018-2024	International Lead, School of Cardiovascular & Metabolic Medicine & Sciences, Faculty Life Sciences & Medicine
1999-2014	Head of Postgraduate Research Studies - School of Biomedical & Health Sciences

Prof GE Mann Publications: Peer-reviewed articles [>190], Book Chapters [39], Books [1]h-index 61, Citations: 13,597 by 11,231 documents

Transcriptional activation of NRF2 antioxidant genes in endothelial cells under physiological oxygen levels: implications for improved clinical translation

Giovanni E. Mann

In vivo, vascular and other cell types are exposed to physiological oxygen levels ranging from to 2 - 13 kPa O2, while cells cultured in vitro in standard CO2 gassed incubators are routinely exposed to hyperoxic oxygen levels (18 kPa O2). Although recent evidence highlights the importance of studying cellular redox signaling under physiological O2 levels, few studies have examined the effects of short- or long-term adaptation of cells to different pericellular O2 levels (see Keeley & Mann, Physiol. Reviews 2019;99:161-234). As molecular mechanisms regulating NRF2 mediated redox signaling have primarily been studied in cells exposed to hyperoxia, we characterised NRF2 gene targets in endothelial cells following 5 d adaptation to hyperoxia (18 kPa), physiological normoxia (5 kPa) or hypoxia (1 kPa) in an O2 regulated Scitive workstation. Gene profiling established that activation of NRF2 and induction of GSH related genes were insensitive to alterations in O2, whereas upregulation of HO-1 and NQO1 in response to electrophiles or nitric oxide (NO) was diminished under 5 kPa O2 due to an upregulation of the NRF2 repressor Bach 1 (Chapple et al. Free Radic Biol Med 2016;92:152-62). We further established that a PP2A mediated feedback mechanism regulates Ca2+ dependent endothelial NO release (Keeley et al. FASEB J 2017; 31:5172-5183) and NO bioavailability (Sevimli et al. Redox Biol. 2022; 53:102319) under 5 kPa O2, and that enhanced SERCA activity under 5 kPa O2protects endothelial cells against calcium overload (Keeley et al. FASEB J 2018;32:2531-2538). We recently employed ICP-MS and LA-ICP-MS to measure changes in total metal content in human coronary artery endothelial cells cultured long-term under 18, 5 or 1 kPa O2 and then subjected to ischemia reoxygenation injury, highlighting the importance of zinc in redox signaling (Smith et al. Redox Biol 2023;62:102712). Our recent Expert Recommendation (Sies et al. Nature Rev Mol Cell Biol 2022;23:499-515) emphasizes the importance of maintaining physiologically relevant O2 levels in cell culture to mimic redox reactions associated with specific cell types in vivo.

PLENARY LECTURE 7

Sunday | 08:30-09:00 | Guorui Hall

Speaker: Geert Schmid-Schonbein

Geert W. Schmid-Schönbein is Distinguished Professor in the Department of Bioengineering at the University of California San Diego (UCSD). He teaches bioengineering and biomechanics of living tissues, microcirculation, lymphology and biorheology, cell and molecular biomechanics with application to human diseases. Schmid-Sch√∂nbein was President of the Microcirculatory Society and serves as consultant for the National Institute of Health, is Founding Member of the American Institute for Medical and Biological Engineering, and was Chair of the World Council for Biomechanics.

The current research focus of his team is to answer a fundamental question: What are the trigger mechanisms for inflammation that cause diverse tissue injuries and organ failures? His team discovered a mechanism for cell and organ dysfunctions due to pancreatic digestive enzymes, they designated as “Autodigestion”. It is due to leak of pancreatic digestive enzymes across the mucin/epithelial barrier out of the gastrointestinal tract into the systemic circulation and into peripheral organs. The team provided evidence that cell dysfunctions in the Metabolic Syndrome X are due to an unchecked activity by pancreatic digestive proteases leaking in relatively low concentrations out of the gastrointestinal tract. The digestive enzymes activate secondary proteases and cause cleavage of the extracellular domain of membrane receptors, for example insulin resistance due to proteolytic cleavage of the insulin receptor ectodomain or capillary rarefaction due to cleavage of endothelial growth factor receptors and endothelial apoptosis in addition to other cell dysfunctions. Furthermore, the team showed in acute hemorrhagic and septic shock pancreatic digestive enzymes leak in high concentrations out of the gastrointestinal tract and cause severe cell dysfunction leading to complete organ failures. The team has shown that enteral blockade of pancreatic digestive enzymes serves to attenuate acute cell dysfunctions in shock and reduce morbidity. The team proposes that Autodigestion may be a fundamental mechanism for disease and death.

PL-07

Microvascular Dysfunctions and Organ Failure by Autodigestion

Geert Schmid-Schonbein

The concentrated, fully activated, and relatively non-specific digestive enzymes synthesized by the pancreas and transported in the intestine are designed to break down proteins, lipids, long-chain carbohydrates, and nucleotides from food sources. During normal digestion, these powerful pancreatic enzymes are compartmentalized in the lumen of the small intestine by the mucin/epithelial barrier. Any compromise to this barrier with elevated permeability to molecules the size of digestive enzymes allows their escape into the wall of the intestine and into the circulation and tissues outside the intestine. Digestive enzymes activate secondary degrading enzymes (e.g. proMMPs into MMPs) and initiate enzymatic degradation of numerous cell and organ functions. For example, pancreatic serine proteases degrade plasma proteins and membrane receptors and consequently compromise their functions, such as elevated endothelial permeability due to cleavage of VE-cadherin, vasodilation and blood pressure reduction after cleavage of alpha-adrenergic receptors or acute loss of insulin signaling after cleavage of the insulin receptor. The escape of digestive enzymes into peripheral organs is the common denominator for cell and organ failure in hemorrhagic shock and multiple models of sepsis. Enteral blockade of pancreatic serine proteases in experimental shock with different inhibitors significantly attenuates the characteristic multiorgan dysfunctions in shock and sepsis. This new form of intervention against acute multiorgan failure is now tested in Phase II and III clinical trials. These results suggest that pancreatic digestive enzymes may play a central role in acute as well as chronic diseases. While required for normal digestion, their escape out of the small intestine leads to autodigestion with far-reaching consequences.

PLENARY LECTURE 8

Sunday | 09:00-09:30 | Guorui Hall

Speaker: Yoshikazu Tsuzuki

Educational and professional background

Mar 1989 Graduated from Keio University School of Medicine, Tokyo, Japan
June 1998 Postdoctoral fellow, Massachusetts General Hospital,
Harvard Medical School, USA
June 2001 Medical Fellow, Second Department of Internal Medicine,
National Defense Medical College, Saitama, Japan
April 2003 Assistant Professor, Second Department of Internal Medicine, National Defense Medical College
Apr. 2017 Associate Professor, Department of Gastroenterology, Saitama Medical University, Saitama, Japan. (concurrently in charge of General Internal Medicine)
Dec. 2022 Professor, Department of Gastroenterology, Saitama Medical University
(concurrently serving as Professor of General Internal Medicine)

Qualifications

Board Certification in Internal Medicine, Japanese Society of Internal Medicine
Board Certified Trainer in Internal Medicine, Japanese Society of Internal Medicine
Board Certified Trainer in Japanese Society of Internal Medicine
Board Certified Trainer in Japanese Society of Gastroenterology
No. 22212 Date of certification: December 1, 1995 - Present
Board Certified Trainer in Japanese Society of Gastroenterological Endoscopy,
Date of certification: December 1, 1998 - Present
Fellow of American college of Gastroenterology(FACG) 1999
Board Certified Doctor, Japanese Society of Hospital General Practitioners, 2017
Board Certified Trainer in General Practice, Japan Medical Specialty Organization Specially Board Certified Trainer in Gastroenterology, Japanese Society of Gastroenterology 2021.11.1

Awards

1999 Travel award for young investigator (AACR)
2002 Japanese Society of Microcirculation Award
2006 Japanese Society of Gastroenterology Award for Encouragement
2020 Japanese Society of Internal Medicine Teaching Advisor Award

PL-08

Mucosal microcirculation in inflammatory bowel disease

Yoshikazu Tsuzuki

The pathogenesis of inflammatory bowel disease (IBD) is unknown, however, one of the characteristics in IBD is continuous inflammation in intestinal mucosa. The accumulation of inflammatory lymphocytes and the production of cytokines are crucial in this process. We have reported the observation for lymphocyte trafficking in postcapillary venules in Peyer's patches in small intestine and submucosal venules in intestinal mucosa. By in vivo observation under intravital microscope, we compared lymphocyte kinetics in normal and inflammatory mucosa in various rat and mouse models and observed increased T cell accumulation in inflammatory conditions induced by lipopolysaccharide (LPS) due to upregulation of cytokine-induced adhesion molecules such as integrins on lymphocytes and counterparts on endothelial cells.

On the other hand, in clinical setting, the concept of ‚ÄòTreat to Target' (T to T) strategy, in which treatment goals are set has been widely spread for the management of IBD including ulcerative colitis (UC) and Crohn's colitis (CC). The goal of treatment has shifted from symptom improvement to mucosal healing (MH). In addition, treatment is intensified if the goals are not achieved through monitoring.

Although serum or fecal biomarkers are developed and periodically examined in the management of UC, nevertheless, colonoscopy (CS) is the gold standard for monitoring UC activity.

It is possible to observe microvessels in colonic mucosa by CS in combination with image enhancing endoscopy (IEE) such as narrow band imaging (NBI) and Linked color images (LCI). LCI has been developed to detect very mild inflammation and adapted for UC monitoring in T to T by emphasizing red color. The LCI-CS was scored on a 5-point scale, with total-LCI being the sum of the 5 colorectal inflammation scores and max-LCI being the site of highest activity. We also investigated blood and stool biomarkers (WBC: White blood cell count, CRP, albumin, NLR: Neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, fecal calprotectin) that correlate with mucosal inflammation evaluated by LCI-CS endoscopic score and can be used in combination for monitoring.

In addition to IEE, ultra-high magnifying endocytoscope (ECS: x520, Olympus, Tokyo) has been developed and combination with narrow-band imaging (NBI; EC-NBI) enables in vivo visualization of mucosal regular capillary network in normal colonic mucosa. We attempted to use ECS in the evaluation of UC inflammation. We present two cases with recurrence of UC and observed the architecture of vasculature in inflammatory UC colonic mucosa. Case1 was 66-year old male who showed bloody diarrhea of 5-6 times a day and abdominal pain. CS demonstrated diffuse inflammatory and edematous mucosa from the rectum to the descending colon and diagnosed as left-sided UC. ESC showed narrow and irregular blood vessels with coarse distribution in ulcer scar. On the other hand, irregular and tortuous blood vessels was observed in active inflammatory mucosa in the rectum consistent with MES (Mayo endoscopic score)1. Treatment was changed based on T to T. Cases2 was 81-year old female who showed bloody stool. CS demonstrated continuous diffuse inflammatory mucosa from the rectum to the descending colon and diagnosed as left-sided active UC. ESC showed irregular and tortuous blood vessels with dense distribution showing MES1 activity. Biologics was administered based on T to T.

In conclusion, in vivo observation for lymphocyte microcirculation by intravital microscope is a powerful tool in the investigation for pathogenesis of mucosal inflammation in the basic experiments. In clinical practice, LCI-CS and endocytoscope which can monitor microcirculation and vascular irregularity in colonic mucosa in combination with serum and fecal biomarkers may be useful tools for evaluating and monitoring inflammation in UC activity.

PLENARY LECTURE 9

Sunday | 09:30-10:00 | Guorui Hall

Speaker: Congying Wu

Congying Wu is an associate professor at School of Basic Medical Sciences, Peking University.

She received her Ph.D. from the University of North Carolina at Chapel Hill and did postdoctoral research at HHMI/UNC Lineberger Cancer Center. Her research group focuses on the mechanical regulation of cell structure and function in disease and development, and related work has been published in Cell, Developmental Cell, Nature Communications and other international academic journals. She was selected into the youth project of the overseas high-level talent introduction program, won the “Excellent Qing” project of the National Natural Science Foundation of China, and undertook the key research and development plan young scientist project as the project leader.

PL-09

Mechanical instability generated by Myosin 19 contributes to mitochondria cristae architecture and functions

Congying Wu

The folded mitochondria inner membrane-cristae is the structural foundation for oxidative phosphorylation (OXPHOS) and energy production. By mechanically simulating mitochondria morphogenesis, we speculate that efficient sculpting of the cristae is organelle non-autonomous. It has long been inferred that folding requires buckling in living systems. However, the tethering force for cristae formation and regulation has not been identified. Combining electron tomography, proteomics strategies, super resolution live cell imaging and mathematical modeling, we reveal that the mitochondria localized actin motor-myosin 19 (Myo19) is critical for maintaining cristae structure, by associating with the SAM-MICOS super complex. We discover that depletion of Myo19 or disruption of its motor activity leads to altered mitochondria membrane potential and decreased OXPHOS. We propose that Myo19 may act as a mechanical tether for effective ridging of the mitochondria cristae, thus sustaining the energy homeostasis essential for various cellular functions.

SATELLITE SYMPOSIUM 1

Traditional Chinese Medicine and Microcirculation

13:30-15:00 | Guorui Hall

S01-1

The ameliorative effect of salvianolic acid A, one main water-soluble component of salvia miltiorrhiza, on Lipopolysaccharide-Induced Leukocyte Recruitment and Oxidative Stress in Mesenteric Venules in Rats

Chun-Shui Pan [1], Jun Guo [1], Yu-Ying Liu [1], Bai-He Hu [1], Xin Chang [1], Jing-Yu Fan [1], Jing-Yan Han [1,3]*

[1] *Tasly Microcirculation Research Center, Peking University Health Science Center, Beijing, China*
[2] *Department of Integration of Traditional Chinese and Western Medicine, School of Basic Medical Sciences, Peking University, Beijing, China*

Background and Aim: Lipopolysaccharide (LPS) causes microvascular barrier disruption resulting in a range of disastrous sequence. This study aimed to investigate the effect of salvianolic acid A (SalA), a main ingredient of Salvia miltiorrhiza, on LPS -elicited leukocyte recruitment and oxidative stress in mesenteric venules of rat in vivo, and its underlying mechanism in HUVECs in vitro.
Methods: SalA was continuously infused starting either from 20 min before or 20 min after LPS infusion. Human umbilical vein endothelial cells (HUVECs) were treated by LPS with or without SalA.
Results: SalA significantly reduced leukocyte adhesion to and emigration across the venular wall, peroxide production in venular wall in rats induced by LPS. Additionally, in vitro experiments revealed that treatment with SalA inhibited the expression of CD11b and CD18 on rat neutrophils caused by LPS, and reduced adherent neutrophils to HUVECs exposed to LPS.
Conclusion: This study demonstrates that protection of SalA against LPS is a process involving ameliorating oxidative stress.

S01-2

MALT1/NF-κB Study on the regulatory mechanism of microglia-mediated neuroinflammation after cerebral ischemia and the intervention effect of Dengzhanshengmai Formula

Jingjing Zhang [1,2], Guangzhao Cao [1], Hongjun Yang [1]

[1] *Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China*
[2] *Chinese Institute for Brain Research, Beijing 102206, China*

Microglia (MGs) polarization-mediated neuroinflammation is the core link of cerebral ischemia, and NF- κ B pathway plays a key role in regulating this process. The applicant found that Dengzhanshengmai Prescription alleviated cerebral ischemia injury, inhibit neuroinflammation, and promote the polarization of MGs from M1 to M2. Single cell sequencing (scRNA-seq) found that this prescription regulated MALT1, which was the potential key targets of MGs, and modulated NF- κB pathway. And siMalt1 decreased cerebral ischemia injury in rats and promoted the polarization of MGs to M2 type. Therefore, we hypothesized that MALT1/NF-κB pathway increased neuroinflammation in ischemic stroke through regulating the polarization of MGs, and Dengzhanshengmai Formula alleviated ischemic stroke injury and inhibited MGs-mediated neuroinflammation through regulating MALT1/NF- κB pathway. Thus, we systematically explore the role of MALT1/κB pathway in regulating MGs-based neuroinflammation and the mechanism of Dengzhanshengmai Formula in regulating this pathway in the middle cerebral artery occlusion animal model and lipopolysaccharide-induced cell model through adenovirus transfection, small interfering RNA technology and related molecular biological technology. This research provides new targets for ischemic stroke, deepens the understanding of the pathological mechanism of cerebral ischemia, and provides basic research support for the clinical application of Dengzhanshengmai Formula.

S01-3

Compound Danshen Dripping Pill inhibits vascular calcification in ApoE-deficient mice as well as VSMCs and ECs

Hui Xiong [1], Yanfang Yang [2], Liying Yuan [2], Wenjia Wang [1], Shuiping Zhou [1,3], He Sun [1,3], Shuang Zhang [4,5], Yajun Duan [4], Yunhui Hu [1]

[1] *Tasly Pharmaceutical Group Co., Ltd., Tianjin 300410, China*
[2] *College of Life Sciences, State Key Laboratory of Medicinal Chemical Biology, Key Laboratory of Bioactive Materials of Ministry of Education, Nankai University, Tianjin 300071, China*
[3] *The State Key Laboratory of Core Technology in Innovative Chinese Medicine, Tasly Academy, Tasly Holding Group Co., Ltd., Tianjin 300410, China*
[4] *Department of Cardiology, the First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, Hefei 230001, China*
[5] *Key Laboratory of Metabolism and Regulation for Major Diseases of Anhui Higher Education Institutes, College of Food and Biological Engineering, Hefei University of Technology, Hefei, 230009, China*

Vascular calcification (VC) is characterized by the formation of mineral deposits on the walls of arteries and veins, resulting in the hardening of the arteries and the narrowing of the arterial lumen. It is one of the most common pathological characterize of atherosclerosis, aortic stenosis and aging. Previous research has suggested that Compound Danshen Dripping Pill (CDDP) may be capable of inhibiting thickening of the vascular intima and improving atherosclerosis. However, it is unknown whether it can inhibit VC. In this study, we investigated the therapeutic efficacy and underlying mechanism of CDDP in treating VC both *in vivo* and *in vitro*.
Based on the published omics data of human aortic valve calcification, we calculated the network proximity between vascular calcification and CDDP targets from its specific expression genes and protein levels, respectively. The results reveal that CDDP targets are closely related to the disease module gene network of vascular calcification from a network perspective (zscore: -2.53 and -1.74), indicating that CDDP has a potential therapeutic effect on vascular calcification. The development of VC is a complex process that is linked with a multitude of signaling pathways and is associated with dysfunction of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), as well as cellular senescence. It has been reported that the Wnt/β-Catenin pathway, which is involved in atherosclerosis, and Sirtuin-1 (Sirt1), a deacetylase protein involved in cellular senescence, contribute to VC. The Wnt/β-Catenin pathway plays an important role in the osteogenic phenotypic trans-differentiation by influencing the expression of RUNX2 in VSMCs. Then we explored the mechanisms underlying the anti-VC effect of CDDP, including its anti-aging, and anti-inflammatory effect, as well as its regulation of the Wnt/β-Catenin pathway. Aortic calcification was induced in ApoE-deficient ($ApoE^{-/-}$) mice through the administration of a high-fat diet, while calcification in ECs (HUVEC and HAEC) and VSMCs (HASMC) was induced by calcification medium (CM) containing elevated levels of $PO4^{3-}$ and Ca^{2+}. CDDP reduced aortic calcification and lipid deposits in mice as well as osteoblastic transition markers (ALP, OPN, BMP2 and RUNX2) of VC in ECs and VSMCs, through its actions of anti-inflammatory, anti-aging properties and inhibition of Wnt/β-Catenin pathways. Mechanistically, our previous study has shown that CDDP inhibited the activity of Wnt/β-Catenin pathway, which is significantly activated in mice and cells with calcification. Conversely, CDDP inhibited Wnt/β-Catenin pathway by up-regulating the expression and secretion of DKK1 (Dickkopf-related protein 1), a Wnt inhibitor. The effect could be abolished by using small interfering RNA to knockdown DKK1. Furthermore, VC is a hallmark of vascular stiffness and aging. Sirt1 has a protective effect on VC by inhibiting oxidative stress and inflammation in the vascular wall. It has been reported that the active ingredients of CDDP have the effect of activating Sirt1. VC contributes to vascular aging by increasing senescence parameters (β-Gal, p21 and p16) and inducing inhibition of Sirt1, while the anti-aging by CDDP was achieved by decreasing the senescence parameters and increasing Sirt1 expression. CDDP also reduced pro-inflammatory cytokines and the senescent-associated secretory phenotype (SASP), such as IL-18, IL-1β, IL-6, and TNF-α in calcified mice. The specific inhibitor of Sirt1, EX527, could reverse

the anti-aging and anti-VC effect of CDDP. Taken together, our study suggests that CDDP can be an effective therapy for reducing atherosclerosis-induced VC.

S01-4

Advanced technologies for cellular targets identification of neuroprotective agents

Ke-Wu Zeng [1]

[1] *State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University*

Identification of the cellular targets of drugs is crucial for understanding the molecular mechanisms and side effects. Thus, novel methods for identification of target proteins are largely required in modern drug discovery. In this study, we reported several bioactive compounds from traditional medicinal resources using bioassay-guided separation. Then, we developed a series of technologies especially affinity purification strategy to capture the potential target proteins from cell or tissue lysates using these bioactive natural compounds as chemical probes. For example, we showed that brazilin (BZ) was a natural small-molecule from *Caesalpinia sappan* L., and exhibited obvious anti-ischemic stroke effect. Then, DOHH was identified as a crucial cellular target of BZ using affinity purification strategy-coupled with HuProt™ human proteome microarray. In mechanism, BZ induced DOHH conformation changes to increase DOHH activity for neuroprotection. Moreover, we found a natural bioactive compound echinacoside (ECH) from *Cistanche deserticola* with a significant neuroprotective effect. Then, we used ECH as a chemical probe to identify casein kinase 2 (CK2) α′ subunit (CK2α′) as a direct cellular target for neuroprotection via affinity purification strategy. In particular, we revealed that ECH regulated CK2α′ conformation change to induce basic transcription factor 3 (BTF3) binding, thereby inducing β-catenin nuclear translocation to activate TCF/LEF transcription for neuroprotection. Collectively, our studies provide the advanced approaches for cellular targets identification of neuroprotective agents. Moreover, these targets also contribute to the development of novel drugs with unique biological mechanisms.

SATELLITE SYMPOSIUM 2

From Microcirculation and Vascular Biology to Drug Target

15:00-16:30 | Guorui Hall

S02-1

Fatty acid-binding proteins 3 and 5 mediate the mitochondrial damage in brain ischemia

Kohji Fukunaga [1], Qingyun Guo [1,2], Ichiro Kawahata [1]

[1] *CNS Drug Innovation/Tohoku University*

[2] *Hainan Medical University*

Fatty acid-binding proteins (FABP) 3, 5 and 7 function as the transporter of long-chain fatty acids and mediate the fatty acid metabolism, inflammation, cell differentiation and proliferation in brain. We previously reported that brain ischemia induces the upregulation of these FABPs in the brain. FABP3 and FABP5 were expressed in injured neurons and FABP7 was expressed in glial cells. However, the pathophysiological relevance of FABP3 and FABP5 in neuronal injury remains unclear. Overexpressing either FABP3 or FABP5 aggravated the reduced mitochondrial membrane potential and induced cell death in human neuroblastoma SH-SY5Y cells during oxidative stress (Redox biology, 2023;59: 102547). Following rotenone stimulation, BAX was overexpressed and moved to FABP5-containing mitochondria in SH-SY5Y cells. FABP5 mediates lipid peroxidation and generates toxic by-products (i.e., 4-HNE) in SH-SY5Y cells. FABP3 and FABP5 were accumulated in the mitochondria and caused oxidative stress following mouse brain ischemia. The novel FABP3/5 inhibitor significantly reduced cerebral infarct volume and blocked FABP3/5-induced mitochondrial damage, including lipid peroxidation and BAX-related apoptotic signaling. Thus, FABP3 and FABP5 are key players in triggering mitochondrial damage in ischemic neurons. In addition, the novel FABP inhibitor may be a potential neuroprotective treatment for ischemic stroke to ameliorate mitochondrial damages.

S02-2

The role of endothelial Sema3G on vascular remodeling and spine formation

Ying-Mei Lu [1]

[1] *Nanjing Medical University, China*

The proper interactions between blood vessels and neurons are critical for maintaining normal brain function. However, the precise molecular events underlying these interactions remain largely unknown. Here, we firstly confirmed the specific expression of semaphorin 3G (Sema3G) in retinal endothelial cells, and Sema3G coordinated the functional interaction between β-catenin and VE-cadherin by increasing β-catenin stability in the endothelium through the neuropilin-2 (Nrp2)/PlexinD1 receptor. Sema3G supplementation enhanced healthy vascular network formation and promoted diseased vasculature regression during blood vessel remodeling. Moreover, we also show that Sema3G increased excitatory synapse density via neuropilin-2/PlexinA4 signaling and through activation of Rac1, which regulates synaptic plasticity and hippocampal-dependent memory. Our findings highlight the role of vascular endothelial molecule Sema3G in regulating vascular remodeling and cognitive function through intercellular communication between endothelium and neurons.

S02-3

Analysis Platform for disease-oriented drug discovery by drug repurposing

Katsuhisa Horimoto [1]

[1] *SOCIUM Inc., Japan*

Identifying the causal relationship between events at the molecular level in cells and at the individual level is a great challenge. In fact, drug discovery that changes the state of an individual by administering a molecule is fraught with great difficulty. In drug discovery, molecules

(therapeutics) have been discovered through many trials and errors. We have built a platform to discover drug candidates as rationally and logically as possible by implementing recent comprehensive measurement data of intracellular molecules and mathematical analysis such as AI. Our approach does not identify a single target molecule of a drug candidate, but rather exploits patterns of molecular group variation in existing drugs and the target disease. Thus, drug candidates for diseases for which the target molecule is unknown or difficult to identify can be discovered from existing drugs and their core-structures of compounds. In fact, we have discovered a promising existing drug candidate for ALS and obtained permission from the Japanese government to start phase II of clinical trial. We have also developed the world's first comprehensive intracellular phosphorylation measurement system. In conjunction with the above data analysis platform, this system can be used for drug discovery utilizing signaling pathways, especially in the development of anti-cancer drugs. The workflow for the above developments will be explained with specific examples.

S02-4

Tissue optical clearing for vascular structure and function imaging

Dan Zhu [1]

[1] *Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology*

Biomedical optical Imaging, as a powerful tool has been applied for observing biomedical tissue structural and functional information with high resolution and contrast unattainable by any other method. However, the high scattering of turbid biological tissues limits the penetration of light, leading to strongly decreased imaging resolution and contrast as light propagates deeper into the tissue. Fortunately, Recently, tissue optical clearing techniques have emerged to reduce the scattering for deep biological imaging, which include the organic solvent-based clearing methods and the solvent-based clearing methods. The former one could make tissue transparent with relatively short time, but lead to fluorescence quenching, and the latter show good fluorescence preserving ability, but often require long incubation time. In this presentation, I will show some progress in tissue optical clearing methods and their applications on whole organs vascular network imaging. In addition, we also invented an easy-to-handle, switchable, and safe optical clearing skull windows without craniotomy by topical application of skull optical clearing agents. It is not only suitable for imaging cortical structures at synaptic resolution, but also for vascular structure and function by combining with various optical imaging techniques. Through the transparent skull window, laser not only successfully induced cortical BBB opening, but also caused vascular obstruction based on the PDT. Thus, it has the potential for use in basic research on the physiological and pathologic processes of cortical vessels.

LUNCH LECTURE 1

12:50-13:30 | Guorui Hall

LL-01

Efficacy and Safety of Angoing Niuhuang Pill as an Adjunct Therapy for thrombolytic treatment for ischemic stroke

Hansen Chen [1], Bing Tsoi [1], Qiaohui Du [1], Jiangang Shen [1]

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Angong Niuhuang Pill (AGNHP) is a classical formula used in Traditional Chinese Medicine (TCM) practice over century in China. In modern clinical practice, AGNHP is approved by SFDA for acute stroke, trauma brain injury and clinical syndrome with high fever, convulsion and coma, etc. However, the scientific basis, molecular targets and clinical efficacies remain to be further elucidated. Particularly, AGNHP contains several mineral materials named cinnabar and realgar. Cinnabar is mercuric sulfide (> 96% HgS) whereas realgar is mainly composed of arsenic sulfide (>90% As4S4). With those mineral materials, scientific community raises safety concerns for its use clinically. In the present study, we first performed literature review on the adverse drug reactions (ADR) and adverse events (AE) to assess the safety of AGNHP. The results revealed that AGNHP carries a relatively low risk of ADR/AE if it is used according to the guideline. Furthermore, meta-analysis revealed the efficacies of AGNHP on improving neurological deficit scores and coma index in both ischemic and haemorrhagic stroke patients. Subsequently, we systematically investigated the neuroprotective effects and safety of AGNHP against cerebral ischemia-reperfusion injury with or without thrombolytic treatment. Male SD rats were subjected to 5 h of middle cerebral artery occlusion (MCAO) with or without t-PA infusion (10 mg/kg) plus 19 h reperfusion. AGNHP and the modified formula removing cinnabar or realgar were orally administrated at 2 h of MCAO equivalent to adult human dose. We evaluated the outcome including mortality, neurological deficits, infarction volume, blood-brain barrier (BBB) permeability, haemorrhagic transformation (HT), neurological deficit and apoptotic cell death. We also studied the antioxidant and anti-inflammation effects including MPO, MMP-9, iNOS, NADPH oxidases, 3-nitrotyrosine and ONOO-. Furthermore, we investigated its anti-inflammatory and immunomodulation effectiveness against ischemic brain injury. To address its safety concerns, we assessed body weight, organ index, liver and kidney functions and plasma arsenic and mercury concentrations in the rats after oral administration. AGNHP treatment reduced the BBB damage, brain oedema, reduced haemorrhagic transformation, enhanced neurological function, and reduced mortality rate in the ischemic stroke rats with t-PA treatment. AGNHP revealed antioxidant, anti-inflammatory and immunomodulation, inhibited MMP-9 activity, and preserved tight junction proteins in the ischemic brains. Depletion of cinnabar or realgar from AGNHP abolished the effects of AGNHP. Regular doses used for 7 days had no influence on body weight, organ index, liver and kidney function. A small amount of arsenic was found in the blood and liver. Importantly, AGNHP revealed to reduce the mortality and neurological deficit scores for the ischemic stroke rats with delayed t-PA treatment, potentially extending therapeutic window for t-PA in ischemic stroke treatment. Taken togather, AGNHP is effective and safe TCM formula for stroke treatment and could be used as an adjunct therapy with t-PA for ischemic stroke treatment.

SYMPOSIUM 1

KCa Channels as Regulators of Vascular Function

08:30-10:00 | Room 1

001-SS1

Vascular control by ion channel trafficking

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Arterial smooth muscle and endothelial cells express a variety of surface ion channels that control membrane potential and intracellular Ca2+ concentration to regulate contractility, regional organ blood flow and systemic blood pressure. The current amplitude (*I*) generated by a population of surface ion channels is the product of their number (*N*), open probability (P_o) and single channel current (*i*), such that $I=N.P_o.i$. Previous studies have identified mechanisms that regulate the activity (P_o) of ion channels in these cell types. In contrast, mechanisms that regulate the number of surface ion channels and its functional significance is less clear. I will discuss our recent work where we have identified mechanisms by which physiological vasoactive stimuli rapidly modulate surface amounts of ion channel subunits in the vascular wall and its functional significance. First, I will summarize some our published studies where we have shown that vasodilators and vasoconstrictors rapidly regulate the trafficking of large-conductance calcium-activated potassium (BK) channel subunits in arterial smooth muscle cells. Similarly, I will show that hypertension is associated with impaired trafficking of BK channel subunits. These trafficking mechanisms regulate BK channel activity ($N.P_o$) to control arterial contractility. I will also describe mechanisms by which intravascular pressure regulates posttranslational SUMOylation of transient receptor potential polycystin 1 (TRPP1, PC-2) channels in arterial smooth muscle cells. This mechanism regulates TRPP1 surface abundance to regulate arterial contractility. I will then discuss more recent work where we have investigated the physiological functions of ion channel trafficking in endothelial cells. Physiological vasodilator stimuli activate ion channels in endothelial cells to produce vasodilation. Whether physiological vasodilators also modulate the surface abundance of ion channels in endothelial cells to elicit functional responses is unclear. Our data demonstrate that vasodilators rapidly deliver an intracellular pool of small-conductance Ca2+-activated potassium (SK3) channels to the vicinity of surface TRPV4 channels in ECs. This trafficking mechanism produces vasodilation. In summary, I will describe mechanisms by which physiological stimuli rapidly alter the surface abundance of ion channels in arterial smooth muscle and endothelial cells to regulate arterial contractility.

001-SS2

Endothelial KCa channels as therapeutic targets in Type 2 Diabetes

Ramesh C Mishra [1], Rayan Khaddaj Mallat [1], Cini M John [1], Darrell D Belke [1], Heike Wulff [2], Andrew P Braun [1]

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[2] Department of Pharmacology, University of California Davis

The vascular endothelium dynamically regulates systemic blood pressure and tissue perfusion by generating vasoactive signals (e.g., nitric oxide (NO), prostaglandins and endothelium-dependent hyperpolarization (EDH)) that act on the adjacent smooth muscle to regulate arterial diameter. In type 2 diabetes (T2D), endothelial cell dysfunction, particularly in the microcirculation, is an early pathogenic event that impairs blood pressure regulation and local blood flow, leading to cardiovascular disease and tissue damage. Clinical efforts to reverse endothelial dysfunction in T2D have achieved limited success, thus highlighting the urgent need for new approaches. Endothelial Ca^{2+}-activated K^+ (KCa) channels (i.e. KCa2.3 and KCa3.1) act as key “drivers” of arterial diameter by controlling

EDH and NO synthesis, which predominantly regulate stimulus-evoked vasodilation, peripheral blood flow and blood pressure. In myogenically active resistance arteries from rodents and humans exhibiting T2D-associated endothelial dysfunction, we have shown that pharmacological "priming" of KCa2.3 and KCa3.1 channel activity with the KCa channel positive modulator SKA-31 (A Sankaranarayanan et al, Mol Pharmacol 2009) can restore agonist-stimulated dilation back to normal levels (RC Mishra et al. Metabolism 2021). This strategy also improves endothelium-dependent dilation and arterial flow in the intact coronary circulation of non-obese T2D Goto-Kakizaki (GK) rats (RC Mishra et al, J Mol Cell Cardiol 2014). Moreover, we have further observed that prolonged treatment of 18-month old male rats with a low dose of SKA-31 improved endothelial function and reversed age-related decline of cardiac performance (CM John et al, Pharmacol Res 2020). Our recent studies now show that prolonged administration of 10 mg/kg SKA-31 to instrumented, adult male, T2D GK rats for 12 weeks prevented blood pressure elevation and improved cardiac ejection fraction and fractional shortening compared with vehicle treated GK rats. SKA-31 administration further augmented endothelium-dependent dilation in small mesenteric arteries and increased the expression of endothelial KCa channels, eNOS, IP3R1 and SERCA2. These findings are thus consistent with improvement of endothelial function *in vivo*. Importantly, prolonged SKA-31 administration did not negatively affect peripheral immune cell populations, plasma cytokine profiles, metabolic status and tissue morphometrics/viability in T2D GK rats, suggesting that SKA-31 treatment was well tolerated and did not produce adverse effects. Collectively, our observations suggest that pharmacological "priming" or facilitation of endothelial KCa channel activity *in vivo* may represent a novel and effective strategy to reduce cardiovascular dysfunction associated with T2D.

001-SS3

Role of Na+/K+ ATPase in Pulmonary Hypertension

Junting Zhang [1], Xiaowei Nie [1], Jinsong Bian [2]

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[2] *Department of Pharmacology, School of Medicine, Southern University of Science and Technology, Shenzhen 518055, China*

Pulmonary hypertension (PH) is an incurable disease, characterized by pulmonary vascular remodeling and right heart failure, which often leads to death. The Na^+/K^+ ATPase (NKA) maintains cellular function by maintaining ion concentration gradients between the intracellular and extracellular environments, and its malfunction contributes to the development of many serious diseases. In the present study, we investigated the biological role and molecular mechanism of NKAα1 in PH pulmonary vascular remodeling. We found that NKA expression was significantly decreased in the distal pulmonary arteries in PH patients. This was further confirmed in mouse PH models induced by hypoxia alone or hypoxia combined with Su5416 injection (SuHx). Inhibition of NKAα1 aggravated PH progression and promoted proliferation, migration and angiogenesis of pulmonary artery endothelial cells (PAECs). In addition, NKAα1 knockdown further aggravated the PH of mice induced by hypoxia combined with Su5416 (SuHx). Immunocoprecipitation combined with mass spectrometry showed that NKAα1 binds to mitophagy receptor Prohibitin 2 (PHB2). Loss of NKAα1 in the cell membrane promotes PHB2 transfer to mitochondria and nucleus. The recruitment of PHB2 in mitochondria induces PAECs mitophagy and dysfunction. We demonstrate for the first time that NKAα1 contributes to the PH development through regulates the expression and distribution of PHB2. Therefore, our study provides a novel target for treatment of PH and the evidence for NKAα1 antibodies and peptides are potential medicine for the treatment of this disease.

001-YS1

The Functions of Vascular KCa Channels in Aging

Erik Behringer [1]

[1] *Department of Basic Sciences, School of Medicine, Loma Linda University, Loma Linda CA*

Gerontology experts have projected that individuals aged ≥65 years will comprise approximately 20% of the global population by 2030. Cardiovascular disease remains the leading cause of death in the world with age-related vascular endothelial "dysfunction" as a key risk factor. As an organ in and of itself, vascular endothelium is distributed over 100,000 kilometers throughout the body to coordinate blood flow to all other organs and tissues (e.g., brain, heart, kidneys, liver, skeletal muscle, gut) in accord with metabolic demand. Regardless of type of signaling input, the cross-talk between endothelial Ca^{2+} ($[Ca^{2+}]_i$) and membrane potential (V_m) is a "master regulator" of moment-to-moment blood flow control throughout the microcirculation. The most direct bridge linking increases in endothelial $[Ca^{2+}]_i$ to higher V_m is endothelium-derived hyperpolarization (EDH) resulting from activation of small- and intermediate-conductance Ca^{2+}-activated K^+ (SK_{Ca}/IK_{Ca}; or $K_{Ca}2.3$/$K_{Ca}3.1$) channels. In turn, EDH spreads to surrounding smooth muscle through myoendothelial gap junctions, whereby vascular relaxation and enhanced blood flow takes place. We have also identified a reverse role for K_{Ca} channels, by which their activation facilitates Ca^{2+} influx into the cell interior through open non-selective cation (e.g., transient receptor potential; TRP) channels in accord with robust electrical (hyperpolarized intracellular V_m) and concentration (~20,000-fold) transmembrane gradients for Ca^{2+}. Such an arrangement supports a feed-forward activation of EDH while potentially boosting production of vasodilatory nitric oxide. Furthermore, in vascular types expressing TRP channels but deficient in functional K_{Ca} channels (e.g., collecting lymphatic endothelium), there are profound differences relative to blood vessel endothelium such as downstream depolarizing ionic fluxes and the absence of dynamic hyperpolarizing events. SK_{Ca}/IK_{Ca} channels can also fine tune the spread of cell-to-cell electrical signals through gap junctions as hyperpolarization and depolarization along the vascular wall to convey vasodilation and vasoconstriction respectively. In such manner, it is optimal to have brief bursts of ion channel activity to initiate local, discrete events in tandem with sustained gap junction patency along endothelial cells (i.e., high membrane resistance & low axial resistance). Vascular aging disrupts this balance whereby local vasoreactivity is preserved but conduction is diminished via enhanced oxidative signaling and membrane current "leak" through chronically open SK_{Ca}/IK_{Ca} channels. Thus, with a restricted spatial domain of blood flow control during aging, the resilient activity of endothelial SK_{Ca}/IK_{Ca} channels may be calibrated as needed to help fulfill a healthy integration of oxidative, Ca^{2+}, and electrical signals. Accordingly, we will be able to address vascular aging and co-development of morbidities such as neurodegeneration, diabetes, hypertension, kidney disease, heart failure, and cancer.

SYMPOSIUM 2

Ion Channels in Pulmonary Microcirculation in Health and Disease

08:30-10:00 | Room 2

002-SS1

Endothelial Piezo1 channels in pulmonary hypertension

Jason Yuan [1]

[1] *Department of Medicine/University of California, San Diego*

Piezo1 is a mechanosensitive cation channel responsible for stretch-mediated Ca^{2+} and Na^{+} influx in multiple types of cells including pulmonary arterial endothelial (PAEC) and smooth muscle (PASMC) cells. The lung vasculature is constantly under mechanical stimulation due to respiration (airway radial traction) and cardiac output (RV ejection). The numerous vascular junctions or bifurcations in the pulmonary vascular beds also make PAEC and microvascular/capillary endothelial cells exposure to flow shear stress. In this presentation, I will present some of our recent work on the potential role of Piezo1 channels in PAEC in the development and progression of pulmonary arterial hypertension (PAH). Our data show that Piezo1 is significantly upregulated in PAEC from patients with idiopathic PAH and animals with experimental pulmonary hypertension (PH) compared with normal controls. Membrane stretch by decreasing extracellular osmotic pressure or by cyclic stretch (18% CS) increases Ca^{2+}-dependent phosphorylation (p) of AKT and ERK, and subsequently upregulates expression of Notch ligands, Jagged1/2 (Jag-1 and Jag-2), and Delta like-4 (DLL4) in PAEC. siRNA-mediated downregulation of Piezo1 significantly inhibited the stretch-mediated pAKT increase and Jag-1 upregulation, whereas downregulation of AKT by siRNA markedly attenuated the stretch-mediated Jag-1 upregulation in human PAEC. Furthermore, the mRNA and protein expression level of Piezo1 in the isolated pulmonary artery, which mainly contains PASMC, from animals with severe PH was also significantly higher than that from control animals. Intraperitoneal injection of a Piezo1 channel blocker, GsMTx4, ameliorated experimental PH in mice. Taken together, our study suggests that membrane stretch-mediated Ca^{2+} influx through Piezo1 is an important trigger for pAKT-mediated upregulation of Jag-1 in PAEC. Upregulation of the mechanosensitive channel Piezo1 and the resultant increase in endothelial Notch ligands (Jag-1/2 and DLL4) may play a critical pathogenic role in the development of pulmonary vascular remodeling in PAH and PH.

002-SS2

Acid-sensing ion channels in pulmonary hypertension

Nikki Jernigan [1], Megan Tuineau [1], Selina Garcia [1], Jay Naik [1], Thomas Resta [1]

[1] *Department of Cell Biology and Physiology, University of New Mexico School of Medicine*

During pulmonary hypertension (pHTN), a chronic shift in cellular metabolism from mitochondrial oxidative phosphorylation to aerobic glycolysis underlies the hyperproliferative and anti-apoptotic phenotype of pulmonary vascular disease. These metabolic derangements are accompanied by H^{+} extrusion, creating an alkalotic intracellular pH while acidifying the extracellular microenvironment; prime conditions for activating the Na^{+}/Ca^{2+}-conducting ion channel, acid-sensing ion channel 1a (ASIC1a). Our previous findings demonstrate ASIC1a is an important constituent of the active vasoconstriction, arterial muscularization, and right ventricular hypertrophy associated with chronic hypoxia (CH)-induced pHTN. While CH does not transcriptionally regulate the expression of ASIC1, we found CH causes greater localization of ASIC1 at the plasma membrane of pulmonary arterial smooth muscle cells (PASMC) and loss of ASIC1 in the mitochondria, where ASIC1 has been shown to contribute to oxidative cell death. Therefore, we *hypothesize* that ASIC1 contributes to metabolic dysfunction in pHTN due to altered subcellular localization and regulation of PASMC plasmalemmal and mitochondrial membrane potential. Using whole-cell patch-clamp and sharp electrode electrophysiology, we show that increased Na^{+} currents through ASIC1 contribute to plasmalemmal membrane potential depolarization in PASMC following CH. CH and deletion of ASIC1a (*Asic1a*$^{-/-}$) leads to mitochondrial membrane hyperpolarization that is restored upon lentiviral transfection of mitochondrial-targeted ASIC1a. CH decreased active caspase-3 in pulmonary arteries from *Asic1a*$^{+/+}$, but not *Asic1a*$^{-/-}$ mice. Furthermore, active caspase-3 was lower in pulmonary arteries from *Asic1a*$^{-/-}$ compared to *Asic1a*$^{+/+}$ mice under normoxic conditions. These data suggest ASIC1 plays an essential role in regulating plasmalemmal and mitochondrial membrane potential and the hyperproliferative and apoptosis-resistant phenotype of PASMCs in pHTN.

002-SS3

Critical role of mechanosensitive ion channel Piezo1 in endothelial biology

Jing Li [1]

[1] *Faculty of Biological Sciences, University of Leeds*

Mechanotransduction of shear-stress has a key role in cardiovascular physiology andpathophysiology. But the mechanisms by which physical forces regulate endothelial cells to determine the complexities of vascular structure and function are enigmatic. Piezo1 proteins as subunits of calcium permeable non-selective cationic channels for detection of mechanical stimulation has been discovered recent years. Here we show Piezo1 channels as sensors of frictional shear stress and determinants of vascular structure in both development and adult physiology. Global or endothelial-specific disruption of mouse Piezo1 profoundly disturbed the developing vasculature and was embryonic lethal within days of the heart beating. Haploinsufficiency was not lethal but endothelial abnormality was detected in mature vessels. The importance of Piezo1 channels as sensors of blood flow was shown by Piezo1 dependence of shear-stress-evoked ionic current and calcium influx in endothelial cells and the ability of exogenous Piezo1 to confer sensitivity to shear stress on otherwise resistant cells. Downstream of this calcium influx there was protease activation and spatial reorganization of endothelial cells to the polarity of the applied force. Our data suggest that Piezo1 channels function as pivotal integrators in vascular biology.

002-YS1

Impaired Endothelial Piezo1-Pannexin1-TRPV4 Channel Signaling Reduces Flow-Induced Dilation of Resistance Pulmonary Arteries in Pulmonary Hypertension

Zdravka Daneva [1], Yen-Lin Chen [1], Maniselvan Kuppusamy [1], Eliska Klimentova [1], Swapnil Sonkusare [1,2]

[1] *Robert M. Berne Cardiovascular Research Center, UVA*
[2] *Department of Molecular Physiology and Biological Physics, UVA*

Introduction: Endothelial Ca^{2+} signaling mechanisms are essential regulators of flow-induced dilation in the vasculature. Resistance-sized pulmonary arteries (PAs) are a “high-flow” vascular bed; however, the mechanisms for flow-induced dilation of PAs remain unknown. We recently reported that adenosine triphosphate (ATP) efflux through endothelial Pannexin 1 ($Panx1_{EC}$) activates endothelial transient receptor potential vanilloid 4 ($TRPV4_{EC}$) ion channels through purinergic P2Y2 receptor ($P2Y2R_{EC}$) signaling to dilate PAs. We hypothesized that impaired $Panx1_{EC}$—$P2Y2R_{EC}$—$TRPV4_{EC}$ pathway mediates flow-induced dilation of PAs and its impairment contributes to endothelial dysfunction in pulmonary hypertension (PH).
Methods: Inducible endothelium-specific TRPV4EC-/-, Panx1EC-/-, P2Y2REC-/- mice and respective control mice, and C57BL6/J mice were used. Ca2+ imaging in en face PAs (~ 50 mm diameter) was used to record elementary Ca2+ influx signals via TRPV4EC channels (TRPV4 sparklets). Flow/shear stress (F/SS, 4-15 dynes/cm2)-induced dilation was studied in small PAs pressurized at 15 mm Hg in pressure myography experiments. Flow was regulated using flow indicator and peristaltic pump. For flow-induced ATP release, the luminal outflow was collected and ATP levels were quantified by an ATP bioluminescence

assay. Exposure to chronic hypoxia (CH, 10% O2 for 4 weeks) and sugen 5416 (Su+CH, 20 mg/kg; s.c., once a week for the initial 3 weeks) in mice was used as a model of PH.

Results: Increase in F/SS (4-15 dynes/cm2) induced an endothelium-dependent dilation of PAs. The F/SS-induced dilation was drastically reduced in PAs from Panx1EC-/-, P2Y2REC-/-, and TRPV4EC-/- mice, suggesting that Panx1EC—P2Y2REC—TRPV4EC signaling mediated the physiological dilation to flow. Baseline and F/SS-induced ATP efflux through Panx1EC were reduced in PAs from mice exposed to Su+CH compared to normoxic mice, indicating a reduced basal and F/SS-induced activity of Panx1EC in PH. Ca2+ imaging studies showed that the activity of TRPV4EC channels is reduced in PAs from Su+CH mice compared to normoxic mice. Additionally, Ca2+ imaging studies showed that basal and ATP-induced activation of TRPV4EC channels was also reduced in Su+CH mice, suggesting an impairment of P2Y2REC—TRPV4EC channel signaling in PH.

Conclusion: Together, these data suggest that flow-induced Panx1EC—P2Y2REC—TRPV4EC vasodilator signaling is impaired in PH. Future studies will assess the F/SS—Panx1EC and P2Y2REC—TRPV4EC signaling linkages in PH.

SYMPOSIUM 3

Endothelial Glycocalyx in Health and Disease

08:30-10:00 | Room 4

003-SS1

The impact of intravenous fluid resuscitation on sepsis-associated glycocalyx dysfunction

Eric Schmidt [1]

[1] *Massachusetts General Hospital*

In this keynote talk, Dr. Schmidt will discuss the importance of the endothelial glycocalyx to vascular homeostasis. Accordingly, heparanase-mediated degradation of the endothelial glycocalyx during sepsis contributes to local vascular injury (leading to ARDS and acute kidney injury) as well as the release of biologically-active glycosaminoglycans into the circulation that selectively penetrate memory centers of the brain, leading to long-term cognitive impairment. Dr. Schmidt will then discuss animal and human investigations of how fluid resuscitation practices may alter endothelial glycocalyx degradation, potentially impacting both short-term and long-term sepsis outcomes. These findings may lead to new, precision-medicine approaches to sepsis treatment.

003-SS2

Determining the structure, function and compositional relationship in capillary walls

Kenton Arkill [1]

[1] *Medicine/University of Nottingham*

Many micro-vessels incorporate a biophysical approach to molecular exchange by balancing vascular wall hydraulic and solute resistances and the pressures. The wall is made up of several layers: Endothelial glycocalyx, endothelial cells, basement membrane and underlying cells all having different roles and can be physiologically manipulated accordingly depending on tissue needs. Molecular exchange is a concern in many conditions either directly (e.g. diabetic retinopathy or nephropathy) or indirectly (e.g. for effective drug delivery), yet there are multiple difficulties for study: Firstly the endothelial glycocalyx structure is often lost in processing. Secondly, the structure and function of the walls tends to require a physiological setting limiting use of cell culture models. Thirdly the glycosaminoglycans in the extracellular layers are notoriously difficult to quantify on a subcellular scale. Here I will discuss multiple imaging approaches including correlative light (for function), electron (for structure) and imaging mass spectrometry (for composition) approaches to discern the structure-composition-function relationship in the microvasculature wall.

Light microscopy, particularly fluorescence, has revolutionised tissue characterisation and can be used to trace molecules as they transit the capillary wall and allows functional permeability calculations. As an example this can be performed repeatedly over a period of time in the rodent retina relatively non-invasively. Tissue can be taken for electron microscopy, and by using perfusion of lanthanides or equivalent can visualise the endothelial glycocalyx. Here we explore how to interpret the staining after tissue processing that collapses the endothelial glycocalyx. Of course, the endothelial glycocalyx layer has other functions that also depend on its molecular composition, such as mechanistic roles or shear stress detection. To discern the glycosaminoglycan components is clearly important but antibody staining has limited robustness. We are now able to decern using our secondary ion mass spectrometry ($[3Bi]^+$ cluster source with time of flight analyser) from paraffin embedded sections, such as patient biopsies, different glycosaminoglycan components from each layer of the vascular wall giving an alternative to antibody or other fluorescent staining methodologies.

003-SS3

Endothelial glycocalyx degradation and microvascular hyperpermeability

Jerome Breslin [1]

[1] *University of South Florida*

The endothelial cells of the postcapillary venules play an active role in controlling leakage of plasma components. Subcellular structures including the cytoskeleton, intercellular junctional protein complexes, focal adhesion complexes, and the glycocalyx surface layer all play key roles in endothelial barrier function. In recent years, much focus has turned to the glycocalyx, which has been shown to become compromised in the context of shock or sepsis. This talk will focus on hemorrhagic shock-induced glycocalyx degradation and the potential role of mitochondrial stress on glycocalyx integrity and overall endothelial health. Lastly, the ability of sphingosine-1-phosphate (S1P) to protect the endothelial glycocalyx will be discussed.

003-YS1

Restoration of Glycocalyx by sphingosine 1-phosphate

Ye Zeng [1]

[1] *Institute of Biomedical Engineering, West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University*

Sphingosine 1-phosphate (S1P) protects glycocalyx against shedding, playing important roles in endothelial functions. We previously found that glycocalyx on endothelial cells was shed after plasma protein depletion. In the present study, we investigated the role of S1P on the recovery of glycocalyx, and tested whether it is mediated by phosphoinositide 3-kinase (PI3K) pathway. After depletion of plasma protein, endothelial cells were treated with S1P for another 6 h. And then, the major components of glycocalyx including syndecan-1 with attached heparan sulfate (HS) and chondroitin sulfate (CS) on endothelial cells were detected using confocal fluorescence microscopy. Role of PI3K in the S1P-induced synthesis of glycocalyx was confirmed by using the PI3K inhibitor (LY294002). Finally, we analyzed the S1P and syndecan-1 levels in ApoE-/- atherosclerotic mice using ELISA kits. We found that syndecan-1 with attached HS and CS were degraded with duration of plasma protein depletion. S1P induced recovery of syndecan-1 with attached HS and CS. The PI3K inhibitor LY294002 abolished the effect of S1P on recovery of glycocalyx. Thus, S1P induced synthesis of glycocalyx on endothelial cells and it is mediated by PI3K pathway. In addition, the protective role of S1P on glycocalyx is challenged by elevated S1P levels and shedding of syndecan-1 in atherosclerosis.

SYMPOSIUM 4

Anti-Cancer Treatments and Endothelial Dysfunction: Mechanisms and Clinical Implications

10:00-11:30 | Room 1

004-SS1

Accelerated vascular aging induced by common chemotherapeutic agents: Understanding underlying mechanisms to inform future therapeutics strategies

Zachary Clayton [1]

[1] *Department of Integrative Physiology; University of Colorado Boulder*

Advancing age is the primary risk factor for cardiovascular diseases (CVD). Increased CVD risk with aging is mediated primarily by vascular dysfunction, including impaired vascular endothelial function and increased large elastic artery (primarily aortic) stiffening. These changes in vascular function are largely due to excessive reactive oxygen species (ROS) as a result of increased mitochondrial superoxide production, which reduce bioavailability of the vasodilatory molecule nitric oxide (NO) and induce structural changes in the arterial wall. However, the integrative mechanistic events regulating these processes are incompletely understood. Cellular senescence, a physiological state of largely-permanent cell cycle arrest coupled with the secretion of pro-inflammatory factors (i.e., the senescence-associated secretory phenotype [SASP]), has recently been established by us and others to be a key mechanism of age-related vascular dysfunction.

Interestingly, young adults who have undergone cancer treatment with doxorubicin (DOXO) chemotherapy have vascular dysfunction (e.g., lower endothelial function and greater aortic stiffness), similar to or even worse than what is observed in older adults without disease. Moreover, the mechanisms underlying DOXO-induced vascular dysfunction are similar to those with advancing age, including greater mitochondrial ROS and lower NO bioavailability. As such, DOXO chemotherapy is viewed as a model of accelerated vascular aging, but like with naturally aging, the integrative mechanistic events governing these cellular processes have not been established. Over the last three years, we have tested the hypothesis that cellular senescence is a novel therapeutic target for the prevention and/or treatment of accelerated vascular aging following DOXO chemotherapy treatment. Our preliminary results suggest that genetic clearance of excess senescent cells, in mice, following administration of DOXO chemotherapy can preserve endothelial function and prevent aortic stiffening, ultimately establishing cellular senescence as a viable therapeutic target for novel treatment strategies. To follow up on these results, we have treated mice with synthetic and natural senolytic agents (compounds that can selectively clear excess senescent cells) to establish the translational potential for targeting cellular senescence to preserve and/or improve vascular function following DOXO chemotherapy. The results of these studies advance our understanding of the effects of cancer treatment on aging outcomes and provide new insight into cellular senescence as a novel therapeutic target to reduce vascular dysfunction and CVD risk in DOXO-treated cancer survivors.

004-SS2

iPSC Models Uncovering Statin's Epigenetic Role in Vascular Health Protection

Chun Liu [1,2]

[1] *Department of Physiology, Cardiovascular Center, Cancer Center, Medical College of Wisconsin*

[2] *Stanford Cardiovascular Institute, Stanford University*

The pleiotropic benefits of statins in cardiovascular diseases that are independent of their lipid-lowering effects have been well documented, but the underlying mechanisms remain elusive. Here we show that simvastatin significantly improves human induced

pluripotent stem cell-derived endothelial cell functions in both baseline and diabetic conditions by reducing chromatin accessibility at transcriptional enhanced associate domain elements and ultimately at endothelial-to-mesenchymal transition (EndMT)-regulating genes in a yes-associated protein (YAP)-dependent manner. Inhibition of geranylgeranyltransferase (GGTase) I, a mevalonate pathway intermediate, repressed YAP nuclear translocation and YAP activity via RhoA signaling antagonism. We further identified a previously undescribed *SOX9* enhancer downstream of statin–YAP signaling that promotes the EndMT process. Thus, inhibition of any component of the GGTase–RhoA–YAP–SRY box transcription factor 9 (SOX9) signaling axis was shown to rescue EndMT-associated endothelial dysfunction both in vitro and in vivo, especially under diabetic conditions. Overall, our study reveals an epigenetic modulatory role for simvastatin in repressing EndMT to confer protection against endothelial dysfunction.

004-SS3

Moesin and its Phosphorylation in VE-cadherin Expression and Distribution in Endothelial Adherens Junctions

Qiaobing Huang [1,3], Bingyu Li [2], Xiaoxia Huang [1], Zhuanhua Liu [1], MaoMao Sun [1,3], Xing Zhou [1], Zhenfeng Chen [1], Xiaohua Guo [1]

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Background and Aim: Vascular endothelial cadherin (VE-cadherin) is an important element of adherens junctions (AJs) between endothelial cells. Its expression and proper distribution are critical for AJ formation and vascular integrity. Our previous studies have demonstrated that moesin phosphorylation mediated the hyper-permeability in endothelial monolayer and microvessels. However, the role of moesin and its phosphorylation in VE-cadherin expression and distribution is not clear.

Methods and Results: *In vivo*, expression of VE-cadherin was significantly reduced in retina and other various tissues in moesin knock out mice (*Msn*$^{-/Y}$). *In vitro*, by regulating moesin expression with siRNA and adenovirus transfection, we verified that moesin has an effect on VE-cadherin expression in HUVECs, while transcription factor KLF4 may participate in this process. In addition, treatment of advanced glycation end products (AGEs) induced abnormal distribution of VE-cadherin in retinal microvessels from C57BL/6 wild type mice, and in vitro studies indicated that moesin Thr558 phosphorylation had a critical role in AGE-induced VE-cadherin internalization from cytomembrane to cytoplasm. Further investigation demonstrated that the inhibition of F-actin polymerization with cytochalasin D could abolish AGE- and Thr558 phosphor-moesin-mediated VE-cadherin internalization.

Conclusion: This study suggests that moesin regulates VE-cadherin expression through KLF4 and the state of moesin phosphorylation at Thr558 affects the integrity of VE-cadherin-based AJs. Thr558 phosphor-moesin mediates AGE-induced VE-cadherin internalization through cytoskeleton reassembling.

004-YS1

Anti-cancer therapies induce human microvascular endothelial toxicity through direct and secondary signaling mechanisms

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Cardiotoxicity is a complication of several anti-cancer therapies, including doxorubicin and trastuzumab. Treatment-induced cardiotoxicity impacts treatment decisions and contributes to elevated risk of adverse cardiovascular outcomes in breast cancer patients and survivors. Microvascular dysfunction has recently emerged as a consequence of anti-cancer therapeutics with implications for the heart and other vital organs, although few studies have investigated treatment-induced microvascular dysfunction in humans.

In a longitudinal study of breast cancer patients undergoing therapy with at least one cycle of doxorubicin and/or trastuzumab, endothelial function was severely impaired in adipose arterioles isolated from patients during therapy and one-month after treatment cessation compared to pre-treatment baseline. Flow-induced production of nitric oxide was suppressed one month after treatment, whereas production of mitochondrial hydrogen peroxide was elevated. A complementary cross-sectional study revealed a similar magnitude of microvascular endothelial dysfunction that persisted for at least six months after treatment cessation. Endothelial function began to recover in arterioles obtained from patients 12–24-months post treatment.

We next investigated the direct impact of doxorubicin, trastuzumab, and paclitaxel – a chemotherapeutic agent with minimal risk of cardiotoxicity – on endothelial function in arterioles isolated from healthy donors. Acute, *ex vivo* exposure to clinically relevant doses of doxorubicin and trastuzumab largely abolished endothelial function, whereas paclitaxel had no effect on endothelial function. Vascular smooth muscle vasodilatory function was not affected by exposure to any agent. Evidence from prior studies in rodent models indicates that vascular endothelial growth factor B (VEGF-B) gene therapy preserves endothelial function and protects the heart against doxorubicin-induced cardiotoxicity (https: //doi.org/10.1073/pnas.1616168113). In the present study, VEGF-B overexpression prevented the detrimental impact of doxorubicin on healthy human arterioles *ex vivo*.

Finally, we sought to investigate indirect effects of anti-cancer therapy on the microvascular endothelium. Several agents used to combat cancer induce mitochondrial DNA (mtDNA) damage, which stimulates release of circulating, cell-free mtDNA fragments capable of activating Toll-like receptor 9 (TLR9). Arterioles from healthy donors were exposed to plasma obtained from breast cancer patients one month after treatment completion. Overnight incubation with plasma from cancer patients who had undergone anti-cancer therapy conferred endothelial dysfunction in healthy arterioles, which was prevented by TLR9 siRNA.

Collectively, these findings indicate that cardiotoxic anti-cancer therapies induce microvascular endothelial dysfunction through direct endothelial toxicity and secondary signaling mechanisms in humans. We provide proof of principle regarding isolated vessel preparations and gene therapy approaches as means to investigate underlying mechanisms. Results from longitudinal and cross-sectional studies of breast cancer patients demonstrate prolonged microvascular endothelial dysfunction, which may represent an opportunity for monitoring and intervention in patients at elevated risk of adverse cardiovascular outcomes.

SYMPOSIUM 5

Capillary Sensing

10:00-11:30 | Room 2

005-SS1

Electro-metabolic signaling via capillaries regulates blood flow in heart

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Exquisite regulation of local blood flow in the heart is crucial for meeting the high metabolic demands of the heart tissue and for fulfilling its non-stop pumping task. Our proposed Electro-Metabolic Signaling (EMS) theory for heart suggests that ventricular myocytes (VM's) play a vital role in this regulation by delivering electrically encoded metabolic signals to the capillaries. This is thought to be done through electrical connections between VM's and capillary endothelial cells (cECs) and the low pass filtering effect of this network. Thus, the resulting small but important membrane potential changes of the cECs acts on multiple cell types connected to the cECs through gap junction including contractile pericytes (CPs) and arteriolar smooth muscle cells (ASMCs). When metabolic demand increases in heart and the rate of ATP consumption in VMs exceeds production, there is a drop in $[ATP]_i$ with an increase in $[ADP]_i$ to activate ATP-sensitive K^+ channels in VM's. Even small changes in $[ATP]_i$ and $[ADP]_i$ have meaningful effects in VMs because of the extreme abundance of K-ATP channels in VM's. This leads to sequential membrane hyperpolarization, first in VMs, then in cECs, CPs, and ASMCs, attributable to the electrical spread of the hyperpolarizing signal. Additionally, there is the local effect of increased extracellular $[K^+]$ that is tissue and cell-type dependent. Such increased extracellular $[K^+]$ may lead to additional hyperpolarization of cECs due to a combination of the inward-rectifier K^+ channels (Kir) affected, the shape of the current-voltage relationship and the resting potential of the cECs. Both will result in upstream arteriolar dilation and increased blood flow to meet the metabolic needs of VMs. Unlike what has been found in cerebral blood flow, Kir in heart seems to play a minor role in heart blood flow regulation - a finding supported by recent experiments in the pressurized mouse right ventricle papillary muscle (Z-Prep) and freshly isolated cECs.

005-SS2

Cell-cell crosstalk in limb ischemia microenvironment

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Background: Peripheral artery disease is a major issue for persons who lost peripheral organs. Angiogenesis and tissue regeneration are the key recovery mechanisms for limb ischemia, in which comprehensive analyses of the ischemic repair niche are lacking. It is imperative to draw a cellular map of the angiogenesis and regeneration of skeletal muscle in response to ischemic stimulation.
Methods: Single-cell RNA sequencing was used to map the cell landscapes of the mouse and human limb ischemia microenvironments. Blood flow was measured by Laser Doppler imaging. Lineage tracing mice and bone marrow transplantation were used to elucidate the contribution of CD34+ cells from different sources to this niche. Focusing on the fibroblasts and macrophages, key secretory signal regulatory switches during the ischemia/repair process was identified and then further confirmed by flow cytometry, immunofluorescence, and other analyses.
Results: Seventeen different cell subsets contributed to human and mouse muscle ischemia microenvironments respectively, after unbiased clustering performed with Seurat canonical correlation analysis. Analysis of intercellular receptor-ligand pairs showed that the crosstalk among different cell types existed much more widely with increased number of inferred interactions by ischemia, in which the signal between fibroblasts and macrophages was dramatically stronger. Blood-derived macrophages with antigen-presenting function migrated to the ischemic site, while resident macrophages mainly exhibiting M2 phenotype tended to undergo apoptosis. The macrophage oncostatin M (OSM) regulatory pathway was specifically turned on by ischemia. Regarding fibroblasts, a group of pro-regenerative fibroblasts, partly from bone marrow, was identified. They responded to macrophage OSM secretion signals and in turn acted on endothelial cells through the angiopoietin-like protein (ANGPTL) signaling. In addition, scRNA-seq of samples from Cd34-CreERT2;R26-tdTomato mice showed that CD34+ cells were the primary source of these pro-regenerative fibroblasts after ischemia. Depletion of CD34+ cells using diphtheria toxin-induced cell ablation and blocking OSM signaling with AAV-9 or a neutralizing antibody markedly inhibited angiogenesis and regeneration in ischemic tissues.
Conclusions: These findings provided mechanisms on the cellular events and cell–cell communications during limb ischemia and regeneration, and provided evidence that CD34+ cells serve as fibroblast progenitors promoting tissue regeneration.

005-SS3

Spatiotemporal manipulation of capillary network flow

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Background: Capillary flow is governed by a complex interplay between blood cells, endothelial cells, and other perivascular cells. Much effort has been put into elucidating the signal mechanisms between these cells in controlling capillary flow, but little is known about the spatial and temporal fluctuation of flow and thus of the distribution of flow on capillary networks. Here, we investigated the spatiotemporal coherence of the diameter changes in capillaries and blood cell flow for local vasoconstrictive stimulation in the brains of anesthetized rodents.
Method: Two-photon microscopy was used to map the flow structures of blood plasma and red blood cells labelled fluorescently. To manipulate the systemic level of hematocrit, the animals were subjected to dehydration by restricting water supply. The measurement of capillary diameters and flow speeds was done using a custom-written Matlab software. The flow map was made using a kymograph image with Radon transform. Animal use and the experimental protocols were approved by the institutional laboratory animal care and use committee, and all experimental procedures were performed following guidelines established by the Institute for the Humane Care and Use of Laboratory Animals in compliance with ARRIVE guidelines.
Results and Discussion: The diameter changes were concentrated at the stimulated spot, but the flow speed changes were observed to spread over the entire capillary. Despite the speed changes, the inter-cell distance between blood cells was relatively unchanged, which suggest that the plasma components packed between the cells were isolated. The flow speed depended on the package of blood cells in the capillary, and thus the speed change occurred inside the branched capillaries next to the point of branching. The results suggest that the power of spontaneous flow fluctuations in the capillary beds represents the number of the branches in the capillary networks. Under dehydration conditions, spatial heterogeneity of flow distribution was enhanced, leading to a more synchronized flow distribution across the capillaries.

Conclusions: The findings showed that local changes in capillary diameter lead to spatiotemporal modulation of capillary flow distribution. This remote effect of flow changes in capillary networks should be taken into consideration to better understand the mechanisms for regulating capillary flow structures.

005-YS1

Piezo1 Is a Mechanosensor Channel in Central Nervous System Capillaries

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Capillaries are equipped to sense neurovascular coupling agents released onto the outer wall of a capillary, translating these external signals into electrical/Ca2+ changes that play a crucial role in blood flow regulation and ensuring that neuronal demands are met. However, control mechanisms attributable to forces imposed onto the lumen are less clear. Here, we show that Piezo1 channels act as mechanosensors in central nervous system capillaries. Electrophysiological analyses confirmed expression and function of Piezo1 channels in brain cortical and retinal capillaries. Activation of Piezo1 channels evoked currents that were sensitive to endothelial cell–specific Piezo1 deletion. Using genetically encoded Ca2+ indicator mice and an ex vivo pressurized retina preparation, we found that activation of Piezo1 channels by mechanical forces triggered Ca2+ signals in capillary endothelial cells. Collectively, these findings indicate that Piezo1 channels are capillary mechanosensors that initiate crucial Ca2+ signals and could, therefore, have a profound impact on central nervous system blood flow control.

SYMPOSIUM 6

Novel Mechanisms of Regulation of Endothelial Cell Function

10:00-11:30 | Room 4

006-SS1

Regulation of blood brain barrier function in Alzheimer's Disease

Ka Ka Ting [1,2], Paul Coleman [1,2], Hani Jieun Kim [4], Yang Zhao [5], Jocelyne Mulangala [1], Ngan Ching Cheng [1], Li Wan [6], Dilini Gunatilake [1], Daniel M. Johnstone [7,8], Lipin Loo [1,9], G. Gregory Neely [1,9], Pengyi Yang [4], Jürgen Götz [3], Mathew Vadas [1], Jennifer R. Gamble [1,2]

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Alzheimer's disease (AD) is an age-related disease, with loss of integrity of the blood-brain barrier (BBB) being an early feature. Cellular senescence is one of the reported nine hallmarks of aging. Here we show for the first time the presence of senescent cells in the vasculature in AD patients and mouse models of AD. Senescent endothelial cells and pericytes are present in APP/PS1 transgenic mice but not in wild-type littermates at the time of amyloid deposition. *In vitro*, senescent endothelial cells display altered VE-cadherin expression and loss of cell junction formation and increased permeability. Consistent with this, senescent endothelial cells in APP/PS1 mice are present at areas of vascular leak that have decreased claudin-5 and VE-cadherin expression confirming BBB breakdown. Further, single cell sequencing of endothelial cells from APP/PS1 transgenic mice confirms that adhesion molecule pathways are among the most highly altered pathways in these cells. At the pre-plaque stage the vasculature shows significant signs of breakdown, with a general loss of VE-cadherin, leakage within the microcirculation, and obvious pericyte perturbation. Although senescent vascular cells were not directly observed at sites of vascular leak, senescent cells were close to the leak area. Thus, we would suggest in AD there is a progressive induction of senescence in constituents of the neurovascular unit contributing to an increasing loss of vascular integrity. Targeting the vasculature early in AD, either with senolytics or with drugs that improve the integrity of the BBB maybe valid therapeutic strategies.

006-SS2

Nedd4 controls lymphatic endothelial cell sprouting and adhesion by regulating sphingosine 1-phosphate receptor activity

Genevieve Secker [1], Drew Sutton [1], Melinda Tea [1], Jan Kazenwadel [1], Kelly Betterman [1], Briony Gliddon [1], Hiroshi Kawabe [5], Quenten Schwarz [1,2], Dejana Elisabetta [3], Stuart Pitson [1], Sharad Kumar [1,2], Harvey Natasha [1,2]

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The lymphatic vasculature is a crucial component of the cardiovascular system, with vital roles in tissue homeostasis, immune cell trafficking and absorption of lipids from the digestive system. Growth and remodelling of lymphatic vascular networks during development requires precise and dynamic coordination of endothelial cell adhesion. While the assembly and remodeling of adherens junctions must be precisely tuned to facilitate the expansion of vascular networks while maintaining vessel integrity, little is known about the molecular mechanisms controlling this tuning, especially in lymphatic endothelial cells. Our work has revealed that the ubiquitin ligase NEDD4 is crucial for morphogenesis of the lymphatic vasculature during mouse embryogenesis by regulating lymphatic endothelial cell sprouting, migration and adhesion. Nedd4 deficient mice exhibit striking defects in lymphatic vascular development as a result of key roles for NEDD4 in the regulation of VEGFR trafficking and adherens junction remodelling. Our analysis has identified an important mediator of the balance between lymphatic vessel sprouting and quiescence, sphingosine 1-phosphate receptor, S1PR1, as a target of NEDD4 in lymphatic endothelial cells. NEDD4 regulates the levels and activity of S1PR1, resulting in increased adherens junction stability and tighter cell-cell adhesion in the lymphatic vasculature of Nedd4 deficient mice. Our data reveal novel roles for NEDD4 and S1PR1 in developmental lymphangiogenesis and highlight the potential for targeting these molecules in the setting of pathological lymphangiogenesis.

006-SS3

New regulators of Vegfc-driven lymphangiogenesis and vascular proliferation

Kazuhide Shaun Okuda [1,2,3,4], Scott Patterson [2,3,4], Huijun Chen [3], Katarzyna Koltowska [3,5], Gregory Baillie [3], Cas Simons [3], Kelly Smith [3,6], Benjamin Hogan [2,3,6]

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Lymphatic vessels are important for the regulation of tissue fluid homeostasis, immune surveillance and dietary fat absorption, and are closely associated with various pathological conditions such as cancer, inflammation and lymphoedema. Studies in both zebrafish and mouse have revealed that lymphatic precursor cells predominantly originate from veins and the vascular endothelial growth factor c (VEGFC)/ VEGF receptor 3 (VEGFR3) pathway play essential roles in lymphatic precursor cell specification, sprouting and migration. However, genes associated with the vast expansion of lymphatic endothelial cells as they sprout from the vein and form mature lymphatic networks are hugely unknown. Recently, we identified Ddx21 and downstream ribosome biogenesis as selective regulators of lymphatic endothelial cell proliferation. Ddx21 function is essential for Vegfc/Vegfr3 driven endothelial cell proliferation and in its absence, endothelial cells show reduced ribosome biogenesis, p53 and p21 up-regulation, and cell cycle arrest that blocks lymphangiogenesis. From a zebrafish forward genetic screen, we identified top3a mutant, which also lacks lymphatic vessels but not blood vessels. In a *vegfc*-overexpression background, *top3a* mutation results in reduced *vegfc*-mediated venous endothelial cell proliferation, identifying *top3a* as a necessary downstream component of the Vegfc/Vegfr3 pathway. Interestingly, deletion of *tp53*, which is required for the activation of cellular responses to abnormalities in DNA replication and damage, in *top3a* mutants rescued its lymphatic phenotype, suggesting that lack of Top3a results in p53-mediated lymphatic endothelial cell death, similar to ddx21 mutants. Taken together, we identified *top3a* as a novel modulator of Vegfc/Vegfr3-mediated lymphatic endothelial cell proliferation.

006-YS1

Mechanisms of Capillary Signaling to Arterioles to Regulate Oxygen Delivery

Paulina Kowalewska [1], Stephanie Milkovich [1], Daniel Goldman [1], Shaun Sandow [2], Christopher Ellis [1], Donald Welsh [1]

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Red blood cell (RBC) flow through the microvasculature is closely matched to tissue O_2 requirements. At a fundamental level, O_2 demand-supply coupling entails the sensing of PO_2, and the generation of a stimulus that alters upstream arteriolar tone. However, where and how O_2 needs are sensed in the microcirculation is presently contested. One idea centers on hypoxia triggering the release of K^+, activating endothelial $K_{IR}2.1$ channels and initiating a hyperpolarization that conducts upstream via gap junctions, comprised of connexins (Cx). We tested this idea in skeletal muscle where we controlled the local tissue O_2 environment using live animal imaging in *Cx40*$^{-/-}$ and endothelial *K*$_{IR}$*2.1*$^{-/-}$ mice. The extensor digitorum longus muscle positioned overtop a gas control chamber allowed second-by-second monitoring of capillary RBC flow responses as O_2 was altered around its physiological set point of 53 mmHg. A stepwise drop in PO_2 at the muscle surface (53 to 15 or 0 mmHg) increased RBC supply rate in control capillaries while elevated chamber O_2 elicited the opposite response; these capillaries robustly expressed Cx40. The RBC flow responses were rapid and tightly coupled to O_2 levels as readily observed when chamber O_2 was oscillated in a sinusoidal manner. In contrast, this blood flow response was significantly diminished in *Cx40*$^{-/-}$ mice and translated into lower capillary RBC O_2 saturation. *K*$_{IR}$*2.1*$^{-/-}$ mice, on the other hand, had normal resting RBC O_2 saturation and reacted normally to O_2 changes, albeit an oscillation or a sustained stepwise decrease. Furthermore, we confirmed that RBC flow responses are conserved in endothelial *K*$_{IR}$*2.1*$^{-/-}$ mice even when the low O_2 challenge is applied to a restricted number of surface capillaries in the muscle; interestingly, these responses were dominated by capillary hematocrit changes in both control and endothelial *K*$_{IR}$*2.1*$^{-/-}$ mice. In conclusion, we demonstrate that microvascular O_2 responses depend on coordinated electrical signaling via gap junctions comprised of Cx40 and that endothelial $K_{IR}2.1$ channels do not drive the initiating electrical event. These findings reconceptualize our understanding of blood flow regulation and how O_2 initiates this process at the capillary level independent of metabolite production.

SYMPOSIUM 7

Hemodynamic Characterization of the Coronary Microvasculature

15:00-16:30 | Room 1

007-SS1

Mechanosensors and Their Significance in Vascular Diseases

Jing Zhou [1]

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Mechanotransduction in vascular smooth muscle cells (VSMCs) plays crucial roles in maintaining vascular homeostasis and the development of diseases. Yet the molecules responsible for sensing forces remain largely unknown. The discoidin domain receptor 1 (DDR1) tyrosine kinase is fundamental for proper embryonic development and organogenesis and also implicated in the progression of several diseases including various cancers, atherosclerosis and fibrotic diseases. It is mechanoresponsive to the stiffness of extracellular matrix (ECM) but remains functionally unknown in coordinating VSMC mechanosensation. Our study identified DDR1 as a primary mechanosensor and is required for stiffness/ligand-induced dephosphorylation and nuclear translocation of yes-associated protein (YAP), a major player in the development and progression of large artery stiffening. We uncovered that DDR1 underwent stiffness/ligand-stimulated liquid-liquid phase separation (LLPS) and co-condensed with LATS1, the Hippo pathway kinase large tumor suppressor 1. In mouse models, YAP activity was positively correlated with collagen I expression and arterial stiffness. LATS1 inhibition reactivated the YAP signaling in Ddr1-deficient vessels and abrogated the arterial softening effect of Ddr1 deficiency. Our findings establish a previous uncharacterized role of VSMC DDR1 in directly sensing forces and offer a mechanism by which VSMC activation of DDR1 promotes vascular diseases.

007-SS2

Multiparametric evaluation of coronary microvascular dysfunction in heart transplantation patients

Annagrazia Cecere [1], PLM Kerkhof [2], Giovanni Civieri [1], Annalisa Angelini [3], Antonio Gambino [4], Angela Fraiese [4], Tomaso Bottio [4], Elena Osto [5,6], Giulia Famoso [1], Marny Fedrigo [3], Enrico Giacomin [1], Giuseppe Toscano [4], Roberta Montisci [7], Sabino Iliceto [1], Gino Gerosa [4], Francesco Tona [1]

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Background: Coronary microvascular dysfunction (CMD) leads to a worse prognosis in heart transplanted (HT) patients. Coronary flow velocity reserve (CFVR) estimates the physiological impact of allograft disease on the coronary circulation in HT patients. We aimed to determine the mechanisms of CMD in HT patients and their prognostic implications.
Methods: We enrolled 134 patients, surviving at least 5 years, with normal systolic function and no evidence of allograft vasculopathy or rejection. 50 healthy volunteers without cardiovascular diseases, and matched for age and sex, served as a control group. All enrolled patients underwent echocardiographic evaluation of microvascular function by the assessment of rest and hyperemic coronary diastolic peak flow velocity (DPV_r and DPV_h); CFVR; companion of CFVR (CCFVR), which is based on the quadratic mean: $CCFVR=\sqrt{\{(DPV_r)^2+(DPV_h)^2\}}$; basal and hyperemic coronary microvascular resistance (BMR and HMR). A CFVR ≤ 2.5 was considered abnormal; the median value of DPV_h (75 cm/sec) and CCFVR (80 cm/sec) were selected as cut-offs to classify patients.
Results: Based on CFVR and DPV_h, HT patients can be assigned to four endotypes: endotype 1 (n=32), discordant with preserved CFVR (3.1±0.4); endotype 2 (n=60), concordant with preserved CFVR (3.4±0.5); endotype 3 (n=31), concordant with impaired CFVR (1.8±0.3), and endotype 4 (n=11), discordant with impaired CFVR (2.0±0.2).
Intriguingly, endotype 1 showed lower DPV_r and DPV_h (both $p < 0.0001$) than controls with lower CFVR and CCFVR (both $p < 0.0001$) than controls. Moreover, both BMR and HMR were higher in endotype 1 than in controls ($p=0.001$ and $p<0.0001$, respectively), suggesting structural microvascular remodeling. Conversely, endotype 2 was comparable to controls. A 13/32 (41%) patients in endotype 1 died in a follow-up of 28 years and mortality rate was comparable to endotype 3 (14/31, 45%). However, CCFVR was <80 cm/s in all 13 deaths of group 1 (characterized by preserved CFVR).
At multivariable analysis, CMD, DPV_h< 75 cm/s, CCFVR <80 cm/s were independent predictors of mortality in HT patients. The inclusion of CCFVR<80 cm/s to models with clinical indicators of mortality permitted better prediction of survival in HT patients, compared to only adding CMD or DPV_h< 75 cm/s ($p<0.0001$ and $p=0.03$, respectively).
Conclusions. This study is the first to demonstrate that the CFVR alone is not sufficient to completely predict long-term survival in HT patients. CCFVR provides a significant improvement in survival prediction in long-term HT patients. The proposed multiparametric approach could provide more complete clinical information on coronary microvasculopathy and guide HT patient management.

007-YS1

Rb1 attenuates cardiac microvascular hyperpermeability and hemorrhage after ischemia and reperfusion injury through restoration of microvascular endothelial cell junction and basement membrane

Xin-Mei Huo [1,2], Li Yan [2], Kai Sun [2], Ping Huang [2], Wang Xiao-Yi [1,2], Li An-Qing [1,2], Li De-Xin [1,2], Yang Dong-Min [1,2], Han Jing-Yan [1,2]

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Background and Purpose: Myocardial ischemia and reperfusion (I/R) injury and cardiac microcirculation disturbance are associated with microvascular barrier injury. Previous studies have shown Ginsenoside Rb1 (Rb1) can protect I/R-induced myocardial injury via regulation of energy metabolism. The purpose of this study is to clarify the effect and mechanism of Rb1 in attenuating cardiac microvascular hyperpermeability and hemorrhage after I/R injury.
Method: We detected the effect of Rb1 on albumin leakage from coronary venules, the integrity of cardiac microvascular, the expression and distribution of junction proteins in I/R-induced rats.
Result: The results showed that Rb1 could attenuate cardiac microvascular hyperpermeability after I/R injury, alleviate the degradation of cardiac microvascular endothelial cells connexins, attenuate abnormal expression of cytoskeleton protein, and improve vascular basement membrane integrity through reducing the expression of MMP2/9.
Conclusion: These results indicated that Rb1 may attenuate cardiac microvascular hyperpermeability and hemorrhage through improving connexin of vascular endothelial cells, F-actin polymerization and basement membrane.

007-YS2

Spinning disk confocal intravital imaging revealed platelet and neutrophil dynamics in microvascular obstruction following ischemia-reperfusion injury and their synergistic interventions

Zengrong Chen [1], Pengfei Xu [1], Xiao Yu [1], Xuejian Yang [1], Qing Wan [1], Haojie Rao [1], Jianfeng Yang [1], Hong Chen [1], Miao Wang [1]

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Objective: Microvascular obstruction is associated with poor outcome in patients with acute myocardial infarction, however the underlying cell dynamics is unclear. We report that phospordiesterase-4 inhibition by roflumilast improves microcirculation following myocardial ischemia-reperfusion (I/R) injury. This study aimed to elucidate the cell dynamics in microcirculation following I/R.

Approach and Results: In eight-week-old C57B6 mice, 30min coronary ischemia followed by reperfusion resulted in impaired microcirculation, as assessed by laser Doppler flow. This I/R response was also reproduced with hind-limb I/R. Micro-vessels and capillaries (with diameter of 10-25 μm and <10 μm, respectively) were non-invasively imaged at the plantar skin area of hind-limb extremity by spinning-disk confocal intravital microscopy. The impaired microcirculatory perfusion following I/R was exemplified with platelet aggregation, platelet-neutrophil aggregate (PNA) formation, neutrophil adhesion, and enhanced vascular permeability. Platelet aggregation and neutrophil adhesion were often spatially different from each other in capillaries. Aspirin treatment suppressed the I/R induced platelet aggregations and PNA formation, whereas roflumilast, without affecting platelet aggregation, attenuated the neutrophil adhesion and PNA formation, and both treatments reduced vascular permeability. Furthermore, treatment with aspirin and roflumilast each ameliorated microvascular obstruction after I/R injury, and combination of the two drugs provided synergistic protection.

Conclusions: I/R triggers microvascular obstruction attributable to platelet aggregation, neutrophil activation and increased permeability. Pharmacological interventions of platelets and neutrophils synergistically improve microcirculation post I/R injury, implicating their potential clinical application.

Keywords: Ischemia-reperfusion injury; Microvascular obstruction; Microcirculation; Platelet; Neutrophil; Aspirin; Roflumilast; Spinning disk confocal imaging

SYMPOSIUM 8

Microcirculation in Gastrointestinal Cancer and Inflammation

15:00-16:30 | Room 2

008-SS1

Movement of Innate lymphoid Cells from Intestinal Mucosa to mesenteric lymph node through lymph collecting ducts in rats

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Introduction: Innate lymphoid cells (ILCs) are classified as ILC1, ILC2, and ILC3, according to the gene transcription factor for each type. Recently, it has been also demonstrated that dysregulation of ILC1, ILC2, and ILC3 may be a causative factor for inflammatory bowel diseases. In contrast to the abundant distribution of ILCs in the intestinal mucosa, the number of ILCs in the peripheral blood is much lower than lymphocytes. Thus, ILCs have been believed to be stayed within the one organ and do not migrate to the other organs. Luminal antigens, nutrients, metabolites from commensal bacteria, bile acids or neuropeptides influence function and trafficking of immune cells in the intestine. Among the immune cells in the gut, innate lymphoid cells, play an important role for the maintenance of intestinal homeostasis through a rapid immune response to luminal pathogens. Recently, it was reported that water intake increases the number of ILC3 in MLNs and decreases the number of intestinal ILC3 in rats, suggesting that luminal ILC3 travel from the intestinal mucosa to the MLNs in response to luminal stimulation. Other group showed that ILC3 moved to the mesenteric lymph nodes (MLNs) depending on CCR7 expression by using Kaede mice. Herein, ILCs were directly obtained from intestinal lymph using a lymph fistula rat model and analyzed under physiological and pathological conditions.

Methods: Lymphocytes flowing through mesenteric lymphatic vessels (MLVs) were collected by cannulation into the thoracic duct of Wistar rats (9 weeks) that had received a mesenteric lymphadenectomy 4 weeks before. The collected ILCs were classified according to gene transcription factors and analyzed by flow cytometry. Rats were treated by indomethacin to induce small intestinal injury. To induce intestinal allergy, ovalbumin treatment was induced to the rats. To activate ILC2 directly, recombinant IL-25 was administered to the rats.

Results: The proportion of total ILCs in the peripheral blood was very few. The proportion of total ILCs in the MLV (MLV-ILCs) was significantly higher than that among thoracic duct lymphocytes (TDLs) Physiologically, there were several significant differences in the MLV-ILCs compared with TDL-ILCs, including the proportion of ILC2 and ILC3, and the proportion of α4 integrin-positive cells. IL-25 significantly increased the proportion of MLV-ILC2 after 3 days. Indomethacin-induced intestinal injury increased the proportion of MLV-ILC3 in the early phase within 12 hours.

Conclusion: We successfully isolated ILCs in the thoracic duct through which ILCs moved from intestinal mucosa to the MLN. The altered mobilization of MLV-ILC after stimuli suggests that ILCs were involved in mucosal immune response after luminal antigens by migrating to the secondary lymph nodes.

008-SS2

The role of heme oxygenase-1 in intestinal ischemia/reperfusion injury in mice

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Background: Intestinal ischemia-reperfusion (I-R) injury is a complex,

multifactorial, pathophysiological process with high morbidity and mortality, leading to serious difficulty in treatment, especially in human. Although the mechanisms involved in the pathogenesis of intestinal I-R injury have not been fully elucidated, it is generally believed that oxidative stress and subsequent inflammation play an important role. One of the antioxidant enzymes, heme oxygenase (HO), is a rate-limiting enzyme catalyzing the degradation of heme to biliverdin, free iron, and carbon monoxide (CO). In particular, HO-1 (an inducible form) is believed to confer cytoprotection by inhibiting inflammation, oxidation, and apoptosis, and maintaining microcirculation. Then, we investigated the role and potential mechanisms of HO-1 on modulation of inflammatory responses in murine intestinal I-R injury. In addition, the role of BTB and CNC homolog 1 (Bach1), which is a transcriptional repressor of HO-1, Nuclear factor-erythroid 2-related factor 2 (Nrf2), which has been known to be a transcriptional factor of HO-1, and CO, one of the by-products of heme degradation by HO were investigated in the present study.

Materials and Methods: Intestinal damage was induced by clamping the superior mesenteric artery for 45 min followed by reperfusion in male wild type (WT) mice, Bach1 deficient mice and Nrf2 deficient mice. CO-releasing molecule (CORM)-3 was intraperitoneally administered 1 h before induction of ischemia. Subsequently, intestinal damages were evaluated macroscopically, histologically, and biochemically 4h following reperfusion.

Results: Luminal inflammatory markers such as luminal protein and hemoglobin, tissue levels of TNF-alpha and KC were significantly elevated in I-R-induced intestine of WT mice. These changes were significantly attenuated in Bach1 deficient mice or treatment with CORM-3, and obviously deteriorated in Nrf2 deficient mice. In addition, the treatment with HO-1 inhibitor resulted in the reverse of these attenuations in I-R-induced injury of Bach1 deficient mice.

Conclusion: These findings indicate that HO-1 has protective role against murine I-R-induced intestinal injuries, and may be valuable targets against intestinal I-R injury.

008-SS3

Inflammation and microvascular sensitivity to insulin and flow

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A common characteristic of inflammation is presence of an increased activity of the enzyme a disintegrin and metalloproteinase-17 (ADAM17). Shedding of tumor necrosis factor-alpha (TNFα, an inflammatory cytokine) is a canonical feature of ADAM17. However, ADAM17 is capable of cleaving multiple other components on the cell surface. These components include cellular receptors for a variety of ligands and proteins members of the glycocalyx. Recently, it was shown that the extracellular portion of the insulin receptor (IRα) and the mechanosensor glypican-1 (a glycocalyx component) are substrates of ADAM17. In the setting of pro-inflammatory states, such as obesity and type 2 diabetes, there is an increased amount of ADAM17 in the vascular wall which coincides with endothelial dysfunction, characterized by decreased agonist- and flow-mediated vasodilatory responses. We hypothesized that ADAM17 activity causes endothelial dysfunction in part by its capacity to shed IRα and mechanosensitive components of the glycocalyx to reduce endothelial production of nitric oxide (NO) in response to insulin or shear stress. Experiments to test this hypothesis used endothelial cells in culture and isolated omental arteries from humans. Results show that activation or overexpression of ADAM17 in endothelial cells reduces the presence of IRα on the cell surface and augments it in the cell culture supernatant. Congruently, ADAM17 activation or overexpression impairs insulin signaling as determined by diminished phosphorylation of Akt and endothelial NO synthase, as well as NO production. Overexpression of ADAM17 also results in shedding of known mechanosensitive components of the glycocalyx from endothelial cells including glypican-1. These findings in cultured endothelial cells were supported by experiments in human isolated vessels, which show that increased ADAM17 activity reduces insulin- and flow-induced vasodilation. All this indicates that increased ADAM17 activity, as present in pro-inflammatory states, sheds a variety of components from the surface of endothelial cells, contributing to endothelial dysfunction and reduced vasodilatory capacity. We posit that targeting ADAM17 sheddase activity such as that occurring in type 2 diabetes represents a potential therapeutic approach to reduce endothelial dysfunction and associated cardiovascular disease incidence and mortality.

008-YS1

Current status of magnifying endoscopy for digestive neoplasms according to microvessel findings

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Magnifying endoscopy has been an evolving and promising technique for the assessment of digestive neoplasms. This technique involves the use of magnification endoscopes that allow for enhanced visualization of the microvessels (MVs) and microstructures in the gastrointestinal mucosa. Especially, observing these MVs enables endoscopists obtain valuable information for neoplastic characterization and depth of invasion. Here, I would like to review current status of magnifying endoscopy for digestive neoplasms with a focus on MV findings.

Endoscopic treatment for superficial esophageal squamous cell carcinoma (SESCC) is less invasively procedure than surgical esophagectomy. The risk of lymph node metastasis in SESCC was reported to be related to the depth of invasion of the primary SESCC. Japanese guidelines for the diagnosis and treatment of esophageal carcinoma also recommend that invasion to the epithelium (T1a-EP) or lamina propria mucosa (T1a-LPM) is an indication for endoscopic resection, invasion to the lamina muscularis mucosa (T1a-MM) or submucosa to a depth ≤200 μm (T1b-SM1) is a relative indication. Therefore, precise preoperative diagnosis is essential for a therapeutic strategy of SESCC.

Image-enhanced endoscopy, such as narrow-band imaging (NBI), has been reported to be a useful technique for the detection and diagnosis of superficial esophageal squamous cell carcinoma (SESCC). Moreover, magnifying endoscopy with NBI (ME-NBI) was reported to be useful for identifying the depth of invasion of SESCC by focusing on the MVs on the surface of the lesion. Magnifying endoscopy with blue laser imaging (ME-BLI) have also been reported to be useful for pathological diagnosis of SESCC.

Gastric cancer is the major common cause of cancer-associated deaths. Early detection and treatment have led to improved survival rates, with esophagogastroduodenoscopy (EGD) proving to be the most useful method of diagnosis for early gastric cancer (EGC). However, it is often difficult to diagnose gastric superficial adenocarcinomas using conventional endoscopy with white-light imaging (C-WLI). Many clinical studies have reported on the diagnostic performance of EGC by IEE techniques such as NBI and BLI. ME-NBI and ME-BLI enable a detailed examination of the MVs and microsurface patterns in the gastric mucosa, aiding in the differentiation diagnosis between benign and malignant lesions and guiding targeted biopsies. Yamada et al. showed that the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of M-NBI after C-WLI for the diagnosis of small depressed lesions were excellent at 95, 97, 97, 79, and 99 %, respectively. Dohi et al. showed that the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of M-BLI were also excellent at 93.8%, 91.6%, 92.1%, 78.9%, and 97.7 %, respectively. Furthermore, Ueyama et al. reported that dynamic diagnosis with MV blood flow rate using ME may be useful for the differential diagnosis of EGC and patchy redness. Magnifying endoscopic assessment of dynamic processes within the gastric mucosa is expected to facilitate the diagnosis of EGC.

SYMPOSIUM 9

Mitochondria / Endoplasmic Reticulum and Microcirculation

15:00-16:30 | Room 4

009-SS1

Coronary microcirculation: novel mechanisms and therapeutic targeting

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Microcirculation is a major determinant of coronary heart disease. Timely and complete reperfusion is the most efficient treatment for patients with acute myocardial infarction (AMI). However, the efficacy is limited by myocardial ischemia-reperfusion (MI/R) injury, and the associated microvascular obstruction predicts adverse outcome. Therapeutic targeting of MI/R injury has been largely unsuccessful, necessitating mechanistic insights into coronary microcirculation. We report that prostaglandin E_2, through acting its Gs protein-coupled receptor EP4, protects microcirculation in MI/R injury and that activation of EP4 constrains MI/R injury. Recently, we identified a downstream target—phosphodiesterase subtype 4B (PDE4B), which specifically hydrolyzes intracellular cyclic adenosine monophosphate, as a novel regulator of coronary microcirculation. Genetic deletion or pharmacological inhibition of PDE4B improved cardiac microvascular perfusion and suppressed neutrophil inflammation, preventing heart failure after MI/R injury in mice. PDE4B mediated neutrophil–endothelial cell interaction and protein kinase A-dependent expression of cell adhesion molecules, neutrophil cardiac infiltration, and release of proinflammatory cytokines. Meanwhile, PDE4B promoted coronary microcirculatory obstruction and vascular permeability in MI/R, without affecting flow restriction-induced thrombosis. PDE4B blockade increased flow-mediated vasodilatation and promoted endothelium-dependent dilatation of coronary arteries in a protein kinase A- and nitric oxide-dependent manner. Incubation with sera from patients with AMI impaired acetylcholine-induced relaxations in human coronary micro-arteries, which was abolished by PDE4 inhibition. Similar protection against MI/R-related coronary injury was recapitulated in mice with PDE4B deletion or inhibition, but not with sodium nitroprusside. Microvascular reactivity and inflammation critically regulate microcirculation dysfunction, leading to MI/R injury. Selective inhibition of PDE4B protects against microvascular injury and suppresses inflammation, representing a promising target for cardioprotection in AMI patients designated for reperfusion therapy. The role of aspirin and its interaction with PDE4B and bioactive lipids in coronary microcirculation will also be discussed.

009-SS2

Cardiac mitochondria elongate as a physiological adaptation towards necroptosis

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Background: Cardiovascular disorders remain the main cause of death and disability worldwide. Necroptosis – a form of programmed cell death, has been implicated in various cardiovascular disorders. Nonetheless, the underlying mechanisms involved in cardiac necroptosis, particularly the changes to mitochondrial morphology, remain elusive. We investigated the changes to cardiac mitochondria during the occurrence of nectoptosis and whether manipulating mitochondrial morphology protect against necroptosis.

Methods: The H9c2 cardiac cell was subjected to 50 ng/ml TNF-α and 20 μM zVAD-fmk (zVAD) to induce necroptosis over a 24-hours period. Necroptosis was monitored using lactate-dehydrogenase (LDH)-assay and propidium-iodide (PI)-staining. Mitochondrial morphology was observed using confocal-microscopy whilst the mitochondrial-shaping proteins' levels were detected using qPCR/Western blot (WB). In order to study the association between mitochondrial morphology and necroptosis, pharmacological agents modulating cardiac mitochondrial morphology (Erythropoietin (EPO) and mitochondrial fusion promoter, M1 for fusion; hydrogen peroxide (H_2O_2) and ionomycin for fission) were utilised.

Results: H9c2 cells subjected to TNF-α/zVAD had a LDH-activity of 33±4% and PI-staining of 63±5% vs 2±1% and 4±1%, respectively for non-treated cells. The proportion of cells with elongated mitochondria increased from 8±1% (0 hour) to 23±2% (24 hours) post-TNF/zVAD. The levels of Mfn1 and phosphorylated-Drp1 (Ser-637) were increased as detected by qPCR and WB. Administration of 10 U/ml EPO at 2- and 6-hours post-TNF/zVAD treatment reduced LDH-activity to 24±1% and 27±3%, respectively, versus 45±3% for control cells. Similarly, administration of 10 μM M1 at 2- and 6-hours post-TNF/zVAD treatment reduced LDH-activity to ~31% versus 50±1% for control cells. Fragmenting the cardiac mitochondria using H_2O_2 or ionomycin did not cause any significant reduction to the LDH-activity.

Conclusion: Our data suggests that the cardiac mitochondria elongate via Mfn1 upregulation as a form of physiological adaptation towards necroptosis. Pharmacological modulation of mitochondrial elongation may serve as a novel therapeutic target towards inhibiting necroptosis in the heart.

009-YS1

QiShenYiQi Pills improves retinal microvascular exudation in type 2 diabetic mice through restoration of energy metabolism

Zheng Wang [1], Jing-Yan Han [1], Jian Liu [1]

[1] *Peking University Health Science Center*

Objectives: The conventional treatment for diabetic retinopathy include anti-VEGF drug therapy, laser photocoagulation, surgical removal of the lens, etc. However, all the above therapies have side effects includes retinal hemorrhage, detachment and cataract. Therefore, safe and effective therapy is still needed for diabetic retinopathy. This study aims to investigate the protective effects and possible mechanism of compound Chinese medicine QiShenYiQi (QSYQ) pills on diabetic retinopathy in type 2 diabetic db/db mice.

Methods: 8-week-old male C57BL/6J mice and db/db mice were used in this study. To explore the therapeutic effect of QSYQ, db/db mice were intragastrically administered with physiological saline or QSYQ daily. All the groups were treated for 6 consecutive weeks before sacrificed. H&E staining was used to examine the histology of microvessels in the retina; retinal exudation was observed by FITC-dextran fluorescence; retinal morphology was observed by optical tomography; retinal microvessels and pericyte detachment were observed by PAS staining. Proteinomics was used to reveal the mechanism of the inhibition of retinal microvascular exudation by QSYQ. Western Blot was used to detect the expression of cell junction proteins Claudin-5, Occludin, junction adhesion molecule (JAM-1) and vascular endothelial cadherin (VE-Cadherin).

Results: QSYQ significantly decreased retinal microvascular exudation in the retina of db/db mice as shown by FITC-dextran fluorescence. Besides, QSYQ also significantly decreased the number of retinal acellular blood vessels as shown by PAS staining. Proteinomics study showed that QSYQ significantly restored the expression of proteins related to mitochondrial energy metabolism, fatty acid and glucose metabolism and cytoskeleton. Western blotting demonstrated that QSYQ upregulated the expression of Claudin-5 and Occludin but not JAM-1 and VE-Cadherin in retinal tissue.

Conclusion: QSYQ can inhibit retinal microvascular exudation in type 2 diabetic mice. This effect is probably mediated by upregulation of proteins related to energy metabolism and cytoskeleton, and restoration of the expression of endothelial junction protein Claudin-5 and Occludin.

009-YS2

Role of mitochondrial quality control in cardiac microvascular ischemia/reperfusion injury

Zhou Hao [1]

[1] *Chinese PLA General Hospital*

As reperfusion therapies have become more widely used in acute myocardial infarction patients, ischemia-induced myocardial damage has been markedly reduced, but reperfusion-induced cardiac injury has become increasingly evident. The features of cardiac ischemia–reperfusion (I/R) injury include microvascular perfusion defects, platelet activation and sequential cardiomyocyte death due to additional ischemic events at the reperfusion stage. Microvascular obstruction, defined as a no-reflow phenomenon, determines the infarct zone, myocardial function and peri-operative mortality. Cardiac microvascular endothelial cell injury may occur much earlier and with much greater severity than cardiomyocyte injury. Endothelial cells contain fewer mitochondria than other cardiac cells, and several of the pathological alterations during cardiac microvascular I/R injury involve mitochondria. Mitochondrial quality control (MQC) machineries respond to a broad array of stress stimuli to regulate fission, fusion, mitophagy and biogenesis in mitochondria. Impaired MQC is a cardinal feature of EC injury and dysfunction. Hence, medications modulating MQC mechanisms are considered as promising novel therapeutic options in cardiac microvascular I/R injury. Here, we provide updated insights into the key role of MQC mechanisms in coronary ECs and microvascular dysfunction during I/R injury. We also discussed the option of MQC as a novel therapeutic target to delay, reverse or repair coronary microvascular damage in cardiac reperfusion injury. Contemporary available MQC-targeted therapies with potential clinical benefits to alleviate coronary microvascular injury during MI are also summarized.

SYMPOSIUM 10

Myeloid Cell Interactions in the Tumor Microvasculature

17:40-19:10 | Room 1

010-SS1

Neutrophil trafficking in tumors

Sven Brandau [1]

[1] *University Hospital Essen*

Cancer-related inflammation influences almost all elements of neutrophil biology by tumor-induced or tumor-secreted factors. As a consequence, the production, expansion, recruitment, function and life-cycle of neutrophils is altered in the tumor-bearing host.
Many of these changes are also clinically relevant. This relevance is illustrated by strong correlations between high frequencies of intratumoral neutrophils and poor outcome in the majority of human cancers. Recent high-dimensional analysis of murine neutrophils provides evidence for unexpected plasticity of neutrophils in murine models of cancer and other inflammatory non-malignant diseases. New analysis tools enable deeper insight into the process of neutrophil differentiation and maturation. These technological and scientific developments led to the description of an ever-increasing number of distinct transcriptional states and associated phenotypes in murine models of disease and more recently also in humans. At present, functional validation of these different transcriptional states and potential phenotypes in cancer is lacking. Current functional concepts on neutrophils in cancer rely mainly on the myeloid-derived suppressor cell (MDSC) concept and the dichotomous N1-N2 paradigm. In my presentation I will discuss earlier and more contemporary concepts of neutrophils and MDSC in cancer against the background of our own work.

010-SS2

Galectins in cancer-associated inflammation and thrombosis

Elmina Bach [1]

[1] *Walther Straub Institute for Pharmacology and Toxicology, Ludwig Maximilian University*

Galectins are carbohydrate-binding proteins involved in numerous physiological processes, including immune defense, cell proliferation, and phagocytosis. Cancer is one of the pathological conditions that can alter the gene expression of galectins, and these changes contribute to neoplastic transformation, angiogenesis, or tumor metastasis. During hematogenous metastasis, invasive tumor cells enter the bloodstream, where they can establish physical and functional interactions with platelets, red blood cells, and vascular endothelium. These interactions facilitate the metastatic spread of cancer cells, promoting their survival and proliferation in distant organs. We show that cancer metastasis is significantly influenced by tumor-resident galectins (galectin-3 and galectin-4) that interact with glycoproteins on the surface of platelets and red blood cells. Galectin-3 promotes platelet adhesion and activation by binding to platelet glycoprotein VI, thereby enhancing tumor cell extravasation and subsequent metastasis. In addition, these interactions also contribute to the pro-inflammatory environment of the vasculature and the surrounding tissue, further supporting the invasive and metastatic potential of cancer cells.

010-SS3

Platelet functions in cancer

Monika Haemmerle [1]

[1] *Martin-Luther University Halle-Wittenberg, Institute of Pathology*

Platelets are anucleate blood cells derived from megakaryocytes. Besides their function in limiting blood loss and promoting wound healing, experimental evidence has highlighted platelets as active players in all steps of tumorigenesis including tumor growth, tumor cell extravasation and metastasis. Additionally, thrombocytosis is

associated with adverse patient survival in cancer. Correlations between high platelet counts and shorter disease-specific survival are often described for lung, colon, breast, pancreatic, kidney and gynecologic cancers. Due to the secretion of large amounts of microparticles and exosomes as well as growth factors, platelets are well positioned to coordinate both local and distant tumor-host crosstalk. Moreover, tumor-educated platelets might be an important source for liquid biopsy in cancer patients.

010-SS4

Platelets misguide immune cell responses in cancer

Bernd Uhl [1,2], Johanna Schaubaecher [1,2], Florian Haring [1,2], Bojan Smiljanov [1,2], Katja Steiger [4], Simone Ballke [4], Joshua Luft [1,2], Vera Schneewind [1,2], Jonas Hildinger [1,2], Martin Canis [2], Laura Mittmann [1,2], Constanze Braun [1,2], Gabriele Zuchtriegel [1,2], Wilko Weichert [4], Kirsten Lauber [3], Christoph Reichel [1,2]

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[4] Department of Pathology, Technical University Munich, Munich, Germany

Platelets are increasingly recognized to contribute to the pathogenesis of malignant tumors in addition to their essential role in hemostasis and inflammation. Reciprocal interactions with platelets are well-known to support the extravasation of immune cells to the perivascular tissue under inflammatory conditions. The role of platelets for the regulation of immune cell responses in malignant tumors, however, is still elusive. Employing advanced *in vivo* microscopy techniques in different animal models of cancer, various *ex vivo* as well as *in vitro* assays, and human data, we sought to define the functional relevance of microvascular platelet-leukocyte interactions in cancer.

Here, we report that the presence of platelets in the cancer microvasculature relates to pro-tumorigenic immune cell activity and impaired survival. Mechanistically, tumor-released molecules attract platelets into the tumor microvasculature where these cell fragments deliver specific pro-inflammatory and anti-inflammatory molecules. This concomitantly promotes pro-tumorigenic leukocyte responses thus supporting tumor growth. Interference with platelet-leukocyte interactions reduced pro-tumorigenic immune cell infiltration and suppressed tumor progression.

Hence, our data uncover a mechanism of malignant tumors utilizing platelets to induce pro-tumorigenic immune cell responses. Targeting this aberrant multicellular interplay might represent a novel immunotherapeutic strategy in cancer.

010-YS1

A transcriptomic pan-cancer signature for survival prognostication and prediction of immunotherapy response based on endothelial senescence

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Background: The microvascular endothelium inherently controls nutrient delivery, oxygen supply, and immune surveillance of malignant tumors, thus representing both biological prerequisite and therapeutic vulnerability in cancer. Recently, cellular senescence emerged as a fundamental characteristic of solid malignancies. In particular, tumor endothelial cells have been reported to acquire a senescence-associated secretory phenotype, which is characterized by a pro-inflammatory transcriptional program, eventually promoting tumor growth and formation of distant metastases. We therefore hypothesize that senescence of tumor endothelial cells (TEC) represents a promising target for survival prognostication and prediction of immunotherapy efficacy in precision oncology.

Methods: Published single-cell RNA sequencing datasets of different cancer entities were analyzed for cell-specific senescence, before generating a pan-cancer endothelial senescence-related transcriptomic signature termed EC.SENESCENCE.SIG. Utilizing this signature, machine learning algorithms were employed to construct survival prognostication and immunotherapy response prediction models. Machine learning-based feature selection algorithms were applied to select key genes as prognostic biomarkers.

Results: Our analyses in published transcriptomic datasets indicate that in a variety of cancers, endothelial cells exhibit the highest cellular senescence as compared to tumor cells or other cells in the vascular compartment of malignant tumors. Based on these findings, we developed a TEC-associated, senescence-related transcriptomic signature (EC.SENESCENCE.SIG) that positively correlates with pro-tumorigenic signaling, tumor-promoting dysbalance of immune cell responses, and impaired patient survival across multiple cancer entities. Combining clinical patient data with a risk score computed from EC.SENESCENCE.SIG, a nomogram model was constructed that enhanced the accuracy of clinical survival prognostication. Towards clinical application, we identified three genes as pan-cancer biomarkers for survival probability estimation. As therapeutic perspective, a machine learning model constructed on EC.SENESCENCE.SIG provided superior pan-cancer prediction for immunotherapy response than previously published transcriptomic models.

Conclusions: We here established a pan-cancer transcriptomic signature for survival prognostication and prediction of immunotherapy response based on endothelial senescence.

SYMPOSIUM 11

Glial Regulation of Cerebral Blood Flow Responses

17:40-19:10 | Room 2

011-SS1

Astrocyte regulation of the microvasculature in health and disease

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Astrocytes are important mediators of neurovascular coupling—the process by which active brain regions increase their local blood flow. Reduced neurovascular coupling is reported in several neurological disorders, including after ischemic stroke and in dementia, a condition often comorbid with stroke. We find that experimental stroke results in a decrease in neurovascular coupling. Importantly, this decrease occurs in intact cortical regions outside the stroke infarct, which are typically considered clinically asymptomatic. Our results indicate that altered signaling from reactive astrocytes may underlie this deficit in neurovascular coupling. Targeting astrocyte-dependent NVC pathways may be a viable therapeutic intervention to restore healthy cerebrovascular regulation post-stroke and, thus, prevent cognitive decline.

011-YS1

Reduced microvascular reactivity after stroke: the role of reactive astrocytes

Ákos Menyhárt [1,2], Réka Tóth [1,2], Rita Frank [1,2], Ferenc Bari [3], Eszter Farkas [1,2]

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Reactive astrogliosis is the pathological activation of astrocytes in response to the injury of nearby neurons in cerebrovascular diseases. In acute ischemic stroke (AIS), ATP deprivation triggers the malignant swelling of astrocytes that temporally precedes the evolution of reactive gliosis. Swollen astroglia emerge as a target of intervention because their K^+ and glutamate clearance mechanisms are impaired, thus they create a hyperexcitable environment to the vulnerable neurons. We demonstrate in rodents that glial swelling predisposes neurons to secondary pathological phenomena such as spreading depolarizations (SDs) that reduce cerebral blood flow (CBF) and cause perfusion deficit after AIS. We also show in anesthetized mice that reactive astrogliosis is accompanied by the decline of neurovascular coupling 3 days after AIS. Consequently, counteracting glial swelling by specific aquaporin-4 channel (AQP-4) blockade attenuates the SD-caused perfusion deficit, reduces reactive gliosis, and improves NVC 3 days after AIS. We confirm in rat brain slices exposed to osmotic stress, that swollen astrocytes display similar phenotypic alterations to reactive astrocytes. Furthermore, the blockade of AQP-4 channels and Na+/K+/Cl- co-transporters mitigates swelling and SD occurrence *in vitro*. Finally, we show in the mouse water intoxication model of cytotoxic edema that astrocyte swelling is associated with altered astrocyte calcium waves that co-exist with SD evolution and profound vasoconstriction. Our results emphasize the need of glia- specific pharmacological manipulations that attenuate the chronic activation of astrocytes and improve cerebrovascular outcome after AIS.

011-YS2

A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation

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Endothelial hyperpermeability exacerbates multiple organ damage during inflammation or infection. The endothelial glycocalyx, a protective matrix covering the luminal surface of endothelial cells (ECs), undergoes enzymatic shedding during inflammation, contributing to barrier hyperpermeability. A disintegrin and metalloproteinase 15 (ADAM15) is a sheddase capable of cleaving the ectodomains of membrane-bound molecules. Here, we tested whether and how ADAM15 is involved in glycocalyx shedding and vascular leakage during sepsis. Dextran-150kD exclusion assay revealed lipopolysaccharide (LPS) significantly reduced glycocalyx thickness in mouse cremaster microvessels. Consistently, shedding products of glycocalyx constituents, including CD44 ectodomain, were detected with an increased plasma level after cecal ligation and puncture (CLP)-induced sepsis. The direct effects of CD44 ectodomain on endothelial barrier function were evaluated, which revealed CD44 ectodomain dose-dependently reduced transendothelial electric resistance (TER) and caused cell-cell adherens junction disorganization. Furthermore, we examined the role of ADAM15 in CD44 cleavage and glycocalyx shedding. An *in vitro* cleavage assay coupled with liquid chromatography-tandem mass spectrometry confirmed ADAM15 cleaved CD44 at His^{235}-Thr^{236} bond. In ECs with ADAM15 knockdown, LPS-induced CD44 cleavage and TER reduction were greatly attenuated, whereas, ADAM15 overexpression exacerbated CD44 cleavage and TER response to LPS. Consistently, ADAM15 knockout in mice attenuated CLP-induced increase in plasma CD44. Intravital and electron microscopic images revealed ADAM15 deficiency prevented LPS-induced glycocalyx injury in cremaster and pulmonary microvasculatures. Functionally, $ADAM15^{-/-}$ mice with better-preserved glycocalyx exhibited resistance to LPS-induced vascular leakage, as evidenced by reduced albumin extravasation in pulmonary and mesenteric vessels. Importantly, in intact, functionally vital human lungs, perfusion of LPS induced a significant up-regulation of ADAM15, accompanied by elevated CD44 in the effluent and increased vascular permeability to albumin. Together, our data support the critical role of ADAM15 in mediating vascular barrier dysfunction during inflammation. Its mechanisms of action involve CD44 shedding and endothelial glycocalyx injury.

011-SS2

Microglia influence cerebral blood flow via direct and indirect purinergic actions

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Microglia are the main immune cells in the CNS parenchyma with roles extending beyond immunological functions. Microglial activity is altered in common brain diseases, but the mechanisms through which microglia contribute to the maintenance of normal brain function and impact on common neurological disorders are not well understood. We have recently identified novel forms of microglia-vascular and microglia-neuron interactions that possess specialized nanoarchitecture and molecular machinery optimized for purinergic signaling. Microglia form direct contacts with cells of the neurovascular unit, including endothelial cells, pericytes, smooth muscle cells, astrocytes and neurons. Microglial contacts with neuronal somata – termed somatic purinergic junctions - and endothelial cells are formed in the vicinity of mitochondria and are dependent on microglial P2Y12 receptor-mediated actions. We show that microglia shape cerebrovascular responses via compartment-specific purinergic actions, modulating hypcapnia-induced vasodilation, neurovascular

coupling and hypoperfusion. These actions also involve microglial adenosine production, are partially independent of nitric oxide, while the absence of microglia reduces brain pH. Cells of the neurovascular unit produce different purinergic metabolites in a stimulus-dependent manner that are sensed by microglial receptors. These results suggest that motile microglial processes exert fine-tuned actions to influence neurovascular responses via diverse purinergic mechanisms. Understanding these interactions is likely to help the identification of novel therapeutic targets in common neurological disorders.

SYMPOSIUM 12

Molecules Going with the Flow: Physiology and Disease

17:40-19:10 | Room 4

012-SS1

Flow-induced release of multifunction molecules from the endothelium: from fish to humans

Akos Koller [1]

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By ~1980, it was thought that the major mechanisms regulating vascular tone are already known. However, after a somewhat serendipity discovery that endothelium is involved in mediation of vasorelaxation to acetylcholine, a whole new world opened up forcing us to rewriting our concept regarding the regulation of vasomotor tone, vascular function and reveal the physiological and pathophysiological multifunctional roles of these mediator molecules. Several new endothelium-derived mediators were discovered and/or recognized: nitric oxide, metabolites of arachidonic acid (dilator prostaglandins, thromboxane A2, leukotrienes and 20-hydroxyeicosatetraenoic acid (20-HETE), etc.), and endothelial hyperpolarizing factor(s), the nature of which it still debated.

Perhaps more importantly it was discovered that one of the primarily physiological stimuli of the release of these mediators is related to the blood flow itself, more precisely to changes in wall shear stress (when flow increases in the presence of constant diameter). Such condition can happen in the early phase of physical exercise, providing a positive feedback mechanism, which increases blood flow to the heart and skeletal muscle.

Importantly and contrary this “flow sensitive” mechanism via release of 20-HETE acting on TP receptors, contribute to the autoregulation of cerebral blood flow, by eliciting constriction of small cerebral arteries providing and additional power to the myogenic mechanism to limit the increase in cerebral blood flow in the space limited rigid cranium-capsuled brain. In addition, these mediators play roles, not only in arterial. but venous, and lymphatic vessels.

Comparative physiological studies shown that the so called later line of fish is a flow-sensor enabling them to collect information from the surrounding water environment, a great significance in surviving hunting and in general communication underwater.

The human importance of the flow sensitive mechanisms is shown that in hypertension, diabetes and other cardiovascular diseases flow-dilation is impaired, whereas the reduced flow-constriction of cerebral arterial vessels can lead to stroke and microbleeds, and vascular dementia.

Interestingly these endothelium-derived mediators play many other important roles, for example in vascular growth and remodeling, modulation of cellular metabolism and even neural and immune function.

Many roles of these mediators have been shown, not only in experimental studies but in human investigations as well, underlying their translational importance.

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012-SS2

The Pathogenic Role of Cytokine-like Protein FAM3D in Vascular Injury

Yi Fu [1]

[1] *Peking University Health Science Center*

Current anti-hypertensive options still incompletely control blood pressure, suggesting the existence of uncovered pathogenic mechanisms. Here, whether cytokine-like protein FAM3D is involved in hypertension etiology is evaluated. A case-control study exhibits that FAM3D is elevated in hypertensive patients, with a positive association with odds of hypertension. FAM3D deficiency significantly ameliorates angiotensin II (AngII)-induced hypertension in mice. Mechanistically, FAM3D directly causes eNOS uncoupling and impairs endothelium-dependent vasorelaxation, whereas 2,4-diamino-6-hydroxypyrimidine to induce eNOS uncoupling abolishes the protective effect of FAM3D deficiency against AngII-induced hypertension. Furthermore, antagonism of formyl peptide receptor 1 (FPR1) and FPR2 or the suppression of oxidative stress blunts FAM3D-induced eNOS uncoupling. Translationally, targeting endothelial FAM3D by adeno-associated virus or intraperitoneal injection of FAM3D-neutralizing antibodies markedly ameliorates AngII- or DOCA-salt-induced hypertension. Conclusively, FAM3D causes eNOS uncoupling through FPR1- and FPR2-mediated oxidative stress, thereby exacerbating the development of hypertension. FAM3D may be a potential therapeutic target for hypertension.

012-SS3

Permissive role of angiotensin II in the mediation of flow-induced responses

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It is well accepted that increased activation of renin-angiotensin system is related to increased arterial blood pressure due to its various effects on cardiovascular system. However, a number of data suggest, rather controversial that physiological circulatory levels of angiotensin II (ANGII) are crucial in maintaining various vasodilator responses in microcirculation, via its interaction with AT1 receptors (AT1R). Furthermore, suppression circulatory levels of ANGII, such as with high salt diet leads to impaired or attenuated endothelium-dependent vasodilation in many vascular beds. In several subsequent studies we have aimed to elucidate the role of ANGII and AT1R in the mechanisms of flow-induced dilation (FID) in middle cerebral arteries (MCA) and incidence of oxidative stress at the functional, cellular and molecular level in the cerebral vasculature and in the serum of Sprague-Dawley (SD) rats.

For this purpose, eleven-week old, male SD rats were randomly assigned to control group (CTRL, 0.4% NaCl in rat chow); Losartan group (rats on a standard diet given the AT1R blocker losartan (1 mg/mL) in drinking water); high salt (HS) group (7 days 4% NaCl in rat chow) or HS+ANGII group (7 days HS with 3 days ANGII administration via osmotic minipumps (100 ng/kg/min on days 4–7)). To investigate the mechanisms of FID in MCA, FID was determined in absence/presence of the NOS inhibitor L-NAME, the non-selective cyclooxygenases inhibitor indomethacin, and the superoxide dismutase mimetic TEMPOL. Gene and protein expression of enzymes involved in FID mechanisms and antioxidative enzymes were determined by RT-qPCR and Western blot. Vascular NO and superoxide/ROS levels were assessed by direct fluorescence in MCA subjected to no-flow and flow conditions. Serum systemic oxidative stress parameters was measured by spectrophotometry. All experimental procedures conformed to the EU Directive 2010/63/EU.

The results of the studies demonstrated that HS diet or AT1R blockade impaired FID and increased oxidative stress of MCA. Supplementation of ANGII to physiological levels restored the mechanisms of FID in MCA of rats fed HS diet to the ones present in CTRL rats without affecting arterial blood pressure. ANGII restoration decreased systemic oxidative stress and decreased superoxide/ROS levels and increased NO bioavailability in the vascular wall of HS treated rats, by modulation antioxidative enzyme expression. The AT1R blockade resulted in significantly attenuated endothelium-dependent dilation, changed mechanisms of FID, increased vascular and systemic oxidative stress and decreased expression/ activity of antioxidative enzymes.

All of these findings support the conclusion that ANGII is crucial in the preservation of vascular oxidative stress-antioxidant system balance and via AT1R, in maintenance of physiological vasodilation mechanisms of MCA. Suppression of ANGII is a key link between HS intake and development of endothelial dysfunction, and impaired regulation of flow-induced responses.

SYMPOSIUM 13

Atherosclerosis, Sex and Microcirculation: The Influence of Hemodynamics

17:40-19:10 | Room 5

013-SS1

Microvascular endothelial dysfunction in skin is associated with higher risk of heart failure with preserved ejection fraction in women with type 2 diabetes: the Hoorn Diabetes Care System Cohort

Elisa Dal Canto [1], Luca Van Deursen [2], Anna Hoek [2], Petra Elders [2], Hester Den Ruijter [1], Jolanda Van deer Velden [2], Vanessa Van Empel [3], Etto Eringa [2,3], Joline Beulens [2]

[1] *University Medical Center Utrecht*
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[3] *Maastricht University Medical Center*

Background: To investigate if presence and degree of microvascular dysfunction (MVD) in skin relates to markers of left ventricular diastolic dysfunction (LVDD) and risk of heart failure with preserved ejection fraction (HFpEF) in adults with type 2 diabetes, and whether sex modifies this association.
Methods: We recruited 154 participants (50% women) from the Hoorn Diabetes Care System Cohort, a prospective cohort study, for in vivo evaluation of skin MVD, echocardiography and blood sampling. MVD was assessed by laser speckle contrast analysis combined with iontophoresis of insulin, acetylcholine and sodium nitroprusside (SNP). We performed a cross-sectional analysis of the association between perfusion responses to each substance and echocardiographic markers of LVDD and the H2FPEF score by multivariable linear regression analysis adjusted for confounders. Sex was assessed as an effect modifier and the analysis was stratified by sex.
Results: Mean age was 67±6y, mean HbA1c 7.6±1.3%. Women were more frequently obese (54.5 vs 35.1%), had higher NT-proBNP plasma levels (80, IQR: 34-165 vs 46, 27-117 pg/ml) and higher E/E' (13.3±4.3 vs 11.4±3.0) than men. We found that a lower perfusion response to insulin and acetylcholine was associated with a higher HFpEF risk in women, but not men (10% decreased perfusion response was associated with 5.8% [95% confidence interval: 2.3.9.4] and 5.9% [1.7;10.1] increase of the H2FPEF score, respectively). A lower perfusion response to SNP was associated with higher estimated pulmonary arterial systolic pressure in men while a lower perfusion response to acetylcholine associated with higher LV mass index in women and with a lower LV longitudinal strain in the total population.
Conclusions/interpretation: Impaired microvascular responses to insulin and acetylcholine in skin confers a higher risk of HFpEF in women with type 2 diabetes. In vivo measures of systemic MVD could represent novel risk markers for HFpEF, opening new avenues for the prevention of HFpEF in type 2 diabetes.

013-SS2

Metabolism and vascular function

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Metabolism, which people are familiar with, is divided into sugar and lipid metabolism, energy metabolism, etc. The content of metabolic products in the body varies greatly, and the difference in content between two metabolites can exceed a thousand times. The types of metabolic products even exceed the types of proteins. Although metabolic products have the same molecular weight, their structures may be completely different. How to find important pathways for cardiovascular and cerebrovascular diseases in the complex metabolic products that can become drug targets in the future is our opportunity and challenge.
Metabolomics is powerful, but the types of metabolites found are thousands, and it is challenging to find metabolites that play an important role in disease. Because these metabolites have a small molecular weight and are endogenous, their metabolic rate is much faster than protein production, and traditional biotechnology is difficult to study cell metabolism and related pathways. Since human vascular tissue is difficult to obtain, we can only explore from the blood of thousands of patients through mass spectrometry, bioinformatics, and the patient's disease process. We found that the level of succinic acid in the plasma of acute aortic dissection (AAD) patients was specifically elevated and could be distinguished from acute myocardial infarction and pulmonary arterial hypertension patients with similar chest pain symptoms. Mechanistically, the level of succinic acid is regulated by the p38α-CREB-OGDH axis in macrophages, and macrophage-specific knockout of p38α can reduce succinic acid and alleviate the progression of AAD. The relevant results were published in top international cardiovascular journals and received peer reviews from the journal. In addition, we further discovered changes in metabolic components in abdominal aortic aneurysm (AAA) and AAD diseases, especially changes in metabolic components in smooth muscle cells. We found that the intake of putrescine can promote the occurrence and development of AAA. This process is regulated by GSDMD in smooth muscle cells but is not related to pyroptosis. Instead, it causes phenotypic transformation of smooth muscle cells through endoplasmic reticulum stress-related pathways, transforming into a more secretory smooth muscle cell, which exacerbates AAD. We revealed a new mechanism by which metabolic products affect vascular function, discovered new pathogenic principles for certain metabolic products, and expanded the pathogenic theory of metabolic products. Based on these findings, we were invited to write a review on the metabolic mechanism in aortic aneurysms in Signal Transduction and Targeted Therapy.
In addition, we included 1250 unruptured intracranial aneurysms (UIA) patients receiving conservative treatment from 27 regional medical centers across the country and followed up for 7 years, revealing that oleic acid, arachidonic acid, IL-1β and TNF-α are biomarkers for UIA instability in the Chinese population and proposed the first classification model that can be used to assess the natural history of UIA. We proposed a new method for assessing the risk of growth and rupture of intracranial aneurysms and revealed that regulating metabolism and cytokines may be a new direction for delaying intracranial aneurysm rupture. The relevant research results can help clinicians carry out UIA instability risk assessment and are expected to guide UIA stratified management and decision-making for preventive surgical treatment, improving clinicians' and scientists' understanding of the pathological characteristics of intracranial aneurysms in the Chinese population.
Continuing to explore new mechanisms by which metabolic products affect vascular function and expanding the pathogenic theory of metabolic products is an important direction of our research.

013-YS1

Sex-related differences in hemodynamics and atherosclerosis

Jolanda Wentzel [1], Michail Papaflakis [3], Antonios Antoniadis [2], Peter Stone [2]

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Atherosclerosis manifests itself differently in women compared to men, regarding atherosclerotic plaque composition and rupture risk. Plaques derived from women exhibit predominantly fibrous, more stable characteristics, whereas in men plaques are more often lipid rich and present with vulnerable plaque characteristics. These sex-related differences in plaque composition directly link to the risk of cardiovascular events in men and women. Interestingly, culprit lesions do not show much differenes among men and women. Moreover, women present more often, compared to men, with non-obstructive

coronary artery disease because of microvasculature abnormalities leading to ischemia or myocardial infarction.
Another factor that is gaining interest, is the blood flow induced shear stress of the blood at the vessel wall. The shear stress is a very small frictional force of the blood flow at the vessel wall, but nevertheless the endothelial cell are very sensitive to it. Thereby shear stress influences the function of the endothelial cells. At low shear stress locations plaques are initiated and plaque progression is most often observed. The question is whether sex-related differences in prevalence of atherosclerosis can be traced back to differences in shear stress distribution in coronary and carotid arteries in men and women.
During this presentation I will give an overview of the existing knowledge on sex-related differences in plaque composition in coronary and carotid arteries of patients as can be assessed with the different invasive and non-invasive imaging modalities and the shear stress related plaque growth.

013-YS2

Deletion of BACH1 Attenuates Atherosclerosis by Reducing Endothelial Inflammation

Mengping Jia [1], Qinhan Li [1], Jieyu Guo [1], Siyu Ma [1], Xiangxiang Wei [1], Xiuling Zhi [1], Osto Elena [2], Xinhong Wang [1], Dan Meng [1]

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[2] *University of Zurich and University Hospital Zurich Institute of Clinical Chemistry*

Background: The transcription factor BACH1 (BTB and CNC homology 1) suppressed endothelial cells (ECs) proliferation and migration and impaired angiogenesis in the ischemic hindlimbs of adult mice. However, the role and underlying mechanisms of BACH1 in atherosclerosis remain unclear.
Methods: Mouse models of atherosclerosis in endothelial cell (EC)-specific-Bach1 knockout mice were used to study the role of BACH1 in the regulation of atherogenesis and the underlying mechanisms.
Results: Genetic analyses revealed that coronary artery disease-associated risk variant rs2832227 was associated with BACH1 gene expression in carotid plaques from patients. BACH1 was upregulated in ECs of human and mouse atherosclerotic plaques. Endothelial Bach1 deficiency decreased turbulent blood flow- or western diet-induced atherosclerotic lesions, macrophage content in plaques, expression of endothelial adhesion molecules (ICAM1 [intercellular cell adhesion molecule-1] and VCAM1 [vascular cell adhesion molecule-1]), and reduced plasma TNF-α (tumor necrosis factor-α) and IL-1β levels in atherosclerotic mice. BACH1 deletion or knockdown inhibited monocyte–endothelial adhesion and reduced oscillatory shear stress or TNF-α-mediated induction of endothelial adhesion molecules and/or proinflammatory cytokines in mouse ECs, human umbilical vein ECs, and human aortic ECs. Mechanistic studies showed that upon oscillatory shear stress or TNF-α stimulation, BACH1 and YAP (yes-associated protein) were induced and translocated into the nucleus in ECs. BACH1 upregulated YAP expression by binding to the YAP promoter. BACH1 formed a complex with YAP inducing the transcription of adhesion molecules. YAP overexpression in ECs counteracted the antiatherosclerotic effect mediated by Bach1-deletion in mice. Rosuvastatin inhibited BACH1 expression by upregulating microRNA let-7a in ECs, and decreased Bach1 expression in the vascular endothelium of hyperlipidemic mice. BACH1 was colocalized with YAP, and the expression of BACH1 was positively correlated with YAP and proinflammatory genes, as well as adhesion molecules in human atherosclerotic plaques.
Conclusions: These data identify BACH1 as a mechanosensor of hemodynamic stress and reveal that the BACH1-YAP transcriptional network is essential to vascular inflammation and atherogenesis. BACH1 shows potential as a novel therapeutic target in atherosclerosis.

SYMPOSIUM 14

Aquaporins

17:40-19:10 | Room 6

014-SS1

Soluble (pro)renin receptor as a new regulator of collecting duct water reabsorption

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The (pro)renin receptor (PRR), also termed as ATPase H^+ transporting accessory protein 2 (ATP6AP2), was originally cloned as a specific receptor for prorenin and renin [together called (pro)renin]. Given the wide tissue distribution of PRR, PRR was further postulated to act as a regulator of tissue renin. The extracellular domain of PRR is cleaved by proteases to generate soluble PRR (sPRR), which is widely considered as a non-selective biomarker multiple human diseases including diabetes, hypertension, kidney disease, etc. Within the kidney PRR is predominantly expressed in the collecting duct intercalated cells (ICs). In 2016, we for the first time reported that sPRR exerted a biological function in upregulation of aquaporin-2 expression in CD cells via activation of β-catenin signaling and enhancement of urine concentrating capability. In 2017, site-1 protease was reported to be the predominant protease for generation of sPRR by our group and others. We further proposed that within the CD sPRR acts as a paracrine factor to mediate the communication between the IC and the principal cells (PCs) to fine-tune water excretion. In the current presentation, I will review major advances in the field concerning the function of PRR/sPRR axis in regulation of kidney function, particularly urine concentrating capability.

014-SS2

Pathological roles of aquaporin-4 in neurodegenerative disorders

Masato Yasui [1]

[1] *Pharmacology*

Aquaporin-4 (AQP4) is a main water channel protein in the mammalian brain and is distributed with highest density in the perivascular and subpial astrocyte end-feet. AQP4 is a critical component of an integrated water dynamics in the brain. Indeed, AQP4 has been shown to play an important role in brain lymphatic system referred to as “Glymphatic system”. AQP4 was also identified as a target antigen of autoimmune attack in neuromyelitis optica (NMO). We have established several NMO-animal models to elucidate pathological mechanisms of NMO and to develop a new therapy. We also demonstrated that AQP4 deficiency facilitates the progression of Alzheimer disease using mouse models. AQP4, therefore, can be a potential therapeutic target in several neurological conditions.

014-YS1

Physiological roles of aquaporin-3 as glycerol channel

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Aquaporins (AQP), are a family of membrane channel proteins that facilitate the transmembrane diffusion of water and small, non-charged solutes such as glycerol and urea by osmosis or solute gradient. The abnormalities observed in mice lacking AQP provide direct evidence for the physiological importance of AQPs. AQP3, as an aquaglyceroporin, is present in different types of cells in the kidney, skin, and reproductive system. Mice lacking AQP1 or AQP3 exhibit symptoms of diabetes insipidus. In addition, the absence of AQP3 leads to dry skin in mice. To better describe this defect, we generated AQP3 knock-out (AQP3 KO) mice and knock-in mice expressing AQP4 (AQP4 KI) *in situ.* By utilizing the characteristic of AQP4 being

permeable to water only, not other small molecular solutes, our aim is to study the impact of AQP3 on urea and glycerol permeation, as well as its physiological role in different organs. In the basal state, we observed that the knock-out of AQP3 in mice lead to renal tubule dilation and abnormal urine concentration. Interestingly, in AQP4 KI mice, these phenomena were reversed. Specifically, the renal tubule dilation was reduced, urine concentration capacity was restored, urine volume decreases, urine osmolality increases, and urine urea concentration rises. However, we have not observed significant difference in non-urea solute concentrations between different genotypes. Subsequently, we conducted acute urea loading tests and high-protein diet experiments to further stimulate the production and excretion of urea in mice. These experiments aimed to investigate in more depth the role of AQP3 and AQP4 in urea metabolism and renal function. The experimental results demonstrate that both urea loading and high-protein diet had little impact on urine osmolality and urinary urea concentration in AQP3 KO mice. Meanwhile, the urine osmolality and urinary urea concentration in AQP4 KI mice were altered by exogenous administration of urea. Therefore, our data indicates that the absence of AQP3 prevents urea accumulation in the kidneys, leading to the disruption of urine concentration mechanism. The knock-in of AQP4 can restore normal water channel function and help to regulate the balance of water and urea in urine. The water permeability, other than glycerol or urea permaeability, of AQP3 plays important role in urine concentrating mechanism.

014-YS2

KLF5-mediated aquaporin 3 activated autophagy to facilitate cisplatin resistance of gastric cancer

Xudong Dai [2], Yong Chen [1], Ning Chen [1], Jin Dou [1], Haiwen Zhuang [1], Jian Wang [1], Xin Zhao [1], Xiaoyu Zhang [1], Haijian Zhao [1]

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Background: Resistance to chemotherapeutic drugs limits the control of gastric cancer (GC) development. The study intended to probe into the mechanism of aquaporin 3 (AQP3) on the chemoresistance of GC.
Methods: Cisplatin (CDDP)-resistant cells were constructed. Parental AGS and HGC-27 cells and their respective CDDP-resistant cells were transfected with AQP3 overexpression plasmid, AQP3 short hairpin RNA (sh-AQP3) and sh-Kruppel-like factor 5 (shKLF5). The expressions of AQP3 and factors related to autophagy (LC3 I, LC3 II, Atg5, Beclin-1, p62)/epithelial-mesenchymal transition (EMT; E-cadherin and snail) were assessed by Western blot and qRT-PCR. Cell counting kit-8 assay was adopted to test cell viability and half maximal inhibitory concentration (IC 50) was determined. Transwell assay was used for the examination of cell migration and invasion. The regulatory relationship of AQP3 and KLF5 was tested by chromatin immunoprecipitation (ChIP) and dual luciferase reporter assays.
Results: AQP3 was highly-expressed in GC cells and its level was even higher in CDDP-resistant GC cells. AQP3 silencing inhibited viability, autophagy and EMT in CDDP-resistant GC cells, while AQP3 overexpression had the opposite effect. KLF5 positively modulated AQP3 in GC cells resistant to CDDP. KLF5 knockdown reversed AQP3-induced autophagy, viability, migration, invasion and EMT in CDDP-resistant GC cells.
Conclusion: KLF5-modulated AQP3 activated autophagy to facilitate the resistance of GC to CDDP.

SATELLITE SYMPOSIUM 3

Microvascular Network Modeling and Visualization

08:30-10:00 | Guorui Hall

S03-1

Recent Advances in Tumor Microcirculation Visualization and Its Applications in Cancer Research

Meng Yang [1]

[1] *AntiCancer PDOX, LLC*

An increasing body of evidence reveals that tumor microcirculation, characterized by multiple structural and functional abnormalities, plays a crucial role as an integral part of the tumor microenvironment. It supports tumor development and metastasis while negatively impacting treatment outcomes through direct and indirect mechanisms. Therefore, the study of tumor microcirculation, including the morphology, network structures, and functionality of tumor blood vessels, as well as their response to different treatments and the relevant mechanisms, represents an important and active field of biological research.

We have utilized fluorescence molecular imaging technology to conduct a series of visualized, qualitative, and quantitative explorations and studies on tumor angiogenesis and tumor microcirculation at the molecular and cellular levels in intact living organisms. This report aims to provide a detailed introduction to the recent developments in tumor microcirculation research using fluorescence molecular imaging and its applications in cancer research.

S03-2

Modelling Microcirculation System – From Structure to Function

Gangmin Ning [1,2]

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[2] *Research Center for Healthcare Data Science, Zhejiang Lab, China*

Microcirculation is the terminal of the cardiovascular system. It plays an essential role in maintaining the physiological function of living bodies, responsible for facilitating the exchange of substances between tissues and blood. The microcirculation is composed of a complex network comprised of arterioles, veins, capillaries and their interconnections. Presently, it lacks methods for investigating the features of microcirculation network and in practice only a limited number of vascular bifurcations can be observed. Addressing the challenges, a computational model was developed to reconstruct the complete network using data derived from vascular branches, meanwhile analytical methods were proposed to explore the characteristics of the microcirculation network. With animal experimental data, the model was applied in the analysis of microcirculation network, and its structural as well as functional patterns were discovered.

S03-3

Quantitative microvascular angiography and blood flowmetry by optical speckle imaging

Ruolan Li [1,2], Minghui Ma [1,2], Jinling Lu [1,2,3], Pengcheng Li [1,2,3]

[1] *Britton Chance Center and MoE Key Laboratory of Biomedical Photonics, Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology, Wuhan, China*
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[3] *School of Biomedical Engineering, Hainan University, Haikou, China*

Laser speckle contrast imaging is widely used for mapping the spatio-temporal dynamics of blood flow perfusion in vivo, but suffers from a superficial imaging depth and the difficulty in resolving microvascular. Although transmissive imaging can significantly improve both detecting depth and resolution, the ballistic photons directly transmitting forward through tissue without scattering may cause significant error in estimating the decorrelation time of scattered light related to blood flow speed when using a traditional theoretical model of laser speckle contrast imaging. In this paper, we developed a model of temporal laser speckle contrast imaging accounting for the effect of nonscattered light on estimating decorrelation time. Based on this model, a long-short exposure temporal laser speckle imaging method was proposed for simultaneously imaging the angiography and blood flowmetry at microvessels level. Blood-intralipid phantom and in vivo animal experiments demonstrated the potential of this new transmissive laser speckle imaging method for investigating the dynamics of morphology and blood flow speed with high resolution by a simple label-free wide-field imaging modality.

S03-4

Pulsatile Hemodynamics in the Microvascular Networks – Insights from Computational Approaches

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[2] *Department of Biomedical Engineering, Zhejiang University*

The conventional understanding of blood flow in the microcirculation simplifies it as a steady-state process. However, it is crucial to recognize that pulsatility is prevalent in the microcirculation and carries significant physiological implications for microvascular functions. While observing pulsatile hemodynamics in individual microvessels through animal experiments or human tissue is feasible, analyzing the distribution and variations of pulsatility patterns in the microvascular networks has proven challenging. This limitation hampers our comprehension of the physiological roles of pulsatility in the microcirculation. To tackle this challenge, researchers have developed theoretical models that account for pulsatile hemodynamics in the microcirculation. These models have the capability to simulate pulsatile hemodynamics in actual microvascular networks derived from animal experiments. Moreover, they enable the analysis of hemodynamic parameters in each individual vessel, thereby facilitating the examination of pulsatility damping patterns, pulse wave propagation, and the regulatory effects of vasodilators such as nitric oxide. Employing this approach contributes significantly to our understanding of pulsatile mechanical forces and their influence on physiological regulation within the microcirculation.

SATELLITE SYMPOSIUM 4

Hemoglobin-Based Oxygen Carrier and Microcirculation

10:00-11:30 | Guorui Hall

S04-1

Polymerized human hemoglobin enhanced tumor oxygenation: A novel strategy for cancer therapy

Jiaxin Liu [1]

[1] *Institute of Blood Transfusion, Chinese Academy of Medical Sciences & Peking Union Medical College*

Polymerized human hemoglobin as a kind of Hemoglobin based oxygen carriers (HBOCs), is a class of modified products of human hemoglobin. Similar to normal red blood cells (RBCs), HBOCs could carry and release oxygen. HBOCs don't require blood typing before use or have a risk of spreading diseases, with a longer storage time compared with RBCs. Its size is at the nanoscale (approximately 1/100 of that of RBCs), and it can transport oxygen to hypoxic tissues and organs through obstructed small blood vessels that normal RBCs couldn't easily pass through. Due to insufficient blood flow and oxygen supply, most solid tumors often undergo molecular and biological changes during cancer development, leading to radiotherapy and chemotherapy resistance, and accelerating the malignant progression of tumors. Recently, HBOCs, as a potential nanoscale high-efficiency oxygen carrier, were used to increase tissue oxygenation and reduce the expression of Hif-1α during radiotherapy and chemotherapy. The proportion of hypoxic cells could be reduced by oxygenation amelioration, thereby relieving the resistance of radiotherapy and chemotherapy and enhancing its therapeutic effect. However, the sensitization efficacy of HBOCs possibly vary for different types of solid tumors and different phases of tumors. HBOCs combined with radiotherapy and chemotherapy may be a promising method for relieving the hypoxia degree in solid tumors and down-regulating HIF-1α protein, which will be very helpful for subsequent cancer therapy.

S04-2

Study on the role of active ingredient of earthworm in improving microcirculation disorders

Jianbo Sun [1]

[1] *China Pharmaceutical University*

Microcirculation is closely related to cardio cerebral Vascular disease such as cerebral thrombosis, cerebral infarction, post cerebral hemorrhage, coronary heart disease, myocardial infarction, angina pectoris, etc. The clinical application of promoting blood circulation and resolving blood stasis has achieved certain results. As a traditional Chinese medicine for calming the liver and the wind, earthworm has been used for thousands of years. In 1983, Mihara et al. first found that the water extract of Lumbricidae earthworm had the function of directly dissolving fibrin and activating Plasmin, and named it “Lumbrokinase”. Earthworm extract contains fibrinolytic enzymes, biopolysaccharides, and various other bioactive substances. The clinical trial shows that oral earthworm extract has a good health care effect on cardio cerebral Vascular disease of middle-aged and elderly people. This study will summarize the effect of earthworm extract on improving blood microcirculation in the body and elucidate its mechanism of health care for the cardiovascular and cerebrovascular systems.

S04-3

Improvement of microcirculatory perfusion by hemoglobin-based oxygen carriers after experimental cerebral ischemia

Yang Li [1,2,3], Jian Zhang [1,2,3], Yuan Li [1,2,3], Mingfeng Yang [1,2,3], Ying Wang [1,2,3], Jiaxin Liu [1,2,3], Baoliang Sun [1,2,3]

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Acute cerebral infarction has a rapid onset and serious prognosis. The key to its treatment is early reperfusion of the occluded blood vessels to restore effective perfusion to the ischemic brain region. However, both thrombolysis and mechanical thrombectomy have strict time limitations, and exceeding the time window may lead to significant reperfusion injury or irreversible necrosis of brain tissue. Therefore, finding effective methods to partially restore blood oxygen supply before and during transportation to the hospital can effectively prolong the time window for cerebral blood flow restoration and reduce ischemia-reperfusion injury.

Hemoglobin-based oxygen carriers (HBOCs) serve as nanoscale oxygen carriers with potential capabilities to cross the occluded area, providing oxygenation to tissues. In this experiment, a rodent model of focal cerebral ischemia-reperfusion (MCAO/R model) was prepared using the filament method. HBOCs were administered via the femoral vein for preperfusion of the ischemic brain region. Cerebral blood flow changes were observed at different time intervals using a laser Doppler flowmeter. TTC staining was used to assess the volume of cerebral infarction, Longa score was employed to evaluate neurologic function, and Morris water maze was used to assess learning and memory abilities of the animals. Additionally, TUNEL staining, immunofluorescence techniques, and Western blot were utilized to observe neuronal apoptosis.

The results revealed that HBOC infusion before reperfusion validly reduced the volume of cerebral infarction, improved cerebral blood flow, alleviated neurologic dysfunction, enhanced learning and memory abilities, and mitigated neuronal apoptosis. These findings indicate that HBOCs can effectively reach the ischemic brain region, increase oxygen supply, and provide significant protection against ischemia-reperfusion injury.

Keywords: cerebral ischemia; hemoglobin-based oxygen carriers; microcirculation; cerebral blood flow; neuroprotection

S04-4

Effects of compound anisodine on functional status of microvascular vasomotion in rats

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To investigate the effects of compound anisodine (CA) and its components on microvascular vasomotion and microcirculatory blood perfusion. Methods Rats were pretreated with norepinephrine (NE) to induce local arteriole contraction and interdict microvascular blood flow of arteriole in small intestinal walls. And then compound anisodine (CA), anisodine hydrobromide (703), procaine hydrochloride (PHI) and normal saline (NS) were given dropwise respectively. Intravital microscope and Laser Doppler flowmeter were employed to determine the changes of the microcirculatory blood flow and spectrum of microvascular vasomotion at 0 min, 1 min, 5 min, 10 min and 15 min. Results In CA group, the blood flow recovered to the baseline level at 5 min and exhibited a low-frequency and high-amplitude microvascular vasomotion. Compared with CA group, the recovery times of blood flow in 703, PHI and NS groups were significantly longer, companying with low-frequency, low-amplitude or high-frequency and low-amplitude microvascular vasomotion. Conclusions CA restores the microcirculatory blood perfusion and recovery microvascular vasomotion which improving tissue ischemia.

Keywords Compound anisodine; Microvascular vasomotion; Microcirculation; Procaine hydrochloride

SATELLITE SYMPOSIUM 5

Living Complex Fluid and Microcirculation

15:00-16:30 | Guorui Hall

S05-1

Magnetic resonance imaging on structure of living interstitium and fluid behaviour within

Xiaohan Zhou [1], Wentao Liu [1], Dong Han [1]

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The interstitium, a soft material structure composed of fibrous networks and matrix gel, plays a vital role in the regulation of human behavior and health, filling the spaces between cells, functional tissues, and organs to promote interstitial connectivity, fixation, and nutrition. Despite its significance, our understanding of the interstitium's complex structure and mechanism is limited. Recently, tissue channels, green pathway, para-vascular pathways, and the glymphatic pathways have all been identified as interstitial behaviors. Relative researches in this area is still in its early stages, with a limited understanding of the interstitial structure, behavior, and function, as well as a lack of accurate in-vivo imaging and characterization techniques. In highly-interconnected interstitium, complex chemical, mechanical, and physical processes facilitate remote tissue feedback along certain pathways, resulting in a scientific basis for life medical modeling.

Thus, studying the structure of living interstitium and its fluid behavior within provides the best means for intervening in the connection between various systems and the occurrence and development of diseases. This research may serve as a catalyst for developing new diagnostic methods and treatments for chronic diseases.

The objective of this study is to develop new imaging, characterization, and material methods to achieve a better understanding of the structure and behavior of the living interstitium, ultimately advancing our knowledge in this area.

K-T space sectioned imaging (KTSSI) has been proposed to image the solid structure of the interstitium, specifically the fascia. It combines magnetic resonance RF and gradient design to obtain a T2* value map. Human leg scanning experiments using KTSSI established the technology's capability to quantitatively image large-scale fascia structures efficiently. This technique provides a reliable technical method for subsequent research, enabling the continuous and extensive imaging of leg fascia.

In addition, to further explore fluid behavior and function of the extracellular matrix of living organisms, the study proposes a nano-sized contrast agent with high molar relaxivity and slow in vivo metabolism. The contrast agent is composed of polyacrylic acid linked covalently to diethylene triamine molecules. By overcoming limitations of current small molecule contrast agents, such as low molar relaxivity, easy diffusion, and fast in vivo metabolism, this amphiphilic Gd-based contrast agent has promising applications in the field of magnetic resonance imaging. The study's comprehensive approach to understanding the structure, behavior, and function of living interstitium has significant implications for the development of diagnostic and treatment strategies for chronic diseases. The study presents an improved MRI contrast agent that has a higher longitudinal molar relaxivity of 13.94 $mM^{-1}{\cdot}s^{-1}$ than the clinical contrast agent Magnevist. Compared to Magnevist, the new contrast agent has a larger hydrodynamic radius and molecular weight, allowing it to remain in the interstitial fluid circulation structure and avoid leakage through the gaps between fascia or endothelial cells of blood vessels. The contrast agent contains gadolinium, which reacts with azo phosphonate III to form a color reaction, making it distinguishable from other tissues. This characteristic enables dynamic imaging studies and effective combination with pathology.

Inductively coupled plasma mass spectrometry was used to quantify gadolinium's trace amounts, which supplements the lack of information on low-concentration trace analysis in imaging and pathology and confirms the differences in gadolinium distribution caused by tail vein and leg interstitial injection. In the study, the “green channel” of the interstitial long-range communication from the surface to the kidney was also reported, providing experimental support for further understanding of the interstitial tissue behavior.

The study explores the interstitium by “structure-behavior-function” biological activities I to establish a link between body surface, limbs, organs and the regulation mechanism of interstitial tissue for developing diagnostic methods and treatment strategies.

S05-2

Randomized controlled trial of Kuanxiong aerosol to improve coronary microcirculation disorder during PCI

Zihao Liu [1], Hongxu Liu [1], Qi Zhou [1], Aiyong Li [1], Wenlong Xing [1], Zhenmin Zhang [1], Penglu Wei [1]

[1] *Beijing Hospital of Traditional Chinese Medicine, Capital Medical University*

Objective: To evaluate the effect of kuanxiong aerosol on microcirculation during PCI by using invasive diagnostic method of coronary artery microcirculation resistance index (IMR).

Methods: A total of 60 patients with left anterior descending artery (LAD) lesion were selected from the Cardiovascular Department of Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University. They were randomly divided into two groups: the experimental group (kuanxiong aerosol group) and the control group (blank control group) with 30 cases each. The coronary artery microcirculation resistance index (IMR) was measured before and after percutaneous coronary intervention (PCI) in the two groups. The kuanxiong aerosol group was injected with two sprays of kuanxiong aerosol through the mouth before and after the measurement, and the IMR was measured again 1 minute later. Observe the changes of IMR value before and after operation and administration, the occurrence of Maces event 30 days after operation, and the safety indicators (changes of blood pressure and heart rate before and after administration, changes of liver and kidney function and blood coagulation of patients before and after operation).

Results: There was no statistically significant difference in baseline IMR values between the two groups before and after surgery ($P>0.05$). The IMR values in the two groups before and after administration were higher than those in this group before surgery, indicating an increase in coronary microcirculation resistance, with a statistically significant difference ($P<0.05$). The IMR of the test group decreased after postoperative administration compared to that before administration ($P<0.05$), with a statistically significant difference compared to the control group ($P<0.05$). There was no statistically significant difference between the two groups in the occurrence of Maces events and safety indicators 30 days after operation ($P>0.05$).

Conclusion: Kuanxiong aerosol may have the potential to improve coronary microcirculation disorders during PCI perioperative period, and its clinical use has certain safety, which is worth further research.

S05-3

Hypersensitive MR Angiography based on Nanoprobe for Diagnosis of Cardiac-cerebral Vascular Diseases

Yi Hou [1]

[1] *College of Life Science and Technology, Beijing University of Chemical Technology*

Magnetic resonance (MR) angiography is one of the main diagnostic approaches for cardiac-cerebral vascular diseases, which are the major leading causes for neurologic disability and mortality, nevertheless, the no-contrast MR angiography always suffers from its intrinsic problems derived from the blood flow-dependency, while the clinical Gd-chelating MR contrast agents are unsatisfactory due to their rapid vascular extravasation. Aiming at accurately describing the anatomical vascular structure and identifying abnormalities, the strategy of hypersensitive MR angiography with high resolution based on nanoprobes including Fe_3O_4 nanoparticles, $NaGdF_4$ nanoparticles and zwitterionic Gd-chelating polymer (PAA-Gd). A series of animal models of cardiovascular and cerebrovascular diseases, such as ischemic stroke, reperfusion subarachnoid hemorrhage and atherosclerotic plaque, have been built for imaging studies on a 7.0

T MRI scanner with different sequences, as well as the translation potential of these nanoprobes to the clinical settings has been evaluated through MR angiography of swine on a 3.0 T clinical MRI scanner. The current studies therefore offer a promising strategy for precise diagnosis of vascular diseases.

S05-4

Functional MRI of White Matter

John Gore [1]

[1] *Vanderbilt University Institute of Imaging Science*

Blood oxygenation level dependent (BOLD) contrast in MR images has for ≈30 years been exploited for detecting localized neural activity in the cortex using functional MRI (fMRI), and is an essential tool for mapping brain function. BOLD signals represent changes in blood flow, volume and oxygenation, driven by increases in metabolic demands of neurons in the cortex. In addition, correlations between BOLD signals in a resting state are interpreted as depicting functional connectivity between regions. While BOLD signals have been reliably detected in grey matter (GM) in a very large number of studies, such signals have rarely been reported from white matter (WM). However, it is clear from our own and other studies that although BOLD effects are weaker in WM they may be measured. To summarise:

(1) BOLD signals are robustly detectable in WM if appropriate analyses are used; conventional methods throw away sensitivity by using an inappropriate hemodynamic response function (HRF).

(2) Event related measurements show the HRF in WM is different than in GM but can be measured accurately. It often shows a significant negative dip compared to GM.

(3) WM BOLD activity can be evoked by stimulation in task-specific tracts or regions. The magnitude of WM signals in a task reflects those in GM engaged in the same task, and they are modulated by the same task parameters.

(4) At rest, WM tracts show reproducible patterns of connectivity which are summarized in Functional Connectivity Matrices (FCMs) obtained by analyzing resting state correlations between segmented WM and GM parcellations; the FCM relating WM to GM is altered in various pathologies including Alzheimer's disease and schizophrenia in a manner that correlates with behavioral measures.

(5) Distinct, reproducible networks in WM emerge from data-driven analyses in similar manner to cortical circuits. Moreover, comparisons of partial and full correlations between GM regions with inclusion vs exclusion of WM shows the degree of engagement of specific WM tracts in the couplings between cortical volumes.

(6) WM resting state correlations are anisotropic so functional tensors can be constructed and used for tractography.

(7) BOLD signals may also be detected and analyzed in WM tracts in the spinal cord.

This presentation will summarize some of our recent studies that provide evidence that BOLD signals in WM are related to brain functional activity and deserve greater attention by the neuroimaging community. Moreover, recent works suggests that BOLD effects in WM may be driven by different processes than in GM.

YOUNG SYMPOSIUM 1

JSM Young Investigator Symposium

08:30-10:00 | Room 6

Y01-1

Possible association of Proprotein Convertase Subtilisin/Kexin Type 9 expression and inflammation after cerebral reperfusion injury

Atsushi Mizuma

Tokai University School of Medicine, Japan

Y01-2

The smallest unit of capillary activity in the somatosensory cortex of awake mouse

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[1] Graduate School of Informatics and Engineering, University of Electro-Communications

[2] Center for Neuroscience and Biomedical Engineering, University of Electro-Communications

Cerebral capillaries play a crucial role in regulating blood flow distribution to meet neural demand. However, a functional unit of the capillary responses that are the minimum length and coherently respond to vasoactive signals is not well understood. In this study, the spatiotemporal dynamic changes in cerebral capillaries were determined to estimate the smallest functional unit of capillary dilation and constriction for neurovascular coupling.

The skull over a portion of the mouse somatosensory cortex was removed and blood plasma labeled with sulforohdamine 101 was visualized using two-photon microscopy. All experiments were conducted in the awake state, and mechanical stimuli were repeatedly applied to the contralateral whiskers of the observed cortex to induce neural activity. In each location of cortical layers II/III, capillary diameter fluctuations and responses to neural activity were measured. The capillary diameters were quantified using a custom code written in the Matlab software.

Approximately 6,000 to 8,000 measurement points were collected in each animal to measure capillary diameter. Based on resting fluctuations of capillary diameters, the capillaries were segmented at the inflection point of the fluctuation profiles along the individual capillaries. This resulted in the length of 4 ± 4 μm (n = 6,701 segments). Next, the comparison of capillary data based on network structures (i.e., arterial sides to venous sides) showed that capillary diameters and fluctuations are dependent on the pathway from the arterial side to the venous side. In contrast, capillary responses to neural activity are localized irrespective of the arteriovenous axis. Correlation analysis further revealed a spatial coherence of the diameter fluctuations within a single pathway, and the length of these segments was 5 ± 3 μm (n = 2,719 segments).

In conclusion, the minimum length of capillary segments that can be responsive to activity-induced dilation and constriction is around 5 μm.

Y01-3

Endoscopic hemostasis and transarterial embolization in patients with GI bleeding - Microcirculatory study and measures to improve the visibility of the bleeding blood vessels

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[1] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine

The gastrointestinal mucosa is covered with an endless microcirculatory system, and fluctuations in microvascular blood flow lead to bleeding events. Most colonic diverticula are pseudodiverticula lacking the muscularis propria, with only the intestinal mucosa projecting convexly from the gaps in the muscular layer of the large intestine, and its microcirculatory system is also extremely vulnerable to changes in internal pressure, etc., often causing bleeding. Endoscopic hemostasis is usually performed, but if hemostasis is difficult, transarterial embolization (TAE) is performed. Comparing the group that underwent hemostasis only with endoscopy and the group that underwent TAE, the group that underwent TAE had a higher shock index and lower Alb and PT% than the endoscopic hemostasis group. Shock index correlated with Alb and PT%. A shock index greater than 0.740 increases the likelihood of switching to TAE treatment and should also be considered if extravasation is seen on contrast-enhanced CT (J. Clin. Biochem. Nutri. 2022 May;70(3): 283-289). Furthermore, during endoscopic hemostasis, it is effective to slow down the bleeding speed by spraying gel (Endoscopy. 2022 Dec;54(S 02): E1066-E1067). in order to improve the visibility for identifying the bleeding point.

Y01-4

Role of Prostaglandin E2 related pathways in gastric adenocarcinoma

Yuji Nadatani [1], Koji Otani [2], Akira Higashimori [2], Tetsuya Tanigawa [2], Yasuhiro Fujiwara [2], Toshio Watanabe [1]

[1] Department of Premier Preventive Medicine

[2] Department of Gastroenterology

Background and Aim: Prostaglandin (PG) E2 promotes gastrointestinal carcinogenesis and tumor progression. The total amount of biologically active PGE2 in tissues is determined by a balance of PG biosynthesis and degradation pathways, which involve the PG transporter (PGT) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a catabolic enzyme for biological inactivation of PGE(2). We investigated PGT and 15-PGDH in gastric adenocarcinoma by determining its expression pattern and examining associations of PGT and 15-PGDH with prognosis and tumor angiogenesis.

Methods: 15-PGDH and PGT expression was determined by immunohistochemistry in advanced gastric adenocarcinoma specimens obtained from patients who underwent surgical resection. Angiogenesis in the tumor tissue was evaluated by counting the number of microvessels. Human gastric carcinoma cell lines were used for in vitro study. The Ethics Committee of Osaka City University approved this study.

Results: Multivariate analysis revealed reduction of 15-PGDH expression to be an independent predictor of poor survival. The proportion of Ki67-positive cells in 15-PGDH-negative adenocarcinoma was higher than that in 15-PGDH-positive adenocarcinoma. Negativity for PGT expression was also an independent poor prognostic factor. There were more microvessels in PGT-negative tumors than in PGT-positive tumors. Use of specific siRNA to silence 15-PGDH or a specific inhibitor of 15-PGDH enhanced cell proliferation in the gastric cancer cell line AGS. Transfection of AGS and MKN7 gastric cancer cells with PGT-specific siRNA led to increased VEGF mRNA and protein expression accompanied by increased PGE2 in the culture media.

Conclusion: These findings suggest that reduction of 15-PGDH or PGT expression is an independent predictor of poor survival in gastric adenocarcinoma.

YOUNG SYMPOSIUM 2

Exploring the Molecular Events of Cerebrovascular Injury

15:00-16:00 | Room 5

Y02-1

In situ Imaging of Toxic Metabolites Mediating Neurovascular Injuries

Xin Li [1]

[1] College of Pharmaceutical Sciences, Zhejiang University

Neurovascular injury is a basal mechanism in the pathogenesis of stroke, neurodegenerative diseases, and mental disorders. Understanding the mediators and their molecular mechanisms involved in neurovascular injury is critical for the development of novel therapeutics to treat related syndromes. It is well established that the excess production of reactive oxygen species (ROS) is crucially implicated in neurovascular injury; while in sharp contrast, the beneficial roles of antioxidants for neurovascular protection hasn't been solidly achieved in clinical trials. ROS is actually an umbrella term covering a variety of species with distinct reactivity and spatiotemporal distribution profiles. This complexity in combination with their pleiotropic roles in physiology and pathology, advocates new technology to detect each ROS species with precision. We have developed a strategy of "tailored design" for reactivity-based probes to image the ROS of interest in live samples, and multiscale imaging ranging from live cells even to mice are achieved.[1-4] We envision the application of these imaging probes should deepen our understanding on the pathophysiological roles of ROS in neurovascular injury.

Y02-2

Effect of acupuncture on boosting microvascular repair in neurodegenerative disease

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Emerging findings addressed microvascular impairment as one major contributor to the progression of neurodegenerative diseases, such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Thus, microvascular impairment potentially serves as one of early indicators of neurodegenerative diseases, but also as the therapeutic target to prevent subsequent neurological dysfunction. Delivery of vascular growth factors has been wildly studied in preclinical research to boost angiogenesis and cerebral microvascular recovery. However, it remains unavailable in the clinic partially due to the risk of multiple adverse effects. Effective intervention with low cost and side effects is urgently required to prevent microvascular degeneration and neurological dysfunction.

Besides pharmacological intervention, acupuncture has been widely practiced as non-pharmacological medicine for disease prevention and treatment with low cost, high safety and impressive effect. Combined with electrical current to acupuncture needles, electroacupuncture (EA) provides a more accurate and quantitatively controlled approach for acupuncture treatment. Recently, our studies addressed the protective effect of electroacupuncture (EA) on attenuating the early-onset behavioral and neurovascular defects in the AD mice and ALS mice.

In the AD treatment, our study found that high-frequency EA at "ZuSanLi" ST36 acupoints (EAST36) effectively alleviated the olfactory impairment and anxiety-like behavior, and boosted the cerebrovascular repair in AD mice. EAST36 attenuated cerebral microvascular degeneration in AD mice by modulating endothelial cell viability and injury. Consequently, the Aβ deposits and neural damage in AD mice were reversed after EAST36. Mechanistically, we revealed that EAST36 restored melatonin levels in AD mice. Melatonin supplement mimicked EAST36 effect on cerebrovascular protection in AD mice and endothelial cell cultures. Importantly, blockage of melatonin signaling by antagonist blunted EAST36-induced cerebrovascular recovery and subsequent neurological improvement.

In the study of ALS prevention, our findings showed EA at "Jia ji" Ex-B05 acupoints (EAEB05) effectively alleviated motor deficit in ALS mice during onset and progression phase. EAEB05 treatment blocked the inflammatory activation of microvessels in the spinal cord, as demonstrated as the reduction of leukocyte-endothelial interaction and neighbor microglia activation. The microvascular degeneration in spinal cord was inhibited in ALS mice after EAEB05 treatment. In mechanism, our study revealed the crucial role of α 7nAChR in driving the microvascular protection of EA on ALS. Blockage of α 7nAChR obviously abolished the microvascular protection of EAEB05, as showed as the drop of microvascular density and the activation of microvascular inflammation in ALS mice with EAEB05 treatment.

Collectively, our findings demonstrated the impressive effect of EA treatment to boost microvascular repair in AD and ALS mice, providing strong evidence to support EA treatment as a potential non-pharmacological therapy against devastating neurodegenerative disease.

Keywords: Acupuncture, Electroacupuncture, Microvascular impairment, Alzheimer's disease, Amyotrophic lateral sclerosis.

Y02-3

Endothelial Cdk5 Deficit Leads to the Development of Spontaneous Epilepsy Through CXCL1/CXCR2-Mediated Reactive Astrogliosis

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[1] Nanjing Medical University

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Abstract: Abnormal blood-brain barrier function contribute to epileptogenesis after brain injury. Here we report that selective knockout of endothelial *Cdk5* increased the excitability of hippocampal neurons, trigged spontaneous hippocampal epileptic discharges in *Cdh5-Cre;Cdk5$^{f/f}$* mice. The effect was associated with an increase in chemokine CXCL1 expression and a decrease in GLT1 function in astrocytes that impairs glutamate homeostatic functions, which can contribute to neuronal hyperexcitability and seizure generation. Ceftriaxone restored astrocytic GLT1 function and inhibited seizures in endothelial *Cdk5*-deficient mice, and these effects were also reversed after silencing Cxcl1 in endothelial cells and its receptor chemokine (C-X-C motif) receptor 2 (Cxcr2) in astrocytes respectively in the CA1 by AAV transfection. These results reveal a previously unknown link between vascular dysfunction and epilepsy and suggest that endothelial *Cdk5* regulates astrocyte GLT1 and its deficiency may contribute to epileptogenesis in patients with vascular diseases.

Method: We generated three sets of conditional endothelial-specific Cdk5 knockout mice (Cdh5-Cre;Cdk5f/f mice, Cdh5-CreERT2;Cdk5f/f mice, BR1-iCre-Cdk5f/f mice) to investigate the role of endothelial Cdk5 in brain. The behavioral phenotypes were detected by 24-hour video surveillance and EEG recordings. The role of Cdk5 on the excitabilty of hippocampal pyramidal neurons was assessed by patch clamp recording. The signaling mechanisms between endothelial Cdk5 and epilepsy were determined using immunohistochemistry combined with RNAseq, western blot and immuofluorescence.

Result: We showed that *Cdh5-Cre;Cdk5$^{f/f}$* mice showed an age-dependent increase in the prevalence and frequency of seizures using 24-hour video surveillance (8 weeks: 8.3%; 24 weeks: 80%). In contrast, only 1/14 (7%) of *Cdh5-Cre;Cdk5$^{f/n}$* mice and 0/17 *Cdk5$^{f/f}$* mice showed seizures. Additionally, when treated with the convulsant agent pentylenetetrazole (PTZ), *Cdh5-Cre;Cdk5$^{f/f}$* mice showed increased

seizure duration and decreased seizure onset compared to *Cdk5*$^{f/f}$ mice at 4 weeks. The increasing in hippocampal discharges have been caused by an increase in both the amplitudes and frequencies of spontaneous and miniature excitatory postsynaptic current (sEPSC and mEPSC) in *Cdh5-Cre;Cdk5*$^{f/f}$ mice. Furthermore, we demonstrated that deletion of endothelial *Cdk5* induces progressive astrogliosis and impairs astroglial GLT1 function. Next, Using RNAseq combined with qRT-PCR and RNAscope, we found that the *Cdk5* deficiency induces overexpression of endothelial cell-derived CXCL1 and aberrant elevation of endothelial cell-derived CXCL1 is the trigger of astrogliosis. Using viral tools, We demonstrated that CXCL1 reduces GLT1-mediated glutamate uptake by activation of CXCR2 receptors on astrocytes.

Conclusion: In summary, our findings reveal a previously unknown function of the endothelial-derived *Cdk5* signaling in the brain. Endothelial *Cdk5* deficiency induces spontaneous epilepsy in an age-dependent manner. The effect is associated with a decrease in GLT1-mediated glutamate uptake and an increase in excitability of hippocampal pyramidal neurons. Our evidence further suggests that these effects depend on CXCL1 release from ECs and subsequent activation of astrocytic CXCR2 receptors by CXCL1. Importantly, we found that these effects can be reversed by pharmacological restoration of GLT1 function (ceftriaxone), genetic silence or immunoneutralization of CXCL1, or inhibition of the CXCL1 receptor CXCR2 on astrocytes.

Keywords: *Cdk5*; Endothelial Cells; Astrogliosis; GLT1; CXCL1; CXCR2

Y02-4

Uncovering the Role of Fatty Acid-Binding Proteins in Mitochondrial Dysfunction: A Potential Therapy for Dementia and Cerebrovascular Injury

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Dementia is a global issue due to the aging population. While there are various types of dementia, the mechanisms behind their development remain unclear. Fatty acid-binding proteins (FABPs) are responsible for transporting long-chain fatty acids, which are vital for fatty acid metabolism. Our previous study discovered that FABPs are crucial in mitochondrial dysfunction leading to neuronal injury in models of vascular dementia and dementia with Lewy bodies, including Parkinson's disease dementia. We found that FABPs are essential for both neuroinflammation induced by transient cerebral ischemia and α-synuclein-induced neurotoxicity. Specifically, FABP3 contributed to the loss of mitochondrial membrane potential in MPTP-induced neuronal degeneration, while FABP3 and FABP5 accumulated into mitochondria and lost the membrane potential in cerebral ischemia. Additionally, FABP7 was critical in the loss of mitochondrial homeostasis in glial cells. We also discovered that inhibiting FABPs with specific ligands protected against mitochondrial dysfunction and promoted neuronal survival. Therefore, FABPs play a crucial role in initiating mitochondrial damage in cerebrovascular injury and α-synuclein toxicity. The novel FABP ligands may offer a promising therapy for protecting the nervous system against mitochondrial damage, which is common to both ischemic stroke and α-synucleinopathies.

FREE ORAL COMMUNICATION 1

Cancer and Microcirculation

08:30-10:00 | Room 5

F01-1

Arid5b competes with STAU2 regulating BAI1 mRNA stability to regulate breast tumor angiogenesis

Ailing Li [1], Jianqun Han [1], Hongwei Li [1], Xueting Liu [1], Wenbao Lu [1], Ruijuan Xiu [1]

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Tumor angiogenesis is a crucial step for further growth and metastasis of solid tumors. However, the underlying molecular mechanism of tumor-induced angiogenesis remains unclear. Here, we showed that RNA-binding proteins Arid5b and STAU2 were able to antagonistic regulate breast tumor angiogenesis and metastasis by competitively mediating the expression of anti-angiogenic gene *BAI1* (brain-specific angiogenesis inhibitor 1) via controlling its mRNA stability. We demonstrated that Arid5b expression is lower but STAU2 expression is higher in human breast cancer tissues, and their expression levels were significantly associated with survival of breast cancer patients, respectively. The *in vivo* and *in vitro* data showed that Arid5b could significantly inhibit breast tumor angiogenesis and metastasis progression, while STAU2 was able to promote breast tumor angiogenesis and metastasis. Mechanistically, Arid5b physically bound the stem-loop structure in the 3'-untranslated region of BAI1 mRNA through its ARID domain and stabilizing its mRNA, causing increased expression and tumor angiogenesis inhibition. However, STAU2 could competitively bind the same stem-loop structure and degrade *BAI1* mRNA, which in turn suppressed BAI1 expression and promoted tumor angiogenesis. Furthermore, we found that Arid5b and STAU2 expression levels were significantly correlated with BAI1 expression in human breast cancer tissues. Notably, Arid5b and STAU2 expression in tumor samples from breast cancer patients were strongly associated with microvessels density, respectively. Collectively, our results highlight that Arid5b and STAU2 might be a pair of antagonistic regulators that regulate breast tumor angiogenesis by competitively control anti-angiogenic gene BAI1 mRNA stability via binding the same stem-loop structure.

F01-2

AAV-delivery of engineered tRNA-enzyme pairs to overcome nonsense mutation in vivo

Zhetao Zheng [1], Liangzhen Dong [1], Bangyan Kong [1], Zhiyang Dou [1], Qing Xia [1]

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In the past two decades, genetic code expansion has evolved from a fantastic idea to a powerful research tool, enabling not only biosynthesis of proteins with novel or enhanced functions, but also introduction of functionally diverse unnatural amino acids (UAAs) into all types of organisms, from bacteria to mice. To incorporate UAAs into target proteins, several components are needed: a reassigned nonsense codon (UAG, UGA or UAA) in mRNA, an engineered aminoacyl-tRNA-synthase (aaRS)–tRNA pair, and relevant UAAs. Currently, four orthogonal aaRS–tRNA pairs, referred as to the MmPylRS/tRNAMmPyl, MbPylRS/tRNAMbPyl, EcTyrRS/tRNAEcTyr and EcLeuRS/tRNAEcLeu systems, have been developed to specifically recognize a nonsense codon and incorporate a desired UAA in mammalian cells, respectively or simultaneously.

Approximately 11% of monogenic diseases are caused by premature termination codons (PTCs) in human genes, whose transcripts harboring nonsense mutations could be down-regulated by the nonsense-mediated decay mechanism and produce truncated proteins with impaired functions. Duchenne muscular dystrophy (DMD) is a human X-chromosome-linked disease and nonsense mutations in the DMD gene account for about 10% of reported cases, presenting the most prevalent and severe phenotypes characterized by progressive muscle weakness and a shortened life span. Therapeutic methods have been developed to restore the expression of dystrophin encoded by pathogenic DMD, via exon-skipping, genome editing or PTC read-through.

Here we describe specific steps for using engineered UAA incorporation system to read-through the PTC site of DMD transcript and alleviate disease symptoms in mice. We anticipate that this potentially curative method could be repurposed for treating more human nonsense mutation diseases.

F01-3

New Treatment Strategies of Glioblastoma: Targeted Regulation of Blood–Brain Barrier for Enhanced Therapeutic Efficiency of Hypoxia-Modifier Nanoparticles and Immune Checkpoint Blockade Antibodies

Zhouyue Wu [1]

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Introduction: Glioblastoma is the most destructive type of brain cancer. The blood–brain barrier (BBB) is a tremendous obstacle that hinders therapeutic agents, such as chemical drugs and antibodies, from reaching glioblastoma tissues. Meanwhile, the abnormal microenvironment of glioblastoma extremely restricts the expected therapeutic effects of accumulated drugs.

Method: For targeted BBB regulation, we created BBB-regulating nanovesicles (BRN) containing adenosine 2A receptor (A2AR) agonists and perfluorocarbon (PF). A2AR agonists are released in the presence of local ultrasonication (US) and have effects on both F-actin and endothelial cell tight junctions. Subsequently, BBB permeability is temporarily increased and enables small molecules and nanoparticles to enter brain parenchymal tissues. The high affinity between manganese dioxide and temozolomide (TMZ) is utilized to form multifunctional nanoparticles called MT@PAE to ameliorate the hypoxic microenvironment, which yields improved glioblastoma inhibition combined with radiotherapy. Moreover, with the aid of targeted BBB regulation, programmed death ligand-1 (PD-L1) antibody induces a tumor-specific immune response. Statistical significance was performed by two-tail Student's t-test for two groups and one-way analysis of variance (ANOVA) analysis for multiple groups. A value of $p < 0.05$ was considered statistically significant. Data was shown as mean ± SD; $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p < 0.001$.

Results: In this work, we targeted endothelial cells to regulate the BBB permeability for enhanced drug accumulation. RBCM was used to encapsulate NECA, avoiding off-target effects, and NECA was locally released via ultrasonication to increase BBB permeability. Results showed good safety and improved cognitive function in glioblastoma-bearing mice receiving BRN combined with MT@PAE treatments. Subsequently, activated CD8+ T cells were found to be amplified. Therefore, our results suggested that synergistic combination may have the potential in amplifying the therapeutic efficacies of clinical drugs and immune checkpoint blockade antibodies to overcome the therapeutic resistance of glioblastoma.

Conclusions: We developed a pharmacological cooperative strategy of combining targeted BBB regulation with microenvironment amelioration to circumvent multifarious barriers in glioblastoma tissues. Biomimetic nanovesicles were designed to achieve targeted regulation of the BBB in glioblastoma-bearing mice. Increased BBB permeability was achieved via the release of encapsulated NECA during local ultrasonication and provided a therapeutic window for efficient accumulation of therapeutic hypoxia-modifier nanoparticles and immune checkpoint blockade antibodies. Finally, the therapeutic efficiencies of chemoradiation and immune therapy for glioblastoma treatment were significantly improved without additional observable toxicity.

F01-4

Sodium Pentobarbital Suppresses Breast Cancer Cell Growth Partly via Normalizing Microcirculatory Hemodynamics and Oxygenation in Tumors

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Breast cancer remains the leading cause of cancer-related death among women worldwide. Sodium pentobarbital was found to play an inhibitory role in glioma growth in rats. In this study, we aimed to evaluate the effects of sodium pentobarbital on breast cancer growth both in vitro and in vivo, and its impacts on the microcirculatory changes on both skin and tumor surface in mice bearing subcutaneous xenograft. Cell counting
assay was used to assess the antiproliferative effect of sodium pentobarbital on MDA-MB-231 breast cancer cells. Subcutaneous xenograft model was established to study the role of sodium pentobarbital on in vivo tumor growth. Speed-resolved blood perfusion, hemoglobin oxygen saturation (SO_2, %), total hemoglobin tissue concentration (ctTHb, μM), and red blood cell (RBC) tissue fraction (%) were examined simultaneously by using enhanced perfusion and oxygen saturation system to investigate the effects of sodium pentobarbital on microcirculatory hemodynamics and oxygenation. Sodium pentobarbital suppressed breast tumor growth both in vitro and in vivo. Cutaneous blood flux in nutritive capillaries with low-speed flow was significantly increased in tumor-bearing mice, and high dose sodium pentobarbital treatment cause a reduction in this low-speed blood flux, whereas sodium pentobarbital therapy caused an elevated blood flux in larger microvessels with mid and high speed in a dose-dependent manner. Different doses of sodium pentobarbital exerted different actions on SO_2, ctTHb, and RBC tissue fraction. Collectively, the inhibitory effect of sodium pentobarbital on breast tumor growth was at least partly associated with its ability to normalize microcirculatory hemodynamics and oxygenation in tumors.

F01-5

Abrupt disruption of tumor microcirculation to block tumor growth by an innovative anti-CD39 monoclonal antibody

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Background: CD39, ectonucleoside triphosphate diphosphohydrolase-1, expresses at low levels under physiological conditions. While in the tumor, CD39 levels are markedly elevated chiefly on tumor neovasculature and stroma.
Methods: PUR001, a fully human recombinant anti-CD39 monoclonal antibody, rather than focusing on direct inhibition of ectoenzymatic activity of CD39, is designed to specifically target and ablate intratumoral CD39high cells. Antitumor activities of PUR001, alone or in combination with chemotherapy or immunotherapy, were investigated in small animal tumor models using human CD39 knock-in mice. CD39 expression in human tumor samples was evaluated by immunohistochemistry.
Results: CD39 is highly expressed on tumor neovascular cells, tumor-infiltrating immune cells and tumor stroma cells, as noted in various human solid tumors. When tested in vivo, PUR001 selectively ablates the immature neovasculature, disrupts tumor microcirculation and induces massive immunogenic tumor cell death; this effect is further augmented by combination with chemotherapy e.g. Gemcitabine or Cisplatin plus 5-Fluorouracil or immune checkpoint inhibitors e.g. anti-PD-L1. In addition, immediate enhanced immune responses are coupled with removal of intratumoral CD39high suppressor cells (e.g. tumor-associated macrophages – TAMs).
Conclusions: Preclinical studies indicate that PUR001 is safe and well tolerated in both mice and cynomolgus monkeys. PUR001's breakthrough antitumor mechanism-of-action (MOA) uniquely offers the opportunity to have monotherapy efficacy as well as synergism with other I/O agents and with chemotherapies, and potentially to rejuvenate antitumor immunity. To our knowledge, this represents the first report of an anti-CD39 antibody having such innovative MOA in treating solid tumors.

F01-6

Construction of an efficient gene prognosis signature in pancreatic cancer based on microvascular angiogenesis feature

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Tumors rely on a sufficient blood supply to grow and metastasize, and the microcirculation plays a crucial role in this process. The microcirculation is responsible for delivering oxygen, nutrients, and growth factors to the tumor, as well as removing waste products. Angiogenesis, the process of forming new blood vessels, is essential for tumor growth and progression, which is an important factor in the development of pancreatic cancer (PC), a deadly disease that typically progresses rapidly, often with limited treatment options. PC cells release pro-angiogenic factors that stimulate the formation of new blood vessels in microcirculation, leading to the development of an abnormal and chaotic network of vessels. As PC progresses, microvascular angiogenesis stimulates the formation of these microvessels in and around the tumor, allowing it to continue to grow and spread. In addition, these microvessels can facilitate the spread of cancer cells to other parts of the body, making the cancer even more difficult to treat. Understanding the complex relationship between PC and microvascular angiogenesis is crucial for the development of effective cancer treatments, as targeting the microvasculature has shown promise as a therapeutic approach. Thus, our research is aimed to establish a microvascular angiogenesis based gene signature for predicting the prognosis of PC patients. A total of 48 microvascular angiogenesis based genes were identified. The integrated expression level of these genes was significantly negative related with disease free survival (HR = 1.7, p = 0.021). And microvascular angiogenesis score in PC was significantly higher than that in normal pancreas ($p < 0.05$). By performing multi-Cox regression, a total of 11 genes were found to be the independent risk factors for the survival of PC patients, including NPR1 (HR = 0.41, p = 0.004), RNH1 (HR = 0.52, p = 0.019), IL18 (HR = 1.8, p = 0.003), PML (HR = 3.69, $p < 0.001$), CDH13 (HR = 1.34, p = 0.09), SERPINF1 (HR = 0.66, p = 0.013), PROK2 (HR = 4, $p < 0.001$), EGF (HR = 1.35, p = 0.055), C1GALT1 (HR = 0.73, p = 0.081), SHH (HR = 0.68, p = 0.043) and FOXO4 (HR = 0.65, p = 0.118). Subsequently, the Cox proportional-hazards model was constructed (Akaike Information Criterion = 776.25; Concordance Index = 0.72, $p < 0.001$), which could predict the prognosis of PC efficiently. The area under the curve of receiver operating characteristic curve was 0.778 and high risk patients was related to a worse overall survival, significantly ($p < 0.001$). Besides, we constructed a nomogram using these 11 genes with extra clinical characteristics to better evaluate 1-year or 3-year survival time of PC patients, and the calibrated curve was plotted. Differential expressed gene (DEGs) analysis showed KRT6A (FDR < 0.001), S100A2 (FDR = 0.007) and KRT13 (FDR < 0.028) were significantly higher expressed in high risk group than that in low risk group. Pathway enrichment analysis showed tissue morphogenesis, Vitamin D receptor pathway and canonical Wnt signaling pathway were significantly enriched in high risk group. Protein-protein Interaction Enrichment Analysis showed intermediate filament related processes were related to higher microvascular angiogenesis level. Transcriptional Regulatory

Relationships Unraveled by Sentence-based Text mining results suggested that microvascular angiogenesis could be regulated by transcript factor BRCA1. In addition, single-cell RNA-sequencing of PC showed significantly different tumor microenvironment in high microvascular angiogenesis level patients, with altered level of stromal and immune cells. Overall, our research proposed a novel idea that microvascular angiogenesis signature could efficiently predict survival time of PC, which can also affect tumor microenvironment.

FREE ORAL COMMUNICATION 2

Cardiac Microcirculation

08:30-10:00 | Room 7

F02-1

Pulsatile Flow Promotes Microcirculatory Perfusion and Maintains the Endothelial Integrity during Extracorporeal Membrane Oxygenation

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Background: Extracorporeal membrane oxygenation (ECMO) is an important device in critical care medicine, especially during the COVID-19 pandemic. Recent studies found that the impairment of microcirculation is associated with the unfavorable outcome for ECMO patients. Studies revealed that pulsatile modification improves hemodynamics and attenuates inflammation during ECMO support. However, whether flow pattern impacts microcirculation and endothelial integrity is rarely documented. The objective of this work was to explore how pulsatility affects microcirculation during ECMO.

Methods: Canine animal models with cardiac arrest were supported by ECMO, with the i-Cor system used to generate non-pulsatile or pulsatile flow. The sublingual microcirculation parameters were examined using the CytoCam microscope system. Hemodynamic parameters, peak wall shear stress (PWSS), the expressions of endothelial tight junction markers were measured at different time points during ECMO. In vitro pulsatile experiments were also performed in pulmonary vascular endothelial cells (PMVECs) exposed to different magnitudes of pulsatility, with cell viability, the expressions of endothelial tight junction markers, adhesive molecules, endothelial-to-mesenchymal transformation (EndMT) markers, and activities of relevant signaling pathways analyzed.

Results: The pulsatile modification of ECMO enhanced microcirculatory perfusion, attenuated pulmonary inflflammation, and stabilized endothelial integrity in animal models. The pulsatile flow generated more surplus hemodynamic energy and preserved higher PWSS during ECMO. The expressions of syndecan-1 and heparan sulfate were both negatively correlated with PWSS, and significantly lower levels were observed in the pulsatile group. The non-pulsatile flow triggered EndMT in endothelial cells exposed to low pulsatility had the lowest possibility of EndMT. Moreover, arterial pulsatility stabilized the expressions of endothelial tight junction markers zonula occludens-(ZO-) 1 and occludin, followed by modulating the endothelial nitric oxide synthases (eNOS) activity and inhibiting the NF-κB signaling pathway.

Conclusion: The modification of pulsatility contributes to microcirculatory perfusion and endothelial integrity during ECMO. The maintenance of the PWSS by pulsatility during ECMO possesses beneficial effects on endothelial integrity. Moreover, pulsatility prevents EndMT in endothelial cells, and low pulsatility exhibits the best protective effects. The augmentation of pulsatility may be a plausible future direction to improve the clinical outcome in ECMO.

F02-2

Cardiac-Specific BACH1 Ablation Attenuates Pathological Cardiac Hypertrophy by Inhibiting the Ang II Type 1 Receptor Expression and the Ca2+/CaMKII Pathway

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Aims: Transcription factor BACH1 is upregulated in hypertrophic hearts, but its function in cardiac hypertrophy remains largely unknown. This research investigates the function and mechanisms of BACH1 in the regulation of cardiac hypertrophy.

Methods and results: Male cardiac-specific BACH1 knockout mice or cardiac-specific BACH1 transgenic (BACH1-Tg) mice and their

respective wild-type littermates developed cardiac hypertrophy induced by angiotensin II (Ang II) or transverse aortic constriction (TAC). Cardiac-specific BACH1 knockout in mice protected the hearts against Ang II- and TAC-induced cardiac hypertrophy and fibrosis, and preserved cardiac function. Conversely, cardiac-specific BACH1 overexpression markedly exaggerated cardiac hypertrophy and fibrosis and reduced cardiac function in mice with Ang II- and TAC-induced hypertrophy. Mechanistically, BACH1 silencing attenuated Ang II- and norepinephrine-stimulated calcium/calmodulin-dependent protein kinase II (CaMKII) signaling, the expression of hypertrophic genes, and hypertrophic growth of cardiomyocytes. Ang II stimulation promoted the nuclear localization of BACH1, facilitated the recruitment of BACH1 to the Ang II type 1 receptor (AT1R) gene promoter, and then increased the expression of AT1R. Inhibition of BACH1 attenuated Ang II-stimulated AT1R expression, cytosolic Ca2+ levels, and CaMKII activation in cardiomyocytes, whereas overexpression of BACH1 led to the opposite effects. The increased expression of hypertrophic genes induced by BACH1 overexpression upon Ang II stimulation was suppressed by CaMKII inhibitor KN93. The AT1R antagonist, losartan, significantly attenuated BACH1-mediated CaMKII activation and cardiomyocyte hypertrophy under Ang II stimulation in vitro. Similarly, Ang II-induced myocardial pathological hypertrophy, cardiac fibrosis, and dysfunction in BACH1-Tg mice were blunted by treatment with losartan.

Conclusion: This study elucidates a novel important role of BACH1 in pathological cardiac hypertrophy by regulating the AT1R expression and the Ca2+/CaMKII pathway, and highlights potential therapeutic target in pathological cardiac hypertrophy.

F02-3

YiQiFuMai injection inhibits pulmonary interstitial edema after myocardial infarction by protecting the cellular junctions via energy metabolism and ZEB1/PARD3/TBC1D2b pathway

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Background: Myocardial infarction (MI) accompanied by pulmonary interstitial edema (PIE) is a critical clinical challenge. YiQiFuMai injection (YQFM) has shown potent effects in inhibiting MI and suppressing mesenteric and cerebral microvascular exudation induced by lipopolysaccharide. However, the efficacy of YQFM in PIE after MI remains unknown.

Purpose: To investigate the effect and underlying mechanism of YQFM in alleviating PIE caused by MI.

Methods: Male rats had their left anterior descending artery ligated to establish a MI model. YQFM was administrated intravenously for 7 consecutive days. in vitro study was performed in a rat pulmonary microvascular endothelial cell line (PMVECs) subjected to hypoxia. Morphological observation of heart and lung was evaluated by H&E staining; myocardial fibrosis was observed by Masson's trichrome staining; proteomics analysis of lung tissue; ATP, ADP, AMP, BNP levels and SUCLA2 activity were assessed by ELISA; expression of proteins related to energy metabolism and cellular junctions were detected by Western Blotting.

Results: YQFM ameliorated myocardial injury and myocardial fibrosis, and improved cardiac function and energy metabolism. In addition, YQFM attenuated PIE and lung injury, and improved energy metabolism by inhibiting the activity of SUCLA2 and increasing the expression of ATP synthase α and β. YQFM protected tight and adherent junctions through up-regulation of Claudin-5, Occludin, ZO-1, VE-cadherin and down-regulation of β-catenin phosphorylation both in lung tissue and PMVECs. Furthermore, YQFM decreased the expression of ZEB1 and increased the expression of PARD3 and TBC1D2b.

Conclusion: YQFM exerted a therapeutic effect on PIE following MI through inhibition of abnormal energy metabolism and protection of cellular junctions mediated by the ZEB1/PARD3/TBC1D2b pathway in PMVECs.

Keywords: YiQiFuMai injection; myocardial infarction; pulmonary interstitial edema; energy metabolism; cellular junctions

F02-4

Evaluation of the drug-drug interaction potential of neoadjuvant chemotherapy using a physiologically-based pharmacokinetic modelling approach

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Background: A combination of the docetaxel, cyclophosphamide and epirubicin as neoadjuvant chemotherapy agents for breast cancer is intended to shrink tumors for surgery, explore drug sensitivity and guide subsequent treatment. Due to their widespread use and extremely narrow therapeutic window, there are concerns that drug–drug interactions (DDIs) may lead to treatment failure. As cytochrome P450 (CYP) 3A4 is the major enzyme involved in metabolism of docetaxel, cyclophosphamide and epirubicin, physiologically-based pharmacokinetic (PBPK) modeling was applied to predict the 3A4-mediated pharmacokinetic (PK) DDIs potential of docetaxel, cyclophosphamide and epirubicin in cancer patients.

Objective: This study aimed to assess the pharmacokinetic (PK) interactions of docetaxel, cyclophosphamide and epirubicin as neoadjuvant chemotherapy agents for breast cancer using physiologically based pharmacokinetic (PBPK) models.

Methods: The PBPK models for docetaxel, cyclophosphamide and epirubicin were constructed using the GastroPlusTM software (Version 9.8) based on the physicochemical data and PK parameters obtained from literature, in vitro studies and clinical researches, then were optimized and validated in cancer patients to predict the plasma concentration-time profiles of these three drugs and assess the predictive performance of each model. According to analysis of the properties for each drug, the developed and validated PBPK models were subsequently used to assess the extent of DDIs with neoadjuvant chemotherapy agents coadministration.

Results: The developed PBPK models described the concentration-time profiles of docetaxel, cyclophosphamide and epirubicin well, and all the fold errors of Cmax,ss, Tmax, and AUC0-t,ss were between 0.5 and 2.0 of the observed data, indicating the good prediction of the PBPK models. Based on model-based simulations, no DDIs among docetaxel, cyclophosphamide and epirubicin are expected when co-administered as neoadjuvant chemotherapy agents for breast cancer. CYP3A4 induction cyclophosphamide is predicted to have a negligible effect on docetaxel and epirubici exposure. CYP3A4 inhibition docetaxel is predicted to have a weak but negligible effec on cyclophosphamide and epirubicin exposure. The good prediction of DDIs was demonstrated by simulated plasma profiles, DDI AUC0-t,ss ratios and DDI Cmax,ss ratios.

Conclusion: The developed PBPK models adequately predicted the pharmacokinetics of docetaxel, cyclophosphamide and epirubicin, and qualified for DDIs prediction. This study increased our confidence in using PBPK model simulation to optimize clinical DDI study design and can provide reference to evaluate complex DDIs associated with eoadjuvant chemotherapy agents in breast cancer.

F02-5

Clinical study of antibiotic loaded bone cement in treatment of 104 patients with moderate to severe diabetic foot infection

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Objective To explore the clinical efficacy of antibiotic loaded bone cement in the treatment of moderate to severe diabetic foot infection (DFI) patients, and analyze the distribution characteristics of pathogenic bacteria.

Methods 167 patients with moderate to severe DFI were collected from

the Endocrinology Department of Henan Provincial People's Hospital. After admission, the tissue at the base of the wound was taken for bacterial culture to determine the pathogenic bacteria. 63 patients in the traditional group were treated with conventional therapy, while 104 patients in the study group were treated with antibiotic loaded bone cement. The healing rate, healing time, length of hospital stay, number of debridements, hospitalization costs, pain numerical rating scale (NRS) score, patient health questionnaire-9 (PHQ-9) score, generalized anxiety disorder-7 (GAD-7) score and ulcer recurrence rate were compared between the two groups.
Results A total of 132 strains of pathogenic bacteria were cultured from 167 patients, including 72 strains of gram-negative bacteria, 56 strains of gram-positive bacteria and 4 strains of fungi. A total of 78 strains of pathogenic bacteria were cultured in 104 patients in the study group, and 54 strains of pathogenic bacteria were cultured in 63 patients in the traditional group. The most common pathogenic bacteria in the two groups were Staphylococcus aureus and Escherichia coli, which were mainly gram-negative bacteria. The healing rate of the study group was higher than that of the traditional group, and the wound healing time, length of hospital stay, number of debridements, hospitalization cost, NRS score, PHQ-9 score, GAD-7 score of the study group were lower than those of the traditional group ($P<0.05$). There was no significant difference in ulcer recurrence rate between the two groups ($P>0.05$).
Conclusion Antibiotic loaded bone cement can treat wounds of DFI patients, shorten hospital length of stay, reduce medical costs and relieve patients' burden.

F02-6

Physiologically-Based Pharmacokinetic (PBPK) Modeling of midazolam injection in neonates

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Objectives: Midazolam is a short-acting benzodiazepine that can be used for sedation and anti-anxiety in pediatric patients under 6 months of age during diagnosis, treatment, pre-endoscopy, and induction of anesthesia. However, the specific clinical dosage recommended is unclear. Therefore, the objective of this study was to developed physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) models to predict effective doses of midazolam in pediatrics for the treatment of assist sedation.
Methods: A midazolam PBPK model was constructed using a population-based absorption, distribution, metabolism and excretion simulator, GastroPlusTM (Version 9.8), with physicochemical and in vitro data, develop and optimize adult models based on clinical literature data from single dose administration. Considering the ontogeny and physiological anatomy changes of the pediatric population, the developed adult PBPK model was extrapolated to the newborn population to establish the neonatal PBPK model. A popPK model was also developed from PK data obtained from the database search. Combining the adult popPK model with an allometric scaling strategy considering individual physiological development to establish a neonatal popPK model.
Results: The developed PBPK models well described the concentration-time profiles of midazolam, and all the fold errors of AUC, Cmax, Tmax are mostly between 0.5 and 2.0 of the observed data, indicating the good prediction of the PBPK models. The PopPK model of midazolam in pediatric patients was developed. Postnatal age (PNA) significantly affected the pharmacokinetic parameters of midazolam of pediatric patients. The model evaluation results suggested robustness and good predictability of the final model.
Conclusions: Both PBPK and popPK approaches can reasonably predict midazolam exposures in neonate. By exploring the feasibility of neonatal pharmacokinetic extrapolation method in neonates, it provides effective evidence for the application of modeling and simulation techniques in drug study of neonatal population.

FREE ORAL COMMUNICATION 3

Cerebral Microvascular Injury and Microcirculation

10:00-11:30 | Room 5

F03-1

Erythropoietin-derived peptide ARA290 mediates brain tissue protection through the β-common receptor in mice with cerebral ischemic stroke

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Background and purpose: Many experimental studies and some clinical trials in the last two decades have explored neuroprotective function of erythropoietin (EPO) in cerebral ischemic stroke. Unfortunately, the hematopoietic side-effects and the unfavorable interactions with recombinant tissue plasminogen activator (rtPA) limit its clinical application. Previous studies showed ARA290 (also called Cibinetide, 11 amino acid derived from the structure of helix B of the erythropoietin) mediated tissue protection against acute kidney injury and myocardial ischemic injury. However, few studies have investigated the neuroprotective effects of ARA290 on ischemic stroke, the underlying mechanisms and whether the β-common receptor (βCR) was involved are poorly defined. This study investigated the neuroprotective effects of ARA290 in mice following transient focal cerebral ischemia.
Methods: Male C57BL/6J mice were subjected to middle cerebral artery occlusion (MCAO) and reperfusion. ARA290, EPO or equal volume of normal saline was injected intraperitoneally. Neurological function was assessed by Longa test and modified neurological severity score (mNSS). Infarct volume and edema volume of the brains was measured by TTC staining. Neuronal apoptosis was detected by TUNEL staining. ELISA was performed to assess the inflammatory factors. Western blotting was applied to detect the protein level of EPOR and β-common receptor (βCR).
Results: Compared with EPO, ARA290 exerts qualitatively similar effects on reducing brain infraction, and improving neurological function after MCAO. As expected, ARA290 antagonizes the erythropoietic effects of EPO on erythroid cells. The results also showed that ARA290 significantly reduced neuronal apoptosis, and inflammatory cytokines (tumour necrosis factor α, interleukin-1β, and interleukin-6) in the brain 7 days after I/R injury, which might be contribute to the improvement of neurological function and tissue integrity. However, the ARA290's neuroprotective effect was largely suppressed by intracerebroventricular injection of siRNA against βCR.
Conclusion: ARA290 improved neurological function and brain tissue integrity via βCR, and ARA290 also suppressed the neuronal apoptosis and inflammatory reaction in cerebral ischemic mice without motivating erythropoiesis. This study provides novel insight into ARA290 for ischemic stroke intervention.
Keywords: Cerebral ischemia, ARA290, β-common receptor, Neuroprotection

F03-2

Knock down of lncRNA H19 attenuates cerebral ischemia/reperfusion injury by regulating IMP2

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Background: Ischemic stroke, characterized by a high incidence and high disability rate, is one of the leading causes of death worldwide. Long noncoding RNAs (lncRNAs), aberrantly expressed in the central nervous system (CNS), play an important role in the pathophysiological process of acute ischemic stroke and may be potential biomarkers for the diagnosis and treatment of ischemic stroke.
Objective: The present study aimed to explore the effects of knockdown lncRNA H19 on neural function, cerebral blood flow, angiogenesis and blood-brain barrier (BBB) in cerebral ischemia/reperfusion mice, and to explore the regulatory mechanisms of lncRNA H19 in ischemic stroke.
Methods: In our study, male C57BL/6 J mice were used to establish a cerebral ischemia/reperfusion injury model by using middle cerebral artery occlusion/reperfusion (MCAO/R). In addition, sh-NC, sh-H19, sh-IMP2 were injected into the lateral ventricle. Neurobehavioral tests, TTC staining and laser speckle imaging technique were performed to evaluate the neuronal injury, infarcted area and cerebral arteries occlusion and reperfusion following ischemic stroke. Further, the expression levels of tight junction proteins (claudin5, ZO-1) and vascular endothelial cell markers (VEGFR2, CD31) were detected by western blot and immunofluorescence staining.
Results: We found that knockdown of H19 significantly reduced the volume of brain tissue loss, increased cerebral blood flow and promoted the recovery of neurological function. Knockdown of H19 can also promote angiogenesis and reduce BBB injury in cerebral ischemia/reperfusion mice. However, knocking down IMP2 reversed the protection effects of H19 knockdown, indicating that knocking down H19 attenuates cerebral ischemia/reperfusion injury through regulating IMP2.
Conclusion: Taken together, our results demonstrated that knockdown H19 could promote angiogenesis and reduce BBB damage after ischemic stroke by regulating IMP2, suggesting that lncRNA H19 might be a biomarker for the diagnosis and prognosis of ischemic stroke.

F03-3

Electroacupuncture improves post-stroke central pain in rats by regulating miR-21-5p/Smad7 pathway

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Background: Central post-stroke pain (CPSP) is a chronic neuropathic pain caused by central nervous system damage or dysfunction following cerebrovascular injury. It is a difficult-to-treat disease that severely affects patients' physical and psychological health and increases the social and economic burden. Although the underlying mechanism is not yet clear, clinical features of somatic pain and sensory dysfunction suggest that central sensitization is its fundamental mechanism. The interaction between glial cells and neuroinflammation has played a significant role in the pathogenesis of pain. However, the specific mechanism of this interaction is still unclear. miR-21-5p has been found to be a potential therapeutic target for alleviating inflammation-related pain. In addition, Smad7, as a negative regulator of the TGF-β/Smads signaling pathway, and its negative regulation of miR-21-5p, also play an important role in the pathogenesis of pain. In this study, we investigated the regulatory mechanism of electroacupuncture on the miR-21-5p/Smad7-mediated TGF-β/Smads signaling pathway in a rat model of CPSP, providing a basis for the use of electroacupuncture in treating CPSP.
Methods: A rat model of CPSP was induced by intracerebral hemorrhage in young male SD rats, and adenoviral transfection was used to inhibit or overexpress miR-21-5p and Smad7. Pain behavior, glial cell activation, neuroinflammation, and the expression of key proteins in the TGF-β/Smads signaling pathway were evaluated to explore the mechanism by which electroacupuncture mediates the activation of glial cells and neuroinflammation by regulating the miR-21-5p/Smad7-mediated TGF-β/Smads signaling pathway to alleviate post-stroke pain.
Results: Analysis of the perilesional tissue around the thalamus of rats with central post-stroke pain (CPSP) revealed that after electroacupuncture intervention, the pain threshold of CPSP rats increased, the activation of astrocytes was inhibited, and the expression of IL-1β, IL-6, and TNF-α decreased. By transfecting with adenovirus miR-21-5p inhibitor and overexpression plasmid, it was found that inhibiting miR-21-5p increased the pain threshold of CPSP rats, increased the number of neurons, reduced damage, and inhibited the activation of astrocytes and microglia. The expression of IL-1β, IL-6, and TNF-α also decreased. In addition, in vivo and in vitro experiments found that miR-21-5p and Smad7 have a negative regulatory relationship. By transfecting with adenovirus Smad7 inhibitor and overexpression plasmid, it was found that overexpression of Smad7 increased the pain threshold of CPSP rats, inhibited the activation of astrocytes and microglia, and reduced the expression of IL-1β, IL-6, and TNF-α. Conversely, after knocking out Smad7 on the basis of electroacupuncture, compared with the electroacupuncture group, the pain threshold of CPSP rats decreased, the abnormal activation of astrocytes and microglia increased, and the expression of IL-1β, IL-6, and TNF-α increased. Furthermore, in CPSP rats transfected with miR-21-5p inhibitor and overexpression plasmid, it was found that activation of the TGF-β/Smads-mediated neuroinflammatory signaling pathway occurred.
Conclusion: This study provides evidence that the interaction between astrocyte activation and neuroinflammation is involved in the mechanism of CPSP. Considering the previously reported pain and neuroprotective effects of miR-21-5p and Smad7, miR-21-5p inhibitors may be used as a multifunctional method for central neuropathic pain. By negatively regulating Smad7, astrocyte activation, neuroinflammation, and downstream central sensitization can be inhibited.

F03-4

Association of microvascular complications with reduced neuronal activity and cognitive impairment in type 2 diabetes mellitus: a resting-state fMRI study

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Background: Adults with type 2 diabetes are at an increased risk of developing microvascular complications including diabetic nephropathy, retinopathy and neuropathy. Recently, more and more imaging studies of type 2 diabetes mellitus have reported structural and functional abnormalities in a variety of spatially diverse brain regions. The complex network in the human brain is the physiological basis for information processing and cognitive expression. Increasing amounts of data suggest that diabetes-related microvascular dysfunction is associated with a higher risk of cognitive impairment. However, the underlying mechanism is still unclear.
Objective: This study aimed to investigate whether microvascular complications were associated with cognitive performance and brain dynamics in patients with type 2 diabetes mellitus (T2DM) based on resting-state fMRI analysis.
Methods: Ninety eight patients with T2DM (55 diabetic patients without microvascular complications(DM) and 43 diabetic patients with microvascular complications(DM-C)) were recruited for Montreal Cognitive Assessment test (MoCA), Mini-Mental State Examination (MMSE), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS) and neural activity of brain which was measured by rest-state function MRI (rs-fMRI).
Results: Diabetic patients with microvascular complications

displayed a significantly decreased score on MoCA, compared to the DM group (P=0.048). Among rs-fMRI parameters, no significant difference was observed in voxel-based morphometry (VBM). And meanwhile, mean amplitude of low-frequency fluctuations (mALFF) significantly decreased in the right cuneus, right calcarine, right superior occipital gyrus, right inferior occipital gyrus,and bilateral precentra in diabetic patients with microvascular complications, compared to DM patients. Futhermore, compared with DM patients, Diabetic patients with microvascular complications patients showed a significantly decreased mean regional homogeneity (mReho) in the left hippocampu, bilateral calcarine, left inferior occipital gyrus, and increased mReho in the left middle frontal gyrus. The mReho were positively correlated with MoCA (P = 0.009, r = 0.264) in diabetic patients.

Conclusions: Our findings suggest that diabetic patients with microvascular complications displayed more impaired cognition. Decreased neuronal activity in visual network and memory center was well correlated with diabetes-related microvascular dysfunction.

Keywords: cognitive function;MoCA; rs-fMRI; mALFF; mReho

F03-5

Differential impact of factor XII, factor XI and prekallikrein deficiency on thrombosis in mice

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Objective: Factor XII (FXII) initiates the plasma contact system that triggers the intrinsic coagulation pathway and the kallikrein-kinin pathway via factor XI (FXI) and plasma prekallikrein (PK), respectively. The importance of the contact system for thrombosis sparing hemostasis is well established, however a comprehensive head-to-head comparison of the three proteases in arterial thrombosis is missing.

Approach and Results: We produced mice deficient in FXII (F12-/-), FXI (F11-/-) and PK (Klkb1-/-) and compared them in two distinct thrombosis models. While all (100%) of WT mice formed occlusive thrombi upon ferric chloride challenge, carotid artery occlusion was reduced to 0, 4.8, 27.3 % in F12-/-, F11-/- and Klkb1-/- mice (n=14-22), respectively. Upon photochemical-induced cremaster arteriolar thrombosis, occlusion time (s) prolonged to 226.1±60.4, 123.8±32.0 and 87.8±25.3 (mean±SEM, n=10-15) respectively in F12-/-, F11-/- and Klkb1-/- mice, largely exceeding WT levels (38.3±12.1). A discordance was observed between in vivo thrombotic effects of the proteases and their roles for ex vivo coagulation, which ranked FXII≈FXI>PK as assayed by thromboelastography and activated partial thromboplastin time. Activation of FXII promoted thrombosis in WT and Klkb1-/- mice and, impressively, it also accelerated thrombosis in F11-/- mice, increasing activated PK activity and plasma bradykinin formation. Infusion of bradykinin and blockade of degradation of endogenous bradykinin increased platelet-endothelium adhesion and promoted thrombotic occlusions, which involved bradykinin mediated endothelial cell-release of platelet activating factor, rather than direct activation of platelets by bradykinin.

Conclusion: FXII, FXI and PK differentially mediate experimental thrombosis in vivo and FXII/FXI appear as superior targets for thrombosis as compared to PK. PK-bradykinin axis activated by FXII contributes to thrombosis in vivo.

F03-6

Panax notoginseng saponins promotes angiogenesis after cerebral ischemia-reperfusion injury

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Background: Ischemic stroke is a devastating disease that can result in permanent disability and death, and angiogenesis plays a critical role in the recovery and survival of patients and animal models of ischemic stroke. Panax notoginseng has been used as a key herb in the treatment of stroke diseases due to its effect in promoting blood circulation and removing blood stasis. However, the role of Panax notoginseng saponins, in promoting angiogenesis is unclear.

Purpose: This study is aimed to investigate the effect of Xueshuantong (XST) injection, composed of Panax notoginseng saponins in post-stroke revascularization.

Method: In the present study, a middle cerebral artery occlusion/reperfusion model was established in Sprague-Dawley rats, with XST and the positive drug Dl-3-n-butylphthalide (NBP) administered via intraperitoneal injection to observe vascular changes after stroke. The protective and pro-angiogenic effects of XST after stroke were demonstrated by Triphenyltetrazolium chloride staining and optical coherence tomography angiography. Subsequently, network pharmacology and molecular docking techniques, as well as in vitro experimental validation, were used to further analyze the potential mechanism by which XST promotes angiogenesis.

Results: The results showed that XST could reduce the cerebral infarction region in rats. And the neovascularization in the ischemic area of the rat brain significantly increased after 7 or 14 days of XST administration. Furthermore, XST could activate the vascular endothelial growth factor A (VEGFA)/vascular endothelial growth factor receptor 2 (VEGFR2), and hypoxia-inducible factor 1 (HIF-1) signaling pathways.

Conclusion: XST may promote post-stroke angiogenesis by affecting the VEGFA/VEGFR2 and HIF-1 signaling pathways.

FREE ORAL COMMUNICATION 4

Kidney and Lung Microcirculation

10:00-11:30 | Room 6

F04-1

D-Ribose Induces Podocyte NLRP3 Inflammasome Activation and Glomerular Injury via AGEs/RAGE Pathway

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D-ribose levels are demonstrated to be increased in type II diabetes mellitus and increased blood D-ribose is involved in the development of diabetic complications such as diabetic encephalopathy and nephropathy. However, the mechanism mediating the pathogenic role of D-ribose in nephropathy remains poorly understood. Given that D-ribose was reported to induce advanced glycation end products (AGEs) formation, the present study tested whether D-ribose induces NLRP3 activation and associated glomerular injury via AGEs/receptor of AGEs (RAGE) signaling pathway. In vivo, C57BL/6J and Asc−/− mice were treated with D-ribose with or without AGEs inhibitor. Administration of D-ribose daily for 30 days was found to induce NLRP3 inflammasome formation in glomerular podocyte, as shown by increased co-localization of NLRP3 with apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) or caspase-1. This D-ribose-induced NLRP3 inflammasome formation was accompanied by its activation as evidenced by increased IL-1β production, a major product of NLRP3 inflammasome. Corresponding to NLRP3 inflammasome activation, D-ribose led to significant glomerular injury in mice. All these D-ribose-induced glomerular inflammasome and associated pathological changes were markedly attenuated by deletion of Asc gene. Furthermore, the accumulation of AGEs and RAGE was found increased in glomeruli of mice receiving D-ribose. In cell studies, we also confirmed that D-ribose induced NLRP3 inflammasome formation and activation in podocytes, which was significantly blocked by caspase-1 inhibitor, YvAD. Mechanically, AGEs formation inhibition and cleavage or silencing of RAGE gene were shown to suppress D-ribose-induced NLRP3 inflammasome formation and activation, as shown by significant reduction of NLRP3 inflammasome molecular aggregation, caspase-1 activity and IL-1β production. These results strongly suggest that relatively long term administration of D-ribose induces NLRP3 inflammasome formation and activation in podocytes via AGEs/RAGE signaling pathway, which may be one of important triggering mechanisms leading to diabetic nephropathy.

F04-2

The Protective Effects of a Pure Chinese Medicinal Preparation from Eucommia Ulmoides and Pinoresinol Diglucoside on Renal and Intestinal Wall Microcirculatory Blood Perfusion and Vasomotion in Spontaneously Hypertensive Rats

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Objective: To investigate the protective effects of a pure Chinese medicinal preparation from *Eucommia ulmoides* Oliver called Quanduzhong Jiaonang (QDZJN). and pinoresinol diglucoside on renal and intestinal wall microcirculatory blood perfusion and vasomotion in spontaneously hypertensive rats**.**

Methods: 30 spontaneously hypertensive rats (SHRs) were randomly divided into SHR, SHR+ QDZJN, SHR+PDG (L), SHR+PDG (M) and SHR+PDG (H) group, with 6 SHRs per group. 6 WKYs rats were used as the control group. All treatment groups were given intragastric administration of QDZJN or pinoresinol diglucoside (PDG), or pure water. After 2 months of continuous administration, the rats' kidneys and intestine were exposed by surgery. Microcirculatory blood perfusion of renal and intestinal wall was measured and compared by laser Doppler flowmetry (LDF) and laser Doppler perfusion imaging (LDPI) among six groups. Wavelet transform analysis was performed to convert LDF signals into three-dimension time-frequency domains, based on which amplitude spectral scalograms were constructed. The amplitudes of NO-independent endothelial and NO-dependent endothelial oscillators were compared among six groups.

Results: Compared with the control group, renal and intestinal wall perfusion level were significantly decreased in SHRs group ($P<0.0001$). After 2-month treatment, renal and intestinal wall blood perfusion level in SHR+QDZJN group and SHR+PDG group was significantly increased compared with SHR group. The amplitudes of NO-dependent and -independent endothelial oscillators in SHR group were significantly lower than those in control group. PDG (M) and PDG (H) significantly enhanced the amplitudes of SHRs renal NO-dependent and -independent endothelial oscillator. While QDZJN only enhanced the amplitude of renal NO-dependent endothelial oscillator. QDZJN and each dosage of PDG significantly enhanced the amplitudes of NO-dependent and -independent endothelial activity of intestine wall perfusion in SHRs

Conclusion: The microhemodynamics and endothelial function of SHRs kidney and intestinal wall were abnormal, and the treatment of QDZJN and PDG for 2 months could significantly improve the microhemodynamics and endothelial function of kidney and intestinal wall in SHRs.

F04-3

SHR Improves the Prediction of Contrast-Induced Nephropathy in NSTE-ACS Patients Undergoing PCI: A Retrospective Cohort Study

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Background The stress hyperglycemia ratio (SHR), a new indicator of relative hyperglycemia, was significantly associated with increased adverse cardiovascular clinical outcomes and in-hospital mortality. Studies regarding the relationship between SHR and incidence of contrast-induced nephropathy (CIN) in non-ST elevation acute coronary syndrome (NSTE-ACS) patients undergoing percutaneous coronary intervention (PCI) are limited.

Methods A total of 860 participants were recruited and divided into two groups based on the occurrence of CIN. The SHR was calculated using the following equation: SHR = admission blood glucose (mmol/L)/[1.59×HbA1c(%) – 2.59]. Baseline characteristics and incidence of CIN were compared between the two groups. Logistic regression analysis and receiver operating characteristic (ROC) curve were performed to evaluate the relationship between the SHR and CIN.

Results 92 participants (10.7%) developed CIN. Compared with the non-CIN group, the CIN group had a significantly higher SHR [0.713(0.652,0.766) vs. 0.907(0.862,0.998), $P<0.001$]. After adjusting for confounding factors, the SHR was significantly related to the increased risk of CIN, behaving as a J-shaped non-linear association. Moreover, the ROC presented that the risk assessment performance of the SHR was superior to other single hyperglycemic indexes. By incorporating SHR to the baseline model showed an increase in the area under the curve from 0.645(0.612-0.701) to 0.720(0.702-0.759).

Conclusion The SHR is an independent predictor of CIN in NSTE-ACS patients undergoing PCI, and may serve as a better predictor as well as a potential target for tailored glucose-lowering treatment in these patients.

F04-4

Value of contrast-enhanced ultrasound in evaluating foot microcirculation in diabetes

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Background&Objective: Macrovascular and microvascular lesions in the lower limbs can affect the prognosis of diabetes foot. Lower limb vascular ultrasound and ankle brachial index can reflect the condition of lower limb large blood vessels in diabetes patients to a certain extent, while the detection means of foot microcirculation are limited. The purpose of this study was to explore the value of contrast-enhanced ultrasound (CEUS) in assessing microcirculation in patients with diabetic foot.

Methods: This study included 28 patients with diabetic foot. In addition to collecting case data, testing blood glucose, blood lipids, renal function, etc., the lower extremity vascular ultrasound, ankle-brachial index, and toe-brachial index were examined. After intravenous injection of 2ml of sulfur hexafluoride microbubble ultrasound contrast agent, real-time ultrasound contrast was continuously performed using a 2-5MHz convex probe. The development time of popliteal artery and popliteal vein was recorded, and the blood perfusion performance of the first interdigital artery of the right foot was measured by CEUS. The measured parameters include starting time, peak time, peak intensity, peak half-time, area under the curve, average transit time, rising slope and falling slope. According to whether the three lower knee arteries (anterior tibial artery, posterior tibial artery and peroneal artery) are occluded or not, they are divided into occluded group and blood flow unobstructed group. The clinical data, ankle brachial index, toe brachial index, starting time, peak time, peak intensity, peak half-time, area under the curve, average transit time, rising slope and falling slope were compared between the two groups.

Results: The ankle-brachial index in the occlusive group was lower than that in the unobstructed group (0.80 ± 0.38 vs 1.13 ± 0.22, P=0.02), and there was no difference between the two groups (0.48 ± 0.29 vs 0.65 ± 0.25, P=0.132). The development time of popliteal artery in occlusive group was shorter than that in blood flow unobstructed group (21.2 ± 4.5s vs 27.5 ± 6.8s, P=0.019), and the development time of popliteal vein was shorter than that in blood flow unobstructed group (21.2 ± 4.5s vs 27.5 ± 6.8s, P=0.055). The peak intensity, ascending slope and descending slope of contrast-enhanced ultrasound in the occlusive group were significantly different from those in the blood flow unobstructed group (P<0.05), and the area under the curve in the occlusive group was lower than that in the blood flow unobstructed group (P=0.078).

Conclusion: As a non-invasive and valuable technique, CEUS can detect the foot microcirculation of patients with diabetic foot. CEUS showed that the foot microcirculation of diabetic foot patients with lower limb vascular occlusion was worse.

F04-5

Network Pharmacology and Experimental Assessment to Explore the Effects of Shenzhuo Formula against Diabetes Kidney Disease Podocyte Apoptosis

Lili Zhang [1], Yu Wei [1,2], Yishan Huang [1], Runny Miao [1,2], Xinyi Fang [1,2], Linyuan Xue [3], Danni Zhou [4], Xiangyuan Zhang [1,2], Jing Ma [5], Xiangyan Li [6], Linhua Zhao [1], Xiaolin Tong [1]

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Podocyte morphology and function abnormalities are the main determinants of diabetes kidney disease (DKD). Identifying potential therapeutic drugs by mediating podocyte apoptosis is of great clinical significance. Shenzhuo formula (SZF) is a classic prescription for treating DKD, which has a substantial renal protection effect on DKD patients, but the mechanism of this protection remain unclear. The study aims to investigate the mechanism of SZF against DKD. We first conducted UHPLC/Q-TOF-MS to clarify the material basis of SZF, and applied network pharmacology and target organ localization to predict that SZF may exert renal protective effects by inhibiting cell apoptosis and improving microcirculation. Subsequently, db/db mice and zebrafish were used as research objects. The results suggested that SZF could reduce urinary albumin excretion of db/db mice, inhibit renal podocyte injury and apoptosis, improve microcirculation, and delay the progression of DKD. In addition, SZF can improve microvascular dysfunction and hemodynamics by improving the diameter of internode vessels of zebrafish, preventing thrombosis, increasing blood flow velocity and cardiac output, and thus improving microcirculation. In conclusion, SZF may reduce albuminuria, protect renal function and delay the progression of DKD by inhibiting podocyte apoptosis and improving microcirculation.

F04-6

Inhibition of Endothelial-to-Mesenchymal Transition and Capillary Injury With TFA Alleviates Renal Fibrosis in Diabetic Kidney Disease

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The total flavones of *Abelmoschus manihot* (TFA) is an anti-inflammatory compound extracted from a Chinese herbal medicine, A*belmoschus manihot*, which has been widely used in the treatment of diabetic kidney disease (DKD) in China. Recently, endothelial-to-mesenchymal transition (EndMT) has been proved to promote renal fibrosis (RF) and capillary injury in microcirculation disorder in DKD. Our previous studies showed that TFA can improve DKD. However, the underlying mechanisms remain unclear. Therefore, this study investigated the effects of TFA on RF in DKD and its possible new mechanisms regarding EndMT and capillary injury. In this study, we used db/db mice and high-glucose (HG)-induced human glomerular endothelial cells (GenCs) as the models in *vivo* and in *vitro*, respectively. We also used western blot (WB), immunohistochemistry (IHC) and immunofluorescence (IF) staining to detect the protein expression levels, which are related to EndMT and autophagy. The mechanisms of TFA on RF in DKD were revealed using Tandem Mass Tag (TMT)-based proteomics analysis. In addition, the roles of histone deacetylase 1 (HDAC1) in the GEnCs under a state of HG were clarified by transfecting with small interfering RNA (siRNA). After TFA treatment for eight weeks, the DKD models' renal dysfunction, massive extracellular matrix (ECM) deposition, and capillary injury were significantly improved, respectively. In the HG-induced GenCs, cellular EndMT was attenuated by the activation of autophagy. TFA restored autophagy and decreased EndMT *in vivo* and *in vitro*. The results of proteomics analysis indicated that HDAC1 was significantly downregulated in the 136 mg/kg/d TFA group when compared with the DKD model group. Transfection of the GenCs with SI-HDAC1 partially blocked HG-induced EndMT and restored autophagy. In addition, TFA inhibited the phosphorylation of PI3K/Akt/mTOR signaling pathway. Finally, we found that rapamycin (RAP), a specific inhibitor of mTOR, inhibited HDAC1 overexpression in the HG-induced GenCs, which was verified the association between mTOR and HDAC1. In conclusion, this study demonstrated that TFA alleviates RF in DKD by inhibiting EndMT and capillary injury and restoring autophagy through regulating the PI3K/Akt/mTOR/HDAC1 signaling pathway. This study provides a novel understanding of how TFA can reduce RF in DKD.

FREE ORAL COMMUNICATION 5

Endoplasmic Reticulum, Mitochondria and Cell Death

15:00-16:30 | Room 6

F05-1

Vascular endothelial cell-specific arginase 2 is involved in vasculopathies through regulating mitochondrial dynamics in diabetes

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Aims: Elevation of arginase activity has been linking to vascular endothelial dysfunction in various diabetic complication. Arginase 2(Arg2), one of the arginine proteases, is only expressed in mitochondria, but the mechanism of its role in diabetic vascular complications remains unclear. Mitochondrial dysfunction plays one of the key characteristics in endothelial cell dysfunction under a variety of cardiovascular and cerebrovascular diseases. The aim of this study is to investigate whether diabetes-induced blood circulation damage and vasculopathies are mediated by Arg2 in vascular endothelial cells (ECs), which occur through mitochondrial dysfunction.
Methods and results: To test this proposition, we performed a series of experiments including laser doppler, cardiac ultrasound and electromyography in mice of overexpression and knockdown Arg2 in ECs to assess blood circulation and vascular damage. We found that the overexpression of Arg2 in ECs impaired vascular function and blood circulation, whereas endothelial Arg2 knockdown had no significant effect on that. Meanwhile, we established the diabetic mouse model using STZ to determine the effect of Arg2 knockout on the vasculature of diabetic mice. Knockout of Arg2 in ECs can partially protect the damage of macro-circulation and micro-circulation, and also has a certain improvement on vascular stiffness, abnormal vascular permeability and endothelial impairment caused by diabetes. In addition, we further found that knockdown of Arg2 in human umbilical vein endothelial cells not only prevented vascular endothelial dysfunction, but also balanced mitochondrial dynamics in a diabetic model. Combined with in *vivo* and in *vitro* experiments, it was demonstrated that reducing Arg2 in ECs could improve mitochondrial respiration, reduce mitochondrial fragmentation, and restore the endothelial damage under the high glucose condition.
Conclusion: Overexpressed Arg2 in ECs can cause blood circulation damage and vasculopathies and endothelial Arg2 deletion can prevent vascular damage from diabetes through modulating mitochondrial dynamics. This finding indicates that endothelial Arg2 is a critical regulator of mitochondrial dynamics and thereby affecting endothelial vascular function and blood circulation. Specific deficiency of Arg2 may represents a novel therapy for vascular injury and cardiovascular disease.

F05-2

TFEB nitration alleviating autophagy is involved in vascular endothelial cell senescence in hyperhomocysteinemia

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Endothelial senescence has been identified as an important factor in various cardiovascular and metabolic diseases. Hyperhomocystinemia(HHcy) is a known factor for multiple organ damage, and the organ damage caused by HHcy may be secondary to endothelial senescence, but the mechanism is unclear. There is sufficient evidence that stimulation of autophagic flow extends both healthspan and lifespan. TFEB is a master regulator of autophagy-lysosome biogenesis, and regulation of TFEB mainly occurs at the post-translational level. HHcy stimulates the increased level of nitrative stress in vivo, which causes nitrative modification of aromatic amino acid residues of proteins, leading to the change of protein functional activity. In this study, we established the HHcy rat model by feeding a 2.5% methionine diet. Both the large arteries represented by the thoracic aorta or the small arteries represented by the mesenteric arteries showed endothelial systolic dysfunction with increased collagen deposition in the vessel wall, upregulation of cell cycle arrest protein P16 / P21 / P53, and downregulation of autophagy level. However, autophagy was up-regulated by overexpression of TFEB or ATG5, partially reversing homocysteine-induced endothelial senescence. HHcy vessels showed increased 3-NT level(a form of nitrative modification of tyrosine residues), and nitrative modification of TFEB was increased. Further studies showed that nitration of TFEB at Tyr33(TFEB^{Y33}) inhibits nuclear translocation and autophagy. The elevated level of TFEB nitration, especially nitration at TFEB^{Y33}, is an important target for combating homocysteine-induced endothelial senescence. Our present work provides new preventive strategies for rescuing vascular endothelial senescence to prolong healthy lifespan.

F05-3

Serpina3c derived from peripheral adipocytes alleviates atherosclerosis by inhibiting perivascular adipose tissue inflammation

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Background: Perivascular adipose tissue (PVAT) inflammation promotes atherosclerosis (AS). Serpina3c is a secretory serine protease inhibitor associated with AS which is highly expressed in adipocytes, but it is unclear whether it can affect AS by regulating PVAT inflammation.
Purpose: The present study aimed to investigate the effect of Serpina3c derived from perivascular (PV) adipocytes on PVAT inflammation and AS.
Methods: ApoE-/- mice were ligated the right common carotid artery and transplanted epididymis white adipose tissue (eWAT) around the artery, then fed with high fat diet for 4 weeks. The transplanted eWAT was taken from Serpina3c knockout mice and injected with an adenoviral vector containing its human homolog kallistatin (KS) gene (3cKO/Ad.HKS) or adenoviral vector alone (3cKO/Ad.Null). AS plaque and adipose tissue inflammation were evaluated by Oil Red O staining, Haematoxylin-Eosin (HE) (H&E) staining, immunohistochemistry, western blot and qRT-PCR.
Results: The Serpina3c content in the adventitia of abdominal aorta in ApoE-/- mice was significantly higher than that in the intima. Serpina3c in the PVAT around abdominal aorta in ApoE-/- mice decreased after HFD. The expression level of serpina3c in adipocytes was markedly higher than that in endothelial cells and vascular smooth muscle cells, and macrophages almost didn't express Serpina3c. The TLR4/NF-κB pathway and the pro-inflammatory factor TNF-α and IL-17 reduced, meantime the anti-inflammatory factor adiponectin and vaspin increased in 3cKO/Ad.HKS eWAT compared with 3cKO/Ad.Null eWAT under HFD condition. Most importantly, the carotid AS plaque in 3cKO/Ad.HKS mice was significantly lightened than 3cKO/Ad.Null mice. There were no difference in body weight, blood glucose and lipids between the two groups.
Conclusion: Serpina3c in mainly comes from PV adipocytes and its expression is down-regulated after HFD, which enhances the TLR4/NF-κB pathway, thereby promoting PVAT inflammation and AS progress.

F05-4

Semaglutide alleviates endothelial cell injury induced by high glucose and fat through regulating mitochondrial energy balance

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Semaglutide, a long-acting Glucagon-like peptide-1 receptor agonist (GLP-1RA), was approved for treating type 2 diabetes in adults in China in April 2021. Many clinical studies have demonstrated that GLP-1RA can improve cardiovascular outcomes in diabetic and non-diabetic patients, but the specific mechanism has not been revealed. In this study, human aortic endothelial cells (HAEC) were treated with semaglutide in vitro, and mitochondrial membrane potential(MMP) was evaluated by flow cytometry. ATP content was detected by the fluorescence probe method. The mitochondrial dynein protein Drp1 was tested by immunofluorescence. The results showed that semaglutide in vitro could alleviate the decrease of MMP ($P<0.05$), increase ATP content ($P<0.05$), and reduce the abnormal over-expression of Drp1 ($P<0.05$) in HAEC injury induced by high glucose and fat. These studies suggested that semaglutide can alleviate HAEC injury induced by high glucose and fat by regulating mitochondrial energy balance.

Keywords: Semaglutide; Energy metabolism; High glucose and fat; Vascular endothelial cells

F05-5

The mechanism of HDAC4 regulating mitophagy of fibroblasts on wound healing of diabetic foot ulcers

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Background: Diabetic Foot Ulcer (DFU) is one of the serious chronic complications that cause disability and death in diabetic patients. Up to 15%~25% of DM patients will have protracted chronic ulcers. DFU is the leading cause of amputation incidence and mortality. Currently, there is no effective treatment for DFU. Moreover, the underlying molecular mechanisms for the development of DFU have not been clearly described. In an in vitro culture of peripheral blood mononuclear cells in diabetic patients, it was shown that the level of DFU histone acetylatase HDAC4 was elevated compared to the control group. However, the molecular mechanism of HDAC4 in DFU has not been elucidated. Mitophagy plays an important role in maintaining cell functional homeostasis, in acute injury, the autophagic lysosomal system can effectively remove damaged components and harmful substances, but with the extension of time, the autophagic system will inevitably lead to excessive loss of cellular components, which will be detrimental to the subsequent recovery of cells. Whether this is the cause of the difficulty of wound healing in DFU patients needs further study.

Purpose: Investigating whether HDAC4 delays wound healing in DFU patients through mitochondrial autophagy

Methods: The skin tissues of DFU patients and traumatized healthy patients were collected, and the expression of HDAC4 factors in different Wagner grade DFU patients was verified by immunohistochemical experiments. The quantitative real-time polymerase chain reaction (qPCR) and western blot (WB) was used to identify the impact of the concentration of glucose on the expression of HDAC4 at the cell level, and detect the expression of mitophagy-related proteins (PINK1, BNIP3) after HDAC4 being inhibited. Targeting mt-Keima with mitophagy reporter gene was transfected into fibroblasts to verify the relationship between HDAC4 and mitophagy. Transcriptome sequencing was then performed to look for possible signaling pathways in which HDAC4 regulates mitophagy.

Results: HDAC4 is expressed in different Wagner grade DFU patients. As glucose concentration increases, HDAC4 factor expression increases. After inhibition of HDAC4, the expression of mitophagy-related proteins decreased, indicating that inhibition of HDAC4 can reduce mitophagy, thereby reducing the damage of cellular components caused by prolonged mitophagy injury, which may help wound healing in DFU patients.

Conclusions: Together, our results established that HDAC4-mediated mitophagy plays an important role in DFU wound healing.

F05-6

The crude polysaccharide of Fructus Ligustri Lucidi relieved renal fibrosis of UUO mice and I/R mice by alleviating kidney mitochondrial injury

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Background: The incidence of acute kidney injury (AKI) is increasing dramatically worldwide. AKI manifests as an acute decline of kidney function and is mostly triggered by renal ischemia, tubular obstruction, and renal toxic substances. Fructus Ligustri Lucidi (FLL), the fruit of *Ligustrum Lucidum* Ait. (Oleaceae), belongs to kidney-tonifying herb in principle of traditional Chinese medicine. It has now gained broad attention as an alternative medicine in treating various kidney diseases due to its actions on nourishing kidney and liver. This study aimed to elucidate the therapeutic effects and pharmacological mechanisms of the crude polysaccharide (CP) of FLL for AKI.

Methods: The CP of FLL was extracted using the method of alcohol extraction-water precipitation. The mice underwent the surgeries of unilateral ureteral obstruction (UUO) or ischemia-reperfusion (I/R) after oral administration of CP in two dosages (75 mg/kg and 225 mg/kg) for 7 days. The UUO mice was administered with CP continuously for 7 days prior to sacrifice, while the I/R mice were killed after 24 h post I/R operation. Renal fibrosis was assessed by Periodic Acid-Schiff (PAS) staining and Masson's trichrome staining in paraffin-embedded slides. RT-PCR, immunoblotting, and immunofluorescence staining were performed to detect the molecular expression. The content of ATP in kidneys was determined to assess the quality of the mitochondria. The mitochondrial mass and ROS were detected by the Mito Tracker deep red stain and the Mito SOX stain, respectively.

Results: The administration of CP to UUO and I/R mice resulted in a significant reduction in the area of interstitial tubular fibrosis and markedly ameliorated the glomerular sclerosis of the kidney. Meanwhile, the protein and mRNA abundance of profibrogenic factors such as fibronectin, CTGF, and VEGF, and the inflammatory factors MCP-1 and Rantes, was significantly decreased in those mice. As expected, the ATP content was significantly downregulated in the UUO and I/R groups, whereas the CP treatment reversed the decline. Additionally, the mass of mitochondria in UUO and I/R mice kidneys was substantially suppressed, while the low-dose and high-dose CP group mice showed a dramatically elevating abundance of mitochondria in the kidneys. Moreover, mitochondrial ROS production was significantly suppressed by CP in the kidneys of UUO mice and I/R mice.

Conclusion: The crude polysaccharide of FLL could prevent renal fibrosis of mice with AKI. The underlying mechanism might be attributed to its maintainance on homeostasis of renal mitochondria.

FREE ORAL COMMUNICATION 6

Pericyte

15:00-16:30 | Room 7

F06-1

HDAC1 regulates peripheral neuropathy to affect diabetic foot wound healing

Xinyi Kong [1], Yuetong Li [2], Yang Liu [1], Yanping Zhang [1], Wanwen Lao [2], Kaming Yang [2], Zhenlin Li [2], Jianhua Zhong [2], Jiaxin Li [2], Shitong Zhang [3], Changlong Bi [2], Aixia Zhai [1]

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Diabetic foot ulcer (DFU) is one of the most common chronic complications in diabetic patients with poor prognosis, high mortality and disability rate. 19-34% of diabetic patients develop DFU, and 85% of them eventually have to choose amputation. Approximately 50% of them die within 5 years after amputation. Meanwhile, it causes a heavy economic burden on patients, families and society. Diabetic peripheral neuropathy (DPN) is the most common cause of DFU. About 60-70% of diabetic patients have mild, moderate or severe DPN, of which painless neuropathy often leads to small, unnoticeable foot skin lesions due to the loss of protective sensation, resulting in foot ulcers. The appearance of foot ulcers, aggravated by subsequent amputation, leads to disability. Therefore, we speculate that the mechanism of peripheral nerve repair may be a breakthrough point in the study of DFU wound healing. In recent years, it has been found that the expression level of histone deacetylase (HDAC) family is closely related to the progression of DFU, and the expression of HDAC1 is significantly upregulated in peripheral blood mononuclear cells of DFU patients, which may inhibit the angiogenesis and wound healing of DFU by downregulating NRF2. Meanwhile, HDAC1 was found to be involved in neurodegeneration, which is associated with neurotoxicity. However, studies addressing the mechanism of HDAC1 regulating peripheral neuropathy and affecting diabetic foot wound healing have not been reported. We found through experiments that the mRNA and protein expression levels of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and other neurorepair-related factors were increased after the knockdown of HDAC1 in skin fibroblasts, while their expression levels were decreased after the overexpression of HDAC1. It is consistent with previous speculation that HDAC1 can affect the expression levels of neurorepair-related factors and the nerve repair in DFU wound healing. Meanwhile, it demonstrated that the expression level of HDAC1 was increased with the increase of grade according to Wagner classification in DFU patients through immunofluorescence experiments on clinical tissue samples. It confirmed that the expression level of HDAC1 has clinical significance, and it is promising to be conducive to the clinical treatment by exploring the mechanism of HDAC1 on peripheral nerve repair and wound healing in diabetic foot. The primary skin fibroblasts were isolated from the skin tissues of diabetic foot patients and healthy individuals, cultured and infected with shRNA lentivirus of HDAC1. After constructing stable expression cell lines, the RNA-sequence and proteomic sequencing were performed to explore the specific mechanism that high glucose-induced HDAC1 affects nerve repair and wound healing in diabetic foot, thus providing new ideas for the treatment of DFU.

F06-2

Glycation of fibronectin inhibits PDGF-BB signaling activation by uncoupling PDGF receptor-β-α5β1 integrin cross-talk

Wang Liqun [1], Wu Jianbo [1]

[1] Southwest Medical University

Glycation of extracellular matrix proteins has been demonstrated to contribute to the pathogenesis of vascular complications. However, no previous report has implicated glycated fibronectin (FN) in the control of platelet derived growth factor-BB (PDGF-BB) signaling and PDGF-BB-induced recruitment of smooth muscle cells (SMCs) and pericytes. To explore whether the glycation of FN affects PDGF-BB signaling and to understand the molecular mechanisms involved, we synthesized glycated FN by incubating FN with methylglyoxal (MGO) in vitro and identified the formation of glycated FN by an LC–ESI–MS/MS-based method. We tested the hypothesis that glycation of FN downregulates PDGF receptor-β (PDGFR-β) activation by uncoupling the interaction between PDGFR-β and α5β1. Unmodified and MGO glycated FN were used as substrates for rat aortic smooth muscle cells (RASMCs) and mouse brain vascular pericytes (MBVPs). The effects of glycated FN on PDGF-BB signaling were investigated. The glycation of FN inhibited PDGF-BB-induced phosphorylation of PDGFR-β and the intracellular signaling pathway downstream of PDGFR-β. Glycated FN inhibited the binding of PDGFR-β to α5β1 integrin. Furthermore, glycation of FN significantly decreased PDGF-BB-induced proliferation and migration of RASMCs and MBVPs in vitro. Glycated FN also remarkably inhibited PBDGF-BB-induced recruitment of RASMCs and MBVPs to endothelial cells in 3D collagen matrices. Collectively, these data indicate that the glycation of FN inhibits PDGF-BB-induced PDGFR-β activation by uncoupling PDGFR-β-α5β1 integrin cross-talk. This may provide a mechanism for the failure of collateral sprouting in diabetic microangiopathy.

F06-3

Single-cell profilling of pericytes in adult mouse and identifying cell-type specific molecular change in Alzheimer's disease

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Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder characterized impaired cognition, memory and language. It is the most common cause of dementia. As the global population ages, the incidence of AD is increasing. For decades, amyloid beta (Aβ) was viewed as the driver of AD, triggering neurodegenerative processes such as inflammation and formation of neurofibrillary tangles (NFTs). Unfortunately, though many novel drugs targeting Aβ have entered clinical trials, none have been successful at altering the trajectory of the disease.

Recent studies suggest a critical role of the microvasculature in AD progression. The capillary constriction is a significant contributor to reduced cerebral blood flow, and the blood-brain barrier (BBB) damage may initiate or precede dementia. Pericytes are a type of vascular mural cells localized in the basement membrane of microvascular. They participate in various neurovascular functions including BBB formation and maintenance, vascular stability and angioarchitecture, regulation of capillary blood flow, and clearance of toxic cellular by-products. Moreover, the role of the pericytes in contributing to AD-related neurovascular dysfunction has recently been suggested. However, there is a lack of investigation of the heterogeneity of pericytes in brain, which precludes the in-depth analysis of its importance in AD.

To this end, we performed scRNA-seq to wild-type and APP/PS1 AD mice. By using fluorescence-activated cell sorting (FACS), we isolated primary pericytes from micro-dissected brain regions of mice and analyzed a total of 7 samples by droplet microfluidics (10X Genomics) to reveal the transcriptomes of 73174 cells. Clustering on these cells generated nine pericytes subtypes and we experimentally validate their spatial locations and expression patterns. Comparison between conditions, we discovered a number of remarkable changed genes in diffferent celltypes, such as X-inactive Specific Transcript (XIST), a long non-coding RNA that up-regulated in eight subtypes, and the immune-related gene, Jund that down-regulated in six subtypes. These results could be used as essential candidates for down-stream validation. We aimed at Xist to preliminarily explore its role in dysfunction of pericytes

in AD. Collectively, this study presented here provides an initial analysis revealing keys principles of the molecular diversity of different pericytes subtypes and lays an important foundation for understanding the roles of pericytes in AD and other neurodegenerative diseases.

F06-4

High glucose mediates diabetic peripheral neuropathy by inducing Schwann cell apoptosis through the Dgkh/PKC-α signaling pathway

Linhui Zuo [1]

[1] *Xiangya Hospital Central South University*

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, and DPN occurs in >50% of diabetic patients. The increased apoptosis of Schwann cells (SCs) induced by hyperglycemia through various pathological processes plays an important role in the pathogenesis of DPN, but the specific mechanism remains unclear. Diacylglycerol kinase eta (Dgkh), a member of the diacylglycerol kinases (DGKs) family, plays a significant part in glucose uptake, utilization, and energy homeostasis, but its role in DPN has not been reported. Our results showed that mechanical pain thresholds and thermal pain thresholds were significantly decreased in DPN rats induced by STZ. We first found increased apoptosis of the sciatic nerve in diabetic rats accompanied by increased Dgkh expression. Meanwhile, it was also confirmed in cell experiments that hyperglycemia-induced increased apoptosis of HSC by increasing Dgkh expression. Knockdown of Dgkh can reverse HSC apoptosis induced by high glucose. In addition, our results indicated that the expression of PKC-a in the sciatic nerve and HG-treated HSC decreased in the DPN group, and Dgkh mediated HSC apoptosis under high glucose conditions by inhibiting PKC-a expression. And knockdown of Dgkh reverses hyperglycemia-induced PKC-a downregulation. Interestingly, we intervened HSC cells with PKC-a agonist PMA and showed that PMA reversed HSC apoptosis induced by high glucose, but did not affect Dgkh expression, suggesting that Dgkh expression is not regulated by PKC-a. More importantly, we found that the apoptosis of HSC cells reversed by Dgkh knockdown disappeared after the addition of the PKC-α inhibitor Ro-318220. In conclusion, Dgkh expression was increased under high glucose conditions and induced apoptosis of SCs promoting DPN via the PKC-a/Bcl-2/Bax signaling pathway.

F06-5

Endothelial TFEB signaling-mediated autophagic disturbance initiates microglial activation and cognitive dysfunction

Yaping Lu [1]

[1] *Department of Physiology, School of Basic Medical Sciences, Nanjing Medical University*

Cognitive impairment caused by systemic chemotherapy is a critical question that perplexes the effective implementation of clinical treatment, but related molecular events are poorly understood. Herein, we show that bortezomib exposure leads to microglia activation and cognitive impairment, this occurs along with decreased nuclear translocation of transcription factor EB (TFEB) which is linked to autophagy disorder, signal transducers and activators of transcription-3 (STAT3) phosphorylation and interleukin-23 subunit alpha (IL23A) expression. Pharmacological enhancement of TFEB nuclear translocation by digoxin restores lysosomal function and reduces STAT3-dependent endothelial IL23A secretion. As a consequence, we found that brain endothelial-specific ablation of *Il23a* ameliorated both microglia activation and cognitive dysfunction. Thus, endothelial TFEB-STAT3-IL23A axis in the brain represents a critical cellular event for initiating bortezomib-mediated aberrant microglial activation and synapse engulfment. Our results suggest the reversal of TFEB nuclear translocation may provide a novel therapeutic approach to prevent symptoms of cognitive dysfunction during clinical use of bortezomib.

Keywords: autophagy; endothelial cells; TFEB; digoxin; cognitive dysfunction; IL23A; microglia.

F06-6

Epitranscriptomic mechanisms of N6-methyladenosine methylation regulating mammalian hypertension development by determined spontaneously hypertensive rats pericytes

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Aim: Pericytes maintain homeostatic functions in the blood–brain barrier. N6-methyladenosine (m6A) is critical for various biological processes, but the role of mRNA m6A methylation in hypertension has not been fully elucidated

Methods: The m6A methylation levels of Wistar Kyoto rat pericytes and sponta-neously hypertensive rat pericytes were detected via m6A high throughput sequencing.

Results: The m6A methylations were more enriched in the coding sequence region, 3'UTR and 5'UTR of mRNAs, with the m6A motifs being relatively conserved across the different conditions investigated. The average m6A abun-dance of spontaneously hypertensive rat pericytes exhibited global reductions in the pericytes.

Conclusion: This study revealed the m6A landscapes and identified an epitranscriptomic mechanism during the devel-opment of mammalian hypertension.

LUNCH LECTURE 2

12:50-13:30 | Guorui Hall

LL-02

Mechanisms of Qi Tonifying and Blood Activating Compound Chinese Medicine in Improving Myocardial Microcirculation Dysfunction, Myocardial Injury, and Myocardial Fibrosis Induced by Ischemia-Reperfusion

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Interventional therapy is an effective method for treating acute coronary syndrome, capable of saving the lives of 90% of patients with acute coronary syndrome. However, approximately 32% of treated patients developed heart failure within one year. Even under standard treatment, the five-year survival rate of heart failure patients is less than 50%. The inhibition of myocardial ischemia-reperfusion (I/R) injury after interventional treatment and the prevention of myocardial fibrosis remains unresolved clinical challenges that urgently need solutions.

During the period of coronary artery occlusion, the myocardium lacks oxygen and nutrient supply, leading to decreased aerobic metabolism, increased anaerobic glycolysis, abnormal electron transfer in the myocardial mitochondrial respiratory chain, low expression of ATP synthase, reduced ATP content, F-actin depolymerization, myocardial fiber rupture, and decreased myocardial contractility. After vascular recanalization, blood supply of large vessels is restored, but due to decreased activity of mitochondrial respiratory complex, abnormal electron transfer leads to electron leakage from mitochondrial complexes I and II, generating reactive oxygen species and causing oxidative stress damage. On the other hand, mitochondrial complex V and its subunit ATP5D are downregulated, impairing ATP synthesis, and leading to continuous F-actin depolymerization and myocardial fiber rupture.

Injured myocardium releases chemotactic factor S19, which acts on monocytes C5a receptor, inducing their migration out of microvessels, and polarization into M1 and M2 macrophages. M2 macrophages release TGF-β1, which acts on fibroblast TGF-βII receptor, activates Smad2/3,4, initiates collagen-related genes and collagen secretion, and promotes myocardial fibrosis.

Our research confirms that pre-treatment with QiShenYiQi pills, composed of Astragalus, Salvia Miltiorrhiza, Panax Notoginseng, and Lignum Dalbergiae Odoriferae, can alleviate myocardial energy metabolism and myocardial fiber rupture during the ischemic period in rats. It also reduces myocardial cell apoptosis and myocardial fiber rupture after reperfusion, inhibits low expression of myocardial mitochondrial ATP synthase, suppresses ATP content reduction and F-actin depolymerization, improves rat cardiac function and coronary flow, and reduces myocardial infarct size. When post-treatment with QiShenYiQi 3 hours after reperfusion, can inhibit myocardial fibrosis in rats on day 7 after reperfusion. This effect is associated with the inhibition of chemotactic factor S19 release, prevention of S19 binding to monocyte C5a receptors, inhibition of monocyte migration out of microvessels, and suppression of their polarization into M1 and M2 macrophages. It also inhibits the release of TGF-β1 by M2 macrophages, prevents TGF-β1 from binding to fibroblast TGF-βII receptor, inhibits activation of Smad2/3,4, and suppresses collagen secretion.

In this presentation, we will combine our research results to elucidate the mechanisms by which Qi tonifying and Blood activating compound Chinese medicine improves myocardial microcirculation dysfunction, myocardial injury, and myocardial fibrosis induced by I/R.

SYMPOSIUM 15

Metabolism and Vascular Diseases

08:30-10:00 | Room 1

015-SS1

Adaptor protein HIP-55-mediated signalosome protects against ferroptosis in myocardial infarction

Yunqi Jiang [1,2,3,4], Yuhui Qiao [1,2,3,4], Dan He [1,2,3,4], Aiju Tian [1,2,3,4], Zijian Li [1,2,3,4]

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Ischemic heart disease is a leading cause of death worldwide. Myocardial infarction (MI) results in cardiac damage due to cell death and insufficient cardiomyocyte self-renewal. Ferroptosis, a novel type of cell death, has recently been shown as a key cause of cardiomyocyte death after MI. However, the complicated regulation mechanisms involved in ferroptosis, especially how ferroptosis is integrated into classical cell survival/death pathways, are still unclear. Here, we discovered that HIP-55, a novel adaptor protein, acts as a hub protein for the integration of the ferroptosis mechanism into the classical AKT cell survival and MAP4K1 cell death pathways for MI injury. The expression of HIP-55 is induced in MI. Genetic deletion of HIP-55 increased cardiomyocyte ferroptosis and MI injury, whereas cardiac-specific overexpression of HIP-55 significantly alleviated cardiomyocyte ferroptosis and MI injury. Mechanistically, HIP-55 was identified as a new AKT substrate. AKT phosphorylates HIP-55 at S269/T291 sites and further HIP-55 directs AKT signaling to negatively regulate the MAP4K1 pathway against MI injury in a site-specific manner. S269A/T291A-mutated HIP-55 (HIP-55AA), which is defective in AKT phosphorylation and significantly decreases the interaction between HIP-55 and MAP4K1, failed to inhibit the MAP4K1/GPX4 ferroptosis pathway. In line with this mechanism, cardiac-specific overexpression of HIP-55WT mice, but not cardiac-specific overexpression of HIP-55AA mice, protected cardiomyocytes against MI-induced ferroptosis and cardiac injury in vivo. These findings suggest that HIP-55 rewired the classical AKT (cell survival) and MAPK (cell death) pathways into ferroptosis mechanism in MI injury. HIP-55 may be a new therapeutic target for myocardial damage.

015-SS2

Role of GPCRs in hepatic triglyceride and cholesterol metabolism

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As a center of lipid synthesis, expenditure, and circulation, the liver is critical for lipid homeostasis. Under physiological conditions, the balance between lipid synthesis, β-oxidation, and export is precisely controlled by a series of pathways ranging from hormones and G protein-coupled receptors (GPCRs) to nuclear receptors and transcription factors. Identification of key GPCRs critical for hepatic triglyceride and cholesterol metabolism will provide novel strategy for intervention of lipid dysfunction and its associated chronic diseases including cardiovascular disorders. Our studies have defined GPR180 and leucine-rich repeat G protein-coupled receptor 4 (LGR4) as novel GPCRs in hepatocytes crucial for the synthesis of triglyceride and cholesterol. Deficiency of GPR180 in hepatocytes decreased the synthesis of triglyceride and cholesterol by suppression of SREBP proteins, including precursor and mature SREBP1 (pSREBP1, mSREBP1), pSREBP2, and mSREBP2. As a consequence, adiposity and liver steatosis induced by high fat diet was significantly ameliorated. On the other hand, LGR4 functions to suppress cholesterol synthesis via the AMPKα-SREBP2 pathway. LGR4 and its endogenous ligands

Rspondin(Rspo) 1 and 3 were abundantly expressed in hepatocytes and their expressions were sensitive to energy states. Activation of LGR4 by Rspo1 and Rspo3 reversed OA-induced cholesterol synthesis, accompanying with increased the phosphorylation of AMPKα Thr172, reduced SREBP2 nuclear translocation, and Srebf2 mRNA expression. Conversely, hepatic LGR4 knockdown increased hepatic cholesterol synthesis and decreased the phosphorylation of AMPKα both in vitro and in vivo. Activation or inhibition of AMPKα significantly abolished the effects of LGR4 deficiency or Rspos, respectively, on cholesterol synthesis. Knockdown of AMPKα1 or/and AMPKα2 repressed Rspos-induced inhibition on cholesterol synthesis. Our study indicates that GPR180 and LGR4 may counteract each other to precisely regulate cholesterol synthesis in hepatocytes.

015-SS3

Effect And Mechanism Of Silibinin To Improve Non-Alcoholic Fatty Liver Disease

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Background: Recent years, non-alcoholic fatty liver disease (NAFLD) and type 2 diabetic mellitus (T2DM) have been major diseases that threaten the health of public health in China and consume medical finance, and more than half of patients with T2DM are accompanied by NAFLD. As two major hormones secreted by the liver and adipose tissue, fibroblast growth factor 21 (FGF21) and adiponectin (ADPN) are key regulators of the crosstalk between liver and adipose tissue and play important roles in regulating lipid and glucose metabolism. Clinical studies have shown that there are higher circulating FGF21 concentration and lower circulating ADPN concentration in patients with NAFLD and T2DM, which may be in FGF21 resistance. Silybum marianum is a plant of the Asteraceae family, which has been used as a therapeutic herb for more than 2000 years. Silymarin is a mixture of flavonolignans extracting from the dried seeds and fruits of silybum marianum, of which silibinin is the primary bioactive ingredient. Shui Lin Jia is a kind of phospholipid complex of silibinin, which was approved by the State Food and Drug Administration (SFDA) in 2004 (Approval No. H20040299) and used for the treatment of acute and chronic hepatitis and NAFLD in China. Our team has shown that Shui Lin Jia attenuated HFD-induced NAFLD in hamsters, which implicated hepatic de novo lipogenesis pathway and hepatic fatty acids (FAs) β-oxidation pathway. However, whether Shui Lin Jia can improve T2DM with NAFLD is still unclear. Therefore, we studied the effect of Shui Lin Jia on glucose and lipid metabolism in db/db mice and its mechanism.

Methods: In the in vivo experiment, 8-week-old male diabetic db/db mice and normoglycemic db/m mice were randomly divided into five groups: control group (db/m + saline), background group (db/m + 50 mg/kg silibinin), model group (db/db + saline), low-dose Shui Lin jia group (db/db + 50 mg/kg silibinin) and high-dose Shui Lin Jia group (db/db + 100 mg/kg silibinin). All of them were given gastric gavage once a day for eight weeks, respectively. In the in vitro experiment, the mouse hepatic cell line AML12 was selected and divided into three groups: control group, equal concentration dimethyl sulfoxide (DMSO) incubation; model group, 250 μmol/L oil acid (OA) incubation; treatment group, 250 μmol/L OA and 50 μmol/L silibinin incubation. Each of group was cultured for 48 hours and then lipid droplets in hepatocytes were observed by oil red O staining; mitochondrial oxygen consumption and electron leakage during oxidative phosphorylation were measured by Oxygraph-2k.

Results: The weight gain and the increase of total and visceral adipose tissue volume in db/db mice were inhibited with the treatment of Shui Lin Jia. Shui Lin Jia can improve central obesity phenotype; activate the expression of phosphorylation of AKT, improve glucose tolerance and insulin sensitivity; up-regulate the expression of FAs β-oxidation-related genes, down-regulate the expression of lipogenesis-related genes to attenuate hepatic lipid accumulation; improve the activity of mitochondrial Complex II, reverse the decrease of ATP/ADP and ATP/AMP ratios and alleviate the inflammation and oxidative stress; improve FGF21 sensitivity, up-regulate the expression of ADPN, activate p-AMPK and inhibite mTOR-S6 signaling pathway.

Conclusions: The study demonstrated that Shui Lin Jia could improve central obesity and NAFLD, glucose tolerance and insulin sensitivity in db/db mice. The mechanism of Shui Lin Jia attenuated hepatic lipid accumulation and insulin resistance were likely related to the promotion of FAs β-oxidation-related genes, the inhibition of lipogenesis-related genes, the improvement of mitochondrial respiratory chain, the alleviation of oxidative stress injury and the regulation of FGF21-ADPN-K-MTOR-S6 pathway.

015-SS4

Single base-edited stem cell derived endothelial cells for modelling arteriovenous malformation

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Most arteriovenous malformations (AVMs) arise sporadically and could be deadly when the abnormal vessels rupture within the brain. It appears that AVMs are most likely affected by inappropriate activation of signaling pathways including MAPK due to the somatic mutations in endothelial cells (ECs). Treatments have been very limited and the lack of robust disease models are hindering the discovery of new therapeutics. Here, we established a novel single base-editing protocol to introduce the point mutation into the patient derived induced pluripotent stem cells (iPSCs) for recapitulating the heterozygous MAP2K1^{K57N} somatic mutation. Since the AVM phenotypes are mainly driven by hyperactivation of MAPK/ERK signaling in endothelial cells, we then derived the MAP2K1^{K57N} iPSCs into vascular endothelial cells and observed the increased proliferation and vascular hyperbranching and enlargement compared to the wild type ECs in several vascular assays including tube formation on Matrigel and vasculogenesis within fibrin gel in vitro. When we implanted stem cell derived ECs into immune-deficient mice, those mutant MAP2K1^{K57N} ECs generated vascular lesions with dilated blood-filled lumens covered by very few smooth muscle cells, recapitulating the patients' phenotype. Moreover, we performed a high-throughput screen based on ECs proliferation and we identified Trametinib as a factor that efficiently suppressed the ERK phosphorylation and rescued the disease phenotype. In summary, by leveraging on the single-base genome editing and stem cell technology, we generated a novel personal AVM model which enabled the development of precise treatment options for AVM patients.

SYMPOSIUM 16

MCS Presidents' Perspectives for Future Discoveries

08:30-10:00 | Room 2

016-SS1

Innovative Views of early RBC interactions in forming rouleaux and in dispersing rouleaux

Mary Frame [1], Lesley Frame [2], Samantha Weber-Fishkin [1], Alexander Eichert [1], Yuxuan Li [1], Harrison Seidner [1], Geoffrey Gunter [1], Anna Eligulashvili [2]

[1] *Biomedical Engineering / Stony Brook University*
[2] *Materials Science Engineering / University of Connecticut Storrs*

In many pathologies, red blood cells (RBC) first form stacked structures termed rouleaux well before the clotting cascade is initiated. The aggregation is poorly understood, as is the disaggregation phase. We investigated both the aggregation and disaggregation phases in relation to local shear rate, plasma vs protein solution, and RBC surface charge in the absence of clotting factors. To examine the role of band 3 and the actin cytoskeleton we further promoted actin polymerization and de-polymerization, as well as use of the band 3 inhibitor, DIDS. Lastly, we examined the role of echinocyte formation and morphology in rouleaux formation and with these treatments.

016-SS2

Innovative Views for Watching Cell Dynamics During Microvascular Growth

Walter Murfee [1]

[1] *Department of Biomedical Engineering/University of Florida*

Understanding angiogenesis, similar to other physiological processes, requires identifying multiple cell, system, and environmental interactions. A challenge is identifying these dynamics when you cannot observe them using traditional experimental approaches. Fundamental questions still remain unanswered. What cells are involved? Where do cells come from? Where do cells go? This presentation will highlight the impact of biomimetic model development for making new discoveries about the cellular dynamics involved in adult microvascular network remodelling and the growth of new blood vessels. Novel observations made possible by time-lapse imaging of intact cultured tissues motivate new paradigms related to endothelial cell jumping from one vessel to another, the lineage of vascular pericytes, lymphatic-blood vessel plasticity, and the vasculogenic potential for stem cell populations. Altogether the presentation will serve to frame an appreciation for how new "views" can encourage vascular biologists and physiologists to rethink what we know about angiogenesis.

016-SS3

In Silico Views of Angiogenesis During Tissue Fibrosis

Shayn Peirce-Cottler [1]

[1] *Biomedical Engineering, University of Virginia*

The most prevalent, devastating, and complex diseases of our time, such as diabetes, cardiovascular disease, cancer, and infectious diseases, involve the dynamic interactions of cells with one another and with their changing environment. However, the drugs we typically use to treat diseases target a single protein and disregard the fact that cells within tissues are highly heterogeneous and have individualized responses that contribute to the tissue-level outcomes. To bridge the gap between protein and multi-cell/tissue-levels of spatial scale, my lab develops agent-based computational models and uses them in combination with experiments and machine learning approaches to predict how individual cell behaviors give rise to tissue-level adaptations. We have used agent-based modeling to simulate the structural adaptations of microvessels in the settings of physiological development, complications of diabetes, and cardiac and lung fibrosis. Our studies have suggested new mechanistic hypotheses and provided guidance for the design of novel therapies that account for the dynamic and heterogeneous interactions between different cell types within diseased and regenerating tissues.

SYMPOSIUM 17

Leukocyte Recruitment in Microvascular Inflammation

08:30-10:00 | Room 4

017-SS1

Contributions of leukocyte beta2 integrins in myocardial ischemia-reperfusion injury

Wei Liu [1], Chunxia Cronin [2], Lai Wen [3], Klaus Ley [4], Bruce Liang [2], Zhichao Fan [1]

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Leukocyte recruitment and their mediated inflammatory responses are critical for cardiovascular diseases, including myocardial ischemia-reperfusion (I/R) injury, which accounts for 9% mortality and 10% morbidity rates in ischemic heart disease patients. Blocking leukocyte recruitment in mouse knockouts (KO) of beta2 integrin (CD18) or blocking beta2 integrin with anitibodies in multiple animals significantly reduced infarct size after myocardial I/R injury. However, the cell-specific contribution of leukocyte beta2 integrin to I/R injury is unknown. In this study, we used the newly established $CD18^{flox/flox}$ (hITGB2 KI) mouse strain to address this knowledge gap. We crossed them to CSF1R-cre (CD115) and MRP8-cre (S100A8) and tested the KO of beta2 integrins in different leukocyte populations. Interestingly, CSF1R-cre $CD18^{flox/flox}$ unexpectedly deleted beta2 integrins in all peripheral blood leukocyte populations, including blood neutrophils, monocytes, CD4 T cells, CD8 T cells, B cells, and NK cells. It also elevated the cell number of these leukocyte populations in peripheral blood. In MRP8-cre $CD18^{flox/flox}$ mice, beta2 integrins were only knocked out in neutrophils but not other peripheral blood leukocytes. And only neutrophil number was elevated in peripheral blood. After 35 minutes of myocardial ischemia and 24 hours of reperfusion, we found both CSF1R-cre $CD18^{flox/flox}$ and MRP8-cre $CD18^{flox/flox}$ mice have significantly reduced infarct size compared to cre- controls. However, if we distinguish the sex in analysis, we only found a significant alleviation in female but not male CSF1R-cre $CD18^{flox/flox}$ mice. In contrast, we observed a significant alleviation only in male but not female MRP8-cre $CD18^{flox/flox}$ mice. These results suggested sex-specific and immune-cell-specific contributions of beta2 integrins in myocardial ischemia-reperfusion injury and provided new insights into beta2 integrin targeting therapies.

017-SS2

Regulation of immune cell trafficking by adhesion signaling

JianFeng CHEN [1]

[1] *Shanghai Institute of Biochemistry and Cell Biology*

Integrins are the major metazoan receptors that mediate cell-cell, cell-matrix interactions and bidirectional signaling across the plasma membrane. Lymphocyte integrins control tissue-specific homing of lymphocytes, playing vital roles in immune surveillance and host defence. α4 integrins (α4β7 and α4β1) are heterodimeric lymphocyte homing receptors that mediate lymphocyte adhesion and migration by interacting with their ligands. The dynamic regulation of integrin-ligand binding by extracellular stimuli is essential to integrin-mediated lymphocyte trafficking. One research interest in my lab is the regulation of integrin adhesion and signaling by different extracellular microenvironment factors. My talk will focus on two of our most recent findings: the switch of integrin ligand specificity by different chemokines, and the regulation of integrin-mediated lymphocyte adhesion and migration by febrile temperature.

017-YS1

Fishing for microRNAs and their targets that regulate neutrophil migration

Qing Deng [1]

[1] *Biological Sciences/Purdue University*

Neutrophil migration is essential for inflammatory responses to kill pathogens and cause tissue injury. To discover novel therapeutic targets that modulate neutrophil migration, we performed a neutrophil-specific microRNA overexpression screen in zebrafish, and identified eight microRNAs as potent suppressors of neutrophil migration. Among those, miR-199 decreases neutrophil chemotaxis in zebrafish and human neutrophil-like cells. Intriguingly, in terminally differentiated neutrophils, miR-199 alters the cell cycle-related pathways and directly suppresses cyclin-dependent kinase 2 (cdk2), whose known activity is restricted to cell cycle progression and cell differentiation. Furthermore, miR-199 overexpression or CDK2 inhibition significantly improves the outcome of lethal systemic inflammation challenges in zebrafish. Another microRNA, miR-99, suppresses RORalpha to support neutrophil migration. Together, our results reveal previously unknown functions of microRNAs and their targets in regulating neutrophil migration and provide new directions in alleviating systemic inflammation.

017-YS2

CD34+ Cell-derived Fibroblast–Macrophage Crosstalk Drives Limb Ischemia Recovery through the OSM–ANGPTL Signaling Axis

Yuwei Song [1,6,7], Junyao Yang [2], Tianrun Li [3], Kai Sun [6,7], Jingyan Han [6,7], Guangxin Yang [3], Yanhua Hu [4], Wei Kong [1], Xian Wang [1], Hongkun Zhang [5], Qingbo Xu [4], Juan Feng [1,3,6,7]

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Background: CD34+ cells improve the perfusion and function of ischemic limbs in humans and mice. However, there is no direct evidence of the differentiation potential and functional role of these cells in the ischemic muscle microenvironment.
Methods: By utilizing a murine model of hindlimb ischemia and collecting amputation samples from patients with peripheral artery disease, we used single-cell RNA sequencing to map the cell landscapes of the mouse and human ischemic/repair muscles. Lineage tracing mice and bone marrow (BM) transplantation were used to elucidate the contribution of CD34+ cells from different sources to this niche. Focusing the analysis on fibroblasts and macrophages, we identified the key secretory signal regulatory switches during the repair process.
Results: We identified 17 different cell subsets in the human and mouse muscle microenvironments respectively, of which fibroblasts and macrophages were the main subsets and were significantly expanded under ischemia. BM-derived macrophages with antigen-presenting function migrated to the ischemic site, while resident macrophages underwent apoptosis. The macrophage oncostatin M (OSM) regulatory pathway was specifically turned on by ischemia. Simultaneously, CD34+-derived pro-regenerative fibroblasts were recruited to the ischemia niche, where they received macrophage-released OSM, and promoted angiopoietin-like protein (ANGPTL)-associated angiogenesis. In addition, Depletion of CD34+ cells or

OSM blockade significantly limited ischemic tissue repair.
Conclusions: This study reveals the complexity of the cell atlas and cell-cell interactions in the ischemic/repair tissue microenvironment at the single-cell level and defines a CD34+ cell-derived pro-regenerative fibroblast subset regulated by the macrophage-released OSM that ultimately promotes angiogenesis and tissue regeneration through ANGPTL.

SYMPOSIUM 18

Image-Based" Vascular Systems Biology and Emerging Technologies

08:30-10:00 | Room 5

018-SS1

Image-based Vascular Systems Biology: A New Frontier Beckons

Arvind Pathak [1]

[1] *Depts. of Radiology and Biomedical Engineering/The Johns Hopkins University School of Medicine*

This lecture will highlight how interdisciplinary research at the interface of engineering, medicine and design is needed to develop new hardware, software, and "wetware" tools for characterizing the structural and functional changes in the vascular microenvironment (VME). I will illustrate how one can leverage multiscale and multimodality imaging approaches in conjunction with novel computational and visualization tools to revolutionize our understanding of the vasculature in the preclinical (i.e. animal models) setting. This lecture will showcase the development of new "image-based" computational biology approaches that employ imaging data as the substrate for biophysical models of the microcirculation in cancer. It will then highlight the design and development of novel mini-microscopes capable of imaging different aspects of the neurovasculature in the brains of awake, freely moving animals. Finally my lecture will culminate with a description of a new multimodality and multiscale imaging and visualization pipeline for vascular systems biology called "VascuViz". In summary, this lecture will demonstrate how advances in multiscale imaging, data visualization and computing in together with transgenic animal models of disease are ushering in a new era of "image-based" vascular systems biology – the next frontier in microcirculation research.

018-SS2

Image-based Patient-Specific Characterization of Cancer Hemodynamics

Thomas Yankeelov [1,2]

[1] *Departments of Biomedical Engineering, Diagnostic Medicine, and Oncology*
[2] *Oden Institute for Computational Engineering and Sciences*

Our lab is focused on developing tumor forecasting methods by integrating advanced imaging technologies with mathematical models to predict tumor growth and treatment response. The imaging methods we use extend from time-resolved microscopy to longitudinal MRI and PET scans, while the modeling methods rely mostly on ordinary and partial differential equations. In this presentation, we will focus on how quantitative magnetic resonance imaging (MRI) data can be employed to calibrate mathematical models built on first-order effects related to well-established "hallmarks" of cancer including proliferation, migration/invasion, vascular status, and drug-related tumor growth inhibition and cell death. In particular, we will present some of our recent results through four vignettes focusing on breast and brain cancer: 1) incorporating patient-specific data into mechanism-based mathematical models, 2) predicting and optimizing outcomes via patient-specific digital twins, 3) guiding interventions through applications of optimal control theory, and 4) updating predictions through data assimilation. The long-term goal of this set of studies is to provide a rigorous methodology that is practical enough for predicting and optimizing, therapeutic interventions on a patient-specific basis.

018-YS1

VascuViz: A Multimodality and Multiscale Imaging and Visualization Pipeline for Vascular Systems Biology

Akanksha Bhargava [1], Manisha Aggarwal [1], Arvind Pathak [1]

[1] *Department of Radiology and Radiological Science/Johns Hopkins University School of Medicine/Johns Hopkins University*

Recent innovations in imaging and data visualization methods have

significantly advanced our understanding of the role of microcirculation in health and disease. However, to characterize a vascular system completely requires that structural and functional properties of blood vessels are integrated across multiple spatial scales ranging from the whole-organ level down to single cells. Integration of multiscale imaging data is often challenging due to differences in sample preparation, image contrast mechanisms, spatial resolution, and fields of view. As a result, combining vascular data with complementary contrasts from other modalities (e.g. MRI), simulations (e.g. hemodynamics) or measurements (e.g. protein expression) has also remained challenging. We have recently developed VascuViz which is a new multimodality, multiscale imaging, and visualization workflow for image-based vascular systems biology applications. It makes blood vessels simultaneously visible in MRI (~40 µm), CT (~5-7 µm) and optical microscopy (< 1 µm) by employing a unique contrast agent combination providing multiscale vascular fiducials for integration of these imaging data with other contrasts or assays. This enables generation of novel multiscale imaging data for the creation of multicontrast atlases of vascular structure and function. VascuViz-derived multiscale data can also be incorporated into computational biology models for quantification and visualization of emergent microcirculatory phenomenon e.g. blood flow, oxygenation, and drug transport. In this talk, I will present how VascuViz can be adapted to applications in neuroscience, cancer, and computational biology and it can help answer important questions about the role of microcirculation in biological systems from the scale of the entire organism down to that of endothelial cells.

018-YS2

A bioengineered 3D platform to dissect cell-cell interactions in tumour angiogenesis

Akhilandeshwari Ravichandran [1], Anna Jaeschke [1], Maria Koch [1], Laura Bray [1]

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The tumour microenvironment is a key contributor to cancer development and progression. Reciprocal interactions between the epithelium and the adjacent stroma are essential for malignant transformation. Cancer-associated fibroblasts (CAFs) are a fundamental component of the tumour stroma. CAFs contribute to cancer progression through altered paracrine signalling as well as by remodelling of the ECM. The arising aberrant biochemical, biomechanical, and topographical cues promote invasiveness and migration of tumour cells. It is crucial to consider stromal and endothelial features in *in vitro* cancer models to understand the role of the tumour microenvironment in cancer progression. The majority of previous studies examining the process of tumour angiogenesis have utilised easy to isolate human umbilical vein endothelial cells and mesenchymal stromal cells. In this research, bioengineered experimental models provided a more physiologically relevant platform for tumour angiogenesis research *in vitro*. Primary tissue-specific endothelial and fibroblast cells (non-malignant fibroblasts (NFs) and CAFs) were used to study differential influences of these cell types on tumour angiogenesis and epithelial plasticity within a tissue-specific context. Distinct biomechanical and cytoskeletal characteristics of patient-matched NFs and CAFs were elucidated. Utilising a co-culture model, a decreased cellular stiffness was found in benign epithelial cells grown in the presence of CAFs, which coincided with a more invasive and proliferative phenotype. To mimic early cancer angiogenesis in vitro, tissue-specific microvascular cells were cultured in the presence of NFs or CAFs within 3D semi-synthetic hydrogels. Confocal imaging assessed cellular morphology and vascular network formation. An open source software package was developed to quantify morphological features. Cell heterogeneity within the tissue-specific tumour angiogenesis model was assessed using high-throughput techniques such as RNA sequencing and cytokine arrays. On the molecular level, angiogenesis-related pathways were found upregulated in the presence of CAFs indicating a stimulatory effect. Overall, this works contributes to the understanding of the tumour microenvironment by providing novel insights into the differential characteristics between the healthy and the malignant tumour microenvironment.

SYMPOSIUM 19

The Cerebral Microcirculation as a Novel Target to Treat Dementia

08:30-10:00 | Room 7

019-SS1

TRPV4 and hypertension associated cognitive impairment

Laura Chambers [1], William Jackson [1], Swapnil Sonkusare [2], Anne Dorrance [1]

[1] *Michigan State University*
[2] *University of Virginia*

Transient receptor potential vanilloid 4 (TRPV4) channels are critical for appropriate vascular function and are impaired during hypertension and chronic cerebral hypoperfusion. In rodent models, hypertension impairs TRPV4-mediated dilation in cerebral parenchymal arterioles (PAs), and this is associated with cognitive impairment. Global TRPV4 deletion results in PA dysfunction and severe cognitive impairment. Due to the ubiquitous expression of TRPV4, the cell-type specific contribution of the channel to vascular and cognitive function is unclear. We tested the hypothesis that endothelial TRPV4 channel deletion ($TRPV4_{EC}^{-/-}$) will result in cognitive decline and increased markers of neuroinflammation. Male and female 30-35-week-old $TRPV4_{EC}^{-/-}$ mice and littermate controls were used. Cognitive function was assessed by an open field arena, a novel arm test, a spontaneous alternation test in the Y-maze, and a nesting test. To assess neuroinflammation, an anti-glial acidic fibrillary protein (GFAP) antibody was used to assess the quantity and morphology of cortical astrocytes. $TRPV4_{EC}^{-/-}$ mice spent more time in the center of the open field arena compared to littermate controls, with no changes in locomotor activity, indicating a reduction in anxiety-like behavior. Memory function was also impaired in $TRPV4_{EC}^{-/-}$ mice, demonstrated by less time spent exploring the novel arm in the Y-maze and impaired spontaneous alternation behavior compared to controls. Male $TRPV4_{EC}^{-/-}$ mice had more GFAP-positive cortical astrocytes with greater arborization compared to those from littermate controls, indicating an increase in neuroinflammation after $TRPV4_{EC}$ deletion. Taken together, these data suggest $TRPV4_{EC}$ channels are essential for the maintenance of cognitive function, and their dysfunction may increase dementia risk.

019-SS2

YangxueQingnao Wan ameliorates hippocampal neuron injury by regulating cerebral arteriole constriction and cerebral microvascular hyperpermeability

Ying-Qian Jiao [1,2], Chun-Shui Pan [2], Jian Liu [1], Kai Sun [2], Pin Huang [2], Xiao-Yi Wang [1,2], Li Yan [2], Hui-Yu Chen [1,2], Ruo-Lin Yang [1], Ding-Zhou Weng [1,2], Yuan Wang [3], Zhi-Zhong Ma [1], Jing-Yan Han [1,2]

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Background: Current antihypertensive drugs are unable to attenuate microvascular hyperpermeability caused by hypertension. YangXue QingNao Wan (YXQNW) is a Chinese herb compound preparation which consists 11 Chinese herbs, used for the treatment of headache, dizziness, insomnia and dreaminess. It is not clear whether YXQNW can improve cerebral microvascular hyperpermeability and neuron damage caused by hypertension and the underling mechanisms.
Methods: We used spontaneously hypertensive rats (SHR) as model, with Wistar Kyoto (WKY) rats as control. YXQNW, enalapril and nifedipine (EN+NF) were administrated orally for 4 weeks. Effects and mechanisms were studied in rat brain microvascular endothelial cells and rat brain artery smooth muscle cells, both induced by Angiotensin II and hypoxic reoxygenation.
Results: SHR exhibited higher blood pressure, Evans blue

extravasation, albumin leakage, increased brain water content, decreased cerebral blood flow, perivascular edema, and neuronal apoptosis in the hippocampus and cortex, all of which were attenuated by YXQNW treatment. After YXQNW administration, 11 components were texted in peripheral blood of SHR. The results showed that Aurantio-obtusin and Rchophylline in YXQNW could relax constriction of arteriole, while, Caffeic Acid could inhibit cerebral post-capillary venule hyperpermeability, inhibit intercellular endothelial tight junction and adhesive junction injury, and Tetrahydropalmatine had double effects.

Conclusion: The overall result shows the potential of YXQNW to attenuate blood pressure and hippocampal neuron injury in SHR, which involves different components absorbed into blood of YXQNW by inhibiting arteriole contraction and post-capillary venule hyperpermeability.

019-YS1

BKca nitrosylation is associated with micro- and neurovascular dysfunction in a mouse model of Alzheimer's Disease

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Background: Vasculopathy and oxidative stress are present in patients with Alzheimer's disease (AD) and may contribute to disease progression and severity. Large conductance calcium activated K+ channels (BKCa) plays an important role in vasodilatory responses and maintenance of myogenic tone in resistance arteries. Opening of BKCa channels occurs upstream from localized intracellular Ca2+ release events (Ca2+ sparks), and results in K+ efflux, vascular smooth muscle cell hyperpolarization and vasorelaxation. In a pro-oxidative scenario, BKCa can be modified, resulting in decrease activity and exacerbation of contractile responses, which can compromise cerebral blood flow regulation, generating an environment that may accelerate neurodegeneration. We hypothesized that reduction in BKCa-dependent vasodilation in cerebral arteries, as consequence of oxidative stress, results in neurovascular dysfunction in the 5x-FAD model of AD.

Methods: Posterior communicating arteries (PComA) from 5 months-old male and female 5x-FAD and wild-type (WT) littermates were isolated and studied ex vivo using pressure myography. Ca2+ transients in smooth muscle cells were evaluated by spinning-disk confocal microscopy. Oxidative stress was assessed by total and oxidized glutathione levels in the brain using a colorimetric enzymatic assay. BKCa expression was assessed by qPCR. Nitrosylated BKCa was evaluated using a pull-down assay and Western blot. Basal cortical perfusion and functional hyperemia were evaluated by laser speckle contrast imaging. Data are means ± SEM, analyzed by two-tailed Student's t-test or Mann Whitney test.

Results: In females, PComA from 5x-FAD showed higher spontaneous myogenic tone than WT (Myogenic tone: 24.48 ± 3.20 vs 16.09 ± 0.93%, $p < 0.05$, N = 7). Constriction to the BKCa blocker iberiotoxin (30 nM) was smaller in 5x-FAD than WT, suggesting lower basal BKCa activity (Vasoconstriction: -4.252 ± 0.429 vs -9.220 ± 2.556%,$p < 0.05$; N=5), which was independent of alterations in intracellular Ca2+ transients (Frequency: 0.51 ± 0.30 vs. 0.62 ± 0.33 Hz, 5x-FAD vs WT, $p > 0.05$, N=3-4). These vascular changes were associated to higher levels of oxidative stress in whole brain homogenates of 5x-FAD ([oxidized glutathione]: 7.83 ± 0.62 vs 5.27 ± 0.74 µM, 5x-FAD vs WT, $p < 0.05$, N=8) and higher level of S-nitrosylation in the BKCa α-subunit ([S-Nitrosylated BKCa]: 0.68 ± 0.04 vs 0.41 ± 0.03, 5x-FAD vs WT, $p < 0.05$, N=5). There were no differences on BKCa expression between 5x-FAD and WT, however, female 5x-FAD mice showed increased expression of iNOS mRNA ([2-ΔΔCT]: 10.64 ± 5.40 vs 0.74 ± 0.19, 5x-FAD vs WT, $p < 0.05$, N=6) and lower resting cortical perfusion atop the frontal cortex (Perfusion: 345.9 ± 16.43 vs. 415.5 ± 23.15 PU, 5x-FAD vs WT, $p < 0.05$, N = 6), and impaired functional hyperemia responses after whisker stimulation (increase from baseline: 3.82 ± 0.64 vs. 9.91 ± 1.41%, 5x-FAD vs WT, $p < 0.05$, N = 6). No significant differences were observed between male 5x-FAD and WT for all parameters above.

Conclusions: Cerebrovascular impairments were more pronounced in female 5x-FAD mice, observed as an increase in spontaneous myogenic tone, likely due to reduction in smooth muscle cell BKCa activity associated to an increase in brain oxidative stress and S-Nitrosylation of the channel. These alterations were linked to reduced basal cortical perfusion and blunted neurovascular coupling responses. Together, they identify post-translational modifications of BKCa as a putative target to improve cerebral microvascular function in AD.

019-YS2

Influence of Hypertension with Multiple Risk Factors on Brain Tissue Pathomorphology and Cognitive Impairment-Related Biomarkers

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Background: Hypertension is the most common chronic disease in the elderly. In China, according to a survey conducted in 2012–2015, the prevalence rate of hypertension in people aged ≥60 years was 53.24%, and for people aged ≥80 was 60.27%. Not only is hypertension the primary cause of stroke in China, it is also a risk factor for cognitive impairment diseases such as vascular dementia and Alzheimer's disease (AD). Compared with healthy people, patients with hypertension have a 1.4-fold increased risk of developing dementia. Therefore, it is important to study the characteristics of hypertension models to reveal the potential and changeable etiologies and risk factors and to slow the progress of cognitive impairment through systemic intervention, especially for vascular cognitive impairment, and prevent AD. Hyperlipidemia, diabetes mellitus, and a high-salt diet are risk factors for hypertension and cognitive impairment. It is essential to explore how these diseases injure cognitive function by assessing the pathological changes and biomarkers.

Purpose: Using a spontaneously hypertensive rat (SHR) model of metabolic syndrome (hyperlipidemia, diabetes mellitus, salt-sensitive) by feeding SHRs complex model diets (high-fat diet, high-glucose diet, and salt-sensitive diet), we assessed changes in brain tissue pathomorphology and cognitive impairment-related biomarkers.

Materials and Methods: Thirty-two male SHR were randomly divided into four groups (n=8 rats per group): SHR group (fed routine diet), HFD–SHR group (fed high-fat diet), HSD–SHR group (fed high-salt diet), and the DM -SHR group (fed high-fat, high-glucose mixed diet and injected with streptozotocin, 25 mg/kg). Eight male Wistar–Kyoto (WKY) rats (that share the same genetic background with SHR) comprised the blank control group. After 24 weeks, blood plasma was collected by the abdominal aortic method, and the plasma levels of interleukin (IL)-6, IL-1β, and hypersensitive C-reactive protein were assessed. Cortex and hippocampal homogenate was used to determine levels of inflammatory factors, acetyl cholinesterase, acetylcholine, and β-amyloid protein (β-AP). Meanwhile, pathological changes in the CA1 area of the hippocampus and the cortical histopathological structure were observed under light microscopy following hematoxylin and eosin staining, Nissl's staining, and Golgi-Cox staining.

Results: Compared with WKY controls, the level of inflammatory and cholinergic factors in the blood and brain tissue of the four model groups decreased significantly ($P<0.05$), whereas the amount of β-AP increased ($P<0.05$). Changes in the 3'H' model group were more obvious; however, there was no significant difference among the model groups. Compared with WKY group, other groups were obseved the decrease in the number of neurons, space broadening, a disorganized structure, and pyknosis and condensed nuclei by HE

staining. Decreasing in the number of Nissl bodies in the CA1 area were observed by Nissl's staining.

Conclusion: Hypertension combined with lipid metabolism disorders, diabetes, or a high-salt diet can result in pathological changes to the brain tissue and influence the levels of cognitive impairment-related biomarkers. This study presents interactions between multiple risk factors and the increase in the degree of vascular dementia. And it is of great significance for identifying biomarkers to aid in the early intervention or delaying the progress of cognitive deficits caused by hypertension.

SYMPOSIUM 20

Infection and the Microcirculation: Lessons From COVID-19

10:00-11:30 | Room 2

020-SS1

Ruscogenin improves sepsis-induced lung injury

Junping Kou [1]

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Sepsis is a life-threatening organ dysfunction caused by the imbalance of the body's response to infection, and it is the ultimate common death path of serious infections, including bacterial blood infection, malaria, dengue fever, lower respiratory tract infection, diarrheal diseases and systemic fungal infection. Epidemiological research reports show that the incidence of sepsis in the world is about 48.9 million per year, and the number of sepsis-related deaths is about 11 million, accounting for about 20% of the total number of deaths in the world. The structural and functional integrity of endothelium is very important for maintaining vascular homeostasis. Endothelial dysfunction is an early core event in the pathological process of sepsis. It plays an important role in the pathogenesis of sepsis by enhancing vascular permeability, promoting the activation of coagulation cascade and inflammatory reaction, and damaging the perfusion of important organs. Therefore, improving endothelial dysfunction is an important strategy for treating sepsis. Here, we report that ruscogenin (RUS), an effective steroid aglycone in Ophiopogon japonicus, can significantly improve the destruction of organ vascular endothelial barrier in septic mice induced by cecal ligation and perforation (CLP), and alleviate the destruction of pulmonary endothelial barrier induced by lipopolysaccharide (LPS) by mediating the interaction between non-muscle myosin heavy chain IIA (NMMHC IIA) and Toll-like receptor 4 (TLR4). Mice were treated with LPS (5 mg/kg) by intratracheal instillation for 24 h to induce pulmonary endothelial cells injury in model group. RUS (three doses: 0.1, 0.3, and 1 mg/kg) was administrated orally 1 h prior to LPS treatment. Through *in vivo* and *in vitro* experiments, we observed that RUS can significantly improve the pathological injury of lung tissue, evans blue leakage, protein and leukocyte leakage in alveolar lavage fluid, pulmonary endothelial cell apoptosis and the degradation of adhesion protein VE-cadherin triggered by LPS. And we observed that RUS could inhibit the activation of TLR4/MYD88/NF-κB pathway in pulmonary endothelium after LPS treatment. In murine lung vascular endothelial cells (MLECs), we further confirmed that RUS (1 μmol/L) markedly ameliorated MLECs apoptosis and barrier function destruction by suppressing TLR4 signaling. In addition, we also confirmed that RUS directly targeted the N-terminal and head domains of NMMHC IIA by tandem affinity chromatography, molecular docking, biological layer interferometry and micro-scale thermal electrophoresis analysis. Down-regulating the expression of endothelial NMMHC IIA *in vivo* and *in vitro* eliminated the protective effect of RUS. It was also observed that NMMHC IIA in pulmonary vascular endothelial cells was separated from TLR4 after LPS treatment, and then Src/VE-cadherin signal downstream of TLR4 was activated, which could be recovered by RUS. These results provide pharmacological evidence that RUS could inhibit the TLR4 pathway by targeting NMMHC IIA and mediating the interaction between NMMHC IIA and TLR4, thus alleviating the dysfunction of pulmonary vascular endothelial barrier induced by LPS. We also found that NMMHC IIA was highly expressed in blood samples of clinical sepsis patients and renal endothelial cells of septic mice, and it was verified in lung tissue of CLP mice. *In vivo* experiments showed that RUS could significantly improve the mortality, hypothermia, the increase of inflammatory factors and organ damage related factors (ESM-1, IL-1β, IL-6, TNF-α, IFN-α, IFN-β, CXCL1, CK, CRP, BUN, ALT, LDH), lung tissue pathological damage and evans blue leakage in CLP mice. Collectively, the above research shows that RUS can

significantly improve sepsis-induced lung injury by targeting NMMHC IIA.

Keywords: Sepsis, lung injury, endothelial barrier, NMMHC IIA, TLR4, Ruscogenin

020-SS2

Protein-based Inhibition of SARS-CoV-2 Binding to ACE2

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The COVID-19 pandemic fundamentally changed the world. Although SARS-CoV-2 vaccination is the primary preventative intervention, there are few antiviral therapies available, with current drugs decreasing viral replication once the virus is intracellular. Adding novel drugs to target additional points in the viral life cycle is paramount in preventing future pandemics. Our group has developed a novel protein, the recombinant rod domain of vimentin (rhRod), that serves to interrupt SARS-CoV-2 replication through its interaction with the spike protein. We created rhRod in *E. coli*. Using biolayer interferometry (BLI), we measured the K_D of SARS-CoV-2 S1S2 spike protein and rhRod (500 ± 44 nM; R^2 >0.95), using heat inactivated rhRod as a negative control for non-specific binding (indeterminant binding). We then used BLI to determine whether rhRod blocked ACE2-Spike S1S2 interactions. Regardless of whether the immobilized ligand was ACE2 or Spike S1S2 protein, increasing rhRod concentrations decreased ACE2-Spike S1S2 interactions with an IC50 of 33.6 ± 7.6 nM (R^2=0.984; immobilized ACE2) and 139.3 ± 17.4 nM (R^2=0.996; immobilized Spike S1S2). We measured rhRod's effect on SARS-CoV-2 replication in Vero E6 cells and found that daily administration of rhRod at increasing concentrations significantly decreased viral replication after 48 hours. Finally, we evaluated rhRod's effect on lung injury in K18-hACE transgenic mice infected with a high lethal dose of ancestral SARS-CoV-2. Mice that received treatment throughout their infection course had significantly decreased lung injury scores compared to control treated animals. Based on our data, rhRod decreases SARS-CoV-2 replication *in vitro*, likely through its ability to bind to immobilized spike S1S2 protein and blocking spike-ACE2 interactions. Future studies will need to evaluate the protective effects of rhRod against viral variants and multiple doses to identify the optimal dose that both prevents viral replication and host lung injury.

020-SS3

Induction of alarmin S100A8/A9 mediates activation of aberrant neutrophils in the pathogenesis of COVID-19

You Fuping [1]

[1] *Peking University*

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic poses an unprecedented public health crisis. Evidence suggests that SARS-CoV-2 infection causes dysregulation of the immune system. However, the unique signature of early immune responses remains elusive. We characterized the transcriptome of rhesus macaques and mice infected with SARS-CoV-2. Alarmin S100A8 was robustly induced in SARS-CoV-2-infected animal models as well as in COVID-19 patients. Paquinimod, a specific inhibitor of S100A8/A9, could rescue the pneumonia with substantial reduction of viral loads in SARS-CoV-2-infected mice. Remarkably, Paquinimod treatment resulted in almost 100% survival in a lethal model of mouse coronavirus infection using the mouse hepatitis virus (MHV). A group of neutrophils that contributes to the uncontrolled pathological damage and onset of COVID-19 was dramatically induced by coronavirus infection. Paquinimod treatment could reduce these neutrophils and regain anti-viral responses, unveiling key roles of S100A8/A9 and aberrant neutrophils in the pathogenesis of COVID-19, highlighting new opportunities for therapeutic intervention.

SYMPOSIUM 21

Microcirculation in Diabetes

10:00-11:30 | Room 4

021-SS1

Microvascular Insulin Resistance and Diabetes

Zhenqi Liu [1]

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Endothelium, acting as a barrier, protects tissues against factors that provoke insulin resistance and type 2 diabetes and itself responds to the insult of insulin resistance inducers with altered function. Endothelial insulin resistance and vascular dysfunction occur early in the evolution of insulin resistance-related disease, can co-exist with and even contribute to the development of metabolic insulin resistance, and promote vascular complications in those affected. The impact of endothelial insulin resistance and vascular dysfunction varies depending on the blood vessel size and location, resulting in decreased arterial plasticity, increased atherosclerosis and vascular resistance, and decreased tissue perfusion. Thus, reducing endothelial insulin resistance and improving endothelial function in the conduit arteries may reduce atherosclerotic complications, in the resistance arteries lead to better blood pressure control, and in the microvasculature lead to less microvascular complications and more effective tissue perfusion. Multiple diabetes therapeutic modalities, including medications and exercise training, improve endothelial insulin action and vascular function. This action may delay the onset of type 2 diabetes and/or its complications, making the vascular endothelium an attractive therapeutic target for type 2 diabetes and potentially type 1 diabetes.

021-SS2

AI-based screening of diabetic retinopathy

Zilin Sun [1]

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Diabetic retinopathy (DR) affects 25% of Chinese patients with diabetes, but screening rates for DR in China are currently low. The onset of DR is not inevitable; its development can be halted through aggressive primary and secondary prevention. However, the traditional methods of DR screening through fundus photography highly relies on the participation of ophthalmologists, which are severely underrepresented in China to meet the demand for screening. AI technology can provide a fast, accurate, and cost-effective alternative for DR screening. Unfortunately, there is a lack of large-scale research on AI screening for DR in China.

In recent years, we have evaluated the effectiveness of AI technology based on deep learning models for early DR screening in China using fundus photographs of a natural population of 8948 individuals from six ethnic groups across the country. We performed dilatation-free fundus photography on subjects and scored fundus photographs according to ETDRS scoring criteria, and found that the prevalence of any DR in the natural population was 3.9%, severe DR was 0.04%, and DR requiring referral was 0.60%. In the newly diagnosed diabetes population, the prevalence of any DR was 12.46%, severe DR was 0.22%, and DR requiring referral was 3.85%. We then evaluated these fundus photographs using AI and found that AI was efficient in screening patients with DR requiring referral in both the general (AUC 0.936, sensitivity 94.21%, specificity 94.21%) and newly diagnosed diabetes populations (AUC 0.911, sensitivity 93.98%, specificity 88.27%).

We further conducted a larger study of early DR screening using AI for the diabetes population. Through the China Diabetic Retinopathy Screening and Prevention Project grading platform (screening and prevention demonstration centers, screening and prevention centers, grassroots screening and prevention demonstration units, and grassroots screening stations), we performed dilatation-free fundus

photography on two million diabetic patients from 270 hospitals in 110 cities across China between October 2016 and July 2020 and analyzed these fundus photos by AI and co-diagnosed with ophthalmologists to determine whether they are DR and whether they need to be referred to ophthalmology for further treatment. We analyzed 219,739 of these diabetic patients with complete data and found that the positive rate of DR screening in diabetic patients was 31.6%, and the proportion of moderate to severe DR requiring referral to ophthalmology for treatment was 13.6%. Therefore, the mechanism of AI combined with ophthalmology referral can not only promote prevention and improve DR screening rates but also can detect serious DR patients early, which will help reduce the harm of DR to the vision of diabetes patients. In the China Diabetic Retinopathy Screening and Prevention Project, in addition to already verified risk factors for DR, we also found in the subgroup analysis that regardless of the duration of diabetes, the risk of DR was highest in diabetic patients aged 50-70 years; among patients in the same age group, the risk of DR was highest in patients with 10-15 years of diabetes. This suggests that early DR screening should be carried out among those at high risk of DR. Considering that early DR screening on a large scale cannot be achieved by ophthalmologists alone, the timing of screening should be shifted forward to endocrinology and down to primary care in DR early screening because, in China, a large number of patients with DR are first seen in endocrinology or primary care.

In conclusion, the China Diabetic Retinopathy Screening and Prevention Project empowers endocrinologists and primary care general practitioners to screen for DR at an early stage through AI technology, changing the traditional DR screening model and improving the effectiveness of DR screening and prevention.

021-SS3

Redox regulation of endothelial dysfunction in diabetes

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Endothelial progenitor cells (EPCs) are a circulating, bone marrow-derived cell population that participate in both vasculogenesis and vascular homeostasis. Recent studies have shown that EPCs are both reduced and dysfunctional in diabetes. However, the molecular and cellular mechanisms underlying EPC dysfunction are poorly understood. Our studies have focused on in vitro and in vivo aspects of oxidative stress regulation of EPC dysfunction and angiogenesis in diabetes. Our findings demonstrate that a significantly reduced endogenous manganese superoxide dismutase (MnSOD) results in EPC reduction and dysfunction, contributing to wound healing impairement in diabetets. Importantly, epigenetic regulation on MnSOD of EPCs, especially by angiogenic microRNAs, may provide a mechanistic retionale for EPC-based cell therapy strategy on diabetic vascular complications such as impaired wound healing.

021-YS1

TRPC6 mediated podocyte foot process effacement in early diabetic kidney injury

BINGCHEN LIU [1]

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Glomerular podocyte injury is a key factor that contributes to progression of diabetic nephropathy. Podocyte foot process effacement is a specific pathological change of early injury, the regulatory mechanism of which is significance for the research of early reversible diabetic nephropathy. We have previously shown that TRPC6 channels are involved in the regulation of podocytes apoptosis, so whether and how TRPC6 is mediated in the regulation of foot process effacement is an important question to be solved. Our preliminary studies suggest that high glucose reduces expression of podocin, a slit diaphragm structural protein in cultured human podocytes by stimulating TRPC6 that increases intracellular calcium. And recent studies have shown that calcium-dependent cysteine protease calpain-1 is a cleaving enzyme for structural proteins. Co-IP immunoprecipitation assay demonstrated that Calpain-1 does not interact directly with nephrin, but it does interact with podocin. In a mouse model of type 2 diabetes mellitus (db/db T2D), TRPC6 expression was increased and podocin expression was decreased in a cholesterol-rich lipid raft (Cav-1) compared with mice without diabetes (db/m). The application of Calpain-1 inhibitor Calpeptin can reverse the degradation of podocin, which proves that Calpain-1 can cleave podocin in the functional region of cell membrane. Therefore, the following hypothesis was proposed: High glucose leads to increased calcium influx through activation of TRPC6, which activates Calpain-1 to cleave the core protein podocin of the slit diaphragm, and activates the positive feedback damage loop of TRPC6 activation -podocin degradation leading to foot process effacement.

SYMPOSIUM 22

Cerebrovascular Diseases and BBB Permeability: Molecular Targets and Therapeutic Strategies

10:00-11:30 | Room 5

022-SS1

Cerebral tissue oxygenation and blood brain barrier damage in ischemic stroke

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Stroke is a leading cause of death and adult disability. Acute ischemic stroke results in heterogeneous changes in cerebral blood flow and brain metabolism in the affected region, leading to severe neuronal and neurovascular injury. No-flow phenomenon in animal models of ischemic stroke has shown that brain microcirculation did not recover to physiological level even though blood clot has been removed. Recent clinical studies demonstrate that recanalization, including both thrombolysis and thrombectomy, significantly improves the outcome of stroke patients. However, there are still nearly 50% patients, who undergo recanalization, do not have good outcome, suggesting that recanalization does not mean complete reperfusion and, thus, improving microcirculation is critical after recanalization. Our animal studies found that cerebral pO_2 level could be modulated by changing the percentage of oxygen content in the breathing gas, and that 95% O_2 was able to raise penumbral interstitial pO_2 close to the physiological (pre-ischemic) value during ischemia. Importantly, normobaric hyperoxia (NBO) treatment immediately after an ischemia increased tissue pO_2, reduced infarction volume, alleviated blood brain barrier damage, and improved the neurological function of the animal. Most significantly, our randomized controlled clinical trial with acute ischemic stroke patients shows that NBO combination with vascular recanalization could reduce infarct volume, reduce neurological deficits within 24-48h, and reduce risk of poor prognosis and improve mRS score at 90 days. The combined therapy also may reduce the incidence of intracranial hemorrhage at 24 hours and the mortality at 90 days. The encouraging outcome from NBO plus recanalization may indicate the beginning of a new era for recanalization-based combination therapy.

022-SS2

Acute Alteration of Brain Microvasculatures following Hypoxic-Ischemic Brain Injury Model

Hong-Shuo Sun [1]

[1] *University of Toronto*

Neonatal hypoxic-ischemic brain injury (HIBI) poses a large risk in infant survival and resultant neurodevelopmental complication deficits, such as hypoxic-ischemic encephalopathy (HIE), mental retardation, cerebral palsy, and epilepsy. HIE can have long-lasting impacts on affected individuals. The cerebral microvasculature plays an important role in maintaining proper cerebral blood flow and facilitating proper neurodevelopment, while changes in the cerebral microvasculature have been linked to certain brain disease progression and recovery.

In visualizing and quantifying 3D microvascular changes in the developing brain following HIBI, we use neonatal mouse hypoxic-ischemic brain injury model to employ *ex vivo* two-photon microscopy to evaluate the 3D cerebral microvasculature architecture changes in 3, 6, and 24 h after the HIBI. A microvessel segmentation algorithm, incorporating vesselness filtering and binarization, was subsequently used to quantify the 3D microvascular parameters.

We showed a significant reduction in cerebral microvascular segment density, vessel length density, and percent blood volume following the HIBI in both cortical and subcortical regions of the ipsilateral hemisphere. These microvascular changes were observed as early as 3 h post-HIBI. Compared to sham controls, the contralateral hemisphere of the HIBI animals exhibited an increase in cerebral microvascular length density and cerebral blood volume in the subcortical regions at 24 h post-HIBI, suggesting a potentially re-establishment of cerebral microvasculature which may promote recovery after the HIBI.

Our study offers the comprehensive characterization of 3D cerebral microvascular alterations following neonatal HIBI, thereby advancing our understanding of the intricate cerebral microvascular architecture in the developing brain after the hypoxic-ischemic brain injury model.

022-SS3

Ion channels as therapeutics targets in the cerebral microcirculation

William Jackson [1]

[1] *Pharmacology and Toxicology, Michigan State University*

Blood flow to the brain is exquisitely regulated to meet the metabolic demands of active neurons and glial cells through the process of neurovascular coupling. Vascular ion channels play a central role in this form of functional hyperemia. Plasma membrane and intracellular ion channels provide the major source of activator Ca^{2+} that controls contraction (tone) of vascular smooth muscle cells and pericytes; production of endothelial autacoids (NO, PGI_2, Epoxides of arachidonic acid, etc.) that modulate smooth muscle and pericyte function; and gene expression in all vascular cells. Ion channels also importantly determine membrane potential. In smooth muscle cells and pericytes membrane potential controls the activity of voltage-gated Ca^{2+} channels which provide a major source of activator Ca^{2+}. In endothelial cells, membrane potential serves as an important signal for long-distance communication along endothelial cells which are tightly coupled by homocellular gap junctions. Heterocellular gap junctions between endothelial and smooth muscle cells or pericytes allow radial spread of this signal to control the contractile state of these overlying mural cells. Endothelial and smooth muscle cell inward rectifier K^+ (KIR) channels are an excellent example of an ion channel whose function is disturbed in diseases that result in dementia. These channels are activated by physiological changes in extracellular K^+ and thus sense neuronal and glial activity. The resulting smooth muscle KIR-induced hyperpolarization deactivates voltage-gated Ca^{2+} channels in these cells producing vasodilation and an increase in blood flow. K^+-induced activation of capillary endothelial cell KIR channels produces endothelial cell hyperpolarization that is conducted retrogradely along capillaries through endothelial-endothelial cell gap junctions towards feeding arterioles. In this process the endothelial cell KIR channels also serve as amplifiers of endothelial cell hyperpolarization because of their negative slope conductance. Heterocellular gap junctions allow the endothelial cell hyperpolarization to be radially transmitted to overlying contractile pericytes or smooth muscle cells to promote relaxation of these mural effector cells increasing blood flow to the activated capillary segment. These important K^+ channels have been shown to be crippled in a model of Alzheimer's disease mediated by a decrease in phosphatidylinositol 4,5 bisphosphate (PIP_2) resulting in impaired neurovascular coupling. Studies have shown that supplementation with exogenous PIP_2 restores endothelial KIR channel function and neurovascular function, but it has not been shown that treatment with PIP_2 restores cognition. These data and others in the literature suggest that vascular ion channels may provide new targets to treat dementia.

022-SS4

Regulatory role of caveolin-1 in the proliferation and differentiation of neural stem cells in post-ischemic brain

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Caveolin-1 (Cav-1) is an important modulator for adult neurogenesis in post stroke brain repair but its underlying mechanisms are largely unknown. In the present study, we report that endothelial Cav-1 inhibits neuronal differentiation of neural stem/progenitor cells (NSCs/NPCs) in post ischemic brain via regulating vascular endothelial growth factor (VEGF) and NeuroD1 signaling pathway. We first investigated the dynamic change of Cav-1 and its impact on neuronal differentiation in rat and mouse models of 2 h transient middle cerebral artery occlusion (MCAO) plus 1, 7, 14, 21 and 28 day of reperfusion. We then studied the roles of endothelial Cav-1 in modulating the neuronal differentiation of NPCs which were co-cultured with brain microvascular endothelial cells (BMVECs) under 2 h oxygen-glucose deprivation plus 5 days reoxygenation (OGD/R). The major discoveries include: (1) Cav-1 expression in the hippocampal dentate gyrus (DG) was down-regulated on day 1 after 2 h cerebral ischemia, and gradually recovered with reperfusion time, accompanied with transient increased but gradually reduced neuronal differentiation of NPCs marked by doublecortin (DCX). (2) Cav-1 knockout mice exhibited the increased DCX and VEGF at the granular cell layers of hippocampal DG in post-ischemic brains. (3) Co-cultured with BMVECs, NPCs had remarkably decreased neuronal differentiation under OGD/R. Knockdown of Cav-1 in the BMVECs increased VEGF secretion into the medium and NeuroD1+ cells, and rescued the neuronal differentiation of NPCs without affecting astroglial and oligodendroglial differentiation. (4) Cav-1 exosomes released from BMVECs inhibited neuronal differentiation of NPCs via decreasing the expression of VEGF, p44/42MAPK phosphorylation and NeuronD1 upon OGD/R insults. Taken together, endothelial Cav-1 serves as a niche regulator to inhibit neuronal differentiation via negatively modulating VEGF, p44/42MAPK phosphorylation and NeuronD1 signaling pathway.

SYMPOSIUM 23

Microcirculation From Bench to Bedside: Translational Newest Findings

15:00-16:30 | Room 1

023-SS1

Sex in microcirculation: concepts from cardiovascular research

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Coronary microvascular dysfunction (CMD) is assessed as abnormal coronary flow reserve (CFR) and is a condition more prevalent in women compared to men. CMD is associated with increased cardiovascular morbidity and mortality, independently from traditional cardiovascular risk factors.

Factors that may contribute to higher risk of CMD development in women are a. higher levels of systemic inflammation with high oxidative stress

b. stronger innate and adaptive inflammatory responses compared to males and c. higher expression of pro-inflammatory genes at cardiac/vascular tissue level. CMD has been proposed to play a key pathogenetic role also in heart failure with preserved ejection fraction. In our talk we will summarize main concepts from vascular research. Concerning endothelial cells, we know that sex-dependent differences exist at the genetic level and in the endothelial response to sex hormones and vasoactive molecules, however, a better investigation of disease-specific patho-physiology of endothelial dysfunction as a contributing factor in CMD is needed. A better patho-physiological understanding and an early diagnose of CMD is a prerequisite to improve cardiovascular risk management and treatment.

023-SS2

Coronary microvascular dysfunction in immunometabolic disorders

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Coronary microcirculation is a frequent site of cardiac involvement in systemic immunometabolic disorders, whose presence triggers the development of structural and functional abnormalities known as coronary microvascular dysfunction (CMD). CMD limits the increase of the coronary blood flow in response to myocardial oxygen demand and is functionally expressed as the reduction of the coronary flow reserve (CFR). CMD has a high prevalence in metabolic disorders. In diabetic patients, for example, hyperglycemia is associated with significantly reduced endothelial-dependent vasodilation and contributes to the activation of an endothelial pro-inflammatory state. In these patients, CMD is a strong predictor of adverse cardiovascular outcome even before the evidence of macrovascular complications. Overweight and obesity, common in diabetic patients, can also lead to CMD through increased oxidative stress and low-grade systemic inflammation. Indeed, also in obese individuals without other metabolic comorbidities, adipose tissue secretes adipokines that have an impact on the control of the microvascular tone. Interestingly, appropriate interventions were found to reduce obesity-induced endothelial dysfunction. Regarding immune disorders, their impact on coronary microcirculation is also mostly mediated by systemic inflammation. The effects of psoriasis on the heart, for example, go beyond atherosclerotic disease and there is often an early impairment of coronary microvascular function. This impairment correlates with disease duration, disease severity and degree of systemic inflammation. Also in systemic sclerosis, especially in the diffuse form, patients show impaired CFR, even in absence of other signs of cardiac disease. In these clinical scenarios, assessment of CMD allows not only diagnosis of cardiac involvement but has strong prognostic implications: indeed, in both psoriasis and

systemic sclerosis impaired CFR is associated with a worse outcome. Moreover, CFR can be used as a surrogate marker of systemic efficacy during specific therapies, such as treatment with monoclonal antibodies, and the observed improvement in CMD was found to be correlated with reduction of biomarkers of inflammation. This allows to identify responders to medical therapy. Psoriasis and systemic sclerosis are, however, only some examples of the long list of immune-mediated and autoinflammatory conditions associated with CMD, that range from other rheumatic disorders (such as rheumatoid arthritis) to gastroenterological and hepatological disease (such as inflammatory bowel disease and primary biliary cholangitis). In immunometabolic disorders, CMD represents a major form of cardiac involvement and is associated with impaired prognosis. Moreover, still limited but valid evidence shows that an accurate control of the immunometabolic disorder and of its pro-inflammatory profile allows to reverse CMD.

023-YS1

The sublingual glycocalyx and perfused boundary region in health

Andrew Forbes Brown [1,2], Kim Gooding [1,2], Dave Mawson [1,2], Kuni Aizawa [1,2], Chris Kelsall [1,2], Claire Ball [2], Alina Govier [2], Silvia Balma [2], Darcy Watkins [2], Anna Barnes [2], John Kirkwood [2], Mark Gilchrist [1,2], Angela Shore [1,2]

[1] *University Of Exeter Medical School*
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Introduction: The sublingual microvasculature is an accessible vascular bed increasingly utilised in research. Recent development of red blood cell (RBC) column imaging has allowed estimations of endothelial glycocalyx (EG) integrity. Specifically, the perfused boundary region (PBR) indicates the capacity of EG to restrict RBC movement toward the vessel wall. EG is vital for vascular health. Previous research has demonstrated associations between EG loss and various conditions, including endothelial dysfunction, diabetes, kidney disease, and sepsis. Factors relating to EG integrity in health remain under-researched. Thus, this project aimed to assess associations between PBR and factors impacting EG.

Method and Material: Anthropometric data, blood samples, blood pressures and sublingual images were collected from participants without diabetes or cardiovascular disease under standardised conditions. Sidestream darkfield microscopy paired with Glycocheck software was used for PBR assessment, calculated from the 50th and 90th percentile RBC column width, where higher PBR represents poorer EG integrity. Results Images were obtained from 71 participants (59.2% male, mean age (SD):69.3±5.9 range:47-83years, BMI:26.9±4.5kg/m2, systolic BP:134.1±14.5mmHg, diastolic BP:75.4±9.1, resting HR: 62.1±8.8bpm). PBR was assessed in vessels 5-25μm in diameter (mean:1.96±0.22μm), and subcategories of 5-9μm (1.11±0.85), 10-19μm (2.17±0.24), and 20-25μm (2.34±0.38). Mean PBR (5-25μm) was lower in men than women (1.91, 95% CI [1.85, 1.97], vs. 2.03 95% CI [1.94, 2.11], p=0.02). This observation was more evident in vessels 5-19μm, and in 20-25μm vessels did not reach statistical significance. In all participants, positive correlations were seen between PBR (5-25μm) with age (Rs=0.27, p=0.02, Spearman's), and resting HR (r=0.27, p=0.03, Pearson's). Positive correlation between systolic BP and PBR was present, but in larger vessels (20-25μm) only (r=0.25, p=0.04). No associations were seen between PBR and, anthropometric measurements, glycaemic control (HbA1c, fasting glucose) or kidney function (eGFR).

Conclusion: Within this older non-diabetic cohort, EG integrity decreased with age, and in larger microvessels with SBP. Women possessed a higher PBR, particularly in the smaller vessels. Resting HR may be interpreted as a marker of physical activity/fitness. This association could indicate a protective effect of exercise on EG integrity, though further research is required to examine this.

023-YS2

Vascular age is not only atherosclerosis, it is also arteriosclerosis

Rosa Maria Bruno [1]

[1] *Université Paris Cité*

Vascular ageing is a process that can capture the early (generally asymptomatic) features of vascular degeneration. While there is no universally agreed definition for vascular age, it involves the deterioration in arterial structure and function over time, which ultimately leads to damage of the heart, brain, kidney, and other organs and established cardiovascular disease. Vascular age includes a large spectrum of alterations affecting the functional and structural components of the arterial wall irrespective of size, traditionally included in the definitions of atherosclerosis and arteriosclerosis. Though chronological age is a major determinant of vascular age, many other conditions, including classical and emerging cardiovascular risk factors as well as genetic and environmental conditions, contribute to vascular age, which can be thus largely different from chronological age. Increasing evidence shows that biological or vascular age is a better predictor of cardiovascular disease than chronological age, leading to the introduction of the concept of early vascular age or EVA. On the other side, individuals with inappropriately healthy arteries compared to their risk profile, a phenomenon recently described as supernormal vascular ageing or SUPERNOVA, are protected from premature cardiovascular disease.

Given that a measure of vascular age encompasses the cumulative effect of all cardiovascular risk factors on the arterial wall over the life course, compared to more traditional risk factors which may fluctuate in time, a measure of vascular age may help identify those at elevated cardiovascular risk. Because factors influencing vascular age are numerous and their impact on vascular health varies between individuals, a direct, noninvasive assessment of vascular health is advisable.

Carotid ultrasound, ankle-brachial index, and coronary artery calcium score are recommended according to European guidelines for CVD prevention because of their reclassification potential in addition to traditional risk scores, whereas American College of Cardiology/American Heart Association guidelines recommend only coronary artery calcium

score. However, these biomarkers represent the atherosclerotic component of vascular aging, which is only one side of the coin. Arteriosclerosis is equally relevant as a mechanism of age-related diseases. Arterial stiffness (determined via carotid-femoral pulse wave velocity or other techniques) also has reclassification potential and can be measured with simple, noninvasive, increasingly available techniques. Nevertheless, a number of unmet needs are limiting the measurement of arteriosclerosis in routine clinical practice, which the VascAgeNet Cooperation in Science and Technology (COST) Action is currently working to address.

SYMPOSIUM 24

Cross-Talk Between Microcirculation and Microrheology of Blood Cells in Arterial Hypertension and Diabetes Mellitus

15:00-16:30 | Room 2

024-SS1

Microcirculatory and hemorheologic alterations in diabetes mellitus measured in vitro and in vivo by different optical techniques

Andrei Lugovtsov [1], Petr Ermolinsky [1], Matvey Maksimov [1], Anastasiya Romanova [1], Danila Umerenkov [1], Yury Gurfinkel [2], Alexey Muravyov [3], Irina Tikhomirova [4], Alexander Priezzhev [1]

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Nowadays the number of people suffering from diabetes mellitus (DM) increases rapidly mainly due to unhealthy nutrition and lifestyle. This disease can lead to severe alterations of vitally important systems of the human organism including the cardiovascular system and results in a damage to blood vessels and capillaries, impairment of blood hemorheology and microcirculation. Enhanced aggregation of red blood cells (RBC) and platelets is one of key factors, which determines the blood flow alteration and thereby affects the blood rheology. The ability of RBC to deform in shear flow conditions is the second major property that affects the blood microcirculation. Alterations in these properties lead to changing the blood viscosity and, consequently, to changes in capillary blood flow. This can lead to significant impairment of blood function, which increases a risk of occurrence of vascular concomitant diseases, and even the mortality.

The main goal of this work is to interrelate and assess the deformability (dependance of RBC elongation on shear stress) and aggregation properties of RBC (hydrodynamic strength of RBC aggregates, characteristic time of RBC aggregates formation, aggregation index, forces of pair aggregation of RBCs and aggregation rate), platelets aggregation rate and degree in the blood samples drawn from patients suffering from DM and from healthy donors. The measurements were performed *in vitro* using the techniques of diffuse light scattering, turbidimetry, laser diffractometry, laser trapping and manipulation. Digital capillaroscopy was used *in vivo* to visualize the capillaries and quantitatively evaluate the capillary blood flow in the nailfold vessels.

It was shown that in DM patients, the ability of RBC to deform is slightly reduced while the aggregation rate and forces of the cells interaction are significantly increased relative to those in the control group. The degree and rate of platelets aggregation in patients suffering from DM are increased compared with people without DM. The activation of platelets occurs more intensively and rapidly in case of DM. The blood microcirculation in nailfold capillaries is impaired as well. We have shown that the alterations of the parameters measured *in vivo* and *in vitro* for patients with different stages of these diseases are interrelated. Good agreement between the results obtained with different techniques, and their applicability for the diagnostics of abnormalities of rheological properties of blood were demonstrated.

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024-SS2

Effect of Traditional-Chinese-medicine-based blood-regulating therapy on abnormal vascular function in psoriasis

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Psoriasis is a common, chronic papulosquamous skin disease that occurs worldwide and can affect individuals of any age. Its immunological pathogenesis suggests that underlying genetic and environmental factors lead to an autoimmune inflammation in skin lesions involving multiple immune cells. However, abnormal vascular inflammation also plays a significant role throughout its development and progression, including the appearance of tortuous blood vessels and dermal microvascular angiogenesis in the initial stages, endothelium inflammation with increased vascular permeability in the progressive stages, and persistent microvascular non-regression in the static stages. Therefore, regulating vascular function can be an effective approach in the treatment of psoriasis.

According to Traditional Chinese medicine (TCM) theory, psoriasis is induced or aggravated by the accumulation and transformation of evil heat from genetics or external infection which results in toxic heat in the blood. Thus, the basic principle for treating psoriasis is to address the blood syndrome. Blood syndrome of psoriasis in TCM is classified into three types: blood-hotness, blood-dryness, and blood-stasis syndrome, corresponding to the initial stage, progressive stage, and static stage of psoriasis respectively. TCM apply cooling-blood herbs for blood-hotness syndrome, nourishing-blood herbs for blood-dryness, and promoting-blood circulation herbs for blood-stasis. Meanwhile all syndromes combine detoxification herbal medicine. Therefore, blood-regulating therapy including cooling blood, nourishing-blood and promoting-blood circulation, is regarded as the most essential therapy principle for treating psoriasis.

This report summarizes the mechanisms of vascular changes at different stages of psoriasis and the therapeutic effects of blood-regulating therapy. Firstly, a total of 105 psoriasis cases were examined, revealing that the serum VEGF level was higher in the psoriasis group compared to the control group. Among these cases, there were 48 with blood-hotness syndrome, 32 with blood-dryness, and 25 with blood-stasis. After 8 weeks of corresponding treatment, significant down-regulation of serum VEGF levels was observed in both the blood-hotness and blood-dryness syndrome groups.

LXJD formula for blood hotness syndrome is mainly composed of *Lithospermum, Rehmannia, Red peony root, Smilax glabra, Sophora japonica.L, etc.* Clinical studies have shown that after 8 weeks of treatment, the effective rate of LXJD formula reached up to 57.8%, with a total effective rate of 98.3%. In addition, there was a significant decrease in serum levels of TNF-α, IL-8, IFN-γ, and VEGF after treatment. In vitro studies also showed that the LXJD formula inhibited both medium and small blood vessel growth in chicken embryo chorioallantoic membrane and prevented endothelial cells (ECs) migration and tube formation.

S-Nitrosoglutathione reductase (GSNOR), an enzyme regulating nitric oxide bioavailability, was found overexpressed in skin lesions of both psoriasis patients and IMQ-induced psoriasis-like mice. Knockdown of GSNOR gene reduced psoriatic lesions and decreased inflammatory cytokines and vascular-related factors. LXJD formula showed a reduced PASI score, as well as decreased the expressions of vascular and inflammatory cytokines. Additionally, LXJD decreased GSNOR protein expression and increased nitrosylation level of NF-κB protein.

YXJD formula for blood-dryness syndrome is mainly composed of *Salvia miltiorrhizae, Angelica sinensis, Scrophulariae, etc.* In K14/VEGF mice model, YXJD formula decreased PASI score, relieved the excessive blood perfusion, and reduced the number of blood vessels by inhibiting ERK/NF-kB pathway, as well as reduced VEGF/VEGFR and ANG/TIE expression. Moreover, YXJD formula reduced ECs apoptosis caused by Survivin overexpression, reduced VEGF secretion by inhibiting AKT and GSK-3β phosphorylation, β-catenin production.

Here concludes, blood-regulating therapy can alleviate psoriasis by modulating vascular function at different stages of the disease.

024-SS3

Transcription factor FOXO1 and diabetic complication

LU TIE [1]

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Refractory wounds in diabetic patients constitute a serious complication that often leads to amputation with limited treatment regimens. Transcription factor FOXO1 is a key angiogenic regulator and plays a pathologic role in progression of diabetes. The present study was designed to determine the involvement of FOXO1 in impaired EC function and post-ischemic neovascularization in diabetes and investigate underlying mechanisms. We found that FOXO1-selective inhibitor AS1842856 improved blood flow recovery and capillary density in ischemic hindlimb, and rescued the delay of wound closure with a concomitant augmentation of mean perfusion rate in diabetic mice. *In vitro*, treatment with AS1842856 or FOXO1 siRNA abrogated high glucose–induced apoptosis and ameliorated capillary tube formation in human umbilical vein endothelial cells (HUVECs). FOXO1 inhibition relieved alterations in mitochondrial networks and significantly suppressed the overproduction of mitochondrial reactive oxygen species (mtROS) induced by high glucose in ECs. Expression of dynamin-relatedprotein-1 (Drp1) and phosphorylation at Ser616, a protein required for mitochondrial fission, were enhanced by hyperglycemia, which could be neutralized by FOXO1 inhibition. Moreover, the transcription of Rho-associated coiled-coil containing protein kinase 1 (ROCK1), which phosphorylates Drp1 at Ser616, was shown by luciferase assay to be directly regulated by FOXO1. These findings suggested that FOXO1 is critical to preserve mitochondrial quantity and function in ECs, and FOXO1 may serve as a therapeutic target for microvascular complications of diabetes.

024-YS1

Microhemorheological and microcirculatory profile of hypertensive patients

Petr Ermolinskiy [1], Matvey Maksimov [1], Andrei Lugovtsov [1], Gurfinkel Yury [2], Alexander Priezzhev [1]

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Blood plays crucial role in delivering oxygen and other substances to body tissues. Red blood cells (RBC) as blood component are the most abundant cells in the blood. RBCs interact with each other resulting in formation of RBCs linear or 3D aggregates. The process of RBC aggregates formation is referred to as RBC aggregation and it mainly determines the blood viscosity. RBC spontaneous aggregation and shear forced RBC disaggregation depend on a variety of medium and cell factors. Blood coagulation mainly depends on platelet aggregation. Platelet aggregation also depends on a variety of factors and determines hemostasis. Deviation of RBC and platelets aggregation parameters from the healthy conditions can significantly impair blood microcirculation in the body, as well as lead to the development of vascular pathologies and comorbidities. Elevated RBC and platelet aggregation were be found in the blood of patients suffering from type 2 diabetes mellitus, cardiovascular diseases, cerebrovascular disorders, and other pathologies [A. Maslianitsyna, et al. Diagnostics (Basel) 11(1): 76 (2021)]. The aim of this study is to show the comprehensive microhemorheological and microcirculatory patterns of hypertensive patients obtained by modern and simple optical techniques.

In this study, light scattering techniques were used to measure RBC and platelet aggregation properties in vitro. These methods are based on the dependence of scattered light intensity on particle size and allow for the registration of RBC and platelet aggregation kinetics. RheoScan-AnD300 device (RheoMedTekh, Republic of Korea) was used to measure several RBC aggregation parameters. Biola-230LA (Biola, Russia) was used to determine the platelet aggregation under adenosine diphosphate activation. Digital capillaroscope Kapillaroskan-1 (AET, Russia) was used to visualize the terminal blood capillaries in the nail bed of patients in vivo and to calculate blood flow velocities therein.

Comprehensive study of 50 patients confirms the hypothesis of increased RBC and platelet aggregation in the blood samples of patients suffering from arterial hypertension compared to that of healthy donors. Our results also clearly demonstrate the possibility of using light scattering techniques to assess changes in microrheological (RBC aggregation and platelet aggregation) and, therefore, microcirculatory parameters (capillary blood flow velocity etc.). In future, changes in RBC and platelets aggregation parameters measured in vitro can be used to correct and develop the therapy protocols for patient suffering from hypertension.

The study was supported by the Russian Science Foundation Grant No. 22-15-00120.

SYMPOSIUM 25

The Advantage of Traditional Chinese Medicine in Treating COVID-19

15:00-16:30 | Room 4

025-SS1

Deciphering the covalent SARS-CoV-2 3CLpro inhibitors from herbal medicines via integrating chemoproteomic and biochemical approaches

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The 3C-like proteases ($3CL^{pro}$s) play crucial roles in polyprotein processing in various β-coronaviruses (CoVs), thus have been validated as key targets to develop broad-spectrum anti-CoVs drugs. $3CL^{pro}$s are cysteine-rich homodimeric proteins and can be covalently modify by numerous natural and synthetic compounds, which in turn, block the proteolytic activity or the formation of enzymatically active dimeric forms. Although herbal medicines have been widely used to treat COVID-19, deciphering the key herbal constituents that can covalently modify $3CL^{pro}$s remains a big challenge. Herein, to efficiently discover covalent SARS-CoV-2 $3CL^{pro}$ inhibitors from herbal medicines, we construct a comprehensive approach by integrating fluorescence-based $3CL^{pro}$ inhibition assay, global analysis of herbal constituents, and chemoproteomic profiling of cysteine-modified peptides. Following testing the anti-SARS-CoV-2 $3CL^{pro}$ effects of 104 herbal medicines, we found that *Ginkgo biloba* extract 50 (GBE50), *Lonicera japonica* extract (LJE) and *Rhodiola Crenulata* extract (ERC) potently inhibited SARS-CoV-2 $3CL^{pro}$ in dose- and time-dependent manners.

A total of 38 constituents were identified from GBE50 by UHPLC-Q-Exactive Orbitrap HRMS, while 26 peptides modified by 18 constituents were identified by chemoproteomic profiling. The anti-SARS-CoV-2 $3CL^{pro}$ effects of 18 identified covalent inhibitors were then validated by performing time-dependent inhibition assays. The results clearly demonstrated that most tested constituents showed time-dependent inhibition on SARS-CoV-2 $3CL^{pro}$, while gallocatechin and sciadopitysin displayed potent anti-SARS-CoV-2 $3CL^{pro}$ effects. UHPLC-Q-Exactive Orbitrap HRMS analysis identified 51 constituents in LJE, while chemoproteomic profiling revealed that 22 constituents in LJE could covalently modify SARS-CoV-2 $3CL^{pro}$. Biochemical assays showed that gallic acid, quercetin and cynaroside displayed strong anti-SARS-CoV-2 $3CL^{pro}$ activity in a dose- and time- dependent manners, with IC_{50} values of less than 20 μM. The K_I value of gallic acid was determined as 5.63 μM. Covalent docking simulations were also used to elucidate the inhibitory mechanism. A total of 48 constituents were identified from ERC by UHPLC-TOF-MS/MS, while a total of 40 peptides covalently modified by 26 constituents were detected. Further investigations demonstrated that at least 17 constituents in ERC showed time-dependent inhibition against SARS-CoV-2 $3CL^{pro}$. Among them, rhodiosin, herbacetin, rhodionin, gallic acid, catechin gallate, and epigallocatechin gallate showed strong inhibition on SARS-CoV-2 $3CL^{pro}$, with the IC_{50} values were less than 10 μM, while inactivation kinetics analyses and covalent docking simulations were performed to further elucidate the inhibitory mechanisms of these constituents. Finally, the synergistic effects of various covalent SARS-CoV-2 $3CL^{pro}$ inhibitors and the underlying synergistic mechanisms were also investigated.

Overall, this study established a novel strategy for efficiently discovering the covalent inhibitors of $3CL^{pro}$ from herbal medicines by integrating mass spectrometry-based approaches and biochemical assay, which will greatly facilitate the discovery of covalent SARS-CoV-2 $3CL^{pro}$ inhibitors from herbal products.

025-SS2

Further understanding of anti-SARS-CoV2 by using TCM: attach equal importance to antiviral and anti-inflammatory therapies

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In recent years, new respiratory infectious diseases have continuously emerged, such as SARS, MERS, novel H1N1 influenza, H7N9 avian influenza, COVID-19, etc. The new respiratory pathogens have characteristics of high variability, strong infectivity, and high susceptibility, making it easy to cause outbreaks and epidemics. Traditional Chinese medicine has significant advantages in the prevention and treatment of respiratory infectious diseases. Its advanced concepts of treating the disease before it occurs and holistic approach are in line with the core of modern infectious disease prevention and control, that is, early warning, early detection, and early intervention. It can provide effective methods, strategies, and drug choices for the prevention and treatment of new respiratory infectious diseases, and enhance the ability to prevent and control major respiratory infectious diseases.

Over the years, we have persisted in combining the advanced TCM concepts of "holistic view" and "treating before the onset of illness" with advanced Western virology techniques to achieve breakthrough results in the prevention and treatment of respiratory infectious diseases. (1) Based on the pathogenesis of "internal and external evil", a common evaluation system for antiviral Chinese medicine was created, confirming the advantages of single or compound drugs such as Banlangen and Lianhua Qingwen with "one drug, multiple targets" or "multiple drugs, multiple targets", and breaking through the bottleneck of unclear evaluation and mechanism of antiviral Chinese medicine; (2) In order to further reveal the development and evolution laws of newly emerging respiratory infectious diseases and to reflect the characteristics of "internal and external evil", successful models of non-human primates and tree shrews that simulate virus replication and inflammation were developed; (3) Under the guidance of the theory of "internal and external evil" causing severe illness, the applicant led and participated in the screening, research and clinical evidence-based application of Chinese medicine for the treatment of SARS-CoV-2 in China, first discovering and confirming the therapeutic effects of Lianhua Qingwen, Liushenwan, and Xuebijing on SARS-CoV-2, timely translating them into clinical treatment, and the pharmacological achievements were the first in the world. The potential for the anti-SARS-CoV-2 effect of the Chinese medicine monomer Lianqiao glycoside was discovered, providing hope for new specific Chinese medicine for the treatment of SARS-CoV-2, supporting the combination of Chinese and Western medicine in clinical prevention and treatment.

025-YS1

Qing-Fei-Pai-Du-Tang, a Chinese medicine formula, attenuates lipopolysaccharide-induced pulmonary microcirculatory disturbances in rats

Shuya He [1,2], Chunshui Pan [2], Li Yan [2], Ping Huang [2], Lulu Yan [2], Rong Huang [2], Quan Li [2], Xinmei Huo [1], Jian Liu [1,2], Jingyu Fan [2], Wei Liu [3], Chaoran Wang [4], Guangbo Ge [3], Weidong Zhang [3], Kai Sun [2], Jingyan Han [1,2]

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Background and Aim: A Chinese medicine formula Qing-Fei-Pai-Du-

Tang (QFPDT) is recommended to prevent COVID-19 patients from exacerbation in China with effectiveness. However, the underlying mechanism remains unclear. The present study was to assess the role of QFPDT in a lipopolysaccharide (LPS)-induced acute lung injury (ALI) attempting to disclose the rationale behind the effect of QFPDT.
Methods: Male Wistar rats were intraperitoneally injected with lipopolysaccharide (7.5 mg/kg), QFPDT (6 g/kg) was given by gavage 10 minutes before (pre-treatment) or 6 hours after (post-treatment) LPS injection. Leukocyte adhesion to pulmonary microvessels, microvascular hyperpermeability, pulmonary endothelial apoptosis were detected, and the underlying mechanisms were explored.
Results: The results revealed that 6 and 24 hr after injection of LPS (7.5 mg/kg) induced an increase in leukocyte adhesion to pulmonary microvessels accompanied with high expression of CD18/CD11b and ICAM-1. Besides, LPS induced an increase in FITC-dextran leakage from pulmonary microvessels, Evans blue extravasation and lung edema, along with a downregulated expression of tight junction and adherent junction proteins and deceased ATP/ADP and ATP/AMP ratio. Moreover, there was a downregulated expression of basement membrane protein laminin, and an activation of TLR-4, Src, focal adhesion kinase (FAK) and Cathepsin B in lung tissue after LPS. Importantly, all the insults were attenuated by pre- and post-treatment with QFPDT. Moreover, QFPDT attenuated the increase of malondialdehyde and 8-hydroxy-2-deoxyguanosine, the decrease of glutathione peroxidase and superoxide dismutase, and the increase of TUNEL positive cells in lung tissue.
Conclusion: QFPDT improves LPS-induced lung injury through attenuating leukocyte adhesion to pulmonary microvessels and inflammatory cell infiltration due to the inhibition of adhesion molecules, as well as maintaining pulmonary microvascular barrier integrity which is related to the inhibition of energy metabolism abnormality and intercellular junction disruption, TLR-4/Src/FAK/ Cathepsin B mediated vascular basement membrane injury, and oxidative stress mediated pulmonary endothelial cell apoptosis.

025-YS2

Understanding the mechanism of Qing-Fei-Pai-Du decoction in coronavirus-induced pneumonia based on omics approaches

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Qing-Fei-Pai-Du decoction (QFPDD) is a recommended therapy for patients with COVID-19 in China, but the mechanism remains unclear. In this study, we evaluated the therapeutic effects of QFPDD in pneumonia model mice and performed16S rRNA gene sequencing and metabolomic analysis to explore the underlying mechanisms. Our results suggest that QFPDD can restore the richness and diversity of gut microbiota, and many of them are significantly associated with immune-inflammation-related indicators. In addition, various types of lipid metabolism changes were observed in serum and lung tissue metabolome, especially glycerophospholipids and fatty acids. Interestingly, these differential metabolites showed a good correlation with the gut microbiota affected by QFPDD. The results suggest that QFPDD can improve the immune function and reduce inflammation in pneumonia model mice possibly by remodeling gut microbiota and host metabolism.

SYMPOSIUM 26

Vascular Redox Signaling and Oxidative Stress

15:00-16:30 | Room 5

026-SS1

Vascular redox signaling and oxidative stress

Katrin Schröder [1]

[1] *Goethe-University Frankfurt, Faculty of Medicine, Germany*

A major component of vascular redox signaling is the family of NADPH oxidases (Nox). The family of NADPH oxidases consists of 7 members whose only function is, to produce superoxide anions or hydrogen peroxide. All members represent with a specific expression pattern and intracellular localization. While endothelial cells mainly express Nox2 and Nox4, smooth muscle cells express Nox1 and Nox4. In line with different modes of activity and intracellular localization, the individual NADPH oxidases modify specific signal transduction pathways.
Nox4 contributes to long lasting effects such as differentiation and cellular homeostasis. In contrast, Nox1 and 2 modify acute cellular responses to cytokine stimulation.
The talk will cover the way how Nox2 modifies signaling in erythropoietin stimulated endothelial progenitors and how Nox4 mediates endothelial differentiation.

026-SS2

Cross-talk between oxidized LDL, oxidative stress and renin-angiotensin-aldosterone system: Impact on microcirculation and atherosclerosis

Henning Morawietz [1]

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Rationale and Objective: Hypertension and hypercholesterolemia are important risk factors of endothelial dysfunction, atherosclerosis and coronary artery disease. Previous studies suggested a crosstalk between an activated renin-angiotensin system (RAS), reactive oxygen species (ROS) and oxidized low-density lipoproteins (LDL) in atherosclerosis, but the underlying molecular mechanisms are not well understood. We here identify a new signaling pathway controlling the molecular crosstalk of the RAS with ROS and the atherosclerotic environment.
Methods and Results: We demonstrate that oxidized low-density lipoprotein (oxLDL) modulates angiotensin II (Ang II) type-1 receptor (AT_1R) expression via Oct-1 transcription factor signaling in human microvascular and aortic endothelial cells *in vitro*, with concomitant validation in the heart of obese C57BL/6 mice and cardiac and aortic tissue of AT_{1a}/AT_{1b} double knockout mice. AT_1R promoter activation studies upon Ang II- and oxLDL-stimulation in endothelial cells revealed that Ang II and oxLDL activate AT_1R signaling through G protein $G\alpha_{12/13}$, followed by activation of ERK1/2 MAP kinases, and transcription and translation of Oct-1, resulting in up-regulation of AT_1R, LOX-1 and NOX2 expression, which could be antagonized by specific inhibitors at each step of the identified signaling cascade. Male C57BL/6 mice fed a high-fat diet exhibited upregulation of Oct-1 levels in cardiac tissues, compared to normal controls, while AT_{1a}/AT_{1b} double knockout mice demonstrated downregulation of Oct-1, AT_1R, LOX-1, and NOX2 on mRNA and protein level in cardiac and aorta tissue, thus confirming the identified signaling cascade *in vivo*.
Conclusions: Oct-1 is an essential transcription factor for Ang II- and oxLDL-induced upregulation of AT_1R and LOX-1 expression in endothelium, thus identifying a novel molecular cross-talk of oxLDL with ROS signaling and the RAS contributing to development of endothelial dysfunction and atherosclerosis.

026-YS1

HIF-2α mediates regulation of Endothelium-derived semaphorin 3G expression via Nrp2/PlexinD1 pathway under hypoxia

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Aims: The poorly understood mechanisms underlying vascular remodeling in retinal neovascular diseases associated with ischemic retinopathy highlight the urgent need to improve current pharmacological treatment modalities.

Methods: In this study, we investigated the mechanism of Sema3G-mediated physiological vascular recovery and pathological vascular pruning using a combination of gene-modified mice, hypoxia models, immunofluorescence staining, RNA in situ hybridization, RNA sequencing, bioinformatics analysis, and pharmacology/genetic regulation techniques. Specifically, we employed an oxygen-induced retinopathy (OIR) mouse model, in which newborn mice were exposed to 75% oxygen at postnatal day 7 (P7) until P12, resulting in significant blood vessel loss and vaso-obliteration in the center of the retina. Upon returning to normoxia, these mice developed extraretinal neovascularization during P12 to P17, followed by vessel regrowth and regression of preretinal neovascularization during P17 to P25.

Results: To investigate the involvement of Sema3G in pathological retinal angiogenesis, retinas from Sema3G knockout mice were analyzed at various phases of OIR. Our findings indicate that endothelial Sema3G deficiency delays the regression of pathological vasculature and inhibits vascular normalization in OIR retinas. These results suggest that the expression of endothelial Sema3G is regulated in a HIF-2α–dependent manner in response to hypoxia. We further investigated the sequence characteristics of the Sema3G promoter and identified three putative HRE sites from the JASPAR database. Our data suggest that HIF-2α directly binds to the Sema3G promoter and activates its transcription in response to hypoxia, but not HIF-1α.

To gain deeper insight into the intracellular molecular mechanisms, we utilized transcriptome sequencing to analyze the effects of silencing endogenous Sema3G expression in human retinal microvascular ECs (HRMECs). Our integrated bioinformatics analysis revealed that the downregulation of Sema3G expression affects cell adhesion molecules, Wnt signaling pathways, and focal adhesions. These results collectively suggest that Sema3G may protect the stabilization of β-catenin from degradation, thereby sustaining cadherin-mediated adhesion in ECs. To provide additional evidence that β-catenin is a downstream regulator of Sema3G in pathological angiogenesis, we characterized the expression patterns of β-catenin and VE-cadherin in endothelial-specific deletion of Sema3G mice in the OIR model. Our findings demonstrate that Sema3G attenuates ischemic retinopathy by preventing β-catenin degradation, which targets the vasculature for vascular normalization. Furthermore, our results suggest that β-catenin is required for Sema3G to attenuate ischemic retinopathy.

To further validate the receptors of Sema3G in ECs, we investigated the direct binding of Sema3G-AP to siControl or siPlexinD1-transfected HRMECs. We observed that the binding signal was decreased in the absence of Nrp2, indicating that the Nrp2/PlexinD1 complex is the functional cell-surface receptor of Sema3G. We also developed an adeno-associated virus–mediated (AAV-mediated) receptor knockdown method in OIR mice, which revealed that Sema3G attenuates ischemia-induced pathological neovascularization through PlexinD1.

Conclusion: In a word, we demonstrate that HIF-2α directly regulates Sema3G expression under hypoxic pathological conditions and that Sema3G protects vascular stability by enhancing the stabilization of endothelial β-catenin and VE-cadherin through the Nrp2/PlexinD1 signaling pathway. Cumulatively, our study sheds light on the intricate mechanisms by which Sema3G regulates vascular stability and remodeling, particularly during the vascular regression phase in vasculopathy. These findings have significant clinical implications and provide new insights and drug targets for the treatment of ischemic retinopathy. Our study not only unravels the endothelial-derived Sema3G-dependent events but also clarifies the protective effect of Sema3G in ischemic retinopathy, opening up new avenues for further research in this field. Ultimately, our work provides an important foundation for the development of novel therapeutic strategies for the treatment of ischemic retinopathy.

026-YS2

Inhibition of endothelial nitrosative stress attenuates cisplatin-induced neurotoxicity in the arcuate nucleus

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Objective Severe anorexia limits the clinical application of cisplatin, and even leads to the discontinuation of treatment. To elucidate the exact mechanism of cisplatin-induced neurotoxicity and feeding behavior disorder.

Methods We measured neuronal activity in the arcuate nucleus (Arc) of mice after cisplatin administration by *in vivo* electrophysiological recording. We used *ex vivo* electrophysiology to record the resting membrane potential and action potential (AP) of the neurons in acute separated cerebral slices. RNA sequencing analysis of cells was used to elucidate the molecular mechanisms underlying neuronal oscillation dysfunction mediated by cisplatin.

Results Cisplatin could affect neuronal gamma oscillations and induce abnormal neuronal theta-gamma phase-amplitude coupling in the Arc, which were associated with significantly decreased food intake and weight loss in mice. Chemogenetic activation of AgRP neurons in the Arc reversed the cisplatin-induced food intake reduction in mice. Furthermore, endothelial peroxynitrite ($ONOO^-$) formation in the Arc induced nitrosative stress following cisplatin treatment via a previously uncharacterized pathway involving neuronal caspase-1 activation. Strikingly, treatment with $ONOO^-$ scavenger uric acid (UA) reversed the reduced AP frequency of AgRP neurons and increased the AP frequency of POMC neurons induced by SIN1, a donor of $ONOO^-$. Moreover, UA treatment effectively alleviated cisplatin-induced dysfunction of neuronal oscillations and neuronal theta-gamma phase-amplitude coupling in the Arc of mice.

Conclusion These results suggest that targeting the overproduction of endothelial $ONOO^-$ can regulate cisplatin-induced neurotoxicity through neuronal caspase-1, and thereby serve as a potential therapeutic approach to alleviate chemotherapy-induced anorexia and weight loss.

Keywords: Cisplatin; Endothelial cell, Peroxynitrite; Neuronal oscillations; Arcuate nucleus.

SATELLITE SYMPOSIUM 6

Microcirculation and Ocular Diseases

08:30-10:00 | Guorui Hall

S06-1

Retinoschisis with multiple abnormal blood vessels in high myopia

Weihong Yu [1]

[1] *Peking Union Medical College Hospital*

Objective: To report two rare cases of high myopic retinoschisis with abnormal blood vessels, reveal related characteristics of the lesion, and report the effectiveness of vitrectomy and laser treatment.

Methods: This study included three eyes of two patients with high myopic retinoschisis with or without foveal detachment, accompanied by retinoschisis at the vascular arcade with abnormal retinal vessels. Vitrectomy were performed to one eye and focal laser to two eyes. Morphological changes of the abnormal retinal vessels after the treatment were evaluated by color fundus photograph (CFP), optical coherence tomography (OCT), optical coherence tomography angiography (OCTA) and fundus fluorescein angiography (FFA).

Results: Both patients were middle-aged women with high myopia. After a thorough ophthalmologic examination, all three eyes of both patients were diagnosed with retinoschisis with abnormal blood vessels near the vascular arcade, and one eye had macular retinoschisis with fovea detachment. The one eye with macular retinoschisis with fovea detachment was treated with vitrectomy combined with fovea-spared inner limiting membrane peeling and air tamponade, and the other two eyes were treated with local retinal laser photocoagulation. The abnormal vessels in all three eyes completely regressed within 1-3 months after treatment.

Conclusion: This article reports clinical manifestations of retinoschisis with multiple abnormal vessels near the vascular arcade in high myopia, and both laser and vitrectomy treatment can make abnormal vessels regressed successfully.

S06-2

Deep learning for identification of choroidal microcirculation activity in age-related macular degeneration

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Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the elderly in developed countries, affecting 10% of people aged ≥65 years (Jager et al. 2008). Neovascular AMD (nAMD) accounts for two-thirds of prevalent late-stage cases; however, it is responsible for over 80% of severe vision loss and blindness attributable to AMD (Wong et al. 2008). Optical coherence tomography (OCT) is a noninvasive technique to show the status of macular lesions, such as choroidal neovascularization (CNV), which is a characteristic of choroidal microcirculation (Gualino et al. 2019). Nonetheless, OCT lacks the ability to manifest the vascular structure and to detect leakage. Recently, the introduction of optical coherence tomography angiography (OCTA) has provided a noninvasive system to better assess the microvascular morphology of CNV (Coscas et al. 2015). This study aimed to determine the efficacy of a multimodal deep learning (DL) model using OCT and OCTA images for the assessment of CNV activity in AMD.

This retrospective and cross-sectional study was performed at a multicenter, and the inclusion criteria were age >50 years and a diagnosis of typical neovascular AMD. The OCT and OCTA data for an internal data set and two external data sets were collected. A DL model was developed with a novel feature-level fusion (FLF) method utilized to combine the multimodal data. The results were compared with identification performed by an ophthalmologist. The best model was tested on two external data sets to show its potential for clinical use.

Our best model achieved an accuracy of 95.5%and an area under the curve (AUC) of 0.9796 on multimodal data inputs for the internal data set, which is comparable to the performance of retinal specialists. The proposed model reached an accuracy of 100.00% and an AUC of 1.0 for the Ningbo data set, and these performance indicators were 90.48% and an AUC of 0.9727 for the Jinhua data set. The FLF method is feasible and highly accurate, and could enhance the power of the existing computer-aided diagnosis systems. The bi-modal computer-aided diagnosis (CADx) system for the automated identification of CNV activity is an accurate and promising tool in the realm of public health.

S06-3

Natural-Language Diagnostic Report Generation by Multi-Modal AI for Macular Diseases

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Purpose: to investigate the multi-modal methodology to automatically generate natural language diagnostic reports for macular diseases. This involves both the rule-based approach and deep learning-based approach of natural-language processing (NLP) techniques.

Methods: we collected 3342 eyes from patients who visited the Department of Ophthalmology of Peking Union Medical College Hospital in 2020. Each eye consisted of 1 colorful fundus photographs (CFP) and 12 optical coherence tomography (OCT) B-scan images. The sample included 833 healthy eyes and 2509 eyes affected by various macular diseases including epiretinal membrane, dry age-related macular degeneration (AMD), wet AMD, and diabetic retinopathy (DR). Ten ophthalmologists with specialized training provided diagnostic reports for each image, encompassing lesion description, diagnosis and recommendations. Subsequently, we employed three pre-trained deep learning networks to establish a multi-modal artificial intelligence (AI) recognition system. Based on the fundus lesions and diseases detected by AI, a rule-based NLP algorithm would automatically produce a report encompassing lesion description, diagnosis and recommendations. Simultaneously, we developed a deep learning-based NLP model for natural language reports generation utilizing a training set of 659 images and a test set of 255 images. To assess the effectiveness of the aforementioned models, two junior ophthalmologists majoring in fundus diseases will independently wrote generate diagnostic reports for the collected images. A questionnaire was designed and cooperatively judged by two retina specialists to quantitatively grade each report's readability, correctness of diagnosis, lesion description and recommendations. To avoid bias, all reports involved in the evaluation process were anonymized. Sensitivity and specificity of diagnostic reports were also analyzed.

Results: The rule-based NLP reports achieved higher grades over junior ophthalmologists in correctness of diagnosis and recommendations, with a sensitivity and specificity of 0.74 (95% CI, 0.66 - 0.82) and 0.94 (95% CI, 0.91-0.98), respectively. Moreover, the deep learning-based NLP reports achieved a comparable level to that of junior ophthalmologists in lesion description, correctness of diagnosis and recommendations. In relation to readability, the deep learning-based reports exhibited better performance compared to junior ophthalmologists, with scores of 10 points versus 9.9 points, albeit lacking statistical significance (p=0.083).

Conclusion: The application of a multi-modal AI system, coupled with NLP algorithm, has demonstrated a competence in generating reports for macular diseases compared with junior ophthalmologists. This finding highlights the prospective of this innovative concept in primary eye service.

S06-4

The therapeutic application of autologous ozonized blood transfusion (AOBT) in diabetic vascular ldisease through improvement of microcirculation

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Objective: Autologous ozonized blood transfusion (AOBT), an autologous blood transfusion treatment that mixes anticoagulant blood with a certain concentration and volume of medical ozone in vitro, is widely used in clinical medicine. AOBT might improve microcirculation in Systemic Sclerosis Patient in a recent literature. However, there is a lack of country-wide guidelines or other special procedures to follow. The aim of this clinical study is to investigate the therapeutic application of ABOT in diabetic microangiopathy.
Methods: This clinical study was conducted in Jinjiang Hospital, Jiujiang City, China. A total of 12 cases of diabetic foot and fundus lesions in diabetes mellitus were treated with ABOT daily for 30 days between July 2018 to March 2023. The efficacy and improvement of related symptoms were observed.
Results: In this clinical investigation. all 11 patients showed significant improvement in symptoms after ABOT. 1 patient showed partial improvement. The total effective rate was 100%. Autologous ozonized blood transfusion (AOBT), an autologous blood transfusion treatment that mixes anticoagulant blood with a certain concentration and volume of medical ozone in vitro, was effective in improvement of microcirculation. In diabetic vascular disease.
Conclusion: The effect of ABOT on the treatment of microcirculation dysfunction in diabetic mellitus of is remarkable, and this treatment is simple and easy to implement.
Keywords: Autologous ozonized blood transfusion (AOBT), diabetic vascular lesions diabetic mellitus

SATELLITE SYMPOSIUM 7

Microcirculation and Hemorheology in Shock

10:00-11:30 | Guorui Hall

S07-1

Oxidative stress mediates hippocampal neuronal apoptosis through ROS/JNK/P53 pathway in rats with PTSD triggered by high-voltage electrical burn

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The pathogenesis of post-traumatic stress disorder (PTSD) triggered by high-voltage electrical burn (HVEB) remains unclear and the oxidative stress likely plays a role in this process. To investigate the underlying mechanism of oxidative stress in PTSD induced by HVEB. The PTSD rat model was developed by stimulating with high voltage electric and screened using behavioral performance including Morris water maze (MWM), elevated plus-maze (EPM) and open-field test (OFT). The reactive oxygen species (ROS) generation was measured by DHE fluorescence staining or flow cytometry. Western blotting assay was used to detect the proteins of p-JNK, JNK, P53, PUMA, Bcl-2 and Bax in hippocampal tissue or HT22 cells treated with electrical stimulation. The serum MDA and 8-OHdG levels were increased ($P < 0.001$), while the SOD and CAT activity were decreased ($P < 0.001$) significantly in patients with HVEB. Behavioral test results showed that high-voltage electric stimulation induced the PTSD-like symptoms and the ROS-JNK-P53 pathway was involved in the neuronal apoptosis in rats with PTSD induced by HVEB. In vitro experiments further confirmed the electrical stimulation induced neuronal apoptosis through ROS/JNK/P53 signaling pathway and the antioxidant NAC could rescued the ROS generation, activation of JNK/P53 proteins and improved the cell apoptosis rate in HT22 cells. Finally, the JNK inhibitor SP600125 could significantly inhibited the percentage of HT22 cell apoptosis induced by electrical stimulation ($P < 0.001$). These results indicated that oxidative stress mediates hippocampal neuronal apoptosis through ROS/JNK/P53 pathway in rats with PTSD triggered by HVEB.

S07-2

Luseogliflozin, a SGLT2 inhibitor, does not affect glucose uptake kinetics in renal proximal tubules of live mice

Anqi Zhang [1], Daisuke Nakano [2], Wararat Kittikulsuth [2], Yuka Yamashita [2], Akira Nishiyama [2]

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Proximal tubules (PTs) take up most of the glucose in the glomerular filtrate and return it to peritubular capillary blood. Sodium-glucose cotransporter 2 (SGLT2) at the apical membrane takes up glucose into the cell. Glucose then flows across the cells and is transported to the interstitium via glucose transporter 2 (GLUT2) at the basolateral membrane. However, glucose transport under SGLT2 inhibition remains poorly understood. In this study, we evaluated the dynamics of a fluorescent glucose analogue, 2-NBDG, in the PTs of live mice treated with or without the SGLT2 inhibitor, luseogliflozin. We employed real-time multiphoton microscopy, in which insulin enhanced 2-NBDG uptake in skeletal muscle. Influx and efflux of 2-NBDG in PT cells were compared under hypo-, normo-, and hyperglycemic conditions. Luseogliflozin did not exert significant effects on glucose influx parameters under any level of blood glucose. Our results suggest that blood glucose level per se does not alter glucose influx or efflux kinetics in PTs. In conclusion, neither SGLT2 inhibition nor blood glucose level affect glucose uptake kinetics in PTs. The former was because of glucose influx through basolateral GLUT2, which is an established bidirectional transporter.

S07-3

Surface-anchored framework for generating RhD-epitope stealth red blood cells

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Rhesus D (RhD) is one of the most important immunogenic antigens on red blood cells (RBCs). However, the supply of RhD-negative blood frequently faces critical shortages in clinical practice, and the RhD antigen's positive-to-negative transition remains a great challenge. Here, we developed an alternative approach for sheltering the epitopes on RhD-positive RBCs using a surface-anchored framework, which is flexible but can achieve an optimal shield effect with minimal physicochemical influence on the cell. An ultrathin and uniform nano gel layer composed of polysialic acid and tyramine was generated on individual RBCs through catalysis by surface-anchored enzymes. The chemical framework completely obstructed RhD antigens on the cell surface, and assessments of both allogeneic blood transfusion in a mouse model and xenogeneic blood transfusion with human RhD-positive RBCs in a rabbit model confirmed the RhD-epitope stealth characteristics of the engineered RBCs. The physical and biological properties, tissue distribution, and biocompatibility of the engineered RBCs were similar to those of the native RBCs, indicating the promise of the application using a cell surface-anchored framework. This work provides an efficient methodology for cell surface improvement for universal blood transfusion and generally indicates the potential of rationally designed cell surface engineering for transfusion and transplantation medicine.

S07-4

Biomechanical Risk Stratification for Cardiovascular Diseases

Zhiyong Li [1]

[1] *Ningbo University*

This introduces the image-based computational modelling techniques which can accurately quantify the biomechanical parameters that are associated with plaque vulnerability. Our results from patient data demonstrated this approach could better detect the vulnerable plaques. I will summarize our work in imaging-based computational modelling and simulation of the interaction between blood flow and atherosclerotic plaque. I will also discuss our recent developments in multiphysical modelling of plaque progression and destabilization. The model development builds upon current understanding of plaque vulnerability to develop patient-specific models for the individual quantification of plaque progression. The computational analysis can be incorporated into medical imaging technology, leading to a considerable advancement of medical imaging technology and industry. The developed patient-specific model and the new risk factors can be used to better assess plaque vulnerability, make more accurate predictions for plaque rupture, and allow actions to be taken in a timely manner to reduce risk of eventual fatal events on an individual basis. Other applications of our computational methods and models, including brain aneurysm and atrial fibrillation will also be discussed in the talk.

SATELLITE SYMPOSIUM 8

Endovascular Intervention of Peripheral Vascular Microcirculation Dysfunction Diseases

15:00-16:30 | Guorui Hall

S08-1

Current strategy for femoropopliteal artery in-stent restenosis

Yang Zhang [1]

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Data regarding the safety and long-term efficiency of the combination of Rotarex catheter device and drug-coated balloon(DCB) catheter in treatment of femoropopliteal artery in-stent restenosis(FP-ISR). A series of consecutive clinical data of 32 FP-ISR cases undergoing combined therapy of Rotarex catheter device and DCB from June 2016 to July 2017 were retrospectively analyzed. The primary endpoint was primary patency of target lesion and freedom from clinically-driven target lesion revascularization (CD-TLR) at 5 years after interventional treatment. The secondary endpoint included the rate of major adverse limb events (MALE), amputation and mortality. The primary functional endpoint was assessed by Walking Impairment Questionnaire (WIQ). The rate of technical and procedural success were all 100%. 5-years follow-up data were achieved for 26 cases(81.3%). Mean ABI increased from 0.45±0.14 before surgery to 0.77±0.12 at 5 years after surgery($p<0.05$). WIQ score improved from 30.45±21.14 before surgery to 49.28±24.62 at 5 years after surgery ($p<0.05$). Primary patency rate and freedom from CD-TLR rate at 5 years analyzed by Kaplan-Meier estimate were 76.9% and 80.8% respectively. Satisfactory long-term outcome was achieved in FP-ISR cases undergoing combined therapy of Rotarex device and DCB.

S08-2

Study on the diagnostic value of interleukins in deep vein thrombosis

Yongkang DANG [1], Weiguang JIANG [1]

[1] *Inner Mongolia Chifeng City Hospital*

Deep vein thrombosis (DVT) refers to abnormal blood clotting in the deep vein, which causes lumen stenosis and leads to venous return obstruction. DVT is a common peripheral vascular lesion in vascular surgery, which can lead to lower limb swelling, pain, ulcer necrosis, disability, secondary pulmonary embolism and even death.

At present, the diagnosis of DVT is mainly through the combination of clinical symptoms and signs imaging and laboratory examination. At present, venous angiography is recognized as the gold standard for the diagnosis of DVT due to its high accuracy. However, due to its invasive nature, patients may be allergic to contrast media and its high cost, its application scope is limited Color Doppler ultrasound has high sensitivity and accuracy, which is currently an important means of early diagnosis and therapeutic effect evaluation of DVT. However, due to the complex anatomy of lower limb blood vessels, its accuracy is affected by the experience and level of the examiner In terms of laboratory examination, D-dimer is mainly used as the primary screening project for thrombotic diseases. Among the biomarkers used in the diagnosis of DVT, D-dimer in plasma has a high sensitivity of up to 95% in the diagnosis of DVT and PE, but D-dimer is susceptible to multiple factors, such as surgical tumors Inflammation, etc,with poor specificity and a very low positive prediction rate, can only be used for the early auxiliary diagnosis of suspected DVT cases. Therefore, the search for biomarkers suitable for early diagnosis has become a hot topic in related research fields In terms of biomarker studies, the value of other biomarkers in predicting DVT is still uncertain except for the relatively reliable negative prediction rate of plasma D-dimer. In view of this, the search for new biomarkers related to the formation of DVT can provide a basis for early clinical diagnosis.

Previous studies show that interleukin (IL), a multipotent, pro-

inflammatory cytokine that regulates cytokines and inflammatory molecules released by many types of cells, plays a role in the development of DVT and is associated with inflammation and platelet aggregation A recent study has shown that elevated serum IL levels in rats are positively correlated with DVT formation, suggesting that abnormal IL levels may be a key pathological feature of DVT. However, whether IL plays a role in lower limb DVT formation by mediating platelet activation and aggregation has not been clarified.
The search for specific sensitive DVT to predict and diagnose IL can provide more targeted and individualized prevention and treatment, so as to reduce the occurrence of thrombosis and reduce the incidence and mortality of pulmonary embolism. The study on the changes of IL in patients with DVT is intended to provide a new perspective for the early diagnosis of DVT.

S08-3

Quality-of-life endpoints are associated with coronary microvascular resistance in patients with hypertrophic cardiomyopathy

Jie Ma [1], Lihong Ma [1], Yue Lan [1], Anqi Wang [1]

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Objectives: Hypertrophic cardiomyopathy (HCM) is a phenomenon of left ventricular wall thickening that cannot be completely explained by abnormal cardiac load. HCM affects about 1/500 people in the population.The ultimate pathogenesis of HCM is caused by the combined effect of gene mutation, personal genetic background and environmental factors, resulting in asymmetric left ventricular hypertrophy, abnormal energy metabolism of myocardial cells, microvascular ischemia, myocardial fibrosis, diastolic dysfunction and multi-source arrhythmia. The purpose of this study was to investigate the relationship between microvascular resistance and KCCQ-12 and Borg scales in hypertrophic cardiomyopathy.
Methods: HCM was confirmed by echocardiographic septal hypertrophy (defined as a maximum septal thickness of 15mm). Inclusion criteria: (1) Age of 18-80 years old. (2) Patients underwent diagnostic coronary angiography. Exclusion criteria: (1) Unqualified patients with incomplete data (2) Phenotypical HCM patients. Angio-derived microvascular resistance(AMR)≥2.5 as the positive cutoff value. The cohort was grouped according to the Three-vessel AMR tertile values or the number of microvascular disorders. The endpoint were KCCQ-12 and Borg scale after a 6-minute walk test with a 1-year follow-up. Group differences for KCCQ-12 and Borg scales were determined using Turkey's Method.
Results: Finally, 342 patients diagnosed with HCM in Fuwai Hospital from January 2017 to November 2021 were included in this study. The mean age of the patients was 49.74±13.61 years old, of which 197 (57.60%) were male. There were 236 patients (69.00%) with different degrees of positive microvascular resistance. The KCCQ-12 and Borg scores were significantly different between High 3V-AMR and AMR≥2.5 in all 3 vessels and the other groups (all p-value<0.01).
Conclusions: High 3V-AMR and AMR≥2.5 in all 3 vessels are predictive factors for quality of life in HCM patients.

S08-4

Endovascular treatment of long CTO lesions in femoropopliteral artery

Shenghan Song [1]

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Background: The incidence of arteriosclerosis obliterans (ASO) in the lower extremities has been increasing year by year as the general standard of living in society has improved and the population has aged. It is manifested as arteriosclerosis obliterans of the lower extremities, which is actually one of the manifestations of systemic arteriosclerosis. Atherosclerosis involves arteries in the lower extremities, causing arterial stenosis and occlusion, which can lead to limb ischemia. The clinical manifestations are cold or numbness in the affected limb, weakness, intermittent claudication. In severe cases, it can lead to resting pain, ulcers, gangrene and even amputation. ASO is a disease that causes disability and seriously affects the quality of life of patients. The superficial femoral artery and popliteal artery are the arteries most commonly involved, and most of them are long and multi-segmented lesions. With the growing development of interventional techniques, endovascular intervention has become the first choice for the treatment of ASO.
The challenges in the treatment of femoropopliteal long-segment Chronic Total Occlusion (CTO) are as follows: Recanalization of the occluded segment is usually difficult, so the process may be time-consuming. Multiple guidewires and balloons or stents are often needed during the procedure and the cost is high. The longer the lesion, the worse the long-term patency rate, leading to poor efficacy and prognosis. Restenosis after femoropopliteal artery stenting and symptomatic recurrence have always been great challenges for doctors and patients. In-stent restenosis (ISR) refers to the re-stenosis of the vascular lumen after stent implantation, and the diameter stenosis rate > 50%. The leading causes of ISR are intimal hyperplasia, thrombosis, and stent fracture. ISR is particularly common in long lesions and in vessels of small diameter.
The devices used in endovascular treatment include simple balloon (POB), drug-coated balloon (DCB), bare stent, drug eluting stent (DES), covered stent, etc. In addition to PTA and stent implantation, the treatment options also include catheter-directed thrombolysis, mechanical debulking, etc., or a combination of multiple interventional techniques. A few cases were successfully treated by hybrid surgery combined with open surgery and endovascular techniques.
Methods: In this paper, by the cases treated by the authors themselves, the process and results of endovascular treatment were demonstrated in solving lower limb ischemia and improving microcirculation, so as to provide a basis for the basic research of microcirculation and to explore clinical treatment methods.
Occlusion: Endovascular treatment of long CTO lesions of femoropopliteal artery is still one of the difficult problems in vascular surgery. How to improve the success rate of endovascular treatment is one of the concerns worth studying. DCB provides a better treatment option by inhibiting intimal hyperplasia and leaving nothing in the body. The efficacy of DCB in the treatment of in-stent restenosis has been confirmed by several clinical trials. Mechanical debulking in combination with DCB may be a more effective treatment for ISR with long segments and total occlusions, but more clinical evidence for this result is needed. Some cases require the use of rescue stents after DCB. At the same time, the importance of antithrombotic drug therapy in preoperative preparation, prevention of thrombosis during operation and prevention of recurrence after operation was emphasized.

YOUNG SYMPOSIUM 3

Young Symposium of Diabeto-Mircrocirculation

10:00-11:30 | Room 6

Y03-1

Advanced glycation end products induce endothelial hyperpermeability via β- catenin phosphorylation and subsequent up- regulation of ADAM10

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Endothelial hyperpermeability is the initial event in the development of diabetic microvascular complications, and advanced glycation end products (AGEs) are suggested to cause much of the endothelial hyperpermeability associated with diabetes mellitus, but the molecular mechanism remains to be characterized. β- catenin reportedly plays dual functions in maintaining normal endothelial permeability by serving both as an adhesive component and a signal transduction component. Here, we found that AGEs induced the phosphorylation of β- catenin at residues Y654 and Y142 and the endothelial hyperpermeability was reversed when the two residues were blocked. In mechanism, phosphorylation of Y654 was blocked by Src inactivation, whereas phosphorylation of Y142 was reduced by a focal adhesion kinase inhibitor. β- catenin Y654 phosphorylation induced by AGEs facilitated the dissociation of vascular endothelial (VE)- cadherin/β- catenin and the impairment of adherens junctions (AJs), whereas β-cateninY142 phosphorylation favoured the dissociation of β- catenin and α- catenin. Further investigation revealed that β- catenin Y142 phosphorylation was required for AGEs-m ediated β- catenin nuclear translocation, and this nuclear- located β- catenin subsequently activated the TCF/LEF pathway. This pathway promotes the transcription of the Wnt target, ADAM10 (a disintegrin and metalloprotease 10), which mediates VE- cadherin shedding and leads to further impairment of AJs. In summary, our study showed the role of β- catenin Y654 and Y142 phosphorylation in AGEs-mediated endothelial hyperpermeability through VE- cadherin/β- catenin/α- catenin dissociation and up-r egulation of ADAM10, thereby advancing our understanding of the underlying mechanisms of AGEs- induced microvascular hyperpermeability.

K E Y W O R D S
advanced glycation end products, β- catenin, ADAM10, adherens junctions, hyperpermeability

Y03-2

Early intensive insulin therapy in patients with type 2 diabetes: transforming current understanding to real-world clinical benefits

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In recent years, the reversal of diabetes has attracted much attention. Short-term intensive insulin therapy (SIIT) is a unique approach for diabetes reversal, which can induce remission in more than 50% newly diagnosed type 2 diabetes patients. SIIT has been incorporated in the management of newly diagnosed type 2 diabetes in Chinese guidelines for the past decade. Unlike the widely adopted weight-loss lifestyle intervention, SIIT can induce diabetes remission in patients with only mild overweight but with significantly hyperglycemia, and its effects are not entirely dependent on weight loss but highly dependent on the maximum clearence of glycotoxicity, suggesting its unique mechanism of action. In recent years, there have been significant advancements in the field of SIIT, including the exploration of its potential mechanisms, implementation details, combination and sequential therapies, and long-term management strategies. Clarifying these aspects will help translate current understanding of SIIT into clinical benefits for patients and integrate it with other diabetes reversal therapies, maximizing the benefits of long-term remission for patients.

Y03-3

Direct Activation of the Angiotensin II Type-2 Receptors Enhances Muscle Microvascular Perfusion, Oxygenation and Insulin Delivery in Male Rats

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Angiotensin II receptors regulate muscle microvascular recruitment and the delivery of nutrients, oxygen and insulin to muscle. While the angiotensin type-1 receptor antagonism increases muscle microvascular perfusion and insulin action, angiotensin type-2 receptor blockade markedly restricts muscle microvascular blood volume and decreases muscle delivery of insulin. To examine the effects of direct type-2 receptor stimulation using Compound 21 (C21) on microvascular perfusion, insulin delivery and action, and tissue oxygenation in muscle, overnight fasted adult male rats were infused with C21 systemically. C21 potently increased microvascular blood volume without altering microvascular flow velocity or blood pressure, resulting in a net increase in microvascular blood flow in muscle. This was associated with a significant increase in muscle interstitial oxygen saturation and insulin delivery into the skeletal and cardiac muscle. These effects were neutralized by co-infusion of the type-2 receptor antagonist or nitric oxide synthase inhibitor. Superimposing C21 infusion on insulin infusion increased insulin-mediated whole body glucose disposal by 50%. C21 significantly relaxed the pre-constricted distal saphenous artery *ex vivo*. We conclude that direct type-2 receptor stimulation markedly increases muscle microvascular perfusion through nitric oxide biosynthesis and enhances insulin delivery and action in muscle. These findings provide a novel physiologic mechanistic insight into type-2 receptor modulation of insulin action and suggest that type-2 receptor agonists may have a therapeutic potential in the management of diabetes and its associated complications.

Y03-4

Clinical characteristics and mechamism of carbapenem resistant Acinetobacter baumannii in diabetic foot

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Aim: With the increase of Acinetobacter baumannii (AB) in diabetic foot ulcer (DFU), most of them are carbapenem resistant Acinetobacter baumannii (CRAB). We investigated Clinical characteristics and mechamism of CRAB in diabetic foot.

Methods: Culture results were from deep wound tissue of inpatients with DFU for 2 years.Antibiotic resistance was analyzed, and its influence on prognosis was followed up. Six CRAB strains and there carbapenem-sensitive AB (CSAB) strains were selected, carried genome sequencing, then analyzed the mechamism of CRAB.

Results: A total of 1451 strains were cultured from 749 patients with DFU, and 241 AB were cultured from 171 patients. AB accounted for 16.61%, accounting for the first in Gram-negative bacteria. CRAB had 200 strains (82.99%), among which, 191 strains (79.25%) were Multi-

drug resistant AB(MDRAB) (resistance ≥3 categories), among which 85 strains (35.27%) were XDRAB. In the case of CRAB, penicillins, second and third generation cephalosporins and cephalomycin were almost resistance, but cefoperazone/sulbactam (36.25%) and cefepime (39.38%) were sensitive or intermediate and could be used. Minocycline resistant rate was low, oral is convenient and effective. Tigecycline and colistin were not commonly used due to side effects. Electron microscopy showed CRAB would produce biofilm and aggravate antibiotic resistance. MLST (Pasteur) showed CRAB as ST2, CSAB as ST1014. CRAB carried OXA-66 and OXA-23, CSAB carried OXA-51 and OXA-424. However, the above genes didn't constitute to carbapenem resistance. Analysis using a Comprehensive Antibiotic Resistance Database found that CRAB in diabetic foot wounds had its own characteristics. There were 107±5 antibiotics resistant genes.34±1 genes were associated with carbapenem resistance. It is mainly divided into three categories: first, 2 genes that affected the permeability of bacterial cell membrane (membrane pore protein). One is CarO, which specifically affects the entry of carbapenems into bacteria, the other is oprD, which has an effect on all 5 β-lactam antibiotics. Second, 2 genes that affect antibiotic target changes, including PBP3 and PBP1a. The above two categories' genes were no different between two groups. Third, 30±2 genes associated with efflux pumps. Related to carbapenem was RND efflux pump. The following genes mexB, mexJ, mexK, mexN, adeK, adeJ, adeI, adeH, adeF, adeG, adeL, adeN, adeS, adeR, adeA, adeB, semS, semR, semF, CRP, AbuO, SoxR were no difference in both CRAB and CSAB. However, AdeC and acrD only belonged CRAB.However, CRAB generally did not cause severe infection or elevated amputation, but delayed wound healing. Timely debridement combined with cefoperazone/sulbactam with minocycline or aminoglycoside could speed up wound healing.

Conclusions: Most AB in DFU are CRAB, even MDRAB to XMDRAB, easy to form biofilm. But the mortality does not increase. Debridement combined with a variety of sensitive antibiotics can accelerate healing. AdeC and acrD are specific resistant genes of CRAB.

YOUNG SYMPOSIUM 4

A Window into the Microcirculation - Using Imaging to Unravel Physiological Mechanisms

15:00-16:30 | Room 6

Y04-1

Getting to the Heart of the Matter: Intravital and Laser Speckle Contrast Imaging of the coronary microcirculation in the injured and diabetic beating heart

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Introduction: Type 2 diabetes mellitus (T2DM) is associated with poorer outcomes following flow-restoring procedures in myocardial infarction (MI) patients. This may result from hyperglycaemia predisposing the coronary microcirculation to enhanced damage. However, no study has directly imaged the microcirculation of the hyperglycaemic heart *in vivo*.

Aims: This study used intravital microscopy (IVM) and laser speckle contrast imaging (LSCI) to assess the impact of high-fat diet (HFD)-induced hyperglycaemia on coronary microvessels, both basally and after ischaemia-reperfusion injury (IRI). Secondly, we determined *whether expression of IL-36 cytokines, and its receptor (IL-36R), varied in hyperglycaemic animals. Finally, we investigated whether an IL-36 receptor antagonist (IL-36Ra) could confer vasculoprotection and reduce MI.*

Methods: Myocardial IRI was induced in mice fed either normal diet or HFD for 16 weeks. Some mice were treated with a IL-36Ra (15μg/mouse). The beating heart was imaged using IVM, multiphoton, and Laser Speckle Contrast Imaging (LSCI), to assess: neutrophil and platelet recruitment, functional capillary density (FCD), and overall perfusion respectively. Infarct size was measured using TTC/Evans Blue staining. Myocardial IL-36/IL-36R/VCAM-1 expression and oxidative stress were investigated immunohistochemically and using flow cytometry. *IL-36R, VCAM-1, oxidative stress and ROS generation were also investigated in human coronary microvascular endothelial cells (HCMECs) treated with varying glucose concentrations (5-50mM) ± hypoxia-reoxygenation ± IL-36γ (30ng/ml).*

Results: In the beating heart, neutrophil and platelet presence was increased, primarily within coronary capillaries, in HFD mice compared to normal diet mice ($p<0.001$). Neutrophil and platelet recruitment increased further ($p<0.01$) in HFD mice undergoing IRI. FCD and overall perfusion were reduced to the highest degree in HFD+IRI hearts. IL-36/IL-36R/VCAM-1 expression and oxidative stress increased ($p<0.001$) in HFD hearts and furthermore in HFD+IRI hearts. IL-36Ra treatment reduced neutrophil recruitment ($p<0.01$), infarct size ($p<0.0001$), VCAM-1 ($p<0.001$) and oxidative stress ($p<0.001$) in HFD+IRI hearts, as well as enhancing FCD and overall perfusion ($p<0.0001$). Hyperglycaemic culture conditions increased ($p<0.05$) oxidative stress and ROS generation in HCMECs, with both further increased with hypoxia-reoxygenation and/or IL-36 addition. IL-36R/VCAM-1 expression on HCMECs was not affected by hyperglycaemia but modified by hypoxia-reoxygenation/IL-36 exposure.

Conclusion: *Our findings suggest enhanced coronary microcirculatory perturbations associated with hyperglycaemia may underlie the poorer outcomes in T2DM patients after MI. We have previously shown that targeting IL-36 was vasculoprotective in aged IRI hearts; we now show that this strategy remains effective in hyperglycaemia patients. Therefore, IL-36 inhibition may potentially be a novel therapy for the treatment of MI in patients with various comorbidities.*

Y04-2

Imaging inflammation and tissue damage in ex vivo human liver tissue using multiphoton microscopy

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Inflammation and acute injury within the liver is associated with immune cell recruitment from general circulation to the site of insult within the parenchyma. This recruitment and subsequent behaviour of immune cells can be monitored in real time by combining animal models of liver injury with intravital microscopy. However, these models rarely recapitulate human disease, which creates difficulties in translating findings to clinical settings. We aimed to develop and validate a novel methodology of imaging *ex vivo* human liver tissue as an alternative to intravital microscopy.

We used 3D-printing and pump-based circuits to create an *in-situ* system which allowed reproducible, simultaneous normothermic perfusion and imaging of human liver tissue using multiphoton microscopy. Using this system with *ex vivo* human tissue obtained from the Queen Elizabeth Hospital, Birmingham, UK, we demonstrated tissue viability in both non-cirrhotic donor livers and end-stage disease explants using reporters of mitochondrial membrane potential and nuclei labelling. Vasculature and parenchymal architecture were broadly identified using fluorescent dyes and the tissue was imaged in three dimensions to a depth of >100 µm. Individual cell types within the liver were also identifiable using cell-specific labels and fluorophore-conjugated antibodies. The same strategy was used to image *ex vivo* mouse liver lobes, which provided comparable images to those obtained using intravital microscopy.

We next aimed to visualise aspects of diseased tissue related to liver inflammation and tissue damage. To demonstrate that the recruitment of immune cells to the liver could be documented in real-time using our system, immune cells were labelled with fluorescent dyes and then infused into pre-labelled liver tissue whilst simultaneously imaging. With this strategy, we showed that the recruitment of patient-matched liver-infiltrating mononuclear cells (LIMCs) was faster compared to that of non-matched peripheral blood mononuclear cells (PBMCs). Additionally, we could identify collagen-rich areas of fibrosis using second harmonic generation (SHG) and non-viable regions within the hepatic nodules using dyes requiring enzymatic cleavage. Finally, we could observe cellular responses to acute injury by cauterisation, including the internalisation of hepatocytes by their neighbouring cells. Overall, we have developed a new methodology to image *ex vivo* human liver tissue; it permits the identification of specific cell types, the observation of responses to injury, and recruitment of infused immune cells. This provides a new platform for the study of authentic human disease and a strategy for reducing and replacing the use of animals for observing immune cell behaviour in the liver.

Y04-3

Multi-scaled molecular imaging modalities reveal contributions of the bone matrix in the sexual dimorphism of the skeletal vasculature

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Objectives: Physiological bone formation during development and repair is regulated by osteoblast (OB)-derived vascular endothelial growth factor (VEGF) and is critical for angiogenic-osteogenic coupling throughout life. Recently, OB-derived VEGF has been shown to be responsible for the divergent regulation of the intracortical vasculature, microarchitecture, and mineralisation via its actions on vascular endothelial cells1. The aim of our study was to determine whether this vascular dimorphism was driven by inherent differences in the bone extracellular matrix (ECM) that arise as the result of divergence in OB activities. Herein, we employed a multi-scaled approach to characterise the influence of VEGF on bone extracellular matrix (ECM) organisation and composition using a combination of Raman spectroscopy (RS) with polarisation-resolved second harmonic generation microscopy (P-SHG).

Methodology: OB-derived VEGF was conditionally deleted in 16-week-old male and female mice expressing floxed alleles of VEGF (*Vegf$^{fl/fl}$*; wildtype, WT) and Cre-recombinase controlled by the osteocalcin promoter (OcnVEGFKO). Bones were embedded in polymethyl methacrylate and sectioned at the tibiofibular junction (TFJ) ahead of RS and P-SHG microscopy (N=75 spectra and N=9 regions from 3 bone sections per sex and genotype). VEGF expression was deleted *in vitro* in primary OB cultures isolated from male and female *Vegf$^{fl/fl}$* mice using a Cre-recombinase expressing adenovirus (OBVEGFKO) for RS (N=50 spectra from 10 cells per group) and gene expression analyses.

Results: P-SHG revealed a sex-specific macrolevel disorganisation of the TFJ bone matrix following OcnVEGFKO in males versus females, attributed by; regionalised reductions in collagen fibre number (-1.16-fold, P=0.006), extensive patches of osteoid and enhanced cortical porosity. Further alterations to the collagen matrix were observed following polarisation anisotropy measurements, with reductions in fibrillar anisotropy around the endosteal regions in female OcnVEGFKOs (-4.19-fold, P=0.01) and in the periosteal and perivascular regions (-1.97-fold, P=0.03; -2.64-fold, P=0.03 respectively) in OcnVEGFKO males versus WT. Nanoscale sexual dimorphism in molecular ECM signatures in OcnVEGFKO animals were detected by RS. B-type carbonate levels were 2.79-fold lower in females (P<0.0001) and elevated by 1.21-fold (P<0.0001) in male OcnVEGFKOs versus WT. Collagen-specific proline was exclusively elevated in male OcnVEGFKO bones (+1.21-fold, P<0.0001) whereas collagen-specific hydroxyproline was reduced in both male and female OcnVEGFKO matrices (-2.43-fold, P<0.0001; -1.25-fold, P=0.01). Collagen intra-strand stability was exclusively reduced in male OcnVEGFKOs (-3.06-fold, P<0.0001) while hydroxyapatite mineralisation was reduced in both sexes following VEGF loss (males; -1.07-fold, P<0.05; females; -1.26-fold, P<0.0001). RS identified 1.31-fold elevations in collagen-specific proline in female OBVEGFKO cultures (P<0.0001) and 1.15-fold reductions in male OBVEGFKO cells versus WTs (-1.15-fold, P<0.0001). In contrast, collagen intra-strand stability was reduced in female OBVEGFKO cells (-2.26-fold, P<0.0001) but increased in male OBVEGFKO cells (+1.19-fold, P<0.0001) versus WTs. Further dimorphism was detected in immature (amorphous calcium phosphate, ACP) and mature (carbonated apatite, CAP) mineral precursors of hydroxyapatite. Here, ACP levels were elevated in male

OBVEGFKOs cultures (+23.6-fold, P<0.0001) while, conversely, high levels of CAP were detected in female OBVEGFKOs (+10.5-fold, P<0.0001) versus WTs. Gene expression screening revealed these sex-specific ECM signatures were underpinned by divergence in the regulation of regulation of genes involved in matrix formation and mineralisation (Col1a1, Itgae and Spp1), matrix remodelling (Adamts2, Mmp13 and Sparc) and angiogenesis (Lama1, Mmp1a, Thbs1) following OBVEGFKO versus WTs.

Conclusions: Our results highlight a role of OB-derived VEGF in the divergent regulation of the skeletal vasculature via the bone matrix. The methods employed herein demonstrate the utility of label-free and non-destructive approaches in the identification of sex-specific variations in the ECM arrangement and composition, which could be employed for the clinical assessment off bone health. Further, defining the mechanisms that underpin sex-specific OB- ECM production could offer new therapeutic routes to effectively target pathological skeletal angiogenesis in men and women.

Y04-4

Structural and functional studies of erythrocyte membrane-skeleton by super-resolution microscopy and microfluidics

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Human mature erythrocytes are well known to exhibit an elegant and mystery biconcave shape, with strong deformation and stability, to ensure millions of circulation in the body without damage. Absence of nuclei and transcellular cytoskeletons, erythrocytes rely on the membrane-skeleton system to maintain their unique biconcave shape and extreme deformability. Here, we explored the nanoscale architecture of erythrocyte membrane skeleton and the deformability of individual erythrocytes by super-resolution microscopy and microfluidics. Firstly, utilizing single-molecule localization microscopy (SMLM), we resolved the ultrastructure of erythrocyte cytoskeleton under near-physiological conditions. We determined an ~80-nm junction-to-junction distance (*Cell R*eports, 2018, 22: 1151). This length is consistent with relaxed spectrin tetramers and theories based on spectrin abundance. Furthermore, by combination of ultrastructure expansion microscopy (U-ExM) with SMLM, we developed a method of U-ExSMLM, reaching a molecular resolution of ~6 nm. Based on this new approach, we strikingly found spectrin skeleton in the erythrocyte dimple region is longer than that in the rim region, while the density of the spectrin skeleton in the dimple region is greater than that in the rim region. These results provided direct molecular resolution evidence for skeleton asymmetry in human erythrocytes, which may be an explanation for the formation of their biconcave shape (Small Methods, 2023, 7: 2201243). On the other hand, the extreme deformability of erythrocytes helps them to squeeze through narrow capillaries, which is also closely associated with their membrane-skeleton. We designed and constructed different types of microfluidic assemblies to mimic in vivo environments and investigate the influence of hydrogen peroxide, ethanol and pentoxifylline on the deformability of erythrocytes based on transit velocity measurements. It was shown that hydrogen peroxide decreased erythrocyte deformability in a dose-dependent manner, while ethanol or pentoxifylline exhibited a biphasic effect. Therefore, our microfluidic designs propose a promising strategy for the measurement of erythrocyte deformability (Biochem. Biophys. Res. Commun., 2019, 512: 303). Taken together, our work based on super-resolution microscopy and microfluidics will provide new information and innovative methods for the exploration on the ultrastructure and function of erythrocyte membrane-skeleton, as well as contribute to further understanding on the unique biconcave shape and extreme deformability of human erythrocytes.

FREE ORAL COMMUNICATION 7

Inflammation

08:30-10:00 | Room 6

F07-1

Cathepsin B inhibition ameliorates leukocyte-endothelial adhesion in the BTBR mouse model of autism

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Aims: Autism spectrum disorder (ASD) is a wide range of neurodevelopmental disorders involving deficits in social interaction and communication. Unfortunately, autism remains a scientific and clinical challenge owing to the lack of understanding the cellular and molecular mechanisms underlying it. Several studies have found reduced levels of adhesion molecules including the soluble platelet-endothelial adhesion molecule-1 (sPECAM-1) and soluble platelet selectin (sP-selectin), which are thought to largely contribute to the attachment of leukocytes to the endothelium, which in adults will lead to high-functioning autism.This study aimed to investigate the pathophysiological mechanism underlying leukocyte-endothelial adhesion in autism-related neurovascular inflammation.

Methods: Male BTBR T+tf/J mice were used as an autism model. The dynamic pattern of leukocyte-endothelial adhesion in mouse cerebral vessels was detected by two-photon laser scanning microscopy (TPLSM). Using FACS, RT-PCR, and Western blotting, we explored the expression of cell adhesion molecules, the mRNA expression of endothelial chemokine, the protein levels of cathepsin B, and inflammatory mediators.Significant differences were determined by either unpaired two-tailed Student's test or one-way analysis of variance (ANOVA), followed by a post hoc Dunnett's comparison of Tukey's test to the control.

Results: We found a significant increase in leukocyte-endothelial adhesion in BTBR mice, accompanied by elevated expression of the adhesion molecule neutrophils CD11b and endothelial ICAM-1. Our data further indicate that elevated neutrophil cathepsin B levels contribute to elevated endothelial chemokine CXCL7 levels in BTBR mice. The pharmacological inhibition of cathepsin B reverses the enhanced leukocyte-endothelial adhesion in the cerebral vessels of autistic mice.

F07-2

The role and mechanism of exosomal miR-486-3p after subarachnoid hemorrhage

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Background: Inflammation is a potential crucial factor in the pathogenesis of subarachnoid hemorrhage (SAH). MicroRNAs (miRNAs) are involved in the regulation of diverse aspects of neuronal dysfunction. In our previous study, we have detected four exosomal miRNAs are associated with the prognosis of patients with SAH. So we injected modified exosomes (Exo) delivered miRNAs to the brains of mice with SAH and detected the level of neuroinflammation damage also explored the potential mechanism with this.

Methods: We peripherally injected RVG/Exo/miR-486-3p to achieve delivery of miR-486-3p to the brain of mice with SAH. The effects of miR-486-3p on SAH were assayed using a neurological score, brain water content, blood-brain barrier (BBB) injury, and Fluoro-Jade C (FJC) staining. Western blotting analysis, enzyme-linked immunosorbent assay (ELISA), and qRT-PCR were used to measure various proteins and mRNA levels. Confocal laser was used to detected the fusion levels of mitochondria and lysosomes and electron microscopy was used to observe the level of mitophagy in brain tissue of mice after SAH.

Results: RVG/Exo exhibited improved miR-486-3p targeting to the brains of SAH mice. MiR-486-3p suppressed the expression and activity of sirt2, which decreased the level of mitophagy. Finally, miR-486-3p treatment mitigated the neurological behavioral impairment, brain edema, BBB injury, and neurodegeneration induced by SAH, and reduced the level of PINK1, Parkin and in mitochondria of mice after SAH.

Conclusions: Exo/miR-486-3p treatment attenuated the inflammatory response by reduced the level of mitophagy via suppressed expression and activity of sirt2. These effects alleviated neurobehavioral impairments and neuroinflammation following SAH.

Keywords: Subarachnoid hemorrhage, Neuroinflammation, Exosomes, Mitophagy, Sirt2

F07-3

Association of microglia- and neutrophil-derived inflammatory factors with neurological injury in severe CVT

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Background: Severe cerebral venous thrombosis (CVT) has more severe clinical manifestations and a worse prognosis, with the underlying pathogenesis remaining unclear. Inflammation is involved in regulating the pathogenesis of severe CVT, and pro-inflammatory factors are significantly associated with poor prognosis, while anti-inflammatory factors play a neuroprotective role. Microglia and neutrophils are the fastest responding immune cells in the center and periphery after brain injury respectively, and their secretion of inflammatory factors is associated with a balance of pro- and anti-inflammatory signaling. Studying the expression of inflammatory factors of both cells, their correlation with neurological damage, and their changes after glucocorticoid treatment is useful to discover the temporal and phenotypic changes of immune cells in severe CVT.

Objective: This study explores the association between microglia-secreted Osteopontin (OPN) and insulin-like growth factor binding protein-4 (IGFBP-4), as well as neutrophil gelatinase-associated lipocalin (NGAL) and Myeloid-related protein 8/14 (MRP8/14) derived from neutrophils, and neurological function at admission and discharge in acute/subacute CVT patients, and changes in expression after anticoagulation combined with glucocorticoids therapy.

Methods: A total of 48 patients with acute/subacute CVT were included, and they were divided into severe and non-severe groups according to the occurrence of venous cerebral infarction/hemorrhage, with 24 cases each of severe and non-severe CVT. The severe group was treated with glucocorticoids in combination with standard anticoagulation. Peripheral blood was collected from all patients on admission, and again from the severe group about 2 weeks after glucocorticoid pulse treatment, and OPN, IGFBP-4, NGAL, and MRP8/14 levels were measured. Inflammatory factor levels were compared between the two groups, and before and after glucocorticoid therapy in the severe group. The correlation between the above inflammatory factor and patients' neurological deficits (NIHSS and mRS scores) at the time of admission was analyzed.

Results: Compared to the acute/subacute non-severe CVT group, serum OPN [44174.9800 (30951.52, 91166.22) VS 83890.77 (67113.45, 118802.09),P<0.01], NGAL [3509.43 (26175.93, 55348.60) VS 659479.90 (368086.30, 814937.60), P<0.001] was significantly lower in the severe CVT group at admission; whereas IGFBP-4 and MRP8/14 did not change significantly. At admission, NGAL and MRP8/14 were significantly negatively correlated with NIHSS (NGAL, r=-0.348, P=0.038; MRP8/14, r=-0.344, P=0.037) and mRS (NGAL, r=-0.672, P=0.000; MRP8/14, r=-0.379, P=0.024). At admission, the correlation between OPN, IGFBP-4, and NIHSS, mRS was not yet significant (p>0.05). Compared with the admission levels, serum OPN [59239.92 (43825.77, 91147.25) vs. 43476.56 (30172.15, 87312.18), P < 0.05] was significantly higher in the severe CVT group after glucocorticoids therapy, and NGAL, MRP8/14 and IGFBP-4 levels tended to increase but did not reach statistical differences (P>0.05).

Conclusions: Both central microglia-derived (OPN) and peripheral neutrophil-derived inflammatory factors (NGAL) were significantly different in CVT severe or not; microglia-derived inflammatory factors (OPN) changed more significantly before and after treatment; neutrophil-derived inflammatory factors (NGAL, MRP8/14) were more significantly correlated with neurological injury, which provides more ideas for the study of the temporal and phenotypic evolution of central and peripheral immune cells in severe CVT.

Keywords: severe CVT, inflammation, microglia, neutrophil

F07-4

Xuebijing injection inhibited NETs formation to improve pulmonary microcirculation in septic mice

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Sepsis is a life-threatening multiple organ dysfunction syndrome (MODS) caused by the host's malfunctioning immune response to microbial invasion with unacceptably high mortality, posing a serious threat to human health. The lung is the first and most frequent organ to fail during sepsis, in which pathological coagulation frequently develops into disseminated intravascular coagulation (DIC), causing organ failures and high mortality. Pulmonary thrombosis frequently observed in sepsis exacerbates sepsis-induced acute respiratory distress syndrome (ARDS). Polymorphonuclear leukocyte neutrophils serve as the major initiator of acute inflammation. Under pathological condition, activated neutrophils release their nuclear contents including histones, myeloperoxidase (MPO), neutrophil elastase (Elane), and DNA fragments to form neutrophil extracellular traps (NETs), which are linked to the activation of platelets and coagulation. Though Xuebijing injection (XBJ) alleviated the clinical symptoms of COVID-19 and sepsis patients, its working mechanisms in the lung remain to be unveiled.

We found that XBJ effectively reversed lung injuries and pulmonary coagulation-triggering events, such as reducing the expression levels of tissue factor (TF), thrombin-antithrombin complex (TAT) and D-Dimer in septic mice. Strikingly, XBJ restrained neutrophils recruitment to lung and downregulated key proinflammatory chemokines. Furthermore, we also found that XBJ evidently reduced the expressions of NETs component proteins, including citrullinated histone H3 (CitH3), myeloperoxidase (MPO), and neutrophil elastase (Elane). Gasdermin D (GSDMD) contributes to the production of NETs and further triggers the microcirculation disorder in sepsis. Notably, XBJ exhibited a reduced effect on the expressions of GSDMD and its upstream regulators. When disulfiram (DIS), a GSDMD inhibitor, was co-administered to septic mice, the inhibitory effects of XBJ on NETs formation and coagulation were reversed. Collectively, we found XBJ relieved sepsis-induced lung injury and pulmonary microcirculation by reversing the GSDMD-related pathway to inhibit NETs formation.

Keywords: Xuebijing injection (XBJ), sepsis-induced lung injury, pulmonary thrombosis, Neutrophil extracellular traps (NETs), Gasdermin D (GSDMD)

F07-5

Beinaglutide alleviates weight and reduces adipocyte differentiation by inhibiting JNK signaling

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Objective: Obesity, a chronic metabolic disease, is closely related to chronic inflammation and adipocyte differentiation. Beinaglutide is a recombinant glucagon like peptide-1 receptor agonists which is fully homologous to human GLP-1 and has been approved for the treatment of type 2 diabetes mellitus. However, whether the weight loss is related to improving chronic inflammation and reducing adipocyte differentiation remains unclear. The present study aimed to evaluate the effect of beinaglutide on weight, inflammation, adipocyte differentiation and to elucidate the underlying mechanisms.

Materials and Methods: We recruited non-diabetic obese patients who met inclusion and exclusion criteria, and constructed a high-fat diet induced obese mouse model and adipocyte model, with beinaglutide as intervention. In recruited non-diabetic obese patients: We measured body weight, body fat, metabolic indexs, and serum lipopolysaccharide (LPS), TNF-α, and IL-6. In animal experiments: After 10 weeks of high-fat diet, C57/BL 6J mice were administered with beinaglutide or saline, then we measured body weight, body fat, energy intake, and blood glucose along with serum LPS, adipose tissue inflammation, intestinal permeability. In vitro experiment: We performed MDI differentiation medium to induce adipocyte differentiation, and intervened with beinaglutide or solvent control at the same time. We examined the mRNA expression of lipogenesis-related genes, lipolysis-related genes and pro-inflammatory factors, oil red O staining and isopropanol extraction to detect adipocyte differentiation and lipid deposition, and NF-κB and MAPK signaling pathways. TLR4 agonists and JNK agonists were used to confirmed their relationship to the anti-adipogenic effects of beinaglutide.

Results: For 25 recruited non-diabetic obese patient: beinaglutide significantly reduced body weight and body fat rate, and the effective rate of weight loss (weight loss percentage ≥5%) was 80%. And beinaglutide significantly reduced serum LPS, TNF-α and IL-6. In addition, beinaglutide significantly improved blood glucose, blood lipid and other metabolic indexes. In animal experiments: Beinaglutide reduced body weight, visceral fat weight and food intake and decreased serum lipopolysaccharide and visceral fat pro-inflammatory cytokine levels in HFD mice. Beinaglutide also improved the increase of intestinal mucosal permeability and increased the expression of intestinal mucosal tight junction protein ZO-1 and Occludin. In vitro experiment: Beinaglutide reduced adipocyte differentiation and lipid deposition, decreased the mRNA expression of lipogenesis-related genes and upregulated lipolysis-related genes. And beinaglutide also inhibited the NF-κB and JNK signal pathways. The activation of NF-κB signaling did not affect adipocyte differentiation and lipid deposition while the activation of JNK signaling pathway promoted adipocyte differentiation and lipid deposition, and impaired the anti-adipogenic effect of beinaglutide.

Conclusion: In conclusion, beinaglutide can significantly reduce body weight, body fat, inhibit appetite, alleviate inflammation and adipocyte differentiation. The inflammation mediated by NF-κB pathway did not affect the anti-adipogenic effect of beinaglutide.We speculated that the anti-adipogenic effect of beinaglutide was attributed to the inhibition of JNK signaling.

Keywords: high-fat diet, inflammation, NF-κB signaling, JNK signaling, beinaglutide

F07-6

Therapeutic mechanism of classical formula Zhishi Xiebai Guizhi Decoction against Pulmonary hypertension in rats

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Pulmonary hypertension (PH) is severe cardio-pulmonary vascular disease lacking high-efficiency therapeutics, and classified into “Chest obstruction” in traditional Chinese medicine according to its clinical symptoms. ZhishiXiebaiGuizhi Decoction (ZXGD) is a classic formula for treating Chest obstruction (Xiongbi in Chinese) recorded in *Synopsis of Golden Chamber*. Our studies delineated that ZXGD significantly decreased pulmonary artery pressure, alleviated pulmonary vascular remodeling and decreased serum level of TC and LDL-C, thus to ameliorate PH in rats. Moreover, network pharmacology results suggested that key therapeutic targets of ZXGD against PH mainly accounted for apoptosis pathway, lipid and atherosclerosis as well as IL-17 signaling pathway, and neohesperidin and naringin were the bioactive components of ZXGD against PH. We further verified that ZXGD promoted pulmonary arterial smooth muscle cells (PASMCs) apoptosis in vivo and vitro, decreased cholesterol in serum and promoted synthesis of lipid droplet in PASMCs, inhibited inflammatory

factors, and regulated the biomarker of mitochondrial dysfunction. Neohesperidin and naringin have the same capacity of inhibiting pulmonary vascular remodeling as ZXGD in PASMCs. These results suggested ZXGD facilitated PASMCs apoptosis, modulated cholesterol esterification, inhibiting inflammation and protecting mitochondrial function, thus to inhibit vascular remodeling and decrease pulmonary hypertension. Taken together, we first deciphered the bioactive compounds and therapeutic mechanism of ZXGD against PH.

Keywords: ZhishiXiebaiGuizhi Decoction; Pulmonary hypertension; Bioactive compounds; Apoptosis; Lipid droplets; Inflammation.

FREE ORAL COMMUNICATION 8

Stroke

10:00-11:30 | Room 1

F08-1

Effects of Drag-Reducing Polymers on Microcirculation and Tissue Oxygenation in Rats with Traumatic Brain Injury of Varying Severity: Gender and Dosage Differences

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Background: Traumatic brain injury ultimately leads to a reduction in cerebral metabolic rate for oxygen due to ischemia and/or metabolic depression. An increasing body of evidence suggests that cerebral blood flow differs between males and females in the intact and injured brain. Previously, we showed that two ppm of drag-reducing polymers (DRPs) in blood improve hemodynamic and oxygen delivery to tissue in a rat model of mild-to-moderate traumatic brain injury (TBI). **Aim:** To evaluate sex-specific and dose-dependent effects of drag-reducing polymers on microcirculation and tissue oxygenation in rats after traumatic brain injury of different severity. Material and methods: In-vivo two-photon laser scanning microscopy over the rat parietal cortex was used to monitor the effects of DRP on microvascular perfusion, tissue oxygenation (NADH) and blood-brain barrier permeability. Brain and rectal temperatures, MAP, blood gases and electrolytes were monitored. Lateral fluid-percussion TBI (1.5 ATA-moderate or 2.5 ATA-severe, 100 ms) was induced after baseline imaging and followed by 4 hours of monitoring. DRP was injected at 1, 2, or 4 ppm within 30 minutes after TBI induction. Data analysis was done by GraphPad Prism 7. Differences between groups were determined using a two-way ANOVA analysis for multiple comparisons and post hoc testing using the Mann-Whitney U test.

Results: Moderate TBI progressively decreased microvascular circulation leading to tissue hypoxia in the pericontusion zone ($p<0.05$). The i.v. injection of DRP increased near-wall flow velocity and flow rate in arterioles, leading to an increase in the number of erythrocytes entering capillaries, enhancing capillary perfusion in a dose-dependent manner without distinguishable difference between males and females ($p<0.01$). The severe TBI resulted in intracranial pressure increase (31±3.2 mmHg, $p<0.05$), leading to microcirculation redistribution to non-nutritive microvascular shunt (MVS) flow and stagnation of capillary flow. Tissue hypoxia was more prominent, especially in male rats; the pericontusion zone was 25±5.2% larger than after moderate TBI ($p<0.01$). Both were reverted by DRP in a dose-related manner with better efficiency in females ($p<0.01$). After severe TBI, BBB degradation was faster and more prominent. DRP was more efficient in attenuating the progression of permeability increase in moderate TBI ($p<0.05$). Discussion: DRP at 4 ppm was most efficient, with a better effects in female rats. Supported by NIH/NINDS R01NS112808

F08-2

Menaquinone-4 attenuates early brain injury after subarachnoid hemorrhage by inhibiting neuronal iron death through upregulation of DHODH

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Background: Ferroptosis is an iron-dependent pattern of cell death due to lipid peroxidation and massive accumulation of reactive oxygen radicals, which plays an important role in early brain injury (EBI) after subarachnoid hemorrhage. Our study aimed to determine the expression pattern and role of dihydroorate dehydrogenase (DHODH) in subarachnoid hemorrhage (SAH) and to investigate whether menaquinone-4 (MK-4) can inhibit ferroptosis by upregulating DHODH in neurons.

Methods: Firstly, we used hemoglobin (Hb) to stimulate mouse cortical primary neurons to establish an in vitro model of SAH. Neurons were treated with BQR, a specific inhibitor of DHODH, to demonstrate the protective effect of DHODH against ferroptosis; neurons were treated with MK-4, or MK-4 and BQR simultaneously, to explore the protective effect of MK-4 against ferroptosis, and its dependence on DHODH. Then, we used intravascular perforation to establish a mouse model of subarachnoid hemorrhage to further demonstrate the therapeutic effects of MK-4. Finally, we measured the levels of MK-4 in the cerebrospinal fluid of SAH patients.
Results: In vivo experiments, inhibition of DHODH was shown to further exacerbate ferroptosis. MK-4 was shown to inhibit ferroptosis by upregulating DHODH, and, this protective effect was abolished in the DHODH-inhibited state. The therapeutic effect of MK-4 in inhibiting ferroptosis and improving neurological function was also demonstrated in vitro experiments. Furthermore, our results suggest that MK-4 levels are significantly elevated in the cerebrospinal fluid of SAH patients and could serve as a potential prognostic biomarker.
Conclusions: Our experiments demonstrate that DHODH plays a protective role in ferroptosis after SAH, and MK-4 treatment can inhibit ferroptosis by upregulating DHODH expression.

F08-3

A cold case of thrombolysis: Cold recombinant tissue plasminogen activator confers enhanced neuroprotection in experimental stroke

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Background: Thrombolysis and endovascular thrombectomy are the primary treatment for ischemic stroke. However, due to the limited time window and the occurrence of adverse effects, only a small number of patients can genuinely benefit from recanalization. Intra-arterial injection of recombinant tissue plasminogen activator (rtPA) based on arterial thrombectomy could improve the prognosis of acute ischemic stroke patients, but it could not reduce the incidence of recanalization-related adverse effects. Recently, selective brain hypothermia has been shown to offer neuroprotection against stroke. To enhance the recanalization rate of ischemic stroke and reduce the adverse effects such as tiny thrombosis, brain edema, and hemorrhage, we described for the first time a combined approach of hypothermia and thrombolysis via intra-arterial hypothermic rtPA.
Methods: We initially established the optimal regimen of hypothermic rtPA in adult rats subjected to middle cerebral artery occlusion (MCAO). Subsequently, we explored the mechanism of action mediating hypothermic rtPA by probing reduction of brain tissue temperature, attenuation of blood-brain barrier damage, and sequestration of inflammation coupled with untargeted metabolomics.
Results: Hypothermic rtPA improved neurological scores and reduced infarct volume, while limiting hemorrhagic transformation in MCAO rats. These therapeutic outcomes of hypothermic rtPA were accompanied by reduced brain temperature, glucose metabolism, and blood-brain barrier damage. A unique metabolomic profile emerged in hypothermic rtPA-treated MCAO rats characterized by downregulated markers for energy metabolism and inflammation.
Conclusion: The innovative use of hypothermic rtPA in enhancing their combined, as opposed to stand-alone, neuroprotective effects, while reducing hemorrhagic transformation in ischemic stroke.

F08-4

Administration of intramuscular AAV-BDNF and intranasal AAV-TrkB promotes neurological recovery via enhancing corticospinal synaptic connections in stroke rats

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Stroke causes long-term disability in survivors. BDNF/TrkB plays an important role in synaptic plasticity and synaptic transmission in the central nervous system (CNS), promoting neurological recovery, but current research primarily focuses on its regulation of synaptic plasticity of the hippocampal neurons, spinal cord, and promotes motor function recovery after intracerebral hemorrhage. In this study, we performed non-invasive treatment methods focused on overexpression of BDNF and TrkB in the spinal cord contralateral to the side of injury significantly promoted synaptic plasticity of the corticospinal connections and motor functional recovery after middle cerebral artery occlusion (MCAO).
In a permanent rat middle cerebral artery occlusion (MCAO) model, we investigated a non-invasive treatment method in rats utilizing intramuscularly injecting adeno-associated virus (AAV) vectors encoding BDNF into the stroke impaired forelimb muscles targeting the motor neurons in the anterior horn of the spinal cord, and intranasally administering AAV-TrkB targeting the cortical neurons and the axonal terminals of CST in the gray matter of the spinal cord. We assessed the effects of combination therapy with AAV-BDNF and AAV-TrkB on motor functional recovery and synaptic plasticity of the corticospinal connections through behavioral tests, electrophysiological analysis, immunofluorescence staining, transmission electron microscopy, qRT-PCR, BDA anterograde tracing CST and other methods.
Our results showed that BDNF or TrkB gene transduced in the spinal anterior horn neurons and cerebral cortical neurons. Compared to AAV vector treatment alone, behavioral and electrophysiological results showed that the combination therapy significantly improved upper limb motor functional recovery and neurotransmission efficiency after stroke. BDA tracing, immunofluorescence staining, qRT-PCR, and transmission electron microscopy of synaptic ultrastructure results revealed that the combination therapy not only potently increased the expression of Synapsin I, PSD-95, and GAP-43, but also promoted the axonal remodeling and restoration of abnormal synaptic structures. These findings provide a new strategy for enhancing neural plasticity and a potential means to treat stroke clinically.
The present study shows that the combination of intramuscular administration of AAV-BDNF and intranasal administration of AAV-TrkB significantly enhances behavioral outcomes and increases synaptic plasticity and reorganization in the denervated gray matter of the spinal cord after ischemic stroke in rats. This provides a novel strategy for the treatment of stroke patients and may provide ideas for the treatment of other central nervous system diseases.
Keywords: Stroke; BDNF; TrkB; Synaptic plasticity

F08-5

Antagonism of histamine H3 receptor promotes angiogenesis following focal cerebral ischemia

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It is known that enhancement of angiogenesis facilitates neurogenesis

and neurological recovery for ischemic stroke. Although histamine showed angiogenic activity, whether antagonism of histamine H_3 receptor (H_3R), which activates histaminergic neurons, boosts angiogenesis after ischemia remains unclear. In the present study, we found that H_3R antagonist thioperamide (THIO) and H_3R gene knockout (*Hrh3*$^{-/-}$) improved angiogenesis and neurological function at late stage after cerebral ischemia. The promotion of angiogenesis conferred by thioperamide was reversed by the H_3R agonist, but not by histidine decarboxylase inhibitor a-FMH, H_1 receptor and H_2 receptor antagonists or histidine decarboxylase gene knockout (*HDC*$^{-/-}$), suggesting the promotion on angiogenesis conferred by H_3R antagonism was independent of activation of histaminergic neurons. Moreover, either thioperamide or H_3R knockdown facilitates vascular endothelial cells migration and tube formation after oxygen glucose deprivation (OGD) *in vitro*. H_3R antagonism reduced the interaction between H_3R and Annexin A_2, while knockdown of Annexin A_2 abrogated the promotion of H_3R antagonist on angiogenesis. Annexin A_2 overexpressed mice displayed more blood vessels at the ischemic boundary zone, which was reversed by H_3R agonist. In conclusion, this study indicates that H_3R antagonism promotes angiogenesis after cerebral ischemia, which is independent of histaminergic neurons, but related to the H_3R on vascular endothelial cells and its interaction with Annexin A_2. H_3R antagonists might be superior drug candidates to improve angiogenesis and neurological recovery after ischemic stroke.

F08-6

C/EBPβ predict the infection followed by acute ischemic stroke onset within a week

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Background: Acute ischemic stroke (AIS) can trigger immune depression and promote infections, which may influence the outcome of AIS. Early identifying the infection may improve the outcome.
Method: We reviewed the data of the patients who were diagnosed with AIS and admitted to hospital within 24 hours of onset. The clinical characteristics were described using a chi-square test and Kruskal-Wallis test. The factors related to the occurrence of infection within a week of AIS onset were assessed using multivariable logistic regression analysis. Mann-Whitney U test was used to assess the relationship between C/EBPβ and the related inflammation factors in the brain of MCAO models.
Results: 316 patients were finally enrolled. Logistic regression analysis show that the higher the C/EBPβ level, the more likely it was for patients to experience a infection after AIS onset within a week. The animal experiments results show that C/EBPβ increases TNF-α, IL-6 and IL-1β in the brain of MCAO models. Inhibiting the expression of C/EBPβ can inhibit the related inflammation factors.
Conclusion: C/EBPβ participates in the inflammation after AIS onset. C/EBPβ may serve as a therapeutic target of the inflammation followed by AIS and a potential biomarker for identifying the infection after AIS onset within a week.

FREE ORAL COMMUNICATION 9

Shock

10:00-11:30 | Room 7

F09-1

Mechanisms underlying regional vascular hypo-responsiveness in sepsis

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Background: Sepsis is a leading cause of death in intensive care units accounting for nearly 11 million global deaths each year. A frequent unresolved clinical complication of sepsis is reduced responsiveness to vasopressor drugs leading to life-threatening falls in blood pressure, multi-organ failure and death. The lack of treatments to reverse sepsis-induced vasoplegia is largely due to a poor understanding of its complex pathophysiology. In this study, we investigated the mechanisms underlying vascular hypo-responsiveness in isolated renal and mesenteric resistance arteries using a clinically relevant sheep model of hypotensive sepsis-induced acute kidney injury.
Methods: Sepsis was induced in female sheep (1.5-2.0 years of age) by intravenous (IV) infusion of live Escherichia coli for 32 hours (a Gram-negative bacterial strain isolated from a septic patient). By 32 hours of sepsis, sheep developed a hemodynamic profile similar to human sepsis characterised by hypotension, increased cardiac output, tachycardia, hyperlactatemia, tachypnoea and acute kidney injury (n=8). Sheep were humanely euthanised at 32 hours of sepsis, and the third order mesenteric arteries and renal interlobar arteries were isolated. Arteries were also collected from a separate group of naïve, healthy (control) animals (n=8). The outside diameter of mesenteric arteries was ~330 μm and for renal interlobar arteries it was ~360 μm. Ring segments of artery with endothelium intact were mounted on a 4-channel wire myograph for measurement of tension development. In other experiments, spiral strips of artery denuded of endothelium were prepared for the simultaneous recording of cytoplasmic free calcium and contraction.
Results: Contraction evoked by phenylephrine was significantly impaired in mesenteric arteries (P=0.002) but not in renal interlobar arteries from septic sheep. The impaired contraction in mesenteric arteries was reversed by blockade of vascular ATP-sensitive potassium channels (KATP) with PNU-37883. In contrast, contraction evoked by depolarization with physiological saline containing 100 mM potassium (HiK+ PSS) was not altered in sepsis in arteries from either vascular bed. In strips of endothelium-denuded mesenteric and interlobar renal arteries, reintroduction of Ca2+ to Ca2+-free PSS evoked concentration-dependent increases in cytosolic free Ca2+ and contraction. In arteries from septic sheep, the contraction evoked by re-introduction of Ca2+ was impaired in mesenteric arteries (p=0.001), but not in renal interlobar arteries. Similarly, reintroduction of Ca2+ in the presence of phenylephrine evoked a smaller contraction in mesenteric arteries of septic sheep. Total endothelium-dependent relaxation was unaltered in either artery in sepsis.
Conclusion: In a clinically relevant large mammalian model, Gram-negative sepsis induced region-dependent resistance artery dysfunction. In small mesenteric arteries, the vasoconstrictor responses were profoundly supressed in sepsis, mediated in part by an influence of KATP channels and by reduced sensitivity of the smooth muscle contractile apparatus to Ca2+. In contrast, contraction of renal interlobar arteries was retained in sepsis. Treatment strategies to reverse sepsis-induced hypotension need to take into consideration the regional differences in vascular responsiveness to vasopressor agents. Our study highlights potential mechanisms for targeted drug development aimed at improving circulatory management of patients with sepsis.

F09-2

STING-regulated macrophage ferroptosis exacerbates sepsis via its interaction with NCOA4

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Ferroptosis is a non-apoptotic form of regulated cell death triggered by the accumulation of reactive oxygen species (ROS) depended on excess iron. Although most research focus on the relationship between ferroptosis and cancer, ischemia/reperfusion injury, research on ferroptosis induced by immune-related inflammatory diseases, especially sepsis, is scarce. STING, a highly evolutionary and stress-responsive protein, is critically involved in defense against infectious disease. Nevertheless, the underlying function of *Sting* in inflammation-mediated ferroptosis in the immune system remains uncertain. We employ Cre-Loxp approach to generate *Sting* knockout mice. Using single-cell transcriptomic, we show that macrophage develop a molecularly distinct, pro-inflammatory state following injury. This transient inflammatory macrophage state significantly upregulates ferroptosis metabolism genes, making the cells vulnerable to ferroptotic stress. Furthermore, we show that STING promotes macrophage ferroptosis in a cGAS- and TBK1-independent manner. Mechanistically, STING interacts with cytoplasmic nuclear receptor coactivator 4 (NCOA4), triggering ferritinophagy-mediated macrophage ferroptosis. Simultaneously, their interaction maintains STING dimer stability, which in turn lessens NCOA4 nuclear localization, impairing its function as a transcription factor coregulatory of PPAR. Our study broadens the roles of STING stress from being a trigger of ferritinophagy to include ferroptosis.

F09-3

Spinning disk confocal imaging of immune-induced microvascular hyperpermeability

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Objective: Anaphylaxis is a potentially life-threatening hypersensitivity reaction that occurs rapidly after allergen irritation to sensitized individuals, which typically manifests with severe pathophysiological symptoms associated with microcirculation dysfunction. However, the pathophysiological dynamics of microcirculation during anaphylaxis remain unclear.

Approach: Six-week-old female mice were sensitized subcutaneously on day 0 with bovine serum albumin in complete Freund adjuvant and boosted on day 7 and day 14 with 50 μg BSA in incomplete Freund adjuvant. One week after the last sensitization, mice were intravenously injected with 15 μg BSA to elicit systemic anaphylaxis. The spinning disk confocal imaging system was used to detect microvascular structure and permeability, and blood cell dynamic actions during immune complex-induced acute anaphylaxis. Real-time microcirculatory perfusion of the hindlimb was monitored by laser-Doppler perfusion imaging system and the degree of microvascular permeability in different tissues was evaluated after i.v. injection of Evans blue.

Results: Albumin leakage was the most striking change during immune complex-induced anaphylaxis, along with increased leukocyte adhesion to the venular wall, decreased blood flow velocity, and decreased microvascular diameter. Five minutes after BSA challenge, we observed obvious microvascular leakage, and this phenomenon aggravated over time. Microcirculatory perfusion of the hindlimb continued to decrease upon BSA challenge. About 50% of blood flow was lost within 10 minutes, likely due to increased vascular permeability. Eighty minutes after BSA challenge, microcirculatory perfusion decreased to ~20% of the baseline. During anaphylaxis, Evans blue leakage was systemic, particularly in the lung, heart, liver, and intestine.

Conclusions: Immune complex induced acute and systemic microvascular hyperpermeability, leading to severe fluid extravasation and tissue hypoperfusion. Microvascular hyperpermeability represents a major pathological process of anaphylaxis.

Keywords: anaphylaxis, microvascular leakage, immune complex

F09-4

Alteration of N6-methyladenosine-tagged circular RNA in the rats' hippocampus with PTSD triggered by high-voltage electrical burn

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Objective To investigate the differential expression of circular RNA (circRNAs) and differential methylation modification of m6A in rat hippocampus with PTSD (Post Traumatic Stress Disorder) triggered by HVEB (High Voltage Electrical Burn), which provides scientific evidences for revealing the relationship between epigenetic modifications of circRNAs and PTSD.

Methods A transcranial high-voltage electric burn rat model was established using 2 kV for 3 sec high-voltage electric shock, and a rat model of SPS (single prolonged stress) was made as a positive control group for PTSD. The rats in each group were randomly divided into Sham group, SPS group and HVEB group. Behavioral tests included Morris water maze (MWM) (orientation navigation test and Spatial search test), the elevated plus maze (EPM) and the open field test (OFT) to assess PTSD-like symptoms in each group. Rats' hippocampus was subjected to methylated RNA immunoprecipitation sequencing (MeRIP-seq) and transcriptome sequencing (RNA-seq) using the Illumina high-throughput sequencing platform. Differential analysis of circRNAs was done using the EdgeR package, and enrichment analysis of GO and KEGG signaling pathways was done in R.

Results A total of eight rats in the SPS group were used as positive controls for PTSD, and 10 rats were finally obtained after screening in the high-voltage electrical burn group. MWM results showed that, compared with the sham group, the average time to find the platform and percentage of time spent in the target quadrant in SPS group and HVEB group both were significantly longer(P<0.01). SPS group and HVEB group were no significant difference(P>0.05). The rats in SPS group and HVEB group in the EPM spent less time percentage into open arms (P<0.01) and had less percentage of entries into open arms(P<0.01). Percentage of time spent into open arms and percentage of entries into open arms between SPS group and HVEB group were no significant difference(P>0.05). The open field test results showed that percentage of distance moved in the center zone and percentage of time spent in the center zone in SPS group and HVEB group both were significantly shorter in comparison with the sham group. Percentage of distance moved in the center zone and percentage of time spent in the center zone between SPS group and HVEB group were no significant difference(P>0.05). Compared with the sham group, the m6A levels of total RNA in HVEB group increased(P<0.05). According to the results of MeRIP-seq sequencing, a total of 38 differential m6A peaks in circRNAs (FC>1.5, P<0.05) were identified, which were mainly distributed on chromosomes 1, 5 and 7. The RNA-seq sequencing results showed tha a total of 751 differential circRNAs were screened, of which 465 were upregulated and 286 were down-regulated (FC>1.5, P<0.05). GO analysis showed that target genes for differential circRNAs mainly involved in biological processes such as embryonic skeletal system development, rough endoplasmic reticulum and transmembrane transporter activity. KEGG pathway enrichment analysis indicated that the differential circRNAs target genes mainly were related to metabolic processes and signaling pathways such as alanine, aspartate and glutamate metabolism,

glyoxylate and dicarboxylate metabolism and basal transcription factors. Finally, combination analysis of m6A differential methylation modification and differentially expressed circRNAs showed that a total of 11 circRNAs with m6A differentiated modification and differential expression were obtained.

Conclusion Behavioral manifestations of PTSD appeared in rats in the HVEB group. High-throughput sequencing screened out differential m6A-modified and differentially expressed circRNAs, and the various pathways involved in their target genes were analyzed, which provided a potential targeting site for the diagnosis and treatment of PTSD diseases caused by high voltage electrical burns.

F09-5

Transcriptome analysis of parabiotic tissues in high-voltage electrical burns

Jiawen Hao [1], Mengyuan Lv [1], Congying Li [1], Xuegang Zhao [1], Meixiu Li [1], Wenfei Yang [1], Chenyang Ge [1], Lihong Tu [1], Yanfen Xu [1], Qingfu Zhang [1]

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To analyze the potential mechanism of progressive injury through transcriptome sequencing of parabiotic muscle tissue in rats with high-voltage electrical burns. SD rats were randomly divided into electric burn group and control group, with 3 rats in each group. The animal model of electric burn group was established by high voltage electric burn. The parabiotic muscle tissue between the burn entrance of rats in the burn group and the healthy muscle tissue in the corresponding part of rats in the control group were collected 8 hours after the electric burn. The total RNA of the tissue was extracted by Trizol method and sequenced by BGI CNBSEQ platform. The differentially expressed genes were screened and subjected to Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway functional enrichment analysis. Then the joint analysis of transcriptome data and the construction of ceRNA network were performed. Compared with the control group, 2460 mRNA, 54 lncRNA and 136 miRNA were differentially expressed in the parabiotic muscle tissue of the electric burn group. It was significantly enriched in the pathways related to programmed cell death. The competing target mRNA of ceRNA in the lncRNA-miRNA-mRNA interaction network were mainly enriched in PI3K-Akt signaling pathway and Tumor necrosis factor signaling pathway. Multiple signaling pathways related to programmed cell death are involved in the mechanism of parabiotic muscle tissue progressive injury caused by high-voltage electrical burns. miR-23a-5p and miR-370-3p may be potential targets for the intervention of progressive parabiotic muscle tissue injury.

F09-6

A case of residual gangrene of the feet caused by sepsis and literature review

Jie Gao [1]

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Sepsis is a systemic inflammatory response syndrome caused by infection that can progress to severe sepsis and septic shock. The condition of sepsis was stable after treatment, and gangrene was left behind. Such cases were rare. In this paper, a case of gangrene left over from sepsis was reported, and the causes of gangrene were analyzed (considering the local microcirculation disturbance caused by bacterial plug colonization, local microcirculation thrombosis, combined with diabetic vascular disease). The literature on sepsis and its anticoagulant therapy was reviewed. Progress in the diagnosis of disseminated intravascular coagulation, the use of pressor drugs in the rescue of septic shock, changes in microcirculation during septic shock.

FREE ORAL COMMUNICATION 10

New Methods and New Techniques

15:00-16:30 | Room 7

F10-1

Design and application of probes targeting different molecules of nitrosative stress during cerebral ischemia

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In vivo real-time imaging of nitrosative stress in the pathology of stroke has long been a formidable challenge due to both the presence of the blood-brain barrier (BBB) and the elusive nature of reactive nitrogen species, while this task is also informative to gain a molecular level understanding of neurovascular injury caused by nitrosative stress during the stroke episode. So, in order to track the changes of various molecules involved in the nitrosative stress, we designed corresponding probes for NO release, S-nitrosylation, and $ONOO^-$ production, respectively.

Nitric oxide donors (NODs) are indispensable in biological research and disease treatment. NODs had been utilized to treat cardiovascular diseases in clinic and many others are under trial. Thiols are typically required for these donors to release NO. Yet, their mechanism is complex and often lead to resistance. Herein, we reported that N-nitrosated electron-deficient dyes are capable of NO release with one-electron reduction. A fluorophore is generated simultaneously, whose fluorescence is harnessed to monitor the profile of NO release. Through electrochemical and spectral studies, NOD f3 was found to exhibit good biocompatibility and high reduction efficiency and its potentials in cell-protection in oxygen and glucose deprivation (OGD) models were showcased with endothelial cells. S-nitrosylation is a posttranslational modification of protein cysteine residues leading to the formation of S-nitrosothiols and its detection is crucial to understanding of redox regulation and NO-based signaling. Prototypical detection methods for S-nitrosylation are always carried out *ex situ*. However, the reversible nature and the tendency of transnitrosylation highlight the necessity of its probing in intact live biological contexts. Herein we provide a fluorogenic chemical probe for the detection of S-nitrosylation in live endothelial cells. The probe is weakly emissive alone and becomes highly fluorescent only after undergoing a reaction with S-nitrosothiols in live cellular environments. This probe features high degrees of specificity and desirable sensitivity. Furthermore, it has been successfully applied to image the dynamic change of protein S-nitrosylation in live endothelial cells.

NO reacts rapidly with superoxide (O^{2-}) and generates a large amount of peroxynitrite ($ONOO^-$) in a short time. Accumulating evidence suggests that formation of $ONOO^-$ in the cerebral vasculature contributes to the progression of ischemic damage, while the underlying molecular mechanisms remain elusive. Herein, we have developed a fluorogenic probe B545b for imaging $ONOO^-$ during the onset of stroke through a physicochemical-property guided probe design strategy. The probe demonstrates an extremely weak background signal but significant brightness upon $ONOO^-$ stimulation. Moreover, due to its desirable physicochemical properties including its partition coefficient between water and oil and moderate water solubility, B545b can be administered intravenously to mice and it readily penetrates the brain blood barrier. These advantages make B545b sensitive enough to track the $ONOO^-$ flux in clotted microvessels. After accomplishing its imaging mission, the probe is easily metabolized and therefore won't cause safety concerns. These desirable features make the probe competent for the straightforward visualization of nitrosative stress progression in stroke pathology. However, direct visualization of $ONOO^-$ fluxes in the cerebral vasculature of live mice remains a challenge. Therefore, we present a fluorescent switch-on probe (NP3), which exhibits good specificity, fast response, and high sensitivity toward $ONOO^-$ both in

vitro and in vivo. Moreover, NP3 is two-photon excitable and readily blood–brain barrier penetrable. These desired photophysical and pharmacokinetic properties endow NP3 with the capability to monitor brain vascular $ONOO^-$ generation after injury with excellent temporal and spatial resolution.Due to these favorable properties, NP3 holds great promise for visualizing endogenous peroxynitrite fluxes in a variety of pathophysiological progressions in vitro and in vivo.
In light of the versatility exemplified, theses probes hold great promise for exploring the role of nitrosative stress in the pathophysiological process of a variety of vascular diseases.

F10-2

Profile as an interpretable ECG based algorithm to analyze and predict mental stress induced myocardial ischemia

Dantong Li [1]

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Importance: A thorough analysis and novel method based on ECG data hold promise to provide additional insights for mental stress induced myocardial ischemia (MSIMI) diagnosis. Utilizing easily available ECG data for accurate MSIMI prediction can enhance the management of high-risk individuals, ultimately improving prognosis through preventive measures.
Objective: To evaluate the potential of ECG for efficient MSIMI diagnosis including different stages before and after mental stress tasks and developing suitable prediction techniques.
Design, Setting, and Participants: This prospective cohort study recruited 120 age-matched female participants with angina symptoms without obstructive between 2019 and 2021. An additional 33 participants were recruited in 2022. During the participants' engagement in the mental stress tasks, PET/CT and ECG data were collected, with PET/CT being utilized as a precise diagnosis.
Main Outcomes and Measures: The ECG data from participants were categorized into Rest, Stress, and Recover based on the start and end times of their mental stress tasks. A profile method that utilizes Pearson correlation coefficient to demonstrate the distance between participants for further classification was developed. The accuracy of this approach was compared against the current ECG diagnostic criteria.
Results: A total of 80 participants and 39 controls were included in the study, with an additional 33 participants used for independent validation. Among the interpretable ECG variables obtained from the Rest, Stress, and Recovery stages of the mental stress tasks, 119 variables were found to be statistically significant, with 37 of these variables being from the Recovery stage and 96 based on HRV. Based on the selected variables and their variations between the continuous stages, basic profile and Δprofile were constructed. The profile was found to be highly correlated with MSE, SDNN, DFAα1, D2, and SampEn, which are indexes that are highly associated with depression and cardiovascular risks. The approach demonstrated higher agreement with PET/CT in the validation set (Kappa = 0.713) compared to the current ECG diagnostic criteria (Kappa = 0.134).
Conclusions and Relevance: Through this prospective cohort study, we demonstrated that more interpretable variables based on HRV, and those obtained from the Recovery stage, contain valuable information for the diagnosis of MSIMI. Based on these selected variables, we proposed a profile method that is tailored to MSIMI, providing an improved early diagnosis tool for high-risk individuals.

F10-3

A three-dimensional microcirculation culture system was established to simulate and analyze the bone marrow hematopoietic niche

Liu Runjin [1], Yang Qinqin [1], Zhu Yiman [1], Li Chungong [1], Dang Qi [1], Chen Dong [1], Zhu Hongliang [1], Wang Xiang [1]

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A three-dimensional microcirculation culture system was established to simulate and analyze the bone marrow hematopoietic niche

Runjin Liu, Qinqin Yang, Yiman Zhu, Chungong Li, Qi Dang, Dong Chen, Hongliang Zhu, Xiang Wang*

Objective: The bone marrow, situated in three-dimensional (3D) porous cancellous bone with a complicated spatial structure and microcirculation environment, is the primary location for adult hematopoietic stem cell (HSC) maintenance and hematopoiesis. Constructing 3D dynamic microcirculation environment *in vitro* enables efficient expansion and differentiation of HSC.
Methods: Natural decellularized cancellous bone scaffolds were prepared, and their structure was characterized using micro-CT scanning techniques. Construction of idealized 3D models with different pore (round, square, hexagonal) morphology and different porosity (55%, 70%, 85%) using CAD methods combined with structural features of cancellous bone. Porous model permeability, wall shear stress (WSS) stent morphology, and imposed flow conditions in relation to the microcirculation environment within the stent were all calculated. 3D microcirculation culture system was established using a collagen (Col) and hyaluronic acid (HA) -coated scaffold structure to simulate the matrix environment. A suitable inlet flow rate was imposed to analyze the effect of the combination of structural and mechanical stimulation of dynamic microcirculation system on HSC differentiation.
Results: Stent porosity significantly affects stimulation and permeability within the stent. The 85% circular pore scaffold has the scaffold with the closest permeability to human cancellous bone of all the scaffold structures. The WSS decreases with increasing porosity when the pore shape of the stent is the same. Calculating the WSS values for the stent at various flow rates, the results show that the WSS in the stent positively correlates with the applied inlet fluid velocity. Controlling the flow rate can adjust the WSS in the stent. The stent is coated with Col/HA in a complex 3D structure, and the 3D perfusion microcirculation system can provide a suitable flow rate. This system simulates human blood microcirculation in several directions. The expansion and differentiation of HSC in the system will be thoroughly studied.
Conclusion: Porosity 85% hexagonal pore scaffolds are more suitable for HSC culture due to higher permeability and uniform WSS distribution. Simulating the microcirculatory environment of HSC in vivo substantially impacts HSC amplification and differentiation. The results of this study provide a theoretical basis for the mechanics of 3D scaffolds in the in vitro hematopoietic microenvironment. A 3D perfusion microcirculation system was designed and applied for HSC expansion and differentiation.

F10-4

Recapitulating influenza virus infection and facilitating antiviral and neuroprotective screening in tractable brain organoids

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Background: Human pluripotent stem cell derived brain organoids offer an unprecedented opportunity for various applications as in vitro model. Currently, human brain organoids as models have been used to understand virus-induced neurotoxicity.
Objective: To investigate the neurotropism of non-neurotropic viruses for human central nervous system, and screen potential neuroprotectives in our tractable brain organoids.
Methods: The brain organoids were separately challenged by multiple viruses including influenza viruses (H1N1-WSN and H3N2-HKT68), Enteroviruses (EV68 and EV71) and Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV) to investigate the impaired effect of these viruses on human brain development.
Results: The brain organoids challenged by influenza viruses had decreased overall organoid size, while enteroviruses infected brain organoids displayed the opposite result. Then, we found WSN preferentially infected MAP2+ neurons compared to SOX2+ neural stem cells (NSCs) and GFAP+ astrocytes in brain organoids, and induced apoptosis of NSCs and neurons, and released inflammatory factors (TNF-α, INF-γ, and IL-6), facilitating brain damage. Furthermore,

transcriptional profiling revealed several co-upregulated genes (CSAG3 and OAS2) and co-downregulated genes (CDC20B, KCNJ13, OTX2-AS1) after WSN infection for 24 hpi and 96 hpi, implicating target for antiviral drugs development. Finally, we explored compound PYC-12 could significantly suppress virus infection, apoptosis, and inflammatory responses.

Conclusions: Collectively, we established a tractable experimental model to investigate the impact and mechanism of virus infection on human brain development. By the way, we will utilize our novel vascularized cerebral organoids model with microfluidic device, which promotes the generation of more matured organoids, to better simulate the real situation of viral infection in human CNS in further plans.

F10-5

The glymphatic system delivery enhances the transduction efficiency of AAV1 to brain endothelial cells in adult mice

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Aims: Recombinant adeno-associated virus (rAAV) is increasingly applied in neuroscience research or gene therapy. However, there is no simple and efficient tool for specific transfection of rAAV into cerebrovascular tissues. It has been reported that fluorescent tracers or beta-amyloid protein can enter the brain through perivascular spaces, named as “glymphatic system”. This study was to explore whether rAAV could transduce the cerebral vasculature through the glymphatic pathway.

Method: An AAV1-GFP vector suspension (15 μL) was injected into the intracisternal space of anesthetized mice and 5 μl was injected into the bulbus medullae. As controls, 15 μl of artificial cerebrospinal fluid (aCSF) was injected into the cisterna magna. The endothelial specific transduction was verified by Glut1 or PDGFRβ immunofluorescent staining. Immunofluorescence images for all groups were captured with a laser microscope.

Results: It was observed that the administration of rAAV1 vectors encoding green fluorescence protein through cisterna magna injection in adult mice has resulted in a successful cerebrovascular transduction compared to intra-parenchymal injection or aCSF at a 30-day post-transduction interval. Additionally, the immuno-fluorescence data indicates that GFP co-localizes with Glut1. These findings suggest that the delivery of rAAV1 vectors through the glymphatic system enhances the transduction efficiency of AAV1 to brain endothelial cells. In comparison to other approaches, the glymphatic pathway offers a simpler and more efficient method for transducing cerebral endothelial cells using the AAV1 vector.

Conclusion: After analyzing the results of this study, it is clear that rAAV1-based vectors hold tremendous promise for advancing research and developing gene-based therapies that target endothelial cells in neurologic diseases. However, these findings should not be taken as a definitive conclusion, but rather as a starting point for further exploration and investigation. Deeper inquiry into the long-term safety, efficacy, and ethical implications of using these vectors will be necessary to fully realize their potential and ensure their responsible application in clinical settings. Ultimately, by pursuing thoughtful and rigorous research, we can continue to unlock the transformative power of genetic therapies and improve the lives of patients affected by neurologic diseases.

F10-6

Exploring the Magnetocardiographic Characteristics of Myocardial Infarction with Non-obstructive Coronary Artery Disease

Yijing Guo [1], Hong Shen [1], Jian Ma [1], Shulin Zhang [2], Chengxing Shen [1]

[1] Department of Cardiology, Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine
[2] Shanghai Institute of Microsystem and Information Technology

Objective: To explore the characteristics of myocardial infarction with non-obstructive coronary artery disease (MINOCA) based on magnetocardiography (MCG).

Methods: A total of 6 patients diagnosed as MINOCA and 78 healthy controls from July 2021 to August 2022 in Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine were selected as the research objects. The 1: 1 propensity score matching method was used to control the general data of patients, while SPSS21.0 was used to analyze the MCG parameters data.

Results: Before matching, the age of patients showed statistically significant difference between MINOCA group and control group, which became opposite after matching along with other data parameters. Dynamic MCG analysis showed significant difference between two groups. The analysis of MCG data revealed 36 parameters with statistically significant difference and 21 parameters with risk ratio more than one. Only one MINOCA patient showed positive result in previous coronary heart disease MCG model, while other MINOCA patient as well as controls showed negative results. Three MCG parameters, named t_ch16_power_A4_, qrs_qrs_max_magni_skewness, qrs_qrs_center_minmax_x_std, showed positive correlation with myocardial injury in correlation analysis.

Conclusion: Our study proved significant changes of MCG data in MINOCA, which build a good foundation for MINOCA diagnose by MCG in the future.

LUNCH LECTURE 3

12:50-13:30 | Guorui Hall

LL-03

The Effect and Mechanism of YangXueQingNaoWan Attenuating Blood Brain Barrier Disruption after Thrombolysis with Tissue Plasminogen Activator in Ischemia Stroke

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Ischemic stroke is a major cause of death and disability, patients with acute ischemic stroke are currently treated with tissue plasminogen activator (tPA)-mediated thrombolysis within 4.5 hours of stroke onset. However, when administered after 4.5 hours of cerebral infarction, rtPA thrombolysis can lead to cerebral hemorrhage (CH) in 10% of patients and result in a 5% fatality rate. The blood-brain barrie (BBB) damage caused by rtPA thrombolysis after 4.5 hours of ischemic stroke remains a clinical challenge.

Following 4.5 hours of obstruction, cerebral infarction causes ischemia and hypoxia, leading to abnormal mitochondrial respiratory chain function and energy metabolism in vascular endothelial cells. This results in reduced ATP content, F-actin depolymerization, decreased expression of gap junction proteins in vascular endothelial cells, and leakage of plasma albumin. Thrombolysis with rtPA further increases oxidative stress damage to vascular endothelial cells. The release of matrix metalloproteinase (MMP) by adhering of leukocyte to brain microvessels, as well as endothelial cells affected by rtPA on vascular, damages the vascular basement membrane, exacerbating BBB damage and microvascular bleeding.

YangXueQingNaoWan (YXQNW), a compound Chinese medicine, has been widely used for dizziness, irritability, insomnia, and dreaminess caused by blood deficiency and liver hyperactivity in China. Our previous studies have confirmed that YXQNW can attenuate cerebral perfusion flow and microvascular hyperpermeability in spontaneously hypertensive rats (SHR), inhibit BBB damage in SHR induced by ischemia-reperfusion. However, it is still unclear whether YXQNW can alleviate the BBB damage after thrombolysis in ischemic stroke.

SYMPOSIUM 27

Lymphatic Functions in Cardiovascular Disease

08:30-10:00 | Room 1

027-SS1

Renal Lymphatic Roles in Blood Pressure Regulation

Brett Mitchell [1]

[1] Texas A&M University College of Medicine

The kidney plays an important role in long-term blood pressure regulation. By altering sodium, other solutes, and fluid, the kidney, and the lymphatic vessels within the kidney, ensures proper volume homeostasis and organ perfusion throughout the body. Disruptions in these functions can lead to an elevation in blood pressure, or hypertension. Renal injury, interstitial inflammation, and immune cell infiltration play an important role in the development and maintenance of hypertension. In renal inflammatory conditions as well as hypertension, expanded lymphatic vessels attenuate inflammation by trafficking activated immune cells and excess fluid from the interstitial space to lymph nodes. This talk will discuss the evidence by which renal lymphatic vessels contribute to blood pressure regulation. Topics will cover how augmenting lymphangiogenesis in the kidney can decrease particular immune cells, improve kidney function, and lower blood pressure.

027-SS2

Extracellular vesicles and lymphatic function in chronic inflammatory conditions

Catherine Martel [1]

[1] Department of Medicine/Montreal University/Montreal Heart Institute

We have reported that extracellular vesicles (EVs) are present in mouse lymph, and that lymphatics are a route of dissemination for platelet content. Depending on the cells they are pertaining from and the tissues/organs they are in, EVs might display distinct roles. Therefore, whereas platelet EVs can be either friend or foe in the blood circulation, we rather hypothesize that platelet EVs are beneficial for lymphatic function. Platelets per se are essential to instigate and preserve lymphatic function at the embryogenic stage and throughout life. Our results suggest that platelet EVs enhance lymphatic transport by acting directly on lymphatic endothelial cells. Altogether, our data suggest that a specific subset of EVs might potentiate lymphatic integrity and boost lymphatic function. Ultimately, enhancing lymphatic function with our newly identified subpopulation of EVs might become a new therapeutic option in the treatment of chronic inflammatory diseases where lymphatics are known to be defective, such as atherosclerosis.

027-YS1

Enteral Treatment with a Mitochondrially-targeted Antioxidant Preserves Pulmonary Lymphatic Function in an Ovine Model of Congenital Heart Disease with Increased Pulmonary Blood Flow

Wenhui Gong [1], J.H.N. Soares [3], Eric G. Johnson [3], Samuel Chiacchia [1], Elena K. Amin [1], Jason T. Boehme [1], Emin Maltepe [1], Gary W. Raff [2], Jeffrey R. Fineman [1], Sanjeev A. Datar [1]

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[2] Departments of Surgery and Pediatrics, University of California, Davis
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Persistent respiratory dysfunction in patients with congenital cardiac defects has been well described in patients with defects that result in increased pulmonary blood flow (PBF). For example, although complete surgical repair of a ventricular septal defect (VSD) during infancy is considered to be associated with good long-term outcomes, many of these children continue to have deficits in long-

term respiratory mechanics that last into adulthood, worsen with age, and are an independent risk factor for mortality. The underlying cause of this abnormal respiratory physiology is not completely understood. We have previously used a clinically relevant large animal model of congenital heart disease (CHD) with increased PBF (shunt) to demonstrate that chronically increased PBF results in abnormal pulmonary lymphatic flow and function, and decreased lung compliance by pulmonary function testing. Associated with these aberrations, these lambs have increased mitochondrial reactive oxygen species (mtROS)-driven hypoxia inducible factor-1α (HIF-1α) activity and metabolic reprograming to support lymphatic endothelial cell growth and proliferation; and a HIF-1α/KLF2-dependent decrease in nitric oxide (NO) signaling. We hypothesized that in the setting of CHD with increased PBF, dysfunctional pulmonary lymphatics contribute to persistently impaired respiratory mechanics, and that in vivo treatment with a drug to inhibit mtROS could prevent these metabolic and functional derangements by preserving lymphatic endothelial function in shunt lambs. We found that a daily oral treatment with a mitochondrially-targeted antioxidant (mitoquinone, MitoQ): 1) reversed the HIF-1α-mediated shunt LEC phenotype in vitro, 2) restored lymphatic endothelial function in isolated lymphatic vessels, 3) normalized levels of bioavailable NO in pulmonary lymph, 4) preserved pulmonary lymphatic clearance and minimized pulmonary lymphatic congestion in vivo, and 5) improved lung compliance by pulmonary function testing. These results suggest that inhibition of mtROS can preserve lymphatic endothelial function in the setting of increased PBF, including CHD, pneumonectomy and other vascular abnormalities, and hold real promise for a safe, effective, and affordable therapy to improve the quality of life in these patients.

027-YS2

Estrogen activates its receptors to improve lymphatic contractility through suppression of endoplasmic reticulum stress induced by hemorrhagic shock

Jia-Yi Zhai [1,2], An-Ling Kang [1,3], Cai-Juan Li [1], Zhen-Ao Zhao [1,4], Hui-Bo Du [1,4], Li-Min Zhang [1,4], Chun-Yu Niu [1,4], Zi-Gang Zhao [1,4]

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[3] Department of Pathology, Bayannur Hospital
[4] Hebei Key Laboratory of Critical Disease Mechanism and Intervention

Lymphatic contractility dysfunction is associated with the deterioration of hemorrhagic shock (HS). Endoplasmic reticulum stress (ERS) has been demonstrated to be involved in HS-induced organ injury, while estrogen alleviates HS-induced ERS and organ injury. However, whether estrogen improves lymphatic contraction through inhibition of HS-induced ERS remains unclear. We hypothesized that estrogen activation of its receptors (ERs) promoted mesenteric lymphatic contractility through suppression of HS-induced ERS in lymphatic smooth muscle cells (LSMCs). In a rodent model of HS, 17β-estradiol (E2) administration abrogated HS-induced upregulation of GRP78 in lymphatic tissues. Either E2 or ERS inhibitor 4-phenylbutyric acid (4-PBA) promoted the survival HS rats in the first 72 hours after resuscitation. E2, ER-α agonist PPT, ER-β agonist DPN, GPR30-selective agonist G-1, 4-PBA significantly enhanced the contractility of mesenteric lymphatics following HS *in vivo* and *in vitro*. In contrast, ICI 182,780 (ERα and ERβ selective inhibitor) and G-15 (GPR30-selective inhibitor) partly abolished the beneficial effects of E2. Furthermore, ERS agonist XCT-790 abolished the beneficial effects of E2, PPT, DPN, and G-1 on lymphatic contractility. Additionally, E2, PPT, DPN, and G-1 inhibited ERS, and thus ameliorate ERS agonist tunicamycin-induced hypo-contractility in primary LSMCs. Taken together, the data indicates that E2 promotes the lymphatic contractility after HS by inhibiting ERS and estrogen receptor activation mediates the beneficial effect of E2.

SYMPOSIUM 28

Novel Functions of Pericytes in the Microcirculation

08:30-10:00 | Room 2

028-SS1

Pericyte in heart microcirculation

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The outside surface of the capillaries are embroidered with the cell bodies and processes of pericytes, specialized cells that have captured the interests of numerous physiologists for over a century. Pericytes are believed to play a crucial role in regulating blood flow and vascular function in the microcirculation of the cardiovascular system. They have also been implicated in various pathological conditions such as hypertension, diabetes, and heart disease. Despite significant developments in molecular tools and instrumentation, our understanding of the structural hierarchy and molecular mechanisms underlying pericyte function in the heart microcirculation remains limited. Here we focus on discussing our current understanding of the structural profiles of pericytes and highlight recent advances in our knowledge of their physiological roles in the heart microcirculation. The discussions and overviews are supported by our new imaging data obtained from the pressurized and perfused mouse right ventricle papillary muscle (Z-Prep) and electrophysiological results collected from freshly isolated pericytes.

028-SS2

Brain capillary pericytes as metabolic sentinels in the control of brain blood flow

Thomas Longden [1]

[1] Department of Physiology, School of Medicine, University of Maryland Baltimore, USA

Despite the abundance of capillary thin-strand pericytes and their proximity to neurons and glia, little is known of the contributions of these cells to the control of brain hemodynamics. I will discuss our recent findings that KATP channels equip thin-strand pericytes to dilate upstream penetrating arterioles and arteriole-proximate capillaries, and increase capillary blood flow. I will also show that decreasing extracellular glucose in vivo flips a mechanistic energy switch driving rapid KATP-mediated pericyte hyperpolarization to increase local blood flow. Our data support the concept of capillary pericytes as metabolic sentinels that respond to local energy deficits by increasing blood flow to neurons to prevent energetic shortfalls.

028-SS3

The Pericyte Microenvironment in Health and Disease

John Chappell [1]

[1] Fralin Biomedical Research Institute at Virginia Tech-Carilion

Surrounding pericytes (PCs) and endothelial cells (ECs) within capillary walls, the extracellular matrix (ECM) plays an essential role in regulating vessel homeostasis. This structure also serves as a dynamic interface between PCs and ECs in development as well as during pathology. We recently explored the roles that the ECM plays as (i) a provisional scaffold in regulating vessel formation during vasculogenic and angiogenic remodeling, and (ii) a mature structure surrounding vessels that becomes reorganized under certain conditions. In a developmental model of vessel formation, we found that hypoxia influenced the spatial deposition of Type IV Collagen (Col-IV) as embryonic stem cell (ESC)-derived PC and EC precursors organized into basic vascular structures. A similar spatial restriction of Col-IV (and Type III Collagen, Col-III) was observed during angiogenic

sprouting within various developing tissues including mouse retina and brain. Ultrastructural analysis revealed that these ECM components ultimately maintain the vascular basement membrane (vBM) of mature brain capillaries at a consistent thickness (~150-300nm). Furthermore, we found that inducing the hypoxia-sensing pathway in mouse kidney vasculature caused a profound increase in Col-IV transcript and protein levels, coincident with transcriptional changes in mural cell markers. Subjecting brain vessels to static conditions also altered vBM-related mediators such as matrix metalloproteinase-9 (MMP9), an enzyme that targets Col-IV, and vitronectin, an ECM component that may influence EC junctions. Overall, these experiments highlight the importance of the ECM in mediating PC/EC dynamics during developmental and pathological vessel formation and remodeling.

028-YS1

Intraluminal pressure elevates intracellular calcium and constricts central nervous system pericytes

Nicholas Klug [1]

[1] *Pharmacology/University of Vermont*

Arteriolar smooth muscle cells (SMCs) and capillary pericytes dynamically regulateblood flow in the central nervous system in the face of fluctuating perfusion pressures.Pressure-induced depolarization and Ca2+ elevation provide a mechanism for regulationof SMC contraction, but whether pericytes participate in pressure-induced changes inblood flow remains unknown. Here, utilizing a pressurized whole-retina preparation,we found that increases in intraluminal pressure in the physiological range induce contractionof both dynamically contractile pericytes in the arteriole-proximate transitionzone and distal pericytes of the capillary bed. We found that the contractile response topressure elevation was slower in distal pericytes than in transition zone pericytes andarteriolar SMCs. Pressure-evoked elevation of cytosolic Ca2+ and contractile responses inSMCs were dependent on voltage-dependent Ca2+ channel (VDCC) activity. In contrast,Ca2+ elevation and contractile responses were partially dependent on VDCC activityin transition zone pericytes and independent of VDCC activity in distal pericytes. Inboth transition zone and distal pericytes, membrane potential at low inlet pressure (20mmHg) was approximately –40 mV and was depolarized to approximately –30 mV by anincrease in pressure to 80 mmHg. The magnitude of whole-cell VDCC currents in freshlyisolated pericytes was approximately half that measured in isolated SMCs. Collectively,these results indicate a loss of VDCC involvement in pressure-induced constriction alongthe arteriole-capillary continuum. They further suggest that alternative mechanismsand kinetics of Ca2+ elevation, contractility, and blood flow regulation exist in centralnervous system capillary networks, distinguishing them from neighboring arterioles.

SYMPOSIUM 29

Vascular Adaption in Aging, Obesity, and Metabolic Syndrome

08:30-10:00 | Room 4

029-SS1

Potential Role of Neurovascular Senescence in Cognitive Decline

Anna Csiszar [1]

[1] *Neurosurgery/ University of Oklahoma Health Sciences Center*

Age-related phenotypic changes in cerebromicrovascular endothelial cells contribute to the dysregulation of cerebral blood flow and disruption of the blood-brain barrier, thereby promoting the development of vascular cognitive impairment (VCI). In recent years, there has been growing recognition of endothelial cell senescence as a potential underlying mechanism driving microvascular abnormalities. This realization has paved the way for exploring the potential of senolytic drugs in preclinical research to improve cererbromicrovascular function and structure and positively impact cognition.

In order to identify senescent endothelial cells within the aging mouse brain, we used single cell RNA Sequencing to meticulously examine cells derived from enriched fractions of cerebromicrovascular endothelial cells and other components of the neurovascular unit. These samples were obtained from both young (3-month-old) and aged (28-month-old) C57BL/6 mice. We characterized and delineated 13 distinct transcriptomic cell types. Subsequently, we correlated transcriptomic signatures associated with cellular senescence to endothelial cells, relying on their specific gene expression profiles.

Our investigation revealed a notable elevation in the proportion of senescent endothelial cells within the cerebral microcirculation of aged mice. This phenomenon was further validated using spatial transcriptomics, which confirmed the heightened presence of senescent cells within key regions such as the hippocampus and cortex of the aged mouse brain.

To test the efficacy of a clinically relevant senolytic treatment regimen, we administered the BCL-2/BCL-xL inhibitor senolytic drug ABT263/ Navitoclax to aged mice. Encouragingly, our findings indicate that Navitoclax intervention leads to an enhancement in neurovascular coupling and decreased blood brain barrier permeability among aged mice, which in turn correlates with discernible improvements in cognitive performance.

These findings collectively underscore the potential therapeutic utility of senolytic drugs across various age-related cerebrovascular conditions, as underscored by our preclinical investigations. By shedding light on the role of endothelial cell senescence and its modulation, our results open the avenue to the therapeutic exploitation of senolytic drugs in multiple age-related cerebrovascular pathologies in preclinical studies.

029-SS2

High fat diet provokes distinct responses in male and female adipose endothelial cells

Tara Haas [1]

[1] *School of Kinesiology and Health Science, York University*

Impaired angiogenesis is associated with adipose dysfunction and metabolic complications during the development of obesity. We previously showed that female mice have higher angiogenesis in the adipose tissue than males upon high-fat diet feeding, which is consistent with greater resistance of females to development of metabolic dysfunction. To look at underlying mechanisms, we have focused on comparing the properties of adipose endothelial cells (EC) from male and female mice that may explain these distinct angiogenic responses. Transcriptome analyses reveal that genes upregulated in female adipose ECs are associated with cellular proliferation, oxidative phosphorylation, and chromatin remodeling, indicating a predominantly proliferative state. Higher proliferative activity of female ECs is also maintained in culture, in the absence of sex hormones. In

contrast, male adipose ECs display significant enrichment for genes related to inflammation and a senescence-associated secretory phenotype. They also are more sensitive to inflammatory stimuli in culture. These sex-specific transcriptional profiles also can be detected in ECs from aged mice, suggesting that our findings may be applicable for understanding the molecular mechanisms that underpin sex disparities of ECs in other pathophysiological states.

029-SS3

Increased circulating microparticles contribute to severe infection and adverse outcomes of COVID-19 patients with diabetes

Haoyu Sun [1], Yong Du [1], Rinki Kumar [2], Nicholas Buchkovich [2], Pingnian He [1]

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[2] Department of Microbiology and Immunology, College of Medicine, Pennsylvania State University, Hershey, PA, 17033

COVID-19 patients with pre-existing diseases, especially diabetes, have adverse outcomes and greater mortality than those without the comorbidities, but the underlying mechanisms accounting for this disparity remain unknown. Our recent study revealed novel facilitators that contribute to the severe infection and adverse outcomes of COVID-19 in patients with diabetes. Converging clinical and animal studies demonstrated that microparticles (MPs), the cell membrane-derived vesicles released into the circulation upon cell activation, are largely increased in patients with cardiovascular diseases including diabetes and serve as vectors to propagate inflammation in the vasculature. To date, many mechanisms have been postulated for the increased severity of COVID-19 in patients with diabetes, but the contributions of the excessive MPs in patients with diabetes to the severe COVID-19 have been overlooked. Our study characterized human plasma MPs from normal subjects and type 2 diabetic patients with poor glycemic control (HbA1C 6-9%) and quantified their amount, cell origins, surface adhesive properties, ACE2 expression, spike protein binding capacity, and their roles in SARS-CoV-2 infection. Our study provides the first evidence that over 90% of the human plasma MPs express ACE2 that have high binding affinity to the S protein of SARS-CoV-2. Importantly, plasma MPs in diabetic patients increased 13-fold in quantity and 11-fold surface adhesiveness when compared with those in normal subjects. The majority of human plasma MPs were derived from platelets (~65%), endothelial cells (~12%), and leukocytes (~7%). Our microvessel-on-a-chip study illustrated that the S protein-bound MPs from diabetic patients, not normal subjects, could adhere to and endocytosed into endothelial cells through their adhesive surface. Furthermore, the perfusion of in vitro microvessels with diabetic patients' plasma and pseudotyped SARS-CoV-2 virus resulted over 4 times higher cell infection rate than that of normal plasma perfusion, demonstrating diabetic MP-mediated additional viral entry mechanisms that enhance SARS-CoV-2 infection in diabetic patients. Results also showed that plasma of diabetic patients has significantly higher tissue factor content than that in normal subjects and over 85% of the largely increased platelet-derived MPs in diabetic plasma carry tissue factor. The hypercoagulable state of diabetic patients could initiate and accelerate thrombotic process with severe vascular complications when infected with SARS-CoV-2. Our study revealed a dual role of diabetic MPs in promoting SARS-CoV-2 entry and propagating vascular inflammation, which contributes to adverse outcomes of COVID-19. These findings provide novel mechanistic insight into the high prevalence of COVID-19 in diabetic patients and their propensity to develop severe vascular complications. Supported by HL130363, HL144620, and DK132394.

029-YS1

Obesity as a Premature Aging Phenotype – Implications for Skeletal Muscle Function

Joshua Butcher [1]

[1] Physiological Sciences/Oklahoma State University

In recent decades, two key pathologies have insidiously crept to the forefront of Western civilization: obesity and aging. The purpose of this work was to highlight common pathologies that present with obesity, along with the underlying risk factors, that have remarkable similarity to what is observed in the aged. These include skeletal muscle dysfunction, increases in adiposity, autonomic dysfunction, reduction in nitric oxide bioavailability, increases in reactive oxygen species and inflammation, dysregulation of glucose homeostasis, and mitochondrial dysfunction. As aging is an inevitability and obesity prevalence is unlikely to significantly decrease in the near future, these two phenotypes will ultimately combine as a multidimensional syndrome (a pathology termed sarcopenic obesity). Unfortunately, sarcopenic obesity is challenging to describe as a distinct pathology; it is a multidimensional syndrome that is loosely described as a state in which a patient presents simultaneously with muscle weakness and increases in adiposity. Whether the pre-mature aging indices accompanying obesity are additive or synergistic upon entering aging is not yet well defined, but the goal of this work was to illustrate the potential consequences of a double aged phenotype in sarcopenic obesity. Thus, the conjunction of two diseases (obesity and sarcopenia) termed sarcopenic obesity has created a demanding field that merits further exploration and discussion.

SYMPOSIUM 30

Microcirculation, Stem Cells and Tissue Repair

08:30-10:00 | Room 5

030-SS1

Critical role of mitochondrial integrity in the vascular endothlium in development of cardiac dysfunction

Cristhian A. Gutierrez Huerta [1], Karen C. Clark [1], Shelby N. Hader [1], Andreas M. Beyer [1]

[1] *Cardiovascular Center, Medical College of Wisconsin, Milwaukee, WI*

Endothelial dysfunction is an important predictor of future major adverse cardiac events and a direct contributor to coronary artery disease (CAD). Under physiological conditions, an increase in blood flow stimulates the release of endothelial-derived nitric oxide (NO) resulting in microvascular dilation. Under pathological conditions, such as CAD, vasodilation is instead achieved by the release of mitochondria-derived hydrogen peroxide (H_2O_2), a reactive oxygen species (ROS).

Mitochondrial dynamics is an important homeostatic process that regulates mitochondria's main functions: ATP production and ROS formation. DRP1 mediates mitochondrial fission, the process of splitting mitochondria into smaller fragments, while MFN2 mediates mitochondrial fusion, the process of combining mitochondria. Mitochondrial fission promotes ROS production, but fusion results in improved ATP production. We hypothesize that mitochondrial fission/fusion is an important contributor to the phenotype switch from NO- to H_2O_2-mediated vasodilation in individuals with CAD.

Microvessels were obtained from surgical discard tissue from patients with <1 co-morbidities (non-CAD) and with CAD. Expression of DRP1 and MFN2 were quantified by western blot and the mitochondrial network of the endothelium was assessed by confocal immunofluorescent microscopy. To assess the functional role of mitochondrial dynamics, microvessel diameter was measured by video microscopy and levels of DRP1/MFN1&2 manipulated genetically (siRNA knockdown or AAV mediated overexpression.

Our results show that microvessels from individuals with CAD had higher levels of DRP1 and lower levels of MFN2 compared to non-CAD. Confocal images confirm that the endothelial mitochondria from individuals with CAD were more fragmented compared to non-CAD. Promoting mitochondrial fission (achieved by either upregulating DRP1 or downregulating MFN2) in microvessels from non-CAD promotes H_2O_2-mediated vasodilation in non-CAD vessels. Promoting. Downregulation of DRP1 or upregulation of MFN2 restores NO-mediated vasodilation in microvessels from individuals with CAD.

Our data suggests that the balance between mitochondrial fission/fusion may be an important contributor to H_2O_2-mediated vasodilation in the microvessels of individuals with CAD. We hence argue that targeting mitochondrial dynamics in the endothelium may be an important therapeutic tool that can improve CAD outcomes.

030-SS2

Microvascular Regeneration Following Skeletal Muscle Injury

Steven Segal [1]

[1] *Medical Pharmacology and Physiology / University of Missouri*

Skeletal muscle comprises nearly half of body mass and is subject to injuries that disrupt its microcirculation along with myofibre damage. While regeneration of myofibres is well described, less is known of microvascular regeneration, which may vary with the nature of injury. In the mouse gluteus maximus (GM) muscle, local injection of the myotoxin barium chloride ($BaCl_2$) depolarizes myofibres to initiate proteolysis and disruption of the sarcolemma, which leads to capillary fragmentation and loss of blood flow at 1 day post injury (dpi). While efferocytosis removes cellular debris, basal laminae persist. Endothelial cell sprouts from surviving microvessel fragments appear within 3 dpi, coincident with the onset of myofibre regeneration and the transition from M1 (damage) to M2 (repair) macrophage phenotype. Nascent capillary networks become perfused with blood by 5 dpi, remain disorganized through 10 dpi, and remodel into microvascular units aligned with regenerated myofibres by 21 dpi. Vasomotor tone, vasodilation to acetylcholine, and vasoconstriction to phenylephrine recover over a similar (21-day) time course. In contrast to myotoxin injury, punch biopsy (diameter, 2 mm) of the GM creates subthreshold volumetric muscle loss (VML). The void becomes filled with a primordial matrix infiltrated with immune (CD45+) and fibroadipogenic progenitor (PDGFRα+) cells within 24 hours. At 7 dpi, endothelial cell sprouts project centripetally from the edges of the wound and perfused microvascular networks span the wound by 14 dpi. Myofibres are regenerating at wound edges by 14 dpi and span the wound by 21 dpi; however, microvessels and myofibres remain disorganized. We suggest that, compared to myotoxin injury, the delay in regeneration with angiogenesis preceding myogenesis following VML reflects removal of basal laminae, which may otherwise provide guidance cues that promote and coordinate regeneration and reorganization of microvessels with the myofibres that they supply.

030-SS3

Improving vasculoprotective effects of MSCs in coronary microvessels – benefits of 3D culture, sub-populations and heparin

Kobkaew Bumroongthai [1], Dean Kavanagh [1], Paul Genever [2], Neena Kalia [1]

[1] *Institute of Cardiovascular Sciences, University of Birmingham*
[2] *Department of Biology, University of York*

Aims: Treatment of myocardial infarction (MI) focuses on rapidly re-establishing reperfusion following blockage in one or more coronary arteries. However, despite successfully opening occluded coronary arteries using interventions such as stents, a significant number of patients still subsequently proceed to develop muscle damage and heart failure. This is partly due to reperfusion paradoxically leading to damage of the delicate coronary microvessels through a process called myocardial ischaemia-reperfusion (IR) injury. Although mesenchymal stromal cells (MSCs) have the potential to limit this injury, clinical success remains limited. This may be due to (i) poor MSC homing to the heart (ii) infused MSCs, even if derived from the same site, being a heterogeneous population with varying therapeutic efficacy and (iii) conventional 2D culture of MSCs decreasing their homing and beneficial properties. This study investigated whether 3D culture of two distinctly different bone marrow (BM)-derived MSC sub-populations could improve their homing and coronary vasculoprotective efficacy.

Methods: Two clonally-derived human BM-MSC lines, namely CD317neg MSCs-Y201 and CD317pos MSCs-Y202, were cultured using conventional monolayer and 3D hanging drop methods. Intravital imaging of the anaesthetised mouse beating heart was used to investigate the trafficking and microvascular protective effects of these MSC sub-populations in the coronary microcirculation in vivo. The mouse beating heart was prepared for intravital imaging as previously described [1-2]. Myocardial IR injury was performed by temporarily ligating the LAD artery for 45 minutes. The ability of 3D culture to change MSC homing and their subsequent coronary recruitment, neutrophil and platelet adhesion as well as functional capillary density (FCD) in IR injured mouse hearts was assessed intravitally.

Results: 3D culture consistently improved the adhesive behaviour of MSCs-Y201 to various substrates in vitro and both MSCs-Y201 and MSCs-Y202 to coronary capillaries in vivo. However, only 3D cultured MSCs-Y201 reduced neutrophil recruitment within the IR injured heart in vivo. Since 3D cultured MSCs-Y201 did not reduce platelet microthrombus formation in the injured heart, they were delivered as a dual therapy combined with heparin. This maintained their anti-neutrophil effect but also conferred an anti-platelet effect which resulted in improved ventricular FCD and perfusion. Consequently, this dual therapy led to the greatest salvage of viable myocardium and the smallest infarct size. Therapeutic benefit could mechanistically be explained by reductions in coronary endothelial oxidative stress and ICAM-1/VCAM-1 expression and also by 3D cultured MSCs-Y201

being the most potent sub-population at reducing serum levels of several pro-inflammatory cytokines.
Conclusion: Protecting coronary microvessels in the immediate aftermath of a heart attack could maximise salvage of viable myocardium. This could potentially be achieved with cellular therapy using BM-derived MSCs. However, clinical success using MSCs has remained elusive. This novel study highlights the importance of not only 3D culture, but also of a specific and more superior CD317neg MSC sub-population, as being critical to realising their full coronary vasculoprotective potential in the injured heart. Since the smallest coronary blood vessels are increasingly recognised as a primary target of reperfusion injury, therapeutic interventions must be able to protect these delicate structures and maintain adequate perfusion in the heart. MSCs are potentially powerful therapeutic cells. Hence, their clinical use should not be disregarded particularly if their translational benefit could be improved by relatively feasible technical modifications.

030-SS4

Regulation of Photomodulation in Angiogenesis

Jianbo Wu [1]
[1] *Southwest Medical University*

Novel therapeutic methods increase neovascularization in ischemic tissue. Experimental studies revealed that adipose-derived stem cells (ASCs) therapies are emerging as a promising approach to therapeutic angiogenesis. However, the delivery of stem cells remains a critical hurdle for the clinical translation in current approaches. Our study demonstrated that mass spectrometry revealed that light-treated ASCs conditioned medium retained a more complete pro-angiogenic activity with significant upregulation of angiogenesis related proteins. Light-activated ASCs-Exos can promote angiogenesis via miR-3572-5p-mediated targeting of ELVAL1. Photoactivated-ASCs increased functional blood flow perfusion and neovascularization in a murine ischemia hindlimb model. These results suggest that light activation is an effective method for generating the functionality of ASCs-Exos, and miR-3572-5p could be a potential therapeutic target for angiogenesis.

SYMPOSIUM 31

Cerebral Microvascular Injury and Pharmacological Intervention

10:00-11:30 | Room 1

031-SS1

Cerebral micro-blood vessels were changed in neuronal degenerative diseases

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The patients of neuronal degenerative diseases such as Alzheimer's disease, Parkinson disease and so on are more and more with the aging in China and also in most countries in the world. However, the etiology of these diseases is unclear till now. The proteins of beta-amyloid, tau phosphorylation and Louie's body were known highly related with above diseases. Recently it was found that the blood supply is also an important factor in development of during neurodegenerative diseases. In the present study we investigated the cerebral micro-blood vessels changed in aging and AD and PD transgenic animal models using the fMOST techniques. The APP/PS1 mice of aged 4, 7 and 12 month as well as A53T mice of aged 12 month were used in this study. The micro blood vessels were marked with the LEL-dylight 561/637. The 3D high resolution (0.35x0.35x1.0 μm) whole brain images were generated and analyzed by using the Imaris, Amira and TD Polygon and so on. The results showed that in APP/PS1 mice the volumes of hippocampus and cortex were significant reduced with the aging. The density, length and diameter of the blood vessels were also marked decreased in these cerebral regions. The PD animals were also seen the micro blood vessels changed in various brain regions during the disease developing.
Conclusion: It indicated that in neuronal degenerative diseases normally with aging, the cerebral blood vessels changed very often, it might be an important factor to aggravate the disease process of AD and PD. Therefore, to improve the cerebral blood supply will be important in treatment of neuronal degenerative diseases.
Keywords: neurodegenerative diseases, AD, PD, cerebral blood vessels, micro-structure image.

031-SS2

Pharmacological target of neurovascular unit in cerebrovascular disease

Feng Han [1]
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Neurovascular unit is a new breakthrough in the study of the mechanism of severe brain disease, and it will also promote clinical translational research. Brain neurovascular unit must be fully taken into account as a functional ensemble in the clinical pathological process for its cross-cell communication mechanism and related pathological molecular events of brain diseases, which is essential for the identification of biomarkers and therapeutic drug targets. In order to elucidate the role of neurovascular units in the pathogenesis, development and prognosis of diseases, we need to explore the precise regulation of endothelium injury and cerebral microcirculation with new techniques and methods. On the basis of neurovascular unit research, we are trying to examine the pathological process of brain diseases, identify effective drug therapeutic targets, screen candidate drugs and develop new physical intervention technologies, it will provide solutions for the early diagnosis and clinical treatment of severe brain diseases.

031-SS3

Mineralocorticoid Receptor Antagonists as Therapeutic Strategies for Vascular Cognitive Impairment

Laura Chambers [1], Janice Diaz-Otero [1], Anne Dorrance [1]
[1] *Michigan State University*

Strong evidence links the development of midlife hypertension to cognitive decline later in life. This connection is thought to result from impaired vascular function and chronic cerebral hypoperfusion. Elevated plasma aldosterone has been linked to essential hypertension, and mineralocorticoid receptor (MR) antagonists have beneficial effects on vascular function even when aldosterone levels are not markedly elevated. We have shown that MR antagonists can prevent cerebrovascular injury associated with hypertension development. Still, it is unclear if these beneficial effects are sustained when treatment begins after the onset of hypertension, as would be the case when hypertensive humans are treated. To assess this, adult (20-22-week-old) male stroke-prone spontaneously hypertensive rats (SHRSP) were treated with the MR antagonist eplerenone (EPL; 100 mg/kg daily) or vehicle for four weeks and compared to age-matched normotensive Sprague-Dawley rats. Endothelium-dependent dilation was impaired in the cerebral parenchymal arterioles from SHRSP, and MR antagonism improved this without affecting myogenic tone. Impairments in PA dilation in SHRSP were associated with cognitive decline, microglial activation, reactive astrogliosis, and increased mRNA expression of neuroinflammation markers. The cognitive and inflammatory changes were improved with MR blockade. These data advance our understanding of the effects of hypertension on cerebral arterioles using a clinically relevant model and treatment paradigm. Our studies suggest that the MR is a potential therapeutic target to improve cerebrovascular function and cognition during hypertension.

031-YS1

Ameliorative Effects of YangXueQingNao Wan, a compound Chinese Medicine, on Cerebral Microcirculation Disturbance in Diabetic Mice

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Background and Purpose: Diabetes mellitus (DM) is a severe metabolic disease with significant complications involving multiple organs. Diabetes-related cerebral microvascular dysfunction and the blood-brain barrier (BBB) disruption are reported to be closely associated with neurological complications in the central nervous system. YangXueQingNao Wan (YXQNW) is a compound Chinese medicine widely used in China to deal with cerebrovascular diseases, such as dizziness, headache or vertigo. However, it is unknown whether YXQNW is favorable for diabetes-induced cerebral microcirculatory disturbance and BBB damage. This study was designed to investigate the ameliorating effect of YXQNW on cerebral microcirculatory disturbance and BBB disruption in db/db diabetic mice.
Methods: In this study, male db/db mice were treated with YXQNW daily by gavage for 4 weeks. Blood glucose was measured every week. We tested the effects of YXQNW on microvascular permeability, reactive oxygen species and mitochondrial complex activity in diabetic mice.
Results: Compared to the control group, diabetic mice showed higher blood glucose, increased FITC-dextran leakage, decreased cerebral blood flow (CBF), decreased expression of junction proteins claudin-5, occludin, zonula occludens-1 (ZO-1) and vascular endothelial cadherin (VE-cadherein), increased expression of caveolin-1, suppressed activities of mitochondrial respiratory chain complexes, and increased malondialdehyde. All of the above parameters were ameliorated by YXQNW treatment except blood glucose.
Conclusion: This study indicates YXQNW as a potential regime to attenuate diabetes-related cerebral microangiopathy, which involves inhibiting oxidative stress, attenuating cerebral microvascular hyperpermeability and protecting the integrity of the BBB.

SYMPOSIUM 32

Adaptations in Pregnancy in Health and Disease

10:00-11:30 | Room 2

032-SS1

Preeclampsia and the maternal brain

Marilyn Cipolla
University of Vermont, USA

032-SS2

Microvascular significance in the newborn; an evolving paradigm

Ian Wright [1,2], Yvonne Eiby [1]
[1] *The University of Queensland* [2] *James Cook University*

Cardiovascular support for preterm infants has focused on the heart and major vessels but our research demonstrates the critical role of the immature microvasculature. Preterm infants are at risk of cardiovascular deterioration on the first day after birth and this is a major contributor to their high rates of adverse neurodevelopmental outcome. Current interventions to support preterm cardiovascular function such as blood volume expansion or administration of inotropes are based on adult physiology and do not effectively improve brain outcomes. However, these remain the mainstay of clinical practice as no effective alternatives are available. An understanding of the unique cardiovascular physiology of preterm infants is essential to the development of effective interventions.
We use an established pre-clinical model, the preterm piglet model of intensive care, to test why current interventions have failed and to develop novel strategies. These new insights highlight the critical role of the microvasculature - immature capillaries are excessively leaky and whole plasma is rapidly lost from the circulation after birth. Preterm newborns also have a limited capacity to vasoconstrict and the preterm heart is unable to maintain cardiac output in the face of these low preload conditions. This functional hypovolemia cannot be detected nor treated under standard care practices. In parallel, we are also currently examining pathways for fluid loss from the circulation using electron microscopy and undertaking the first ever studies of lymphatic function in preterm newborns. We have developed a new method for measuring blood volume in preterm newborns to facilitate the development and testing of several novel therapeutic strategies to provide effective cardiovascular support.
This shift away from the role of the heart and major vessels to the critical importance of the microvasculature provides immense opportunities for research that is generating novel therapeutic strategies to support blood volume and prevent cardiovascular deterioration in this vulnerable population.

032-SS3

Uterine vascular RAGE in gestational diabetes

Timothy Murphy [1], Sandra Lowe [2], Stephen Horrowitz [2], Leo Leader [2],

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Gestational diabetes (GD) is an increasingly prevalent complication of pregnancy which alters foetal growth patterns and increases the likelihood of future metabolic disease. Many of the health impacts of GD may arise from impaired uterine and placental vascular function, including impaired blood flow and increased capillary permeability (1). The hyperglycemia characteristic of GD results in the excessive plasma accumulation of advanced glycated end-products (AGE) and increased activity of their receptor, RAGE. This study examined the expression of RAGE and AGE-binding proteins, and effects of AGE on funtcional responses in myometrial and omental arteries from women with normoglycemic pregnancies and gestational diabetes.

Pieces of myometrium and omentum were collected from consenting normoglycemic (NG) women and others with GD (fasting glucose >8 mmol/L) and small arteries (internal diameter ~200 µm) dissected free. RAGE, AGER-1, NLRP3 and galectin-3 mRNA and protein expression was investigated using rt-qPCR and immunofluorescence (IF), respectively. Functional studies examining the effects of AGEs on the arteries were performed using pressure myography. Arteries were pre-constricted with vasopressin (1-10 nM) and endothelium-dependent responses examined using bradykinin. AGE were generated by incubating human serum albumin (10 mg/ml) with methylglyoxal (9 mM) in phosphate-buffered saline for 4 days at 37°C.

In myometrial arteries from GD women (n = 8), the mRNA expression of RAGE, AGER-1, NLRP3 and galectin-3 was not significantly changed compared with those from NG women (n = 9). IF studies suggested RAGE protein expression was increased in both smooth muscle and the endothelium of myometrial and omental arteries of GD women, while galectin-3 protein expression was also increased in the smooth muscle and endothelium of omental arteries only. Functional studies demonstrated that AGEs (0.1mg/ml) inhibited endothelium-dependent, bradykinin-induced dilation of myometrial arteries from GD women (bradykinin pEC_{50} 6.57 ± 0.08) compared with NT women (7.30 ± 0.16; n = 4 for each, P<0.05). AGEs also caused a slowly-developing contraction of the myometrial arteries. Preliminary studies (n=1) suggest the RAGE antagonist FPS-ZM1 (1 µM) prevented this effect of AGEs.

These observations imply AGEs inhibit endothelium-dependent hyperpolarization of the myometrial arteries, as nitric oxide/prostanoid-mediated dilation in these vessels was abolished in established GD (2). Combined with the effects of AGEs alone on vascular tone, AGEs may interact with RAGE to impair uterine blood flow in GD.

032-YS1

Cholesterol depletion alters human myometrial artery compliance in normal pregnancy, but not preeclampsia

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Introduction: Inappropriate remodelling of the uterine arteries in response to pregnancy occurs in preeclampsia (PE), and is associated with compromised uteroplacental tissue perfusion and placental blood flow in multiple vascular beds. This study determined the characteristics of uterine myometrial radial arteries in normotensive (NT) and preeclampsia (PE) patients. The effects of arterial cholesterol depletion on vessel characteristics vary, which likely reflect tissue type and specific function, disease and experimental state.

Aims: This study determines the effect of cholesterol modulating drugs pravastatin and methyl-β-cyclodextrin (MβCD) in vitro on indicators of uterine microvascular remodelling and compliance, as well as the comparative effects on vessels from healthy NT pregnancy and the PE disease state.

Methods: Myometrial radial arteries (those that immediately precede the spiral arterioles) from caesarean-section NT and PE patients were incubated with pravastatin (2 mM/6h) or MβCD (10 mM/1h) in vitro. Internal (ID) and external diameter (OD) were obtained for arteries over a 5-120 mmHg pressure range under passive (zero [Ca2+] conditions); and metrics which characterized vessel structure and function were subsequently derived. Transmission electron microscopy was performed to determine gross vessel morphology including circumferential internal elastic lamina (IEL) length (µm), and the number of smooth muscle cell (SMC) layers at 4 randomly determined areas ~90o apart for each 'n'. Functional data were analysed via two-way ANOVA with Sidak's post-hoc comparison to assess significance; and anatomical data analysed via one-way ANOVA with Tukey's post-hoc comparison. P<0.05 taken as significant.

Results: In PE (n=9), changes in vessel stress correlated with lower vessel strain compared to NT (n=12), indicating increased stiffness (P<0.05). Increased wall thickness (WTk) and WTk to lumen ratio (WTk: ID) to increased intralumenal pressure was seen in PE, compared to NT at all pressures examined (P<0.05). PE vessels displayed no difference in ID relative to intralumenal pressures, compared to NT (P>0.05). NT vessels incubated with the cholesterol depleting agent MβCD (n=10) exhibited decreased passive distensibility (P<0.05), compared to NT untreated. Vascular WTk (P<0.05) and WTk: ID (P<0.05) relative to pressure were reduced in NT following MβCD incubation. MβCD incubation of NT vessels displayed increased ID at 5 mmHg (68.8 ± 6.2µm from untreated levels 44.3 ± 8.1µm; P<0.05). In PE neither pravastatin (n=5) nor MβCD (n=6) incubation altered stress-strain relationships (P>0.05), ID (P>0.05), mean vascular WTk (P>0.05) or WTk: ID (P>0.05) compared to untreated tissues. Gross morphological examination of myometrial radial artery cross-sections revealed PE and NT vessels contain a similar number of SMC layers (4.3 ± 0.2; n=4; 3.8 ± 0.3; n=4, PE and NT, respectively; P>0.05). IEL measurements allowed for calculation of unpressurised vessel diameter, being comparable between NT (89.5 ± 14.2µm; n=4) and PE (82.6 ± 8.7µm; n=4) (P>0.05). Dense collagen layers were present between each SMC layer as well as at the adventitial surface.

Discussion: Data show that treatment of healthy NT human myometrial radial arteries with cholesterol depleting MβCD can negatively impact vessel compliance, an effect which is not seen in already less compliant vessels from PE pregnancy with either MβCD or pravastatin cholesterol removal. Data suggest a potential link between cholesterol dysregulation and reduced vessel compliance in PE. Human uterine radial arteries have an atypical structure, as compared to 'standard' resistance vessels in which collagen is absent between SMC layers.

SYMPOSIUM 33

Microcirculation and Cardiovascular Diseases

10:00-11:30 | Room 4

033-SS1

Regulatory role of non-coding RNAs on microcirculation in myocardial infarction

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Rationale: Ca^{2+} homeostasis-a critical determinant of cardiac contractile function-is critically regulated by SERCA2a (sarcoplasmic reticulum Ca^{2+}-ATPase 2a). Our previous study has identified ZFAS1 as a new lncRNA biomarker of acute myocardial infarction (MI).

Objective: To investigate the effects of ZFAS1 on SERCA2a, as well as explore the interplay between Ca2+ homeostasis, cardiac contractile function, and microcirculation in the setting of MI.

Methods and results: ZFAS1 expression was robustly increased in cytoplasm and sarcoplasmic reticulum in a mouse model of MI and a cellular model of hypoxia. Knockdown of endogenous ZFAS1 by virus-mediated silencing shRNA partially abrogated the ischemia-induced contractile dysfunction. Overexpression of ZFAS1 in otherwise normal mice created similar impairment of cardiac function as that observed in MI mice. Moreover, at the cellular level, ZFAS1 overexpression weakened the contractility of cardiac muscles. At the subcellular level, ZFAS1 deleteriously altered the Ca^{2+} transient leading to intracellular Ca^{2+} overload in cardiomyocytes. At the molecular level, ZFAS1 was found to directly bind SERCA2a protein and to limit its activity, as well as to repress its expression. The effects of ZFAS1 were readily reversible on knockdown of this lncRNA. Notably, a sequence domain of ZFAS1 gene that is conserved across species mimicked the effects of the full-length ZFAS1. Mutation of this domain or application of an antisense fragment to this conserved region efficiently canceled out the deleterious actions of ZFAS1. ZFAS1 had no significant effects on other Ca^{2+}-handling regulatory proteins.

Conclusions: ZFAS1 is an endogenous SERCA2a inhibitor, acting by binding to SERCA2a protein to limit its intracellular level and inhibit its activity, and a contributor to the impairment of cardiac contractile function and microcirculation in MI. Therefore, anti-ZFAS1 might be considered as a new therapeutic strategy for preserving SERCA2a activity and cardiac function under pathological conditions of the heart.

033-SS2

The role and mechanism of non-coding RNAs in cardiac remodeling

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Purpose Cardiac remodeling leads to changes in the structure and function of the heart and is the primary risk factor for heart failure. Non-coding RNAs, including lnRNAs and microRNAs, have various biological functions, and their vital role in the regulation of cardiac remodeling still needs to be explored. The aim of this study was to evaluate the regulatory role of LncRNAs in cardiac remodeling and elucidate its molecular mechanism.

Methods The cardiac remodeling model was induced by MI and TAC surgery. The adeno-associated virus vector AAV9-Plscr4 and AAV9-miR-26a was injected through the tail vein, the mouse heart function was detected by echocardiography after 4 weeks. Apoptosis and mitochondrial membrane potential was evaluated by TUNEL and JC-1 staining. The degree of myocardial fibrosis was evaluated by HE and Masson staining, and myocardial hypertrophy was evaluated by WGA staining. At the cellular level, AngII and H_2O_2 was used to induce hypertrophy and apoptosis of primary cardiomyocytes. Western blot, qRT-PCR and immunofluorescence staining were used to detect the changes of myocardial hypertrophy and apoptosis.

Results We demonstrated that lncRNA Plscr4 was upregulated in hypertrophic mice hearts and in Ang II–treated cardiomyocytes. Overexpression of Plscr4 attenuated TAC-induced cardiac hypertrophy. Conversely, the inhibition of Plscr4 gave rise to cardiomyocyte hypertrophy. Finally, we demonstrated that Plscr4 acted as an endogenous sponge of miR-214 and forced expression of Plscr4 downregulated miR214 expression to promote Mfn2 and attenuate hypertrophy. Moreover, we found the downregulation of miR-26a both in the heart of MI mice and in H2O2-treated cardiomyocytes. Forced expression of miR-26a protected against MI-induced cardiac injury and attenuated cardiac apoptosis. Further studies showed that miR-26a inhibited apoptosis through regulation of Bak1. Furthermore, MIRF decreased ATP content and MMP through regulating miR-26a, which then promoted the cardiomyocyte apoptosis.

Collectively, these findings identify lncRNA Plscr4 and MIRF as a regulator of cardiac hypertrophy and cardiomyocyte apoptosis in vivo and in vitro, suggesting that lncRNA Plscr4 and MIRF might act as a therapeutic target for the treatment of cardiac remodeling.

033-YS1

Cardiotonic Pills, a traditional Chinese medicine, ameliorates isoproterenol-induced cardiac injury and fibrosis via regulating myocardial metabolism

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Cardiotonic Pills (CP), a compound Chinese medicine with good efficacy in treating coronary angina pectoris, has passed phase II, and is undergoing phase III clinical trials for treatment of ischemic cardiovascular disease by the US FDA. However, there is little data regarding the beneficial role of CP in isoproterenol (ISO)-induced cardiac injury. The present study aimed to evaluate the effect of CP and the contributions of its major components on ISO-induced cardiac injury, and to explore the underlying mechanism. Male Sprague-Dawley rats received subcutaneous injection of ISO saline solution at 24 h intervals for the inchoate 3 consecutive days and then at 48 h intervals for the later 4 to 15 days. Along with ISO, rats were gavaged with CP, salvia miltiorrhiza (SM), panax notoginseng (PN), and their respective main active monomers DLA (3, 4-dihydroxyphenyl lactic acid) and notoginsenoside Rg1 for 15 consecutive days. CP obviously improved ISO-induced low survival rate, attenuated ISO-evoked cardiac injury and myocardial fibrosis, as evidenced by heart function and morphological reservation. SM, PN and their active monomers DLA and Rg1 administration exhibited similar effects as CP but to a lesser extent. Quantitative proteomics revealed that the cardioprotective effect of CP relied on the regulation of metabolic pathways, including glycolipid and energy metabolism. CP inhibited the enhancement of glycolysis, promoted fatty acid oxidation, and restored mitochondrial oxidative phosphorylation by regulating Eno1, Mcee, Bdh1, Ces1c, Apoc2, Decr1, Acaa2, Cbr4, ND2, Cox6a, Cox17, ATP5g, and ATP5j. Further proteomics and Western blotting results verified that as same as CP, DLA and Rg1 both upregulated the decline of Cox 6a and Cox17. Besides, DLA showed more effective in regulating glycolipid metabolism, manifested as its modulation on BDH1 and Cbr4, while Rg1 could specifically enhance ATP5g and ATP5j, suggesting Rg1 has more advantages for ATP synthesis. In conclusion, DLA and Rg1 could improve myocardial metabolism after ISO from different aspects. As the combination of DLA and Rg1, CP exerted a more potent cardioprotective effect than any of its components on ISO-evoked cardiac injury.

033-YS2

The Effect and Mechanism of QishenYiQi and its Effective Ingredients on Pressure Overload-induced Myocardial Fibrosis

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Purpose: Heart failure (HF) is a leading cause of morbidity and mortality worldwide, and it is characterized by cardiac hypertrophy and fibrosis. However, effective treatments are not available to block cardiac fibrosis after cardiac hypertrophy. The QiShenYiQi pill (QSYQ) is an effective treatment for chronic HF. However, the underlying mechanism remains unclear.
Methods: In the present study, a pressure overload-induced cardiac hypertrophy model was established in rats by inducing ascending aortic stenosis for 4 weeks. QSYQ was administered for 6 weeks, and its effects on cardiac fibrosis, myocardial apoptosis, RP S19 release, macrophage polarization, TGF-β1 production, and TGF-β1/Smad signaling were analyzed. In vitro studies using H9C2, Raw264.7, and RDF cell models were performed to confirm the in vivo study findings and evaluate the contribution to the observed effects of the main ingredients of QSYQ, namely, astragaloside IV (ASIV), notoginsenoside R1, 3,4-dihydroxyl-phenyl lactic acid (DLA), and Dalbergia odorifera T. C. Chen oil (DO). The role of four-and-a-half LIM domains protein 2 (FHL2) in cardiac fibrosis and QSYQ's effects were assessed by small interfering RNAs (siRNAs).
Results: QSYQ ameliorated cardiac fibrosis after pressure overload-induced cardiac hypertrophy and attenuated cardiomyocyte apoptosis, low FHL2 expression, and TGF-β1 release by the injured myocardium. QSYQ also inhibited the following: release of RP S19 from the injured myocardium, activation of C5a receptors in monocytes, polarization of macrophages, and release of TGF-β1. Moreover, QSYQ downregulated TGF-βR-II expression induced by TGF-β1 in fibroblasts and inhibited Smad protein activation and collagen release and deposition.
Conclusion: The results showed that QSYQ inhibited myocardial fibrosis after pressure overload, which was mediated by RP S19-TGF-β1 signaling and decreased FHL2, thus providing support for QSYQ as a promising therapy for blocking myocardial fibrosis.

SYMPOSIUM 34

Novel Treatment Targets for Brain Disorders

10:00-11:30 | Room 5

034-SS1

Neurovascular unit and Stroke: metabolic response of astroglia

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Normal brain function is dependent on microcirculation which provides continuous supply of glucose and oxygen, indispensable energy substrates. In addition to brain microvessels and neurons, glial cells play pivotal roles in the regulation of brain microcirculation and metabolism. Astroglia are one of the three types of glial cells in the brain: astroglia (astrocytes), oligodendroglia (oligodendrocytes), and microglia. Astroglia are the most abundant cells in the human brain and outnumber neurons by a factor of 1.4 in the human cerebral cortex. In addition, their unique anatomical location, which is interposed between neurons and cerebral microvessels and was depicted more than 100 years ago in a sketch by a legendary neuropathologist, Santiago Ramón y Cajal, has been attracting the attention of many neuroscientists. Neurons, microvessels, and astroglia form the "neurovascular unit (NVU)", a conceptual framework that was originally used to better understand the pathophysiology of cerebral ischemia. Now, the NVU is a tool that can be used to understand normal brain physiology as well as the pathophysiology of numerous neurological disorders. Therefore, NVU could be a prime target of brain disorders like ischemia, demyelination, neuroinflammation, or neurodegeneration. In fact, the metabolic responses of astroglia in the NVU can be either protective or deleterious. This review focuses on three major metabolic compartments: (i) glucose and lactate; (ii) fatty acid and ketone bodies; and (iii) D- and L-serine. Both the beneficial and the detrimental roles of compartmentalization between neurons and astroglia will be discussed. A better understanding of the astroglial metabolic response in the NVU is expected to lead to the development of novel therapeutic strategies for diverse neurological diseases.

034-SS2

Neurovascular unit in multiple sclerosis: New gateway to disease modification?

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system affecting millions of young adults across the globe. Neurodegeneration and consequent brain atrophy are increasingly recognized as a key driver for the progressive nature of MS. While precise mechanisms underlying neurodegeneration in MS remain elusive, oxidative stress induced by inflammation and neuroinflammation, exacerbated by iron depositions, causes serious mitochondrial injury in axons, leading to "virtual hypoxia" of MS lesions. In this talk, I will review reported roles of neurovascular unit (NVU) in MS pathophyisiology in a hope that these dots become lines to open a new gateway to disease modification in the future.

034-YS1

Alzheimer's Disease and Glymphatic System

Itsuki Hasegawa [1]

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Amyloid β protein (Aβ) is a 40/42 amino acid peptide, and abnormal accumulation of Aβ in the brain parenchyma is associated with the development of Alzheimer's disease. Pathways by which Aβ is excreted include transcytosis through the blood brain barrier, degradation by Aβ-degrading enzymes from neurons and by microglia, and excretion

through the glymphatic system, but the details are not yet known. Disposition of Aβ into the perivascular space of the cerebral cortex has been recently suggested as a major source of its clearance, and its disturbance may be involved in the pathogenesis of cerebral amyloid angiopathy and Alzheimer's disease.

The glymphatic system has been proposed as one of the factors affecting clearance. In the first report in 2012, it had already been shown that perfusion of the glymphatic system is reduced in aquaporin4 (AQP4) channel knockout mice and that Aβ injected into the brain parenchyma and cisterna magna is distributed in the perivascular space and its excretion is delayed in AQP4 knockout mice. It has already been reported that concentrations of Aβ and tau in the cerebrospinal fluid are higher during wakefulness and change to the lowest level during sleep. It has been pointed out that the glymphatic system may be involved in the clearance of this old excretory product during sleep.

In the future, this system may become a potential therapeutic target for various proteinopathies, including Alzheimer's disease. Although anti Aβ antibody drugs are about to enter clinical use, it is difficult to achieve a complete therapeutic effect by themselves. Therapeutic targeting of the clearance of abnormal proteins may allow for nonselective elimination. There are also reports indicating that intrathecal administration of drugs results in drug efflux in the awake state, which may contribute to the determination of administration methods that take into account drug distribution to the brain.

Recently, we conducted experiments based on the hypothesis that amyloid-β behaves differently in the perivascular space depending on its degree of polymerization. We explored the *in vivo* dynamics of Aβ in the perivascular space of anesthetized mice. Live images were obtained with two-photon microscopy through a closed cranial window. Either fluorescent dye-labeled Aβ oligomers prepared freshly or Aβ fibrils after 6 days of incubation at 37 °C were placed over the cerebral cortex. Accumulation of Aβ was observed in the localized perivascular space of the penetrating arteries and veins. Transportation of the accumulated Aβ along the vessels was slow and associated with changes in shape. Aβ oligomers were transported smoothly and separately, whereas Aβ fibrils formed a mass and moved slowly. Parenchymal accumulation of Aβ oligomers, as well as Aβ fibrils along capillaries, increased gradually. In conclusion, Aβ placed on the cortical surface was slowly transported to the deeper parenchyma through the perivascular space. Loose polymerization may affect the speed of its transportation

In this symposium, we will present the association between the glymphatic system and Alzheimer's disease, with our report on the differences in the behavior of oligomers and polymers in the perivascular space.

034-YS2

Post-Sepsis Microcirculatory Dysfunction Alleviation by Drag-Reducing Polymers

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Introduction: Sepsis and septic shock in multiorgan dysfunction syndrome (MODS) are characterized by inflammation, coagulopathy, and vascular collapse with microvascular endothelial dysfunction, the leading cause of in-hospital mortality. Novel approaches are needed to prevent the consequences of sepsis. We showed that nanomolar concentrations of intravascular blood soluble drag-reducing polymers (DRPs) significantly improved microvascular perfusion and tissue oxygenation and protected neurons in a rat brain suffering traumatic brain injury and hemorrhagic shock. DRPs reduce blood flow microvortices at vessel bifurcations resulting in a reduction in the pressure gradient across arterioles, thereby increasing precapillary pressure and the number of erythrocytes entering capillaries, decreasing capillary stasis and increasing tissue oxygenation. We hypothesized that DRPs alleviate panvascular dysregulation of microvascular blood flow in sepsis and MODS and tested the hypothesis in a C57BL/6J mouse model of lipopolysaccharide (LPS)-induced sepsis.

Methods: In-vivo 2-photon laser scanning microscopy (2PLSM) was used to monitor cerebral (parietal cortex) and peripheral (ear) microcirculation and blood-brain barrier (BBB) permeability (i.v. fluorescein isothiocyanate dextran), mitochondrial respiration and brain tissue oxygen supply (nicotinamide adenine dinucleotide autofluorescence, NADH), and oxidative stress (i.v. Hydroethidine, HE, 1 mg/kg) at a baseline and during 4 hours after septic shock induction. After baseline imaging, LPS (Salmonella Thyphosa, 10 mg/kg) was administered to induce acute sepsis. DRPs (5 ppm or saline were i.v. injected. Statistical analyses were done using GraphPad Prism by Student's t-test or Kolmogorov-Smirnov test where appropriate. Differences between groups were determined using a two-way analysis of variance (ANOVA) for multiple comparisons with post hoc testing. The statistical significance was set at $p<0.05$.

Results: LPS-induced sepsis substantially impaired cerebral and peripheral microcirculation without difference between groups. The number of functioning capillaries decreased from 1009±51 and 955±48 per mm3 at a baseline to 627±49 and 638±52 per mm3 in the brain cortex and ear skin, respectively ($p<0.05$). Capillary red blood cell flow velocity fell from 1.3±0.18 and 1.21±0.19 mm/s to 0.81±0.19 and 0.86±0.2 in the brain and skin, respectively ($p<0.05$). The microcirculatory impairment reduced tissue oxygen supply inversely reflected by an increase in NADH (1.13±0.04 and 1.16±0.05 normalized units in the brain and ear, respectively, $p<0.05$). Cerebral and peripheral ischemia was associated with increased oxidative stress; the number of Het-positive cells per 0.075 mm3 increased from ~0 to 44.5±9.7 and 45.3±10.2 in the brain and skin, respectively, $p<0.05$. DRPs alleviated microthrombosis formation, microvascular dysfunction, tissue hypoxia, and oxidative stress in the brain and peripheral tissue compared to saline ($p<0.05$). By the end of the monitoring period, the number of functioning capillaries further decreased to 431±41 and 439±44 per mm3 in the saline group and increased to 782±68 and 699±52 per mm3 in the DRPs group in the brain and skin, respectively ($p<0.05$). Capillary blood flow velocity fell to 0.57±0.18 and 0.62±0.19 mm/s in the saline group and increased to 1.01±0.21 and 0.96±0.19 mm/s in the DRPs group in the brain and skin, respectively ($p<0.05$). In the saline group, degradation of microcirculation led to an increase in tissue hypoxia (1.22±0.06 and 1.28±0.07 normalized units in the brain and ear, respectively, $p<0.05$) and oxidative stress (119±14 and 121±16 Het-positive cells per 0.075 mm3 in the brain and ear, respectively, $p<0.05$). In the DRP group, in contrast, microcirculation improvement partially restored tissue oxygen supply (1.05±0.03 and 1.1±0.04 normalized units in the brain and skin, respectively, $p<0.05$) mitigating oxidative stress (89±12 and 91±14 Het-positive cells per 0.075 mm3 in the brain and skin, respectively, $p<0.05$).

Conclusions: DRPs effectively improved cerebral and peripheral microcirculation, reducing microthrombosis, microvascular dysfunction, tissue hypoxia, and oxidative stress in sepsis.

SYMPOSIUM 35

Vascular and Intravascular Components of Microcirculation in Norm and Disease

15:00-16:30 | Room 1

035-SS1

Vascular aging in health and disease: consequences for Nrf2 redox signalling

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Vascular dysfunction contributes to age-related cardio- and cerebrovascular diseases including cognitive decline, dementia, heart failure and atherosclerosis. Maintenance of vascular health function through dietary and lifestyle interventions reduces the incidence and severity of these age-related diseases through enhancing resilience against cellular dysfunction and senescence. The pathobiology of brain ageing includes neurovascular inflammation and blood-brain barrier disruption arising from enhanced oxidative stress and impaired endogenous antioxidant defences. Nrf2 (Nuclear factor erythroid 2-related factor 2) is the master regulator of redox homeostasis and controls the transcription of a panel of antioxidative and anti-inflammatory genes. Aging is associated with perturbations in regulation of the Nrf2 pathway, and increasing evidence demonstrates the role of Nrf2 in mitigating brain and heart ageing processes leading to dementia and cardiac conditions. Studies on models of cognitive decline and neurodegeneration have shown that targeting Nrf2 can restore endothelial function and preserve blood-brain barrier integrity, reducing oxidative stress and neurovascular inflammation. We have shown that fluid shear stress and the endothelial glycocalyx play a crucial roles in maintaining Nrf2 activity and antioxidant gene expression. The Nrf2 pathway continues to be an important area of research to identify lifestyle and therapeutic interventions for vascular dysfunction in heart and brain ageing and to promote healthy longevity. Supported by UK Biotechnology and Biological Sciences Research Council, Stavanger University Hospital, Norway and Ageing Research at King's College London.

035-SS2

Structural and functional state of various parts of skin microcirculation at an early stage of hypertension in working-age men

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Study purpose: to conduct a cross-sectional study on the structural and functional characteristics of various parts of skin microcirculation in working-age men with newly diagnosed hypertension (HTN).

Materials and methods: the study included 118 male participants (ages 30 to 60) who were not regularly taking any medicine, had no medical complaints, and subjectively considered themselves healthy at the time of study. All participants underwent a cross-sectional comprehensive medical examination. The following tests were performed: complete blood count, biochemical blood tests, video capillaroscopy (VCS), laser Doppler flowmetry (LDF) and photoplethysmography (PPG) on the left hand fingers, determination of flow-mediated vasodilation of the brachial artery, echocardiography, ultrasound of extracranial and femoral arteries, 24-hour ambulatory blood pressure monitoring (ABPM). According to ABPM data, the participants were divided into two equal groups called a control group(CG) and a hypertension group(HG). There were 59 participants with normal BP in CG, and 59 participants with newly diagnosed HTN in HG.

Results: nailfold VCS of the ring finger revealed no significant differences between the groups at the level of exchange microvessels. According to LDF data, there was no decrease in tissue perfusion and signs of an increase in the activity of endothelial, neurogenic, and myogenic regulation of the tone of precapillary arterioles in the HTN group. According to PPG of the index finger,in contrast to CG,HTN participants had significantly higher values of the following parameters: normalized augmentation index (Alp75) – 3.8% and -5.25% ($p<0.005$), stiffness index (SI) – 7.6 m/s and 7.35 m/s ($p<0.05$), reflection index (RI) – 36.5% and 28.4% ($p<0.005$), respectively.

Discussion: working-age men in the early stage of HTN have neither capillary rarefaction nor an increase in the tone of skin precapillary arterioles. The largest contribution to peripheral vascular resistance in the onset of HTN is most likely made by large muscular arterioles, in which the neurogenic regulation of vascular tone predominates.

035-SS3

Extracellular matrix regulation of vascular homeostasis and disease

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Extracellular matrix (ECM), mainly composed of elastic fibers, various types of collagen, proteoglycans and glycoproteins, is the major component of vascular microenvironment modulating vascular homeostasis. These ECM proteins not only form complex matric structures that contribute to vascular elasticity, tensile strength and integrity, but also directly interact cell surface receptors or extracellular molecules to influence cellular behaviors. Meanwhile, extracellular proteases degrade or cleave ECM proteins contributing to ECM turnover as well as various pathological vascular diseases. Our recent study showed that an extracellular matrix protein, namely cartilage oligomeric matrix protein (COMP), acts as an endogenous allosteric biased modulator of the angiotensin II receptor type 1 (AT1) signaling receptor, and its deficiency results in activation of AT1a-β-arrestin-2 signaling and subsequent exclusive abdominal aortic aneurysm (AAA) formation. And we also revealed basement membrane protein nidogen-2 as a novel endogenous protective ECM protein in blood vessels, which is essential for the maintenance of contractile phenotype in vascular smooth muscle cells (VSMCs) and the inhibition of vascular calcification. We also developed a peptide vaccine against ADAMTS-7 (a disintegrin and metalloproteinase with thrombospondin type 1 motif 7), a metalloprotease degrading COMP, and confirmed its efficacy in alleviating atherosclerosis and postinjury neointima hyperplasia. Therefore, targeting ECM is a pivotal therapeutic strategy for vascular diseases.

035-SS4

The new formula for cell supply in tissues with the help of blood circulation is a fact. Let's talk about the consequences of this Law and Order in the Theory of Microcirculation

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Life is chemistry, life is physics, statics and kinematics, life is cybernetics, computer science and much more. What is life not? That's why physiology is called the mother of all sciences and the physiologist is above all a scientist who has to act between the different sciences. For over a century, circulatory physiologists have focused on their field and developed their own knowledge and rules. It is important to know that in fluid mechanics one cannot simply write the equations as one pleases. There is „law and order" in science, especially in this sense that the laws of nature and the peculiarities of fluid mechanics must be observed in the tissue.

When one writes an equation, that equation belongs only to a specific tissue model and, conversely, to a specific tissue model belongs 100% to a single equation specific to that model. In this context, the Starling equation only applies to interstitials with infinite compliance.
A porous tube like the blood capillary must be calculated correctly by approximating the capillary length slice by slice by “finite elements” to an equivalent circuit diagram. The result is surprising because a) In the closed interstitium the porous capillary automatically finds an equilibrium for different values of blood pressure (P_{CA}-P_{CV}) over the whole capillary b) The pressure at the capillary end PCA, the pressure at the capillary end P_{CV}, the capillary conductance $K_{f\mu}$ and the colloid osmotic pressure difference Δπ=COP give a new relationship for the local flow through the capillary wall $J_{v\mu}$:

$$J_{v\mu}=M_{f\mu}(P_{CA}-P_{CV})+\sum_{j=1}^{N} n_{j\mu}.\Delta\pi_{j\mu}. \quad (1)$$

In this equation, the interstitial hydraulic pressure P_i=IHP is missing because it is derived from the pressure P_{CA} and P_i is not an active parameter. However, Pi is reduced by the amount Δπ by the COP=Δπ. In the state of equilibrium the second summand results to zero, so that the local current $J_{v\mu}$ through the capillary wall is independent of the COP=Δπ:

$$J_{v\mu}=M_{f\mu}(P_{CA}-P_{CV}), \quad (2)$$

$$P_{i\mu}=N_{f\mu}(P_{CA}-P_{CV})-\Delta\pi. \quad (3)$$

The colloid osmotic pressure of the blood COP does not appear in the tissues as an opponent of the blood pressure, rather the COP supports the supply of the cells. In the lungs, COP enables respiration; in the whole body, the COP effect against the development of oedema is of extraordinary importance. Since the early days of circulatory physiology 125 years ago, circulatory physiologists have believed that this function of COP is possible because, according to Starling’s equation, COP as an opponent of blood pressure Pc would reduce filtration into the interstitium.
However, COP also enables these effects as an opponent of interstitial fluid pressure (IFP). To understand this, it is first important to understand the situation with IFP. The IFP is a passive parameter and arises from the summative effect of the blood pressure Pc and the COP=(πc-πi), see equation (3). According to the definition
Pressure= Force × Area,
there is no independent force in the interstitium that could cause spontaneous IFP.
In the previous theory of microcirculation, the wrong tissue approximation was used, the wrong equation was calculated, and there was an irrational idea of how interstitial fluid pressure (IFP) arises and how it must be measured. They also used the wrong method to determine CFC. How could one arrive at a correct result in this case? The damage that the Starling teaching has done in 125 years cannot be overlooked.
The Time of the Three-Axis Starling-Landis-Pappenheimer is over!

SYMPOSIUM 36

Integrated Traditional Chinese and Western Medicine for Cerebrovascular Disease

15:00-16:30 | Room 2

036-SS1

Microcirculatory Disturbance in Dementia

Yoshiaki Itoh [1]

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Alzheimer's disease (AD) is the leading cause of dementia around the world. Even though AD is regarded as a neurodegenerative disease, increasing number of reports have suggested vascular involvement in the pathogenesis.
First, many epidemiological studies reported that risk factors for AD included hypertension, dyslipidemia, diabetes, and obesity in addition to genetic factors. These factors are well-known risk factors to atherosclerosis of the vessels. Although relative risk ratios and treatment effects to prevent its occurrence are low compared to cardiovascular diseases, they are mostly significant. In addition, we previously reported that white matter lesion in AD was negatively associated with cognitive function. All these epidemiological and neuroimaging data suggest circulatory disturbance in AD.
Second, disposition of amyloid β protein (Aβ) through cerebral vessels may be impaired in AD, that may trigger pathological cascades of AD (amyloid cascade theory). We previously reported a family of AD, in which deposition of Aβ was not detected with PiB-PET (Shimada et al. Int J Mol Sci. 2020 Jun; 21(12): 4443). Animal model of the same mutation confirmed that oligomer of Aβ is toxic to neurons and may initiate further pathophysiological processes.
Pathways by which Aβ is excreted include 1) transcytosis through the blood brain barrier, 2) degradation by Aβ-degrading enzymes from neurons and by microglia, and 3) excretion through the glymphatic system. Disposition of Aβ into the perivascular space of the cerebral cortex has been recently suggested as a major source of its clearance, and its disturbance may be involved in the pathogenesis of cerebral amyloid angiopathy and Alzheimer's disease. Iliff et al. reported that glymphatic system was impaired aquaporin4 (AQP4) channel knockout mice, showing that clearance of Aβ injected into the brain parenchyma and cisterna magna was delayed in AQP4 knockout mice.
Recently, we conducted experiments based on the hypothesis that amyloid-β behaves differently in the perivascular space depending on its degree of polymerization (Hasegawa et al. Int J Mol Sci 2022; 23, 6422). We explored the *in vivo* dynamics of Aβ in the perivascular space of anesthetized mice. Live images were obtained with two-photon microscopy through a closed cranial window. Either fluorescent dye-labeled Aβ oligomers prepared freshly or Aβ fibrils after 6 days of incubation at 37 °C were placed over the cerebral cortex. Accumulation of Aβ was observed in the localized perivascular space of the penetrating arteries and veins. Transportation of the accumulated Aβ along the vessels was slow and associated with changes in shape. Aβ oligomers were transported smoothly and separately, whereas Aβ fibrils formed a mass and moved slowly. Parenchymal accumulation of Aβ oligomers, as well as Aβ fibrils along capillaries, increased gradually. In conclusion, Aβ placed on the cortical surface was slowly transported to the deeper parenchyma through the perivascular space. Loose polymerization may affect the speed of its transportation
Third, we reported that expansion of tau distribution from the parahippocampal gyrus to the cerebral cortex was observed with advancing AD, whereas Aβ distribution was already advanced in the earliest stage. A novel PET tracer for tau, PBB3, may be useful in determining stages in AD based on tau distribution. Although tau accumulates primary in neurons, tau aggregates excreted from degraded neurons may spread through perivascular spaces.
Finally treatment of AD with anti- Aβ, including lecanemab, has just been available. One of major concerns for its safety is a microcirculatory disturbance including AREA-H and AREA-E. Microcirculatory

inflammation and damage to the blood-brain barrier is suspected in these processes.
In this symposium, pathophysiology of microcirculatory disturbance in dementia will be presented and its relevance for its treatment will be discussed.

036-SS2

Reactive nitrogen species are critical therapeutic targets for reducing delayed thrombolysis-mediated hemorrhage transformation and improving therapeutic outcome in ischemic stroke

Jiangang Shen [1]

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Stroke is a major disease burden worldwide and over 85% incidences are ischemic stroke. Tissue plasminogen activator (t-PA) is the only FDA approved drug for acute ischemic stroke, but its use is limited with the restrictive time window within 4.5 hours and the complications of the blood brain barrier (BBB) disruption and hemorrhagic transformation (HT). Exploring molecular targets to reducing the BBB permeability and HT incidence is timely important to develop novel therapeutic approaches for reducing the complications and increasing outcome in ischemic stroke.
Oxidative/nitrosative stress and neuroinflammation are two crucial pathological processes in ischemic stroke. Reactive nitrogen species (RNS) and high mobility group box 1 protein (HMGB1) are important cytotoxic factors contributing to cerebral ischemia-reperfusion injury. Peroxynitrite ($ONOO^-$) is a representative RNS but its roles in mediating inflammation signaling in the blood-brain barrier (BBB) damage and hemorrhagic transformation (HT) in ischemic brain injury remain unclear. In this study, our group has tested the hypothesis that $ONOO^-$ could directly mediate HMGB1 signaling in ischemic brains with delayed t-PA treatment. In clinical studies, we found that plasma nitrotyrosine (NT, a surrogate marker of $ONOO^-$) was positively correlated with HMGB1 level in acute ischemic stroke patients. Plasma levels of nitrotyrosine and HMGB1 were increased in t-PA-treated ischemic stroke patients with hemorrhagic transformation. In animal experiments, FeTmPyP, a representative $ONOO^-$ decomposition catalyst (PDC), significantly inhibited the activations of HMGB1/TLR2/MMP-9 signaling cascades, preserved collagen IV and tight junction claudin-5 in ischemic rat brains with delayed t-PA treatment. $ONOO^-$ donor SIN-1 directly induced HMGB1/TLR2/MMP-9 signaling cascades in naive rat brains in vivo and brain microvascular endothelial b.End3 cells in vitro. Those results suggest that $ONOO^-$ could activate HMGB1/TLR2/MMP-9 signaling, contributing to the BBB disruption and HT in ischemic brain injury. We also demonstrate that $ONOO^-$ mediated MMPs and NLRP3 inflammasome could aggravate the BBB damage and HT, and induce poor outcome in ischemic stroke with hyperglycemia. Thus, the interactions of $ONOO^-$ and inflammation factors play crucial roles in the BBB disruption and HT. Furthermore, we found that peroxynitrite Scavengers from Traditional Chinese Medicine (TCM) and a classic TCM formula significantly decreased the mortality rate, attenuated the BBB disruption, HT, brain swelling, and improved neurological outcomes in the ischemic stroke rat model with delayed t-PA treatment. In conclusion, targeting peroxynitrite-mediated inflammation signaling cascades could be a potential adjuvant therapy to prevent hemorrhagic transformation and improve outcome in ischemic stroke with delayed t-PA treatment, potentially extending the therapeutic window for thrombolysis.
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036-SS3

Cognitive impairments and blood-brain barrier damage in a mouse model of chronic cerebral hypoperfusion

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Chronic cerebral hypoperfusion (CCH) is commonly involved in various brain diseases. Tight junction proteins (TJs) are key components constituting the anatomical substrate of the blood-brain barrier (BBB). Changes in cognitive function and BBB after CCH and their relationship need further exploration. To investigate the effect of CCH on cognition and BBB, we developed a bilateral common carotid artery stenosis (BCAS) model in *Tie2-GFP* mice. Mice manifested cognitive impairments accompanied with increased microglia after the BCAS operation. BCAS mice also exhibited increased BBB permeability at all time points set from D1 to D42. Furthermore, BCAS mice showed reduced expression of TJs 42 d after the operation. In addition, correct entrances of mice in radial arm maze test had a moderate negative correlation with EB extravasation. Our data suggested that BCAS could lead to cognitive deficits, microglia increase and BBB dysfunction characterized by increased BBB permeability and reduced TJs expression level. BBB permeability may be involved in the cognitive impairments induced by CCH.

036-YS1

YiQi FuMai Lyophilized Injection Attenuates Blood-Brain Barrier Disruption and Hemorrhagic Transformation and Improves Neurological Outcome in Ischemic Stroke mice with Delayed t-PA Treatment

Quan Li [2], Xiao-Yi Wang [1,2], Shu-Qi Yao [1,2], Li Yan [2], Jing-Yan Han [1,2]

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Background: Stroke has become the first leading cause of death among Chinese people. Ischemic stroke accounts for about 60% to 80% of all the strokes. Tissue plasminogen activator (tPA) remains the only approved drug for acute ischemic stroke. However, thrombolysis with tPA may lead to increased risks of brain edema and hemorrhage. Yiqi FuMai injection (lyophilized) (YQFM) is a freeze-dried powder injection of Shengmai San (red ginseng, schisandra chinensis, ophiopogon japonicus) with controllable quality, which was approved for marketing in 2006 (GYZZ Z20060463). It has the roles of replenishing qi, promoting fluid production, and consolidating the vital energy. However, whether YQFM could ameliorate the damage of blood brain barrier induced by tPA is unclear.
Methods: In this study, the mice model of ischemic stroke prepared by ferric chloride chemical stimulation and the cell model of hypoxia and reoxygenation were used to explore the improvement effect of YQFM on the damage of blood brain barrier induced by tPA.
Results: The results showed that, the combination therapy of YQFM and tPA significantly reduced hemorrhage, infarction, brain edema, Evans blue extravasation, FITC-dextran leakage, leukocyte adhesion, MMP-9 expression, and leukocyte infiltration at 28.5 hours after stroke. The combination also significantly improved functional recovery, cerebral blood flow, tight and/or adherens junction proteins expression, and basement membrane proteins expression.
Conclusion: Our results showed that YQFM inhibits tPA-induced brain edema and hemorrhage by protecting the blood-brain barrier integrity. The present study supports YQFM as an effective adjunctive therapy to increase the safety of delayed tPA thrombolysis for ischemic stroke.

SYMPOSIUM 37

The Impact of Microvascular Aging on Brain Neural Functions: Experimental and Theoretical Approaches

15:00-16:30 | Room 4

037-SS1

Neurogenic control of brain vasculature

Harumi Hotta [1]

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Cognitive decline in dementia patients and the elderly involves a decrease or dysfunction of basal forebrain cholinergic neurons. The stimulation of the basal forebrain nucleus (nucleus basalis of Meynert: NBM), the origin of cholinergic axons widely distributed to the cerebral cortex, increases extracellular acetylcholine (ACh), resulting in a marked increase in regional cerebral blood flow through muscarinic and nicotinic receptors in the cerebral cortex in rodents. The blood flow increase is observed in widespread cortices without accompanying changes in glucose metabolism. In contrast, sensory stimulation increases both blood flow and metabolism in the same localized region. Therefore, the cholinergic system was proposed to be a neurogenic vasodilative system (Sato et al., 1995).

Using two-photon microscopy, we have shown that penetrating arterioles dilate in a layer-dependent manner during NBM stimulation (Hotta et al., 2014). This was a feature consistent with the distribution density of cholinergic endings. This feature is again in contrast to the fact that somatosensory stimulation dilates both pial arteries and penetrating arteries. A gap junction blocker, carbenoxolone, attenuated forepaw stimulation-induced dilation of the pial artery but not that of the penetrating artery (Watanabe et al., 2018), suggesting that the regulatory mechanisms of the two arteries are different. NBM activity not only acts on parenchymal arteries but also on cortical neurons to increase NGF secretion via nicotinic receptors, but the response is greatly reduced in aged rats (Hotta et al., 2009).

NBM activation is involved, at least in part, in increases in cortical blood flow associated with daily activities such as chewing and walking. However, our results in which the masticatory motor area was stimulated under muscle relaxant showed that it is not only due to peripheral sensory input resulting from movement but also commands from the motor cortex that activate the NBM via neural circuits within the forebrain (Hotta et al., 2020). Somatosensory input generated by chewing and walking, as well as motivation to eat and walk, may activate the NBM and help maintain cognitive function.

037-YS1

Multiphysics modeling of cellular and tissue-scale oxygen distribution in cerebral cortex

Satoshi Ii [1]

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Oxygen and glucose are continuously supplied to cerebral tissues through microcirculation. In the microcirculation, the flow and erythrocytes distribution are closely related to oxygen transport to tissues. Although the relationship between vascular resistance and microhemodynamics due to neurovascular couplings becomes to be unraveling [1], much is unknown for erythrocytes distribution. Recently, various hypotheses have been proposed regarding how waste products are transported and discharged in/from the brain parenchyma, which does not have lymphatic vessels, along with water transport in the brain parenchyma [2]. Elucidation of these physical mechanisms is expected to deepen our understanding of homeostasis of cerebral circulatory and metabolic functions, and to provide insights for active control toward functional regeneration. In this study, we introduce mathematical modeling approaches for prediction of cerebral microcirculation using ideal and actual geometry of cerebral microvasculature.

Two mathematical models were constructed to express circulation and oxygen transport in the cerebral cortex. The first is a blood flow model including transport of erythrocytes, which captures spatiotemporal changes in flow resistance due to congestion of red blood cells flowing in microvessels. Our simulations suggest that erythrocyte flow/distribution may have a passive regulation mechanism of microblood circulation. The second model is an interstitial flow model that considers water penetration between blood vessels and the interstitial tissue, which can capture interstitial fluid flow driven by osmotic flow that depends on blood flow distribution. It was shown that even in cerebral capillaries with a blood-brain barrier, a certain degree of interstitial fluid flow occurs due to the filtration effect due to the difference in oncotic pressure.

037-YS2

Perfusion changes in response to microvascular disturbances across scales and brain areas

Franca Schmid [1]

[1] *ARTORG Center, University of Bern, Switzerland There is increasing evidence that changes at the microvascular level contribute to blood flow impairment during aging and pathologies like dementia and Alzheimer's disease. However, as the energy storage capacities of the brain are limited, a robust and well-balanced blood supply via the vasculature is indispensable. Microvascular alterations might impair the functionality of this intricate supply system. As such, quantifying the impact of such disturbances on perfusion, oxygen, and nutrient availability is important but also not trivial. This is because microvascular flow is highly heterogenous and fluctuating (1), and in vivo studies are often limited to small regions of interest.*

Here, we use a previously established *in silico* blood flow model (1) that allows us to describe perfusion changes in realistic microvascular networks (MVNs) both directly at the site of disturbance and in larger surrounding areas. In this framework, we test three microvascular alterations ranging from single vessel occlusions to ~1000 affected capillaries in two realistic MVNs from the mouse somatosensory cortex (2).

The smallest scale of disturbance is the occlusion of a single capillary. Our results showed that the cortical capillary bed has an inherent robustness to single capillary occlusions (3). This is achieved by the interconnected nature of the capillary bed. More precisely, the smallest perfusion changes are observed for the occlusion of a capillary with a divergent bifurcation upstream and a convergent bifurcation downstream (*1-in-1-out*). Interestingly, with a frequency of 43%, this is by far the most common local capillary configuration. While single capillary occlusion likely does not cause severe tissue hypoxia, each occlusion causes a drop of flow rate by 20-70% in neighboring capillaries. As such, an accumulation of occlusions is expected to have a synergistic effect on the impairment of blood supply and vascular adaptability locally.

At the intermediate scale, we investigated blood flow redistribution in response to dilating sets of ~15 connected capillaries (4). This mimics vasodilations in response to the ablation of three consecutive pericytes and is motivated by reduced pericyte density and plasticity during aging (4). Such multi-capillary dilations induce a redistribution of blood flow that is characterized by increased flow rates in the dilated vessels, and flow increases (70%) and decreases (30%) in surrounding vessels. Moreover, perfusion heterogeneity increases in the dilated capillaries, which might hinder flow homogenization as observed during neuronal activation (5).

Recent evidence suggests that capillary density reductions, as observed during aging, are not homogeneous over depth (6). In addition to reduced capillary density, age-related vasoconstrictions may occur. As deeper cortical layers are more vulnerable, our focus is on vascular alterations in layers 4-6. Preliminary simulation results indicate that layer-specific reductions of capillary density by 10% only slightly impact overall perfusion within the cortical layer. In contrast, layer-specific constrictions exert a significant impact on the integral perfusion per layer.

So far, our investigations have been limited to realistic MVNs embedded in a tissue volume of 1mm^3. However, it is well-established that not

all brain areas are affected equally during aging. Consequently, we currently extend our simulations to whole-brain reconstruction of the microvasculature of the mouse (7). This will enable insights into the sensitivity of different brain areas to the aforementioned alterations and, additionally, allow us to quantify the baseline flow field in deeper brain areas that are difficult to assess in *in vivo* imaging.

037-YS3

Therapeutic Effect and Mechanisms of AnGongNiuHuang Wan in Ameliorating LPS-Induced Cerebral Microvascular Injury and Edema

Bo-Tong Liu [1,2], Quan Li [2], Kai Sun [2], Chun-Shui Pan [2], Xin-Mei Huo [1,2], Ping Huang [2], Li Yan [2], Li-Jun Zhong [3], Meng-Lei Hu [1,2], An-Qing Li [1,2], Ying-Qian Jiao [1,2], Shuang Zhang [1,2], Jing-Yan Han [1,2]

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Background: lipopolysaccharide (LPS) induced cerebral microvascular injury can result in significant tissue edema, subsequently leading to cellular damage. At present, there is no established therapeutic approach to mitigate cerebral edema associated with LPS induced injury. This study aims to explore the therapeutic effect and mechanisms of AnGongNiuHuang Wan (AGNHW) in this field.
Method: Pharmacodynamics include assessing survival rates, brain water content, Evans Blue leakage, microcirculatory dynamics, observation of endothelial cell-cell junctions, and determination of caveolae phosphorylation status. Mechanistic research employs liquid chromatography-mass spectrometry for the identification of drug components in the bloodstream, and proteomics analyses to monitor alterations in protein. Network pharmacology is utilized to elucidate the specific mechanism by which the drug components modulate protein to ameliorate LPS induced cerebral edema.
Results: The study found that AGNHW significantly reduced LPS induced mortality and mitigated brain edema. This therapeutic effect seemingly was mediated by augmenting the expression of the intercellular junction protein and vascular endothelial cadherin (VE-cadherin), reducing the phosphorylation of caveolae, alleviating microcirculatory hyperpermeability and inhibiting leukocyte adhesion.
Conclusion: The results underscore the therapeutic promise of AGNHW in addressing cerebral microvascular damage resulting from sepsis and advocate for further exploration utilizing integrative multi-omics approaches. Sustained research efforts in this field are anticipated to generate significant and influential outcomes.

SYMPOSIUM 38

Micro- and Macro-Circulatory Dysfunction in Disease

15:00-16:30 | Room 5

038-SS1

Effect of stroke beyond the brain

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Ischaemic stroke is one of the leading contributors to morbidity and mortality worldwide. Despite its recognised debilitating neurological deficits, stroke is associated with various non-neurological medical complications, including pneumonia and bowel dysfunction. These complications contribute to extended hospital stay, poor neurological outcome, development of further complications, and even death. Our group is interested in understanding how an injury in the brain induced by stroke triggers a series of peripheral impairments, and we believe revealing these pathways will pave the way for new and targeted therapeutic strategies for stroke patients. We discovered an intricate communication network between the brain and the gut, and between the brain and the lung. Disruptions of the brain-gut and brain-lung axes contribute to altered intestinal homeostasis and impaired pulmonary antibacterial defence, respectively. These stroke-induced peripheral effects worsen disease outcome. In this presentation, I will outline our recent findings on the impact of stroke on the peripheral microvasculature.

038-SS2

Novel therapeutics for pulmonary arterial hypertension

Kara Hetherington [1,2], Himanshu Chuglani [1], Jordyn Thomas [1,2], Stephen Nicholls [2], Barbara Kemp-Harper [2,3], Scott Levick [4], Kristen Bubb [1,2]

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Background: Pulmonary arterial hypertension (PAH) is a severe disease characterized by remodelling of the pulmonary vasculature, resulting in increased pulmonary vascular resistance which leads to progressive and fatal right heart failure. Endogenously produced vasodilators and vasoconstrictors are imbalanced in PAH and the majority of approved drugs target nitric oxide, prostacyclin and endothelin signalling pathways. However, current treatments are sub-optimal; they result in improved quality of life, but only a marginal increase in life expectancy. Substance P is a neuropeptide released from sensory C fibres. It is vasoactive and generally causes systemic vasodilation, thereby lowering blood pressure. However, in the pulmonary circulation, substance P can be either a vasodilator or constrictor depending on the conditions. Interestingly, substance P is increased in the lungs during experimental PAH. Substance P can induce pulmonary vascular remodelling in ex vivo lung slices and activation of the receptor for substance P, neurokinin (NK) 1 increases pulmonary pressure. We hypothesised that NK1 receptor (Tacr1) deficiency would attenuate PAH.
Aims: We aimed to assess whether PAH could be prevented in Tacr1-/- mice and whether established PAH would be attenuated by treatment with an NK1 receptor antagonist, aprepitant.
Methods: Tacr1-/- and Tacr1+/+ mice were placed into a hypoxia chamber (10% oxygen) for 5 weeks, with injections of vascular

endothelial growth factor inhibitor, Su5416, (20 mg/kg/day) once per week for the first three weeks. Right ventricular systolic pressure (RVSP) was assessed on the final day by catheterisation with a 1.4F pressure transducer. Pulmonary vascular remodelling was assessed in lung sections stained with Masson's trichrome by measuring wall thickness, lumen diameter and perivascular fibrosis (collagen). We repeated similar experiments in C57BL6J mice treated with aprepitant for the last 3 weeks of hypoxia (0.14 mg/kg/day, oral). Proof-of-concept studies were conducted using human pulmonary artery smooth muscle cells. Cells were treated with substance P and NK1 receptor inhibitor R67580 (10 mM) and proliferation was determined over 72 hours.

Results: Tacr1+/+ mice had significantly elevated RVSP after Su5416/hypoxia (Hpx) compared with Tacr1+/+ control mice. Tacr1-/- mice had similar baseline RVSP but after Hpx RVSP was attenuated in Tacr1-/- compared to Tacr1+/+ mice (mean ± SEM mmHg: Tacr1+/+ control 24.7 ± 0.9, Hpx 46.8 ± 1.7; Tacr1-/- control 25.6 ± 0.7, Hpx 39.9 ± 1.0, n=10-13, analysed by 1-way ANOVA). Treatment with aprepitant attenuated RVSP in Hpx mice (mmHg: control vehicle 29.9 ± 1.9, control aprepitant 30.0 ± 0.4, Hpx vehicle 51.5 ± 2.2, Hpx aprepitant 41.9 ± 2.7, n=4). There were no changes in mean arterial blood pressure in any groups, suggesting selectivity for the pulmonary circulation. Pulmonary vascular remodelling was evident after Hpx, with thicker artery walls and increased wall to lumen ratio (Tacr1+/+ control 0.033 ± 0.001, Tacr1-/- control 0.027 ±0.002, Tacr1+/+ Hpx 0.054 ± 0.003, Tacr1-/- 0.031 ± 0.002) and there was a trend towards attenuated remodelling after aprepitant treatment but this did not reach significance with n=4. Substance P treatment stimulated proliferation in isolated pulmonary artery smooth muscle cells and this was prevented by NK1 receptor inhibition (fold change from 0-48 hours: control 2.04 ± 0.09, substance P 2.97 ± 0.27, substance P + RP67580 1.98 ± 0.22).

Conclusion: We have demonstrated that NK1 receptor deficiency or inhibition attenuates pulmonary vascular remodelling and PAH. This may involve reduced smooth muscle cell proliferation and regulation of collagen deposition and ongoing work will unravel the precise mechanisms underpinning this.

038-SS3

Importance of extracellular vesicles in microvascular pathologies

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The microvascular endothelium is at the centre of inflammatory process, which underpins the pathogenesis of most diseases. We have focused our attention on immunopathological complications of infectious diseases. Extracellular vesicles (EV) include exosomes, microvesicles and apoptotic bodies. They are now acknowledged as major players in cell-cell communication and, thereby, in homeostasis and pathophysiology. While EV have been described originally in the nineteen-sixties, it is only recently that they have been examined from the angle of disease pathogenesis. The release of EV is an integral part of any immune response. As such, overproduction of EV from all immune cell types, including endothelial cells and platelets, has been documented in numerous inflammatory diseases.

In this talk, we will, first, define the various EV subtypes and focus on our current understanding of the heterogeneity of microvesicles and exosomes; second, we will present recent data on EV characterisation by flow cytometry, nanoparticle tracking analysis and vibrational spectroscopic techniques [Fourier-transform infra-red (FTIR) and attenuated total reflection (bio-ATR) spectroscopies], and share experimental data supporting the central role of EV as mediators of immunopathology – with particular attention to the mechanisms by which EV modify their target cells and those by which they are modified by pathogens - in some bacterial, parasitic and viral infections.

038-YS1

Bench-to-bedside translation of mega-dose sodium ascorbate to reverse sepsis-induced brain and kidney micro-circulatory dysfunction

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Background: Sepsis is a major clinical problem, the greatest cause of multiple-organ dysfunction and death in intensive care units and lacks effective treatments. Recently, there has been an increasing interest in the use of intravenous vitamin C in sepsis due to its beneficial pleiotropic effects including, as an antioxidant, anti-inflammatory, innate immune stimulant, and a cofactor for noradrenaline synthesis. We investigated the effects of the sodium salt of vitamin C, sodium ascorbate, on vasopressor requirements, cerebral and renal microcirculatory tissue perfusion and oxygenation and plasma ascorbate levels in a clinically relevant ovine model of Gram-negative sepsis.

Methods: Sheep were surgically instrumented with laser-Doppler and oxygen-sensing probes in the cerebral cortex, renal cortex, and renal medulla to measure microcirculatory tissue perfusion, oxygen tension (PO2), and temperature. The carotid artery and jugular vein were cannulated for measuring blood pressure, heart rate, arterial blood sampling and intravenous fluid and drug infusions. Non-anesthetized sheep received an intravenous infusion of live Escherichia Coli for 31 hours. After 23 hours of established Gram-negative sepsis, sheep received intravenous fluid resuscitation (30 mL/kg/30-min; sodium lactate) before randomisation to intravenous sodium ascorbate (0.5 g/kg bolus over 30-minute + 0.5 g/kg/h for 6.5-hours; N=6) or fluid-matched vehicle treatment (n=6). Noradrenaline was titrated to restore mean arterial pressure to 70-80 mmHg.

Results: In ovine sepsis there were decreases in mean arterial pressure (85±2 to 64±2 mmHg) and plasma levels ascorbate (27±2 to 15±1 µmol/L), while core (39.4±0.1 to 41.5±0.3 °C) and brain tissue (39.1±0.2 to 41.1±0.2 °C) temperatures increased (all P<0.001). Sepsis caused cerebral microcirculatory tissue ischemia (901±58 to 396±40 laser-Doppler blood perfusion units (BPU)) and hypoxia (34±1 to 19±3 mmHg tissue PO2), renal medullary microcirculatory tissue ischemia (987±63 to 353±72 BPU) and hypoxia (42±5 to 22±2 mmHg) and increased plasma creatinine (71±2 to 155±22 µmol/L) (all P<0.001). Compared with vehicle, mega-dose sodium ascorbate permitted withdrawal of noradrenaline therapy while the target mean arterial pressure was achieved at 70-80 mmHg (PTreatment<0.001). Furthermore, sodium ascorbate restored cerebral microcirculatory tissue perfusion (to 703±121 BPU) and tissue PO2 (to 30±2 mmHg) and markedly elevated plasma ascorbate levels (to 20,000±3,000 µmol/L) (all PTreatment<0.05). It normalised body temperature (to 39.4±0.3 °C), renal medullary tissue microcirculatory perfusion (to 866±141 BPU) and medullary tissue PO2 (to 46±4 mmHg) and normalised plasma creatinine (to 33±5 µmol/L) (all PTreatment<0.05).

Conclusion: In a clinically relevant large mammalian model of Gram-negative sepsis, megadose sodium ascorbate improved vasopressor sensitivity and reversed brain and kidney microcirculatory ischemia and hypoxia and acute kidney injury. We have recently completed a double-blind Phase Ia randomised controlled clinical trial in 30 patients with sepsis at Austin Health receiving intravenous mega-dose sodium ascorbate or placebo [ACTRN12620000651987p]. The results from this clinical trial are currently being analysed by a blinded biostatistician and will be presented at this conference.

SATELLITE SYMPOSIUM 9

Diabetes and Microcirculation

08:30-11:30 | Room 7

S9-1

Diabetes and gastroparesis

Rayner Chris [1]

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Gastroparesis is an important complication of diabetes, because it is associated with troublesome gastrointestinal symptoms and impaired nutrition. Moreover, in type 1 and insulin-requiring type 2 patients, it contributes to poor glycaemic control by causing a mismatch between the action of injected insulin and the emptying of carbohydrates from the stomach.

This presentation will focus on recent developments in our understanding of the pathogenesis of diabetic gastroparesis, as well as the clinical consequences. It will review the tools used for diagnosis, and will provide an update on management, including pharmacotherapy - both prokinetic and entiemetic medications - as well as gastric electrical stimulation, and novel endoscopic therapies including G-POEM.

S9-2

New target for prevention and treatment of diabetic retinopathy

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Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes and the main cause of non-traumatic blindness in adults. Studies have shown that the pathogenesis of diabetic retinopathy includes inflammation, oxidative stress, neurodegeneration, and epigenetic changes. Inflammation plays a crucial role in the pathogenesis of retinopathy. How to prevent and treat DR Has become a major social and public health problem facing China and even the whole world.

Related zoological research were conducted in different stages of diabetic retinopathy, from non-proliferative to proliferative. Non-proliferative diabetic retinopathy models were constructed in KKAy mice and HFD+STZ mice. Pancreatic Kallikrein intervention can increase the level of retinal bradykinin, activate the expression of B1R and B2R, reduce the level of retinal oxidative stress, inflammation and apoptosis, and improve the thickness and vascular exudation of non-proliferative diabetic mice. Inhibit the formation of nonfunctional capillaries.

It is well known that VEGF plays an important role in the occurrence and development of DR, which can destroy the blood-retinal barrier and promote pathological neovascularization. For the treatment of proliferative neovascularization, laser photocoagulation and anti-VEGF antibody injection are mainly performed on the premise of basic treatment. By using oxygen-induced ischemic retinopathy (OIR) mouse model to simulate diabetic proliferative retinopathy, inhibition of angiogenic factor AGGF1 can reduce inflammation and pathological neovascularization in proliferative retinopathy, providing a new target for clinical treatment of diabetic retinopathy.

S9-3

Kallikrein kinin system and diabetic microvascular complications

Zhaoyun Zhang [1]

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The kallikrein-kinin system has been shown to be involved in the development of diabetic nephropathy and cardiomyopathy, but specific mechanisms are not fully understood. Here, we determined the renal-n and cardiac-protective role of exogenous pancreatic kallikrein in diabetic mice and studied potential mechanisms in db/db type 2 diabetic and streptozotocin-induced type 1 diabetic mice. After the onset of diabetes, mice were treated with either pancreatic kallikrein (db/db+kallikrein, streptozotocin+kallikrein) or saline (db/db+saline, streptozotocin+saline) for 16 weeks, while another group of streptozotocin-induced diabetic mice received the same treatment after onset of albuminuria (streptozotocin+kallikrein, streptozotocin+saline). Db/m littermates or wild type mice were used as non-diabetic controls. Pancreatic kallikrein had no effects on body weight, blood glucose and blood pressure, but significantly reduced albuminuria among all three groups. Pathological analysis showed that exogenous kallikrein decreased the thickness of the glomerular basement membrane, protected against the effacement of foot process, the loss of endothelial fenestrae, and prevented the loss of podocytes in diabetic mice. Renal fibrosis, inflammation and oxidative stress were reduced in kallikrein-treated mice compared to diabetic controls. The expression of kininogen1, tissue kallikrein, kinin B1 and B2 receptors were all increased in the kallikrein-treated compared to saline-treated mice. In the heart, we observed similar improvement in inflammation, fibrosis and oxidative stress. Thus, exogenous pancreatic kallikrein both prevented and ameliorated diabetic nephropathy and cardiomyopathy, which may be mediated by activating the kallikrein-kinin system.

S9-4

Mitochondrial oxidative stress and diabetic nephropathy

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Mitochondrial function is essential in bioenergetics, metabolism and signaling; is compromised in diseases such as proteinuric kidney diseases; and contributes to the global burden of kidney failure, cardiovascular morbidity and death. The key cell that prevents proteinuria is the terminally differentiated glomerular podocyte. Here, we identify the importance of mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH), located on the inner mitochondrial membrane, in regulating podocyte function and glomerular disease. Specifically, podocyte-dominated mGPDH expression was downregulated in glomeruli in patients and mice with diabetic kidney disease and adriamycin (ADR) nephropathy. Podocyte-specific depletion of mGPDH in mice exacerbated diabetic or ADR-induced proteinuria, podocyte injury and glomerular pathology. RNA sequencing revealed that mGPDH regulated the receptor for advanced glycation end-product (RAGE) signaling pathway, and inhibition of RAGE or its ligand S100A10 protected against the impaired mitochondrial bioenergetics and increased reactive oxygen species generation caused by mGPDH knockdown in cultured podocytes. Moreover, RAGE deletion in podocytes attenuated nephropathy progression in mGPDH-deficient diabetic mice. Rescue of podocyte mGPDH expression in mice with established glomerular injury (diabetes or ADR nephrotoxicity) led to a significant improvement in their renal function. In summary, our study proposes activation of mGPDH induces mitochondrial biogenesis and reinforces mitochondrial function, which may provide a potential therapeutic target for preventing podocyte injury and proteinuria in glomerular disease.

S9-5

Postprandial hypotension – prevalence, pathophysiology and approaches to treatment

Karen Jones [1]

[1] *Adelaide Medical School, The University of Adelaide*

Postprandial hypotension (PPH) is a common clinical disorder which predisposes to syncope and falls, and in more severe cases, death. PPH, defined as a fall in systolic blood pressure (SBP) of greater than 20mmHg, within 2 hours of a meal, occurs in ~ 15% of healthy asymptomatic older people more than 65 years of age, ~25% of people with type 2 diabetes and ~40-50% of nursing home residents. While PPH is much more common than orthostatic hypotension, it has

received relatively little attention and management remains suboptimal. The magnitude of the postprandial fall in BP is related directly to the rate of nutrient delivery to the small intestine, so that faster gastric emptying is associated with a greater fall in BP. Conversely, gastric distension attenuates the fall in BP. More recently, the incretin hormone glucagon-like peptide -1 (GLP-1), which slows gastric emptying, has been shown to reduce the postprandial fall in BP. In an acute study, slowing of gastric emptying by the short-acting GLP-1 receptor agonist, lixisenatide, was associated with a marked attenuation in the fall in BP after an oral glucose load in type 2 diabetes. Furthermore, in a more recent study, 8 weeks treatment with the long-acting GLP-1 receptor agonist, exenatide once weekly in type 2 diabetes, was shown to slow gastric emptying of a mashed potato meal and reduce the postprandial fall in SBP.

PPH occurs frequently in older people and those with type 2 diabetes. Strategies targeted at slowing of gastric emptying and maximising gastric distension are likely to prove beneficial in its management, including the use of GLP-1 receptor agonists.

S9-6

Type 2 diabetes and Alzheimer's disease in China

Yan Bi [1,2]

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Cognitive impairment associated with dementia represents a key clinical feature of diabetes central neuropathy and is categorized by severity into mild cognitive impairment (MCI) and dementia. Diabetes not only increases the risk of dementia but also accelerates the disease process. In 2019,Alzheimer's disease underwent a substantial surge in the rankings among leading causes of death, climbing from the 10th to the 5th position. Despite being a leading cause of mortality in the country, these interconnected conditions are frequently overlooked, underscoring the imperative for heightened awareness and prioritization.

The escalating incidence rates of diabetes and dementia in China pose a considerable challenge to the national healthcare infrastructure. Such a scenario engenders substantial socio-economic ramifications, not only affecting society at large but also imposing strains on individual families. In China, the prevalence of dementia among elderly individuals over the age of 60 is approximately 6.0%, whereas it is 10.2% in individuals with type 2 diabetes. The development of Alzheimer's disease occurs gradually and is difficult to cure, caregivers who support individuals with Alzheimer's disease experience immense physical and mental burdens due to a lack of social support and adequate training to help them overcome the challenges they face. Compounding the issue is the insufficient awareness and competency among healthcare professionals, which frequently culminates in suboptimal patient care, delayed disease diagnosis, and missed opportunities for efficacious treatment. To address this critical issue, it is incumbent upon healthcare systems to implement systematic training for physicians, equipping them with the requisite diagnostic, management, and treatment skills to enhance patient outcomes.

As a result, early screening and diagnosis of cognitive dysfunction are crucial to improving patient outcomes. However, there is no effective treatment available, highlighting the importance of early diagnosis to delay progress. We pioneered the task-based fMRI scans to quantitatively assess odor-induced brain function in type 2 diabetes, revealing decreased olfactory threshold and impaired olfactory brain activation and functional connectivity in the preclinical stage of cognitive impairment. And through a prospective randomized controlled three-arm parallel clinical trial, we conducted the effects of three antidiabetic medications GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors on cognitive function in diabetes. The results demonstrated that only GLP-1 receptor agonists improved impaired cognitive domains. Besides, the domestic study points out implementing lifestyle interventions , engaging in regular physical and mental activities, and ensuring a consistent biological rhythm have been shown to effectively reduce the risk of Alzheimer's disease in individuals with diabetes. Targeted therapy for central nervous system diseases remains a global challenge. We have firstly reported a novel mechanism of communication between adipose tissue and the brain, involving extracellular vesicles released by adipose tissue and their miRNA cargo, targeting the brain through a membrane protein-dependent mechanism and with enrichment in the hippocampus. This study proposes that targeting adipose tissue vesicles or their miRNA cargo may preserve a novel therapeutic strategy for diabetes-related cognitive dysfunction.

In recent years, China's government has been confronted with an increasing number of patients as well as significant financial burdens. In response, strategic action plans and targets were formulated and substantial efforts were made to train specialists and set up memory clinics. According to incomplete statistics, over 300 hospitals currently boast memory clinics that provide a wide range of meticulous evaluations. The memory clinic has significantly enhanced patients' awareness of their disease. Our hospital is well aware of the importance of addressing diabetes-related cognitive dysfunction and has taken proactive steps to establish the dedicated diabetes memory clinic aimed at providing high quality services for patients by ensuring early identification of diabetes-related cognitive dysfunction and providing precise personalized interventions and management.

S9-7

Lactic acid: metabolic waste or signaling molecules?

Xiaoyan Hannah Hui [1]

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Adipose tissue is no longer considered to be an inert tissue that stores fat. As one of the largest endocrine organ in the body, adipose tissue secrets a panel of bioactive molecules, whose levels are tightly controlled and coordinated in response to the changing physiological and pathophysiological conditions.

Over-nutrition arouses a low grade, chronic inflammatory response in adipose tissue, ensued by a myriad of metabolic complications. During this event, adipose tissue macrophage (ATM) polarization to the “M1-like” phenotype is a key culprit leading to adipose inflammation. But the metabolic cues that drive ATM polarization is not characterized. Our recent study demonstrates that in adipocytes, elevated lactate production, previously regarded as the by-product of anaerobic or aerobic glycolysis, serves as a metabolic signal to dictate ATM polarization to the M1 status in the context of over-nutrition. Adipocyte-selective deletion of lactate dehydrogenase A (*Ldha*) gene, the enzyme converting pyruvate to lactate, protects mice from diet-induced glucose intolerance and insulin resistance, accompanied by a lower percentage of M1-like ATM and reduced production of proinflammatory cytokines. Mechanistically, adipocyte-derived lactate directly binds to the catalytic domain of prolyl hydroxylase domain-containing2 (PHD2) and thereby stabilizes hypoxia inducible factor (HIF-1a). Lactate-induced IL-1b was abolished in PHD2-deficient macrophages. Human adipose lactate level is positively linked with local inflammatory features and systemic insulin resistance index independent of the body mass index (BMI). Our study establishes a critical role of adipocyte-derived lactate in shaping the pro-inflammatory microenvironment in adipose and identifies PHD2 as a direct sensor of lactate, which functions to connect energy metabolism and chronic inflammation.

S9-8

The Adipokine Tetranectin Inhibits Insulin Secretion from β Cells in Diabetes

Jingjing Zhang [1]

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Pancreatic β cell failure is a hallmark of diabetes. However, our understanding of the causes of β cell failure remains incomplete. Disturbance of microcirculation in islets plays important role in pancreatic β cell failure. Here we report the identification of an adipokine

tetranectin (TN) that inhibits insulin secretion in β cells in diabetes. Circulating TN levels are significantly elevated in diabetic humans and mice compared to their respective controls. In addition, TN treatment greatly exacerbates hyperglycemia in mice and suppresses glucose-stimulated insulin secretion in human and mouse islets. Conversely, knockout of TN significantly improves insulin secretion and glucose tolerance via inhibition of disturbance of microcirculation in islets in high fat diet-fed mice. Mechanistically, TN binds with high selectivity to β cells and inhibits insulin secretion by blocking L-type Ca2+ channels. Collectively, these results uncover a new adipocyte-β cell crosstalk mechanism that contribute to β cells dysfunction in diabetes.

SATELLITE SYMPOSIUM 10

Advanced Technologies and Translational Medicine in Tumor Microcirculation

10:00-11:30 | Guorui Hall

S10-1

STAT1 lactylation induced by Helicobacter pylori activates GNB4 expression to promote gastric carcinogenesis

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Background: Helicobacter pylori (H. pylori) infection is a high-risk factor for the development of gastric cancer. Although lysine lactylation has received more attention as an emerging posttranslational modification, its role in H. pylori-induced gastric cancer (GC) has yet to be fully investigated.
Methods: Proteomic quantification of lysine lactylation was conducted in human GC tissues and adjacent normal tissues by mass spectrometry. The mRNA and protein levels of STAT1 in GC and adjacent normal tissues were analyzed by qRT-PCR and western blot, respectively. The expression of K193-lactylated signal transducer and activator of transcription 1(STAT1) was measured in GC tissue microarray by the K193 lactylated-specific antibody. H. pylori infection was induced in in vitro and in vivo models. RNA-seq was used to screen for lactonized STAT1-acting downstream genes. The interaction between STAT1 and GNB4 was measured by co-immunoprecipitation (co-IP). The effect of K193-lactylated STAT1 on tumor growth and metastasis was evaluated by in vitro and in vivo experiments.
Results: Total, 224 lysine lactylation sites in 159 proteins were identified. Differentially modified proteins were significantly enriched in the glycolytic pathway. STAT1, the key regulator of the glycolytic pathway, was found highly lactylated at K193 in GC. Intriguingly, H.pylori infection activates lactylation at the K193 site of STAT1 in vitro and in vivo. Lactylation-mimic mutant of STAT1 inhibit GC cell proliferation, invasion, and migration. Mechanistically, lactate is translocated intracellularly via MCTs in a p300/CBP-dependent manner to promote STAT1 K193 site lactylation. Lactylated STAT1 targets GNB4 to activate the Wnt/β-catenin pathway to promote gastric cancer progression.
Conclusions: Our study reveals an important role of STAT1 lactylation in the development of H. pylori-associated GC. Our findings demonstrate that H. pylori infection activates glycolysis/lactate generation-p300/CBP-STAT1 lactylation-GNB4 axis, which may be a potential therapeutic target for GC.

S10-2

Intrinsic and microenvironmental factors promotes temozolomide resistance of glioblastoma

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Glioblastoma (GBM) is the most common primary brain tumor in adults and one of the most lethal malignancies due to its aggressive and highly infiltrative nature. Temozolomide (TMZ) is an alkylating agent and has been considered as the first-line chemotherapy agent for postoperative GBM in recent years. Resistance to TMZ is one of the major challenges for glioblastoma (GBM) therapy while the underlying mechanisms demand further exploration. Various intrinsic and microenvironmental factors have been reported to be involved in TMZ resistance. Here we employed multi-omics analyses on GBM tissues,

cell lines and enriched tumor repopulating cells (TRCs) and revealed new intrinsic and microenvironmental molecules that may play important roles in TMZ resistance. Further phenotypic and mechanistic experiments indicate that the newly discovered molecules can promotes TMZ resistance both in vivo and in vitro. Our study provides novel targets and rationale to overcome TMZ resistance of GBM.

S10-3

Lymphangiogenesis-related gene model in microcirculation for predicting prognosis and immune microenvironment of pancreatic cancer

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Pancreatic cancer (PC) is known to be an aggressive malignancy that is characterized by early metastasis to distant organs and poor prognosis. One of the key mechanisms that contribute to the metastasis and poor prognosis of PC is the formation of lymphatic vessels in microcirculation, a process known as lymphangiogenesis. Lymphangiogenesis is the formation of new lymphatic vessels from pre-existing lymphatic vessels, which are specialized vessels that play a critical role in the transport of immune cells and fluid. In PC, the tumor cells can stimulate the formation of new lymphatic vessels by releasing lymphangiogenic growth factors, such as vascular endothelial growth factor C (VEGFC). These growth factors promote the migration and proliferation of lymphatic endothelial cells, leading to the formation of new lymphatic vessels. The newly formed lymphatic vessels in PC can facilitate the spread of tumor cells to regional lymph nodes and distant organs, leading to metastasis. The lymphatic vessels can serve as a conduit for the transport of cancer cells to the blood vessels, allowing for further dissemination and spread of cancer. Additionally, the newly formed lymphatic vessels can also remodel the tumor microenvironment of PC, leading to suppressive conditions and accelerating the growth of tumor cells. However, the relationship between lymphangiogenesis and the prognosis of PC patients is unknown. Therefore, the purpose of our research is to develop a model for predicting the prognosis of PC based on lymphangiogenesis in microcirculation. With the help of Molecular Signatures Database, we identified a collection of genes related to regulation of lymphangiogenesis in microcirculation, including CCBE1, EPHA2, VASH1, FOXC1 and VEGFC, all of which expressed higher in PC tissue than in normal pancreas. Besides, higher expression of CCBE1 (HR = 1.3, p = 0.25), EPHA2 (HR = 2.04, p = 0.002), FOXC1 (HR = 1.83, p = 0.003) and VEGFC (HR = 1.28, p = 0.29) were related with worse prognosis of PC patients, whereas higher expression of VASH1 (HR = 0.4, p < 0.001) was significantly related with better prognosis. The lymphangiogenesis-related gene signature could affect overall survival (HR = 1.4, p = 0.093) and disease-free survival (HR = 1.8, p = 0.012) of PC patients, which suggested a pro-tumor role of lymphangiogenesis. The lymphangiogenesis score in PC was significantly higher than that in normal pancreas (p < 0.05). Subsequently, we developed a lymphangiogenesis-related gene Cox proportional-hazards model in microcirculation, which could help to discriminate high lymphangiogenesis group and low lymphangiogenesis group. The area under the curve of receiver operating characteristic curve was 0.728 and high lymphangiogenesis group was significantly related to a worse prognosis (p < 0.001). Nomogram was constructed according to the features contained in the lymphangiogenesis-related model to predict survival time of PC patients, which was further optimized with the introduction of clinical features. By analyzing differently expressed genes (DEGs) with the DEseq2 method, we found high lymphangiogenesis group expressed significantly higher SPRR1B (FDR = 0.003) and SPRR2D (FDR = 0.041), and significantly lower RFX6 (FDR < 0.001) than low lymphangiogenesis group. Enrichment analysis of DEGs showed positive regulation of cell cycle-related pathway were significantly enriched in high lymphangiogenesis group, such as mitotic cell cycle, positive regulation of cell cycle and cell population proliferation. Single-cell RNA-sequencing results suggested a diverse immune infiltration pattern in high lymphangiogenesis PC patients, leading to a suppressive immune microenvironment. In general, we developed a model for predicting the prognosis of PC based on lymphangiogenesis in microcirculation successfully. Targeting lymphangiogenesis in microcirculation may represent a potential therapeutic strategy for the treatment of PC.

S10-4

Apply CRISPRomics in Cancer Target discovery

Shaokun Shu [1]

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BET bromodomain inhibitors (BBDIs) are candidate therapeutic agents for triple-negative breast cancer (TNBC) and other cancer types, but inherent and acquired resistance to BBDIs limits their potential clinical use. Using CRISPR and small-molecule inhibitor screens combined with comprehensive molecular profiling of BBDI response and resistance, we identified synthetic lethal interactions with BBDIs and genes that, when deleted, confer resistance. We observed synergy with regulators of cell cycle progression, YAP, AXL, and SRC signaling, and chemotherapeutic agents. We also uncovered functional similarities and differences among BRD2, BRD4, and BRD7. Although deletion of BRD2 enhances sensitivity to BBDIs, BRD7 loss leads to gain of TEAD-YAP chromatin binding and luminal features associated with BBDI resistance. Single-cell RNA-seq, ATAC-seq, and cellular barcoding analysis of BBDI responses in sensitive and resistant cell lines highlight significant heterogeneity among samples and demonstrate that BBDI resistance can be pre-exist- ing or acquired.

SATELLITE SYMPOSIUM 11

Myocardial Perfusion: From Pericardial Vessel to Microcirculation

15:00-17:30 | Room 7

S11-1

Noninvasive detection of myocardial ischemia: Diagnostic value of magnetocardiography for coronary artery disease

YiXian Lin [1]

[1] *Hong Kong canossa hospital*

Background: Magnetocardiography (MCG) is a non-contact, noninvasive, contrast-free, and radiation-free multi-channel mapping technique to record cardiac electromagnetic activity with high resolution.
Methods: To find diagnostic value for coronary artery disease, we reviewed our research from past to present. A direct comparison of MCG to different cardiac imaging for predicting the presence of significantly obstructive CAD.
Results: There was no incremental diagnostic value of combined MCG and ECG to detect coronary artery disease (p = 0.357). The best cut-off value of the percent change of ST-segment fluctuation score was -39.0% with sensitivity of 86.7% and specificity of 73.9%. the incorporation of non-dipole phenomenon into a model with the percent change of ST-segment fluctuation score significantly improved C-statistics, indicating the enhancement of diagnostic performance in the detection of significant CAD (0.790 to 0.930; p<0.001). Sensitivity, specificity, diagnostic accuracy, and the area under the receiver-operator characteristics curve of bull's-eye mapping for the detection of significant CAD were 90.5%, 92.3%, 91.5%, and 0.914 on a patient basis and 90.0%, 93.8%, 92.3%, and 0.919 by coronary territory, respectively.
Conclusion: MCG is a useful, noninvasive strategy for the diagnosis and assessment of ischemia in patients with suspected CAD or after PCI. MCG has been proposed as a noninvasive technique with high accuracy for the functional diagnosis of myocardial ischemia by fractional flow reserve.

S011-2

Non-Invasive Magnetocardiography for the Early Diagnosis of Coronary Microcirculation Dysfunction

Jian Ma [1], Cheng xing Shen [1]

[1] *Department of Cardiology, Shang hai sixth people's hospital*

Background: Coronary microcirculation dysfunction(CMD) is a frequently-occurring disease, which significantly affects patients' life quality and increases psychological burden. Repeated medical treatment often increased economic burden due to unclear diagnosis. Clinical evaluation of CMVD was mostly invasive or radioactive, which was complicated and harmful to patients, further limited its application. The magnetocardiograph(MCG) is a medical diagnostic equipment for imaging by detecting the magnetic field of human heart, which has the advantages of non-invasive, non-radiation, non-contact, high sensitivity and excellent early diagnosis ability. The aim of the present study was therefore to evaluate the efficacy of magnetocardiography (MCG) for diagnosis of CMD in patients with chest pain.
Methods and Results: In the present retrospective study, 164 patients with the suspected CMD were selected. Significant CMD disease was defined as a stenosis<50% in all of 16 segments of the 3 major coronary arteries and their branches, and results of exercise electrocardiography was positive. The MCG recordings were obtained at resting state using a 36-channel MCG system in a magnetically shielded room. The presence of significant CMD was identified with a sensitivity of 92.0% and a specificity of 85.0%, compared to 44.7% and 89.8% on ECG. Positive predictive value was 0.76.
Conclusions: MCG was acceptably sensitive and specific in identifying patients with CMD even in the absence
of specific findings on ECG and positive biomarker tests. Thus, MCG seems beneficial for the early diagnosis of patients with CMD.
Keywords: Coronary Microcirculation Dysfunction; Coronary artery disease; Magnetocardiography; Non-invasive detection

S011-3

Magnetocardiography Based Detection of Acute Myocardial Infarction with Single-vessel Disease

Yijing Guo [1], Hong Shen [1], Jian Ma [1], Chengxing Shen [1]

[1] *Department of Cardiology, Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine*

Objective: To explore the magnetocardiographic characteristics of acute myocardial infarction with single-vessel disease.
Methods: A total of 66 patients diagnosed as acute myocardial infarction with single-vessel disease and 78 healthy controls from June 2021 to June 2022 in Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine were selected as the research objects. The 1: 1 propensity score matching method was used to control the general data of patients, while SPSS21.0 was used to analyze the MCG parameters data.
Results: Before matching, the age of patients showed statistically significant difference between AMI group and control group, which became opposite after matching along with other data parameters. Dynamic MCG analysis showed significant difference between two groups. The analysis of MCG data revealed 12 parameters with statistically significant difference and 14 parameters with risk ratio more than one. Subgroup analysis showed significant changes of TT segment in LAD related AMI, while QR changed dramatically in RCA related AMI. Folowing logistic regression generated three AMI model with different vessel disease, which achieved high AUC.
Conclusion: Our study proved significant changes of MCG data in AMI with single-vessel disease, which provided great diagnose models by MCG.

S011-4

On-Site Computed Tomography-Derived Fractional Flow Reserve to guide management of patients With stable coronary artery disease using a machine learning: The TARGET Randomized Trial

Yundai Chen [1]

[1] *PLA General Hospital*

Background: Computed tomography-derived fractional flow reserve (CT-FFR) using on-site machine learning enables identification of both the presence of coronary artery disease and vessel-specific ischemia. However, it is unclear whether on-site CT-FFR improves clinical or economic outcomes when compared with the standard of care in patients with stable coronary artery disease.
Methods: In total, 1216 patients with stable coronary artery disease and an intermediate stenosis of 30% to 90% on coronary computed tomographic angiography were randomized to an on-site CT-FFR care pathway using machine learning or to standard care in 6 Chinese medical centers. The primary end point was the proportion of patients undergoing invasive coronary angiography without obstructive coronary artery disease or with obstructive disease who did not undergo intervention within 90 days. Secondary end points included major adverse cardiovascular events, quality of life, symptoms of angina, and medical expenditure at 1 year.
Results: Baseline characteristics were similar in both groups, with 72.4% (881/1216) having either typical or atypical anginal symptoms. A total of 421 of 608 patients (69.2%) in the CT-FFR care group and 483 of 608 patients (79.4%) in the standard care group underwent invasive coronary angiography. Compared with standard care, the proportion of patients undergoing invasive coronary angiography without obstructive coronary artery disease or with obstructive disease not undergoing intervention was significantly reduced in the CT-FFR care group (28.3% [119/421] versus 46.2% [223/483]; P<0.001). Overall, more patients underwent revascularization in the CT-FFR care group than in the standard care group (49.7% [302/608] versus 42.8% [260/608]; P=0.02), but major adverse cardiovascular events at 1 year did not differ (hazard ratio, 0.88 [95% CI, 0.59-1.30]). Quality of life

and symptoms improved similarly during follow-up in both groups, and there was a trend towards lower costs in the CT-FFR care group (difference, -¥4233 [95% CI, -¥8165 to ¥973]; P=0.07).

Conclusions: On-site CT-FFR using machine learning reduced the proportion of patients with stable coronary artery disease undergoing invasive coronary angiography without obstructive disease or requiring intervention within 90 days, but increased revascularization overall without improving symptoms or quality of life, or reducing major adverse cardiovascular events.

S011-5

The Clinical Research and Application of FFR in STEMI Complicated with Multi-vessel Disease

ChengXing Shen [1]

[1] *Shang hai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine*

Background: Previous studies have shown that for patients with ST-segment elevation myocardial infarction (STEMI) complicated with multi-vessel disease, after successful treatment of IRA, PCI at the same time can achieve complete revascularization, which can significantly improve the prognosis of patients compared with IRA alone. In this study, the effects of non-criminal vessel (IRA)PCI guided by blood flow reserve fraction (FFR) and coronary angiography (CAG) on the prognosis of patients with acute myocardial infarction (AMI) complicated with multi-vessel coronary artery disease were discussed.

Methods: Patients with AMI complicated with multivessel lesions who have been successfully treated by direct or emergency PCI were randomly assigned to receive FFR-guided non-IRA PCI(FFR≤0.80) or CAG-guided non-IRA PCI (non-IRA diameter stenosis > 50%). Both groups underwent complete revascularization, however, the timing of immediate treatment of non-IRA during direct or emergency PCI or phased treatment of IRA during the same hospitalization allowed doctors to decide for themselves. The main end points were all components of the primary end point, cardiac death, PCI-related myocardial infarction, spontaneous myocardial infarction, non-IRA revascularization and stent thrombosis.

Results: The all-cause mortality of FFR guidance group was significantly lower than that of CAG group. Cardiac death, myocardial infarction in FFR guidance group were significantly lower than CAG group. The incidence of cardiac death, spontaneous myocardial infarction or revascularization in FFR group was significantly lower than that in CAG guidance group.

Conclusions: In patients with AMI complicated with multi-vessel diseases, compared with choosing non-IRA lesions for PCI only according to the stenosis degree of vessel diameter shown by CAG, choosing non-IRA lesions (FFR≤0.80) for PCI according to the detection results of FFR can significantly reduce the risk of death, myocardial infarction or revascularization.

S011-6

Clinical Research and Application of FFR Combined with Intravascular Imaging

Jian Liu [1]

[1] *Peking University People's Hospital*

Background: In patients with coronary artery disease who are being evaluated for percutaneous coronary intervention (PCI), procedures can be guided by fractional flow reserve (FFR), intravascular ultrasonography (IVUS) or optical coherence tomography (OCT) for decision making regarding revascularization and stent implantation. However, the clinical outcomes when FFR and Intravascular Imaging are used for both purposes are unclear.

Methods: We divided patients who were being evaluated for PCI into precision therapy group and control group on whether to use FFR combined with intravascular imaging. FFR combined with intravascular imaging was to be used to determine whether to perform PCI and to assess PCI success. In the precision therapy group, PCI was to be performed if the FFR was 0.80 or less and minimal lumen area measuring either 3 mm2 or less or measuring 3 to 4 mm2 with a plaque burden of more than 70%. The primary outcome was a composite of death, myocardial infarction, or revascularization at 24 months.

Results: The precision therapy group had a lower frequency of PCI than the control group. There was no significant difference in the major adverse cardiac events between the control group and the precision therapy group. The number of stents placed per patient was significantly higher in the control group than in the precision therapy group.

Conclusions: In patients who were being evaluated for PCI, FFR combined with intravascular imaging reduced the number of lesions treated and stents, and the need for target-lesion revascularization.

S011-7

Application of FFR in the Stent Optimization and Prediction of Long-term Outcomes Post PCI

YaFeng Zhou [1]

[1] *The First Affiliated Hospital of Soochow University*

Background: In patients with multivessel CAD undergoing PCI, coronary angiography is the standard method for guiding stent placement. FFR measured before PCI has been shown to possess prognostic implications. However, the long-term outcomes after PCI with FFR are unclear.

Methods: We divided patients who were being evaluated for PCI into FFR group and control group on whether to use FFR before and after PCI. Patients randomized to control group underwent stenting of all indicated lesions, whereas those randomized to FFR group underwent stenting of indicated lesions only if the FFR was <or=0.80. The primary outcome was a composite of death, myocardial infarction, or revascularization at 12 months.

Results: The FFR group had a significantly lower frequency of PCI and a smaller number of stents than the control group. Despite satisfactory angiographic appearance, some patients demonstrated post-PCI FFR in the ischemic range (FFR ≤0.80). Patients who achieved final FFR >0.80 had significantly lower MACE compared to the final FFR ≤0.80 group. Final FFR ≤0.80 had incremental prognostic value over clinical and angiographic variables for MACE prediction.

Conclusions: FFR before PCI reduced the number of lesions treated and stents. The post-PCI FFR was a powerful independent predictor of long-term outcomes.

S011-8

Brachial and central hypertension in relation to coronary stenosis in patients with coronary angiography

Yu Chen [1], Ming-Xuan Li [2], Ying Wang [2], Xian Jin [1], Liang Liu [1], Zhen-Fa Zhou [1], Feng-Hua Ding [3], Rui-Yan Zhang [3], Yan Li [2], Cheng-Xing Shen [1]

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The clinical significance of central beyond brachial blood pressure (BP) remains unclear. In patients who underwent coronary angiography, we explored whether elevated central BP would be associated with coronary arterial disease (CAD) irrespective of the status of brachial hypertension. From March 2021 to April 2022, 335 patients (mean age 64.9 years, 69.9% men) hospitalized for suspected CAD or unstable angina were screened in an ongoing trial. CAD was defined if a coronary stenosis of ≥50%. According to the presence of brachial (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) and central (systolic BP ≥130 mmHg) hypertension, patients were cross-classified as isolated brachial hypertension (n=23), isolated central hypertension (n=93), and concordant normotension (n=100) or hypertension (n=119). In continuous analyses, both brachial and central systolic BPs were significantly related to CAD with similar standardized odds ratios (OR, 1.47 and 1.45, *P*<0.05). While categorical analyses

showed that patients with isolated central hypertension or concordant hypertension had significantly higher prevalence of CAD and the Gensini score than those with concordant normotension. Multivariate-adjusted OR (95% confidence interval [CI]) of CAD was 2.24 (1.16 to 4.33, *P*=0.009) for isolated central hypertension and 3.02 (1.58 to 5.78, *P*<0.001) for concordant hypertension relative to concordant normotension. The corresponding OR (95% CI) of a high Gensini score was 2.40 (1.26-4.58) and 2.17 (1.19-3.96), respectively. In conclusion, **r**egardless of the presence of brachial hypertension, elevated central BP was associated with the presence and severity of CAD, indicating that central hypertension is an important risk factor for coronary atherosclerosis.

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YOUNG SYMPOSIUM 5

Microcirculation Disturbance of Cardiovascular and Cerebrovascular Diseases and Drug Intervention

10:00-11:30 | Room 6

Y05-1

Subclinical myocardial aging: Physiological and Translational Perspective on Aging-related cardiovascular disease

Heng Ma [1]

[1] *Fourth Military Medical University*

Biological age is the greatest risk factor for nearly every major cause of death and disability, including cardiovascular disease (CVD). However, traditional biomedical research and clinical methods usually focus on waiting for people to get sick before treating individual diseases. Attempts to cure age-related CVD have proven unsuccessful, and the "disease-first" approaches has limited effect. Our research is dedicated to the association mechanism of biological aging and disease in the cardiovascular system, and identifying interventions that directly target the molecular markers of aging. The loss of intrinsic function of myocardial cells caused by aging is an important basis for irreversible myocardial injury. The aging of myocardial structure and function under the "clinical threshold" will seriously affect the clinical course and prognosis of cardiovascular diseases. Therefore, slowing the aging of the heart muscle is more valuable than treating the cardiovascular disease itself. It is of great significance to elucidate the pathogenesis and preventive measures of senile myocardial vulnerability. Using natural aging and genetically modified mouse model, we showed that protein "carbonyl stress" is an important driving force of myocardial aging and myocardial injury. Acetaldehyde dehydrogenase 2 was used as a breakthrough point to clarify its key role in myocardial protein homeostasis, survival and death. Interestingly, Chronic pain is closely related to the aging of the body. We found that chronic pain can induce "carbonyl stress" and lead to myocardial ischemia vulnerability. The targeted intervention of ALDH2 can inhibit the carbonyl stress of myocardium under the condition of chronic pain, effectively protect the myocardial SIRT1-LKB1-AMPK signal from carbonylation inactivation, and then improve the ability of myocardium to resist ischemia injury. Our data highlight a new mechanism of "subclinical myocardial aging" between "old" and "disease" was proposed.

Y05-2

Nanotechnology for the Diagnosis and Therapy of Ischemic Microvascular Diseases

Meng Qin [1]

[1] *National Chengdu Center for Safety Evaluation of Drugs, West China Hospital, Sichuan University, Chengdu, China*

Ischemic stroke is a significant threat to global health due to its high mortality and disability rate. Thrombolysis with intravenous alteplase is a primary therapy for acute ischemic stroke. However, it may trigger haemorrhage and cause secondary victimization to patients. Compensatory cerebral collaterals microvascular that develop in response to ischemic stroke help preserve the penumbral area where neurons are considered salvageable. Precisely evaluating collateral microvascular circulation and predicting the thrombolytic risk of stroke are essential for treatment decision-making and good prognosis. The development of a dual-targeted magnetic resonance imaging (MRI) nanoprobe based on magnetic iron oxide nanoparticles allows for the precise prediction of potential reperfusion haemorrhage through MRI. This noninvasive approach enables the evaluation of collateral microvascular circulation and ischemic inflammation, which are essential for treatment decision-making and good prognosis in acute ischemic stroke. In addition, targeting neuroimmune inflammation using a therapeutic based on nanocapsules of nerve growth factor (NGF) can mitigate oxidative stress and neuronal apoptosis, reshape microglia polarization in infarct sites, and alleviate microvascular microinfarct burden, leading to improved behavioral and cognitive function recovery. Therefore, targeting neuroimmune inflammation holds promise as a novel therapeutic approach for cerebral microinfarcts and other neurological diseases.

Y05-3

Calenduloside E Ameliorates Myocardial Ischemia-Reperfusion Injury through Regulation of AMPK and Mitochondrial OPA1

Min Wang [1], Guibo Sun [1]

[1] *Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College*

Calenduloside E (CE) is a natural triterpenoid saponin isolated from Aralia elata (Miq.) Seem., a well-known traditional Chinese medicine. Our previous studies have shown that CE exerts cardiovascular protective effects both in vivo and in vitro. However, its role in myocardial ischemia/reperfusion injury (MIRI) and the mechanism involved are currently unknown. Mitochondrial dynamics play a key role in MIRI. This study investigated the effects of CE on mitochondrial dynamics and the signaling pathways involved in myocardial ischemia/reperfusion (MI/R). The MI/R rat model and the hypoxia/reoxygenation (H/R) cardiomyocyte model were established in this study. CE exerted significant cardioprotective effects in vivo and in vitro by improving cardiac function, decreasing myocardial infarct size, increasing cardiomyocyte viability, and inhibiting cardiomyocyte apoptosis associated with MI/R. Mechanistically, CE restored mitochondrial homeostasis against MI/R injury through improved mitochondrial ultrastructure, enhanced ATP content and mitochondrial membrane potential, and reduced mitochondrial permeability transition pore (MPTP) opening, while promoting mitochondrial fusion and preventing mitochondrial fission. However, genetic silencing of OPA1 by siRNA abolished the beneficial effects of CE on cardiomyocyte survival and mitochondrial dynamics. Moreover, we demonstrated that CE activated AMP-activated protein kinase (AMPK) and treatment with the AMPK inhibitor, compound C, abolished the protective effects of CE on OPA1 expression and mitochondrial function. Overall, this study demonstrates that CE is effective in mitigating MIRI by modulating AMPK activation-mediated OPA1-related mitochondrial fusion.

Y05-4

Microglial NFAT5 aggravates neuroinflammation via regulating NLRP6 in experimental model of ischemia stroke

Gan Hui [2], Palahati Ailinuer [2], Zhao Jing [1]

[1] *Chongqing Medical University*

[2] *Children's Hospital of Chongqing Medical University*

Ischemic stroke is a severe cerebrovascular disease with high morbidity, high disability rate, and high mortality. Early thrombolysis to achieve vascular recanalization is the most effective way to treat the disease, but the ischemia-reperfusion injury caused by thrombolysis cannot be ignored. Therefore, studying the pathogenesis of cerebral ischemia-reperfusion injury has always been a hot topic in neuroscience field. Inflammatory response plays a key role in aggravating cerebral ischemia-reperfusion injury, and the activation of microglia triggers the inflammatory cascade after cerebral ischemia-reperfusion. Nuclear factor of activated T cells 5 (NFAT5) is a new member of the Rel transcription factor family. Inflammatory stimulus such as lipopolysaccharide (LPS) can promote the increased expression of NFAT5 in microglia, however, the role of microglia NFAT5 in cerebral ischemia-reperfusion injury has not been reported.

In this work, we explored the role of microglial NFAT5 in cerebral ischemia-reperfusion injury. Our results revealed that NFAT5 in microglia was upregulated after Middle Cerebral Artery Occlusion (MCAO) modeling and Oxygen-Glucose Deprivation/Reoxygenation (OGD/R) modeling. Additionally, we applied the recombinant Adeno-Associated Virus (rAAV) to specifically knock down microglial NFAT5 and found that knockdown microglial NFAT5 reduced the pro-inflammatory factors IL-1β, TNF-α and IL-6, decreased the activation of microglia and the numbers of myeloperoxidase (MPO) positive cells

and TUNEL positive cells, improved the loss of Nissl bodies, cerebral infarction and limb grip strength of mice after MCAO. Meanwhile, Hippocampal neuron cell (HT22) was treated with microglia cell line (BV2) conditional culture medium to simulate microglia OGD/R-induced neuronal injury. Our results demonstrated that knockdown of NFAT5 in BV2 cells attenuated the expression and secretion of pro-inflammatory factors and BV2 OGD/R-induced HT22 injury and apoptosis. Thus, microglial NFAT5 aggravated neuroinflammation, neuronal injury and cerebral ischemia-reperfusion injury in OGD/R and MCAO models.

Our previous study confirmed that the activation of NLRP6 inflammasome promotes inflammatory injury after cerebral ischemia-reperfusion, while the upstream regulatory mechanism of NLRP6 inflammasome remain unclear. In this work, we found that NFAT5 regulated the mRNA and protein level of NLRP6 and NLRP6 inflammasome activation. To ask how NFAT5 regulate the expression of NLRP6, we used bioinformatics prediction and found that there were two binding sites of Nlrp6 promoter (-1528bp—-1519bp and -666bp—-657bp) which transcription factor NFAT5 may binds to. To verify this, we truncated and mutated the NLRP6 promoter, the results of Chip-PCR and Dual-luciferase showed that NFAT5 interacted with Nlrp6 promoter, and NFAT5 promoted NLRP6 transcriptional activity by Nlrp6 promoter -1528bp—-1519bp sequence. These results suggested that NFAT5 regulated the mRNA level of NLRP6 at transcriptional level.

Next, we also ask whether NFAT5 regulates the expression of NLRP6 at the post-transcriptional level. To answer this question, Actinomycin D was administrated in BV2 cell to inhibit mRNA synthesis and detect the half-life of mRNA of NLRP6 by PCR. Notably, we observed that the half-life of mRNA of NLRP6 becomes longer after the OGD/R model, and knockdown NFAT5 shorten the half-life of the half-life of mRNA of NLRP6 and reduced the stability of NLRP6 mRNA. Since the stability of mRNA is related to 3'UTR and 5'UTR, we constructed the NLRP6 3'UTR and NLRP6 5'UTR plasmids to explore how NFAT5 affects the stability of NLRP6 mRNA. Our results revealed that NFAT5 may regulated the stability of NLRP6 mRNA via NLRP6 5'UTR.

In conclusion, our study demonstrated that transcription factor NFAT5 could exacerbate neuroinflammation and cerebral ischemia-reperfusion injury via regulating the mRNA level of NLRP6 at transcriptional level and post-transcriptional level.

YOUNG SYMPOSIUM 6

ESM/MCS/ANZMS Young Investigator Symposium

15:00-16:30 | Room 6

Y06-1

Role of Plasmacytoid Dendritic Cells in the Development of Macro- and Microvascular Dysfunction in Type 2 Diabetic Mice

Kiran Alluri [1], Balaji Srinivas [1], Belmadani Souad [1], Matrougui Khalid [1]
[1] *Physiological Science / EVMS*

Macro- and microvascular dysfunction in type 2 diabetes (T2D) significantly increases the risk of cardiovascular disease. In this study, we investigated the potential role of plasmacytoid dendritic cells (pDCs) in T2D-related vascular dysfunction. We depleted pDCs in male and female db/db mice (a T2D model) with anti-PDCA-1 antibodies for four weeks and found that pDC frequency was higher in db/db mice than in controls. Depleting pDCs did not affect body weight, glucose tolerance, or running distance but significantly improved vascular endothelial function and increased phosphorylation of endothelial nitric oxide synthase (eNOS). Our in vitro findings showed that pDCs from db/db mice blunted endothelial cells' eNOS phosphorylation in response to ATP compared to pDCs from control mice. The CD4+ population (progenitors of pDCs) and pDCs from db/db mice and isolated pDCs from control mice stimulated with high glucose and lipids mixture overnight display a significant increase in markers of ER stress, inflammation, and apoptosis. These data suggest that the frequency and function of pDCs are impaired in T2D and contribute significantly to vascular endothelial dysfunction independently of body weight and glucose metabolism. Our study highlights the potential therapeutic value of targeting pDCs for protecting against T2D-induced vascular dysfunction, suggesting a new avenue for intervention in managing T2D complications.

Y06-2

STIM1 disruption in regulatory T cells protects against renovascular hypertension-induced vascular endothelial dysfunction

Balaji Srinivas [1], Kiran Alluri [1], Jacob O'Regan [1], Souad Belmadani [1], Khalid Matrougui [1]
[1] *Physiological Science / EVMS*

Background: Regulatory T cells (Tregs) are critical in the development of cardiovascular diseases, but the role of STIM1 expression in Treg cells in renovascular hypertension-induced cardiovascular complications has not been studied. This study aims to investigate the effects of STIM1 disruption in Treg cells on macrovascular and microvascular dysfunction and cardiac structural complications induced by renovascular hypertension.

Methods: Male and female mice were randomly divided into six groups: control knockout male mice (Stim1Treg-/-), Stim1flx/flx male mice subjected to 2-kidney-1-clip (2K1C) surgery for four weeks, Stim1Treg-/- male mice subjected to 2K1C surgery for four weeks, control Stim1Treg-/- female mice, Stim1flx/flx female mice subjected to 2K1C surgery for four weeks, and Stim1Treg-/- female mice subjected to 2K1C surgery for four weeks. Body weight, blood pressure, running performance, cardiac hypertrophy and fibrosis, lung edema, inflammation, vascular endothelial function, and signaling were examined.

Results: Male and female Stim1flx/flx mice subjected to 2K1C for four weeks developed hypertension, cardiac hypertrophy, lung edema, diminished running performance, dysfunction of vascular relaxation endothelium-dependent, and cardiac hypertrophy and fibrosis. In contrast, male and female Stim1Treg-/- mice subjected to 2K1C for four weeks were protected from renovascular hypertension pathogenesis. Furthermore, in vitro data showed that isolated and cultured Treg cells from Stim1Treg-/- stimulated with angiotensin II overnight were protected from apoptosis compared to those from Stim1flx/flx.

Conclusion: This study highlights the crucial role of STIM1 in Treg

cells in the pathogenesis of renovascular hypertension. Targeting STIM1 in Treg cells may have potential therapeutic benefits in protecting against renovascular hypertension-induced complications.

Y06-3

Choriocapillaris perfusion correlates with retinal capillary perfusion in all three retinal vascular plexuses in type 2 diabetes

Natalia Rolinska [1,2], Kim Gooding [1,2], Silvia Balma [2], Andrew Forbes-Brown [1,2], Claire Ball [2], Christopher Kelsall [1,2], David Mawson [1,2], Kunihiko Aizawa [1,2], Alina Govier [1,2], Mark Gilchrist [1,2], Roland Ling [3], Angela Shore [1,2]

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[3] Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK

Background and aims: Reduced capillary perfusion are recognised hallmarks of diabetic microvascular damage, such as in the retina. *In vivo* choriocapillaris (CC) perfusion assessments are novel, and the relationship between the choroidal and retinal capillaries in type 2 diabetes (T2DM) is unknown. This study aims to investigate correlations between retinal and choroidal capillary perfusions in individuals with T2DM.
Materials and Methods: Fifty patients with type 2 diabetes mellitus (T2DM) were included in the study. An eye was randomly selected for each patient for optical coherence tomography angiography imaging. Developed ImageJ® macros assessed CC perfusion (CC flow void [FV] count, CC FV average area, and CC vessel perfusion density [CCVPD]) and retinal capillary perfusion [VPD], flow impairment zone [FIZ] count, and FIZ average size. Retinal capillary perfusion was calculated in the superficial, intermediate, and deep capillary plexuses (SVP, ICP, and DCP). Correlation (Pearson's/ Spearman's) were performed between markers of CC and retinal capillary perfusion.
Results: Mean CC FV count, CCVPD, and CC FV mean size were 1358 (SD=432), 56.22 (5.52)%, and 0.0025(0.0011)mm2, respectively. Across three retinal plexuses, mean retinal capillary VPD ranged from 27.38 (2.79)% to 34.84 (3.60)%, median FIZs counts from 6 (3, 10) to 9 (5, 15), median average FIZ areas from 0.0287 (0.0246, 0.0325)mm2 to 0.0339 (0.0259, 0.0441)mm2. In all plexuses, VPD was significantly positively correlated with CC FV count and CCVPD (correlation coefficients between 0.266 and 0.508, p-values ≤ 0.043) and negatively with FV size in SVP and ICP. FIZ mean area correlated significantly negatively with CCVPD only in ICP. FIZ count correlated negatively and positively with CC FV count and FV mean size, respectively, in SVP and ICP. After body fat (%), HDL-cholesterol, and systolic blood pressure adjustment, all correlations between retinal capillary perfusion and CCVPD remained significant. All plexuses followed the same direction of correlations with CC perfusion markers.
Conclusions: Generally, across the three plexuses, better retinal perfusion (higher VPD, VLD, FD) is associated with better CC perfusion (more numerous but smaller CC FVs and higher CCVPD), even after adjusting for potential confounders (body fat, blood pressure, HDL-cholesterol). CC perfusion correlated most strongly with retinal perfusion in the ICP.

Y06-4

QSYQ and its core blood component combination ameliorate diabetic peripheral arterial disease by simultaneously regulating T cell-mediated angiogenic and inflammatory processes

Li Peng [1], Shuang He [1], Huanyi Wang [1], Qinhua Shang [1], Yan Zhu [1]

[1] Tianjin University of Traditional Chinese Medicine

Objective: As the most common early-onset cardiovascular complication of diabetes, peripheral arterial disease (PAD) has a high prevalence and is an important cause of disability and death. Low-grade inflammation, congenital and adaptive immune activation are the characteristics of type-2 diabetes mellitus (T2D), characterizing T2D as an autoimmune disease. Since the mechanism of immune regulation for diabetic PAD remains to be fully elucidated, no targeted therapies have been presented to date. A component-based Chinese medicine QiShenYiQi (QSYQ) has been used to treat ischemic cardiovascular disease clinically and the aim of this study is to explore the efficacy and mechanism of QSYQ and its core blood component combinations for diabetic PAD.
Methods: The effects of QSYQ and a combination of its core blood ingredients on T cell activation, inflammation and angiogenesis were investigated in vitro and in vivo. High-glucose-treated human umbilical vein endothelial cell (HUVEC) culture was used to establish endothelial cell damage model in which cell migration and tube formation were evaluated by high content cell imaging. Hindlimb ischemia was performed in db/db and Db/m mice to establish a diabetic PAD model in which blood flow recovery, blood glucose and muscle fat content were measured by laser Doppler flowmetry, ELISA and microCT scan, respectively. Transcriptome and network pharmacology analyses were carried out, and derived gene targets were validated by real-time reverse transcription-polymerase chain reaction (RT-PCR), flow cytometry, and ELISA using ischemic muscle tissue samples or peripheral blood serum.
Results: In vitro, high glucose damaged the angiogenic capability of HUVEC with reduced tube-formation and migration. QSYQ treatment and its Qi-benefiting or blood-activating core blood ingredient combinations significantly restored these capacities. In a hindlimb ischemia model of diabetic db/db mice, QSYQ significantly accelerated the blood flow recovery, lowered blood glycose level, increased brown fat content, as well as trending reducing visceral fat. Transcriptome analysis of db/db mouse ischemic muscle tissues revealed that 1152 genes were downregulated, and 261 genes were upregulated significantly after QSYQ administration. Among the most prominently affected genes are those for the activation of CD4 T subtypes Th1 and Th2 pathways, indicating that the infiltration of CD4 T cells in the ischemic site was significantly changed after QSYQ administration. Indeed, treatment with T cell-depleting monoclonal anti-CD4 antibody GK 1.5 ablated the QSYQ effect on promoting blood flow recovery. QSYQ significantly upregulated the expression of pro-angiogenic genes PECAM, vWF and VEGF while downregulated the expression of anti-angiogenic gene TSP-1. Accordingly, GK1.5 antibody eliminated QSYQ regulation of these angiogenesis-related gene expression in the ischemic site of db/db mice. QSYQ also significantly reduced the CD4 T cell -associated gene expression of IFNγ, FOXP3, IL-4, IL6, TNF, and IL17A in the ischemic sites, as well as reduced the levels of immune factors associated with CD4 T cell infiltration, such as Th1 isotype-associated IFNγ and TNFαwith, Th2 subtype-associated IL6, and Th17 subtype-associated IL17A, in the peripheral blood of diabetic hindlimb ischemic mice.
Conclusion: QiShenYiQi and its core blood ingredient combinations repair high glucose-induced damage and promote angiogenesis in vascular endothelial cells and in ischemic db/db mouse hindlimb. The Qi-benefiting or blood-activating blood ingredient combinations contributed to these effects independently and differentially. Mechanistically, QSYQ acts at least in part by activation of T cell subpopulations at the ischemic site of diabetic mice, which simultaneously regulate angiogenesis and inflammatory genes to exert the vascular repair and anti-inflammatory effect. Our finds shed a new light on the immunoregulation of diabetic peripheral arterial disease and present a therapeutic potential of a component-based Chinese medicine for this complex disease.

Keywords: QiShenYiQi; Peripheral arterial disease; db/db mice; Angiogenesis; CD4+ T cells; Hindlimb ischemic model.

FREE ORAL COMMUNICATION 11

Vascular Hyperpermeability

08:30-10:00 | Room 6

F11-1

Endothelium-derived Cdk5 deficit aggravates air pollution-induced peripheral vasoconstriction through AT1R upregulation

Xiang Chen [1], Feng Han [1]

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Background: Fine particulate matter in the air, specifically those less than 2.5 μm (PM2.5), have been linked to an increased risk of cardiovascular diseases, ischemic stroke, and Alzheimer's disease beyond respiratory issues. PM2.5 air pollution has been shown to cause endothelial dysfunction, leading to various health problems through oxidative stress, systemic inflammation, and angiotensin II type 1 receptor (AT1R) signaling. However, the exact mechanisms behind this damage are not yet fully understood. Cyclin-dependent kinases (CDKs) play a role in cell regulation and proliferation, including in endothelial cells. Recent studies have highlighted the importance of CDK5 in endothelial cell migration and senescence, although its role in cardiovascular disease induced by PM2.5 is not well-known. Further research is needed to determine the function of Cdk5 in endothelial cells and its potential impact on vascular function and neurovascular cross-talk.

Method: We utilized PM2.5 to investigate the impact of fine particulate matter on various physiological processes in mice. Specifically, we examined the effects of PM2.5 on cell viability at the cellular level, as well as its impact on vascular function and cerebral blood flow. Additionally, we explored the novel mechanism of Cdk5 in endothelial dysfunction caused by PM2.5. By examining alveolar and peribronchial lesions in mice, we were able to gain a deeper understanding of the ways in which PM2.5 can impact the body at a cellular and molecular level. Our findings have important implications for public health policy and underscore the need for continued research into the health effects of air pollution.

Results: Exposure to PM2.5 for two months induced bronchial and pulmonary alveolar damage, increased peripheral vasoconstriction, and enhanced the response of medullary arterioles to external pressure mediated by endothelial Cdk5 deficit. The study found that Hangzhou PM2.5 exposure had no effect on AT1R expression in WT mice, but Cdh5-cre;Cdk5f/n mice showed upregulation of AT1R, accompanied by increased peripheral vasoconstriction. CDK5 was identified as a sensitive factor involved in PM2.5 damage to vascular endothelial cells. The study also examined the effect of PM2.5 on cerebral vessels and found no change in tight junction-related proteins of the BBB, but increased myogenic activity in medullary arterioles of Cdh5-cre;Cdk5f/n-PM mice. These findings suggest that Cdk5 deficits increase the sensitivity of vascular endothelial cells to PM2.5 and indicate the potential role of CDK5 in PM2.5-induced damage.

Conclusion: The lack of Cdk5 under conditions of PM2.5 exposure will further cause higher peripheral vasoconstriction and myogenic activity of the medullary arterioles. Therefore, CDK5 plays an important role in the growth, migration, and signal transduction of endothelial cells, which is also a sensitive sensor for the response of vascular endothelial cells to PM2.5.

F11-2

Water molecular using a Near-infrared spectroscope applied to discriminate the early-stage hyperglycemia and the effect of YanXueQingNao (YXQN)

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Introduction: What role does "water," which accounts for 70% of the living organism, play? Water molecules as a solvent are the key to forming specific three-dimensional structures of solutes, called biomarkers, and expressing biological functions. In other words, if we can visualize the interrelationship between solvents and solutes, we can answer the question, "Why do living organisms need water? This study will use a molecular water mirror as a digital biomarker for diagnosis.

Materials and Methods: The mice prepared C57BL mice (control, db/m), early hyperglycemia model (db/db), and treatment of YangXueQingNao (YXQN) 0.8g/kg/day for four weeks on db/db (db/+). Brain section and blood serum were applied to the histological and biochemical analysis and displayed the water molecular using Near-infrared spectroscope.

Results: The initial exacerbation of diabetes was associated with increased oxidative stress in the blood. A dysfunction of blood-brain barrier (BBB) function was observed due to the loss of Claudin5 in brain tissues. On the other hand, diabetic mice with YXQN recover the BBB function due to reduced oxidative stress. These differences in histological and biochemical results also indicated the molecular water patterns using the NIR spectroscope. It visualized the reader chart gram, characterized by water structure and redox-related wavelengths. The water mirror approach is to be used for diagnosis and effects of the medicine.

F11-3

An ex vivo method may evaluate vasoactivity induced by Hemoglobin-Based Oxygen Carriers in resistance vessels

Daoyuan Gao [1], Hang Yu [1]

[1] *Academy of Military Medical Sciences*

Hemoglobin-based oxygen carriers (HBOCs) are one kind of substitutes for red blood cell with oxygen carrying function. HBOCs are promising candidates to provide therapeutic oxygenation as a blood substitute in battles, emergencies, areas with an imbalance in blood supply and demand, or for patients unable to receive blood transfusion for religious or immunological reasons. Hypertension induced by vasoactivity after HBOCs infusion is one of the side effects, which restricts the clinical application of HBOCs. Therefore, it is essential to establish a vasoactivity evaluation method for the development of HBOCs. Resistance vessels are rich in smooth muscle, which plays an important role in regulating the diameter of vessels and systemic vascular resistance and blood pressure. At present, methods for vasoactivity evaluation based on resistance vessels have not been developed. In our study, the rat mesenteric artery (110~160 μm resting diameter), one of the typical resistance vessels, was applied for ex vivo vasoactivity evaluation. Based on the DMT120CP system, a micro-injection pump and a three-way valve were installed at the vascular entrance for device optimization. During the evaluation, noradrenaline was introduced as a vasoactivity magnifier with an optimized concentration ranging from 1×10-6 to 3×10-6 M. Methoxy Polyethylene Glycol Maleimide modified bovine hemoglobin (MalPEG-bHb) was synthesized and perfused to the vessel for vasoactivity evaluation, perfusion of bHb as the positive control, perfusion of PSS as the negative control. The results of vasoconstriction percentage induced by MalPEG-bHb samples synthesized in different batches showed coefficient of variation values less than 5%, indicating good repeatability. Besides, the ex vivo vasoactivity evaluation method established in this study showed higher sensitivity than the in vivo detection method reported in the literature. Thus, a simple and rapid method for the evaluation of vasoactivity induced by HBOCs was provided. The method is expected to be applied for the mechanism study of vasoactivity induction and elimination, promoting the clinical application of HBOCs.

Keywords: vasoactivity evaluation, resistance artery, noradrenaline, HBOCs

F11-4

Effects of sulforaphane on MGO-induced inflammatory response and pyroptosis in Human Umbilical Vein Endothelial Cells

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Sulforaphane (SFN), as a naturally occurring isothiocyanates (ITCs) found in green cruciferous vegetables, has anti-inflammatory actions in addition to antioxidant effects, but the detailed mechanisms is still unclear. NLRP3 inflammasome can sense many different factors derived from not only pathogen but also environment or host. Once recognized, pro-caspase-1is activated by autolystic cleavage and activated Caspase-1 mediates pyroptosis, which was widely participated in various human complicated diseases. This study intends to find out the effects of SFN on MGO-induced inflammatory response and pyroptosis in human umbilical vein endothelial cells (HUVECs) and its molecular regulatory mechanism. Our results revealed that SFN inhibited the MGO-induced decrease in the cell viability of HUVECs. MGO treatment activated the NLRP3 inflammasome signaling pathway, increased expression of NLRP3, ASC, Caspase-1 and cytosolic interleukin pro-IL-1β, and increased the expression of GSDMD-F, a protein associated with pyroptosis. Meanwhile, MGO can enhance the increase of GSDMD-N and IL-1β caused by Caspase-1 cleavage, increase ROS production and decrease the activities of anti-oxidative enzymes, such as SOD, CAT and GSH-Px, thus resulting the oxidative stress damage and further damage mitochondrial function. On the contrary, SFN alleviated MGO-mediated pyroptosis, inflammation and oxidative stress in a concentration-dependent manner, and had a protective effect on HUVECs. SFN attenuated MGO-induced inflammation, oxidative stress and pyroptosis via the Nrf2/HO-1 and NLRP3 inflammation signaling pathways. Conversely, inhibition of Nrf2/HO-1 and NLRP3 in vitro exacerbated MGO-induced pyroptosis, ROS production and vacuolar structure due to mitochondrial cristae membrane rupture, thereby diminishing the protective effect of SFN on MGO-mediated HUVECs. In addition, MGO significantly promoted endothelial injury, vascular cell pyroptosis, activation of NLRP3 inflammasome and high expression of interleukins IL-1β and IL-18. However, this effect was reversed and repaired by SFN. Moreover, SFN enhanced the activity of antioxidant enzymes, such as SOD, CAT, GSH-Px, promoted Nrf2/HO-1 activation and inhibited NLRP3, Caspase-1, GSDMD and IL-1β expression, thus significantly enhancing the protection of vascular endothelial function. Overall, these findings broaden our understanding of the mechanism by which SFN regulates inflammatory response and pyroptosis induced by MGO, with important implications regarding the potential application of SFN for the treatment of atherosclerotic diseases.

F11-5

Quantitative Assessment of OCT and OCTA Parameters in Diabetic Retinopathy With or Without Macular Edema: Single-center Cross-sectional Analysis

Bojun Zhao [1]

[1] *Ophthalmology /Shandong Provincial hospital*

Aim: The retinal and choroidal parameters were analyzed to understand the impairment of micro-circulation of both retina and choroid in patients with diabetic retinopathy (DR).

Methods: Fifty-five treatment naïve non-proliferative diabetic retinopathy (NPDR) patients (75 eyes) with type 2 diabetes mellitus (T2DM), including 28 patients (36 eyes) with DME, 27 patients (39 eyes) without diabetic macular edema (DME), and 14 healthy subjects (25 eyes), were enrolled in this study. The following parameters of DR patients with or without DME were evaluated: the foveal avascular zone area (FAZ-a), FAZ perimeter (FAZ-p), FAZ circularity index (FAZ-CI), total sub-foveal choroidal area (TCA), luminal area (LA), stromal area (SA), choroidal vascularity index (CVI), choriocapillaris flow area percentage, superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Results: SCP, DCP and the percentage of choriocapillaris flow area were significantly different between DR patients with and without DME. The DR patients presented lower LA, CVI and FAZ-CI in either with DME or without DME compared to that of health controls (all $p<0.05$). The percentage of choriocapillaris flow area in DR patients either with or without DME was significantly lower than health controls ($p<0.05$). SCP and DCP were significantly correlated with FAZ-a and FAZ-p but presented insignificant associations with FAZ-CI.

Conclusions: OCT and OCTA parameters, such as LA, CVI, FAZ-CI and the percentage of choriocapillaris flow area were reduced compared to that in controls, indicating the micro-circulations of retina and choroid in macular area were impaired in DR patients regardless with DME or without DME.

Keywords: choroidal vascularity index, diabetic macular edema, fovea avascular zone, OCT, OCTA

F11-6

Is the microvascular responsiveness to the locally delivered glucagon-like peptide-1 analogue, liraglutide, impaired in individuals with type 2 diabetes and retinopathy?

Christopher Kelsall [1,2], Jacqueline Whatmore [1], Katarina Kos [1], Claire Ball [2], Natalia Rolinska [1,2], Martin James [3], Roland Ling [3], Conor Ramsden [3], David Mawson [1,2], Hirut Von Lany [3], Angela Shore [1,2], Kim Gooding [1,2]

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[3] *Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK*

Aims: (1) examine whether the microvascular response to the glucagon-like peptide-1 (GLP-1) analogue, liraglutide, is impaired in individuals with type 2 diabetes and diabetic retinopathy. (2) explore whether the microvascular response is associated with changes in the endothelial glycocalyx.

Methods: Individuals with type 2 diabetes and moderate/advanced retinopathy (DM+DR group, n=24); individuals with type 2 diabetes and no microvascular complications (DM group, n=46); individuals without diabetes (Non-DM group, n=44) were recruited. Liraglutide at 1/10th minimum treatment dose (0.06mg), acetylcholine (ACh, endothelial-dependent vasodilator), saline (0.9%, microinjection control) were microinjected into the dermis of the forearm. Skin perfusion was assessed by laser Doppler imaging at baseline and then every 30seconds for 10minutes following microinjection. Skin perfusion response was expressed as stabilised response (SR, mean perfusion between 7.5-10minutes post-injection). Glycocalyx measures included assessing perfusion boundary region (PBR) of sublingual microvasculature and plasma levels of shed glycocalyx components (e.g. heparan sulphate and hyaluronan).

Results: Skin perfusion response to liraglutide was lower in the DM+DR group compared to non-DM and DM groups (Non-DM group median SR (25th,75th quartiles): 1.14(1.10,1.40)V; DM group: 1.19(1.12,1.34) V; DM+DR group 1.06(0.91,1.17)V, $p<0.01$). Interestingly, the response to the ACh, was attenuated in both DM groups compared to the non-DM group, and was significantly lower in the complicated DM group compared to the uncomplicated group (Non-DM group mean SR (SD): 2.04(0.39)V; DM group: 1.83(0.29)V; DM+DR group 1.68(0.25)V, p values <0.05). Plasma heparan sulfate was higher in the DM+DR group (mean (standard deviation): 121.5(88.9)ng/ml), compared to Non-DM (96.1(24.8)ng/ml) and DM (100.9(82.6) ng/ml) groups ($p<0.05$). PBR alterations in larger microvessels were observed with retinopathy.

Conclusion: Skin microvascular response to liraglutide is attenuated in individuals with type 2 diabetes and moderate/advanced retinopathy, there is also evidence of glycocalyx perturbations in these individuals.

SYMPOSIUM 39

Emerging Mechanisms Underlying Vascular Contributions to Cognitive Impairment and Dementia. (Small Vessels Big Problems)

08:30-10:00 | Room 1

039-SS1

Cerebral microcirculatory dysfunction and age-related cognitive impairments

Zoltan Ungvari [1]

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The maintenance of healthy cognitive function relies on the moment-to-moment adjustment of regional cerebral blood flow through neurovascular coupling (NVC) and a robust blood-brain barrier (BBB). Age-related cognitive decline is associated with impaired NVC responses and BBB disruption. One contributing factor is cellular senescence, a state of irreversible growth arrest associated with a DNA damage-induced cellular stress response. Senescent cells accumulates with age in various tissues, including the cerebral microcirculation. Senescent cells undergo marked phenotypic changes and secrete a range of factors that cause inflammation and tissue damage, collectively referred to as the senescence-associated secretory phenotype (SASP). The SASP can induce senescence in nearby cells, further promoting the spread of cellular senescence in the tissue. In the context of aging, senescent cells have been implicated in a wide range of age-related pathologies, including cancer, cardiovascular disease, and neurodegenerative disorders. In the brain, emerging preclinical evidence suggest that they contribite to age-related NVC impairment and BBB disruption. We have shown that senolytic treatment could improve NVC responses, BBB function, and cognitive performance in aged mice. Aged transgenic senescece reporter p16-3MR mice were treated with ABT263/Navitoclax, a potent senolytic agent known to eliminate senescent cells. The mice were evaluated for spatial memory performance, NVC responses, BBB permeability, and the presence of senescent endothelial cells. NVC was assessed by measuring cerebral blood flow responses in the somatosensory whisker barrel cortex evoked by contralateral whisker stimulation. The study found that NVC responses were significantly impaired in aged mice, but ABT263/Navitoclax treatment effectively eliminated senescent endothelial cells, improved NVC response, BBB integrity, and cognitive performance. These findings suggest that senolytic treatments could be a promising strategy for improving cerebromicrovascular function and preventing aging-induced cognitive impairment.

039-SS2

Enhanced Cerebral Hemodynamics and Cognitive Function Via Knockout of Dual-Specificity Protein Phosphatase 5

Fan Fan [1]

[1] *Medical College of Georgia, Augusta University, Augusta, GA, USA*

Alzheimer's Disease (AD) and Alzheimer's Disease-Related Dementias (ADRD) are neurodegenerative disorders. Recent studies suggest that cerebral hypoperfusion is an early symptom of AD/ADRD. Dual-specificity protein phosphatase 5 (DUSP5) has been implicated in several pathological conditions, including pulmonary hypertension and cancer, but its role in AD/ADRD remains unclear. The present study builds on our previous findings, demonstrating that inhibition of ERK and PKC leads to a dose-dependent dilation of the middle cerebral artery and penetrating arteriole, with a more pronounced effect in *Dusp5* KO rats. Both ERK and PKC inhibitors resulted in a significant reduction of myogenic tone in vessels from *Dusp5* KO rats. *Dusp5* KO rats exhibited stronger autoregulation of the surface but not deep cortical cerebral blood flow. Inhibition of ERK and PKC significantly enhanced the contractile capacity of vascular smooth muscle cells from both strains. Finally, a significant improvement in learning and memory was observed in *Dusp5* KO rats 24 hours after initial training. Our results suggest that altered vascular reactivity in *Dusp5* KO rats may involve distinct mechanisms for different vascular beds, and DUSP5 deletion could be a potential therapeutic target for AD/ADRD. Further investigations are necessary to determine the effects of DUSP5 inhibition on capillary stalling, blood-brain barrier permeability, and neurodegeneration in aging and disease models.

039-SS3

Diminished pericyte remodeling in the aged mouse brain causes prolonged disruptions to capillary flow

Andy Shih [1,2]

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[2] *Departments of Pediatrics and Bioengineering, University of Washington*

Most of the brain's vascular length lies beyond the artery and arteriole in the form of dense capillary networks. Blood cells move single file through capillaries and the diameter of individual capillaries exert a strong influence on blood flow. However, there remains a limited understanding of how blood flow is regulated in capillary networks and the consequence of flow dysregulation during age-related conditions such as Alzheimer's disease (AD) and Vascular Contributions to Cognitive Impairment and Dementia (VCID). In this talk, I will discuss our recent and unpublished findings using in vivo multi-photon imaging to visualize and modulate flow in brain capillaries in live adult and aged mice. Specifically, we have focused on pericytes and their role in control of capillary tone. I will describe the use of single cell optical ablation of pericytes to understand the consequences of pericyte loss on capillary flow dynamics with age, and repair mechanisms that help to restore pericyte coverage. Further, I will discuss our ongoing efforts to provide a more holistic view of brain capillary function using deep in vivo multi-photon imaging of capillary networks in cerebral white matter, a tissue with greater vulnerability in AD and VCID.

039-SS4

Capillary perfusion and mitochondria deficits in age-related neurodegeneration

Kevin Lin [1]

[1] *Louisiana State University*

Alzheimer's disease (AD) is a devastating pathology, which contributes massively to the long-term care burden in the United States. Women are more likely to develop dementia than men and tend to have a more rapid disease progression. While AD-related dementia is associated with tau and amyloid beta proteinopathies, derangements in cerebral blood flow (CBF) have also been observed in humans and mice. Additionally, in the aged AD brain cerebral vascular dysfunction has been shown to augment blood brain barrier (BBB) dysfunction. These changes may be due to the loss of junctional proteins and a subsequent ionic imbalance which contribute to neurovascular uncoupling and cognitive decline. Soluble levels of NOTCH1 is lower in human AD patients may be a factor in the BBB decline seen in AD. Reduced NOTCH1 is linked to blood brain barrier permeability (more leakage) resulting in brain damage. The intersection of the neuronal and vascular NOTCH1 functions make it a promising and target in AD and cerebrovascular pathology. PRMT4 has been shown to be a specific methylator of the intracellular domain of NOTCH1, methylation of this domain leads to its degradation. As stated previously, lower NOTCH1 is associated with BBB compromise. PRMT4 may be an upstream regulator of the NOTCH1 signaling cascade, and this axis can be manipulated through both pharmacological and AAV approaches to improve BBB stability in AD.

Results/Conclusion: Our preliminary data suggest that 3xTg female mice have 1) higher levels of PRMT4 protein and decreased NOTCH1 intracellular domain expression in the hippocampus, 2) enhanced type-1 PRMT methylation of NOTCH1, 3) reduced junctional proteins in the brain, 4) compromised neurovascular coupling, and 5) poor functional outcomes.

SYMPOSIUM 40

China-Japan Joint Symposium of Qi-Blood

08:30-10:00 | Room 2

040-SS1

Imaging metabolomics to decipher cancer metabolic systems in human cancer

MAKOTO SUEMATSU [1]

[1] *Central Institute for Experimental Animals*

Imaging metabolomics is an advanced technique that includes imaging mass spectrometry, functional MRI and surface-enhanced Raman imaging (SERS). We developed gold-nanoparticle-based Raman substrate that enabled to visualize many metabolites under infra-red illumination on tissues without staining or labelling (Shiota M, 2018 Nat Commun). Spatial information of the SERS signals can be achieved in cancer cell and the surroundling stromal regions separately. Investigation of patients-derived post-operative ovarian cancer tissues allowed us to determine polysulfide (PS), a reactive sulfur species generated through glycolysis and cystine via cystathionine beta-synthase (CSE), accounts for a biomarker that determines chemoresistance against anti-cancer cisplatin and post-operative overall survival (Honda K, et al. 2021 Redox Biol). Furthermore, SERS application to needle-biopsied samples of breast cancer revealed that PS detection in cancer-associated stroma, but not in cancer cells, is a hallmark of desmoplastic reaction and thus invasiveness of the cancer. Combining with automated data processing and machine-learning, SERS imaging serves as a powerful diagnostic tool to distinguish ductal carcinoma-in-situ (DCIS) and invasive breast cancer, and benefits for quality-of-life of patients (Kubo A, et al. Antioxidants 2023).

040-SS2

Herbal Medicine and Gastrointestinal Diseases

Hidekazu Suzuki [1]

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The gastrointestinal (GI) tract is controlled by the microcirculatory system and the autonomic nervous system, and is responsible not only for digestion and absorption, which are the front lines of energy metabolism, but also for biological defense and immunity as an organ in contact with the outside world. Therefore, external and internal attacks can lead to organic or functional diseases. There are many aspects to the success of integrative medicine in pathologies involving not only the gastrointestinal wall, but also the luminal environment in contact with it. In particular, herbal medicines are considered one of the most promising therapeutic modalities because they exert multi-step effects on organ networks such as the microcirculatory system, the autonomic nervous system, and the endocrine system, rather than on individual cells and molecules. For example, evaluating the scientific community's interest in herbal medicines in the treatment of functional dyspepsia and reviewing the preclinical pharmacology and clinical trial data of marketed herbal medicines revealed that effects on GI motility, secretory capacity, cytoprotection and psychotropic effects are often reported. Through rigorous clinical trials, many commercial herbal products have also been identified that report efficacy and safety for functional dyspepsia. One of the attractions of herbal medicines is their ability to simultaneously target multiple pathophysiological mechanisms.

040-SS3

Tonifying Qi with QiShenYiQi Prevents Microvascular Hyperpermeability Induced by Ischemia-Reperfusion

Yang Ye[1], Chun-Shui Pan[2], Jing-Yan Han[1,2]

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Microvascular hyperpermeability after interventional therapy for myocardial infarction and cerebral microvascular hyperpermeability after thrombolysis for stroke are still unresolved clinical problems. Based on the theory of Qi deficiency and microvascular hyperpermeability, traditional Chinese medicine (TCM) has developed effective clinical methods for treating microvascular hyperpermeability in the heart and brain by tonifying Qi to prevent hyperpermeability, but the underlying mechanism is not clear.

Qi, consisting of oxygen and nutrients, is utilized by the mitochondria to generate ATP. ATP is used to assemble G-actin into F-actin, which supports cell junctions of endothelial cells in microvessel, playing an important role in preventing microvascular hyperpermeability. In this study, we selected the compound TCM QiShenYiQi Pills (QSYQ), which could tonify Qi and prevent hyperpermeability. Using a rat model of microvascular hyperpermeability induced by ischemia-reperfusion (I/R) in the heart and cerebral microvascular hyperpermeability induced by rtPA thrombolysis 4.5 hours after stroke, we used a fluorescence microscope to observe FITC-labeled albumin leaking through venules, used immunofluorescence staining to observe the expression of intercellular junction proteins in venular endothelial cells, and used transmission electron microscopy to observe the changes in the structure of the wall of venules.

The results showed that QSYQ can inhibit the leakage of FITC-labeled albumin through venules induced by I/R in the rat heart, inhibit the low expression of intercellular junction proteins in microvascular endothelial cells, and inhibit the opening of intercellular junctions. This effect was related to the inhibition of low expression of mitochondrial ATP5D in endothelial cells and low expression of F-actin induced by I/R. QSYQ can also inhibit the leakage of FITC-labeled albumin, Evan's blue extravasation and brain edema after rtPA thrombolysis in the rat brain. This effect was related to the inhibition of low expression of ATP5D in brain tissue and low expression of intercellular junction proteins in microvascular endothelial cells. QSYQ can inhibit cerebral microvascular hemorrhage after rtPA thrombolysis, which is expected to be mediated by inhibiting the adhesion of neutrophils and monocytes to microvascular endothelial cells and their release of MMP2/9.

This study suggests that microvascular hyperpermeability is related to the low expression of ATP5D and the opening of intercellular junctions in microvascular endothelial cells. Tonifying Qi with QSYQ can improve intercellular junctions by upregulating ATP5D and block the leakage of albumin from microvascular intercellular junctions.

040-SS4

Phase-specific mechanism of Qi-benefiting- and blood-activating-components of QishenYiqi for the synergistic protection of ischemic stroke

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Stroke is a leading cause of mortality and disability worldwide, but its effective treatment is still sparse due to our poor understanding of its complex pathological manifestations. QiShenYiQi (QSYQ) is a component-based Chinese medicine with proven efficacy for cardiovascular diseases and a potential for cerebral ischemic disease. We adopted and improved various rodent models to mimic clinically relevant acute, subacute and recovery phases of ischemic stroke and investigated the efficacy and mechanism of QSYQ and its *Qi*-benefiting (Yiqi)- / and blood-activating (Huoxue)-components. **In the acute phase,** QSYQ inhibits neuroinflammatory response via down-regulation of IFNG-γ, IL-6, TNF-α, NF-κB p65, and TLR-4 and up-regulation of TGF-β1, preventing the brain from ischemic damage (Wang et al. B&P 2020). Furthermore, QSYQ attenuates acute thromboembolic stroke and carotid thrombosis, by inhibition of platelet-leukocyte aggregate formation and inhibition of platelet/leukocyte adhesion to endothelial cell via CD62P/PSGL-1 expression. A synergistic anti-thrombotic

effect of QSYQ is attributed to its components, with the *Qi*-benefiting component more inclined to down-regulate PSGL-1 expression in leukocyte, while the blood-activating component more inclined to down-regulate CD62P expression in platelet (Yu et al. B&P 2023). **In the subacute phase,** QSYQ inhibits ischemia-induced upregulation of brain-injury-related inflammatory regulator galectin-3, and pro-inflammatory cytokines TNF-α and IL-6. (Wang et al. Front Pharmacol 2021). Moreover, YQ and HX components of QSYQ differentially and synergistically protect the ischemic brain by regulating galectin-3-mediated inflammation and lysosomal-autophagy signaling (Wang et al. JEP 2022). **In the recovery phase**, QSYQ downregulates ICAM-1 and other inflammation-related factors, facilitating the recovery of motion and memory loss (Liu et al. B&P 2022). Overall, our studies reaffirms that a multi-faceted inflammation response exits through the entire pathologicalprocess of ischemic stroke, to which QSYQ and its components exert a coordinated protective effect via anti-inflammatory, anti-thrombosis and pro-angiogenic actions.

SYMPOSIUM 41

The Vascular Endothelium in Human Gastroenterology and Hepatology Diseases

08:30-10:00 | Room 4

041-SS1

Role of the vascular endothelium in irritable bowel syndrome

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Objective: Postinfectious IBS-D (PI-IBS-D) is difficult to treat due to its unknown pathophysiology. Extracellular vesicles (EVs) derived from human colon tissue and long noncoding RNAs (lncRNAs), including growth-arrest-specific-5 (GAS5), may play a key role in the underlying pathophysiology of PI-IBS-D. At the core of IBS associated pathophysiology changes are gut vascular endothelial cells, whose continual adjustments in gut structure and function coordinate vascular supply, immune cell emigration, and regulation of the colon tissue environment. Expansion of the endothelium in human IBS progression, mediated by post-inflammatory growth factors, cytokines, and chemokines is a hallmark of active human gut disorders and is closely related to human disease severity. The gut endothelium in newly formed or inflamed vessels differs from that in normal vessels in the production of and response to post-inflammatory cytokines, growth factors, and adhesion molecules which alter coagulant capacity, intestinal barrier function, and blood cell recruitment in gut injury. We sought to determine whether altered colonic-EV lncRNA signaling leads to gastrointestinal and vascular endothelial dysfunction and heightened visceral nociception in PI-IBS-D patients.

Design: To investigate the translational role of colonic EV lncRNA in PI-IBS-D patients, human colonoids, PI-IBS-D tissues, and anti-GAS5 Vivo-Morpholinos were used to determine GAS5, VEGF, ICAM1, miR-23a/b, and N-methyl-D-aspartate (NMDA) receptor subunit type 2 (NR2B) signaling. Intraperitoneal injection of colonic EVs from PI-IBS-D patients into wild-type and Rab27a/b$^{-/-}$ mice was performed to determine whether these EVs alter the gut angiogenesis and visceromotor response (VMR) to colorectal distension (CD) in vivo.

Results: Colonic EVs from PI-IBS-D patients, but not controls, had reduced miR-23a/b expression. Increased expression of GAS5, VEGF, ICAM1, and NMDA NR2B correlated with abdominal pain scores, along with significantly enhanced staining of vascular endothelium marker CD31 and vWF. This colonic EV-mediated lncRNA signaling pathway was verified in human cell culture and colonoids. Intraperitoneal injection of PI-IBS-D colonic EVs into mice (P-EV mice) increased the VMR threshold to CD, whereas intraperitoneal injection of oligo-miR-23 precursors into P-EV mice restored the VMR threshold to CD by decreasing NMDA NR2B signaling. Intraperitoneal injection of anti-GAS5-Vivo-Morpholino into P-EV mice increased miR-23 levels, and thus decreased NR2B expression. The surface of gut vascular endothelial cells is covered with cell adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) that mediate the adhesion and extravasation of leukocytes and may play a pivotal role in post-inflammatory response during the development and progression of human IBS. Interestingly, the expressions of ICAM-1 and VCAM-1 were significantly decreased in anti-GAS5-Vivo-Morpholino treated TNBS animals, along with the reductions of leukocyte marker CD18, monocyte marker ly6g and vascular endothelium marker CD31 and vWF.

Conclusions: The novel findings of our current study show that colonic EVs are the mediators of cell-cell communications in PI-IBS-D patients and act as biological messengers that transfer ncRNA to key vascular endothelial and intestinal signaling pathways that drive persistent gastrointestinal symptoms following enteric infections. EVs act as internal messengers that alter gastrointestinal and vascular endothelial function and increase visceral nociception and contribute to the pathophysiology of PI-IBS-D. Key roles for the vascular endothelium in mediating and aggravating post-inflammatory responses in IBS have

also been defined. Strategies to deliver EVs to modulate the GAS5/VEGF/ICAM1/miR-23/NMDA NR2B axis signaling may lead to new and innovative treatments for PI-IBS-D patients.

041-SS2

Hepatocyte ADK Promotes Steatotic Liver Disease and Increases Angiogenesis

Chaodong Wu [1]

[1] *Nutrition*

Steatotic liver disease (SLD, formally non-alcoholic fatty liver disease) is characterized by excessive fat deposition in hepatocyte (steatosis) and progresses to steatohepatitis. The latter is the advanced form of SLD and serves as the most common causal factor of terminal liver diseases. The outcomes from multiple studies involving human subjects with SLD and mouse models of SLD have demonstrated that excessive fat deposition in hepatocytes results from increased fat synthesis/storage and/or decreased fatty acid oxidation/very low-density lipoprotein secretion. In addition, increasing evidence implicates either a detrimental or protective effect of angiogenesis in the pathophysiology of SLD, depending on the types of causal factors and stages of SLD. However, it remains largely unknown how hepatocyte fat metabolic dysregulation arises. It also is not clear whether and how angiogenic program is dysregulated during SLD. As an enzyme that catalyzes the removal of adenosine and helps regulating the methionine cycle, adenosine kinase (ADK) is shown to regulate liver function and angiogenic programs. The current study aimed to elucidate how the ADK in hepatocytes promotes SLD and hepatic angiogenesis in mice. While examining the link between hepatocyte ADK expression and the degrees of steatotic liver diseases using the sections of livers from human subjects, we provided the primary evidence validating that hepatic amount of ADK was significantly increased relative to that in livers from subjects without SLD. Since ADK is expressed at very high levels in hepatocytes, we sought to definitively determine the role played by ADK in hepatocyte using mice in which ADK was over-expressed only in hepatocytes. Compared to control mice, hepatocyte-specific ADK-overexpressing mice displayed significant increases in the degrees of hepatic steatosis and inflammation, as well as adiposity and adipose tissue inflammation. To gain mechanistic insights, primary hepatocytes and liver non-parenchymal cells (NPCs) of the mice were isolated and subjected to RNA sequencing (RNAseq) and single-cell RNAseq, respectively. The combined analyses showed significantly decreased expression of genes for fatty acid oxidation that were associated with increased hepatocyte DNA methylation in PPARa gene. In addition, ADK-driven hepatocyte fat deposition was accompanied by increased hepatic production of double-stranded DNA (mtDNA), leading to increased proinflammatory activation of liver macrophages in a manner involving stimulator of interferon genes (STING). Analysis of hepatocyte-NPC crosstalk indicated increased activation of liver NPCs including endothelial cells in response to ADK overexpression. Consistently, the expression of CD31 in VEGFr in livers from hepatocyte-specific ADK-overexpressing mice was significantly increased compared to that in livers from control mice. Taken together, these results suggest that ADK enhances hepatic angiogenic program while promoting liver aspects of SLD.

041-SS3

Vascular Endothelial Growth Factor Signaling and Angiogenesis in Post-Infectious Irritable Bowel Syndrome

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Background: Irritable Bowel Syndrome (IBS), is a common GI disorder with persistent abdominal pain and alterations in bowel habits. Available IBS treatments are not ideal as the pathophysiologic mechanisms are not fully understood. The etiology of abdominal pain in postinfectious, diarrhea-predominant irritable bowel syndrome (PI-IBS-D) is unknown, and few treatment options exist. Angiogenesis is an important component of pathogenesis of post-inflammatory bowel syndrome. Post inflammation responses are dependent on angiogenesis and this angiogenesis is modulated by inflammatory cytokines in PI-IBS-D. Catechol-O-methyltransferase (COMT), an enzyme that inactivates and degrades biologically active catecholamines, plays an important role in numerous physiologic processes, including modulation of pain perception. Among the regulators of angiogenesis, the role of catecholamines (epinephrine, norepinephrine, and dopamine) is of interest due to their diverse roles in the development and progression of human IBS. Our objective was to determine the mechanism(s) of how decreased colonic COMT in PI-IBS-D patients contributes to the chronic abdominal pain phenotype via VEGF and angiogenesis signaling pathways after enteric infections.

Methods: Colon neurons, epithelial cells, and macrophages were procured with laser capture microdissection from PI-IBS-D patients to evaluate cell-specific colonic COMT, microRNA-155 (miR-155), VEGF, ICAM1, VCAM1, CD11a, CD18, CD31, vWF and tumor necrosis factor (TNF) α expression levels compared to recovered patients (infection cleared: did not develop PI-IBS-D) and control individuals. COMT-/-, colon-specific COMT-/-, and miR-155-/- mice and human colonoids were used to model phenotypic expression of COMT in PI-IBS-D patients and to investigate VAGF and angiogenesis signaling pathways linking abdominal pain. Citrobacter rodentium and trinitrobenzene sulfonic acid animal models were used to model postinflammatory changes seen in PI-IBS-D patients.

Results: Colonic COMT levels were significantly decreased and correlated with increased visual analog scale abdominal pain ratings in PI-IBS-D patients compared to recovered patients and control individuals. Colonic VEGF-A, VEGF-C, ICAM1, CD11a, CD18, CD31, CD34, vWF, miR-155 and TNF-α were increased in PI-IBS-D patients with diminished colonic COMT. COMT-/- mice were used to model phenotypic expression of COMT in PI-IBS-D patients. To investigate the effects of COMT, the inflammatory responses in TNBS-induced post-inflammatory irritable bowel syndrome (PI-IBS) model were defined in systemic and colon specific COMT knockout mice. COMT-/- mice had significantly increased expression of VEGF-A, VEGF-C, ICAM1, CD11a, CD18, CD31, CD34 and vWF in colon tissues with or without TNBS treatment; and enhanced miR-155 and TNF-α expressions in both colon tissues and dorsal root ganglia were observed. Anti-TNF-α antibody (cV1q) or its isotype antibody control were given IP to post-TNBS and post-C. rodentium mice. We tested visceral hypersensitivity at 3 and 7 days following anti-TNF-α treatment compared to isotype control and there was a significant reduction in visceral hypersensitivity. Introduction of cV1q antibody (anti-TNF-α) into mice reversed visceral hypersensitivity after C rodentium and trinitrobenzene sulfonic acid. This data suggests a mechanistic link between abdominal pain and the COMT/VEGF/Angiogenesis/miR-155/TNF-α axis and indicates the possible therapeutic potential of anti-VEGF/angiogenesis, anti-miR-155 or anti TNF-α therapy in PI-IBS-D patients.

Conclusions: Through the present study we acquired a better understanding of how decreased colonic COMT activity interacts with VEGF/Angiogenesis/TNF-α via specific miRNAs to contribute to chronic abdominal pain in PI-IBS-D patients. Achievement of this objective increases our understanding of the mechanisms involved in the development of visceral pain in PI-IBS-D patients. Decreased colonic COMT in PI-IBS-D patients drives abdominal pain phenotypes via the COMT/VEGF/Angiogenesis/miR-155/TNF-α axis. These important findings will allow new treatment paradigms and more targeted and personalized medicine approaches for gastrointestinal disorders after enteric infections. COMT agonist may serve as the angiogenesis modulators for the development of drugs in the therapy for PI-IBS.

041-SS4

Aging associated endothelial dysfunction in chronic liver diseases

Ying Wan [3], Elise Slevin [1,2], Wenjuan Xu [1,2], Xuedong Li [3], Tian Li [3], Yudian Zhang [3], Jennifer Mata Salinas [1,2], Fanyin Meng [1,2]

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Background: Chronic liver diseases including cholestasis can lead to endothelial dysfunction and dedifferentiation of liver sinusoidal endothelial cells (LSECs) with loss of fenestrations, deposition of a basement membrane, and surface expression of CD31 and CD34, a process that has been termed sinusoidal capillarization and that precedes liver fibrosis. MicroRNA-34a (miR-34a) is emerging as an important mediator of aging associated vascular dysfunction and injury. miR-34a increases with aging in vessels and induces senescence and the acquisition of the senescence-associated secretory phenotype (SASP) in vascular endothelial cells and progenitor cells. We aimed to define the aging associated microRNA regulated vascular remodeling, intussusceptive angiogenesis, and liver fibrosis during cholestatic liver injury.

Methods: To demonstrate the overall ultrastructure of the vascular damage during cholestatic liver injury, we injected mice via the portal vein with resin to create vascular corrosion casts of the liver with bile duct ligation (BDL) in aged miR-34a knockout and WT control mice for scanning electron microscopy analysis. CD34+ cells were isolated from mouse liver using laser capture microdissection (LCM). A capture probe covalently bound to an oligonucleotide containing biotin and a color-coded reporter probe were designed for 84 endothelial function-related genes and analyzed with the nCounter Single Cell Gene Expression Assay.

Results: We demonstrated that miR-34a expression was significantly increased in human primary sclerosing cholangitis (PSC) livers along with the enhanced ductular reaction, cellular senescence, and liver fibrosis. Using aging associated BDL mouse model of cholestatic liver injury to evaluate vascular injury and deranged angioarchitecture of the liver by 3-dimensional morphology of the hepatic microcirculation, results showed that BDL induced extensive remodeling of the sinusoids with a plexus-like appearance. Casts revealed pores and endovascular pillars, the corresponding intraluminal structures to the pores of intussusception, the hallmark of intussusceptive angiogenesis after vascular injuries. The process of vascular injury associated angiogenesis, vascular remodeling and rearrangement after BDL led to an increased variation of the sinusoidal diameter and increased branching within the microcirculation. Lack of miR-34a in vivo reversed the serum ALT level, and restored the levels of Sirt1 coupled with decreased NOS3 expression as well as the reduced levels of TNFα, CCl2, IL-1β, IFNβ and IL-7 in LCM isolated CD34+ cells analyzed by nCounter single cell gene expression assay. Depletion of miR-34a in vivo also induced a significant down-regulation of profibrogenic genes and MMPs in total liver tissues and LCM isolated CD34+ cells by single cell gene assay from BDL mice liver, along with the reduced vascular remodeling and intussusceptive angiogenesis.

Conclusion: By 3-dimensional morphology of the hepatic microcirculation and single cell analysis, our discovery that aging associated microRNA-34a as an important signaling pathway in hepatic vascular endothelium that governs vascular structure and function in the liver, regulates intussusceptive angiogenesis, and contributes to liver fibrosis during cholestatic liver injury implicates an exciting field in which the epigenomic microRNAs of endothelial dysfunction may be manipulated with potential therapeutic benefits.

SATELLITE SYMPOSIUM 12

Microcirculation and Osteonecrosis

08:30-10:00 | Room 6

S12-1

Marrow adipogenic lineage precursors (MALPs) facilitate bone marrow recovery after chemotherapy

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Introduction: Chemotherapy-induced hematopoietic toxicity is a multifactorial challenge in the treatment of oncology patients. As a common chemotherapeutic agent, 5-fluorouracil (5-FU) drastically reduces the number of cells in both the myeloid and lymphoid compartments. The resultant bone marrow suppression is an important dose-limiting side effect of chemotherapy. At a low dose, 5-FU-induced bone marrow damage is often recovered over the time. However, the mechanism underlying this recovery is largely unknown. Using single cell RNA-sequencing (scRNA-seq) technique, we previously discovered a novel subpopulation of mesenchymal cells, marrow adipogenic lineage precursors (MALPs), which express adipogenic markers but does not process lipid droplets. Our studies have demonstrated their critical roles in regulating bone marrow microenvironment in healthy and diseased mice [1-3]. Here, we utilized a single dose of 5-FU to damage bone marrow and investigated the role of MALPs in bone marrow recovery after chemotherapy.

Methods: *Animals*- All animal work performed in this report was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania. *Col2-Cre Tomato (Col2/Td)*, *Adipoq-Cre Tomato (Adipoq/Td)*, and *Adipoq-Cre DTR Tomato (Adipoq/DTR/Td)* mice were generated. At 1-2 months of age, mice received a 5-FU injection at 150 mg/kg and their bones were harvested at days 5 and 14 for analysis. To ablate MALPs, *Adipoq/DTR/Td* mice received a 5-FU injection followed by vehicle (1xPBS) or diphtheria toxin (DT) injections (50 μg/kg) every other day for 14 days. *ScRNA-seq analysis*- Sorted Td+ cells from the endosteal bone marrow of 1-1.5-month-old *Col2/Td* male mice with no treatment (control, 2 batches, n=5 mice) or at 5 days after a 5-FU injection (1 batch, n=3 mice) were subjected to library construction and sequencing. Unsupervised clustering was conducted by UMAP to generate cell clusters of the overall cell populations. *Whole mount immunofluorescence*- Bones were processed for 50 μm-thick whole mount cryosections and stained with indicated antibodies. *Statistics*- Analyses were conducted using t-tests by *Prism GraphPad 8.4.3.*

Results: A single 5-FU injection did not alter mouse normal activities but caused acute bone marrow damage, leading to a drastic 93% reduction in cellularity and a 2-fold increase in vessel diameter in femoral bone marrow at day 5 (Fig. 1). Since mesenchymal cells provide niches for hematopoietic cells in bone, we next analyzed mesenchymal lineage cells after 5-FU treatment. *Col2-Cre* labels the entire mesenchymal lineage cells in bone [1]. ScRNA-seq on Td+ cells sorted from bone marrow of *Col2/Td* mice with or without 5-FU treatment generated similar mesenchymal cell clusters consisting of early mesenchymal progenitors (EMPs), late mesenchymal progenitors (LMPs), lineage committed progenitors (LCPs), osteoblasts (OBs), osteocytes (Ocys), and MALPs (Fig. 2A). Merging these 2 datasets revealed that the mesenchymal progenitor pool (EMPs and LMPs) is drastically shrunk while MALP population is greatly expanded after 5-FU injection (Fig. 2B). Analyzing differentially expressed genes (DEGs) found that 5-FU upregulates many myofibroblast markers (*Acta2, Tagln, Myl9* etc) in MALPs, indicating a myofibroblast transformation. Using *Adipoq-Cre* to label MALPs *in vivo*, we observed that 5-FU significantly increases the number of MALPs in bone marrow (Fig. 3). Immunostaining validated the increase of myofibroblast marker expression in MALPs (Fig. 4). By day 14 after 5-FU injection, bone marrow cellularity and vessels were partially recovered in *Adipoq/DTR/Td* mice (Fig. 5). However, DT injections after 5-FU injection eliminated MALPs (Td+ cells) and blocked the recovery of bone marrow.

Discussion: In this study, we demonstrated that transient expansion of MALPs after 5-FU injury facilitates bone marrow repair. This finding revealed the plasticity of MALPs and a novel mechanism for the recovery of 5-FU-induced bone marrow damage and. Our research highlights the potential of seeking new target for alleviating chemotherapy damage on bone.

S12-2

Magnesium-based Orthopaedic Implants Induced Osteogenesis and Angiogenesis through Upregulation of Neuropeptides

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Magnesium-based orthopedic implants have emerged as a promising alternative to conventional metallic implants due to their biodegradability and biocompatibility. The use of these implants can promote bone regeneration and angiogenesis through the upregulation of neuropeptides. Specifically, the neuropeptide calcitonin gene-related peptide (CGRP) has been identified as a key regulator of both osteogenesis and angiogenesis during bone regeneration.

Studies have shown that the biodegradation behavior of magnesium-based implants can promote the osteogenic effects of magnesium ions, which lead to enhanced bone formation. For example, in vivo corrosion of four magnesium alloys has been found to induce an increase in bone response. Furthermore, innovative magnesium-based intramedullary nails have been developed to enhance long-bone fracture repair. These implants release magnesium ions in a controlled manner, leading to increased bone density and improved fracture healing.

Additionally, daily injection of Mg2+ directly to the dorsal root ganglia has been shown to enhance new bone formation at the peripheral cortex of the ipsilateral femur. In vitro studies have also shown that neuropeptide CGRP can enhance mesenchymal stem cells' osteogenic differentiation. This suggests that the upregulation of CGRP by magnesium ions can promote bone regeneration and angiogenesis.

Overall, magnesium-based orthopaedic implants have a unique mechanism of action in promoting bone regeneration and angiogenesis through the upregulation of neuropeptides, making them a promising alternative to conventional metallic implants. However, further research is needed to fully understand the mechanisms underlying the effects of magnesium ions on neuropeptides and bone regeneration. These findings have the potential to revolutionize the field of orthopaedic implants and improve patient outcomes.

S12-3

Advancements in the Application of Platelet-Rich Plasma (PRP) for Musculoskeletal Disorders

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Platelet-rich plasma (PRP) therapy has been gaining increasing attention in recent years as a potential treatment for musculoskeletal disorders. PRP is derived from the patient's own blood and contains a high concentration of growth factors that can stimulate tissue repair and regeneration. This makes it an attractive option for treating injuries and degenerative conditions affecting muscles, tendons, ligaments, and joints.

Several clinical studies have investigated the effectiveness of PRP

therapy for various musculoskeletal conditions, including osteoarthritis, tendinopathy, and muscle injuries. While some studies have reported promising results, others have shown no significant difference between PRP and placebo treatments. The lack of standardization in PRP preparation and delivery methods may contribute to the variability in outcomes across studies.
Despite these challenges, PRP therapy remains a promising avenue for treating musculoskeletal disorders. Further research is needed to optimize PRP preparation and delivery methods and to identify which patient populations are most likely to benefit from this treatment. As the field continues to evolve, PRP therapy may become a more mainstream option for managing musculoskeletal conditions.

S12-4

Autocrine Activity of Extracellular Vesicles Induced by Icariin and Its Effectiveness in Glucocorticoid-Induced Injury of Bone Microvascular Endothelial Cells

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Glucocorticoids could induce injury and apoptosis of bone microvascular endothelial cells (BMECs) in the femoral head, which is associated with the development of osteonecrosis and osteoporosis. Icariin is a prenylated flavonol glycoside isolated from Epimedium brevicornum, serving as the main active pharmaceutical constituent to treat bone loss. Currently, the impact of the autocrine activity of extracellular vesicles (EVs) induced by icariin on the glucocorticoid-induced injury of BMECs is still to be confirmed.
In this study, EVs were isolated from BMECs treated with and without icariin by super-speed centrifugation. Although icariin treatment would not significantly change the size and total protein content of BMECs-derived EVs, expression of EVs-carried vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGF-β1) was enhanced and numerous miRNAs involved in cell proliferation and apoptosis were upregulated (e.g., hsa-miR-1469 and hsa-miR-133a-5p) or downregulated (e.g., hsa-miR-10b-5p) ($p < 0.05$). A total of 29 differentially expressed inflammatory factors were detected between the EVs secreted by BMECs from the Icariin-treated group and the Model group. The EVs secreted by BMECs could improve cell viability, decrease cell apoptosis, and promote cell migration and angiogenesis under the intervention of glucocorticoids. Meanwhile, icariin intervention could reinforce these protective effects of BMECs-derived EVs.
To sum up, the present study indicates that icariin acts as a promising candidate for treating glucocorticoid-induced injury of BMECs and bone diseases, partially through the autocrine activity of EVs. In vivo or animal studies are still required to better understand the function of BMECs-derived EVs.

SATELLITE SYMPOSIUM 13

Microcirculation and Translational Medicine

08:30-10:00 | Room 7

S13-1

Development of high-performance MRI contrast agent for tumor diagnosis and therapy

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Early diagnosis and therapy of critical illness is the huge challenge in medicinal research. Construction of new magnetic resonance imaging (MRI) contrast agent provide a method to overcome this trouble. Based on the requirement of accurate diagnosis and therapy, we focus on developing high-performance and multi-functional MRI contrast agent for basic and translation research. According to the quantum mechanical outer sphere and SBM theory, we developed MRI contrast agent with high T_1 or T_2 relaxivities and proper circulation behavior through adjusting some key parameters. Those are magnetization, size, effective radii, homogeneity of surrounding generated magnetic field, crystal phase, electronic relaxation time, and surface modification of nano-sized MRI contrast agent. Besides, strategies to increase the *in vivo* contrast efficiency of MRI contrast agent have been investigated by endowing their with environment response capacity and optimized interface structure. Based on the MRI contrast agent assistant accurate tumor diagnosis, we further developed novel strategies to improve the efficacy of chemo, chemodynamic, and photodynamic therapy and fulfill imaging-guided radical therapy of cancer.

S13-2

The Interplay between Phase Separation and Enhancer Mechanisms in Disease Progression

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Effective gene regulation is crucial for cellular function, and dynamic control of enhancer repertoires drives stage-specific transcription during tissue development and disease progression. Our research program aims to comprehensively understand the regulation of enhancer dynamics in response to signaling and its impact on gene regulation. By doing so, we seek to develop innovative approaches for preventing and treating enhancer-related diseases. Our research spans multiple levels, from enhancer chromatin organization to the coordination of enhanceosome components and the molecular interactions driving enhancer assembly. Our previous studies have revealed that enhancer dynamics can be induced by 1) acute hormone stimulations, which can build up the active enhancer machinery in just minutes at many chromatin sites to turn on gene expression, and 2) chronic disease progression towards endocrine therapy resistance, which reprograms the ERα cistrome to evade endocrine therapies in breast cancer. These novel observations highlight the contributions of enhancer dynamics in both healthy and disease conditions. While enhancer activation relies on proper enhancer assembly, the molecular mechanisms underlying this process, including protein-DNA and protein-protein interactions, remain unclear. Our research has uncovered important principles of enhancer assembly, including combinatorial interactions of multiple transcription factors on hormone-regulated enhancers, and phase-separated condensation mediated by multivalent interactions of hormone receptors. To further investigate enhancer assembly, we employ diverse genetic, genomic, and imaging-based approaches, including the LacO arrays/LacI-fluorescence proteins system and single-molecule tracking (SMT) imaging to study phase separation of enhanceosome components and their contributions to enhancer assembly.
By unraveling the intricate interplay between phase separation and enhancer mechanisms, our research offers insights into gene regulation during disease progression and paves the way for the development of targeted therapeutic interventions.

S13-3

Identification and validation of autoantibodies against tumor-associated antigens as potential serological biomarkers in osteosarcoma: SERPA combined with protein microarray

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Osteosarcoma (OS) is a primary solid tumor of bone, one of the most common and harmful primary malignant tumors in childhood and teenagers. However, due to the lack of sensitive and specific biomarkers, early diagnosis of OS is difficult. It's important to search for an optimal clinical diagnostic biomarker such as anti-tumor-associated antigen (TAA) autoantibody for early diagnosis of OS. Here we aimed to screen and identify new serum TAAs that could be used as OS diagnostic biomarkers by serological proteome analysis (SERPA) and focused protein microarray, as well as evaluated the diagnostic value of these biomarkers.

SERPA was applied to profile anti-TAA autoantibody response in sera from patients with OS and normal human, as well as explore the difference between this response. And differential expression of autoantibodies in serum from the patients and the control were screened by focused protein microarray with 154 human recombinant proteins based on 138 cancer driver genes. Both of these two technologies can detect autoantibodies that could serve as clinical biomarkers. Then Enzyme-linked immunosorbent assay (ELISA), and Western blotting (WB) were further used to validate the level of identified potential TAAs in sera. Immunohistochemistry (IHC) was used to evaluated the expression of ENO1 in OS tissues. The diagnostic value of each TAA for OS was analyzed by ROC curve.

ENO1 as a 47kD TAA in OS was identified and characterized by SERPA. Analysis of 172 serum samples with OS, osteochondroma (OC) and normal human sera (NHS) by ELISA showed higher frequency of anti-ENO1 autoantibodies in OS sera compared to others (P<0.05). Based on the focused protein microarray, three differential expressed TAAs (GNA11, SRSF2, PIK3CA) were screened out, whose content was higher than the control (P<0.05). According to the results of ELISA, anti-SRSF2 autoantibody was owned higher expression in OS than the control (P<0.05), with the area under curve value of 0.648. Furthermore, the results of WB both showed that nine of twelve sera reacted strongly against purified ENO1 or SRSF2. And the results of IHC further verified the results of ELISA and WB above.

In summary, Anti-TAA autoantibody can be considered as potential serological biomarker in the detection of OS. Both SERPA and protein microarray is a useful technology to search for TAAs. The expression of ENO1 and SRSF2 were able to distinguish OS from the normal, which can serve as potential diagnositic biomarkers for the early detection of OS.

S13-4

Effects of bivalirudin on coronary blood flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention

Dan Jiang [1]

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Objective: To evaluate the reperfusion flow of bivalirudin in patients with acute myocardial infarction after primary percutaneous coronary intervention (PCI). To explore the effect of bivalirudin by intracoronary injection during primary PCI on coronary blood flow and 30 days clinical events in patients with acute ST segment elevation myocardial infarction.

Method: From May 2012 to April 2015,245 patients with acute myocardial infarction underwent primary PCI,The patients were divided into two groups: 122 patients in bivalirudin group and 123 patients in heparin group. The bivalirudin group was randomly divided into two subgroups based on whether bivalirudin was injected into the coronary artery during intervention, the control group (n=60) and the intracoronary bivalirudin injection group (n=62).In the bivalirudin group, All patients were given intravenous maintaining does-bivalirudin by body weight. After restoring coronary blood flow(TIMI≥1) via guide wire or micro catheter, intracoronary bivalirudin was pushed via guide wire or micro catheter for half-does subgroup; while intracoronary bivalirudin was not given for control subgroup then following the normal operation. The main outcome measure was TIMI thrombus grade on coronary angiography, Timi blood flow was obtained immediately after target vessel patency, corrected TIMI frame count (CTFC) and NET clinical adverse events (NACE), major adverse cardiovascular events (Mace), and bleeding events according to the American Federation of Bleeding Academic research criteria (BARC) during hospitalization, 30 days after discharge, and 1 year of follow-up.

Results: Compared with patients in the heparin group, Patients in the bivalirudin group had a faster average heart rate on admission [(79.28 ± 15.75) bpm vs (75.38 ± 12.75) bpm, P=0.034]. There were no significant differences in other general data, laboratory indexes and interventional therapy data between the two groups (P > 0.05). After target vessel patency, no matter TIMI or CTFC, the effect of bivalirudin group was not inferior to that heparin group in controlling the occurrence of slow/no-reflow during primary PCI (P > 0.05). Analysis of the data of the patients during hospitalization showed that, The bivalirudin group was able to obtain a higher activated clotting time (ACT) value (p <0.001) without increasing the risk of decreased platelet count. There was no significant difference in the incidence of MACE and NACE between the two groups after 30 days and 1 year follow-up(P > 0.05). No statistical difference was observed on the CTFC between the two bivalirudin subgroups at the end of PPCI(P > 0. 05) . There was no statistical difference on the clinical events(MACCE and bleeding events) between the two subgroups within 30 days (P > 0. 05)

Conclusion: Bivalirudin is effective and safe in the treatment of acute myocardial infarction with primary PCI,There was no increase in slow flow/no-reflow during primary PCI. Intracoronary injection of bivalirudin has no significant effect on improving coronary blood flow, and there is no effect of intracoronary bivalirudin on the clinical ischemic events and bleeding events within 30 days after PPCI.

YOUNG SYMPOSIUM 7

Selected From Abstract Submission

08:30-10:00 | Room 5

Y07-1

GPR124 facilitates pericyte polarization and migration by regulating the formation of filopodia during ischemic injury

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Abstract: Cerebral microvascular occlusion, is implicated in the induction of stroke. Prolonged occlusion of multiple microvessels causes microvascular injury. Pericytes, which are important components of the neurovascular unit, form the basic structure of microvessels and maintain the stability of the BBB. G protein-coupled receptor 124 (GPR124) is required for maintaining central nervous system (CNS) angiogenesis and blood-brain barrier integrity. Here we confirmed the increased expression of GPR124 in pericytes following microsphere embolism. Morphological analysis showed localization of GPR124 to focal adhesions where GPR124 bound directly to the actin binding protein vinculin and upregulated Cdc42. SIN-1 or OGD treatment redistributed GPR124 to the leading edges of HBVPs where GPR124 signaling was required for pericyte filopodia formation and directional migration. Partial deletion of GPR124 domains decreased SIN-1-induced filopodia formation and cell migration. Taken together, our results provide the first evidence for a role of GPR124 in pericyte migration under ischemic conditions and suggest that GPR124 was essential for Cdc42 activation and filopodia formation.

Methods: A microsphere embolism-induced ischemia model was used to evaluate the expression of GPR124 following microsphere embolism. Immunocytochemistry and stochastic optical reconstruction microscopy imaging were used to assess the expression and distribution of GPR124 in human brain vascular pericytes (HBVPs) and after the treatment with 3-morpholino-sydnonimine (SIN-1) or oxygen-glucose deprivation (OGD). The effect of GPR124 knockdown or overexpression on HBVP migration was analyzed in vitro using wound healing assays and a microfluidic device. GPR124 loss-of-function studies were performed in HBVPs and HEK293 cells using CRISPR-Cas9-mediated gene deletion. Time-lapse imaging was used to assess dynamic changes in the formation of filopodia in an individual cell. Finally, to explore the functional domains required for GPR124 activity, deletion mutants were constructed for each of the N-terminal domains.

Results: We showed that the GPR124 expression was increased in pericytes following microsphere embolism. To clarify the role of GPR124 in pericytes in detail, we cultured human brain vascular pericytes (HBVPs). Result of immunofluorescence staining showed that GPR124 may spatiotemporally link the focal adhesions and the actin cytoskeleton through its interaction with focal adhesions proteins. Additionally, we found that scratch stimulation-induced GPR124 redistribution to the leading edges of the leader pericytes in the migrating monolayer, which suggested that GPR124 at the leading edge may participate in polarized cytoskeletal rearrangements to facilitate directional migration. We further examined the effect of GPR124 overexpression and GPR124 knockdown on HBVPs using a microfluidic migration chamber. Our findings indicated that GPR124-dependent signaling is essential for directional migration of pericytes. Cerebral ischemia is known to cause hypoxia, glucose deprivation, and reactive oxygen or nitrogen species. When treated with the SIN-1 or OGD, GPR124 was redistributed to the leading edges of HBVPs. Furthermore, we demonstrated that genetic GPR124 deletion from pericytes inhibits filopodia formation and cell polarization at the onset of nitrosative stress. Meanwhile, time-lapse imaging reveals that GPR124 contributes to filopodia formation upon nitrosative stress. Next, we constructed a series of deletion mutants for each of the domains thus demonstrated GPR124 might induce Cdc42-dependent directional migration of pericytes via its interaction with ELMO, DOCK and ITSN complexes.

Conclusion: In conclusion, our findings reveal pericyte GPR124 may be a potential therapeutic target for brain diseases involving neurovascular reconstruction. GPR124 is highly expressed in pericytes and located specifically at focal adhesions. Our data demonstrate that, for the first time, GPR124-mediated control over cytoskeletal rearrangement is critical to filopodia formation to promote a polarized migration of pericyte encountering damage factors, which is essential for supporting pericyte polarization and migration in the context of ischemia-like injury.

Keywords: GPR124; Pericytes; Directional migration; Filopodia; Ischemia

Y07-2

Pericyte-derived SENP1 restore neurovascular function after brain Ischemia

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Aims: Stroke is the major cause of acquired adult disability and leading death worldwide. Evidences indicated that pericytes could damage BBB and control vascular constriction around infarction periphery, contributing to the process of ischemia. However, the molecular basis of the mechanisms in pericytes in brain ischemia is poorly understood. The aim of this study is to identify novel mechanism-based targets for stroke.

Methods: We used the mice of the selective knockout of senp1 in pericytes (Cspg4-Cre; senp1f/f) to investigate brain function and neuronal damage evaluation following brain ischemia. Two-photon laser scanning microscopy (TPLSM) was used to examine the cerebral blood vessels of diameter, velocity, and flux were performed in living mice. Biochemical analysis and immunohistochemistry methods were used to address the role and mechanism of pericyte-specific SENP1 in the pathological process of brain ischemia. A coculture model of HBVPs and HBMECs mimicked the BBB in vitro and was used to evaluate BBB integrity after glucose deprivation.

Results: Our results showed that the pericyte-specific deletion of senp1 aggravated the infarct size and motor deficit following focal brain ischemia. Consistently, SENP1 deletion in pericytes accelerated thrombosis formation in brain microvessels and exaggerated the neuronal damage significantly following brain ischemia in mice. Moreover, SENP1 knockdown in pericytes could activate the apoptosis signaling and disrupt the barrier integrity in vitro coculture model.

Conclusions: Our findings revealed that targeting SENP1 in pericytes may represent a novel therapeutic strategy for neurovascular protection in stroke.

Keywords: apoptosis, brain ischemia, pericytes, SENP1, SUMOylation

Y07-3

The association of circulating chemerin levels with mild cognitive impairment in patients with type 2 diabetes mellitus, a cross-sectional study based on resting-state fMRI analysis

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Background: Chemerin, an adipokine secreted by adipose tissue, plays a major role in the control of metabolism and inflammation. Recently, the expression of chemerin receptors has been detected in the central nervous system and it may regulate neuronal activity and brain functions. However, few studies have explored the relationship between chemerin and MCI in human populations.

Objective: This study aimed to investigate whether serum chemerin levels were associated with cognitive performance and brain dynamics

in patients with type 2 diabetes mellitus (T2DM) based on resting-state fMRI analysis.

Methods: Three hundred and one patients with T2DM (179 mild cognitive impairment (MCI) and 122 cognitively normal controls (NC)) were recruited for serum chemerin determination by ELISA. Cognitive functions were assessed using Montreal Cognitive Assessment test (MoCA) and neural activity of brain was measured by rest-state function MRI (rs-fMRI).

Results: Serum chemerin levels were significantly lower in patients with MCI, compared to those without MCI. Spearman's analysis showed that a significant positive correlation between chemerin levels and subscores of visuospatial, language, and delayed recall abilities. Logistic regression analysis showed that lower chemerin levels was associated with elevated risk of MCI and the area under the ROC curve was 0.752 (95%CI: 0.641, 0.862) for serum chemerin as predictor of cognitive impairment stage. Among rs-fMRI parameters, patients in high-chemerin group (chemerin≥103.7076ng/ml) had significantly increased mean amplitude of low-frequency fluctuations (mALFF) in the right lingual gyrus, fusiform gyrus, bilateral middle and superior occipital gyrus, compared to patients in low-chemerin group (chemerin<103ng/ml). The correlation analysis showed mALFF values were positively correlated with serum chemerin levels and subscores of visuospatial, language, and delayed recall abilities in these areas of the brain. Brain network analysis of functional connectivity (FC) revealed that significantly increased FC levels between medial visual network (mVN) and ventromedial prefrontal cortex (vmPFC) as well as between posterior default mode network (pDMN) and the anterior default mode network (aDMN) were observed in high-chemerin group, compared to patients in low-chemerin group. Moreover, FC value between vmPFC and mVN and between pDMN and aDMN showed significant positive correlation with chemerin levels and visuospatial score, respectively. In addition, FC value between vmPFC and mVN was positively correlated with delayed recall score and FC value between pDMN and aDMN was positively correlated with language score.

Conclusions: Our findings suggest that chemerin levels in patients with type 2 diabetes was positively associated with cognitive abilities, mALFF and functional connectivity, supporting the potential protective effect of chemerin on cognitive deficits in diabetes.

Y07-4

Myocardial Mitochondrial Antiviral Signaling Protein Promotes Heart Ischemia-reperfusion Injury via the TAK1/TRAF6 Axis

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Myocardial ischemia-reperfusion injury (MIRI) leads to ventricular fibrillation and markedly reduces survival of patients suffering a myocardial infarct (MI). MIRI is thought to be due to dysfunction of the inner mitochondrial membrane-associated proteins. However, participation of the outer mitochondrial protein, i.e. the myocardial mitochondrial antiviral signaling protein (MAVS), remains unexplored. MAVS-deficient (MAVS-KO) mice or myocardium-specific knockdown of MAVS (MAVS-sh) in wild-type (WT) mice were used to examine the role of MAVS in MIRI *in vivo*; MAVS knockdown or MAVS over-expression in a cardiac myocyte cell line (HL-1) or in cultured primary cardiomyocytes were used to delineate its mechanism of action on key MIRI outcomes in vitro. MAVS expression markedly increased in cardiomyocytes of infarcted myocardium of WT mice *in vivo* and in hypoxia-reoxygenated HL-1 cells *in vitro*. MAVS-KO or myocardium-specific knockdown of MAVS (MAVS-sh) protected mice from acute and chronic MIRI including attenuated cardiomyocyte apoptosis and ventricular remodeling. To gain mechanistic insight into MAVS´ impact, its signaling pathway was explored. MAVS recruited TGF-β-activated kinase 1 (TAK1) and tumor necrosis factor (TNF)-associated factor family 6 (TRAF6) to the outer mitochondrial membrane followed by TAK1/TRAF6 complex formation, TAK1 phosphorylation, MAVS aggregation, K63-type ubiquitination, and phosphorylation of its downstream targets c-jun-NH2 terminal kinase (JNK). Activation of the MAVS signaling cascade was associated with upregulation of apoptosis-associated molecules in cardiomyocytes *in vivo*. *In vitro*, mechanistic studies revealed that MAVS knockdown reduced apoptosis under hypoxic conditions and stabilized mitochondrial membrane potential in HL-1 cells. Moreover, JNK inhibitors reduced myocardial injury specify in WT mice while a JNK agonist eliminated cardio-protection in MAVS-KO mice. MAVS mediates activation of the MAPK/JNK signaling pathway via the TAK1/TRAF6 axis. We conclude that MAVS plays an indispensable role in clinically important features of MIRI via its downstream signaling cascade. This data suggests that MAVS qualifies as a novel unexpected target to treat MIRI.

POSTER SESSIONS ABSTRACTS

Cardiac Microcirculation

P001

Incremental prognostic value of dynamic lactate in critically ill patients with acute myocardial infarction

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Background: Arterial lactates and lactate clearance rate (LC) are strong predictors of mortality of critically ill patients. This study aimed to investigate additional risk stratification benefits of arterial lactate and LC in critically ill patients with AMI.

Methods: The clinical data of patients with AMI were extracted from the MIMIC-IV database. The cut-off values of lactate levels at baseline and after 12±4h, and LC were calculated and formed the standard for the 12h lactate risk index (LRI). In-hospital death was assessed as primary endpoint.

Results: 1,064 patients were enrolled in our training cohort and 336 patients (31.6%) died in the hospital. Patients with higher LRI showed a significantly increase in mortality (16.1%, 28.2%, 58.9% and 83.5% for LRI 0-point, 1-point, 2-point and 3-point respectively, P< 0.001). Univariate Cox analysis identified LRI as an independent prognostic factor ((hazard ratio 1.82, 95% confidence interval 1.61–2.05, P<0.001). By adding LRI to the Sequential organ failure assessment (SOFA) score, C-statistic significantly increased (P<0.001).

Conclusion: We demonstrated the potential to use LRI as an outcome indicator. Score adding LRI to SOFA allows improved discrimination accuracy in predicting in-hospital mortality for critically ill patients with AMI.

P002

Changes in myocardial SOD, MDA, and MPO in rats with high-voltage electrical burns and the effect of NAC intervention

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Objective: To investigate the characteristics of superoxide dismutase (SOD), malondialdehyde (MDA), and myeloperoxidase (MPO) changes in the heart tissue of rats with high-voltage electrical burns and the effect of N-acetylcysteine (NAC) intervention.

Methods: 240 rats were divided into the electric injury group, sham injury group (control group), saline group, and NAC group, each group was divided into six-time phases (n=10) of 0h, 8h, 24h, 48h, 72h and 1w after electrocution, and the rat model of electric shock injury was established by using 3kV high voltage electric shock for 3s. 1mL/kg (100mg/kg) of 10% NAC was injected intraperitoneally into the NAC group for intervention. The saline group was given the same volume of saline, and myocardial tissue was collected according to the time phase after electrocution. SOD assay kit, MDA assay kit, and MPO assay kit were applied to detect the level of oxidative stress in myocardial tissue, and the HE staining technique was used to detect the morphological changes of myocardial tissue.

Results: The levels of SOD, MDA, and MPO in myocardial tissues of rats with electrical injury were higher than those in the sham injury group, with significant differences (P<0.05). HE staining indicated that the intercalated disc structure between myocardial cells was unclear, with edema, blurred transverse lines, disorganized myocardial fiber structure, and increased local fibroblasts during 0-48h after electric shock in the rats. The myocardial histopathological damage reached the heaviest at 48h after electrocution. the edema of myocardial cells in rats was gradually reduced and the degree of the lesion was improved within 72h-1w, and the damage was not further aggravated. the levels of SOD, MDA, and MPO of myocardial tissue in rats after NAC treatment were lower than those in the electrocution group, but there was no significant difference. the myocardial histopathological damage after NAC treatment was not significantly improved.

Conclusion: High-voltage electrical burns can cause myocardial tissue damage in rats, and the degree of damage is closely related to the level of oxidative stress. the intervention effect of NAC in high-voltage electrical burns is not obvious, and further experiments are needed to confirm its efficacy.

P003

Risk stratification and predictive value of serum sodium fluctuation for adverse prognosis in acute coronary syndrome patients

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Background: Serum sodium fluctuation (SF) as an indicator of the extent of changes in serum sodium is associated with increased mortality in hospitalized patients. However, there is no consensus on diagnostic criteria for SF, and its impact on the outcome of patients with acute coronary syndrome (ACS) remains uncertain. We defined SF and assessed its association with adverse prognosis in hospitalized ACS patients.

Methods: Patients diagnosed with ACS were consecutively recruited. The serum SF rate (SFR) was defined as the ratio of the difference between the highest and lowest serum sodium levels during hospitalization to the first serum sodium level on admission. The Cox proportional hazards model was performed to evaluate the association between SFR and mortality. The dose-response relationships of SFR with mortality was characterized by restricted cubic splines (RCS) model. The predictive performance of SF for mortality was assessed by the area under the receiver operating characteristic curves (AUCs).

Results: The study retrospectively enrolled 1856 ACS patients, of which 36 (1.94%) patients dead within 1 year. Multivariate Cox analysis showed that SFR was independently associated with higher risk of 1-year mortality (HR=1.114, 95% CI:1.038-1.195, *P*=0.003). RCS analysis showed the optimal threshold for SFR was 5%, and the 1-year cumulative mortality was higher in the abnormal SF group (SFR ≥ 5%) compared with the normal SF group (SFR < 5%, *P* < 0.01). The AUCs of SF for predicting mortality within 1 month, 6 months, and 1 year were 0.842 (95% CI: 0.781-0.904), 0.830 (95% CI:0.736-0.926), 0.703 (95% CI:0.595- 0.811), respectively. Even in patients with normal baseline serum sodium, abnormal SF group demonstrated a significantly higher 1-year mortality compared to normal SF group (HR=4.95, 95% CI: 1.92-12.8).

Conclusion: The SFR during hospitalization is an adequate predictor of adverse outcomes in ACS patients, independent of serum sodium level at admission. Additional research is warranted to ascertain whether interventions targeting SF confer measurable clinical benefits.

P004

Qishen Yiqi Dropping Dills can Improve Cardiac Function in Rats with Heart Failure by Regulating Metabolism and Inhibiting Inflammation

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Background: The high mortality rate of heart failure (HF) threatens people's health. Because of its complex pathological mechanism [1], it is difficult to obtain satisfactory therapeutic effect by using western medicine alone. Qishen Yiqi Dropping Pills (QDP) is an effective compound traditional Chinese medicine preparation for clinical treatment of HF [2]. Previous studies have reported its mechanism of invigorating qi and activating blood circulation, but its mechanism of action in the treatment of cardiovascular diseases has not been fully clarified due to the characteristics of multi-component, multi-target and multi-path action.

Objective: We used a combination of multiple research methods including single cell transcriptomics, metabolomics, and network pharmacology to explore the therapeutic effects of QDP on HF at the

single cell and global circulation levels, and its pharmacodynamic components respectively, in order to further reveal the mechanism of QDP in treating HF with higher resolution.

Methods: In this study, we conducted single-cell transcriptome sequencing and metabolomic test on the heart tissue and serum of the heart failure rat model induced by myocardial infarction caused by coronary artery ligation, and mined the data related to QDP and HF for network pharmacological analysis.

Results: QDP significantly improved cardiac function in HF rats. ScRNA-seq data analysis annotated 19 cell populations. The difference analysis results showed that the energy metabolism and contractile function of cardiomyocytes in HF rats were impaired, other structural cells such as endothelial cells and fibroblasts, and immune cells such as macrophages and T cells were involved in inflammatory and fibrosis, suggesting that the inflammatory microenvironment damaged the function of cardiomyocytes. QDP administration significantly inhibit inflammatory in multiple cell types, thereby playing a protective role. The results of communication analysis suggested that Il-1 and Tgfb signal change between fibroblasts and M1 type macrophages may promote myocardial fibrosis. The results of metabonomic analysis showed that the circulatory metabolic network of HF rats was disrupted, with the decrease in fatty acid utilization and the increase in glycolytic lactic acid production reflecting the conversion of cardiac substrate utilization, suggesting that impaired energy metabolism affects cardiac function. QDP administration significantly improved the energy supply of TCA. The network pharmacology analysis established the potential "QDP-component-target-path-HF" multi-dimensional relationship network and PPI network for QDP treatment of HF. The combined analysis of single cell transcriptomics and network pharmacology revealed the potential chemical components regulating the differential expression genes in various cell types.

Conclusion: This study found the regulatory effect of QDP on inflammatory response and metabolic network in HF rats at the level of single cell transcription and metabolism, and further explored the potential material basis of drug efficacy. Next, we will further study the changes of key transcription factors and cellular communication networks involved in these regulatory roles, reveal the important targets of QDP in the treatment of HF and carry out experimental verification, so as to provide more accurate basis for the clinical application of QDP.

P005

Trimetazidine alleviated cardiac dysfunction and fibrosis after myocardial infarction in rats

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Abstract: Fibrosis plays a causal role in the development of heart failure (HF) after myocardial infarction (MI). Trimetazidine, as an anti-ischemic and antioxidant agent, has been demonstrated to have several cardio-protective effects. However, whether administration of trimetazidine has an effect on cardiac fibrosis of myocardial infarct rats and the mechanisms underlying the effect have not yet been elucidated. HF model was induced by MI in rat, and then trimetazidine was administered by intragastric means at a dosage of 15 mg/kg/day for a period of five weeks. The left ventricular morphology and function were evaluated by echocardiography,and histological alterations were assessed using HE and Masson staining. Apoptosis in hearts of rats was assessed by Tunnel staining, and the structure of mitochondria was evaluated using a transmission electron microscope. In addition, the oxidative stress was evaluated by examinating the activities of superoxide dismutase (SOD) and GSH peroxidase (GSH-PX). The data showed that trimetazidine signifcantly improved cardiac dysfunction of MI rat. The cardiac fbrosis were attenuated after trimetazidine administration in MI rat. Trimetazidine treatment reduced cardiomyocyte apoptosis, attenuated mitochondrial damage, and increased the activities of SOD and GSH-PX in rats with MI. Furthermore, trimetazidine decreased the expression of inflammatory cytokines IL-6 and TNFα in the heart tissues of MI rats. These results demonstrated that trimetazidine could alleviate cardiac dysfunction and attenuate cardiac fbrosis via inhibition of apoptosis and inflammation.

Keywords: Trimetazidine; Fibrosis; Myocardial infarction; Heart failure; Apoptosis; Inflammation

P006

QiShenYiQi Pills® Protects Myocardial Fibrosis Caused by in Stent Restenosis in Miniature Pigs

Lu-Lu Yan [1], Xiao-Hong Wei [1,2], Qiu-Ping Shi [3], Chun-Shui Pan [1], Kai-Yin Li [3], Bin Zhang [3], Xin-Gang Wang [3], Bo Zheng [3], Ming-Xia Wang [1], Li Yan [1], Ping Huang [1], Jian Liu [2], Jing-Yu Fan [1,2], Huan Li [1,2], Chuan-She Wang [1,2], Ming Chen [3], Jing-Yan Han [1,2]

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Background and Objective: Implantation of stents has increasingly applied for treatment of obstructive coronary artery disease, which, albeit effective, often harasses patients by in stent restenosis (ISR). The present study was to explore the role and mechanism of Chinese medicine QiShenYiQi Pills (QSYQ) in protecting ISR-evoked myocardial injury.

Methods: Chinese miniature pigs of both genders were used to establish an ISR model by implanting obsolete degradable stents into distal left anterior descending arteries. QSYQ was given (0.2 g/kg daily) for one month after successful establishment of the model.

Results: Treatment with QSYQ decreased myocardial infarct size, retained myocardium structure, attenuated myocardial fibrosis, and restored heart function and myocardial blood flow. Western blots revealed that QSYQ attenuated the chronic ischemia-caused energy metabolism disorder, blocked TGF β1 up-regulation and reversed its downstream Smad3,4,6,7 expression, and inhibited the increase of MCP-1, PRS19, MMP-2, MMP-9 and Cathepsin B expression.

Conclusions: Treatment with QSYQ effectively protects myocardial structure and function from ISR challenge, possibly by regulating energy metabolism via inactivation of RhoA/ROCK signaling pathway, and affecting monocyte chemotaxis and TGF β1/Smads signaling pathway.

P007

3, 4-dihydroxyl-phenyl lactic acid attenuated ischemia/reperfusion induced cardiac microvascular endothelial dysfunction through regulating Syndecan-4

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Background and Aim: Myocardial ischemia-reperfusion (I/R) causes damage to coronary capillary endothelial barrier and microvascular hyperpermeability. The degradation of endothelial glycocalyx can damage endothelial barrier. Syndecan proteins are key components of endothelial glycocalyx and are shed during I/R injury. This study aimed to test the effect and mechanism of 3, 4-dihydroxyl-phenyl lactic acid (DLA) against microvascular endothelial dysfunction after cardiac I/R, with a focus on glycocalyx.

Methods: Sprague-Dawley rats with or without pretreatment by DLA were subjected to occlusion of left anterior descending coronary artery followed by reperfusion. Endothelial cells were exposed to hypoxia and re-oxygenation (H/R).

Results: *In vivo*, DLA attenuated microvascular damage and albumin leakage after I/R injury, showing the effect on maintaining endothelial glycocalyx and junctions. The ectodomains of Syndecan-4 (Synd4) was

cleaved during I/R injury, which leaded to degradation of the glycocalyx and endothelial dysfunction. The indicators were ameliorated by DLA. *In vitro* study disclosed that DLA protected endothelial barrier from impairment induced by H/R, via attenuating peroxide production and shedding of Synd4, which leading to glycocalyx degradation.
Conclusions: DLA was able to prevent I/R-induced cardiac microvascular hyperpermeability via a mechanism involving protection of endothelial glycocalyx.

P009

Dynamic Assessments of Coronary Flow Reserve After Myocardial Ischemia Reperfusion in mice

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Aims: This study aimed to assess the dynamic change of the CFR before and after ischemia reperfusion by pulsed-wave Doppler measurements.
Methods: Use a modified parasternal long-axis (PLAX) view to examine the left anterior descending coronary artery. CFR is defined as the ratio of the maximal flow velocity induced by a metabolic or pharmacologic stimulus to the resting left coronary artery (LCA) flow velocity. Measure the coronary flow velocity and CFR again in 1 hour, 3 hours, 5hours, 8 hours and 24 hours, 48 hours after reperfusion, respectively. Compare the measurements to before IR measurements.
Results: Before the IR surgery, the baseline CFR and the mice had a normal CFR value near 2.14±0.43. After the IR surgery, CFR was significantly decreased in reperfusion 1 hour compared to the before IR surgery (1.18±0.14 vs 2.14±0.43), indicating that microcirculation was still not immediately restored even after opening the criminal vessels. As the reperfusion time was prolonged, the CFR values improved, but remained lower than before the procedure. What's more, there was no significant difference between the CFR of reperfusion for 24h and the CFR of reperfusion for 1h. And there were no significant changes in cardiac function of the left ventricle when the CFR was significantly reduced in the mice.
Conclusion: After ischemia reperfusion, the 1-hour CFR was significantly decreased than pre-operation. The CFR has gradually recovered over time, but remains below normal. The systolic function was preserved. Therefore, it is important to establish a practical guide to help doctors detect early microvascular dysfunction and study the progression of cardiovascular disease over time.
Keywords: Coronary Flow Reserve, Ischemia-Reperfusion, Dynamic Assessments, Left Coronary Artery Coronary Microvascular Dysfunction, Coronary artery disease

P010

Ginsenoside Rb1 ameliorates isoproterenol-induced cardiac fibrosis in mice

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Background: Heart failure (HF), characterized by cardiac fibrosis, is the leading cause of morbidity and mortality worldwide. Even with the golden triangle therapy (ACEI/ARNI, BBs, MRA), the 5-year survival rate of patients is still less than 50%. Therefore, novel treatment is still in urgent need. In our past study, ginsenoside Rb1 was found to reveal I/R induced heart failure in SD rats. However, whether it could ameliorate isoproterenol-induced heart failure remains unknown.
Methods: Male Balb/c mice were injected with isoproterenol (ISO, 5 mg/kg) subcutaneously for 7 days. Ginsenoside Rb1 at different doses (20, 40, 60 mg/kg) was administered orally. At the end of the study, cardiac function was observed by echocardiography. Heart tissue were isolated for immunohistochemistry, western-blotting and qPCR.
Results: High doses of Ginsenoside Rb1 (60 mg/kg) remarkably ameliorated ISO induced cardiac dysfunction, increased EF and FS, decreased HW/BW, HW/TL and LVIDs. Ginsenoside Rb1 treatment reduced cardiac hypertrophy, collagen deposition and M2 macrophage infiltration in the interstitial area of heart tissues as shown by HE, Masson trichrome staining and CD206 immunohistochemistry staining. Western blotting and qPCR showed that Rb1 inhibited Collagen 1 and Collagen 3 protein and mRNA levels.
Conclusion: The results showed that ginsenoside Rb1 inhibited isoproterenol-induced myocardial fibrosis through inhibition of macrophage infiltration.

P011

Diagnostic value of magnetocardiography in stable coronary artery disease patients with microvascular dysfunction

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Background: Magnetocardiography is a cardiac magnetic detector that has been shown in previous studies to be highly accurate in the diagnosis of myocardial ischemia, while the value of magnetocardiography as a non-invasive test in the assessment of coronary microvascular dysfunction (CMD) remains unclear.
Methods: A consecutive cohort of 210 patients with stable coronary artery disease with suspected myocardial ischemia was included in this study, and all patients underwent magnetocardiography and coronary angiography. Based on computational flow dynamics principles, coronary angiography-derived the index of microcirculatory resistance (angio-IMR) and fraction flow reserve (angio-FFR) were calculated and angio-IMR ≥25 was defined as CMD. 13 magnetocardiographic parameters were screened according to the presence or absence of CMD using one-way logistic regression analysis ($p < 0.05$) were constructed as logistic prediction models for the diagnosis of CMD.
Results: Among 210 patients, the mean age was 64.3 ± 9.4 years, the mean angio-IMR was 28.5 ± 11.7 and the angio-FFR was 0.90 ± 0.10. The patients with CMD were 116 (55.2%), who's mean angio-IMR was 35.8 ± 9.8 and angio-FFR was 0.93 ± 0.03; the patients without CMD were 94 (44.8%) with an angio-IMR of 18.4 ± 4.3 and an angio-FFR of 0.85 ± 0.14. The results of the magnetocardiographic model showed an area under the receiver operating characteristic curve (AUC) of 0.880 , with a sensitivity of 81.9% and specificity of 80.9%. We included coronary diameter stenosis and angio-FFR in the magnetocardiographic model respectively, angio-FFR significantly increased the AUC of the model to 0.921 ($p=0.007$), whereas coronary stenosis diameter did not($p=0.562$).
CONCLUSIONS: Magnetocardiography can be used as a non-invasive test for the diagnosis of CMD in patients with stable coronary artery disease, and angio-FFR improves the efficacy of the magnetocardiographic diagnostic model.
Keywords: magnetocardiography, coronary artery disease, coronary microvascular dysfunction

P012

Reconstruction of Postinfarcted Cardiac Functions Through Injection of Tanshinone IIA@ Reactive Oxygen Species-Sensitive Microspheres Encapsulated in a Thermoreversible Hydrogel

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Myocardial damage resulting from acute myocardial infarction often leads to progressive heart failure and sudden death, highlighting the urgent clinical need for effective therapies. Recently, tanshinone IIA has been identified as a promising therapeutic agent for myocardial infarction. However, efficient delivery remains a major issue that

limits clinical translation. To address this problem, an injectable thermosensitive poly (lactic acid-co-glycolic acid)-block-poly (ethylene glycol)-block-poly (lactic acid-co-glycolic acid) gel (PLGA-PEG-PLGA) system encapsulating tanshinone IIA-loaded reactive oxygen species-sensitive microspheres (Gel?MS/tanshinone IIA) has been designed and synthesized in this study. The thermosensitive hydrogel exhibits good mechanical properties after reaching body temperature. Microspheres initially immobilized by the gel exhibit excellent reactive oxygen species- triggered release properties in a high-reactive oxygen species environment after myocardial infarction onset. As a result, encapsulated tanshinone IIA is effectively released into the infarcted myocardium, where it exerts local anti-pyroptotic and anti-inflammatory effects. Importantly, the combined advantages of this technique contribute to the mitigation of left ventricular remodeling and the restoration of cardiac function following tanshinone IIA. Therefore, this novel, precision-guided intra-tissue therapeutic system allows for customized local release of tanshinone IIA, presenting a promising alternative treatment strategy aimed at inducing beneficial ventricular remodeling in the post-infarct heart.

Traditional Chinese Medicine and Microcirculation

P013

Unraveling the molecular mechanisms of Qing-Xin-Jie-Yu Formula against coronary heart disease, based on bioinformatics and network pharmacology with molecular docking and dynamic simulation

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Background: Qing-Xin-Jie-Yu Formula (QXJYF) has been extensively applied for the remedy of coronary heart disease (CHD) in clinical practice for about two decades in China. Actually, its principal material basis and focal molecular mechanisms against CHD are still undefined.
Methods: In the interest of distinguishing the potential ingredients and their related targets in QXJYF, network pharmacology technology was employed based on the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database. Subsequently, relevant differentially expressed genes (DEGs) in CHD were discerned from the Gene Expression Omnibus (GEO) database. Then, we established drug-compound-target and protein-protein interaction (PPI) network primarily using Cytoscape 3.9.1 software so that these major material bases and nucleus targets of QXJYF against CHD could be achieved and carried out enrichment analysis of interconnection targets to distinguish biological processes and pathways. Finally, the Discovery Studio platform 2019 (DS2019) was used to validate the correlations between the critical targets and their corresponding ingredients and further analyzed their optimal docking conformation.
Results: To sum up, 139 active components and 2402 corresponding targets were spotted from TCMSP in addition to 1719 DEGs amassed from GEO, of which 54 common targets were obtained. By feat of the PPI network and related literature, 8 crucial targets containing VEGFA, HIF1A, and IL6 were identified. Three critical pathways, including fluid shear stress and atherosclerosis, lipid and atherosclerosis, and HIF-1 signaling pathway, were closely associated with the underlying mechanisms of QXJYF against CHD. Furthermore, the results of DS2019 suggested that these binding affinities between key targets and their related ingredients were very reliable and the binding mode of the optimal docking conformation was stable.
Conclusions: In the present study, integration of microarray data from GEO, network pharmacology from TCMSP with molecular docking and dynamic simulation validated that it was absolutely effective for QXJYF against CHD to mainly depend on eight crucial targets (for instance, VEGFA, VCAM1, IL6, SERPINE1, SELE, HIF1A, EDN1, CCL2), their corresponding compounds and three key pathways including fluid shear stress and atherosclerosis, lipid and atherosclerosis, and HIF-1 signaling pathway, which offers explicit tracks for further experimental studies.

P014

The effect of microbiota mediated Pyroptosis pathway on Diabetic Nephropathy and the intervention mechanism of Jiangtang Decoction

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Diabetic nephropathy (DN) is one of the most common chronic microvascular complications of diabetes. Microbiota dysbiosis and pyroptosis were demonsrated to be involved in DN, and the patented medicine Jiangtang Decoction was confirmed to reduce inflammation and regulate microbiota dysbiosis. Therefore, in this study, we aim to study the role of gut microbiota mediated infammatary pathyway in DN, and confirm whether the anti-inflammatory mechanism of Jiangtang Decoction is related to it. Experiments in vivo and invro will first be donducted to explore the role of gut microbiota mediated pyroptosis in DN, focusing on the changes of microbiota in species level, then aseptic model will be used to verify the role of microbiota in species level in DN. Finally, experiments in vivo and in vitro will be performed to study the mechanism of Jiangtang Decoction on DN. The main methods included Western blot, ELISA, RT-PCR, immunofluorescence, immunohistochemistry and metagenomic next-generation sequencing. The results showed that the abundance of Ruminococcus gnavus was upregulated, with enterotoxin Trimethylamine-N-oxide and pyroptosis pathway activeted in DN, and Jiangtang decoction could ameliorated these changes. These results strongly suggest that microbiota might induce enterotoxin and activate pyroptosis, which may be one of important triggering mechanisms leading to diabetic nephropathy, and Jiangtang decoction JTD might reduce infammation in DN through this pathway.

P015

Gushe Tongluo Formula on glomerular filtration rate in patients with chronic renal failure

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Background In patients with chronic renal failure, the glomerular filtration rate (GFR) is still progressively decreased even after the etiology is removed. Previous medical techniques lack effective measures to improve the GFR. Increased permeability of glomerular vascular basement membrane, continuous deposition of harmful substances outside the basement membrane and microthrombus caused by various factors are the main pathological basis for the decrease of GFR. Based on the theory of traditional Chinese medicine, personal clinical experience and the modern microcirculation study of Han Jingyan et al., this study explored the effect of traditional Chinese medicine Gushe Tongluo Formula (supplementing qi, invigorating kidney and inducing astringency, while dehumidifying dampness, removing blood stasis and dredging collaterals) on the improvement of glomerular microcirculation and filtration function in patients with chronic renal failure.

Methods After screening according to the inclusion criteria, 62 patients with chronic renal failure admitted to xxxx hospital from November 2021 to January 2023 were enrolled in this study and divided into group ① and group ② according to random number table. Patients in group ① were treated with Shenshuaining Tablet on the basis of western medicine treatment, which was to control blood sugar, blood pressure and other basic diseases; patients in group ② were treated with Guhe Tongluo Formula on the basis of western medicine treatment. Patients in both groups were treated continuously for 4 weeks, and renal function was measured once before treatment and 2 and 4 weeks after treatment, respectively. The GFR, serum creatinine, serum uric acid, serum urea nitrogen, B2-microglobulin, cystatin C, hemoglobin, serum calcium and serum phosphorus were compared before and after treatment in each group and between two groups, respectively.

Results After 4 weeks of treatment, according to the "Guiding Principles for Clinical Research of New Chinese Medicines", the effective rate of clinical disease control in group ② was 96.55%, 46.67% higher than that in group ① ($P < 0.01$). The GFR, serum creatinine, serum uric acid and other indexes in patients of group ② before treatment were significantly higher compared with those treated for 4 weeks ($P < 0.01$).There was no significant difference in hemoglobin and serum phosphorus levels of group ② between before treatment and 4 weeks after treatment ($P > 0.05$), as well as the GFR, serum creatinine, serum uric acid, serum urea nitrogen, B2-microglobulin, cystatin C, hemoglobin, serum calcium and serum phosphorus levels in patients of group ① between before treatment and 4 weeks after treatment ($P > 0.05$).

Conclusion Gushe Tongluo Formula can significantly enhance the GFR and implies the improvement of glomerular microcirculation in patients with chronic renal failure. Therefore, this prescription could be used as an essential therapy for chronic renal failure. At the same time, this study provides a useful exploration for the application of traditional Chinese medicine in the treatment of chronic renal failure.

Keywords: Renal failure; Inducing astringency; Dredging collaterals; Microcirculation; Glomerulus; Traditional Chinese medicine.

P016

Discovery of Acupuncture Points to Meridians

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The meridian doctrine is the core theory of traditional Chinese medicine (TCM). TCM literature and the bronze figures for acupuncture and moxibustion and other TCM cultural relics all contain the hypothesis of meridians and acupoints. The standard map of meridians and acupoints for acupuncture and moxibustion usually mark the position of acupoints to the Fourteen Meridians. However, how the meridians and acupoints were discovered remains an eternal mystery, and the authenticity of the meridians and acupoints, was once questioned in the past. Historically, both Chinese martial arts and Taoist internal skills have been inextricably linked to TCM. Li Shizhen, a famous medical scientist in the Ming Dynasty and the author of Examination of the Eight Extraordinary Meridians, agreed that Taoist practitioners could perceive the meridians through the method of Taoist meditation. Obviously, those results of subjective awareness lacks the support from objective evidences. The martial artist practiced Tai Chi in one morning, very accidentally discovered regularly arranged sweat spots on the right sleeve of the gray underwear at 5:10 am the next day. The pattern and location of the sweat spots have an excellent correspondence with the acupoints of the hand Taiyin lung meridian. Through long-term observation and analysis of the sweating pattern of the volunteers from long-term boxing practitioners, the authors found that the sweat spots left on the clothes or sweat drops on the skin corresponded to the acupoints of each of the fourteen meridians, when they practiced boxing, meditated, walked for long distance, and were stimulated by acupuncture, hot springs, hot baths, or by COVID-19 infection. It seemed this phenomenon is more prominent around solar terms than on usual days. This is the first report of observation results about the human body sweating through acupoints. These observations and experiments not only help to uncover the mystery of the discovery of meridians and verify the objective existence of acupoints and meridians, but also are expected to provide a novel approach to deeply explore the essence of meridians.

P017

The research of microcirculation evaluation of rats with Qi deficiency and blood stasis

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Objective: To observe the microcirculation status of the rat model of Qi deficiency and blood stasis syndrome, and establish its evaluation system, which aims at providing experimental evidence for the animal model of TCM syndrome and efficacy study of TCM.

Methods: The experimental animals were divided into a normal group and a model group. Rats with Qi deficiency and blood stasis were reproduced by standing on a small platform in a water environment at a fixed time every day for six consecutive weeks. Physical signs, including hair, color, bearing, size, mental state, body weight, and stool and urine, were observed every week. Blood pressure, pulse amplitude, tongue and pulse images, and blood perfusion volume on the auricle and planta surface were detected every two weeks. At 4w and 6w, Blood was collected from the tail tip, and the white blood cell count, platelet count, and percentage of neutrophils and lymphocytes were analyzed by blood cell counter. The bleeding time of rats was measured by tail amputation method at 6w, and the time of carotid artery and mesenteric artery thrombosis induced by $FeCl_3$ was dynamically observed by a visualization microscope. After 6w of modeling, the mesenteric venules were removed. The microcirculation state was recorded every 10 minutes for 30 minutes from the base 0min by a high-speed camera. The "Image Pro Plus 6.0" software was used for slow replay to measure RBC velocity and tube diameter. Count the number of rolling and adherent white blood cells along the blood vessels. The leakage of FITC-labeled plasma albumin from blood vessels of fine veins was observed by fluorescence microscope.

Results: Compared with the normal group, the body weight of rats decreased significantly, the manner was lazy, the hair color was yellow, the mood was irritable, and the stool was loose. The G-value of the tongue was increased at 2w ($P < 0.05$), while the R-value was significantly decreased at 4w ($P < 0.01$). At 6w, the R, G, and B values of the tongue and plantar showed a decreasing trend. At 6w, the pulse amplitude and blood perfusion volume in the left and right ear were decreased ($P < 0.05$ or $P < 0.01$). At the same time, the bleeding time of the rat tail tip was significantly decreased ($P < 0.01$), suggesting that there may be some changes in platelet status. The thrombosis time of the mesenteric artery observed by visual microscopic was significantly higher than that of the normal group ($P < 0.05$). Mesenteric microcirculation state showed that the flow velocity of mesenteric venule red blood cells was lower than that of the normal group, the number of white blood cells adhering to the blood vessel wall and the rolling white blood cells were significantly higher than that of the normal group ($P < 0.05$ or $P < 0.01$), and there was albumin leakage, suggesting that the integrity of the great blood vessel wall in the model group of Qi deficiency and blood stasis was reduced ($P < 0.01$).

Conclusion: The multi-angle experimental evidence confirms that the rat model of Qi deficiency and blood stasis established by sleep deprivation on the water environment platform shows obvious microcirculatory disturbances, and its change process basically accords with the etiology and pathogenesis of the syndrome of Qi deficiency and blood stasis in TCM clinics, which can be used for the evaluation of the model of blood stasis and the study of the efficacy of traditional Chinese medicine.

P018

Pharmacological manipulation of Ezh2 with Salvianolic acid B results in tumor vascular normalization and synergizes with cisplatin and T cell-mediated immunotherapy

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Tumor vasculature is characterized by aberrant structure and function, resulting in immune suppressive profiles of tumor microenvironment (TME) through limiting immune cell infiltration into tumors. The defective vascular perfusion in tumors also impairs the delivery and efficacy of chemotherapeutic agents. Targeting abnormal tumor blood vessels has emerged as an effective therapeutic strategy to improve the outcome of chemotherapy and immunotherapy. In this study, we demonstrated that Salvianolic acid B (SalB), one of the major ingredients of *Salvia miltiorriza* elicited vascular normalization in the mouse models of breast cancer, contributing to improved delivery and response of chemotherapeutic agent cisplatin as well as attenuated metastasis. Moreover, SalB in combination with anti-PD-L1 blockade retarded tumor growth, which was mainly due to elevated infiltration of immune effector cells and boosted delivery of anti-PD-L1 into tumors. Mechanistically, tumor cell enhancer of zeste homolog 2 (Ezh2)-driven cytokines disrupted the endothelial junctions with diminished VE-cadherin expression, which could be rescued in the presence of SalB. The restored vascular integrity by SalB via modulating the interactions between tumor cells and endothelial cells (ECs) offered a principal route for achieving vascular normalization. Taken together, our data elucidated that SalB enhanced sensitivity of tumor cells to chemotherapy and immunotherapy through triggering tumor vascular normalization, providing a potential therapeutic strategy of combining SalB and chemotherapy or immunotherapy for patients with breast cancer.

P019

Sanpian decoction ameliorates cerebral ischemia-reperfusion injury by regulating SIRT1/ERK/HIF-1α pathway through in silico analysis and experimental validation

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Background and Aims: Cerebral ischemia-reperfusion injury (CIRI) is a complex pathophysiological process involving multiple factors, and becomes the footstone of rehabilitation after ischemic stroke. Sanpian decoction (SPD) has exhibited protective effects against CIRI, migraine, and other cerebral vascular diseases. However, the underlying mechanisms have not been completely elucidated. This study sought to explore the potential mechanisms underlying the effect of SPD against CIRI.

Materials and Methods: High performance liquid chromatography (HPLC) was carried out to determine the active aspects of SPD. A network pharmacology approach combined with experimental verification was conducted to elucidate SPD's multi-component, multi-target, and multi-pathway mechanisms in CIRI occurrence. The pharmacodynamics of the decoction was evaluated by establishing rats model of middle cerebral artery occlusion/reperfusion (MCAO/R). *In vivo* experiments, the therapeutic effect of SPD was performed using TTC, HE staining and Nissl staining. *In vitro* experiments, we used TUNEL staining and flow cytometry to quantify cortex apoptosis. The corresponding protein and mRNA expressions were discovered using RT-qPCR and western blot.

Results: Our research showed that pretreatment with SPD improved neurological function and inhibited CIRI. Network pharmacology revealed that the hypoxia-inducible factor-1 (HIF-1) signaling pathway and mitogen-activated protein kinase (MAPK) signaling pathway-mediated apoptosis may be associated with CIRI. *In vivo* and *in vitro* experiments, we confirmed that SPD increased cerebral blood flow, improved neural function, and reduced neural apoptosis via up-regulating the expression of sirtuin 1 (SIRT1) and down-regulating phospho-extracellular regulated protein kinases (p-ERK)/ERK and HIF-1α levels in CIRI rats.

Conclusion: Taken together, the present study systematically revealed the potential targets and signaling pathways of SPD in the treatment of CIRI using in silico prediction and verified the therapeutic effects of SPD against CIRI via ameliorating apoptosis by regulating SIRT1/ERK/HIF-1α pathway.

P020

Paeoniflorin attenuates limb ischemia by promoting angiogenesis through ERα/ROCK-2 pathway

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Background and Objective: Peripheral artery disease (PAD) is a high-risk vascular disease. Vascular remodeling is considered as a promising therapeutic strategy. However, promoting angiogenesis may simultaneously trigger an inflammatory response. Paeoniflorin (PF) is the principal bioactive compound in the roots of *Paeonia lactiflora*, which is widely applied in activating blood circulation and removing blood stasis. PF has been demonstrated to possess pro-angiogenic and anti-inflammatory activities. In this study, we explored the therapeutic efficiency of PF for treating PAD and determined its mechanisms.

Methods: Mouse model of hindlimb ischemia was established by excising the upper and lower ends of the femoral artery in C57BL/6 mice. Laser Doppler perfusion imaging, hematoxylin-eosin (HE) staining, lectin immunofluorescence, western-blotting, flow cytometry, ELISA and qPCR were performed to determine the function of PF in promoting angiogenesis and inhibiting excessive inflammatory response in PAD. The *in vitro* experiments were applied in human umbilical vein endothelial cells (HUVECs) and the bone marrow derived macrophages (BMDMs) to explore its molecular mechanisms.

Results: The blood flow, capillary density and protein expressions of VEGF-A, MMP2, MMP9 and ERα in mouse ischemic tissue were remarkably elevated by PF in PAD model. Knockdown of ERα expression in HUVECs demonstrated that PF facilitated migration and tube formation of endothelial cells through ERα/ROCK2 pathway. Subsequently, PF was found to promote the phenotypic transformation of macrophages and alleviated grave inflammatory responses during vascular remodeling.

Conclusions: These results improved present acquaintance with the advantageous effects of PF as a potent compound in promoting angiogenesis and mitigating inflammatory responses during revascularization. It provides new alternatives to suffice the therapies for PAD patients hereafter.

Thrombosis and Thrombolysis

P021

YangXueQingNao Wan attenuated blood-brain barrier disruption after tissue plasminogen activator thrombolysis in mice

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Background: Thrombolytic therapy with tissue plasminogen activator (tPA) remains the most effective treatment for acute ischemic stroke, but it can cause brain edema and intracerebral hemorrhage (ICH). This study aimed to assess whether YangXueQingNao Wan (YXQN), a compound Chinese medicine, can attenuate tPA-induced brain edema and hemorrhage in ischemic mouse model.
Methods: Ferric chloride-induced carotid artery thrombosis followed by mechanical detachment of thrombi was performed in male C57BL/6N mice. Then mice were treated with YXQN (0.72 g/kg) followed by administration of tPA (10 mg/kg) at 4.5 h after stroke. Cerebral blood flow (CBF), infarct size, survival rate, neurological score, Evans blue extravasation, cerebral water content, FITC-labeled albumin leakage, hemorrhage, junction proteins and basement membrane proteins expression, proteomics, leukocyte adhesion and matrix metalloproteinases (MMPs) expression were evaluated 24 h after tPA administration.
Results: Compared with tPA treatments, the combination of YXQN with tPA not only significantly reduced infarction, Evans blue extravasation, brain edema, FITC-labeled albumin leakage, hemorrhage, leukocyte adhesion and MMP-9 expression, but also improved CBF, survival rate, junction proteins (occludin, claudin-5, junctional adhesion molecule-1 (JAM-1), zonula occludens-1 (ZO-1), VE-cadherin) and basement membrane proteins (collagen IV, laminin) expression. Proteomics analysis identified Rho GTPase-activating protein 21 (Arhgap21) and Ras suppressor protein 1 (Rsu1) were associated with junction function, which were further confirmed by western blotting.
Conclusion: The combination of YXQN with tPA relieved brain edema and hemorrhage by protecting the integrity of blood-brain barrier (BBB), which was partly attributable to the improvement of Arhgap21-modulated junction and basement membrane proteins degradation by MMP-9 derived from macrophage.

Hemorrhage

P022

the difference of Hb redox forms in cerebral spinal fluid between perimesencephalic SAH and aneurysmal SAH

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Background Compared to aneurysnal subarachnoid hemorrhage (SAH), perimesencephalic SAH exhibits a significantly better clinical course and prognosis, but the bleeding source of which is still unknown.
Objective To explore the difference of Hb redox forms in cerebral spinal fluid between perimesencephalic SAH and aneurysmal SAH.
Methods: A prospective study program was strictly performed in our center. All SAH patients underwent DSA as well as CT, and were classified as PMSAH group and aSAH group. The volume of bleeding was evaluated by the hijdra sum score. Cerebrospinal fluid was collected according to the schedule. And the concentration of oxy-Hb, metHb, heme in the CSF was measured by spectrophotometry.
Results: A total of 72 patients were enrolled. Hijdra sum score of PMSAH group (n=10) was 14.40 ± 0.6360. aSAH patients were divided into two groups according to the amount of bleeding: aSAH-1 group, the blood amount was equivalent to that in PMSAH group (n=53, hijdra sum score: 15.70 ± 0.2807); aSAH-2 group, consisting aSAH patients with high blood amount (n=9, hijdra sum score: 28.44 ± 0.6035). CSF concentration of OxyHb (34.62 ± 8.379 vs 50.28 ± 4.040μM) and metHb (33.35 ± 5.596 vs 77.40 ± 7.533 μM) in PMSAH group were significantly lower than that in aSAH-1 group (P< 0.05), while free heme showed no significant difference between the two groups(8.768 ± 3.189 vs 6.226 ± 1.912, P>0.05). Additionally, the distribution of heme forms in PMSAH and aSAH differs from each other.
Conclusion: It has been a perplexing clinical phenomenon that patients with aSAH were more seriously ill than PMSAH patients with the same amount of bleeding in the subarachnoid. According to our study, higher oxy-Hb and oxidized Hb(metHb), originated from arterial blood rather than venous blood, may be the reason why the clinical manifestations of aSAH patients are more severe than those of PMSAH. More studies are necessary for the future.

P023

QiShenYiQi Pills ameliorates aspirin and clopidogrel induced stomach hemorrhage in rats

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Background: Aspirin and clopidogrel are dual antiplatelet drugs that can cause gastric hemorrhage in patients. This study aimes to explore the protective effect and mechanism of QiShenYiQi Pills (QSYQ), a compound Chinese medicine, on this adverse event.
Method: We established a rat model of gastric hemorrhage induced by oral administration of aspirin and clopidogrel for four weeks. QSYQ was co-administered with the antiplatelet drugs to evaluate its preventive effect. We measured the hemoglobin content and Evans Blue leakage in the stomach to assess the hemorrhage severity. We also examined the expression and distribution of tight junction and basement membrane proteins in the gastric microvasculature by immunofluorescence and Western blotting. To elucidate the mechanism of microvascular barrier dysfunction, we performed proteomic analysis of gastric tissues and focused on mitochondrial energy metabolism and macrophage activation.
Result: QSYQ notably attenuated stomach hemorrhage, hemoglobin content and Evans Blue leakage, restored the expression and ruptured distribution of stomach microvascular junction proteins ZO-1, Claudin-5, VE-Cadherin, Occludin, and basement membrane proteins Collagen IV and Laminin. QSYQ also ameliorated HUVEC endothelial cell monolayer hyperpermeability and low-expression of cell junction proteins induced by aspirin and clopidogrel in vitro. The results of proteomic were further verified in vivo and in vitro, revealing that QSYQ augments energy metabolism and cytoskeletal organization of endothelial cells while suppressing macrophage infiltration.
Conclusion: Our results demonstrated that QSYQ attenuated gastric hemorrhage induced by dual antiplatelet drugs through modulating microvascular barrier integrity, mitochondrial energy metabolism, and macrophage activation. These findings support the potential use of QSYQ as a protective agent for coronary artery disease patients receiving aspirin and clopidogrel therapy.

Obesity and Microcirculation

P024

Arcuate nucleus Kir2.1 protein involved in melanocortin-4 receptor trafficking and control of energy balance

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Objective: Imbalance in energy regulation is a major cause of insulin resistance and diabetes. The central melanocortin system, which includes proopiomelanocortin (POMC), agonistα-melanocyte-stimulating hormone (α-MSH), agonist agouti-related protein (AgRP) and melanocortin-4 receptor (MC4R), plays a critical role in regulation of energy balance. Differential roles of MC4R signaling in specific neural circuits (eg, paraventricular nucleus, dorsomedial, lateral region, lateral parabrachial nucleus) suggest that MC4R signaling at specific sites in the central nervous system (CNS) has synergistic but non-overlapping functions. However, the mechanism by which MC4R in the arcuate nucleus (ARC) region regulates energy balance and insulin resistance remains unclear.
Methods: The MC4R $^{flox/+}$ mice with POMC-Cre mice were crossed to generate the POMC-MC4R$^{flox/+}$ mice. Then the POMC-MC4$^{Rflox/+}$ mice were further mated with MC4R$^{flox/flox}$ mice to generate the POMC-MC4R$^{flox/flox}$ mice in which MC4R is selectively deleted in POMC neurons. Bilateral injections of 200 nl of AAV-sh-Kir2.1 (AAV-sh-NC was used as control) were made into the arcuate nucleus of the hypothalamus. Oxygen consumption, carbon dioxide production, respiratory exchange ratio (RER) and energy expenditure were measured by using the CLAMS; Total, visceral and subcutaneous fat was analyzed using Micro-CT. Co-immunoprecipitation assays (Co-IP) was used to analyze the interaction between MC4R and Kir2.1 in GT1-7 cells.
Results: Our results show that MC4R regulates energy balance and insulin resistance by regulating Kir2.1, a strong inward rectifier potassium channel encoded by the KCNJ2 gene in the ARC region of hypothalamic. Proopiomelanocortin (POMC) neuron-specific ablation of MC4R in the ARC region promoted food intake, impaired energy expenditure, leading to increased weight gain and impaired systemic glucose homeostasis. Additionally, MC4R ablation reduced the activation of POMC neuron, and is not tissue-specific for peripheral regulation, suggesting the importance of its central regulation. Mechanistically, sequencing analysis and Co-IP assay demonstrated a direct interaction of MC4R with Kir2.1. Knockdown of Kir2.1 in POMC neuron-specific ablation of MC4R restored the effect of MC4R ablation on energy expenditure and systemic glucose homeostasis, indicating by reduced body weight and ameliorated insulin resistance.
Conclusions: These findings suggest that hypothalamic Kir2.1 is involved in MC4R trafficking and regulate neuron activation. Kir2.1 represents a new target and pathway that could be targeted in obesity.
Keywords: MC4R, arcuate nucleus, Kir2.1, insulin resistance, energy expenditure

P026

Kallistatin Improves High-fat-induced Insulin Resistance via Epididymal Adipose Tissue-derived Exosomes

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Objective: Studies have found that high expression of human Kallistatin (HKS) in adipose tissue can improve obesity and its associated comorbidities, but the underlying mechanism of specific regulation is unclear.
Methods: An obesity model was built by injecting eight-week-old C57BL/6 mice (n=24) with Ad.Null and Ad.HKS adenovirus into epididymal adipose tissue and fed with a high-fat diet (HFD). Epididymal adipose tissue was isolated after 24 hours for culture, and exosomes were extracted by differential centrifugation. Enzyme-linked immunosorbent assay detected the expression of HKS protein in serum and exosomes.
Results: Our results showed that HFD-induced mice with high expression of HKS in epididymal adipose tissue had slower weight gain, lower serum triglycerides, reduced free fatty acids, and improved insulin resistance compared with the Ad.Null group. We also demonstrated that HKS was enriched in epididymal adipose tissue-derived exosomes and released through the exosome pathway. In PA-induced AML12 cells, insulin resistance was alleviated after incubation of the HKS-related exosome; this effect was reversed with GW4869.
Conclusion: High expression of HKS in epididymal adipose tissue could lead to its exocrine secretion in the form of exosomes and improve hepatic insulin resistance by promoting the phosphorylation of AKT.

P027

Epidermal growth factor receptor (EGFR) dependent on insulin signaling pathway regulates hepatic insulin resistance through insulin activation

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Hepatic insulin resistance is a risk factor for metabolic diseases such as type 2 diabetes (T2D) and obesity. Epidermal growth factor receptor (EGFR) is an important central gene in the regulation of insulin resistance, but its mechanism of regulating hepatic insulin resistance remains unclear. Our study found that the expression of EGFR at RNA and protein levels was significantly reduced in the liver of obese mice fed a high fat diet. IHC results also showed reduced EGFR phosphorylation levels in the liver. It was found that fasting blood glucose level increased, body weight and insulin resistance increased, glucose tolerance decreased significantly in obese mice, while there was no significant difference in normal mice, after injected with EGFR inhibitor AG1478. At the cellular level, EGFR expression in liver cell lines was significantly decreased after incubation with insulin for 24 h to construct insulin resistance (IR) models. Besides, in the presence of AG1478, the glucose content in the medium was significantly increased after 12 h of insulin stimulation. These results indicated that EGFR is associated with hepatic insulin resistance. Moreover, the phosphorylation levels of EGFR and AKT in normal liver cells were significantly increased after insulin stimulation. Reducing EGFR by RNA interference decreased AKT phosphorylation levels in cell stimulated by insulin, while EGFR overexpression had the opposite effect. Interestingly, insulin stimulation had no significant effect on the phosphorylation levels of EGFR and AKT in IR cells incubated with AG1478. In addition, when the cells were stimulated with insulin for 24 h after the overexpression of EGFR, the glucose consumption of the cells and AKT phosphorylation increased significantly, indicating that the cells did not develop insulin resistance. These results demonstrated that insulin can activate EGFR phosphorylation in the liver and initiate insulin signaling pathways. Surprisingly, insulin receptor substrate (IRS) expression was significantly increased after EGFR was overexpressed in cells, while RNA expression of EGFR was not affected after IRS interference, implying that EGFR may regulate IRS expression. Furthermore, the RNA expressions of EGFR and IRS were also significantly decreased under the IR cells, and the RNA levels of EGFR and IRS were significantly decreased in both high-fat and normal mouse liver after AG1478 injection. These results suggested that EGFR regulates insulin signaling through IRS. Above all, our study preliminarily revealed the mechanism of EGFR mediating hepatic insulin resistance. This study provides new evidence that the insulin-EGFR-IRS-PI3K/AKT signal transduction axis plays an important role in the development of hepatic insulin resistance, which is expected to provide new ideas and targets for T2D treatment and drug research.

Diabetes and Microcirculation

P028

Time in range, assessed with continuous glucose monitoring, is associated with brachial-ankle pulse wave velocity in type 2 diabetes: A retrospective single-center analysis

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Aims: The aim of this retrospective single-center is to research the relationship between time in range(TIR), an important novel metric of glycemic control, assessed with continuous glucose monitoring(CGM) and brachial-ankle pulse wave velocity (BaPWV), a unique index of systemic arterial stiffness in type 2 diabetes.
Methods: Study participants included 469 hospitalized patients with

type 2 diabetes and no history of serious cardiovascular disease who underwent CGM and BaPWV measurements. TIR of 3.9-10.0 mmol/L was evaluated with CGM. BaPWV was measured by non-invasive arteriosclerosis detector and high baPWV was defined as a mean baPWV≥1800m/s. The spearman correlation and the partial correlation analysis were applied to analyze the correlation between TIR and baPWV. The binary logistic regression was used to examine the independent association of TIR and high BaPWV.

Results: The presence of high baPWV was 32.2%. Compared with patients of low baPWV, those with high baPWV had significantly reduced TIR(P<0.001). With the increase of TIR tertiles, the prevalence of high BaPWV progressively decreased. Correlation analysis showed that TIR is inversely correlated with BaPWV. In a fully adjusted model controlling for traditional risk factor of CVD, TIR is associated with the presence of high BaPWV independent of HbA1c.

Conclusion: TIR is correlated with BaPWV independent of HbA1c in patients with type 2 diabetes, confirming a link between TIR and arterial stiffness.

P029

Time in range, especially overnight timein range, is associated with sudomotordysfunction in patients with type 1 diabetes

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Background: Time in range (TIR) is advocated as key metric of glycemic control and is reported to be associated withmicrovascular complications of diabetes. Sudomotor dysfunction is among the earliest detectable diabetic peripheralneuropathy (DPN). We set about to research the relationship between TIR including overnight TIR and sudomotorfunction detected by SUDOSCAN with the intention of exploring the correlation of TIR including overnight TIR andearly DPN in type 1 diabetes (T1D).

Methods: 95 patients with T1D were enrolled. TIR including nocturnal TIR of 3.9–10.0 mmol/L was evaluated withCGM. SUDOSCAN measured feet electrochemical skin conductance (FESC) and sudomotor dysfunction was definedas average FESC < 60μS. Logistic regressions were applied to examine the independent association of TIR and overnightTIR with sudomotor function.

Results: The overall prevalence of sudomotor dysfunction was 28.42%. Patients with sudomotor dysfunction hadsignificantly lower TIR for the whole recorded phase and for nighttime. The sudomotor dysfunction prevalence progressivelydeclined with the ascending tertiles of TIR and nocturnal TIR (P for trend < 0.05). Correlation analysis showedthat the relationship between nocturnal TIR and FESC was stronger than that between TIR and FESC with correlationcoefficients were respectively 0.362 and 0.356 (P < 0.001). Finally, logistic regression analysis indicated the independentlynegative relation between TIR and nocturnal TIR and sudomotor dysfunction (P < 0.05), and the correlationbetween nocturnal TIR and sudomotor dysfunction was more statistically significant.

Conclusions: TIR is negatively correlated with sudomotor dysfunction in T1D independent of HbA1c. Furthermore,decreased nocturnal TIR is more closely related to the impaired function of sudomotor nerves in sweat glands.

P030

How does diabetic peripheral neuropathy (DPN) impact patients' burden of illness and the economy? A retrospective study in Beijing, China

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Objective: Diabetic peripheral neuropathy (DPN) carries a heavy burden of illness for patients and negatively affects the economy. The objective of this study is to evaluate the cost and quantity of antidiabetic drugs needed in patients with or without DPN, as well as their variation trends in Beijing between 2016 and 2018.

Methods: This observational cross-sectional study used data on diabetic patients with outpatient medication records obtained from Beijing Medical Insurance from 2016 to 2018. The medications, comorbidities, diabetes-related complications, treatment strategies, and costs of drug treatment were compared between DPN patients and non-DPN patients.

Results: Of the 2853036 diabetic patients included in the study, 375216 (13.15%) had DPN, and 187710 (50.03%) of the DPN patients were women. Compared with non-DPN patients, DPN patients used more mediations (4.7±2.47 vs. 3.77±2.32, p<0.0001, in 2018) to treat related complications and comorbidities (2.03±1.2 vs. 1.71±1.05; 2.68±1.93 vs. 2.06±1.86, p<0.0001, respectively, in 2018). The total annual costs of drug treatment were higher in DPN patients than in non-DPN patients (¥12583.25 ± 10671.48 vs. ¥9810.91 ± 9234.14, p<0.0001, in 2018). The usage of DDP4i increased from 2.55% to 6.63% in non-DPN patients and from 4.45% to 10.09% in DPN patients from 2017 to 2018.

Conclusions: The number of comorbidities, diabetic complications, medications, and annual drug treatment costs was greater in DPN patients than in non-DPN patients.

KEYWORDS

Diabetic peripheral neuropathy (DPN), medications, hypoglycemic therapy, medical costs, burden of illness.

P031

Difference analysis in artery plaque above or below the knee in patients with diabetic foot ulcer and periptery artery disease by proteomics

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Aim: Patients with diabetic foot and peripheral vascular disease have multi-stage extensive plaques, which are more common below the knee, which is difficult to treat and the effect is not satisfactory. This study was performed for proteomic analysis of plaques below or above the knee.

Methods: 3 diabetic foot patients with the plaques below the knee as D1 group, 3 diabetic foot patients with the plaques above the knee as D2 group and 3 non-diabetic patients as C group. During endovascular therapy of the arteries of the lower extremities, plaques were collected by rotary cutting. The plaques were analyzed in different groups by mass spectrometry and bioinformatics.

Results:1. A total of 5292 proteins were obtained, of which the quantifiable proteins were 4464. 2. Quantitative difference analysis showed there were upregulated 1504 proteins and downregulated 1350 proteins between D1 and D2 groups. The number of up-regulated and down-regulated proteins was greater than that of D1 and C, and D2 and C. Cluster analysis showed that the similarity of the three samples was high within each group, and the similarity was very low between groups. 3. The functional difference showed between D1 and D2, the GO enrichment top 3 were nucleic acid binding, primary metabolic process and membrane-enclosed lumen and KEGG pathway enrichment top 3 showed diabetic cardiomyopathy, prion

disease and Alzheimer disease. Among them, diabetic myocardial pathway is the most different. The protein interaction results showed that 5 clusters could be formed between the two groups, but the protein interaction between the differential proteins between D1 and D2 was more complex. 4. The cell localization and domain of D1 and D2 differential proteins are also different from those of the control group.

Conclusions: Plaque proteomics below the knee of patients with diabetic foot and periptery artery disease differs from that of above the knee. From the perspective of the number and function of differential proteins, it has a greater impact on the cardiovascular and cerebrovascular, and the top proteins and pathways are useful for in-depth research.

P032

Bilateral gastrocnemius diabetic myonecrosis: Atypical involvement of a rare complication

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Diabetic myonecrosis, also known as diabetic muscle infarction (DMI), is an extremely rare microangiopathy complication of diabetes. It usually occurs in patient with advanced diabetes who have many diabetic complications such as retinopathy, nephropathy, and neuropathy. The most common affected muscle is quadriceps femoris, unilateral involvement is common. Here we reported an atypical case of DMI with bilateral gastrocnemius involvement and found fatty infiltrate is another MRI manifestation besides edema. Pain can be relieved by control blood glucose, non-steroidal anti-inflammatory drugs (NSAID) for analgesia, anti-platelet aggregation, improve microcirculation and bed rest. But MRI fatty infiltrate and edema change slight meaning imaging changes lagged behind clinical findings. The prognosis of end-stage microangiopathy is terrible. Our patient developed diabetic foot later and eventually accepted surgery to remove the necrosis toe.

P033

Renal fat fraction and its influencing factors in patients with type 2 diabetes mellitus

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Background: Fatty kidney, as an emerging field of nephrology research, plays an essential role in the development of chronic kidney disease and cardiovascular events, especially in patients with diabetes mellitus or metabolic syndrome. We set our sights on exploring the influencing factors of renal fat fraction among patients with type 2 diabetes mellitus (T2DM).

Methods: In this cross-sectional study, we determined renal and hepatic fat fraction by Dixon magnetic resonance imaging. Linear regression analysis was used to determine independent risk factors for the renal fat fraction of patients with T2DM.

Results: A total of 118 participants were enrolled. The renal fat fraction of patients with T2DM in this research was 4.89(4.61, 5.67) %. Moreover, renal fat fraction was positively correlated fasting C-peptide, alanine transaminase, aspartate aminotransferase, uric acid (UA), triglyceride, visceral adiposity index (VAI), lipid accumulation product (LAP), product of triglycerides and glucose (TyG) and hepatic fat fraction, however, it was negatively correlated with high-density lipoprotein cholesterol (HDL-C). In the multivariate linear regression model, UA, HDL-C, LAP, VAI and hepatic fat fraction were ultimately shown as independent factors associated with renal fat fraction in patients with T2DM.

Conclusion: Higher renal fat fraction in patients with T2DM was associated with higher levels of hepatic fat fraction, and with increased metabolic risk factors including abdominal obesity, hyperuricemia and dyslipidemia.

Keywords: renal fat fraction, magnetic resonance imaging, metabolic risk factors, type 2 diabetes mellitus

P034

Mechanism of methylglyoxal damage on microvascular endothelial cell based on metabolomics and possible intervention strategy

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Objectives: The impairment of endothelial cell function is an important initial factor of diabetic vascular complications. Methylglyoxal (MGO) is a highly reactive metabolite produced in the process of glucose metabolism and has a damaging effect on endothelial cell function. In this study, untargeted metabolomics and transcriptomics methods were used to analyze the metabolic pathway changes after MGO intervention in microvascular endothelial cells, which further clarify the mechanism of MGO damage on microvascular endothelial cell function and explore differential metabolites that can improve the detrimental effect of MGO, in order to provide new ideas for the treatment of diabetic vascular complications.

Methods: The microvascular endothelial cells were divided into control group and MGO group. The cell proliferation ability was detected by CCK8. The cell apoptosis was detected by flow cytometry. The cell tubulization function was detected by tube formation assay. The cell migration ability was detected by scratch assay. The supernatant NO content was detected by NO reagent kit. The mRNA expression level of related genes was detected by qPCR. The expression of eNOS protein was detected by WB. The differential genes and involved important signaling pathways were screened by RNA-seq, and the differential metabolites and metabolic pathways were analyzed by non-targeted cell metabolomics. L-Arginine (Arg) was chosed to interfere with MGO-induced microvascular endothelial cells. The experiment was divided into control group, Arg group, MGO group and MGO + Arg group.

Results: Compared with the control group, the activity of cells in the MGO group decreased significantly and the apoptosis level increased significantly. ROS production increased and inflammatory reaction increased significantly in the MGO group. Importantly, the ability of forming tube and migration decreased significantly in the MGO group. Furthermore, the amount of NO in the cell supernatant decreased significantly and the expression of eNOS protein decreased significantly.

The results of the cell transcriptome analysis showed that the gene transcription level of the MGO-intervention group changed significantly. A total of 2844 differentially expressed genes were screened out in the control group and MGO group. A total of 884 genes were up-regulated and 1960 genes were down-regulated, including genes closely related to vascular formation. The KEGG pathway enrichment analysis showed that the cell-extracellular matrix receptor interaction and the local adhesion signal pathway were the two pathways with the most significant enrichment.

The results of the cell non-targeted metabolomics showed that MGO mainly induced the amino acid metabolism reprogramming in microvascular endothelial cells. MGO intervention significantly changed the content of 278 cellular metabolites, including 21 metabolites up-regulated and 257 metabolites down-regulated. KEGG metabolic pathway analysis showed that the significantly different metabolic pathways in the control group and MGO group were mainly the amino acid metabolism pathway and the purine metabolism pathway.

Compared with the MGO group, Arg intervention could significantly improve the vitality of microvascular endothelial cells and reduce the apoptosis induced by MGO. Arg intervention also could significantly promote the tubulization and migration ability of endothelial cells damaged by MGO, as well as significantly increase the content of up-regulating NO in endothelial cells.

Conclusions: MGO intervention significantly damaged the functions of proliferation, tube formation and migration of microvascular endothelial cells. MGO intervention affected the expression of genes related to angiogenesis, and the extracellular matrix receptor interaction and local adhesion signaling pathway were significantly enriched signaling pathways of differentially expressed genes. MGO intervention caused metabolic reprogramming of microvascular endothelial cells, among

which amino acid and purine metabolism pathways showed significant changes, which may be a new mechanism of MGO-induced endothelial cell dysfunction. The differential metabolite of Arg identified by metabolomics could significantly ameliorate the damaging effects of MGO on endothelial cell function.

P035

Pathogenic bacteria distribution and drug sensitivity of diabetic foot ulcer complicated with necrotizing fasciitis of lower extremity

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Objective: To explore the pathogenic bacteria distribution, drug sensitivity and clinical characteristics of diabetic foot ulcer complicated with necrotizing lower extremity fasciitis.
Methods: 26 patients with diabetes mellitus complicated with necrotizing fasciitis of lower extremity were collected and their clinical features, laboratory data and bacterial culture results were analyzed.
Results: No amputation occurred in NF patients without DFU. In NF patients with DFU, the amputation rate was 68.4% and Wagner grade was higher. Staphylococcus aureus and Proteus common are the most common gram-positive and Gram-negative bacteria, respectively. Gram-positive bacteria were more sensitive to Teicoplanin, Linezolid and Tetracycline, while gram-negative bacteria were more sensitive to Biapenem cefoperazone-Sulbactam and Amikacin.
Conclusions: Diabetic foot ulcer with necrotizing lower limb fasciitis is associated with a higher risk of amputation and its empiric treatment should include fungal infection and other microbial infections. Higher Wagenr grade and higher NLR and PLR were associated with amputation.

P036

Liraglutide Improves the Integrated Pancreatic Microcirculation in Type 2 Diabetes Mellitus Mice: Evidence from the Common Microcirculatory Framework

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The pancreatic microcirculation is a highly vascularized and complex system responsible for oxygen and nutrient exchange in both islet and acinar cells. However, an integrated perspective for the assessment of pancreatic microcirculatory function is currently lacking. In the current study, we developed a common microcirculatory framework incorporating multiple microcirculatory parameters and established a multimodal device- and computer algorithm-based monitoring and visualization platform to decipher the complex integrated pancreatic microcirculatory function. Using this common microcirculatory framework, we investigated the integrated pancreatic microcirculatory function in both type 2 diabetes mellitus (T2DM) and liraglutide-treated mice. We observed significant decreases in erythrocyte tissue fraction (C_{RBC}), oxygen saturation (SO_2), hemoglobin concentration (Hb), blood perfusion, and microvascular frequency in the T2DM group. Furthermore, we observed heterogeneity in microcirculatory blood flow distribution in velocity-resolved regions, as well as an imbalance between microcirculatory oxygen and microhemodynamics in type 2 diabetic mice. We found that liraglutide partially restored the microcirculatory profile and coordinated microcirculatory blood flow and oxygen. Our results suggest that the common microcirculatory framework established in this study can serve as a methodological support and a novel paradigm for the analysis of the integrated microcirculatory function of the pancreas. In addition, our findings provide evidence that liraglutide may improve the impaired pancreatic microcirculatory function in T2DM.

P037

Acarbose attenuates endothelial progenitor cell dysfunction in streptozotocin-induced diabetic mice

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Introduction: Acarbose, an α-glucosidase inhibitor, is beneficial for the treatment of hyperglycemia in diabetic patients. To determine whether it ameliorates the commonly associated endothelial dysfunction, we investigated the endothelial progenitor cells (EPCs) function in streptozotocin (STZ)-induced diabetic mice.
Material and methods: C57BL/6 mice were injected with STZ (60 mg/kg/d × 5 d, *i.p.*) to induce diabetes whereas acarbose attenuated the endothelial dysfunction of EPCs. Diabetic mice were treated with or without acarbose (50 mg/kg/d, *i.g.*) for consecutive 14 days.
Results: The number of circulating EPCs was rised significantly in acarbose treated diabetic mice. Capabilities of bone marrow-endothelial progenitor cells (BM-EPCs) including tube formation and migration were impaired in diabetic mice, which were attenuated significantly by acarbose. There was also a decrease in the superoxide anion (O2) production of BM-EPCs in diabetic mice treated with acarbose.
Conclusion: Our study demonstrated that acarbose could attenuate EPC dysfunction in STZ-induced diabetic mice, indicating that acarbose might exert beneficial effects for diabetic endothelial dysfunction.
Keywords: Acarbose; diabetes mellitus (DM); endothelial progenitor cells (EPCs); endothelial dysfunction

P038

Glycine supplement protects against the damage of integrated pancreatic microcirculation in streptozotocin-induced type 1 diabetic mice

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Objective: Type 1 diabetes mellitus (T1DM) is a metabolic disorder, characterized by hyperglycemia and autoimmune antibodies that lead to insulin-secreting pancreatic β-cells failure. Although the pathophysiological basis of T1DM remains not fully clarified yet, the disturbance of the integrated pancreatic microcirculation might contribute to the pathogenesis and development of diabetes. As the microcirculation is highly responsive and complex, the current study aimed to investigate the potential protective role of glycine supplementation on pancreatic islet microcirculation.
Methods: The integrated pancreatic microcirculatory profile was determined using a dual-channel laser Doppler blood perfusion monitoring system and wavelet transform spectral analysis. Serum and pancreatic tissue were collected from control, STZ-induced T1DM, and glycine-supplemented mice (n = 6 in each group). Transmission and scanning electron microscopy were used to characterize the ultrastructure of the pancreatic microcirculation, and serum levels of microcirculation-associated inflammatory cytokines were measured by antibody pair-based assay.
Results: The T1DM group showed disturbed pancreatic microcirculatory oscillation and lower blood perfusion pattern. However, 1% glycine supplementation significantly restored regular biorhythmic contraction and relaxation with a higher scale blood

distribution pattern as evidenced by increased mean blood perfusion, amplitude and frequency of microvascular vasomotion. Analysis of continuous blood flow signals revealed that glycine supplementation significantly reversed the lower amplitudes of endothelial oscillators (especially NO-dependent endothelial oscillators) during T1DM. Moreover, glycine supplementation significantly reversed the ultrastructural deterioration of IMECs, IMPCs, including the destruction of the cytoplasmic membrane and organelles (mainly mitochondria), collagen fiber proliferation, and alleviated the edema of the expanded pancreatic islet-exocrine interface in T1DM mice. In addition, glycine supplementation inhibited the production of cytokines IL-6, TNF-α, IFN-γ, pro-MMP-9, and VEGF-A in T1DM.

Conclusions: This study demonstrates that glycine supplementation can protect against STZ-induced integrated pancreatic microcirculatory dysfunction, providing potential therapeutic benefits for T1DM.

P039

The association of circulating chemerin level with mild cognitive impairment in patients with type 2 diabetes mellitus, a cross-sectional study based on resting-state fMRI analysis

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Background: Chemerin, an adipokine secreted by adipose tissue, plays a major role in the control of metabolism and inflammation. Recently, the expression of chemerin receptors has been detected in the central nervous system and it may regulate neuronal activity and brain functions. However, few studies have explored the relationship between chemerin and MCI in human populations.

Objective: This study aimed to investigate whether serum chemerin level was associated with cognitive performance and brain dynamics in patients with type 2 diabetes mellitus (T2DM) based on resting-state fMRI analysis.

Methods: Three hundred and one patients with T2DM (179 mild cognitive impairment (MCI) and 122 cognitively normal controls (NC)) were recruited for serum chemerin determination by ELISA. Cognitive functions were assessed using Montreal Cognitive Assessment test (MoCA) and neural activity of brain was measured by rest-state function MRI (rs-fMRI).

Results: Serum chemerin levels were significantly lower in patients with MCI, compared to those without MCI. Spearman's analysis showed that a significant positive correlation between chemerin levels and subscores of visuospatial, language, and delayed recall abilities. Logistic regression analysis showed that lower chemerin levels was associated with elevated risk of MCI and the area under the ROC curve was 0.752 (95%CI: 0.641, 0.862) for serum chemerin as predictor of cognitive impairment stage. Among rs-fMRI parameters, patients in high-chemerin group (chemerin≥103.7076ng/ml) had significantly increased mean amplitude of low-frequency fluctuations (mALFF) in the right lingual gyrus, fusiform gyrus, bilateral middle and superior occipital gyrus, compared to patients in low-chemerin group (chemerin<103ng/ml). The correlation analysis showed mALFF values were positively correlated with serum chemerin levels and subscores of visuospatial, language, and delayed recall abilities in these areas of the brain. Brain network analysis of functional connectivity (FC) revealed that significantly increased FC levels between medial visual network (mVN) and ventromedial prefrontal cortex (vmPFC) as well as between posterior default mode network (pDMN) and the anterior default mode network (aDMN) were observed in high-chemerin group, compared to patients in low-chemerin group. Moreover, FC value between vmPFC and mVN and between pDMN and aDMN showed significant positive correlation with chemerin levels and visuospatial score, respectively. In addition, FC value between vmPFC and mVN was positively correlated with delayed recall score and FC value between pDMN and aDMN was positively correlated with language score.

Conclusions: Our findings suggest that chemerin levels in patients with type 2 diabetes was positively associated with cognitive abilities, mALFF and functional connectivity, supporting the potential protective effect of chemerin on cognitive deficits in diabetes.

P040

TIR

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There are 30 male C57B6L/J mice.Six mice was randomly selected as control group, fed with normal diet.The following 24 mice were intraperitonealy injected with streptozotocin (STZ, 75mg/kg) ,combining with high fat diet(carbohydrate 23 %, protein 26 %, fat 35 %, cellulose 6.4 %, mineral 6.4 %, vitamin 0.3 %). Mice fasting tail vein blood glucose levels≥11.1mmol/L were considered as diabetic model. Totally 20 mice were successed to be diabetes mice. Diabetic mice were divided into DM group and DM+RH group (Rhein,120mg/kg/d). After 12 weeks of rhein administraton,all mice were starved over night and record fasting blood glucose and body weight.After euthanasy,the whole heart were quickly removed and weighed and calculate heart-to-body weight ratio(HW/BW). Hematoxylin and Eosin staining was used to observe morphology of heart tissue. Masson trichrome stain was used to estimate myocardial interstitial fibrosis. Transmission electron microscopy were used to detect myocardial mitochondria injury.The mRNA levels of Sirt1, PGC-1α, TFAM, NRF-1, UCP2, ANP, BNP and β-MHC were quantified by RT-qPCR. Sirt1, PGC-1α and TFAM protein level were estimated by Western blot and IHC.

P041

Newly established LC-MS/MS method for measurement of plasma BH4 as a predictive biomarker for kidney injury in diabetes

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Objective: The clinical research on BH4 is limited because of the difficulties on its measurement. In this study, we used our own established LC-MS/MS method to examine the plasma BH4 levels in diabetes to determine whether it could be used as a biomarker for the prediction of kidney injury in those patients.

Methods: Hospitalized diabetes patients in Renmin Hospital of Wuhan University from Jan to Aug 2021 were recruited. To assess the association between plasma BH4 with ACR or eGFR in diabetes, a total of 142 patients with type 2 diabetes (T2DM) were enrolled. They were divided into three groups by albuminuria levels: normo-albuminuria (n = 68), microalbuminuria (n = 48), and macroalbuminuria (n = 26) according to ACR; or into two groups by eGFR: eGFR≥90 or eGFR< 90ml/min) for correlation and logistic regression analysis. Plasma BH4 level was measured by LC-MS/MS along with other biochemical indices.

Results: Plasma BH4 concentrations were decreased as ACR progressed. BH4 (r = – 0.55, P < 0.001) and 2h CPeptide (CP-2h) (r = – 0.248, P = 0.003) levels were negatively correlated with ACR. Moreover, multivariable logistic regression analysis showed BH4 concentrations (B = – 0.468, P < 0.001) and CP-2h (B = – 0.257, P = 0.028) were independently associated with ACR progression. ROC curve showed that BH4 level has a predictive value on ACR (95%CI 0.686–0.841, sensitivity 69.1%, specificity 73%). However, in diabetes patients with eGFR≥90 ml/min, plasma BH4 level (P = 0.008) is higher than those in diabetes with eGFR<90 ml/min, and BH4 was remained independently associated with eGFR after multivariable logistic regression analysis (B = – 0.193, P = 0.048).

Conclusion: Our established LC-MS/MS method could be used on human plasma BH4 measurements and our data suggested that

BH4 level can be used as a biomarker for kidney injury in diabetes indicated by its association with ACR progression and early renal function decline.

Stroke

P042

The CCA repair during reperfusion in MCAO filament model could not replace the ECA cross-sectional MCAO filament model in mice

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Aims: A reliable animal model of cerebral ischemia is essential for understanding the pathophysiology of ischemic stroke. Currently, the standard focal cerebral ischemia models in mice include middle cerebral artery occlusion (MCAO) filament insertion through external carotid artery (ECA) trunk (ECA ligated) and MCAO filament insertion through common carotid artery (CCA) which is ligated after reperfusion (CCA ligated). A modified MCAO model in mice has been established, in which the filament is induced via a direct incision in the CCA and the CCA with subsequent closure of the cut and reperfusion of the artery (CCA repaired). Studies have shown that this CCA repaired MCAO model has potential advantages compared with the CCA ligated model. However, there hasn't been any research to clarify whether the CCA repaired model is better than the ECA ligated model. In this study, the CCA repaired model was compared with the ECA ligated model in mice, so as to provide evidence for selecting the appropriate MCAO model.

Methods: Sixty male C57BL/6 mice (2-month-old) weighting 20~22g were randomly assigned to establish CCA repaired model (n= 34) and ECA ligated model (n=26). The operation duration to create ischemia and reperfusion, body weight, food intake and the number of intraoperative and postoperative deaths of mice were recorded in the two models respectively. mNSS and Bederson scores were used to evaluate neurological function deficits on day 1/3/5/7 after MCAO. Removed brain were sectioned, stained using 2% 2,3,5-triphenyltetrazolium chloride (TTC), fixed and imaged to allow for quantification of ischemic injury on day 7 after MCAO. T test, Mann-Whitney test, F test and Kaplan-Meier curve were used for data analysis.

Results: The establishment of the CCA repaired model required longer operation duration than the ECA ligated model (*P=0.0175), especially time period during reperfusion was significantly different (****P<0.0001). There was no significant difference in body weight and weight change and no significant differences were found in average body weight (P=0.3500) and percentage of weight loss (P=0.4104) between the two groups within 7 d after MCAO. There was no significant difference in food intake and food intake change between the two groups within 7 d after MCAO. No significant differences were found in average food intake (P=0.1869) and decline percentage of food intake (P=0.0624) between the two groups within 7 d. Lesion volume (P=0.2056) and intragroup variability (P=0.4802) showed no significant differences between the two groups. And no significant difference was found between the two groups in neurological function deficit on day 1/3/5/7 after MCAO. There was no significant difference in survival probability between the two groups within 7 d after MCAO (P=0.6396).

Conclusion: CCA repaired model has no significant advantage over ECA ligated model and could not replace ECA ligated model. ECA ligated model is still an important tool for the research of focal cerebral ischemia.

P043

uPAR and cFn: candidates for assisting in guiding whether thrombolysis or not in acute ischemic stroke

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Background And Purpose: Recombinant tissue plasminogen activator (rtPA) is still main therapeutics in acute ischemic stroke (AIS), while the therapeutic effect is unpredictable. In clinical practice, the poor outcome with rtPA and good outcome without rtPA are commonly observed. This article aimed to explore the potential factors that related to the necessity and feasibility of the administration of rtPA.

Methods: Eligible patients from November 2018 to July 2019 who were diagnosed with AIS were enrolled. Baseline characteristics were reviewed. Spearman's correlation test was performed to assess the correlation between uPAR/cFn and the outcome of AIS. The receiver operating characteristic (ROC) curve was generated to assess the prediction efficiency of uPAR/cFn in the outcome of AIS. Logistic regression analysis was used to assess the contribution of uPAR/cFn in guiding the necessity and feasibility of rtPA in AIS. The relationship between uPAR/cFn and rtPA were detected via C57/BL6 mice induced by middle cerebral artery occlusion.

Results: Both uPAR and cFn are positively correlate to the outcome of AIS with the correlation coefficient of 0.302 (P<0.001) and 0.253 (P=0.001). uPAR (AUC:0.66, [95% CI, 0.577–0.744]; P=0.001) and cFn (AUC:0.66, [95% CI, 0.577–0.743]; P=0.001) display a similar result in predicting favorable outcome. cFn was an independent variable that is related to low necessity for rtPA (odds ratio (OR), 1.019[95% CI, 1.007–1.032]; P=0.002). Besides, uPAR (OR, 0.990[95% CI, 0.983–0.998]; P=0.010), cFn (OR, 0.947[95% CI, 0.915–0.979]; P=0.002) and hyperlipidemia (OR, 8.699[95% CI, 1.578–47.967]; P=0.013) were identified as independent variables that are related to low feasibility for rtPA. At 24h and 72h ischemic/ reperfusion, rtPA may decrease the plasma levels of cFn and uPAR.

Conclusions:

Our study suggests that uPAR and cFn may serve as the candidates for assisting in guiding whether thrombolysis or not. Our study suggests that the patients with a relatively higher plasma level of cFn may achieve a good outcome with no need for rtPA. The patients with a lower plasma level of cFn or uPAR may still suffer from a poor outcome with rtPA.

P044

Effect of intracranial venous system on blood-brain barrier permeability in rats with cerebral ischemia/reperfusion injury and improvement of Ginsenoside Rb1 and Emodin combinative interventionon

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Objectives: To investigate the effect of intracranial venous system on neurovascular protection and its mechanisms in I/R rats and the combined effect of GRb1 and Emodin.

Methods: Healthy adult Sprague-Dawley (SD) rats were randomly divided into five groups: sham group, I/R model group, I/R+ Left Internal Jugular Vein Occlusion (LIJVO) model group, Emodin group, GRb1 group and GRb1+ Emodin (GE) group. Each group was further divided into four subgroups according to different time points (6h, 1d, 3d, and 7d after I/R injury). Three days before operation, GRb1 (40 mg/kg) and/or Emodin (25 mg/kg) were administered intraperitoneally into each intervention group once a day until the rats were sacrificed,

while the other groups were administered with same volume of normal saline (NS).Modified neurological seveity scores (mNSS) scale was used to assess the neurological function; Western Blot and qRT-PCR were used to detect the expression of YAP and TAZ around cortical infarction.

Results: The mNSS of the I/R group and the I/R+LIJVO group increased significantly ($P < 0.05$) and the increase was more obvious in the I/R+LIJVO group ($P < 0.05$). The I/R group increased from 6h and peaked on 1d, then declined gradually but still remained higher than sham group at 7d. I/R+LIJVO group began to increase at 6h, the mNSS score was still high at 3d, and decreased at 7d. Compared with the I/R+LIJVO group, three treatment groups had significantly lower mNSS ($P < 0.05$). Compared with the GRb1 or Emodin group, the GE group had the lowest mNSS, with statistical significance at 1d, 3d and 7d after cerebral I/R ($P<0.05$).

The expression of ZO-1 and Occludin had no significant difference in sham group at all time points. In two model groups, the expression of tight junction protein decreased significantly ($P < 0.05$) and the decrease was more obvious in the I/R+LIJVO group ($P < 0.05$). The I/R group decreased from 6h and reached the lowest point on 1d, then increased gradually but still remained higher than sham group at 7d. The I/R + LIJVO group began to decrease at 6h, reached the lowest point on 3d, and then increased. Compared with the I/R+LIJVO group, three treatment groups showed significant higher expression at the same time points ($P < 0.05$).The expression of tight junction protein in GE group was the highest, and there was significant differences between the GE group and each mono-therapy group ($P < 0.05$).

There were no significant changes in YAP and TAZ protein and mRNA levels in sham group at each time point. In I/R model group and I/R+LIJVO model group, the expression decreased significantly ($P < 0.05$) and the decrease was more obvious in I/R+LIJVO model group ($P < 0.05$). The expression of YAP and TAZ in the I/R group began to decrease at 6h, reached the lowest at 1d, then increased, and was still lower than that in the sham operation group at 7d. The expression in the I/R+LIJVO model group began to decrease at 6h, reached the lowest at 3d, and then increased. Compared with the I/R+LIJVO group, three treatment groups showed significant higher expression at the same time points ($P < 0.05$). The expression of YAP and TAZ in GE group was the highest, and there was a significant difference between the GE group and each mono-therapy group ($P < 0.05$).

Conclusions: The disorder of intracranial venous system can aggravate the symptoms of neurological deficit, increase the area of cerebral infarction, aggravate the damage of blood-brain barrier, reduce the expression of YAP and TAZ around cerebral infarction, and delay the recovery of injury to a certain extent. Compared with mono-therapy groups, combination use of GRb1 and Emodin showed a synergistic effect in cerebral I/R injury with lower mNSS, smaller infarction area, the ease of blood-brain barrier injury and higher expression of YAP and TAZ around cerebral infarction. GRb1 and Emodin have synergistic effects on the protection of blood-brain barrier, and their effects are realized through Hippo/YAP pathway.

P045

Total Salvianolic Acid Injection Attenuates Blood-Brain Barrier Disruption and Hemorrhagic Transformation in Ischemic Stroke Mice with Delayed RhPro-UK Treatment

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Background and Purpose: RhPro-UK is effective in treating ischemic stroke but may increase hemorrhagic transformation and blood brain barrier (BBB) disruption.The study aimed to evaluate the impact of Total Salvianolic Acid Injection (TSI), a traditional Chinese medicine, on BBB disruption caused by rhPro-UK treatment in a mouse model of thromboembolic stroke.

Methods: Male mice were injected with thrombin to create a blood clot in the middle cerebral artery. After 4.5 hours, they received rhPro-UK with or without TSI. The effects of treatment on thrombolysis, cerebral blood flow, and BBB damage were observed over 24 hours. We performed in vitro experiments on human brain microvessel endothelial cells (HBMEC) utilizing the glucose-oxygen deprivation (OGD) model. Reactive oxygen species levels were assessed using peroxide probes, NOX2 protein membrane translocation was evaluated via Western blotting, and MMP2 activity was measured using gelatin zymography.

Results: Administration of rhPro-UK effectively improved blood flow in the ischemic area, while TSI reduced the risk of adverse reactions caused by delayed treatment. TSI protected the BBB by inhibiting tight junction proteins disarrangement and downregulation. In vitro experiments on HBMECs showed that TSI decreased MMP2 activity in HBMECs by reducing ROS production following OGD modeling, which may be attributed to TSI's ability to reduce NOX2 membrane translocation.

Conclusions: In conclusion, TSI has a protective effect on the BBB during the ischemia-reperfusion phase of stroke.

P046

Prognostic effect of silybin on patients with liver injury after subarachnoid hemorrhage

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Prognostic effect of silybin on patients with liver injury after subarachnoid hemorrhage

Background: Subarachnoid hemorrhage (SAH) is a disease with rapid onset, high disability rate and high fatality rate, mainly caused by ruptured intracranial aneurysm. Complications after SAH are the main cause of low survival rate or direct death of patients, and ischemic brain injury caused by microcirculation dysfunction is the most serious complication after SAH. Liver injury is common after SAH, which leads to poor prognosis.

Objective: To evaluate the effect of silybin on the prognosis of patients with liver injury after subarachnoid hemorrhage surgery, and to further improve the prognosis after SAH to improve microcirculation disturbance.

Methods: A prospective case-control study was conducted among patients who underwent subarachnoid hemorrhage surgery from March 2023 to March 2024. All indexes of liver function were examined on admission, and patients were divided into mild, moderate and severe liver injury, and propensity matching control study was conducted on patients (silybin vs control: 50 vs 50). All indicators were detected and analyzed statistically.

Results: Compared with the control group, the levels of neutrophils, leukocytes, interleukin-6, procalcitonin, C-reactive protein and malondialdehyde in silybin group were significantly decreased ($P<0.05$), and the level of superoxide dismutase was increased ($P<0.05$).

Conclusions: Silybin can improve liver injury after subarachnoid hemorrhage surgery. Silybin may be considered as a drug to protect the body from inflammation after subarachnoid hemorrhage and further improve microcirculation disturbance.

P047

The Mechanism of Mitophagy Regulated by USP30 in Activation of NLRP3 Inflammasome after Subarachnoid Hemorrhage

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Background: Subarachnoid hemorrhage (SAH) is a kind of disease with high mortality and disability rate. The brain injury (EBI) caused by NLRP 3 inflammasome is initiated after SAH, and the degree of injury is closely related to the prognosis of SAH patients and plays a decisive role. The activation of NLRP 3 inflammasome is closely related to mitochondria. ROS, ATP, mtDNA (mitochondrial DNA), MAV (mitochondrial antiviral signaling protein) released by mitochondrial dysfunction are the main factors for the activation of NLRP 3 inflammasome, and mitophagy can inhibit NLRP 3 inflammasome activation by removing damaged mitochondria. USP 30, a deubiquitinating enzyme localized in the

outer mitochondrial membrane, can inhibit mitophagy by removing the ubiquitin tag. In this study, by inhibiting USP 30 to remove damaged mitochondria, thus alleviating NLRP 3 inflammasome activation, alleviating brain injury after SAH and promoting patient prognosis.
Methods: We used an in vivo model of intravascular perforation and an in vitro model of hemoglobin (HB) exposure to investigate the process of NLRP 3 inflammasome activation after SAH and the specific mechanism by which MTX652 inhibiting USP 30 promotes mitophagy to reduce brain injury after SAH.
Results: Western blot analysis showed that NLRP 3 increased significantly after SAH, and TNF- α and IL-1 β massive accumulation, while the mortality rate of cells and mice increased dramatically. After MTX652 inhibition of USP 30 expression after SAH and after lentiviral overexpression of USP 30, the substrate proteins of mitophagy such as PINK 1 and Parkin increased and decreased, respectively, and obvious changes of more and less autophagosomes could be observed by electron microscopy. After the simultaneous use of MTX652, inflammasomes such as NLRP 3 greatly decreased, and the survival rate of cells and mice increased compared with SAH. Further studies revealed that after USP 30 inhibition, it promoted Parkin-mediated ubiquitination of MFN 1 / 2 for degradation, thus disabling the impaired mitochondrial fusion mechanism and being recognized by effector proteins to initiate mitophagy.
Conclusion: Mitophagy removes damaged mitochondria, alleviates the activation of NLRP 3 inflammasome after SAH, and attenuates brain damage after SAH. As a selective inhibitor of USP 30, MTX652 was able to effectively inhibit USP 30 expression and promote Parkin protein-mediated substrate ubiquitination, thus promoting autophagy in damaged mitochondria. Provide new ideas for the treatment and prognosis of clinical SAH.
Keywords: Subarachnoid hemorrhage,NLRP3,Mitophagy,USP30

P048

Effect of DNA methylation level on the prognosis of patients with subarachnoid hemorrhage

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Background: Because of its high lethality and disability, subarachnoid hemorrhage (SAH) has received widespread international attention. In epigenetics, DNA methylation can affect gene transcription and reduce gene and protein expression levels. Previous research found that patients with SAH and delayed cerebral ischemia (DCI) had higher methylation and lower mRNA expression of various genes compared to SAH patients without DCI, implying that DNA methylation may be responsible for the development of DCI. However, it is unclear how overall methylation levels change after SAH versus non-SAH patients, or what causes the changes in DNA methylation.
Objective: Our purpose was to look into the differences in DNA methylation between SAH patients and non-SAH patients, as well as the mechanisms underlying such changes.
Method: Cerebrospinal fluid was collected from non-SAH and SAH patients, and the supernatant was centrifuged to extract genomic DNA, which was then treated with sodium bisulfite and detected using bisulfite sequencing PCR to compare DNA methylation changes.
Results: Methylation levels in cerebrospinal fluid were significantly higher in SAH patients compared to controls. The degree of methylation was related to the prognosis of patients with SAH, patients with higher methylation levels having a worse long-term prognosis.
Conclusions: SAH causes highly methylated genomic DNA, which inhibits gene transcription and results in lower protein expression levels, affecting proteins' ability to perform their normal functions and ultimately leading to a worse prognosis for patients. Reducing the level of genomic DNA methylation after SAH can improve patients' prognoses.

P049

Effect of glucocorticoid in the treatment of inflammatory response in cerebral venous thrombosis

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Objectives: Cerebral venous thrombosis (CVT) is a rare and high-risk cerebrovascular disease, its onset and prognosis are associated with inflammation closely. This study explored the relationship between granulocyte enumeration, inflammatory factors, and peripheral blood leukocyte DNA in acute/subacute CVT with severity on admission and prognosis of neurological function at discharge, as well as the changes after glucocorticoid treatment.
Method: Patients with acute/subacute CVT were included. Patients were assigned to the severe group or non-severe group according to whether venous cerebral infarction or cerebral hemorrhage occurred. Severe patients received glucocorticoid pulse therapy accompanied by anticoagulation therapy. Intracranial pressure, neutrophil enumeration/percentage, eosinophil enumeration/percentage, hypersensitive C-reactive protein (hs-CRP), and interleukin-6 (IL-6) on admission and discharge were collected from both groups of patients. At the same time, anticoagulant peripheral blood was collected from patients at admission and discharge. White blood cell layers were isolated, DNA was extracted, and the relationship between mitochondrial DNA (mt-ND2), beta-globin DNA, and Telomerase Reverse Transcriptase (TERT) DNA with the severity of CVT ereanalyzed. In the severe group, after treatment with glucocorticoid (methylprednisolone), the correlation between changes in intracranial pressure, inflammatory indicators, and leukocyte DNA abundance with the change of neurological deficits (NIHSS Score and mRS Score) from admission to discharge was analyzed by ordinary least square regression.
Results: 84 cases of CVT were collected, including 53 severe cases and 31 non-severe cases. Upon admission, the eosinophil count (0.02 [0.01, 0.07] vs. 0.06 [0.03, 0.09], p=0.028) and eosinophil percentage (0.4 [0.1, 0.9] vs. 0.7 [0.3, 1.4], p=0.045) in severe CVT patients were significantly lower than those in the non-severe group, while the levels of hs-CRP (16.66 [4.39, 31.95] vs. 3.19 [1.41, 5.44], p=0.005), IL-6 (11.22 [7.3, 18.77] vs. 4.865 [3.405, 8.07], p=0.001), mt-ND2 (1.189 [0.878, 1.466] vs. 1.13 [0.862, 1.739], p=0.001) and TERT-DNA (1.182 [1.003, 1.309] vs. 1.151 [1.012, 1.582], p=0.001) in the severe group were significant, compared with the non-severe group. Steroid therapy was applied to severe CVT patients, and the changes in intracranial pressure (coef=0.037, p=0.02), neutrophil ratio (coef=0.300, p=0.001), hs-CRP (coef=0.315, p=0.000), IL-6 (coef=0.186, p=0.000), β-globin DNA (coef=6.984, p=0.001), and TERT-DNA (coef=7.856, p=0.001) from admission to discharge were positively correlated with the changes in NIHSS score. Analysis of each indicator with changes in mRS score showed that the changes in the neutrophil ratio (coef=0.053, p=0.001), hs-CRP (coef=0.055, p=0.000), IL-6 (coef=0.027, p=0.000), β-globin DNA (coef=0.886, p=0.028), and TERT-DNA (coef=0.906, p=0.046) from admission to discharge in severe CVT patients were positively correlated with changes in mRS score.
Conclusion: Compared with non-severe cases, acute/subacute severe CVT patients exhibited significantly enhanced inflammatory responses (granulocyte count, inflammatory cytokines, and leukocyte DNA levels) upon admission. For severe CVT patients, after glucocorticoid treatment, intracranial pressure, inflammation indicators (granulocyte count, protein, and DNA levels), and neurological dysfunction showed a synchronous decreasing trend. Among them, the expression level of inflammatory genes within leukocytes decreased most significantly, suggesting that steroids may improve CVT neurologic deficits by regulating changes in immune cell proteins and genes.

P050

The alteration profiles of N6-methyladenosine modification of neutrophilic RNA in ischemic stroke

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N6-methyladenosine (m6A) modification participates in the pathogenesis of many diseases including ischemic stroke. Peripheral blood neutrophils are forerunners after ischemic brain injury and exert crucial functions. This study aims to explore the m6A-modified transcriptional profiles in neutrophils of ischemic stroke patients. We found that the expression levels of m6A regulators in the brain and leukocytes of post-stroke mouse models and neutrophils of ischemic stroke patients were notably altered after ischemic stroke. The m6A mRNA&lncRNA epigenetic transcriptome microarray identified 416 significantly upregulated and 500 significantly downregulated mRNA peaks in neutrophils of healthy controls and acute ischemic stroke patients. Moreover, 48 mRNAs and 18 lncRNAs were hypermethylated, and 115 mRNAs and 29 lncRNAs were hypomethylated after cerebral ischemia. Bioinformatic analyses showed that these m6A-modified mRNAs were primarily enriched in calcium ion transport, long-term synaptic potentiation, and base-excision repair. The signaling pathways involved were EGFR tyrosine kinase inhibitor resistance, ErbB, and base excision repair signaling pathway. Validation results showed that NRG1 and GDPD1 were significantly hypermethylated, and LIG1, CHRND, lncRNA NR_046869, and lncRNA NR_104118 were significantly hypomethylated after cerebral ischemia. This study explored the m6A methylation pattern in the neutrophils of ischemic stroke patients, indicating that m6A modification may be the intervention target of epigenetic regulation in ischemic stroke, and its specific regulatory mechanisms need to be further clarified.

P051

LC-MS/MS metabolomic profiling of the protective bu-tylphthalide effect in cerebral ischemia/reperfusion mice

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Cerebral ischemia/reperfusion (I/R) injury can cause serious secondary injuries and high patient mortality. Therefore, finding a more effective treatment method to reduce its incidence and mortality has become a research hotspot. Butylphthalide (NBP) is a chemical constituent of celery oil that exhibits anti-cerebral I/R injury and neuroprotective effects. In this study, a mouse cerebral I/R model was prepared using the middle cerebral artery occlusion method, and neurobehavioral score and 2, 3, 5-triphenyltetrazolium chloride staining experiments were used to confirm the obvious NBP anti-cerebral ischemia effect. The protective effect of NBP in the mouse cerebral I/R model and its metabolic pathway and mechanism were investigated using mouse blood samples. The metabolic profiles of mice in the sham, I/R, and I/R+NBP groups were significantly different. Under the condition that I/R *vs.* sham was downregulated and I/R + NBP *vs.* I/R was upregulated, 88 differential metabolites, including estradiol, ubiquinone-2, 2-oxoarginine, and L-histidine trimethylbetaine, were screened and identified. The related metabolic pathways involved arginine and proline metabolism, oxidative phosphorylation, ubiquitin and other terpenoid-quinone biosynthesis, and estrogen signaling. Metabolomics was used to elucidate the NBP mechanism in cerebral ischemia treatment in mice, revealing synergistic NBP pharmacological characteristics with multiple targets.

P052

AnGong NiuHuang (AGNH) pill alleviates neuro-inflammation in ischemic stroke rat by inhibiting Tyrobp/Syk and Tlr2/Myd88

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Background and Purpose: AnGong NiuHuang (AGNH) pill are a famous prescription in China and has been extensively used to treat ischemic stroke, but its effect and mechanism on cerebral ischemia are still unclear. This study systematically evaluated the effect of AGNH on ischemic stroke and elucidated its mechanism by using multi-omic technologies.

Methods and Results: The neuroprotection of pretreatment, immediate treatment and post-treatment of AGNH on middle cerebral artery occlusion (MCAO)-induced cerebral ischemia damage in rats, and the potential mechanism of post-treatment of AGNH was elucidated by integrating transcriptomic analysis and metabolomics analysis. Pretreatment and post-treatment of AGNH obviously decreased infarction rate, Longa 5 neurological deficient scores; post-treatment of AGNH improved survival rate of rats, increased regional cerebral blood flow(rCBF), enhanced the activity distance and time of the rat as indicated by the open field test; whereas immediate treatment of AGNH only decreased infarction rate. Integrated transcriptomics and metabolomics showed that AGNH intervened in the anti-inflammatory network with Tyrobp, Syk, Tlr2 Myd88, and Ccl2 as the core, inhibited inflammatory response and affected metabolic pathways such as “Arginine and proline metabolism”, “Citrate cycle (TCA cycle)”, “Arginine biosynthesis”, “Glycerophospholipid metabolism”, and “Alanine, aspartate and glutamate metabolism”. Post-treatment AGNH obviously downregulated inflammatory cytokines such as IL-1β, KC-GRO, IL-13, and TNF-α, and decreased Tyrobp, Syk, Tlr2, Myd88 and Ccl2 in both mRNA and protein level.

Conclusion: AGNH ameliorated inflammation in MCAO-induced ischemic stroke by regulating Tyrobp/Syk and Tlr2/Myd88 and multiple metabolic pathways.

P053

Naotaifang formula attenuates ferroptosis and necroptosis following cerebral ischemia/reperfusion injury via regulating HSP90-GCN2-ATF4 signaling pathway

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Background: Cerebral ischemia/reperfusion injury (CI/RI), a complex pathological process, is caused by blood recanalization therapy in ischemic stroke and regulated by several cell death processes, including ferroptosis and necroptosis. Naotaifang formula (NTF) has been proven the potential neuroprotective benefits in CI/RI.

Aims: This research aims to determine the evolution law of ferroptosis and necroptosis in the pathogenesis of CI/RI and investigate whether NTF can alleviate ferroptosis and necroptosis following CI/RI by regulating HSP90-GCN2-ATF4 signaling pathway in HT22 cells.

Methods: First, we verified the evolution law of ferroptosis and necroptosis by assessing pro-ferroptotic and pro-necroptotic changes after different reperfusion time in hippocampus of MCAO/R rats, along with cerebral blood, pathological change, protein, and related factors. To reveal the crosstalk of ferroptosis and necroptosis and demonstrate the neuroprotective effect of NTF, HT22 cells were pretreated with NTF, overexpressed plasmid of HSP90/MLKL/GPX4 (OV-HSP90/MLKL/GPX4) for 24 h when oxygen-glucose deprivation cells suffered re-oxygenation. The crosstalk of ferroptosis and necroptosis and effects of NTF were detected by CCK8, ROS, LDH, GSSG, GSH, and Ferrous iron. Besides, we conducted western blotting analyzes of proteins, including those involved in ferroptosis and necroptosis related signaling pathways.

Results: The cerebral blood flow value of rats during MCAO was significantly lower than that at baseline, and gradually increased with the extension of reperfusion time. The neurological function score and cerebral infarction volume of MCAO/R rats were increased gradually with the extension of reperfusion time, while the number of Nissl bodies was decreased gradually. With the extension of reperfusion time, positive cell rate of perls staining and the contents of factors related to pro-ferroptosis were increased, the levels of factors or proteins

related to inhibiting ferroptosis were decreased, and the expression of proteins related to pro-necroptosis were upregulated. These changes were reversed after MCAO/R-24H. In vitro investigation revealed that compared with HT22 cells treated by OGD/R, OV-HSP90 plasmid upregulated the protein expression of MLKL, HSP90, GCN2 and ATF4, added the levels of GSSG, ROS and ferrous iron, decreased the levels of GSH and GPX4 protein in OGD/R cells. OV-MLKL plasmid had the same regulatory effect as OV-HSP90 plasmid on other factors, except that OV-MLKL did not significantly regulate the expression of HSP90 protein. Moreover, NTF alone or combination with OV-MLKL/OV-HSP90 plasmid could reverse these changes above. Versus OGD/R cell, OV-GPX4 plasmid remarkedly promoted the GXP4 protein and GSH level, increased cell proliferation. Besides, NTF alone or combination with OV-GPX4 plasmid both promoted cell proliferation, decreased OGD/R-induced ROS generation and ferrous iron accumulation, downregulated the expression of factors related to pro-ferroptosis and pro-necroptosis, and reduced the protein expression of HSP90, GCN2 and ATF4.

Conclusions: Our results indicated that the degree of ferroptosis and necroptosis was aggravated gradually with the extension of reperfusion time, and these two-cell death reached the peak at 24h of reperfusion in hippocampus of MCAO/R rats. OV-HSP90/MLKL accelerated ferroptosis and necroptosis via HSP90-GCN2-ATF4 pathway, while OV-GPX4 attenuated ferroptosis, did not significantly affect the protein of P-MLKL and HSP90. The remarkable neuroprotective effects of NTF in alleviating CI/RI were associated with ferroptosis and necroptosis downregulation, and its mechanism was related with suppression of the HSP90-GCN2-ATF4 pathway.

P054

Astragaloside IV and ligustrazine alleviated cerebral ischemia reperfusion injury by regulating mitochondrial dynamics via the Drp1 SUMO/deSUMOylation

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Objective: Imbalance in mitochondrial homeostasis plays an important role in the pathological process of cerebral ischemia-reperfusion injury (CIRI). Drp1 is a key protein that regulates mitochondrial dynamics by governing the processes of mitochondrial fusion and fission through small ubiquitin-like modifier (SUMO)/deSUMOylation, which is essential for maintaining mitochondrial homeostasis. Both astragaloside IV and ligustrazine demonstrate significant potential in the prevention and treatment of CIRI. The present study aimed to investigate the effects and mechanisms of action of astragaloside IV and ligustrazine on CIRI.

Methods: In vivo, male Sprague Dawley (SD) rats were intragastrically administered astragaloside IV or ligustrazine for seven days. After the last administration, the rats were subjected to right middle cerebral artery occlusion/reperfusion (MCAO/R) . The cerebral infarction volume was observed by TTC staining. the cerebral blood flow recovery in the ischemic cortex was observed by laser speckle imaging. the cognitive function of the rats was detected by water maze. the neuronal damage in the ischemic cortex was observed by HE and Nissl staining. the mitochondrial morphology and structure in the ischemic cortex was observed by transmission electron microscopy. Co-immunoprecipitation was used to detect the binding of SUMO1 and SUMO2/3 to Drp1 in the ischemic cortex, and Western blot was used to detect the expressions of Drp1, Fis1, MFF, OPA1, Mfn1 and Mfn2 in the ischemic cortex of rats. In vitro, SY5Y cells were exposed to oxygen-glucose deprivation/reoxygenation (OGD/R). To clarify the mechanism, the SUMO1 and SUMO2/3 transfection upregulated the expression of SUMO1 and SUMO2/3. CCK-8 was used to detect cell viability. Elisa was used to determine the release of LDH, ROS and ATP contents. Mitochondrial membrane potential was detected by JC-1, and the binding of SUMO1 and SUMO2/3 of Drp1 was detected by co-immunoprecipitation. Western blot was used to detect the protein expression of Drp1, Fis1, MFF, OPA1, Mfn1, Mfn2, SUMO1, SUMO2/3, SENP1, SENP2, SENP3, SENP5 and SENP6.

Results: Astragaloside IV, ligustrazine and their combined preconditioning can improve the neural and cognitive functions of CIRI rats, improve the level of cerebral blood flow recovery in ischemic cortex, reduce the volume of cerebral infarction, alleviate the damage of neurons and mitochondria in ischemic cortex, reduce the binding of Drp1 to SUMO1 and increase the binding of Drp1 to SUMO2/3 in ischemic cortex. The expression of Drp1, Fis1 and MFF was inhibited, and the expression of OPA1, Mfn1 and Mfn2 was increased in ischemic cortex. In SY5Y cells, combined with astragaloside IV and Ligustrazine could reduce the inhibitory effect of OGD/R on cell proliferation, enhance cell vitality, reduce LDH release and ROS content, increase ATP content, and reduce mitochondrial membrane potential. The expression of Drp1, Fis1, MFF and SENP3 was decreased, while the expression of OPA1, Mfn1, Mfn2, SENP1, SENP2 and SENP5 was increased. However, overexpression of SUMO1 weakened the protective effect of astragaloside IV combined with ligustrazine on OGD/R-induced SY5Y cells. SUMO2/3 overexpression enhanced the protective effect of astragaloside IV combined with ligustrazine on OGD/R-induced SY5Y cells.

Conclusion: The combination of astragaloside IV and ligustrazine has been shown to reduce the SUMO1 modification of Drp1 and increase the SUMO2/3 modification of Drp1. This leads to the inhibition of mitochondrial division, promotes mitochondrial fusion, and improves the imbalanced mitochondrial dynamics, which helps to maintain mitochondrial homeostasis, thereby providing a protective effect against CIRI. Furthermore, the deSUMO1 modification of SENP1, SENP2, and SENP5 and the deSUMO2/3 modification of SENP3 may contribute to the SUMO1 and SUMO2/3 modification of Drp1.

Keywords: Astragaloside IV, Ligustrazine, Mitochondrial dynamics, SUMOylation, Cerebral ischemia reperfusion injury

P055

Astragaloside IV combined with ligustrazine alleviated cerebral ischemia reperfusion injury by regulating mitochondrial dynamics via the Drp1 SUMO/deSUMOylation

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Objective: Imbalance in mitochondrial homeostasis plays an important role in the pathological process of cerebral ischemia-reperfusion injury (CIRI). Drp1 is a key protein that regulates mitochondrial dynamics by governing the processes of mitochondrial fusion and fission through small ubiquitin-like modifier (SUMO)/deSUMOylation, which is essential for maintaining mitochondrial homeostasis. Both astragaloside IV and ligustrazine demonstrate significant potential in the prevention and treatment of CIRI. The present study aimed to investigate the effects and mechanisms of action of astragaloside IV and ligustrazine on CIRI.

Methods: In vivo, male Sprague Dawley (SD) rats were intragastrically administered normal saline, astragaloside IV, or ligustrazine for seven days. One hour after the last administration, the rats were subjected to right middle cerebral artery occlusion/reperfusion (MCAO/R) modeling. The cerebral infarction volume was observed by TTC staining; the cerebral blood flow recovery in the ischemic cortex was observed by laser speckle imaging; the cognitive function of the rats was detected by water maze; the neuronal damage in the ischemic cortex was observed by HE and Nissl staining; the mitochondrial morphology and structure in the ischemic cortex was observed by transmission electron microscopy. Co-immunoprecipitation was used to detect the binding of SUMO1 and SUMO2/3 to Drp1 in the ischemic cortex, and Western blot was used to detect the expressions of Drp1, Fis1, MFF, OPA1, Mfn1 and Mfn2 in the ischemic cortex of rats. In vitro, SY5Y cells were exposed to oxygen-glucose deprivation/reoxygenation (OGD/R). To clarify the mechanism, the SUMO1 and SUMO2/3 transfection upregulated the expression of SUMO1 and SUMO2/3. CCK-8 was used to detect cell viability. Elisa was used to determine the release of LDH, ROS and ATP contents. Mitochondrial membrane potential was detected by JC-1, and the binding of SUMO1 and SUMO2/3 of Drp1 was detected by co-immunoprecipitation. Western blot was used to detect the protein expression of Drp1, Fis1, MFF, OPA1, Mfn1, Mfn2, SUMO1, SUMO2/3, SENP1, SENP2, SENP3, SENP5 and SENP6.

Results: Astragaloside IV, ligustrazine and their combined preconditioning can improve the neural and cognitive functions of CIRI rats, improve the level of cerebral blood flow recovery in ischemic cortex, reduce the volume of cerebral infarction, alleviate the damage of neurons and mitochondria in ischemic cortex, reduce the binding of Drp1 to SUMO1 and increase the binding of Drp1 to SUMO2/3 in ischemic cortex. The expression of Drp1, Fis1 and MFF was inhibited, and the expression of OPA1, Mfn1 and Mfn2 was increased in ischemic cortex. In SY5Y cells, combined with astragaloside IV and Ligustrazine could reduce the inhibitory effect of OGD/R on cell proliferation, enhance cell vitality, reduce LDH release and ROS content, increase ATP content, and reduce mitochondrial membrane potential. The expression of Drp1, Fis1, MFF and SENP3 was decreased, while the expression of OPA1, Mfn1, Mfn2, SENP1, SENP2 and SENP5 was increased. However, overexpression of SUMO1 weakened the protective effect of astragaloside IV combined with ligustrazine on OGD/R-induced SY5Y cells. SUMO2/3 overexpression enhanced the protective effect of astragaloside IV combined with ligustrazine on OGD/R-induced SY5Y cells.
Conclusion: The combination of astragaloside IV and ligustrazine has been shown to reduce the SUMO1 modification of Drp1 and increase the SUMO2/3 modification of Drp1. This leads to the inhibition of mitochondrial division, promotes mitochondrial fusion, and improves the imbalanced mitochondrial dynamics, which helps to maintain mitochondrial homeostasis, thereby providing a protective effect against CIRI. Furthermore, the deSUMO1 modification of SENP1, SENP2, and SENP5 and the deSUMO2/3 modification of SENP3 may contribute to the SUMO1 and SUMO2/3 modification of Drp1.
Keywords: Astragaloside IV, Ligustrazine, Mitochondrial dynamics, SUMOylation, Cerebral ischemia reperfusion injury

P056

Stellate Ganglion Block Reverses PHSML-induced Vascular Hypo-reactivity through Inhibiting Autophagy-mediated Phenotypic Transformation in VSMCs

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Post-hemorrhagic shock mesenteric lymph (PHSML) return-mediated excessive autophagy of vascular smooth muscle cells (VSMCs) is involved the occurrence of vascular hypo-reactivity. Previous studies confirmed that stellate ganglion block (SGB) inhibited PHSML-induced excessive autophagy in VSMCs and then ameliorated vascular hypo-reactivity following hemorrhagic shock. However, the detailed mechanism remains unclear. In general, VSMCs have contractile phenotype and synthetic phenotype. Contractile phenotype of VSMCs will transformate to synthetic phenotype after stimulation with pathological factors, along with decreased contractility. Furthermore, excessive autophagy also induced phenotypic transformation of VSMCs. Therefore, we hypothesized that SGB ameliorates PHSML-induced vascular hypo-reactivity through inhibition of autophagy-mediated phenotypic transformation in VSMCs. To archive it, hemorrhagic shock model (hypotension of 40±2 mmHg for 90 minutes followed by resuscitation) in conscious rats was employed to observe the effects of SGB treatment or autophagy inhibitor 3-MA intravenous infusion (30 mg/kg) on the intestinal blood flow and autophagy marker proteins and phenotype proteins in mesenteric secondary artery tissues, as well as the effect of PHSML (obtained from anesthesia rats with hemorrhagic shock) intravenous infusion (1 ml/kg) and autophagy agonist rapamycin (RAPA) intraperitoneal injection (10 mg/kg) on the beneficial effect of SGB also was investigated. Further, the rat VSMCs were used for the observation of PHSML or PHSML obtained from rats treated by SGB (PHSML-SGB) (4%) on the cellular contractility and autophagy marker proteins and phenotype proteins, while the effects of 3-MA on PHSML or RAPA on PHSML-SGB were performed. The results showed that hemorrhagic shock decreased intestinal blood flow and enhanced the expressions of LC3 II/I, beclin1, and MMP2 in mesenteric secondary artery tissue, which indicated hemorrhagic shock-induced phenotypic transformation of VSMCs. Treatments with SGB and 3-MA improved intestinal blood flow and decreased the expression of autophagy and synthetic phenotype related proteins in rats with hemorrhagic shock. On the contrary, RAPA or PHSML administrations abolished the beneficial effects of SGB on above indices. Then, PHSML incubation decreased VSMCs contractility and induced autophagy activation and phenotype transformation, while opposite results were shown in the PHSML-SGB group. Importantly, 3-MA administration reversed the adverse effect of PHSML, but RAPA treatment presented the opposite effect to the PHSML-SGB incubation on VSMCs. In summary, the protective effect of SGB on vascular reactivity is achieved by inhibiting excessive autophagy-mediated phenotypic transformation in VSMCs to maintain their contractile phenotype. This study is supported by the Natural Science Foundation of Hebei Province (H2020405012).

P057

Role of bone marrow-derived mesenchymal stem cells on hemorrhagic shock-induced lung injury in rats

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Massive blood loss leads to hemorrhagic shock (HS), which can cause acute lung injury (ALI) through post-hemorrhagic shock mesenteric lymph (PHSML) return. Multiple preclinical studies have supported the potential value of bone marrow mesenchymal stem cells (MSCs) for the treatment of ALI. It is still unknown whether MSCs transplantation could prevent the ALI induced by PHSML. In this study, MSCs were transplanted via femoral vein during resuscitation using rat hemorrhagic shock model and in the PHSML infusion model. We found that rat pulmonary function was improved after MSC infusion, evidenced by increased inspiratory resistance (RI) and decreased mean mid expiratory flow (MMEF), forced expiratory volume in 100 ms (FEV100), peak expiratory flow (PEF). Meanwhile, the wet/dry weight ratio of lung was decreased by MSC infusion, indicating reduced edema. In the shock lungs, the neutrophil marker MPO and endoplasmic reticulum stress (ERS) marker GRP78 were significantly increased, while after MSCs transplantation, these markers were decreased. Similar results were observed in the PHSML infusion model. It suggests that MSC transplantation can decrease neutrophil recruitment and ERS induced by HS and PHSML in the lung tissues. In conclusion, our results indicated that MSC transplantation can effectively alleviate HS- or PHSML-induced ALI.
Keywords: Hemorrhagic shock; Mesenchymal stem cells; Acute lung injury; Post-hemorrhagic shock mesenteric lymph

Hypertension and Microcirculation

P058

To observe the effect of Shexiang Baoxin Pill on coronary microvascular dysfunction in refractory hypertensive patients of young and middle-aged adults with semi-quantitative index of SPECT myocardial perfusion imaging

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Abstract: Objective To observe the effect of Shexiang Baoxin Pills (SBP) on Coronary microvascular dysfunction (CMD) in refractory hypertension(RH) patients of young and middle-aged adults by using semi-quantitative indexes of SPECT myocardial perfusion imaging. Methods A total of 108 young and middle-aged RH patients admitted to the Department of Cardiology of Xuzhou Central Hospital from September 2019 to September 2021 were randomly divided into Shexiang Baoxin Pill group (SBP group) and control group, including 53 patients in SBP group and 55 patients in control group. SBP group was combined with SBP (45mg each time, orally, 3 times a day) on

the basis of routine treatment in the control group. Dynamic blood pressure, total cholesterol (TCH), triglyceride (TG), high density lipoprotein-cholesterol (HDL- Cholesterol) , low density lipoprotein-cholesterol (LDL- Cholesterol),total superoxide dismutase (T-SOD), total antioxidant capacity,(T-AOC), malondialdehyde (MDA), lipid peroxidase (LPO), total-nitric oxide synthase (T-NOS), endothelin-1 (ET-1), nitric oxide (NO), and semiquantitative indexes of myocardial perfusion imaging in SPECT [total stress score (SSS) and transient ischemic dilation (TID)] were observed before and 3 months after treatment in both groups. Results SSS and TID of young and middle-aged RH patients decreased after conventional treatment combined with SBP, and SSS{[3(1-5)] vs 4(2-6), P<0.05} was lower in SBP group compared with the control group. Before treatment, ambulatory blood pressure (24-hour mean systolic blood pressure, 24-hour mean diastolic blood pressure), blood lipid paraments(TCH, TG, HDL, LDL), oxidative stress paraments(T-SOD, T-AOC, LPO, MDA), endothelial function(T-NOS, NO, ET-1), SPECT myocardial perfusion imaging semi-quantitative paraments(SSS, TID) were detected in both groups and there was no statistical difference (P<0.05). Compared to the control group after treatment, the 24-hour mean systolic blood pressure [(136.5±2.1) vs (143.3±2.4) mmHg], 24-hour mean diastolic blood pressure [(84.4±1.3) vs (88.8±1.6) mmHg], TCH[(3.9±0.14) vs (4.15±0.15) mmol/L], LDL[(2.2±0.1) vs (2.54±0.1) mmol/L], T-SOD[(26.08±1.79) vs (18.33±1.59) U/ml], T-NOS[(8.24±0.45) vs (6.98±0.22) U/ml], ET-1[(63.94±3.99) vs (78.41±3.84) U/mL] and NO[(76.57±6.19) vs (58.62±5.38) μmol/L] were improved in the SBP group after treatment, the differences were statistically significant (P< 0.05). Conclusion The results of this study indicate that SBP combined with conventional treatment of hypertension can improve CMD in middle-aged and young RH patients, which may be related to the improvement of vascular endothelial function (T-NOS, NO) and antioxidant stress (T-SOD, T-AOC) levels by SBP. At the same time, SBP can improve dyslipidemia and blood pressure regulation.

P059

Toll-like receptor4 contributes to impaired pancreatic microvascular vasomotion in spontaneously hypertensive rat via mediating endothelial dysfunction

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Objective: The aim of this study was to investigate role of Toll-like receptor 4 (TLR4) on dysfunction of microvascular vasomotion of islet in spontaneous hypertensive rat and its underlying mechanism.

Methods: 8-weeks-age male SHRs were treated with neutralizing anti-TLR4 antibody (Anti-SHR)or Control IgG(1μg/day,Con-SHR) for two weeks, pancreatic islet vasomotion were measured by laser doppler. Wavelet transform analysis was performed to analyze characteristic oscillators derived from endothelial cells. The expression of eNOS in pancreatic islet were analyzed by IHC, the level of IL-6, eNOS and NO/ET-1 in plasma were measured by ELISA kit respectively. Islet microvascular endothelial cells (iMECs)-MS1 were cultured and exposed to high glucose(35mM) with treatment of CLI-095 (TLR4 signaling inhibitor) or not. Wound healing and tube formation analysis were used to analyze the endothelial function.

Results: Anti-TLR4 antibody treatment of SHR attenuated the increased blood pressure including SBP, DBP, MAP and HR significantly. Compared with Con-SHR, Anti-SHR showed an improved vasomotion of pancreatic islet microvaculature including amplitude,frequlency, blood perfusion and velocity (p<0.05 respectively) especially the oscillator part from endothelium-NO dependent resources than endothelium-NO-independent resource according the wavelet transform analysis. There were decreased plasma level of eNOS and expression of eNOS in islet tissue accompanied with a higher NO and lower ET-1 and IL-6 in plasma. CLI-095 treatment improved high glucose-induced endothelial dysfunction with increased migratory capacity, tube formation ability and lower monolayer cell permeability.

Conclusion: Blockage of TLR4 could improve microvascular vasomotion of pancreatic islet of SHR by mechanism involving the alleviation of endothelial dysfunction involving the increased expression of eNOS and re-balanced vasoactive substance.

Dementia and Microcirculation

P060

W1302, a novel drug discovery with new mechanisms for treatment of vascular dementia based on ultrastructure imaging method

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Objective: With the worldwide population aging, the incidence of dementia is increasing. The vascular dementia (VaD) is about 20% of all dementia patients. It is the second serious dementia after Alzheimer's diseases and there is no approved drug for this disease until now. It is known that VaD is mainly induced by cerebral blood vessel diseases. But there might be other mechanisms except improving cerebral blood flow for disease treatment. Recently we investigated the new mechanisms and developed a new drug candidate W1302 to treat VaD.

Results: It was showed that W1302 could improve spatial cognition verified by Morris water maze. It could also increase cerebral blood flow and decrease the volume of cerebral infarct and penumbra injury in the acute cerebral ischemic animal model (MCAO). The mechanism studies showed that W1302 released NO and relaxed cerebral blood vessels, especially the micro-blood vessels around infarct regions. The diameter and volume of the micro-blood vessels in the W1302-treated group were found to be larger than those in the pathological control group through 3D digital analysis of blood vessel ultrastructure imaging. In addition, it was found that W1302 modulated GABA receptor system and partially activated $GABA_A$ activity, which was known as a new neuronal protective mechanism. Furthermore, our results showed that W1302 strongly inhibited neuronal inflammation and reduced the enhancing effect of TNF-α induced by ischemia. The drug candidate was completed all preclinical studies and already accepted by CFDA for IND.

Keywords: vascular dementia; W1302; micro-blood vessels; ultrastructure imaging; NO; IND

P061

Study on the mechanism of Coptis chinensis Franch. and its main active components in treating Alzheimer's disease based on SCFAs using Orbitrap Fusion Lumos Tribrid MS

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Ethnopharmacological Relevance: *Coptis chinensis* Franch. (CCF), as an extensively used traditional Chinese medicine, has therapeutic effects on Alzheimer's disease (AD), but its mechanism of action has not yet been elucidated.

Aim of the Study: This study aims to reveal the mechanism of action of CCF via the gut-brain axis, and provide a new strategy for the clinical treatment of AD.

Materials and Methods: APP*swe*/PS1ΔE9 mice were used as AD models, and were given CCF extract by intragastric administration. Barnes maze was used to test the therapeutic effect of CCF on the treatment of AD. To reveal the mechanism of action of CCF in the treatment of AD, Vanquish Flex UHPLC-orbitrap fusion lumos mass was chosen to detect endogenous differential metabolite; MetaboAnalyst 5.0 was applied to derive relevant metabolic pathways; similarly, to explore the effects of CCF on the gut-brain axis, Vanquish Flex UPLC-Orbitrap fusion lumos mass was utilized to detect the changes in the content of SCFAs in AD mice after CCF administration; the prototype components and metabolites in CCF were identified by

UPLC/ESI/qTOF-MS, then their effects on Bifidobacterium breve were explored.
Results: CCF shortened the latency time of AD mice, improved the target quadrant ratio of AD mice, and made the maze roadmap simpler of AD mice; CCF regulated fifteen potential metabolites of AD mice, interestingly, ILA (indole-3-lactic acid) in SCFAs (short-chain fatty acids) was also included; CCF acted on histidine and phenylalanine metabolic pathways of AD mice; CCF increased the contents of acetic acid and ILA in AD mice; magnoflorine, jatrorrhizine, coptisine, groenlandicine, thalifendine, palmatine, berberine, epiberberine, hydroxylated jatrorrhizine, and 3-methoxydemethyleneberberine in CCF were detected in fecal samples of AD mice; magnoflorine, palmatrubine, 13-methylberberine, berberine, coptisine, and palmatine promoted the growth of Bifidobacterium breve.
Conclusions: we have demonstrated that CCF acts on the gut-brain axis by regulating SCFAs to treat AD.

Cerebral Microcirculation

P062

Qingkailing improves the no-reflow phenomenon of cerebral ischemia-reperfusion in mice by inhibition of RhoA/ROCK pathway in pericytes

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Aim of study: We aimed to investigate whether Qingkailing (QKL) inhibits RhoA/ROCK to reduce the contraction of pericytes to improve the recovery of cerebral blood flow after cerebral ischemia and reperfusion.
Materials and methods: The blood flow recovery effect of QKL after cerebral ischemia reperfusion in mice was observed by laser speckle blood flow imaging system. Bederson score, HE and NISSL staining were used to evaluate the protective effect of QKL on nerve function and neurons. The ultrastructural relationship between pericytes and endothelial cells was observed by transmission electron microscopy. Immunofluorescence was used to observe the different expression and morphological changes of pericytes before and after cerebral ischemia and reperfusion. In addition, the mechanism of QKL on RhoA/ROCK signaling pathway was also studied by ELISA and Western blotting.
Results: QKL improves cerebral blood flow recovery after cerebral ischemia and reperfusion mainly by inhibiting the contractility of pericytes. Compared with I/R mice, QKL significantly improved neural function, inhibited neuronal injury and decreased blood-brain barrier permeability after cerebral ischemia and hypoxia. QKL also increased the blood flow velocity. In addition, QKL reduced the contractile effect of pericytes on endothelial cells and the expression of pericellular marker proteins PDGFR-β and α-SMA. Finally, QKL down-regulated the RhoA/ROCK signaling pathway and reduced the phosphorylation of MLC.
Conclusions: QKL reduced pericellular shrinkage through regulation of RhoA/ROCK signaling pathway to improve the non-reflow phenomenon after cerebral ischemia reperfusion.

Atherosclerosis

P065

Serpina3c alleviates atherosclerosis via inhibiting sphingomyelin secretion from adipose tissue

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Background: We reported that Serpina3c could delay the progression of atherosclerosis by inhibiting the proliferation of smooth muscle cells. Adipose tissue metabolism is closely related to atherosclerosis. Repairing dysfunctional adipose tissue can maintain the metabolic balance of the whole body, thereby alleviating atherosclerosis in mice. Serpina3c is highly expressed in adipose tissue, however, whether serpina3c prevent atherosclerosis by regulating adipose tissue function is unknown, and the specific mechanism needs being clarified.
Objective: To explore the effect and mechanism of Serpina3c in adipose on atherosclerosis.
Methods: Serpina3c knockout mice with ApoE$^{-/-}$ background were constructed (ApoE$^{-/-}$ Serpina3c$^{-/-}$). ApoE$^{-/-}$, ApoE$^{-/-}$Serpina3c$^{-/-}$, ApoE$^{-/-}$ mouse in eight weeks old with epididymal adipose tissue injected in situ with Serpina3c control (ApoE$^{-/-}$-AAV8-shNC) or overexpression of adeno-associated virus (ApoE$^{-/-}$-AAV8-Adipoq-Serpina3c) or knockdown of adeno-associated virus (ApoE$^{-/-}$-AAV8-Adipoq-shSerpina3c). Then, atherosclerosis mice model were constructed. The weight of mice was recorded, and the size of aortic plaque was observed by HE staining, and the lipid deposition in the transverse section of aortic root was detected by oil red O staining. Total cholesterol, triglycerides, and TNFα, IL6 level in serum were detected. qRT-PCR and western blotting were used to detect the expression of inflammatory factors (TNFα, IL1β, MCP1, IL6) in aorta. Adipose tissue around the epididymis of ApoE$^{-/-}$ and ApoE$^{-/-}$ Serpina3c$^{-/-}$ mice were extracted for metabonomic analysis to find key lipid metabolites and key regulatory mechanisms. Primary adipocytes and primary smooth muscle cells were extracted for co-culture to verify relevant phenotypes and mechanisms.
Results: (1) There was no statistical difference in body weight among the six groups of mice; (2) HE staining results showed that the aortic plaques in ApoE$^{-/-}$Serpina3c$^{-/-}$ group and ApoE$^{-/-}$-AAV8-Adipoq-shSerpina3c mice were aggravated compared to the control group, while the aortic plaques in ApoE$^{-/-}$-AAV8-Adipoq Serpina3c mice were alleviated; (3) Oil red O staining showed that lipid deposition in the aorta of ApoE$^{-/-}$Serpina3c$^{-/-}$ group and ApoE$^{-/-}$-AAV8-Adipoq- shSerpina3c mice was increased, while lipid deposition in ApoE$^{-/-}$-AAV8-Adipoq-Serpina3c mice was decreased; (4) The total cholesterol, triglyceride, and the levels of inflammatory factors such as TNFα were significantly increased in the serum of ApoE$^{-/-}$Serpina3c$^{-/-}$ and ApoE$^{-/-}$-AAV8-Adipoq-shSerpina3c mice, while the levels of inflammatory factors and lipids in the serum of ApoE$^{-/-}$-AAV8-Adipoq-Serpina3c mice were decreased; qRT-PCR and western blotting showed that the expression of inflammatory factors in the aorta of ApoE$^{-/-}$Serpina3c$^{-/-}$ and ApoE$^{-/-}$-AAV8-Adipoq-shSerpina3c mice increased, while the expression of inflammatory factors in the aorta of ApoE$^{-/-}$-AAV8- Adipoq-Serpina3c mice was decreased; (5) Metabolomics results showed that SM (d18:1/16:0) in adipose tissue of ApoE$^{-/-}$Serpina3c$^{-/-}$ group was significantly increased. Sphingomyelin synthase (SMS) and Hif1α expression increased in adipose tissue of ApoE$^{-/-}$Serpina3c$^{-/-}$ mice. (6) The level of SM (d18:1/16:0) in ApoE$^{-/-}$-AAV8-Adipoq-Serpina3c mice was reduced, and Serpina3c KO induced smooth muscle cell foam. (7) SM (d18:1/16:0) secreted by primary adipocytes was increased and promoted the foam formation of vascular smooth muscle cells.
Conclusion: Serpina3c knockout activated Hif1α in adipose tissue around the epididymis. The expression of Hif1α promoted the transcription of SMS, and the secretion of SM (d18:1/16:0) was increased in adipose tissue. SM (d18:1/16:0) aggravated the progression of atherosclerosis by promoting foam of smooth muscle cells and increasing inflammation.
Keywords: Serpina3c; Adipose; Atherosclerosis; SM(d18:1/16:0); HIF1α.

P066

Serum Metrnl levels are positively associated with high-density lipoprotein cholesterol in patients with type 2 diabetes mellitus

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Purpose
Meteorin-like (Metrnl), a newly-discovered adipokine in 2014, is highly expressed in adipose tissue and has a beneficial effect on glucose and lipid metabolism. HDL-C is well recognized to be inversely associated with cardiovascular events. However, data on serum metrnl levels and HDL-C levels remains blank in the T2DM population. This study aimed to investigate the association between serum Metrnl levels and high-density lipoprotein cholesterol (HDL-C) in T2DM.
Materials and methods
Eighty-one participants with type 2 diabetes (T2DM) were included in this cross-sectional study. They were divided into two groups according to HDL-C levels: Group1 (lower HDL-C group): HDL-C < 1.04 mmol/L; Group2 (higher HDL-C group): 1.04 < HDL-C < 2.07 mmol/L. Serum Metrnl levels were measured by ELISA. Multivariate linear regression and logistic regression were used to assess the association between serum Metrnl levels and HDL-C.
Results: As compared with lower HDL-C levels groups, serum Metrnl levels were significantly higher in the group with higher HDL-C . Multivariate logistic regression analysis showed serum Metrnl levels were positively associated with HDL-C group after adjustment with sex, age, BMI, FPG, 2hPG, HbAlc, TG. Furthermore, serum Metrnl levels were inversely correlated with HOMA-IR. HDL-C levels were lowest in the group with the lowest Metrnl levels group and remained positively associated with Metrnl after adjustment for sex, age, BMI, TG, and HOMA-IR by using multivariate logistic regression analysis.
Conclusion: Serum Metrnl levels were positively associated with HDL-C levels in patients with T2DM.This suggests that increasing serum Metrnl levels maybe a candidate for improving lipid metabolism and preventing cardiovascular events in T2DM.
Keywords
Meteorin-like; lipid metabolism; high-density lipoprotein cholesterol ;T2DM;ASCVD.

Arterial Stiffness

P067

Hyperlipidaemia initiates vascular calcification via mitochondrial stress-triggered VEC senescence-dependent osteoblastic differentiation in VSMCs and macrophage formation in monocytes

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Background and Aims
Vascular calcification is the most common pathological change in metabolic syndrome patients with hyperlipidaemia. Vascular wall cells and macrophages are essential for keeping the physiological structure and function of blood vessel. Considering that senescence is one of the vital mechanisms of vascular calcification, and vascular endothelial cells (VECs) are the first barrier of vascular pathological changes, the role of VEC senescence in the initiation of vascular calcification deserves further investigation. The aim of this experiment is to elucidate whether mitochondrial stress-mediated VEC senescence-induced vascular smooth muscle cell (VSMC) osteoblastic differentiation and macrophage formation are the potential pathogenic mechanisms of vascular calcification occurrence under hyperlipidaemia condition.
Methods: In vitro, the aging model of primary VECs isolated from rat thoracic aortas was induced by palmitic acid (PA); the calcification model of primary VSMCs isolated from rat thoracic aortas and the macrophage formation model of primary monocytes isolated from rat bone marrow were induced by co-culture with aging VECs in the presence of high phosphorus. In vivo, the vascular calcification model was developed in rats by high-fat diet and vitamin D3 plus nicotine.
Results: In vitro, the high levels of mitochondrial damage and senescence markers in VECs, calcification markers in VSMCs, and macrophage formation markers in monocytes were significantly alleviated by knocking down the specific aging genes; additionally, mitochondria-targeted superoxide dismutase mimetics, MitoTEMPO and MitoQ, showed analogously protective effects. In vivo, the expressions of aging VECs, calcified VSMCs, and macrophage formation in rat thoracic aortas were obviously elevated in hyperlipidaemia-mediated vascular calcification group.
Conclusions: Taken together, this study revealed that hyperlipidaemia triggered mitochondrial stress-mediated VEC senescence is a pivotal mechanism of VSMC calcification, which provides a novel strategy for anti-metabolic abnormality syndrome-associated vascular complications.
Keywords: vascular calcification; hyperlipidaemia; senescence; mitochondria stress

Inflammation

P068

Relationship between fibrinogen to albumin ratio and type 2 diabetic retinopathy

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Purpose: Type 2 diabetic retinopathy is a long-term chronic inflammatory disease. The aim of this study was to investigate the relationship between fibrinogen to albumin ratio (FAR) and retinopathy in type 2 diabetic patients.
Methods: A total of 500 patients with T2DM were included in this study, and were divided into non-type 2 diabetic retinopathy group (NDR, n=297) and type 2 diabetic retinopathy group (DR, n=203) according to fundus examination findings, and the DR group was further divided into non-proliferative retinopathy group (NPDR, n=182) and proliferative retinopathy group (PDR, n=21). Baseline data of patients were collected, and the fibrinogen/albumin ratio (FAR) and neutrophil/lymphocyte ratio (NLR) were calculated to analyze the correlation between FAR and NLR and type 2 diabetic retinopathy.
Results: The FAR and NLR were significantly higher in the DR group compared with the NDR group (both P<0.001). Spearman correlation analysis showed that FAR was positively correlated with NLR and DR (P<0.05). As the FAR quartile increased, the prevalence of DR increased (14.8%, 16.7%, 25.1%, and 43.30%, respectively; P<0.05). Multifactorial logistic regression analysis showed that FAR, diabetic course, SBP and DPN were risk factors for the development of DR in patients with T2DM. the area under the ROC curve for FAR to predict DR progression was 0.708, with an optimal critical value of 7.04. the predictive value of FAR for DR was better than that of diabetic course (AUC = 0.705), SBP (AUC = 0.588).
Conclusion: The FAR index was significantly associated with the risk of developing DR and can be used as an early and effective predictor for the development of DR in patients with type 2 diabetes.

P069

Roukou Wuwei Pills ameliorate depression through attenuating neuroinflammation

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Background: Depression is a mental and emotional disorder, which pathogenesis is closely related to neuroinflammation induced by the abnormal activation of microglia cells in the central nervous system. It affects the synthesis and reuptake of neurotransmitters, and induces depressive symptoms. Roukou Wuwei pills (RKWW) is a compound

medicine, which has been used for treating uneasiness, forgetfulness and upset insomnia with notable antidepressant effect in clinic. However, the mechanisms by which RKWW and its main component exert the effect on depression remain unclear.

Methods: The antidepressant effect of RKWW in mice was synthetically evaluated by the acute depression models and reserpine-induced depression model. BV2 microglia neuroinflammation model was induced by lipopolysaccharide. The cytokine levels and related inflammation signaling pathways were determined by ELISA and Western blot. Reverse virtual screening technology was used to fish the target proteins of the main active component of RKWW, Alantolactone (ATL). Moreover, SPR, CETSA and DARTS technology were used to verify the binding of ATL to its target proteins.

Results: We demonstrated the antidepressant effect of RKWW. It increased the levels of neurotransmitters accumulation in the hippocampus of depression model mice. RKWW can also regulate neuroendocrine, reduce the levels of inflammatory cytokines, and promote the phosphorylation of PKA/CREB pathway. ATL was found to be the main active component in RKWW responsible for anti-neuroinflammation. ATL had higher affinity for mitogen-activated protein kinase 14 (MAPK14), which was verified to be the anti-neuroinflammatory target proteins of ATL.

Conclusion: Our study confirms the antidepressant effect of RKWW, which is likely attributable to its ability to reduce neuroinflammation. The main active component responsible for anti-neuroinflammation is ATL, which targets MAPK14 mainly through hydrophobic interactions, attenuating the activation of NF-κB signaling pathway. This study clarified the underlying mechanisms for the antidepressant effect of RKWW, providing pharmacological evidence for the clinical application of RKWW.

P070

Association between the Neutrophil to High-density Lipoprotein Cholesterol Ratio and Peripheral Artery Disease: Findings from National Health and Nutrition Examination Survey (1999-2004)

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Objective: Neutrophil to high-density lipoprotein cholesterol ratio (NHR) is a predictor of thromboembolic events, but the relationship between NHR and peripheral artery disease (PAD) is unknown. This study aims to investigate the relationship between NHR and PAD in American adults.

Methods: A total of 3 065 participants with completed NHR and ankle brachial pressure index (ABPI) records taken from the National Health and Nutrition Examination Survey (NHANES) cycles from 1999 to 2004 were included in this cross-sectional study. NHR was calculated as [neutrophil counts (109/L) / high-density lipoprotein cholesterol (mmol/L)], and the presence of PAD was defined as ABPI≤0.9. A logistic regression model was used to identify whether NHR was an independent risk factor for PAD, and subgroup analysis was performed to explore interactions that modify relationships.

Results: The weighted average age of all participants was 56.17 (55.61, 56.73) years old, and the weighted percentage of 47.81% (46.27, 49.35) were male. The prevalence of PAD was 4.85%. The multivariable adjusted odds ratios and 95% confidence interval (CI) of highest NHR quartiles were 5.17 (1.80, 14.80), with a trend of P = .003. This relationship was consistent with that of hypertension subgroups.

Conclusion: In conclusion, higher NHR is significantly associated with higher risk of PAD, which could be a marker of PAD.

Cancer and Microcirculation

P071

AIMP2: promising biomarker for therapeutic target and prognosis of Breast Cancer

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Background: Breast cancer has become the most common malignant cancer in women, and among the leading causes of cancer-related deaths worldwide. Unfortunately, current underlying mechanistic understanding of breast cancer remains incomplete. The study aims to utilize specific proteins as new biomarkers for evaluating the development and therapeutic targets of breast cancer.

Materials & methods:

A strategy combining protein label-free quantification technique, bioinformatic analysis and RT-qPCR was used to determine the level of differential expressed proteins in 3 matched breast cancer patients. The expression of AIMP2 was detected in breast cancer tissues compared with adjacent tissues, and MDA-MB-231 cell line, MCF/7 cell line and MCF-10A cells by RT-qPCR. CCK-8 analysis and transwell assays were used to investigate the function of AIMP2 in cell proliferation, invasion and metastasis of breast cancer cells. String was performed to predict the interaction between AIMP2 and downstream pathway.

Results: We profiled the proteins in breast cancer tissues and adjacent tissues by protein label-free quantification technique and detected 549 significantly differentially-expressed proteins. After bioinformatic analysis, AIMP2 was chose to further study. RT-qPCR data showed that AIMP2 was highly expressed in breast cancer cell lines and tumor tissues. Moreover, overexpression of AIMP2 promoted breast cancer cells proliferation and invasion. Mechanistically, String was performed to predict the interaction between AIMP2 and KARS. Kaplan-Meier plots showed higher expression of AIMP2 was connected to poor prognosis in breast cancer patients from TCGA database.

Conclusion: The expression of AIMP2 was found significantly upregulated in breast cancer. Moreover, AIMP2 could promote cell proliferation, invasion and metastasis in breast cancer cells. AIMP2 might be bind to KARS and activate the downstream pathways. Therefore, AIMP2 may be considered as a novel therapeutic target and potential biomarker for breast cancer.

P072

Integrative analysis of transcriptomic and genomic data reveals the correlation between PANoptosis-related genes and tumor immune microenvironment in glioma

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Background: PANoptosis is a newly described inflammatory programmed cell death that highlights coordination between pyroptosis, apoptosis and necroptosis. However, the prognostic value of PANoptosis in glioma is still elusive. This study aims to systemically analysis the potential roles of PANoptosis-related genes in glioma progression and prognosis.

Methods: RNA sequencing data of glioma patients were from TCGA and CGGA database. Consensus clustering was applied to reveal different subgroups of gliomas based on PANoptosis-related genes (PANRGs). Functional enrichment, gene set variation, survival and immune cell infiltration analysis were conducted between different subtypes. PANRG score was established with univariate Cox and LASSO Cox regression analyses. Tumor immune infiltration was investigated via ESTIMATE and CIBERSORTx algorithms. Immune checkpoint blockade (ICB) therapy response was predicted through Tumor immune dysfunction and exclusion (TIDE) algorithm. R package “pRRophetic” and CMap database were applied to predict the chemotherapy reponse and potential drugs . Additionally, The expression and function of PANoptosis-associated predictors were validated in clinical samples and glioma cells by qPCR and cell biology assays.

Results: PANRGs showed a considerably high mutation frequency in glioma samples. Two subtypes of patients divided by PANRGs expression possessed distinct clinicopathological, prognostic, and TME cell-infltrating characteristics. A prognostic PANRG score were conducted with four PANoptosis-associated predictors (MYBL2, C21orf62, TUBA1C, and KCNIP2), which showed a general satisfactory

prediction performance in prognosis of glioma. Moreover, TIDE analysis demonstrated that patients in low-risk group were more likely to respond to immunotherapy. Further analysis indicated a potential correlation between PANRG score and chemotherapy responses. Finally, we confirmed the expression and function of PANoptosis-associated predictors in clinical samples and glioma cells.

Conclusions: In this study, integrative analysis of transcriptomic and genomic data reveals a significant correlation between PANRGs and tumor immune microenvironment in glioma. Our results further revealed that two PANRG predictors (MYBL2 and TUBA1C) could promote the proliferation and migration of glioma cells, thus playing an important role in the progression of this disease. These findings highlighted the pathogenic role and prognostic value of PANRGs in glioma, especially in the immune landscape and therapeutic responses, which may serve as promising targets for individualized treatment of glioma.

P073

Fatty acids reshape the fitness and functionality of tumor-resident CD8+ T cells by maintaining ITM2A expression

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Tissue-resident memory T (Trm) cells are a subset of tissue-resident T cells that are restricted to specific tissues and do not recirculate. Trm cells are derived from effector T cells and require tissue-derived signals for local transformation, including transforming growth factor-β (TGFβ), aryl hydrocarbon receptor (AHR), interleukin-15 (IL-15) and IL -33. Generation and maintenance of Trm cells requires the regulation of a unique set of transcription factors, including Runx3, Notch, Blimp-1, Hobbit and Nurr7. These transcription factors confer long-term existence and maintenance of Trm cells. In addition, Trm cells also highly express some effector molecules, including interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α) and granzyme B (GZMB), which increase the rapid response of Trm cells to stimulation and protective immunity. Trm cells are closely related to the host's anti-tumor immune response, and it is involved in cancer immunosurveillance and immunotherapy responses. These properties give Trm cells great potential in the treatment of cancer. In addition, the presence of Trm and tumor-infiltrating lymphocytes (TILs) cells are also associated with improved prognosis in cancer patients. However, the detailed maintenance and regulation mechanisms of Trm and TILs cells function are incompletely understood.

$CD8^+$ T cell activation, effector differentiation and the formation of memory cells are closely related to cellular metabolic processes. The expansion and effector function of effector T cells arise primarily from aerobic glycolysis, whereas the maintenance of Trm requires mitochondrial metabolism and oxidative phosphorylation. Current studies have also shown that Trm cells utilize exogenous free fatty acids and their oxidative metabolism to persist in tissues and mediate protective immunity. Furthermore, fatty acid metabolism controls Trm survival in gastric cancer and enhances the antitumor response of PD-L1 blockade. Acetyl-CoA from fatty acid metabolism within Trm is also a major source of histone acetylation. Importantly, $CD8^+$ T-cell function is closely related to histone acetylation (eg, H3K9, H3K14 and H3K27) and chromosome accessibility.

Epigenetic mechanisms such as chromatin modifications play important roles in T cell responses to antigens, differentiation and development. Histone acetylation modifies T cell development, differentiation, and T cell-related gene expression by altering chromatin accessibility. HBO1 modifies histone H3 and H4 acetylation and plays a key role in the transcription and regulation of DNA replication. HBO1 exists in two distinct complex types consisting of ING4/5, hEaf6 and the scaffolding proteins JADE1/2/3 or BRPF1/2/3. While both types of scaffolds confer HBO1 to acetylate H3 and H4 in the core histones, they exhibit different specificities in chromatin, with the JADE1/2/3-containing HBO1 complex preferentially acetylating histone H4 and the BRPF1/2/3-containing complexes acetylate histone H3 in nucleosomes. Recent studies have found that HBO1 regulates quiescence and self-renewal of hematopoietic stem cells and plays an important role in the development, survival, differentiation and infiltration of T cells. However, the mechanism by which the HBO1 complex plays a role in Trm or TILs cells remains elusive.

In the present study, we identified that ITM2A, which is exclusively upregulated in Trm, is required for fitness, and polyfunctionality of Trm or TILs cells. On exposure to free fatty acids, activation of the transcription factor PRDM1 sustains high levels of ITM2A, which is required for Trm and TILs cells survival and activation and is highly correlated with better prognosis in various cancers. Mechanistically, ITM2A accumulates on chromatin, and recruits the HBO1-BRPF2-ING4 complex to reprogram T-cell-specific gene expression, thereby enhancing Trm or TILs survival and effector function. Thus, our data demonstrate that ITM2A acts as a positive feedback activator to deregulate $CD8^+$ T cell-mediated antitumor immunity.

P074

NIR-Triggered and ROS-Boosted Nanoplatform for Enhanced Chemo/ PDT/PTT Synergistic Therapy of Sorafenib in Hepatocellular Carcinoma

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Although being the frst-line treatment of advanced hepatocellular carcinoma (HCC), sorafenib (SOR) outcome is limited due to drug resistance and low tumor accumulation. Herein, with MnO2 as photothermal agent and chlorine6 (Ce6) as photosensitizer, a tumor-targeting and NIR-triggered multifunctional nanoplatform loading sorafenib (MnO2-SOR-Ce6@PDA-PEG-FA, MSCPF) was constructed. Owing to oxygen generator M nO2, MSCPF could generate excessive ROS, thus can alleviate tumor hypoxia and improve sorafenib accumulation in cancer cells. Besides, ROS production further strengthens Ce6-mediated PDT and PDA-mediated PTT. By exploiting these features, MSCPF exhibited excellent antitumor efects on HCC in the in vitro and in vivo studies, compared to solo sorafenib or PDT/PTT treatment. Further mechanism experiments suggested that MSCPF could inhibit P-gp expression and induce ferroptosis via deactivation of GPX4 and SLC7A11, which ultimately enhanced the antitumor efcacy of SOR. In summary, our work highlights a promising NIR-triggered and ROS-boosted nanoplatform for enhanced chemo/PDT/PTT synergistic therapy of SOR in HCC treatment.

P075

Autophagy inhibition by chloroquine enhances the anti-tumor effects of bazedoxifene in colon cancer, in vitro and in vivo

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Objectives: Recent studies have found that bazedoxifene (BZA), a third-generation selective estrogen receptor modulator (SERM), displayed significant anti-tumor efficacy including head and neck tumors and pancreatic cancer as well as colon cancer. It was clear from studies in tamoxifen, a first-generation SERM, that the clinical efficacy was reduced by acquired resistance resulting from the induction of autophagy, which increases cancer cell survival. Therefore, the objective of this study is to determine whether BZA also induced autophagy, resulting in reduced cytotoxicity during the treatment of colon cancer, was not yet explored.

Materials and methods: Proliferation, colony formation, scratch migration assay and transwell invasion assay were used to test BZA anti-tumor activity enhanced by chloroquine (CQ) *in vitro*. Cell apoptosis and cell cycle were analyzed by flow cytometry. Western blotting (WB), immunofluorescence assays, transmission electron microscopy (TEM) and confocal fluorescence microscopy (CFM) were used to detect BZA-induced autophagy in HT29 and SW480 cells. Relative mechanism study of the CQ-enhanced BZA cytotoxicity and BZA-induced autophagy was conducted in colon cancer cells and the CQ-enhanced BZA activity was confirmed *in vivo* using xenograft nude mice models.

Results: CQ enhanced BZA anti-tumor activity *in vitro*, and further study indicated that the CQ-mediated enhancement of BZA-induced apoptosis is closely associated with upregulated Bad/Bcl-2 signaling. BZA induced autophagy in HT29 and SW480 cells by inhibiting the PI3K/AKT/mTOR signaling pathway and thereby triggered autophagy. LY294002 and NVP-BEZ235 inhibitors exerted effects similar to those found of BZA. Importantly, CQ promoted BZA cytotoxicity by repressing autophagy was further confirmed *in vitro* and *in vivo.*
Conclusions: BZA-induced autophagy is mediated by the inhibition of the PI3K/AKT/mTOR signaling pathway, and BZA cytotoxicity can be enhanced through its combination with the autophagy inhibitor CQ, indicating that the combination of two established FDA-approved old drugs should be a highly promising approach in the clinical treatment of colon cancer patients.

P076

Triphenyl Phosphate, a common flame retardant however an vicious gastric cancer accelerant

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In recent years, the use of organophosphate ester flame retardants (OPFRs) has gained popularity as an alternative to brominated flame retardants (BFRs) in building materials, textiles, and furniture. Nevertheless, multiple studies have discovered that OPFRs are closely associated with a variety of cancers, which includes prostate cancer, bladder cancer and colorectal cancer. As one of the most widely used OPFRs, the correlation between triphenyl phosphate (TPP) and gastric cancer has not been fully explored. Therefore, in this work, we aimed to evaluate the potential correlation between TPP and gastric cancer. Transcriptome profiles and TPP information were obtained from The Cancer Genome Atlas and the Genotype–Tissue Expression, Comparative Toxicogenomics database and PharmMapper databases. In addition, the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were applied to explore the potential pathways that are closely related to the interactive genes of TPP. The differentially expressed analysis was applied to obtain the genes that play a key role in the gastric cancer patients. Furthermore, the LASSO regression analysis, univariate and multivariate COX regression analysis were used to construct the prognostic prediction model. The multiple immune infiltration analysis methods were involved to explore the immune cell infiltration level of hub genes. The GSEA and GSVA enrichment analysis were further used to explore the key pathways involved in key genes. The cell proliferation and invasive assays were applied to evaluate the role of TPP in gastric cancer cells. As results, the GO and KEGG enrichment analysis showed that interactive genes were mainly enriched in gastric cancer, steroid metabolic process, and steroid hormone regulation. The differentially expressed analysis revealed that multiple genes may play a significant role in gastric cancer patients. In order to further obtain the TPP-related genes that play a key role in gastric cancer patients, we then constructed a 18 genes-based risk model. Each gastric cancer patients were assigned with a risk score as follow: (Riskscore = (0.1007) * NOP56 + (0.0737) * KRT18 + (-0.1738) * MLEC + (0.3562) * MAP4K4 + (-0.0188) * SMC4 + (-0.0506) * MDN1 + (0.038) * EGFL6 + (-0.0507) * TP53 + (0.0653) * SLC5A5 + (0.0369) * PDK4 + (0.1047) * CARTPT + (-0.0581) * PLIN1 + (0.1212) * CD36 + (0.0551) * CIDEC + (-0.0233) * NPY + (-0.0348) * CES1 + (0.0286) * GSTA1 + (-0.0267) * KRT5). The time-dependent ROC curve showed that the model's one-year, three-year and five-year AUC values are 0.637, 0.742 and 0.768 respectively, which suggested that the TPP-related risk model showed great predictive value in gastric cancer cohort. Further, based on the results of prognostic prediction model, we discovered that MLEC are closely associated with the overall survival rate of gastric cancer patients. The results revealed that MLEC is closely related to cell cycle checkpoint, cornification, DNA dependent DNA replication, DNA geometric change, DNA integrity checkpoint and DNA templated transcription elongation. Finally, we performed the cell proliferation and invasion assays. The results demonstrated that the exposure of TPP at the concentration of 10^{-7}uM could significantly promote the cell proliferation and invasion ability of gastric cancer cells. Finally, mice experiments indicated that TPP may promote microcirculation by enhancing formation of microvessels during tumorigenesis. In all, this is the first study to evaluate the correlation between TPP and gastric cancer. Our research provides a new insight for the association between reduction of TPP-exposure and inhibition of gastric cancer progression.

P077

Biomarkers and Prognostic Factors of PD-1/PD-L1 Inhibitor-Based Therapy in Patients with Advanced Hepatocellular Carcinoma

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Background: Programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitor-based systemic therapy has achieved good efficacy in advanced hepatocellular carcinoma (HCC); however, only parts of the treated patients develop an overall response. Therefore, biomarkers and prognostic factors for immunotherapy efficacy and their underlying mechanisms must be identified and better understood. Current studies on biomarkers are focused on the tumor microenvironment, tumor genomics, tumor clinical characteristics, patient blood indicators, and gut microbiota. This article summarizes past and ongoing clinical trials related to HCC immunotherapy, as well as provides an overview of biomarker research for HCC therapy.
Results: Relevant clinical studies of aHCC immunotherapy includes anti-PD-1 monotherapy, anti-PD-1/PD-L1 plus anti-vascular endothelial growth factor (VEGF) antibody or tyrosine kinase inhibitors (TKIs), and dual immunotherapy (anti-PD-1/PD-L1 plus anti-CTLA-4). The PD-L1 expression, tumor-infiltrating lymphocytes, intratumoral stimulatory dendritic cells, conventional DC 1, and intratumoral CD38+CD68+ macrophages are important prognostic factors in HCC immunotherapy. Due to the heterogeneity of the immune microenvironment, single-cell sequencing and spatial transcriptome technology will provide more information for further research. Genomic factors including tumor mutation burdens, copy number alteration, and specific mutation (TP53, β-catenin, etc.) were also reported. Host clinical features were also crucial. The pretreatment factors including Child-Pugh, ALBI scores, ECOG score, and blood serum biomarkers (AFP, CRP LDH), imaging biomarkers were associated with the prognosis. The post-treatment factors such as dynamic changes of AFP, PIVKA-II, NLR, and PLR as well as irAEs also predicted the immunotherapy efficacy. In addition, liquid biopsy (ctDNA, CTCs, and cfDNA) was applied in the biomarker research, and a risk-scoring model was established. Commensal microorganisms have also been shown to correlate with immunotherapy including its diversity, makeup, and dynamic variations.
Conclusions: Systemic therapy using PD-1/PD-L1 inhibitors has been shown to be effective in treating HCC; however, only a subset of patients responds well to this treatment. Therefore, biomarker analysis is crucial for identifying patients who will most likely benefit from this treatment. In the future, cutting-edge non-invasive monitoring methods (such as ctDNA), imaging parameters (such as PET/CT), and the latest multi-dimensional data from sources (such as AI radiomics and single-cell sequencing) could provide a more comprehensive understanding of the mechanisms underlying HCC immunotherapy response and the reasons for drug resistance, which will lead to more personalized treatment.

P078

Synthetic Lethal and Resistance Interactions with BET Bromodomain Inhibitors in Triple-Negative Breast Cancer

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BET bromodomain inhibitors (BBDIs) are candidate therapeutic agents for triple-negative breast cancer (TNBC) and other cancer

types, but inherent and acquired resistance to BBDIs limits their potential clinical use. Using CRISPR and small-molecule inhibitor screens combined with comprehensive molecular profiling of BBDI response and resistance, we identified synthetic lethal interactions with BBDIs and genes that, when deleted, confer resistance. We observed synergy with regulators of cell cycle progression, YAP, AXL, and SRC signaling, and chemotherapeutic agents. We also uncovered functional similarities and differences among BRD2, BRD4, and BRD7. Although deletion of BRD2 enhances sensitivity to BBDIs, BRD7 loss leads to gain of TEAD-YAP chromatin binding and luminal features associated with BBDI resistance. Single-cell RNA-seq, ATAC-seq, and cellular barcoding analysis of BBDI responses in sensitive and resistant cell lines highlight significant heterogeneity among samples and demonstrate that BBDI resistance can be pre-exist- ing or acquired.

Endothelial Cells

P080

Characteristics of inflammatory and normal endothelial exosomes on endothelial function and the development of hypertension

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Objective: To investigate the effects of endothelial cell-derived exosomes on the dermal microcirculation profiles of the spontaneously hypertensive rats (SHRs). The effects of inflammatory cytokine tumor necrosis factor (TNF)-α and exosomes on endothelial function were also investigated.

Methods: Endothelial cell-derived exosomes were isolated from the conditioned media of HUVECs after treatment with (T_{Exo}) or without (C_{Exo}) 20 ng/mL TNF-α. The dermal microcirculation profiles of SHRs and WKY rats were monitored using a Laser Doppler Imager and a Laser Doppler Perfusion and Temperature Monitor. The origin of oscillators was determined with a wavelet transformation and analysis of the Doppler signal. The tube formation of the HUVECs was dynamically monitored at 0 h, 3 h and 6 h after the treatments with or without 20 ng/mL TNF-α, or 10 μg/mL C_{Exo} or T_{Exo}. Angiogenesis-related proteins in the conditioned media of the HUVECs were detected. The level of ROS in the endothelial cells or in the mitochondria was determined. Multiple signaling proteins related with inflammation and ROS were detected by Western blot.

Results: Significant poor vascular perfusion in ears was found in the SHRs compared with that in WKY rats ($P < 0.01$). Increased blood perfusion was observed 6 h and 24 h after the SHRs receiving the C_{Exo}, compared to the baseline of SHRs (both $P < 0.01$). Mean amplitude of endothelial oscillator was significantly decreased in the SHRs compared with that in WKY rats ($P < 0.01$). Significantly increased mean amplitude of endothelial oscillator was observed 6 h and 24 h after the SHRs receiving the C_{Exo}, compared to the baseline of SHRs (both $P < 0.01$). TNF-α, C_{Exo} and T_{Exo} treatment for 6 h significantly promoted the endothelial tube formation compared with control cells ($P < 0.05$ or $P < 0.01$). Higher levels of ENA-78, ANGPT1, MCP-3, and endostatin were found in the conditioned media of HUVECs treated with TNF-α, C_{Exo} or T_{Exo} compared to control. The levels of both total ROS and mtROS were significantly increased after treatment with TNF-α, C_{Exo} or T_{Exo} compared with those in control cells ($P < 0.01$ or $P < 0.05$). TNF-α significantly increased STAT3, p38, JNK, Akt phosphorylation and the level of NF-κB in endothelial cells (all $P < 0.01$). T_{Exo} significantly increased the phosphorylation levels of STAT3, p38, level of NF-κB and decreased the phosphorylation levels of JNK and Erk ($P < 0.01$ or $P < 0.05$). C_{Exo} significantly increased the phosphorylation level of STAT3, and decreased the phosphorylation levels of JNK and Erk (all $P < 0.01$).

Conclusion: C_{Exo} increases the dermal microvascular perfusion in SHRs through an endothelium-dependent way. TNF-α and T_{Exo} induce inflammatory and pathological angiogenesis through NF-κB pathway, and C_{Exo} shows physiologically pro-angiogenic effect on endothelial cells. Increased ROS, interplaying with inflammatory signals, participate in exosomes-mediated changes of endothelial function and behavior in development of hypertension.

P081

Glycyrrhizic acid induces endothelium-dependent relaxation in rat mesenteric artery via PI3K/Akt/eNOS pathway

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Background: Glycyrrhizic acid (GA) is a triterpene found in Glycyrrhiza glabra, which shows anti-viral, anti-inflammatory, and hepatoprotective properties. However, its role in vascular disease remains unclear. Vascular function is primarily controlled by the endothelium through releasing vasorelaxation factors such as NO, PGI_2 and EDHF. The present study intends to investigate the vasorelaxation effect of GA and the underlying mechanism.

Methods: Ex vivo, mesenteric arteries were removed from euthanized rat, placed in ice-cold Krebs solution, and sectioned into ring segments. Isometric tension changes in arterial rings were recorded using a Myograph System. Baseline tension was set at 1 mN, and 10 mmol/L phenylephrine (Phe) was used to induce sustained tension before the addition of 100 μM GA. To identify the factors involved in this function, eNOS, COX, Akt, PI3K Akt, CaMKII, PKA and AMPK inhibitors were applied. In vitro, human umbilical vein endothelial cells (HUVECs) were used to confirm the ex vivo study findings. The phosphorylation levels of various factors were estimated by Western Blot.

Result: GA induced vasodilation in mesenteric arteries in a dose-dependent manner, with a maximal effect at a concentration of 100 μM, which induced approximately 70% dilation. This effect was blocked by eNOS inhibitor L-NAME, Akt inhibitor MK206 and PI3K inhibitor Wortmannin, but not by COX-inhibitor indomethacin and EDHF inhibitor 20 mM K^+. In vitro study in HUVECs showed that, GA increased the phosphorylation of Akt, and eNOS in a time-dependent manner, which could be reversed by the PI3K inhibitor Wortmannin.

Conclusions: These findings suggest the potential of GA as a vascular relaxation agent, acting through the PI3K/Akt/eNOS pathway.

P082

Tumor cell-released autophagosomes (TRAPs) promote lung metastasis through inducing PD-L1 high expression of pulmonary vascular endothelial cells (PVECs) in breast cancer

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Background: Most breast cancer-related deaths are caused by metastasis in vital organs including the lungs. The development of immunosuppressive premetastatic microenvironments is a prerequisite for metastasis. However, the previous mechanisms were mainly focusing on immune cells, not on vascular endothelial cells. Tumor cell-released autophagosomes (TRAPs) are being recognized as critical modulators of host anti-tumor immunity during tumor progression. Our previous research has shown that TRAP preferentially reaches the lung more than breast cancer cells in the mouse model. Could pre-arrival of TRAPs promote the immunosuppressive premetastatic microenvironments by affecting endothelial cells?

Objective: Here, we explored the mechanistic aspects of TRAPs enhancing immunosuppressive premetastatic microenvironments formation through inducing PD-L1 high expression of pulmonary vascular endothelial cells (PVECs) in breast cancer.

Methods: TRAPs-treated ECs were subjected to transcriptome analysis. Flow cytometry detected T cell function after TRAP-treated ECs co-culture with T cells *in vitro*. We injected TRAPs into mice by the tail vein and established endogenous *Beclin1* knockdown 4T1 tumor cells which reduced TRAP release mouse model. Flow cytometry will

be used to analyze PD-L1 expression levels of PVECs, to detect PVEC suppressor T cell function and lung infiltrating T cell function, and to monitor late lung metastases. After anti-PD-L1 therapy, spontaneous lung metastases from in situ tumors or lung metastases after surgical removal of in situ tumors were observed. Antibody blocking assay and *HMGB1* knockdown cell lines were used to detect key DAMP on TRAPs surface. Inhibitor-treated ECs and TLR4 knockout mice were used to detect corresponding functional receptors on the surface of ECs. TRAPs stimulated CD/FillpinIII/CPZ -treated ECs to detect the movement of the cytoskeleton. Activation of signal pathways was detected by Western blot.

Results: HMGB1 on the surface of TRAPs from breast tumor cell lines stimulated PVECs cell up-regulation of PD-L1 via a TLR4–MyD88–p38/STAT3 signal cascade and depended on the movement of the cytoskeleton of ECs. TRAPs-treated ECs suppressed $CD4^+$ and $CD8^+$ T cell IFN-γ secretion and proliferation *in vitro*. TRAPs injection and endogenous *Becn1* KD-4T1 breast tumor mouse model showed that TRAPs promoted PVECs to have a similar phenomenon *in vivo* compared to the control group, and TRAPs resulted in more significant lung metastasis. Anti-PD-L1 treatment upregulated lung T-cell function and reduced lung metastasis in tumor-bearing mice.

Conclusion: These findings elucidate a novel role and mechanism of TRAPs-induced immunosuppression of vascular endothelial cells in the pre-metastatic microenvironment. TRAPs or their surface HMGB1 represent important therapeutic targets to reverse immunosuppressive formation, while also providing a new theoretical basis for the treatment of early breast cancer with PD-L1 antibodies.

P083

DDX24 is essential for placental development and uterine spiral artery remodeling in mice

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Background: The placenta is the essential organ for maintaining normal pregnancy and fetal development. Abnormal placental development can lead to adverse pregnancy outcomes such as preeclampsia, premature birth, restricted fetal growth, and even stillbirth. Previously study have found that DDX24 has a regulatory effect on angiogenesis and vascular development in patients with visceral vascular malformations caused by DDX24 mutations. Further research in gene-edited mouse models revealed changes in the structure and function of the placenta. Most studies on placental development have focused on the placenta itself and less on the influence of maternal factors on placental and vascular development. But how DDX24 regulate the development of placenta have not been elucidated.

Aim and method: To explore whether maternal DDX24 knockout has an effect on placental development, we constructed the DDX24 heterozygous and homozygous knockout pregnancy mouse model, and observe the phenotypes resulting of placenta and embryo, placental vascular structure and uterine spiral artery remodeling. We also exert the Ultra-high frequency photoacoustic multimode imaging system for small animals (FUJIFILM VisualSonics, VevoLAR-X) to measure the fetal umbilical artery blood flow velocity. In order to learn whether the DDX24 deficiency of maternal endothelial cells conduce the dysfunction of placental trophoblast cell, we indirectly co-culture the endothelium of knocked down DDX24 with trophoblast lines.

Result: We found that DDX24 deficiency can lead to insufficient remodeling of the uterine spiral arteries in the mouse placenta, mainly manifested as smaller arterial diameter, limited invasion ability of trophoblast cells, and obstacles to the construction of placenta-fetal circulation, resulting in decreased placental efficiency and restricted fetal blood supply. We detected significantly decrease in fetal umbilical artery blood flow velocity (68.85 mm/s vs 57.99 mm/s vs 46.60 mm/s, $P<0.01$). Furthermore, in vitro co-culture cell model showed that knockdown of DDX24 in endothelial cells downregulate invasion and migration function of trophoblast.

Conclusion: This study elucidates for the first time the important role of maternal DDX24 in placental development and provides new insights for the diagnosis and treatment of placenta-derived diseases.

Keywords: DDX24, placenta, spiral artery, endothelial cells

Vascular Smooth Muscle Cells

P084

Effects of male BPA exposure on offspring placental blood vessels and fetal development

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Background: Bisphenol-A (BPA) is a common environmental toxicant that is known to be associated with fetal growth restriction (FGR). However, the mechanisms of how BPA induce FGR is poorly characterized. It has not been reported whether the occurrence of FGR is related to paternal exposure to BPA. Genomic imprinting is a process of epigenetic modification on the genome that causes silencing of one allele according to its parental origin, resulting in monoallelic expression, without changing the DNA sequence. Therefore, the expression of imprinted genes is greatly affected by exogenous exposure. Identifying the genetic input for fetal growth will help to understand serious complications of pregnancy such as FGR. Imprinted genes are important in mammalian fetal growth and development. Evidence has emerged showing that genes that are paternally expressed promote fetal growth, whereas maternally expressed genes suppress growth. DLK1 is the product of an imprinted gene that is predominantly expressed from the paternally inherited chromosome during fetal development. Several studies have indicated that DLK1 expression levels are related to fetal growth and development. VEGFα is a key gene for vascular development. However, it is completely unknown whether BPA exposure during paternal preparation will affect DLK1 expression and thus interfere with placental vascular development.

Aim and method: To explore whether male BPA exposure affects placenta vascular and fetal development by affecting sperm quality and the expression of sperm imprinted genes. The findings could provide scientific guidance for men's lifestyle and eating habits before pregnancy. To accomplish this purpose, the proteomic analysis of placenta tissues of FGR fetuses and normal weight fetuses was performed to screen the significant differences in proteins between the two groups. The 5-week-old male mice were exposed to 50mg/kg/d BPA or corn oil alone for 4 weeks, and after mating with normal female mice, then offspring embryos and placentas were obtained. The testicular tissue and epididymal tail sperm of male mice were taken at the same time. Total RNA was extracted from testicular tissue of the two groups for RNA seq analysis for differentially expressed genes. Screening for co-annotated differential expression factors in FGR placental proteomics and in sperm RNA seq in BPA exposed groups. Sperm quality, weight of placenta and fetal mice, expression of differential proteins in sperm and placenta tissues were detected in two groups of mice.

Result: Proteomic results indicated that the expression of DLK1 in the placenta tissue of FGR fetuses was significantly decreased compared with that of normal weight fetuses ($P<0.05$). RNA seq results suggested that the expression of DLK1 in the testis of bisphenol A exposed mice was significantly decreased compared with that of the unexposed group ($P<0.05$). After exposure to BPA, the quality of the sperm and the expression of DLK1 in sperm decreased significantly. In addition, when male mice in both the BPA exposed group and the unexposed group mated with normal female mice, both the placenta and fetal body weight of the offspring in the BPA exposed group were lower than those in the unexposed group ($P<0.05$). Compared with unexposed group, the expression of DLK1 and VEGFFα decreased in the placental tissue of mice exposed to BPA.

Conclusion: Paternal BPA exposure will affect the expression of imprinted gene DLK1 and reduce sperm quality, which will be transmitted to offspring, resulting in lower placental DLK1 expression, abnormal placental vascular development, and eventually fetal growth restriction. To ensure the normal development of placenta and fetus, male lifestyle and eating habits should be paid enough attention.

Keywords: BPA; Imprinted gene; Semen quality; Placental vascular development; Fetal growth restriction

Pericytes

P085

The moleoule mechanism of ASK1 on pericytes damage induced by cerebral ischemia and reperfusion

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Objective: cerebral ischemia-reperfusion may result in increased infarct size,no-reflow phenomenon and bleeding transformation. As vascular cells surrounding microcirculation, pericytes are important components of neurovascular units. pericytes contract during ischemia and remain in a contractile state, so that obstructing microcirculation. Even though occlusive vessels reopen after reperfusion.This study targets pericytes to explore new strateges for assessment and treatment for no-reflow phenomenon induced by cerebral ischmia-reperfusion.

Methods: In this study, the middle cerebral artery occlusion/reperfusion model (MCAO/R) was used in adult male SD rats to establish MCAO/R models at different time points. The neurological injury of rats was observed by Longa 5-point neurological function score. TTC staining was used to observe the cerebral infarction volume of rats. And Evans blue extravasation assay were performed to assess blood-brain barrier permeability in vivo. Intracerebroventricular injection of sh-ASK1 in model rats, the changes in the morphology and number of pericytes were compared by immunofluorescence. And the expressions levels of ASK1, p-ASK1 and various proteins proteins such as p38, JNK and c-JUN were detected in pericytes. Primary pericytes were extracted in vitro using OGD/R model to simulate ischemia and hypoxia conditions. Sh-ASK1 was used to down-regulate the expression of ASK1 in cells. Cell proliferation index was detected by CCK8 assay and cell migration ability was evaluated by Transwell migration assay. cell contraction was assessed by collagen gel contraction assay. The expression levels of ASK1, pathway protein, IL-1β, caspase-3 and other proteins were detected by Western Blot assay and immunofluorescence. Primary rat microvascular endothelial cells and pericytes were co-cultured by Transwell system to establish an in vitro blood-brain barrier model, and FITC-Dextran permeability assessed the permeability of the in vitro blood-brain barrier model.

Results: Compared with sham group, the ratio of ASK1/P-ASK1 expressed in pericytes was significantly up-regulated after ischemia/reperfusion in vivo and in vitro. in the MCAO/R group, the infarction volume, neurological deficit scores and blood-brain barrier permeability were increased significantly. in the OGD/R group, the result of CCK8 assay showed that cell vitality were decreased. The results of Western Blot assay and immunofluorescence showed that the expressions of inflammatory factors, apoptotic indicators and related pathway proteins were increased in pericytes. Compared with administration of sh-NC, the down-regulation of ASK1 expression can significantly improve the neural function deficit in MCAO/R rats and reduce the activation of OGD/R cell pathway protein. In vitro experiments, the release of ROS, MDA and SOD were decreased. At the same time, The results showed that cell migration ability was reduced and cell contraction was inhibited, maintaining the integrity of the blood-brain barrier.

Conclusion: ASK1 expressed in pericytes was significantly up-regulated after cerebral ischemia and reperfusion in vivo and in vitro. These changes leads to cell inflammation, apoptosis and continuous contraction through activation of p38 and c-JUN signaling pathways. Our data suggest that ASK1 may serve as a potential target for the assessment and treatment of no-reflow phenomenon after ischemic stroke.

Keywords: Acute cerebral ischemia/reperfusion; Blood-brain barrier; Pericyte; ASK1; Cell contraction.

P086

Combined with Putative Endothelial Progenitor Cells, TFA Reduces Renal Interstitial Fibrosis in Diabetic Kidney Disease by Diminishing Pericyte-Myofibroblast Transition and Capillary Injury

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The total flavones of *Abelmoschus manihot* (TFA) is an anti-inflammatory compound extracted from a Chinese herbal medicine, *Abelmoschus manihot*, that has been widely used in the treatment of diabetic kidney disease (DKD) in China. Recently, putative endothelial progenitor cells (pEPCs) have been confirmed to promote vascular repair in DKD. Our previous studies showed that TFA, combined with pEPCs can improve DKD. However, the mechanistic effects of this combined therapy on renal interstitial fibrosis (RIF) in DKD, which is characterized by massive extracellular matrix (ECM) deposition in renal interstitium and capillary injury in renal microcirculation, remain unknown. Therefore, this study aimed to explore the effect and molecular mechanisms by which TFA+pEPCs acts on RIF in DKD. We isolated pEPCs from murine bone marrow. In the *in vivo* experiment, pEPCs, pEPC-MVs (microvesicles), and TFA were injected by tail vein or administrated by gavage into the DKD mice, respectively. In the *in vitro* experiment, TFA+pEPCs under a state of high glucose (HG) was co-cultured with renal-derived pericytes. Pericyte-myofibroblast transition (PMT) was evaluated using the myofibroblast marker, α-smooth muscle actin (α-SMA), and the pericyte marker, platelet-derived growth factor receptor β (PDGFR-β). Capillary injury was assessed by immunofluorescence (IF). Our results indicated that TFA+pEPCs attenuated RIF by decreasing PMT, reducing ECM deposition, and improving capillary injury in the DKD model; TFA+pEPCs regulated pericytes and their transition into myofibroblasts. In addition, co-culture of pericytes with TFA+pEPCs under a state of HG *in vitro* suggested that TFA+pEPCs inhibited transforming growth factor-β (TGF-β)-induced PMT by a classical paracrine pathway. This study demonstrated that TFA+pEPCs could effectively attenuated RIF in DKD by diminishing PMT and capillary injury through a classical paracrine pathway. This study provides new pharmacological evidence for the combined therapy of TFA+pEPCs in the DKD patients.

P087

Inhibition of Pericyte-Myofibroblast Transition and Platelet-Derived Growth Factor Receptors Activation With Fucoidan Ameliorates Renal Congestive Fibrosis

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Fucoidan (FPS) is a class of fucose-rich sulfated carbohydrates found in brown marine algae and echinoderms, and it was recently identified in *Laminaria japonica*, a traditional Chinese medicine. Recently, research into FPS has continued to gained pace and suggests potential roles in cardio-renal syndrome in China. Previous studies demonstrated that renal congestion due to cardio-renal syndrome results in pericyte detachment from capillaries, leading to pericyte-myofibroblast transformation (PMT) and subsequent renal congestive fibrosis (RCF), which may be associated with platelet-derived growth factor receptors (PDGFRs) activation. Our previous studies showed that FPS can improve renal congestion. However, the underlying mechanisms remain unclear. Therefore, this study was designed to investigate the effects of FPS on RCF and its possible new mechanisms regarding PMT and PDGFRs. *In vivo*, we used male Sprague-Dawley rats with ligated left inferior vena cava between renal veins as a model of renal congestion. Physiological, morphological and molecular methods were used to evaluate the efficacy of FPS, respectively. *In vitro*, The inhibitory effect of FPS on PDGFRs and fibrosis was assessed by co-culture of human pericyte and transforming growth factor β1 (TGFβ1). We found that, increased kidney weight and renal tubulointerstitial

fibrosis (RIF) were observed in the congested kidneys. After ligation of the inferior vena cava in the FPS-treated group rats, the upstream inferior vena cava (IVC) pressure immediately increased to about 20 mmHg. Although the vasa recta dilatation and pericyte detachment were maintained under renal congestion, FPS reduced the increased renal weight and inhibited RIF around the vasa recta. TGFβ1-induced elevation of fibrosis markers in human pericyte was inhibited by FPS and PDGFR inhibitors at the transcriptional level. In conclusion, this study demonstrated that FPS alleviates RCF in renal congestion by inhibiting PMT and PDGFRs activation. This study provides a novel understanding of how FPS can reduce RCF in cardio-renal syndrome.

P088

Combined With Bone Marrow-Derived Mesenchymal Stem Cells, Fucoidan Attenuates Renal Fibrosis in Diabetic Kidney Disease by Inhibiting Pericyte-Myofibroblast Transition and Capillary Injury

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Fucoidan (FPS) is a class of fucose-rich sulfated carbohydrates found in brown marine algae and echinoderms, and it was recently identified in *Laminaria japonica*, a traditional Chinese medicine. Recently, research into FPS has continued to gained pace and suggests potential roles in cardio-renal syndrome in China. Previous studies demonstrated that renal congestion due to cardio-renal syndrome results in pericyte detachment from capillaries, leading to pericyte-myofibroblast transformation (PMT) and subsequent renal congestive fibrosis (RCF), which may be associated with platelet-derived growth factor receptors (PDGFRs) activation. Our previous studies showed that FPS can improve renal congestion. However, the underlying mechanisms remain unclear. Therefore, this study was designed to investigate the effects of FPS on RCF and its possible new mechanisms regarding PMT and PDGFRs. *In vivo*, we used male Sprague-Dawley rats with ligated left inferior vena cava between renal veins as a model of renal congestion. Physiological, morphological and molecular methods were used to evaluate the efficacy of FPS, respectively. *In vitro*, The inhibitory effect of FPS on PDGFRs and fibrosis was assessed by co-culture of human pericyte and transforming growth factor β1 (TGFβ1). We found that, increased kidney weight and renal tubulointerstitial fibrosis (RIF) were observed in the congested kidneys. After ligation of the inferior vena cava in the FPS-treated group rats, the upstream inferior vena cava (IVC) pressure immediately increased to about 20 mmHg. Although the vasa recta dilatation and pericyte detachment were maintained under renal congestion, FPS reduced the increased renal weight and inhibited RIF around the vasa recta. TGFβ1-induced elevation of fibrosis markers in human pericyte was inhibited by FPS and PDGFR inhibitors at the transcriptional level. In conclusion, this study demonstrated that FPS alleviates RCF in renal congestion by inhibiting PMT and PDGFRs activation. This study provides a novel understanding of how FPS can reduce RCF in cardio-renal syndrome.

Neutrophils

P089

Analysis of epidemiological characteristics and risk factors of 86 chronic wound patients

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Objective: To analyze the epidemiological characteristics, relevant clinical indicators and risk factors of chronic wounds inpatients.
Methods: The medical records of 86 patients with chronic wounds who were admitted to the Department of Burns and Plastic Surgery, The First Hospital of Hebei Medical University from August 1, 2018 to August 1, 2021 and 80 healthy personnel who underwent physical examination in the Health Examination Center during the same period were collected. The gender, age, BMI, urban and rural distribution, wounds types and the first related laboratory examination results of patients were analyzed. Data was statistically analyzed with Mann-Whitney U test, chi-square test and multiple factor binary Logistic regression.
Results: 1. In this group, there were 49 males (57.0%) and 37 females (43.0%) in chronic wound patients, with a male to female ratio of 1.32:1. The patients ranged in age from 18 to 89 years old, with a maximum of 46 elderly patients (53.5%). The middle age was followed by 24 cases (27.9%). At least 16 young people (18.6%).2. According to the types of wounds, 33 patients with chronic wounds were pressure ulcers (38.4%), 27 patients with traumatic ulcers (31.4%), 15 patients with other ulcers (17.4%) and 11 patients with diabetic foot (12.8%), and the patients with chronic wounds were mainly pressure ulcers and traumatic ulcers.3. There was no significant differences in gender, age and BMI between chronic wound group and healthy control group (the statistical analysis results were as followed:c2=0.005, P=0.946; Z=1.458, P=0.145; Z=0.087, P=0.930). The difference in urban and rural distribution was statistically significant(=4.268, P=0.039).4.The leukocyte counts, the percentage of neutrophils, platelet counts and hypersensitivity C-reactive protein of patients in chronic wound group which were examined for the first time after admission were higher than those in healthy control group (the statistical analysis results were as followed: Z=5.527, P<0.001; Z=4.880, P<0.001; Z=2.096, P=0.036; Z=8.656, P<0.001). 5. The erythrocyte counts, hemoglobin, total protein and albumin of patients in chronic wound group which were examined for the first time after admission were lower than those in healthy control group (the statistical analysis results were as followed: Z=5.384, P<0.001; Z=6.375, P<0.001; Z=3.230, P=0.001; Z=8.686, P<0.001).6.The fibrin(ogen) degradation product and D-dimer of patients in chronic wound group which were examined for the first time after admission were higher than those in healthy control group (the statistical analysis results were as followed: Z=2.358, P=0.018; Z=3.183, P=0.001).7.The increased leukocyte counts, decreased albumin and increased hypersensitivity C-reactive protein were the risk factors of chronic wound.
Conclusions: In this study, most of the chronic wound patients were male and over 60 years old, and the main types of wounds were pressure ulcers and traumatic ulcers. The leukocyte counts, the percentage of neutrophils, platelet counts, hypersensitivity C-reactive protein, fibrin(ogen) degradation product and D-dimer were increased in patients with chronic wounds, while erythrocyte counts, hemoglobin, total protein and albumin were decreased in patients with chronic wounds. The increased leukocyte counts, decreased albumin and increased hypersensitivity C-reactive protein were the risk factors of chronic wound.

P090

Tumor cell-released autophagosomes (TRAPs) promote neutrophil extracellular traps formation

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Background: Neutrophils are the body's first line of defense against pathogen invasion, in addition to removing pathogens through phagocytosis, degranulation, and production of reactive oxygen species. There is a special form of cell death that differs from necrosis and apoptosis: Neutrophil extracellular traps (NETs). It has been shown that NETs are involved in the progression and metastasis of a variety of malignancies. Our previous studies have confirmed that tumor cell-released autophagosomes (TRAPs) induced immunosuppression TME formation. However, whether TRAPs can induce neutrophils to form NETs and exert immunomodulatory effects remains to be further investigated.
Objective: To investigate that TRAPs mediate neutrophils to form NET and its regulatory mechanism, to provide possible targets for disease treatment.
Methods: Neutrophils were isolated from healthy human peripheral blood or mouse bone marrow, TRAPs were co-incubated with neutrophils for 3 hours *in vitro*, and NETs were observed by scanning

electron microscopy (SEM). Image J software was used to analyze their area and fluorescence intensity (FI) to quantify NETs. Free DNA (cf-DNA) in the cell culture supernatant was quantified by Picogreen staining. Western blot and ELISA were used to quantify MPO-DNA, NE, and cit-H3 which are important components of NETs. Antibody blocking assays and *HMGB1* knockdown cell lines were used to detect key DAMP on the TRAPs' surface. Inhibitor-treated neutrophils and TLR4 knockout mice were used to detect corresponding functional receptors on the surface of neutrophils. Activation of signal pathways was detected by Western blot. *In vivo*, TRAPs were injected into the tail vein of mice, and NETs in plasma were detected by ELISA. *Beclin1* knockdown 4T1 tumor cells engineering to reduce TRAPs release injected into mice subcutaneously. The characteristic molecules of NETs in plasma were detected by ELISA.

Results: After 3 hours of stimulation of neutrophils with TRAPs *in vitro*, a large number of reticular structures (NETs) were observed by SEM. Immunofluorescence staining results revealed that a large amount of MPO, NE, and cit-H3 was released into the extracellular, while cf-DNA, MPO-DNA, and NE were also significantly increased in the cell culture supernatant. TRAPs from breast tumor cell lines induced neutrophil formation of NETs via the HMGB1-TLR4-MyD88-ERK/p38 pathway. Neutrophils treated with TRAPs inhibited the secretion and proliferation of $CD4^+$ and $CD8^+$ T cells IFN-γ *in vitro*. *In vivo*, cf-DNA, and MPO-DNA, were significantly increased in plasma after tail vein injection of TRAPs as well as in 4T1 tumor-bearing mice. In contrast, the above molecules were significantly decreased in the plasma of *Beclin1* knockdown 4T1 tumor-bearing mice.

Conclusions: Tumor cell-released autophagosomes (TRAPs) can mediate the release of neutrophil extracellular traps.

Pulmonary Microcirculation

P091

Hypoxia-induced lactation modification of TG2 to promote pulmonary vascular remodeling in hypoxic pulmonary hypertension

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Background: Pulmonary artery hypertension (PAH) is a serious and clinically lethal disease characterized by pulmonary vascular remodeling (PVR). Hypoxia activates the hypoxia induced factor 1α (HIF-1α) subunit, leading to a marked increase in the aerobic glycolytic pathway, i.e. the Warburg effect, which causes abnormal proliferation and inhibition of apoptosis in PASMCs, resulting in increased PVR and vascular resistance, thus contributing to the development of PAH. As a product of glycolysis, lactate was found to be involved in epigenetic modifications, i.e. lactic acidification modifications. However, the role of lactate in HPH and its possible regulatory mechanisms need to be further explored.

Purpose: (1) To detect the levels of lactate and lactonization modifications under hypoxic (CH) conditions; (2) To explore the effects on the bio behavior of human pulmonary artery smooth muscle cells (hPASMCs). (3) Possible regulatory mechanisms.

Methods: A hypoxia (1% O2, 72 h), lactate dehydrogenase A (LDHA) siRNA-transfected, exogenous lactate intervention cell models of human pulmonary artery smooth muscle cells (hPASMCs) was constructed. endogenous lactate, overall lactation and H3K18la levels were detected in hPASMCs by Western blot. CCK-8, EdU and TUNEL were used to detect proliferation and apoptosis levels in hPASMCs. Co-immunoprecipitation (Co-IP) was used to detect the binding of H3K18la and TG2, and to detect the level of H3K18la modification in the TG2 promoter region.

Results: Our results revealed that hypoxia induced an increase in endogenous lactate levels, overall lactation and H3K18la levels in hPASMCs. Previously, our group has demonstrated that hypoxia promotes the increase of TG2 expression and activity, and that TG2 expression increases after exogenous lactate intervention in hPASMCs. Knockdown of LDHA reduced lactate and H3K18la levels in hPASMCs, and TG2 expression was significantly reduced, as was the level of H3K18la modification in the TG2 promoter region. The addition of exogenous lactate increased the levels of lactate and H3K18la in hPASMCs; similarly, the expression level of TG2 and the level of H3K18la modification in the TG2 promoter region were significantly increased compared to the knockdown group. In a study of the biological behavior of hPASMCs, it was found that knockdown of LDHA inhibited the proliferation of hPASMCs and promoted their apoptosis, while exogenous lactate intervention significantly increased the proliferation and decreased the apoptosis of hPASMCs.

[Conclusion] Aerobic glycolysis during the development of hypoxia pulmonary hypertension (HPH) promotes lactation modification, and induces TG2 expression during proliferation and apoptosis of hPASMCs by mediating the lactation of lysine at histone H3 at position 18 (H3K18), and promotes the development of HPH.

Keywords: Hypoxia; Pulmonary artery hypertension (PAH); Lactation modification; Transglutaminase 2 (TG2); Pulmonary artery smooth muscle cells (PASMCs)

P092

The Therapeutic Effects of Novel Mettl3 Inhibitor STM2457 in Experimental Pulmonary Hypertension

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Background: N6-methyladenosine (m6A) is a well-known post-transcriptional modification and it plays important regulatory roles in diverse biological processes. Previous reports have shown that the level of Mettl3 increased in experimental Pulmonary Hypertension (PH), which might be associated with the occurrence and development of PH. However, the mechanism of Mettl3 in the pathogenesis of PH remain elusive and Mettl3 can be used as a drug target for treating PH is not fully understood.

Methods: Levels of Mettl3 and Rbpj in explants of rat pulmonary artery from lung tissues and pulmonary artery smooth muscle cells (PASMC) were measured by immunofluorescence and western blot analysis. The mRNA expression levels of Mettl3 and Rbpj in PASMCs were quantifed with qRT-PCR. m6A RNA immunoprecipitation was used to seek targeted gene modified by Mettl3. Cell proliferation and cell cycle was assessed by PCNA/cyclinD1/ CDK2 and EdU assays.

Results: Levels of Mettl3 were increased in MCT and hypoxic-associated pulmonary hypertension models. Mettl3 was deleted in vascular smooth muscle in mice using SM22α-Cre/LoxP system. SMC-specific deleted Mettl3 or specific inhibitor STM2457 can alleviate hypoxic-induced pulmonary hypertension in mice. Furthermore, inhibition of Mettl3 can attenuated cell proliferation and migration induced by platelet-derived growth factor-BB(PDGF-BB). m6A RNA immunoprecipitation analysis revealed Rbpj as an m6A-regulated gene in our models. The further results shows that Ythdf1 can recognize and stabilize RBPJ mRNA in an m6A dependent manner. In addition, cell experiments showed that inhibition of RBPJ could alleviate cell proliferation and migration induced by PDGF-BB.

Conclusion: Our study indicated the potential mechanism of Mettl3 in the development of PH. These results suggest that inhibition of Mettl3 may constitute a promising approach for treatment of PH.

Keywords: m6A, STM2457, pulmonary hypertension

P093

Clinical and genetic features of pulmonary sclerosing pneumocytoma: a clinical study of 58 Chinese patients

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Background: Pulmonary sclerosing pneumocytoma (PSP) is a rare benign tumor. In clinical practice, misdiagnosis is common in preoperative and intraoperative differential diagnosis. The aim

of our study was to review the disease characteristics, imaging characteristics, pathological characteristics and differential diagnosis, and to explore the molecular mechanisms of PSP.

Methods: A retrospective analysis of the clinical records of 58 patients with PSP was performed, including radiological data and pathological features. Whole exon sequencing (WES) was performed in 12 patients, revealing the molecular biological characteristics for the occurrence and development of PSP.

Results: We reviewed 58 PSP patients and their clinical characteristics, our study indicated that PSP were more common in middle age females, which account for 93.10%, with the average age of 52.86±11.46 years. The tumor generates more often in left lobes (60.34%). Most tumors had clear borders (91.38%) with round or oval masses on computed tomography (CT), and had rapid and obvious enhancement (25/44) on enhanced computed tomography. The rate of benign and malignant manifestations was 25.86% and 27.59% respectively. The remaining 46.55% were unclear. Only 15.52% (9/58) of patients had symptoms during clinical treatment, which included cough, chest tightness, suffocation, fever and chest pain. VATS was performed in 86.21% of patients. The diagnostic rate of intraoperative rapid pathology was 60.71% (17/28). The average tumor diameter was 2.21cm, ranging from 0.6 to 9cm. Occasional multiple or bilateral ipsilateral lymph node metastases (1.72%) were also present in patients with lung adenocarcinoma (5.17%). According to WES, except the well-known gene AKT1 (42%), there were four genes with driver mutations more than 25%, including COL5A3 (50%), NTRK3 (25%), FUS (25%), and OR9G1 (25%). The mutation rate of COL5A3 was higher than that of AKT1, which was expected to be one of the signature gene features of PSP.

Conclusion: Patients with PSP had good prognoses, local excision or tumor enucleation is enough for patients with a clear preoperative diagnosis. Lymph node dissection is not recommended to expand the scope of surgery. In addition to the well-known gene *AKT1*, *COL5A3* is expected to be one of the signature gene features of PSP.

P094

NAD+ metabolism affects the tumor microenvironment and the cytotoxicity of CD8+T cells

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Purpose: Lung cancer is the most morbidity and mortality malignancy worldwide, with 80%-85% of histological types being non-small cell lung cancer (NSCLC).Despite the promising efficacy of immunotherapy in NSCLC patients, the overall response rate to anti-PD-1 or PD-L1 therapy is only 20%-30%. Biomarkers that can effectively predict the prognosis of immunotherapy are still lacking. NAD+ metabolism pathway has been reported to be closely related to tumor immunity. Therefore, we hope to explore the potential of NAD+ metabolism pathway as a biomarker of immunotherapy for NSCLC and its internal possible mechanism.

Methods: We downloaded a DNA sequencing data and a transcript sequencing data based on immunotherapy for NSCLC patients to examine whether the change of NAD+ metabolism pathway affects the prognosis of patients with non-small cell lung cancer treated with immunotherapy. We downloaded the single-cell sequencing data of tumor infiltrating cd8+T cells and normal peripheral blood T cells from NSCLC patients to analyze the relationship between different NAD+ metabolism patterns and the cytotoxicity of cd8+t cells. Consistent clustering was used to identify the expression patterns of different NAD+ metabolism pathways. ssGSEA was used to calculate tumor immune cell infiltration score. Flow cytometry and co-culture experiments were used to detect the cytotoxicity of CD8+T cells in different NAD+ environments. Flow cytometry was used to detect the degree of cell aging of CD8+T cells in different NAD+ environments. Flow cytometry was used to detect the degree of cell senescence of CD8+T cells in different NAD+ environments.

Results: We found that the mutation frequency of NAD+ metabolism pathway gene was low in patients with NSCLC, but copy number variation was common. However, once a NAD+ metabolism pathway gene mutation occurs in NSCLC patients after immunotherapy, the patients will have a better prognosis. We used the gene expression value of NAD+ metabolism pathway to cluster NSCLC patients in TCGA, and found that there were great differences in the immune microenvironment of patients with different NAD+ metabolism pathway expression patterns. After the same consistent clustering of CD8+T cells, we found that CD8+T cells with different NAD+ metabolic expression patterns have different cytotoxicity, mainly in GZMB, PRF1 and IFNG. So we looked at the correlation between NAD+ metabolism pathway genes and the four indicators representing cytotoxicity of CD8+t cells: GZMB, GZMA, PRF1 and IFNG. The results showed that the key genes of NAD+ salvage pathway included CD38, NAMPT, PARP8, NMRK1 and NT5E, which were correlated with the above four genes.

Due to the limitation of data, we can only see the impact of the expression of CD38 and NT5E on the prognosis of NSCLC patients receiving immunotherapy. The results show that patients with high expression of CD38 have a better prognosis. CD8+T cells under more NAD+ metabolic environment showed higher cytotoxicity and lower cell senescence.

Discussion: Therefore, we found that NAD+ metabolism pathway gene mutations may be used as biomarkers for immunotherapy. Patients in the mutation group have better prognosis and fewer patients with progressive disease(PD). At the same time, patients with high expression of CD38 also have a better prognosis. The internal reason may be that different NAD+ metabolism pathway expression patterns change the microenvironment of tumor invasion. There are huge differences in the two different NAD+ metabolism pathway expression patterns according to the 23 immune cell scores calculated by ssGSEA. At the same time, we also found that the expression pattern of NAD+ metabolism pathway is directly related to the cytotoxicity of CD8+T cells. At the same time, we found that a higher NAD+ metabolism environment can make CD8+T cells show higher cytotoxicity and lower cell senescence.

P095

Influence of different thoracoscopic operations on pulmonary function tests and analysis of related factors

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Background: With the popularization of computerized tomography (CT), the age of patients qualified for lung surgery has been lowered. These people have increasingly higher requirements for postoperative quality of life, which is closely related to pulmonary function (PF). In this study, patients undergoing thoracoscopic surgery were selected as the research subject to analyze the effects of different surgical methods on postoperative PF and the related factors. The findings would help accurately evaluate the patients, provide reference indicators for clinicians, and guide patients in postoperative rehabilitation training to promote their postoperative recovery.

Methods: This study retrospectively analyzed the patients who underwent thoracoscopic lung surgery in Tianjin Medical University General Hospital (China) from May 2020 to November 2020. A total of 171 patients were selected according to the inclusion and exclusion criteria and were classified according to the operation method as follows: unilateral lobectomy (UL) group (N = 74), unilateral sublobectomy (USL) group (N = 67), and other surgical method (OSM) group (N = 30). Other operations included unilateral or bilateral lobectomy and/or sublobectomy. Study indicators mainly included patient general condition at different times. PF indexes at pre-operation, 3 weeks after operation, and 3 months after operation and recovery condition after operation. This study aimed to explore the effects of different surgical methods and related factors on PF under video-assisted thoracoscopy (VATS), compare the model-predicted postoperative PF with the actual measured PF, and further evaluate the application value of the clinical prediction model.

Results: The USL group was in the best condition during and after surgery. The condition of the OSM group was between those of the UL and USL groups. Different surgical operations had no remarkab

effect on PO_2 and PCO_2 before/after oxygen inhalation. However, after operation, the operation method had a significant effect on PO_2 after oxygen inhalation, and the least effect was observed in the UL group. The fluctuation degree of PO_2 and PCO_2 was regular. All the thoracoscopic operations significantly reduced PF except FEV_1/FVC, and the loss of PF in the UL group was significantly higher than that in the USL group. The patients' PF recovered gradually, and this phenomenon is related to the relief of postoperative clinical symptoms and the compensatory regrowth of residual lung tissue after operation. In the long-term observation, the loss of PF after lobectomy was almost the same, except for that in the middle lobe of the right lung. In terms of absolute value, the compensatory capacity of the upper lobe of the lung was better than that of the lower lobe. The prediction model uses only the number of segmental resection or the proportion of PF as basis and thus cannot fully reflect the actual situation of patients after operation. Here, a PF loss assessment table based on clinical data was constructed to correct existing models.

Conclusions: Different surgical methods had significant effects on postoperative blood gas analysis and postoperative survival status, but these changes gradually disappeared with time. Existing PF prediction models cannot fully reflect the actual postoperative PF values of patients who underwent VATS surgery. The patients who were subjected to different surgical methods and different lobectomy procedures had significant differences in PF indexes at 3 weeks after operation, but these differences gradually decreased at 3 months after operation.

P096

GSDME-dependent pyroptosis affects the prognosis and response to immunotherapy in lung adenocarcinoma

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Introduction: lung cancer has been the leading cause of cancer-related deaths in the world, among which lung adenocarcinoma (LUAD) is a common pathological type. Studies have shown that the tumor immune microenvironment of LUAD is rich in a variety of immune cells, and pyroptotic cells will release inflammatory factors to reshape the immune microenvironment. Now the relationship between the two has not been revealed, and it is worthy of our further discussion.

Methods: LUAD patient RNA expression data were obtained from the TCGA database, and 6 prognostic-related differentially expressed genes (DEGs) were identified by univariate cox regression. Lasso cox regression was used to exclude overfitting, and the final 5 DEGs were used to construct the prognostic model. Validation cohort data were obtained from the MSKCC database. Then the above genes were analyzed using consistent clustering analysis to obtain clusters. ESTIMATE and ssGSEA were used to analyze the immune function of each cluster. LUAD immunotherapy response data were obtained from the GEO database (GSE93157). Western blot and ELISA were used to detect the expression of scorch death related proteins.

Results: In LUAD, 5 pyroptosis-related genes were identified to establish a prognostic model. LUAD can be divided into three clusters by consistent clustering analysis of the above genes. Among them, cluster3 had a significantly worse prognosis than the other two clusters. In the immune function analysis, cluster3 had a higher immune score. Similarly, different immune cell subsets were quantified using ssGSEA and cluster3 was found to have more macrophage and Treg cell infiltration. Further, we found that the expression of GSDME in cluster3 was higher than that in the other two clusters, suggesting that GSDME dependent pyroptosis is the main form of pyroptosis in cluster3. ELISA results from the plasma of 12 patients who received immunotherapy at our center and the data from GEO showed that HMGB1 expression levels were lower in patients who responded to anti-PD1 therapy. In A549 and H1299 cell lines, we used CHX and TNF-α to induce pyroptosis and increase the secretion of HMGB1. However, when GSDME expression was knocked down by small interfering RNA, the increase of HMGB1 was also inhibited. This suggests that GSDME-dependent pyroptosis occurs with increased secretion of HMGB1.

Conclusion: We propose a model based on pyroptosis related genes for predicting the prognosis of LUAD patients,and suggest that GSDME dependent pyroptosis may be the cause of poor prognosis in LUAD patients and poor effect in anti-PD1 treatment.

P097

Apatinib added when NSCLC patients get slow progression with EGFR-TKI: a prospective, single-arm study

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Background: EGFR-TKI acquired resistance was an inevitably events in NSCLC treatment. Apatinib, a novel VEGF receptor 2 TKI, has been shown could improve NSCLC patinets' PFS combination with EGFR-TKI, but not ideal. This study aimed to explore if different mode of adding apatinib could prolong PFS further.

Methods: Twelve patients with slow progression after first line EGFR-TKI were enrolled. The enrolled patients received apatinib combined with the original first line EGFR-TKI until disease progression or unacceptable toxicity. Peripheral blood was collected for ctDNA and other detection.

Results: Seven patients were included in the efficacy analysis. The median PFS2 of apatinib combined with EGFR-TKI treatment was 8.2 months (95% CI, 7.3m-NA), and the total PFS can reach 20.9 months (95% CI, 17.3m-NA) when plus PFS1. All the adverse events were manageable. Genetic profiling of baseline samples revealed that the three most frequently mutated genes were EGFR, FAT3, and TP53. The median PFS of patients in the ctDNA clearance group was 8.4 months (95% CI, 8.2-NA), significantly longer than that of patients in the ctDNA not clearance group (7.1 months; 95% CI, 6.9-NA; p=0.0082). The acquired resistance mutations in combination treatment included EGFR T790M, TP53, cell cycle, PI3K-AKT and JAK- STAT signaling pathway genes.

Conclusion: Apatinib combined with EGFR-TKI could be an effective treatment in NSCLC with slow progression after initial EGFR-TKI treatment and the side effects are controllable. ctDNA can be a biomarker for monitoring treatment efficacy.

P098

Exploratory study on prognostic markers of nonsmall cell lung cancer based on ctDNA and high-throughput sequencing

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Background: At present, lung cancer is one of the most common malignant tumors in the world, in order to improve the survival time of lung cancer, the early diagnosis and early treatment of lung cancer is one of the most important factors. Tumor cell necrosis or apoptosis causes circulating tumor DNA (ctDNA) to fall off and release into the bloodstream, so ctDNA may be used for tumor diagnosis, subsequent treatment and prognosis: the so-called liquid biopsy. Circulating tumor DNA (ctDNA) isolated from plasma has been shown to contain genetic mutations found in the DNA (tDNA) of primary tumor tissue. Studies have also shown that the sensitivity of ctDNA detection depends on ctDNA levels. Therefore, ctDNA is not yet used for the diagnosis of early lung cancer, and there is currently no standardized method to identify mutations in ctDNA.

Objective: The diagnostic value of ctDNA for non-small cell lung cancer and clinical monitoring are inconclusive. Through the second-generation gene monitoring technology (NGS), the study selected samples of 60 non-small cell lung patients, analyzed the genetic mutation consistency of plasma ctDNA and cancer tissue tDNA, and discovered new biomarkers to study their possibilities for tumor prediction prognosis and monitoring disease progression, thus further illustrating the diagnostic value and clinical monitoring significance of plasma ctDNA sequencing for non-small cell lung cancer.

Methods: In this study, we collected tissue and plasma samples from patients with non-small cell lung cancer in China, totaling 60 patients. Histopathological materials are obtained surgically. Collected clinical

feature information of patients includes, but is not limited to: name, age, gender, personal history, smoking history, clinical diagnosis, family history, pathological diagnosis, tumor staging, CT results and follow-up data. The paired blood samples (ctDNA) and tissue samples of 60 non-small cell lung cancer patients were collected separately for 546 gene panel capture and sequencing of the target area, and the variants of the disembarkation data were detected to analyze the genetic mutation consistency of ctDNA and tumor tissue. New biomarkers are obtained based on the corresponding data model.

Result: In this study, a total of 60 patients with non-small cell lung cancer were selected, and the sensitivities of the genes that could detect mutations in blood samples were 76%, 63%, 50%, 37% and 24% of the epidermal growth factor receptors EGFR, KRAS, LRP1B, TP53, NOTCH1 and DNMT3A, respectively. Based on specimen characteristics, applying cfSNV (Somatic Single Nucleotide Variant in cfDNA) to cfDNA WES data can yield an effective new biomarker, truncal-bTMB. The results showed that Tr_bTMB could significantly distinguish between PFS and OS beneficiaries in the total population, and PFS beneficiaries in the LUAD subtype, and it was found that in early patients, Tr_bTMB could significantly distinguish between PFS and OS beneficiaries. Therefore, Tr_bTMB have the possibility of early diagnosis and prediction of lung cancer patients as a tumor marker.

Conclusion: CtDNA in plasma can identify clinically relevant driving mutations in patients with non-small cell lung cancer through non-invasive sampling, suggesting that ctDNA detection by NGS can reflect the genetic mutations of tumors in patients to some extent. Precise gene sequencing is recommended to clearly match genes. There are corresponding differences between tissue and ctDNA samples, Tr_bTMB have the potential to become tumor markers to play an important role in the precise diagnosis, therapeutic efficacy, individualized treatment, and prognosis of early lung adenocarcinoma.

Keywords: Liquid biopsy Non-small cell lung cancer ctDNA Second-generation sequencing Tr_bTMB Gene mutations

P099

Chinese patent medicine Zilongjin tablet combined with chemotherapy in the treatment of postoperative adenocarcinoma of lung

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Background: The most common type of lung cancer is adenocarcinoma, which accounts for about 40% of all lung cancer cases. Despite successes in understanding the pathogenesis of the disease and new treatments, unfortunately, lung adenocarcinoma remains one of the most aggressive and rapidly fatal types of tumours, with an overall survival of less than 5 years [1]. It is now common to accept postoperative chemotherapy in patients with early to mid-stage lung adenocarcinoma who have been diagnosed with surgery as the first choice of surgery, helping to improve patients' 5-year survival [2, 3]. Adjuvant chemotherapy provides a significant survival benefit to patients with lung adenocarcinoma, improving overall survival and significant progression-free survival, but patients may suffer from a range of physiological and psychological adverse events (AE) during chemotherapy [4]. Chemotherapy drugs have different degrees of adverse drug reactions to patients, which have a direct impact on the patient's quality of life and functional recovery, usually with multiple complications at the same time [5, 6], and those with severe reactions need to reduce or even stop the drug, or abandon subsequent chemotherapy because they cannot tolerate it. At present, the integrated traditional Chinese and Western medicine treatment model for lung cancer after surgical resection is gradually recognized and promoted in clinical practice. On the basis of chemotherapy, combined with traditional Chinese medicine, it can enhance the effect, reduce toxic side effects and improve the quality of life of patients to a certain extent, so as to ensure that chemotherapy is carried out as scheduled

Objective To explore the efficacy, safety and quality of life of Zilongjin tablet combined with chemotherapy for patients with lung adenocarcinoma after pneumonectomy.

Methods Selected 519 postoperative lung adenocarcinoma patients admitted to our hospital from May 2018 to May 2019 and divided them into a study group (n=196) and a control group (n=323). Both groups of patients were based on clinical staging and pathology Standardized surgery and chemotherapy were performed according to the classification. The plan was: pemetrexed + platinum-based dual-drug combination chemotherapy (CSCO Non-small cell lung cancer diagnosis and treatment guidelines for details). Patients in the study group were treated with Zilong Jinpian on the basis of chemotherapy. The efficacy, adverse reactions, survival status and quality of life of the two groups of patients.

Results There was no significant difference in progression-free survival between the two groups, but there were statistical differences in reducing adverse reactions to chemotherapy and improving the quality of life of patients. The average values of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase in the study group were slightly lower than those of the control group, and the average albumin values were slightly higher than those of the control group. The physical strength PS (ECOG) score and quality of life (EQ-5D) score were different There is statistical significance (P<0.05). The liver function of the study group was compared with that of the control group, and the difference between the two groups was statistically significant. Comparing renal function and other indicators with the control group, there was no statistically significant difference between the two groups. The progression-free survival of patients in the study group and control group were 18.97months and 18.35months, respectively, and the difference was not statistically significant.

Conclusion There is no significant difference in the progression-free survival of patients with lung adenocarcinoma treated with post-operative chemotherapy with Zilongjinpian, but it can improve the quality of life without increasing adverse reactions.

Keywords: Zilongjin tablet; Chemotherapy ; Curative effect ; lung adenocarcinoma;

Macrophages

P101

Anti-colorectal Cancer Activity of Bilobalide in Patient-derived Colorectal Cancer Organoids and AOM/DSS Mouse Model

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Bilobalide has shown strong anti-inflammatory activity. Colorectal cancer (CRC) is closely associated with inflammation. However, no studies have reported on the use of bilobalide for treating CRC. This study aims to evaluate the effect of bilobalide on CRC prevention. Enzyme-linked immunosorbent assay (ELISA), quantitative real-time polymerase chain reaction (RT-qPCR), western blotting, and immunofluorescence showed that bilobalide significantly inhibit the M2 polarization of macrophages dependent on the phorbol 12-myristate 13-acetate (PMA) and interleukin-4 (IL-4). Analysis of signaling pathways showed that phosphorylation of extracellular signal-regulated kinase (ERK), c-jun N-terminal kinases (JNK), and signal transducer and activator of transcription 3 (STAT3) was regulated. In particular, human CRC organoids were established. And western blotting, terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling (TUNEL), and analysis of cell viability and morphology further supported the hypothesis that the anti-CRC effects of bilobalide could be explained by its ability to suppress M2 macrophage polarization and promote M1 transformation. C57BL/6 mice treated with azoxymethane (AOM)/dextran sodium sulfate (DSS) were divided into three groups, i.e. no treatment (0 mg/kg), low (2.5 mg/kg) and high (5 mg/kg). Both groups were administered (intragastric administration, i.g) bilobalide daily from days 8 to 58. High-dose bilobalide markedly inhibited the progression of CRC, as evidenced by the increased body weight, decrease in disease activity index death rate (DAI), and alleviation of colon length reduction and tumorigenesis. According to the in vivo results, the levels of inflammatory cytokines, such as tumor necrosis

factor (TNF-α), IL-6, IL-1β, and IL-10 in the serum were substantially reduced in the bilobalide-treated groups. In addition, expression of proliferating cell nuclear antigen (PCNA), Ki67, cellular Myc (c-Myc), and CD206 was downregulated in the drug-treated groups, as confirmed by the immunohistochemical staining. Collectively, these results indicated that bilobalide administration improve experimental CRC by inhibiting M2 macrophage polarization. Thus, bilobalide may prevent CRC and serve as a potential therapeutic target for CRC.

Platelets

P102

Buyang Huanwu decoction ameliorates myocardial injury and attenuates platelet activation and clot retraction by regulating the Rap1 signaling pathway

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Buyang Huanwu Decoction (BYHWD) is a traditional Chinese prescription to treat with the syndrome of qi deficiency and blood stasis. In the present study, model of left anterior descending coronary artery ligation was applied to investigate the possible effects of BYHWD on modulating ischemic myocardial infarction (MI). The rats were randomly divided into five groups: sham, model, MI with aspirin (positive), MI with a low dosage of BYHWD (BYHWD-ld) and MI with a high dosage of BYHWD (BYHWD-hd) for 28 days. The results revealed that coronary artery ligation prominently induced left ventricle dysfunction, decreased cardiomyocyte fibrosis, which was accompanied by platelets with hyperreactivity, and high levels of inflammatory factors. Furthermore, similar to aspirin, BYHWD obviously reversed cardiac dysfunction together with fibrosis, increased the thickness of the left ventricular wall (LVW), and inhibited platelet aggregation, adhesion, and the expression of the membrane receptor CD62p. BYHWD restored the mitochondrial respiration of platelets after MI, concomitant with an increased telomere expression and decreased inflammation. According to the result of transcriptome sequencing (RNA-seq), we found that 106 differentially expressed genes when comparing the model group with the BYHWD groups. Furthermore, enrichment analysis of the genes finally confirmed their close relationship with the Ras-related protein Rap-1 (Rap1) signaling pathway and platelet activation biological function. Further research was applied by quantitative real-time PCR and western blotting, and the results showed that BYHWD reduced the expression of Rap1/PI3K-Akt/Src-CDC42 genes and attenuated the overactivity of Rap1 signaling pathway. Overall, BYHWD plays a role in regulating inflammation and platelet activation and reducing the risk of inflammatory thrombosis after MI.

Stem Cells

P103

The homing and neuroprotective effects of hair follicle stem cells after cerebral ischemia-reperfusion

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Background and Objective: Stem cell transplantation therapy can provide multiple target network regulation to alleviate nerve damage and promote nerve regeneration, which match for the lack of neuroprotection and repair methods for ischemic stroke. Hair follicle stem cells (HFSCs) originate from the ectoderm, the same with nervous system, have strong neural differentiation potential and neurotrophic effects. In addition, the wide range of sources, easy to access and lifelong differentiation potential, make HFSCs a ideal resource for autologous transplantation treatment. This study explores firstly the therapeutic role of HFSCs in cerebral ischemia-reperfusion in order to obtain a more suitable source of stem cells treatment and promote the development of transplantation therapy.

Materials and methods: A rat model of middle cerebral artery ischemia-reperfusion was established, and $1*10^6$ HFSCswere transplanted intravenously 24 hours after reperfusion. The research mainly explores from three aspects: neural differentiation, immune regulation, and blood brain barrier protection. Firstly, the spatial distribution of HFSCs after transplantation was observed via PKH67 fluorescent tracer labeling method, and the neural differentiation ability of HFSCs was evaluated using immunofluorescence colocalization method; Secondly, immunohistochemical staining was used to evaluate the activation of microglia, and western blot to analyze the inflammatory cytokine TNF-α, IL-6 and IL-4, IL-10 expression; Third, brain water content, evans blue leakage and the content of Occludin and ZO-1 proteins in the infarcted hemisphere were measured to evaluate the degree of damage to the blood brain barrier in the infarcted hemisphere; Finally, the neural function score and TTC staining were used to evaluate the impact of HFSCs transplantation on cerebral infarction area and neurological prognosis.

Results: Firstly, HFSCs migrated asymmetrically to the infarcted hemisphere, while rarely migrate to the healthy hemisphere, suggesting that they have a targeted homing effect. Immunofluorescence colocalization analysis showed that most of the homing HFSCs expressed neuron specific markers DCX or NeuN, suggesting that they have the potential to differentiate into neuron like cells for alternative therapy; Secondly, HFSCs transplantation inhibited the activation and aggregation of microglia in the ischemic penumbra during acute phase, reduced the pro-inflammatory cytokines TNF-α and IL-6, and increased the anti-inflammatory cytokines IL-4 and IL-10, suggesting the ability to regulate the activity of immune cells and inflammatory response in the brain after ischemia reperfusion; Thirdly, the evans blue leakage and content of cerebral water in the infarcted hemisphere of rats in the HFSCs transplantation group were significantly reduced, and the content of tight junction proteins Occludin and ZO-1 in the brain tissue was significantly higher than that in the model group, indicating that they played a protective role in the blood brain barrier and reduced the degree of brain edema after infarction; Finally, after HFSCs transplantation, the neural function of rats with cerebral infarction was significantly improved, while TTC showed a decrease in the area of cerebral infarction. Immunohistochemical and immunofluorescence staining showed a significant increase in the number of surviving neurons in the penumbra region of the transplanted group, suggesting that HFSCs have a neural protective effect and improve prognosis in cerebral ischemia-reperfusion injury.

Conclusion: The results of this study show that HFSCs transplantation during the acute phase of cerebral ischemia-reperfusion has the potential for homing and neural differentiation, and can play a therapeutic role through immune regulation and blood brain barrier protection, suggesting that they have the potential to treat ischemic stroke, but the specific mechanism of action still needs further research in the future.

Mitochondria

P104

Acacetin inhibits mitochondrial impairment in mesenteric arterioles to protect against vascular dysfunction in hypertension

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Background: Mitochondrial dysfunction in the endothelium contributes to the abnormal vasodilation in hypertension. Acacetin is a natural flavonoid compound that has been shown to possess multiple beneficial effects, including vasodilatation. However, whether acacetin could improve endothelial function by protecting against mitochondria-dependent apoptosis remains to be determined.

Aims: To explore the potential mechanisms underlying the protective

effect of acacetin on endothelium-dependent dilation in mesenteric arterioles from hypertension.

Methods: Endothelium-dependent dilation in mesenteric arterioles from WKY and SHR was measured to assess the protective effect of acacetin. Endothelial injury in the pathogenesis of hypertension was modeled in HUVECs treated with Angiotensin II (Ang II). Mitochondria-dependent apoptosis, the opening of Mitochondrial Permeability Transition Pore (mPTP) and mitochondrial dynamics proteins were determined by fluorescence activated cell sorting (FACS), immunofluorescence staining and western blot.

Results: Acacetin administered intraperitoneally greatly reduced MAP in SHR by mediating a more pronounced endothelium-dependent dilatation in mesenteric arterioles, and the vascular dilatation was reduced remarkably by NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthesis. While acacetin administered intragastrically for six weeks had no apparent effect on MAP, but it improved the endothelium-dependent dilatation in mesenteric arterioles of SHR by activating the AKT/eNOS pathway and protected against the abnormalities of endothelial mitochondria. Furthermore, Ang II facilitated the opening of mPTP by increasing the protein expression of Cyclophilin D (CypD), the overproduction of ROS and ATP deficiency, as well as the disturbance of dynamin-related protein 1 (DRP1)/optic atrophy1 (OPA1) dynamics in HUVECs. Meanwhile, the aforementioned effects could be remarkably abrogated by acacetin.

Conclusion: This study suggests that acacetin protected against endothelial dysfunction in hypertension by activating the AKT/eNOS pathway and modulating mitochondrial function by targeting mPTP and DRP1/OPA1-dependent dynamics.

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P105

The protective effect and mechanism of rhein on cardiomyocyte injury in diabetic cardiomyopathy

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Objective: To explore the protective effect of rhein on cardiomyocyte injury in diabetic cardiomyopathy and its possible mechanism.

Methods: A total of 30 male C57 BL/6J mice were randomly divided into control group(n=6) and diabetes mellitus model group(n=24). The control group was fed as normal diet, and the model group was fed with high fat diet. After one week, the control group was injected with citric acid buffer and the model group was daily intraperitoneally injected with streptozotocin (STZ, 75mg/kg). The mice with fasting blood glucose (FBG) levels > 11.1 mmol/L were considered as diabetic mice. Diabetic mice were randomly divided into DM group and DM+RH group. DM+RH groups were administered orally at a daily dose 120 mg/kg for 12 weeks, whereas mice in the control and T2D group were treated with the same volume of sodium cellulose solution. The alterations of weight, blood glucose, and heart weight were assessed respectively. Heart histologic sections in each group were stained with hematoxylin-eosin for general morphological analysis and Masson for collagen deposition. Mitochondrial density and morphology were detected by transmission electron microscopy. The mRNA levels of ANP, BNP, β-MHC, Sirt1, PGC-1α, TFAM, NRF-1 and UCP2 were quantified by RT-PCR. Furthermore, Sirt1, PGC-1α and TFAM protein levels were estimated by Western blot and IHC. H9C2 cells were divided into the following four groups: control group (low glucose, LG, 5.5 mM) , high glucose group (HG,35mM) ,Rhein group (HG+RH, Rhein=10μmol/L) ,and EX527 group (HG+RH+EX527, EX527=20μ mol/L) . Drugs were added directly into culture medium and treated for 48 h. The mRNA levels of Sirt1, PGC-1α, TFAM, NRF-1 and UCP2 were quantified by RT-qPCR. The protein levels of Sirt1, PGC-1α and TFAM were evaluated by western blot.

Results: There was no significant difference between DM+RH group and DM group. The heart-to-body weight ratio (HW/BW) was significantly increased in the DM group compared with the control group; this change was reversed by RH treatment(P<0.01). In the DM+RH group, the myocardial arrangement was relatively regular, with clear myocardial texture, tight connections, and clear nuclei. Increased interstitial fibrosis was evident in the DM group, and the fibrotic changes were attenuated after RH administration. In DM group, myocardial ultrastructure was significantly damaged. The myocardial fibers in DM+RH group were arranged regularly, and the morphology of mitochondria was basically normal. In DM group, mRNA levels of Sirt1, PGC-1α, TFAM, NRF-1, and UCP2 were significantly decreased (p<0.01). Rh prevented this down-regulation(P<0.05). Compared with the control group, Sirt1, PGC-1α and TFAM protein levels were significantly decreased in DM group(P<0.01). Compared with DM group, these protein levels were increased in DM+RH group(P<0.05). The expressions of Sirt1, PGC-1α and TFAM were localized in cytoplasm of myocardial cells. DM+RH group had more brown granules than DM group. H9C2 cell viability was significantly decreased after exposure to high glucose. The protein expressions of Sirt1 and PGC-1α were decreased in 25mM group(P<0.01). H9C2 cell viability was increased after treatment with Rhein. The expressions of Sirt1, PGC-1α and TFAM in high glucose treatment group were significantly lower than the low glucose group (P<0.05), and the expressions were increased after intervention of rhein. EX527 inhibited rhein-induced improvement of mRNA levels of Sirt1, PGC-1α, TFAM, NRF-1 and UCP2(P<0.05). EX527 inhibited Rhein-induced improvement of protein expression of Sirt1, PGC-1α and TFAM(P<0.01).

Conclusions: Rhein exhibits protective effects on diabetic cardiomyopathy both in vivo and in vitro which may be achieved by activating Sirt1/PGC-1α pathway.

P106

The Effect and Molecular Mechanism of Slibinin on Improving Non-alcoholic Fatty Liver Induced by PM2.5

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With the rapid development of the world economy, air pollution has become a major issue threatening everyone's health. Among them, PM2.5 is the main cause of air pollution and has a particularly serious impact on human health. In 2022, the World Health Organization reported that only 10% of the population lives in PM2.5 standard environments that meet air quality guidelines, based on PM2.5 concentration monitoring data from 117 countries (including 6,743 observation points in cities) over the past decade (2010-2019). Numerous studies both domestically and internationally have shown that PM2.5 can penetrate deep into the lungs and enter the bloodstream, causing cardiovascular and respiratory diseases (Thurston et al., 2017) and affecting the immune system, brain and nervous system, cancer, endocrine disorders or metabolic syndrome and other diseases. Among them, the liver, as the largest digestive gland and metabolic center of the human body, is exposed to PM2.5 environments, which can induce the development of metabolic-associated fatty liver disease, a type of reversible disease characterized by liver fat degeneration and inflammatory infiltration that is linked to metabolic dysfunction such as obesity, type 2 diabetes, hypertension, and abnormal blood lipids. Timely treatment can effectively reduce the occurrence of liver cirrhosis and liver cancer. Silybin, a natural antioxidant, has long been used to treat chronic liver disease with unclear pathogenesis, and some studies have shown that it has a protective effect against liver injury induced by CCl4. Our previous studies have also found that silybin

can improve excessive liver fat deposition in high-fat diet-induced hamster liver and lipid metabolism disorders in db/db mice with type 2 diabetes. We established animal and cell models of PM2.5-induced metabolic-associated fatty liver disease and found that silybin has an ameliorative effect on PM2.5-induced metabolic-associated fatty liver disease. Silybin can significantly inhibit triglyceride accumulation in cell models, and the specific mechanism is related to mitochondria, which will provide a more ideal drug for clinical treatment of metabolic-associated fatty liver disease caused by atmospheric particulate matter.

Extracellular Vesicles

P107

Adipocyte-derived exosomal miR-22-3p modulated by circadian rhythm disruption regulates insulin sensitivity in skeletal muscle cells

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Objective: Circadian rhythm disruption leads to dysregulation of lipid metabolism, which further drive the occurrence of insulin resistance (IR). Exosomes are natural carrier systems that advantageous for cell communication. In the present study, we aimed to explore whether and how the exosomal microRNAs (miRNAs) in circulation participate in modulating IR induced by circadian rhythm disruption.
Methods: We established a mouse model of circadian rhythm disruption with at least 10 weeks of 24-h constant light to expolore the relationship of exosomal miRNAs in circulation and IR occurrence. The 3T3-LI cells transfected with sh-Bmal1 were used to mimic the accumulation of lipid drop in adipocytes in the context of circadian rhythm disruption. Then the *in vitro* exosome treatment or the co-culture with C2C12 cells further determined the source and target of the exosomal miR-22-3p. We also performed clinical investigations.
Results: Here, we showed that circadian rhythm disruption led to increased body weight and visceral fat volume, elevated exosomal miR-22-3p in circulation as well as occurrence of IR *in vivo*. Furthermore, exosomal miR-22-3p derived from adipocytes in the context of circadian rhythm disruption could be uptaken by skeletal muscle cells to promote IR occurrence *in vitro*. Moreover, miR-22-3p in circulation was positively correlated with the IR-associated factors clinically.
Conclusions: Collectively, these data showed that exosomal miR-22-3p in circulation may act as potential biomarker and therapeutic target for skeletal muscle IR, contributing to the prevention of diabetes in the context of rhythm disturbance.
Keywords circadian rhythm disruption, exosomes, miR-22-3p, insulin resistance, adipocytes, skeletal muscle

P108

Tumor cell-released autophagosomes (TRAPs) remodel the breast tumor microenvironment by inducing the formation of inflammatory cancer-associated fibroblasts (CAFs)

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Abstract:
Background: Cancer-associated fibroblasts (CAFs) are the most prominent stromal cells in the tumor microenvironment, playing a significant role in tumor initiation, progression, and metastasis. However, the specific mechanisms underlying CAF formation and their role in remodeling the tumor microenvironment are not yet fully elucidated. Previous studies have shown that autophagy-derived exosomes released by in situ breast cancer cells (TRAP) can travel through the bloodstream to lung tissue and regulate the function of lung fibroblasts to create an inflammatory and immune-suppressive tumor microenvironment that ultimately promotes breast cancer lung metastasis.
Objective: To investigate the mechanism by which TRAP induces CAF formation and the immune regulatory role of CAFs in the tumor microenvironment in breast cancer.
Methods: Primary human breast adipose fibroblasts (NFs) were obtained in vitro by differential adhesion, and TRAP was obtained from the supernatant of 4T1 tumor cell culture by high-speed centrifugation. The supernatant was collected after 48 hours of co-culture, and chemokines were measured by ELISA. The expression of PD-L1 on the surface of fibroblasts and the ability to inhibit T cells were measured by flow cytometry (FCM). DAMPs on TRAP surface blocked by antibodies and fibroblasts pretreated with inhibitors were used to detect the ligand receptors between TRAP and NFs. The relevant signaling pathways were examined by Western blotting. In vivo, the following experiments were performed: ① Tumor-bearing mice were constructed using TRAP low-expression cell lines (*Beclin1*KD/*Raba8a* KD); ② NFs and 4T1 cells with or without TRAP stimulation were mixed and implanted in mice to detect the proportion and function of various immune cells and fibroblasts in the tumor microenvironment by FCM. Fibroblasts were separated by magnetic beads, and chemokine expression was measured by qPCR. The ability of fibroblasts to inhibit T cells was measured by FCM.
Results: The results of in vitro experiments showed that the proteins (HSP27/70) on the surface of TRAP bind to TLR4 on NFs surface exerting their functions by secreting more CXCL1/2, CXCL9/10, CCL5 and expressing higher levels of PD-L1, combined WB results indicated that interaction between TRAP with NFs via HSP27/70-TLR4-MyD88-NF-κB signal cascade. In vivo experiments showed the proportion of neutrophils and monocytes in the tumor microenvironment decreased in the *Beclin1* KD/*Raba8a* KD group compared to the normal control (NC) group, while the proportion of T cells increased, and the ability of T cells to secrete IFN-γ partially recovered. The level of PD-L1 on the surface of fibroblasts decreased, and their ability to inhibit T cells weakened. Compared with the 4T1+NFs group, the 4T1+NFs/TRAP group showed reduced T cell function in the tumor tissue.
Conclusion: The formation of inflammatory and immune-suppressive fibroblasts induced by TRAP through secreting CXCL1/2 and CCL5 to chemotaxis neutrophils and monocytes to the tumor microenvironment, and by directly inhibiting T cells, ultimately contributing to the formation of the tumor microenvironment.

Intestinal Microcirculation

P109

Gut microbiota regulates blood pressure by modulating the synthesis of pentosidine in individuals with high-salt diet-induced hypertension

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High-salt diet (HSD) has been linked to gut microbial dysbiosis and can trigger cardiovascular diseases that begin to manifest as vascular endothelial dysfunction. Previous studies have shown that HSD could induce blood pressure elevation and endothelial dysfunction through modulating the gut microbial balance. However, the complex relationships and detailed regulating mechanisms among HSD, blood pressure, and gut microbiota have not been investigated thoroughly, especially the key microbiota in affecting blood pressure. In the present study, we first set out to discover the potential relationship between gut microbiota and HSD induced endothelial dysfunction by conventional (Conv) and then verified by germ-free (GF) C57BL/6J mice. HSD could induce increased blood pressure and endothelial dysfunction, regulate vasoconstriction and vasodilation, immunity and inflammation, intestinal vascular barrier, intestinal perfusion in mice. By integrating the LC-MS/MS metabolomics, we used the metabolic pattern to elucidate the adaptive regulatory mechanism of the gut microbiota. HSD metabolism and the synergistic effects

of gut microbiota primarily depend on the synthesis of primary bile acids and arachidonic acid. We discovered *Dubosiella newyorkensis*, a newly identified gut symbiont that is highly sensitive in HSD induced hypertension development in mice. *Dubosiella newyorkensis* could protect blood pressure, regulate the activation of vascular endothelial active factor, inflammatory reaction, and the intestinal vascular barrier injury in Conv mice induced by HSD. Meanwhile, *Dubosiella newyorkensis* could significantly alter the blood pressure in GF mice induced by HSD. Interestingly, in both metabolic modes, serum pentosidine can function as an important biomarker for *Dubosiella newyorkensis* in response to HSD. Additionally, after pentosidine supplement could promote increased blood pressure and vascular endothelial damage in mice after 4 weeks. This metabolite evidence reveals the HSD metabolic pattern and a potential biomarker of the gut microbiota involved in the adaptive regulation of vascular physiology. This work enriched the understanding of the gut microbial function and its effects on hypertension.

miRNA

P110

Resveratrol alleviates NLRP3 inflammasome activation via miR-217 mediated SIRT1/NOX4-XBP1s axis in naturally aging thoracic aorta and senescent endothelial cells induced by H2O2

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Considering the beneficial effects of resveratrol (RES) as an anti-aging agent in cardiovascular disease, we examined its effects and mechanisms on the NLRP3 inflammasome in aging-induced vascular injury. RES was fed to naturally aged male C57 BL/6 mice at 400 mg/kg/d for consecutive 64 weeks. The mice were weighed once a week, serum NO and ET-1 levels, the expression of genes associated with aging and NLRP3 inflammasome and mmu-miR-217 in the thoracic aorta were measured at the end of experiment. RES and SIRT1 knockdown in the H_2O_2-induced senescent human umbilical vein endothelial cells (HUVECs) were used to detect the effects of RES and SIRT1 on aging and NLRP3 inflammasome. Inhibitor and mimic of hsa-miR-217 were transfected into cells to confirm the effect of miR-217 on SIRT1 expression and senescence of HUVECs. RES decreased body weight, improved endothelial dysfunction, reduced expression of p21, p53, NLRP3, NOX4, IL-1β and mmu-miR-217 in the thoracic aorta of naturally aged mice. RES significantly reduced ROS levels, attenuated the activation of NLRP3 inflammasome and expression of NOX4, CHOP, XBP1s in a dose-dependent manner in H_2O_2-induced senescent HUVECs. SIRT1 knockdown significantly induced cell senescence, the activation of NLRP3 inflammasome, expression of CHOP, XBP1s, NOX4 and hsa-miR-217, this effect was partially reversed by RES addition. Mimic of hsa-miR-217 accelerated cell aging while inhibitor of hsa-miR-217 decelerated cell aging via influencing expression of SIRT1. Our results implicated that RES alleviated activation of NLRP3 inflammasome via miR217 mediated SIRT1/NOX4-XBP1s axis in vivo and in vitro.

P111

MicroRNA-221-3p inhibits the inflammatory response of keratinocytes by regulating the DYRK1A/STAT3 signaling pathway to promote wound healing in diabetes

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Diabetic foot ulcer (DFU), a serious complication of diabetes, remains a clinical challenge. MicroRNAs (miRNAs) affect inflammation and may have therapeutic value in DFU. Here, we found that an miR-221-3p mimic reduces the inflammatory response and increases skin wound healing rates in a mouse model of diabetes, whereas miR-221-3p knockout decreases wound healing rates in mice with or without diabetes. In human keratinocytes cells, miR-221-3p suppresses the inflammatory response induced by high glucose. The gene encoding DYRK1A, an enzyme thought to play a role inflammation, is a target of miR-221-3p. High glucose increases the expression of DYRK1A, but silencing DYRK1A expression decreases high glucose–induced inflammatory cytokine release via dephosphorylation of STAT3, a substrate of DYRK1A. Application of miR-221-3p mimic to human keratinocytes cells not only decreases DYRK1A expression but also inhibits high glucose–induced production of inflammatory chemokines and cytokines to promote wound healing. This molecular mechanism whereby miR-221-3p regulates inflammation through the DYRK1A/STAT3 signaling pathway suggests new targets and therapeutic approaches for treating DFU.

Noncoding RNAs

P112

Tumor-associated macrophages induced circTAM in promoting glycolysis and tumor growth of hepatocellular carcinoma via USP22/HIF-1α

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Objective: To explore whether circRNA intervenes with the link between Tumor-associated macrophages (TAMs) and hepatocellular carcinoma tumor cells.

Methods: In this study, though Transwell co-culture system and circRNA-sequencing

we identified a circRNA: circTAM, which is induced by TAMs. The function of internal ribosome entry site (IRES) was verified by dual luciferase reporter gene assay, and the specific peptide translated by circTAM was verified by liquid chromatography/mass spectrometry-mass spectrometry (LC/MS-MS). The target proteins bounding to the specific peptide were verified by Co-immunoprecipitation (CO-IP) and following LC/MS-MS. Finally, RNAscope technology and immunohistochemistry (IHC) were applied in HCC tissue microarrays to detect the expression levels and interrelationships of circTAM and target proteins, and prognostic predictive values were evaluated respectively.

Results: TAMs induced significant upregulation of circTAM in hepatocellular carcinoma cells to promote progression and glucose metabolism imbalance compared with paratumor macrophages (PMs). Function and animal experiments have shown that circTAM is an important factor in not only promoting the proliferation, migration, invasion of hepatocellular carcinoma cells, but also reprogramming of the glucose metabolism, as well as accelerating the growth of subcutaneous tumors. LC/MS-MS confirmed that circTAM can encode a peptide containing 227 amino acids, circTAM-227aa, which inhibited the degradation of HIF-1α via the ubiquitin-proteasome pathway by binding to Ubiquitin Specific Peptidase 22 (USP22). The levels of circTAM positively correlated with USP22 and the number of infiltrated TAMs, and all of them were independent risk factors to predict the prognosis of hepatocellular carcinoma patients.

Conclusion: circTAM, which was upregulated by TAMs, promoted progression and glycolysis of hepatocellular carcinoma by positively regulating HIF-1α expression levels through encoding a new peptide and the following circTAM-227aa/USP22/HIF-1α pathway.

P113

Screening and biological function validation of circRNA associated with matestasis of hepatocellular carcinoma

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Aim: To investigate the circRNAs inhibited postoperative metastasis of hepatocellular carcinoma (HCC).

Methods: Firstly, circRNA sequencing was performed on the HCC tumor tissues of 30 patients who did not show metastasis after surgery (No Metastasis group) and 30 patients who showed metastasis after surgery (Metastasis group) to draw the circRNA expression profile of HCC. Secondly, qRT-PCR was performed to validate the expression of circRNAs in 200 HCC tumor tissue samples. Finally, in vitro functional expriments were performed to investigate the biological role of circRNA in HCC tumor cell. In vivo mouse model experiments were conducted to detect the effects of circRNA on tumor growth.
Results: The sequencing results revealed that 35 circRNAs were highly expressed in the no metastasis group and 42 circRNAs were highly expressed in the metastasis group. The top 3 highly expression circRNAs in no metastasis group were selected: circHOXA4, circEIF4E, circCTSL. We discovered that the expression of circEIF4E was higher in the no metastasis group and its expression was positively correlated with patient prognosis, while the other two were not. Furthermore, in vitro functional assays revealed that circEIF4E inhibited the ability of tumor cell proliferation, invasion, and colony formation. In vivo mouse model expriment showed that circEIF4E inhibited tumor growth and metastasis. Immunohistochemical staining result of subcutaneous tumor tissues showed lower Ki67 expression in circEIF4E overexpression groups.
Conclusion: circEIF4E inhibits HCC metastasis and was positively correlated with patient prognosis. The result of in vitro functional assays and in vivo experiments revealed that circEIF4E inhibited tumor growth and metastasis.

Aquaporin

P114

The polar distribution of AQP4 is altered by trifluoperazine in rats after intraparenchymal hemorrhage

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Objective: This study examines whether trifluoperazine (TFP) can improve edema after intracerebral hemorrhage (ICH) and the mechanisms involved
Methods: Rats were divided into sham-operated (Sham), ICH and ICH+TFP groups after having collagenase IV injected into their Caudate Putamen (CPu). First, third, and seventh days after ICH, Bederson scores, edema levels, and hematoma volumes were measured . In perihematomal tissues, RT-PCR and western blot were used to measure the expression of AQP4 mRNA and protein. Immufluorescence images were analyzed to assess AQP4 polar distribution. The effect of TFP on brain edema following intracerebral hemorrhage was also investigated on AQP4 knockout mice. An immunofluorescence and confocal study was carried out in vitro to investigate the distribution of AQP4 in astrocytes.
Results: In the first and third days following ICH, TFP significantly reduced brain edema and Bederson scores. Following TFP treatment, rats' perihematomal tissues showed significantly reduced levels of AQP4 mRNA and protein expression. Immunofluorescence results also showed a decrease in AQP4 polar distribution following ICH due to TFP. In AQP4 knockout mice, TFP did not reduce brain edema caused by intracerebral hemorrhage. When low osmolality induced edema astrocytes, TFP inhibited AQP4 membrane distribution.
Conclusion: By inhibiting the polar distribution of AQP4, TFP could prevent edema following ICH. This may provide a potential method for ameliorating cerebral edema after ICH by regulating AQP4 polar distribution.

Oxidative Stress

P115

Changes in pancreatic structure and function in rats with high-voltage electrical burns and intervention effect of N-acetylcysteine

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Objective: To investigate the characteristics and changes of superoxide dismutase (SOD), inducible nitric oxide synthase (iNOS), blood glucose, and N-acetylcysteine (NAC) in pancreatic tissue of rats with high voltage electrical burns.) intervention.
Methods: 240 SD male rats were randomly divided into sham injury group, electric injury group, saline group, and NAC group, each group had 6-time phases (0h post-electricity, 8h post-electricity, 24h post-electricity, 48h post-electricity, 72h post-electricity, and 1w post-electricity), 10 rats in each time phase. The modeling process was completed with 3 kV high-voltage electric shock through the left forelimb and right hindlimb of the rats for 3 s. After electrocautery, the NAC (100 mg/kg) was injected into the NAC group and the saline group was injected with an equal amount of saline. The histopathological conditions, SOD activity, iNOS content, and blood glucose of rat pancreas were analyzed to elucidate the effects of high-voltage electric burns on rat pancreatic tissue.
Results: Compared with the sham injury group, the rats in the electric injury group showed obvious pancreatic pathological injury, increased iNOS expression, increased blood glucose concentration, and decreased SOD activity; NAC had some improvement on the pancreatic injury of rats with high voltage electric burns, but did not reduce blood glucose concentration, iNOS content of pancreatic tissues and did not enhance SOD activity.
Conclusion: High-voltage electrical burns caused pancreatic tissue damage in rats, and the degree of damage was closely related to the level of oxidative stress. the intervention effect of NAC in high-voltage electrical burns was not obvious, and further experiments are needed to confirm its efficacy.

P116

The preventive and therapeutic effects of Qishen Yiqi Drop Pill (QSYQ) and its main components on statin induced rhabdomyolysis syndrome and potential mechanism

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This study aims to explore the preventive and therapeutic effects of Qishen Yiqi Drop Pill (QSYQ) and its main components on statin induced rhabdomyolysis syndrome and potential mechanism.
We set up the control group, the model group (Model) and the treatment group (Model +QSYQ). The model group was given the combined administration of simvastatin and fenofibrate combined with running exercise to create the rhabdomyolysis model (divided into acute model and chronic model), and the treatment group was given QSYQ to improve the muscle side effects. In vivo, an inverted microscope and a high-speed camera system were used to continuously observe the hemodynamics of microcirculation vessels in the lower extremity muscles of mice. After sampling, the muscle tissues were sliced and observed by HE staining, PAS glycogen staining and immunofluorescence staining. The activity of mitochondrial complex subunits was detected by Elisa and O2K techniques to determine mitochondrial function. We applied proteomics technology, combined with the analysis of the composition of QSYQ into the blood, and used network pharmacological tools to conduct a preliminary exploration on the response factors of rhabdomyolysis and the possible mechanism of QSYQ, and verified by PCR and WB.
Our phenotypic study found that QSYQ can significantly improve statin induced weight loss in mice, liver mass/weight increase, gastrocnemius mass/weight decrease, serum creatine kinase (CK) serious increase, liver and kidney function impairment of varying degrees. Morphological study showed that QSYQ improved necrosis and inflammatory cell infiltration of mouse muscle tissue. Molecular biology experiments verified that QSYQ improved the expression levels of mRNA and

protein related to muscle injury, oxidative phosphorylation, energy metabolism, connexin, MAPK-PI3K/Akt-mTOR pathway.

Renal Microcirculation

P117

Role of SGLT2 inhibitor on diabetic renal tubular lipid accumulation

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Background: Glucose cotransporter (SGLT) 2 suppression provides potent renal protective effect during diabetic kidney disease (DKD). This work aimed to explore how empagliflozin (EMPA, the selective and strong inhibitor of SGLT2) affected renal lipid deposition among patients undergoing type 2 diabetes mellitus (T2DM), a T2DM mouse model and human renal proximal tubular epithelial (HK-2) cells.
Methods: This work divided subjects as 3 groups: non-diabetic volunteers, patients treated with metformin and those treated with metformin plus EMPA. In an in vivo study, EMPA was adopted for treating db/db mice that were raised with the basal diet or the high-advanced glycation end products (AGEs) diet. In addition, AGEs and/or EMPA was utilized to treat HK-2 cells in vitro.
Results: Results showed that diabetic patients treated with metformin plus EMPA had lower AGEs levels and renal fat fraction (RFF) than those treated with metformin. Moreover, a significant and positive association was found between AGEs and RFF. Results from the basic study showed that EMPA decreased cholesterol level, tubular lipid droplets, and protein levels related to cholesterol metabolism in AGEs-mediated HK-2 cells, kidneys of db/db mice and those fed
with the high-AGEs diet. Additionally, EMPA decreased AGEs levels in serum while inhibiting the expression of receptor of AGEs (RAGE) in vitro and in vivo.
Conclusion: EMPA inhibited the AGEs-RAGE pathway, thereby alleviating diabetic renal tubular cholesterol accumulation.

P118

Lysosomal regulation of extracellular vesicle excretion during D-ribose induced NLRP3 inflflammasome activation in diabetic nephropathy

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The NLRP3 inflammasome is activated in the cytoplasm of cells and its products such as IL-1β are exported through a non-classical ER-Golgi pathway. Several mechanistically distinct models including exocytosis of secretory lysosomes, microvesicles (MVs) and extracellular vehicles (EVs) have been proposed for their release. In this study, we hypothesized that the NLRP3 inflammasome product, IL-1β in response to exogenously administrated and endogenously produced D-ribose stimulation is released via extracellular vesicles including EVs via a sphingolipid-mediated molecular mechanisms controlling lysosome and multivesicular body (MVB) interaction. First, we demonstrated that both endogenous and exogenous D-ribose induced NLRP3 inflammasome activation to produce IL-1β, which was released via EVs in podocytes. Then, we found that colocalization of marker MVB marker VPS16 with IL-1β within podocytes increased upon D-ribose stimulation, which was accompanied by decreased colocalization of lysosome marker Lamp-1 and VPS16, suggesting decrease in MVB inclusion of IL-1β due to reduced lysosome and MVB interaction. All these changes were mimicked and accelerated by lysosome ATPase inhibitor, bafilomycin. Moreover, ceramide in podocytes was found elevated upon D-ribose stimulation, and prior treatments of podocyte with acid sphingomyelinase (Asm) inhibitor, amitriptyline, acid ceramidase (AC) inducer, genistein, or AC CRISPR/cas9 activation plasmids were found to decrease D-ribose-induced ceramide accumulation, EVs release and IL-1β secretion due to reduced interactions of lysosome with MVBs. These results suggest that inflammasome-derived products such as IL-1β during D-ribose stimulation are released via EVs, in which lysosomal sphingolipid-mediated regulation of lysosome function plays an important role.

P119

Shenzhuo Formula improves microcirculation in the treatment of diabetic kidney disease by regulating lipid metabolism

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Objective: To investigate the therapeutic effects of the traditional Chinese medicine formula Shenzhuo formula(SZF) on renal injury and microcirculation disturbance in diabetic kidney disease (DKD) mice.
Methods: The first animal experiments used male C57BL / 6 mice to establish a diabetes model by high-fat plus streptozotocin intraperitoneal injection. They were divided into the model group (M1), SZF group (S1), irbesartan group (E1), control group (C1).
The second experiments used KKAy mice, a spontaneous DKD mouse model. They were divided into the model group (M2),the SZF group (S2) and the irbesartan group (E2). Male C57BL / 6 mice served as the control group (C2).
The SZF group and the Irbesartan group of the two batches of mice were gavaged with the corresponding drugs, and the model group, the control group, was gavaged with the corresponding volume of normal saline. Blood glucose was detected and urine was collected. Mice were intragastrically gavaged for 16 weeks, and blood was collected from the orbit of the first cohort. The second cohort of mice underwent percutaneous glomerular filtration rate monitoring, intestinal microcirculation detection, OCT fundus photography, microCT detection and OGTT detection.
Results: Compared with the model group, the SZF had no significant effect on the fasting blood glucose, 2-hour postprandial blood glucose of mice in both cohorts. Significantly lower urinary albumin to creatinine ratios as well as 24-hour urinary protein levels were achieved in both cohorts of mice($P < 0.05$). The results of electron microscopy showed that the thickening of glomerular basement membrane and the reduction of podocyte foot process number could be significantly reduced in S1 group ($P < 0.05$). S1 significantly decreased the levels of TG, TC ($P < 0.05$), increased LDL ($P < 0.05$), and increased HDL levels.
S2 group can improve the blood flow rate of intestinal microcirculation and increase the glomerular filtration rate. Decreases visceral fat volume and decreases visceral fat / subcutaneous fat ratio.
Conclusion: SZF can significantly protect renal function and alleviate renal pathological damage. Meanwhile SZF can also improve lipid metabolism and increase blood flow rate in mice. It is suggested that SZF can improve microcirculation and protect renal function by regulating lipid metabolism.

P120

Quantitive proteomic analysis based on iTRAG mass spectrum method reveals the effect of methylglyoxal and carnosine on proximal tubule epithelial cells

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Tubular injury triggered by hyperglycemia is an important pathological characteristic in diabetic nephropathy (DN). Accumulated advanced

glycation end products (AGEs) and their precursor methylglyoxal (MGO) contribute to development of DN. Carnosine has been shown to prevent the development of DN. In this study, we aim to explore the potential proteins and signaling pathways influenced by MGO and carnosine in tubule epithelial cells. HK-2 cells were treated with MGO, carnosine, or combination of both. Differentially expressed proteins (DEPs) between different groups were identified by isobaric tag for relative and absolute quantitation (iTRAQ)-based method. For the comparison MGO vs control, there were 29 DEPs and MGO influenced proteins associated with antioxidation and RNA methylation. For the comparison carnosine vs control, there were 10 DEPs in carnosine group associated with ubiquitin protein ligase activity and RNA metabolism. For the comparison MGO plus carnosine vs MGO, carnosine-induced DEPs given MGO are mainly related to RNA splicing and mRNA processing. The effect of MGO on OSTC expression was inversely changed by carnosine. Carnosine can influence RNA processing and metabolism-related proteins and change MGO's effect on HK-2 cells. Some influenced proteins (OSTC, PRDX5, NEDD4L, and GEMIN2) by MGO and/or carnosine were validated by Western blotting assays in HK-2 cells. This study helps to further identify the downstream proteins of carnosine as therapeutic targets of DN.

P121

Convolutional neural networks for the detection of diabetic nephropathy and membranous nephropathy from retinal fundus images

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Background: As the leading causes of end-stage renal disease worldwide, diabetic nephropathy and membranous nephropathy require early intervention for bettering management and outcomes. The kidney and eye share similar structural, developmental, physiological pathways. Patients with clinically visible retinal microvascular signs are more likely to have kidney disease, which suggests that the retinal fundus images, non-invasive and commonly used could provide screening information to complement existing methods.
Purpose: To develop a deep learning system for automated diabetic nephropathy and membranous nephropathy using retinal fundus images from patients who underwent retinal biopsy.
Methods: VGG16, VGG19, ResNet50 and Inception V3 neural networks were used to develop the system based on 272 images (144 subjects) collected from Chinese PLA General Hospital between June 2018 and February 2020. Meanwhile, laboratory data (blood uric acid, serum albumin, serum creatinine, blood urea, nitrogen, eGFR, and blood glucose) from 61 patients who had undergone kidney biopsy were collected for the assessment of renal function. The area under the receiver operating characteristic curve (AUC), precision, F1-Score, recall, sensitivity and specificity were used to assess the performance of detecting DN and MN.
Results: All convolutional neural networks we established for nephropathy detection achieved AUCs of 0.91–1.00. Among them, VGG16, the network with the best performance, reached AUCs of 0.97-1.00, with sensitivities of 83–100% and specificities of 95–100%.
Conclusion: VGG16 has shown good performance in estimating nephropathy using fundus images, which provides the feasibility of using fundus photography as a risk prediction or opportunistic screening tool for diabetic nephropathy and membranous nephropathy, which may compensate for the limitations of applying renal biopsy for diagnosis.Fully automated neural network algorithms were used to identify fundus photographs with a risk of DN and MN. In particular, the image preprocessing and data enhancement sets we created improved the accuracy of the network to a great extent. Our companion diagnostic system achieves early detection of these optic neuropathies, alleviating the lack of medical resources and providing interpretability for neural networks.

Angiognesis

P123

CD44 impairs vascular basement membrane integrity in pathological angiogenesis

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Background: AGEs accumulate in a variety of diseases and have been shown to be associated with pathological angiogenesis. The continuous and intact basement membrane contributes to the normal physiological function of blood vessels. Here we explored the mechanism of AGEs-induced pathological angiogenesis in terms of vascular basement membrane integrity.
Methods and results: This study found that AGEs can promote angiogenesis in both in vivo mouse retina and in vitro HUVECs, but the new vascular basement membrane has a rough structure and uneven thickness. In the mouse model, AGEs did not affect the retinal tissue protein level of Collagen-IV, a component of vascular basement membrane, but the serum level of Collagen-IV increased significantly in mice treated with AGEs for 6 m, indicating that the morphological changes of the vascular basement membrane caused by AGEs were associated with abnormal assembly of Collagen-IV. Moesin, a linker protein of membrane molecules and cytoskeleton, was phosphorylated after AGE treatment, resulting in abnormal morphology of vascular basement membrane. As an important molecule to maintain the stability of basement membrane, CD44 was up-regulated after AGE treatment in endothelial cells, and accumulated on the cell membrane. At the same time, in cultured endothelial cells, AGEs promoted the translocation of β-catenin into the nucleus and combined with TCF4. The inhibition of their binding resulted in the decrease of CD44 expression, indicating that AGEs increased the expression of CD44 through the β-catenin/TCF4 pathway. In the mouse model treated with AGEs, CD44 co-localized with phosphorylated moesin, implying that AGEs may cause uneven distribution of vascular basement membrane and its structural changes by mediating the clustering of phosphorylated moesin and CD44.
Conclusion: Our study demonstrated that AGEs increase the expression of CD44 in endothelial cells through the β-catenin/TCF4 pathway, and the clustering of CD44 and phosphorylated moesin leads to abnormal assembly of Collagen-IV and mediates the structural changes in the basement membrane of neovessels. (Supported by NSFC.81870210 and Guangdong Basic and Applied Research Foundation 2023A1515010094)

P124

Angiogenic pattern and influencing hemodynamic factors in the developing vitelline vascular network: a computational study

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Background: In the developing vascular networks, the pattern of morphological and topological changes during angiogenesis, as well as the hemodynamic factors influencing this pattern, have rarely been studied. Vitelline membrane of chicken embryo is an established model for studying angiogenesis. We employed the vitelline vascular network to explore the morphological and topological angiogenic pattern by a deep learning-based computer vision approach, and to explore how hemodynamic factors affect the angiogenic pattern by computational hemodynamic analysis.
Methods: Fertilized eggs were incubated for 3 days and opened for intravital microscopy to obtain images of the whole vascular network

at five developmental stages, including 3 days post fertilization (3dpf), 3 days and 6 hours post fertilization (3d6hpf), 3d12hpf, 3d18hpf, and 4dpf. For the analysis of morphological and topological pattern, a convolutional neural network (CNN) was applied to classify the developmental stage of the vascular networks based on the local images of the vasculature. For the hemodynamic analysis, sub-areas of the vascular networks at the same region in the five stages were extracted for reconstruction, with 476, 469, 550, 799, and 788 vessel segments in each sub-area, respectively. On one hand, a computational model following Poiseuille's law was developed for the steady-state hemodynamic simulation. Steady-state hemodynamic parameters were computed. On the other hand, a zero-dimensional dynamic model was developed to simulate the pulsatile properties of the hemodynamic parameters. A relative pulse slope index (RPSI) was calculated as the maximum acceleration rate of the pulsatile profile normalized to the mean value for the pulsatile blood pressure to evaluate the degree of hemodynamic pulsatility.

Results: The proportions of regions predicted as 4dpf in the five stages are 21.65%, 68.87%, 92.68%, 99.10%, and 99.30% respectively, indicating a strong morphological and topological change from 3dpf to 3d12hpf. Correspondingly, the hemodynamic analysis shows significant elevation in both steady-state and pulsatile hemodynamic parameters during this episode. The steady-state simulation obtained an increase in the mean shear stress from 3dpf to 3d12hpf (0.39 Pa, 0.66 Pa, and 0.75 Pa for 3dpf, 3d6hpf, and 3d12hpf, respectively, $p<0.001$ between 3dpf and 3d6hpf), but a decrease in 3d18hpf (0.63 Pa) and 4dpf (0.53 Pa). The RPSI of pressure ($RPSI_P$) was strongly increased from 3dpf to 3d12hpf (3dpf: 12.349 s^{-1}, 3d6hpf: 14.542 s^{-1}, 3d12hpf: 21.506 s^{-1}), and remained at the high level for the 3d18hpf (24.079 s^{-1}) and 4dpf (22.937 s^{-1}) stages.

Conclusion: These results suggest that embryonic development of the vascular system is strong from 3dpf to 3d12hpf and is influenced by both steady-state and pulsatile hemodynamic properties.

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Ferroptosis

P125

M6A Demethylase FTO Affecting the Biological Behavior of Papillary Thyroid Carcinoma by Regulating Ferroptosis

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Background: Papillary thyroid carcinoma (PTC) is the most common type of thyroid tumor. Although the vast majority of PTC can be cured by surgery and 131I therapy, a small number of cases can develop into highly invasive thyroid cancer. Targeted therapy may be a new opportunity to solve this problem. Therefore, exploring new therapeutic targets for thyroid cancer is still the focus of research in this field. Fat mass and obesity-associated (FTO) is the first m6A-related protein discovered. As an m6A demethylase, it can demethylate the m6A-modified bases on RNA. However, our current understanding of the exact mechanism of the demethylase FTO and m6A methylation regulation in PTC is still insufficient.

Methods:

1. Collect tumor samples from 86 patients with thyroid papillary carcinoma who underwent standard thyroidectomy in our hospital and their control normal thyroid tissue samples. Analyze the role of FTO in thyroid papillary carcinoma by analyzing tissue samples and combining with TCGA database
2. To evaluate the effect of FTO on the tumor biology of thyroid papillary carcinoma through in vivo and in vitro experiments
3. Combining RNA-Seq and MeRIP-Seq sequencing analysis, identify downstream target genes that FTO regulates thyroid papillary carcinoma through m6A methylation, and validate them
4. Through TCGA database analysis, it was predicted that FTO regulates the m6A reading protein gene of SLC7A11 through m6A methylation, and it was verified experimentally
5. Analyze the relationship between FTO and SLC7A11 in tissue samples, and evaluate the impact of SLC7A11 on the tumor biology of thyroid papillary carcinoma through in vitro experiments
6. Through transmission electron microscopy and Western Blot experiments, the levels of MDA, GSH/GSSG ratio, GPX, and FE2+were monitored to explore the specific mechanism of FTO affecting the biological behavior of thyroid papillary carcinoma cells through SLC7A11
7. Rescue test to verify whether the inhibitory effect of FTO can be reversed by knocking down SLC7A11

Results:

1. Compared with normal thyroid tissue, the expression level of FTO in tumor tissue samples from patients with thyroid papillary carcinoma is significantly reduced
2. Through in vivo/in vitro experiments, FTO can inhibit the proliferation, migration, and invasion of PTC tumor cells, and induce tumor cell apoptosis, which has an inhibitory effect on the growth of PTC tumors
3. Through the combined sequencing of RNA-Seq and MeRIP-Seq, the gene SLC7A11 may be a downstream target gene of thyroid papilloma regulated by FTO through methylation of m6A, which has been confirmed experimentally
4. FTO modifies the overall m6A level of PTC cells through m6A modification, thereby regulating the tumor biological behavior of PTC
5. Through bioinformatics analysis, RIP experiments, and actinomycin D experiments, it was confirmed that FTO inhibits the stability and expression level of SLC7A11 mRNA by recruiting reading protein YTHDF3 and modifying m6A
6. There is a negative correlation between SLC7A11 and FTO in tumor samples. Through experiments, we found that SLC7A11 has a positive effect on PTC and has the ability to promote proliferation, migration, and invasion
7. Through transmission electron microscopy, Western Blot experiments, and monitoring MDA levels, GSH/GSSG ratios, GPX, and FE2+levels, we found that FTO can promote iron death in papillary thyroid cancer cells by downregulating SLC7A11, thereby inhibiting the biological behavior of papillary thyroid cancer cells
8. Through the rescue function rescue test, we found that SLC7A11 can reverse the decreased cell proliferation, migration, and invasion caused by FTO knockdown

Conclusion: The m6A demethylase FTO recruits the reading protein YTHDF3 to jointly participate in the m6A methylation modification of SLC7A11 to affect its mRNA stability, thereby inducing ferroptosis in PTC and inhibiting the progression of papillary thyroid carcinoma.

P126

Mechanisms of Nrf2 Regulation of Iron Overload and Ferroptosis in Subarachnoid Hemorrhage

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Introduction: Ferroptosis is a mode of cell death that is distinct from autophagy and apoptosis and is characterized by reduced glutathione peroxidase 4 activity(GPx4), increased lipid peroxidation, and mitochondrial dysfunction. Nuclear factor E2-related factors(Nrf2) have been shown to have anti-inflammatory effects and their ability to regulate transcription of multiple factors, and we found that it can mitigate early brain injury(EBI) by regulating GPx4 to inhibit the occurrence of iron death in subarachnoid hemorrhage (SAH), providing a viable target for the treatment of subarachnoid hemorrhage later.

Methods: Sixty adult male C57BL/6 normal rats and 60 Nrf2 knockout mice were used to construct an in vivo model by intravascular perforation, and neurons were extracted and cultured with hemoglobin cells to construct an in vitro model to illustrate the regulatory role of Nrf2 on i Ferroptosis in SAH.

RESULTS

Western blot analysis showed that after Nrf2 knockdown, GPx4 expression further decreased, ROS expression increased, and iron death persisted. The iron staining suggested that the iron overload in neuronal cells was significantly alleviated by the continuous application

of low dose of Nrf2 activator tert-butylhydroquinone after the mice were constructed as a model of SAH, and the ROS and MDA contents in the brain tissue of mice were significantly decreased at 24h after SAH, while the protein expression and activity of GPx4 were significantly increased; in the in vitro experiments, tBHQ treated neurons of SAH model at 6 h after In in vitro experiments, the transcription of genes related to resistance to ferroptosis was increased, while the transcription of genes promoting ferroptosis was decreased.
Conclusion: Nrf2, as an endogenous regulator, can play a role in brain protection by regulating iron overload and iron death; and the mechanism may be that Nrf2 functions by regulating the processes of iron metabolism (iron uptake, excretion, storage, and recycling) and the GPx4-GSH-NADPH system (expression and activation of GPx4, GSH synthesis-related factors, and NADPH transcriptional expression).
Keywords: subarachnoid hemorrhage ; early brain injury ; ferroptosis ; Nrf2

P127

SCD-1 down-regulation mediates hepatocyte ferroptosis and leads to septic liver injury

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Background: Ferroptosis is a type of programmed cell death associated with organ failure in sepsis. Membrane lipid peroxidation is an important feature of ferroptosis, and Stearoyl CoA desaturase-1 (SCD-1) is a key rate-limiting enzyme for the synthesis of monounsaturated fatty acids (MUFA), which may be involved in the development of ferroptosis. This study aims to elucidate the role of SCD-1 in septic liver injury by interfering the expression of SCD-1 and detecting ferroptosis in hepatocytes.
Methods and Results: There were significant liver tissue damage, hepatic dysfunction, iron overload, and hepatocyte ferroptosis in CLP-induced septic mice. The results of transcriptome datasets analysis from liver tissues of septic mice revealed that the lipid metabolism pathway was significantly inhibited, and the expression of genes, including SCD-1, involved in fatty acid synthesis and desaturation were obviously downregulated. By extracting liver tissues from CLP sepsis mice and stimulating primary mouse hepatocytes with LPS, we confirmed that the expression of SCD-1 was downregulated in both *in vivo* and *in vitro* septic models. By knocking down SCD-1 in hepatic cell line AML12 and primary mouse hepatocytes with siRNA, we proved that low expression of SCD-1 led to the suppression of glutathione peroxidase 4 (GPX4), a key regulator of ferroptosis, as well as the increase of ferroptosis in hepatocytes. Overexpression of SCD-1 and exogenous administration of MUFA reduced lipid peroxidation and ferroptosis in hepatocytes, suggesting that SCD-1 alleviates liver injury by regulating lipid metabolism and ferroptosis.
Conclusion: The expression of SCD-1 in septic hepatocytes is decreased, resulting in the blockage of endogenous MUFA synthesis, which leads to the intensification of lipid peroxidation in hepatocyte membrane, thus inducing hepatocyte ferroptosis and liver injury in sepsis. (Supported by NSFC 82172139)

Vascular Permeability

P128

Spinning disk confocal imaging of immune induced microvascular hyperpermeability

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Objective: Anaphylaxis is a potentially life-threatening hypersensitivity reaction that occurs rapidly after allergen irritation to sensitized individuals, which typically manifests with severe pathophysiological symptoms associated with microcirculation dysfunction. However, the pathophysiological dynamics of microcirculation during anaphylaxis remain unclear.
Approach: Six-week-old female mice were sensitized subcutaneously on day 0 with bovine serum albumin in complete Freund adjuvant and boosted on day 7 and day 14 with 50 μg BSA in incomplete Freund adjuvant. One week after the last sensitization, mice were intravenously injected with 15 μg BSA to elicit systemic anaphylaxis. The spinning disk confocal imaging system was used to detect microvascular structure and permeability, and blood cell dynamics actions during immune complex-induced acute anaphylaxis. Real-time microcirculatory perfusion of the hindlimb was monitored by laser-Doppler perfusion imaging system and the degree of microvascular permeability in different tissues was evaluated after i.v. injection of Evans blue.
Results: Albumin leakage was the most striking change during immune complex-induced anaphylaxis, along with increased leukocyte adhesion to venular wall, decreased blood flow velocity, and decreased microvascular diameter. Five minutes after BSA challenge, we observed obvious microvascular leakage, and this phenomenon aggravated over time. Microcirculatory perfusion of the hindlimb continued to decrease upon BSA challenge. About 50% of blood flow was lost within 10 minutes, likely due to increased vascular permeability. Eighty minutes after BSA challenge, microcirculatory perfusion decreased to ~20% of the baseline. During anaphylaxis, Evans blue leakage was systemic, particularly in lung, heart, liver, and intestine.
Conclusions: Immune complex induced acute and systemic microvascular hyperpermeability, leading to severe fluid extravasation and tissue hypoperfusion. Microvascular hyperpermeability represents a major pathological process of anaphylaxis.
Keywords: anaphylaxis, microvascular leakage, immune complex

Vascular Barrier

P129

Mechanism Research of Electroacupuncture for Neuropathic Pain after Sciatic Nerve Injury Based on Blood Nerve / Spinal Cord Barrier

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Objective: The injury of blood nerve barrier (BNB) and blood spinal cord barrier (BSCB) is closely related to neuropathic pain (NP). This study intends to establish a NP and detect the expression of tight junction (TJ) in BNB/ BSCB after EA to reveal the mechanism of EA relieving NP.
Methods: Fifty mice were randomized into 5 groups and each group used different intervention methods. The analgesia effect of EA was evaluated by measuring the paw mechanical withdraw threshold (PMWT), paw withdrawal thermal latency (PWTL) and activation of astrocytes and microglia in spinal cord. The effect of EA on BNB/ BSCB by detecting the expression of tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (ILmodel -6) and TJ.
Results:
1. Compared with the model group, EA group's PMWT and PWTL rose significantly ($P<0.05$)
2. The abnormal activation of astrocytes and microglia in spinal cord was recorded in model group but was inhibited in EA group ($P<0.05$)
3. The expression levels of TNF-α, IL-1β and IL-6 decreased in EA group ($P<0.05$)
4. The expression level of TJ (including Occludin, ZO-1, Claudin3) in BNB/ BSCB increased after EA ($P<0.05$)
5. The results of Evans Blue shows that the vascular leakage of BNB/

BSCB decreased in EA group (P<0.05)
Conclusion: EA can relieve NP by up-regulating TJ expression and alleviating the damage of BNB/ BSCB. And the mechanism may be that preventing inflammatory factors from entering nervous system can inhibit the abnormal activation of astrocytes and microglia in spinal cord.

P130

Paternal bisphenol A exposure induces fetal placental vascular dysplasia and fetal growth restriction in offspring

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Background: Bisphenol-A (BPA) is a common environmental toxicant that is known to be associated with fetal growth restriction (FGR). However, the mechanisms of how BPA induce FGR is poorly characterized. It has not been reported whether the occurrence of FGR is related to paternal exposure to BPA. Genomic imprinting is a process of epigenetic modification on the genome that causes silencing of one allele according to its parental origin, resulting in monoallelic expression, without changing the DNA sequence. Therefore, exogenous exposure has a great influence on the expression of imprinted genes. Identifying the genetic input for fetal growth will help to understand serious complications of pregnancy such as FGR. Imprinted genes are important in mammalian fetal growth and development. Evidence has emerged showing that genes that are paternally expressed promote fetal growth, whereas maternally expressed genes suppress growth. DLK1 is the product of an imprinted gene that is predominantly expressed from the paternally inherited chromosome during fetal development. Several studies have indicated that DLK1 expression levels are related to fetal growth and development. VEGFα is a key gene for vascular development. However, it is completely unknown whether BPA exposure during paternal preparation will affect DLK1 expression and thus interfere with placental vascular development.
Aim and method: To explore whether male BPA exposure affects placenta vascular and fetal development by affecting sperm quality and the expression of sperm imprinted genes. The findings could provide scientific guidance for men's lifestyle and eating habits before pregnancy. To accomplish this purpose, the proteomic analysis of placenta tissues of FGR fetuses and normal weight fetuses was performed to screen the significant differences in proteins between the two groups. The 5-week-old male mice were exposed to 50mg/kg/d BPA or corn oil alone for 4 weeks, and after mating with normal female mice, then offspring embryos and placentas were obtained. The testicular tissue and epididymal tail sperm of male mice were taken at the same time. Total RNA was extracted from testicular tissue of the two groups for RNA seq analysis for differentially expressed genes. Screening for co-annotated differential expression factors in FGR placental proteomics and in sperm RNA seq in BPA exposed groups. Sperm quality, weight of placenta and fetal mice, expression of differential proteins in sperm and placenta tissues were detected in two groups of mice.
Result: Proteomic results indicated that the expression of DLK1 in the placenta tissue of FGR fetuses was significantly decreased compared with that of normal weight fetuses (P<0.05). RNA seq results suggested that the expression of DLK1 in the testis of bisphenol A exposed mice was significantly decreased compared with that of the unexposed group (P<0.05). After exposure to BPA, the quality of the sperm and the expression of DLK1 in sperm decreased significantly. In addition, when male mice in both the BPA exposed group and the unexposed group mated with normal female mice, both the placenta and fetal body weight of the offspring in the BPA exposed group were lower than those in the unexposed group (P<0.05). Compared with unexposed group, the expression of DLK1 and VEGFFα decreased in the placental tissue of mice exposed to BPA.
Conclusion: Paternal BPA exposure will affect the expression of imprinted gene DLK1 and reduce sperm quality, which will be transmitted to offspring, resulting in lower placental DLK1 expression, abnormal placental vascular development, and eventually fetal growth restriction. To ensure the normal development of placenta and fetus, male lifestyle and eating habits should be paid enough attention.
Keywords: BPA; Imprinted gene; Semen quality; placental vascular dysplasia; Fetal growth restriction

Lymphatic Vesse

P131

Lymphatic drainage system of the brain: A novel target for intervention of neurological diseases

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The belief that the vertebrate brain functions normally without classical lymphatic drainage vessels has been held for many decades. On the contrary, new findings show that functional lymphatic drainage does exist in the brain. The brain lymphatic drainage system is composed of basement membrane-based perivascular pathway, a brain-wide glymphatic pathway, and cerebrospinal fluid (CSF) drainage routes including sinus-associated meningeal lymphatic vessels and olfactory/cervical lymphatic routes. The brain lymphatic systems function physiological as a route of drainage for interstitial fluid (ISF) from brain parenchyma to nearby lymph nodes. Brain lymphatic drainage helps maintain water and ion balance of the ISF, waste clearance, and reabsorption of macromolecular solutes. A second physiological function includes communication with the immune system modulating immune surveillance and responses of the brain. These physiological functions are influenced by aging, genetic phenotypes, sleep-wake cycle, and body posture. The impairment and dysfunction of the brain lymphatic system has crucial roles in age-related changes of brain function and the pathogenesis of neurovascular, neurodegenerative, and neuroinflammatory diseases, as well as brain injury and tumors. In this review, we summarize the key component elements (regions, cells, and water transporters) of the brain lymphatic system and their regulators as potential therapeutic targets in the treatment of neurologic diseases and their resulting complications. Finally, we highlight the clinical importance of ependymal route-based targeted gene therapy and intranasal drug administration in the brain by taking advantage of the unique role played by brain lymphatic pathways in the regulation of CSF flow and ISF/CSF exchange.
Keywords: Brain lymphatic drainage; Cerebrospinal fluid; Glymphatic pathway; Interstitial fluid; Meningeal lymphatic vessel; Neurological disease; Olfactory/cervical lymphatic route; Perivascular pathway.

P132

Role of intestinal flora remodeling in stellate ganglion block reducing PHSML-mediated lung injury

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Hemorrhagic shock-induced acute lung injury (ALI) is one of the main causes of death in severe patients, which is related to post-hemorrhagic

shock mesenteric lymph (PHSML) return. Studies have shown that stellate ganglion block (SGB) reduced intestinal barrier dysfunction and structural damage by inhibiting autophagy, thereby reducing PHSML return-induced ALI. This study used the hemorrhagic shock model in conscious rats to clarify that SGB improve intestinal smooth muscle contractions after hemorrhagic shock by inhibiting autophagy. The effects of SGB on intestinal microflora and related metabolites in hemorrhagic shock rats as well as intestinal microflora metabolites in PHSML were detected, and the effect of SGB on intestinal microflora disorder in hemorrhagic shock rats was determined. While the effect of SGB in alleviating ALI induced by intestinal flora related metabolites via mesenteric lymphatic pathway was further investigated.

The results showed that hemorrhagic shock significantly decreased the intestinal contractility *in vitro* and contractile protein p-MLC20 expression, and increased the autophagy proteins LC3-II/I and Beclin-1 expressions. SGB and autophagy inhibitor 3-methyladenine (3-MA) significantly increased intestinal contractility and p-MLC20 expression and decreased LC3-II/I and Beclin-1 expressions in rats following hemorrhagic shock. rapamycin (RAPA), an autophagy agonist, reversed the beneficial effects of SGB on the above indices of hemorrhagic shock.

Subsequently, hemorrhagic shock decreased the intestinal flora diversity, enhanced the relative abundance of gram-positive bacteria *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, and decreased the relative abundance of CF231, *Phascolarctobacterium*, SMB53, p-75-a5 and *Dolella*, which were reversed by SGB. The result of metabolomics showed that SGB increased the levels of creatinine, deoxyribose, 4-aminophenol, 2-methylserine, epigenestone, trans-trans-acacia alcohol, decreased the levels of tetrandrine, carbamoylazide, N-acetyllactamine, 4-guanidine, butyric acid in the intestinal contents of rats with hemorrhagic shock, while reduced prostaglandin G2, deoxyuracil, nucleoside, 9-OxoODE, m-hydroxyphenylacetic acid, o-phosphoethanolamine, l-leucine content in mesenteric lymph.

Based on the three combined omics analysis, D-glucuronic acid (DGA) was a metabolite whose changes in PHSML and intestinal contents were consistent with those of intestinal flora metabolites. At the cell level, DGA alone did not significantly affect the proliferative activity and autophagy levels of pulmonary microvascular endothelial cells (PMVECs), PHSML significantly decreased the proliferative activity of PMVECs and increased the expression of autophagy protein LC3-II/I and Beclin-1. Compared with PHSML, the proliferative activity of PMVECs was increased after PHSML-SGB treatment, and the expression of LC3-II/I and Beclin-1 were decreased. More importantly, DGA treatment significantly inhibited the effect of PHSML-SGB on PMVECs.

These results indicate that SGB improves intestinal contractile by inhibiting intestinal smooth muscle cell autophagy, reversing the changes of intestinal flora and related metabolites, especially the decrease of DGA, finally alleviating ALI by inhibiting the autophagy level of PMVECs mediated by PHSML. The results suggest that intestinal flora imbalance plays an important role in SGB reducing PHSML-mediated lung injury.

P133

Role of mitophagy in estrogen-induced improvement of lymphatic contractility in hemorrhagic shock

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The lymphatic microcirculation dysfunction and induced-lymph transportation capability decline cause tissue edema and aggravate tissue and organ hypoxia in severe shock, which is related to the mitochondrial injury. 17β-estradiol (E2) improves mesenteric lymphatic microcirculation and lymphatic contraction in rats with hemorrhagic shock. The relationship between mitophagy and mitochondrial function and whether E2 can improve the function of lymphatic vessels in hemorrhagic shock by regulating mitophagy, it remains unclear. Therefore, the current study observed the role of mitophagy in E2-induced improvement of lymphatic contractility in hemorrhagic shock. Firstly, we observed whether H/R induces mitophagy of LSMCs, and found that mitophagy occurred in LSMCs after H/R and E2 administration reduced mitophagy of LSMCs. Basing this result, we used the hemorrhagic shock model in conscious rats and investigated the role of mitophagy in E2 improving mesenteric lymphatic contractile, and found that hemorrhagic shock significantly decreased lymphatic contractile, which was improved by E2 or 3-MA, an autophagy inhibitor. RAPA, an autophagy agonist inhibited the beneficial effect of E2. Furthermore, we observed the role of mitophagy using LSMCs. The results showed that H/R treatment significantly decreased LSMC contraction and increased the formation of mitochondrial autophagosomes and expression of mitophagy-related proteins. The negative effects of H/R were significantly reversed by E2 and 3-MA treatments, while RAPA treatments offset some beneficial effects of E2. These results suggest that E2 improves the mesenteric lymphatic contraction by inhibiting mitophagy following hemorrhagic shock.

P134

Stellate ganglion blockage alleviates exosomes payload in post-hemorrhagic shock mesenteric lymph-mediated acute lung injury through autophagy inhibition

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Post-hemorrhagic shock mesenteric lymph (PHSML) return plays an important role in hemorrhagic shock inducing acute lung injury (ALI), and stellate ganglion block (SGB) alleviates hemorrhagic shock-induced intestinal barrier injury. The aim of current study is to investigate the role of autophagy and exosomes payload in PHSML in SGB alleviating PHSML-induced ALI. To achieve it, a conscious rat model of hemorrhagic shock was established. Lung morphology, wet-dry ratio (W/D) and the expressions of LC3 II/I and Beclin 1 of lung were detected following hemorrhage shock. The effects of SGB, autophagy inhibition (3-MA), autophagy agonism (RAPA) and PHSML intravenous infusion on above indices also were investigated. Furthermore, the effects of exosomes on normal rats also were detected. Moreover, after rat pulmonary microvascular endothelial cells (PMVECs) isolating, various mesenteric lymph was co-cultured with PMVECs for the detection of cell viability and the expressions of LC3 II/I and Beclin 1. The Results showed that the hemorrhagic shock induced lung morphology injury and increased the wet-dry ratio (W/D) and LC3 II/I and Beclin 1 expressions, which were abolished by SGB treatment and 3-MA administration. RAPA and PHSML administrations increased the lung morphology injury, W/D and the LC3 II/I and Beclin 1 expressions in rats after hemorrhage treated with SGB. Furthermore, PHSML decreased the cell viability and increased the expressions of LC3 II/I and Beclin 1 in PMVECs. PHSML treated with SGB alleviated the cell injury and downregulated the increased LC3 II/I and Beclin 1. Exosomes in PHSML caused the lung morphology injury and increased W/D of rats and decreased cell viability of PMVECs. Exosomes in PHSML treated with SGB reversed the injury. Collectively, the inhibition of excessive autophagy is involved in the mechanism by which SGB alleviated PHSML-mediated ALI. Moreover, exosomes in PHSML maybe the important components of SGB in alleviating ALI induced by hemorrhagic shock.

Hepatic Microcirculation

P135

Targeting PTP1B to investigate the amelioration of hepatic lipid accumulation and microcirculation dysfunction in mice

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Hepatic lipid accumulation, the first stage of Non-alcoholic fatty liver disease (NAFLD), is considered as the metabolic syndrome manifested in liver, and usually accompanied with microcirculation dysfunction and insulin resistance. Protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin/leptin signal pathways, catalyzes the dephosphorylation of the insulin receptor and subsequently reduces insulin sensitivity. It also mediates microcirculation dysfunction by impairing endothelial cell angiogenic responses through endoplasmic reticulum (ER) stress. As a small molecular probe, compound CX08005, which is a strongly competitive inhibitor of PTP1B with IC_{50} of 7.81×10^{-7} M and directly enhances insulin action in vitro and in vivo, was used to investigate the amelioration of hepatic lipid accumulation and microcirculation dysfunction. As the results, PTP1B inhibitor significantly reduced the hepatic triglyceride content and echo-intensity attenuation coefficient in the liver B-ultrasound analysis in KKAy mice; decreased plasma triglyceride and/or total cholesterol levels, respectively, in both KKAy and DIO mice. Moreover, after the PTP1B inhibitor administration, the hepatic microcirculation dysfunction was ameliorated by increased RBCs velocity and shear rate of the blood flow in central veins and in the interlobular veins, enhanced rate of perfused hepatic sinusoids in central vein area, as well as decreased the adhered leukocytes both in the center veins and in the hepatic sinusoids area, respectively, in DIO mice. Additionally, the phosphorylation of IRβ/Akt in insulin pathway and PERK, eIF2α in ER stress pathway were restored, respectively, under the administration of the probe in HepG2 cells induced by sodium oleate, but the expression of factors associated with lipid De novo synthesis pathway, like SREBP1c, ACC, and FAS, were not significant change, respectively, compared to those without the stimulation of PTP1B inhibitor.

In conclusion, with PTP1B inhibition, the hepatic lipid accumulation associated with NAFLD was reduced in mice, as well as the microcirculation dysfunction was also improved. Besides the enhance of insulin sensitization of PTP1B inhibitor, the main mechanism maybe involved activating the PERK-eIF2α pathway in ER adaptive stress. It is supposed that PTP1B may represent a promising target for the treatment of NAFLD, as well as haptic microcirculation dysfunction.

Keywords: PTP1B; small molecular probe; endoplasmic reticulum stress; hepatic lipid accumulation; microcirculation dysfunction

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P136

Mechanism of Wnt/β-catenin signaling pathway promoting immune evasion in hepatocellular carcinoma

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Background & Aims: Immune checkpoint blockade therapy has shown therapeutic efficacy in various cancer patients. However, only a minority of hepatocellular carcinoma patients respond to PD-1/PD-L1 blockade therapy and immune escape *mechanisms remain* unclear. We investigated the mechanisms of liver tumor resistance to PD-1/PD-L1 blockade therapy.

Methods: We tested the effect of the combination treatment with anti-PD-1 and ICG-001 (inhibitor of the WNT/*β*-catenin signaling pathway) in C57/BL6 mice with subcutaneous tumors grown from mouse hepatocellular carcinoma (HCC) cell lines Hepa1-6 and H22. Tumors were collected and analyzed by immunohistochemistry, immunofluorescence, quantitative RT-PCR and western blot. We used ICG-001 to treat HepG2 and SNU449 human HCC cell lines and analyzed cells by quantitative RT-PCR, western blot, immunoprecipitation and dual luciferase reporter gene assay. We co-cultured cell supernatants or chemokines with Dendritic cells (DCs) and analyzed cells by dendritic cell migration assay and immunofluorescence. We knocked down or overexpressed IKZF1 in HepG2 and SNU449 and analyzed cells by quantitative RT-PCR and western blot. We analyzed 90 HCC patient samples in a tissue microarray by immunohistochemistry.

Results: The combination of anti-PD-1 with ICG-001 suppresses tumor growth, increases the infiltration of T cells and DCs. The increase in CCL5 via the inhibition of the WNT/*β*-catenin signaling pathway recruits DCs through CCR5 receptor, which consequently increases T cell infiltration into the tumor microenvironment (TME), resulting in enhanced antitumor immune responses. Tissue microarray analysis of HCC patient samples showed a positive correlation between levels of CCL5 and CD8.

Conclusions: Our findings indicate that the combination of anti-PD-1 with ICG-001 has far stronger antitumor efficacy. The combination of anti-PD-1 with WNT/*β*-catenin signaling pathway inhibitor may be useful for the treatment of hepatocellular carcinoma patients.

Keywords: *β*-catenin, CCL5, dendritic cells, immune evasion, hepatocellular carcinoma.

P137

Nitrative NCOA4 promotes liver injury induced by homocysteine

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Homocysteine(Hcy) is an intermediate product of methionine metabolism by hepatocytes. It is known that homocysteine is a multiple organ damage factor, including liver, kidney and nerve damage. When hepatocyte metabolism is blocked, Hcy accumulates, which increases plasma Hcy concentration through liver microcirculation, further aggravating liver injury. Therefore, exploring the effect of Hcy on liver injury will be an important solution to reduce the damage to other organs. We constructed high-methionine-fed model mice with hyperhomocysteinemia(HHcy), and performed quantitative TMT protein-omics analysis of their liver tissues, suggesting abnormal iron metabolism in the liver of HHcy mice. Experiments using perls staining and a tissue iron content kit confirmed that Hcy induced liver injury through iron overload in hepatocytes. Further studies revealed that the reduced activity of ferritinophagy receptor NCOA4, is an important cause of iron overload in hepatocytes. Recently report that the functional activity of NCOA4 is regulated by its posttranslational modification. Our group found that nitrative modification of NCOA4 can affect its ability to interact with ferritin. The application of peroxynitrite scavenger can reduce the level of nitrification stress and reduce the degree of liver injury. Our present work provides a new preventive strategy for rescuing the liver injury caused by Hcy metabolic abnormalities in order to maintain a healthy hepatic microcirculation.

P138

Clinical and genetic characteristics of Chinese patients with hepatic hereditary hemorrhagic telangiectasia

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Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder that can involve the liver diffusely

in the form of vascular malformations associated with progressive biliary disease, high-output cardiac failure and portal hypertension. Two genes in the transforming growth factor-beta (TGF-β) signaling pathway, ENG and ACVRL1, were discovered in up to 85% of HHT almost two decades ago. More recently, two additional genes in the same pathway, SMAD4 and GDF2, have been identified in a much smaller number of patients with a similar or overlapping phenotype to HHT. However, little is known about the clinical features or genetic background of Chinese patients with hepatic HHT (HHHT).

Subjects and Method: We have screened a total of 8 unselected Chinese patients with the tentative diagnosis of HHHT according to the Curac¸ao Criteria. One of two different molecular diagnostic approaches (Sanger Sequencing or Next Genetation Sequence) was chosen for a family proband based on the evaluation of targeted medical history, physical examination, and multi-generation family history. Whole exome sequencing (WES) was ready for patients with negative results. Positive results were re-evaluated by individual Sanger Sequencing.

Results: A clinically confirmed (4/8) or suspected (4/8) diagnosis of HHT was made in all patients and liver dynamic computed tomography (CT) scan performed allowed the diagnosis of hepatic arteriovenous malformations in each case. Abdominal pain (6/8) is the most common symptoms. Abdominal vascular murmurs was presented in each patient on auscultation. The typical clinical presentations related to liver involvement included high-output heart failure (5/8), portal hypertension (3/8), and biliary disease (5/8). We identified 3 different ACVRL1 mutations in 4 HHHT patients and their family members, two of which were novel. Yet, there were still 4 patients with compelling evidence of a hereditary telangiectasia disorder, but no identifiable mutation in a known gene even by WES. The genotype-phenotype correlation was consistent with a higher frequency of hepatic arteriovenous malformations in patients with ACVRL1 mutations in our collective.

Conclusion: Despite the small number of patients investigated, our findings have revealed the clinical phenotype and molecular genetic features of Chinese patients with hepatic HHT, which show significant phenotypic variability and genetic heterogeneity. Unrecognized factors may determine the clinical spectrum of hereditary hemorrhagic telangiectasia including the hepatic manifestations.

P139

Prognostic efficacy and prognostic factors of TACE combined with TKI and ICIs in the treatment of unresectable hepatocellular carcinoma: a retrospective study

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Hepatocellular carcinoma (HCC) remains a global challenge due to its high morbidity and mortality rates as well as poor response to treatment. Local combined systemic therapy is widely used in the treatment of unresectable hepatocellular cancer (uHCC). This retrospective study was to investigate the prognostic effect and prognostic factors of transcatheter arterial chemoembolization (TACE) plus tyrosine kinase inhibitors (TKI) with immune checkpoint inhibitors (ICIs) in the treatment of uHCC. A retrospective analysis of 171 patients with uHCC were performed in our hospital from April 27, 2015 to October 18, 2021. According to different treatment options, patients were divided into TACE group (n=45), TACE+TKI group (n=76) and TACE+TKI+ICIs group (n=50). In this study, we found that, the median overall survival (mOS) of TACE+TKI+ICIs group was significantly better than TACE+TKI group and TACE group [24.1 (95% CI 15.1-33.1) months vs 14.9 (95% CI 10.7-19.1) months vs 11.4 (95% CI 8.4-14.5) months, hazard ratio (HR) 0.62; 95% CI 0.47-0.81; P=0.002]. A visible difference in the median progression-free survival (mPFS) interval between the groups was discovered [10.6 (95% CI6.5-14.7) months in TACE+TKI+ICIs group vs. 6.7 (95% CI 5.5-7.9) months in the TACE+TKI group vs. 6 (95% CI 2.3-9.7) months in the TACE group (HR 0.66; 95% CI 0.53-0.83; P<0.001)]. The objective response rates (ORR) in the TACE group, TACE+TKI group, and TACE +TKI+ICIs group were 31.1%, 35.5%, and 42%, and the disease control rate (DCR) were 51.1%, 65.8%, and 80%. There were no adverse events (AEs) of arthralgia, diarrhea, rash, and pruritus in the TACE group. The incidence of grade 3 AEs (Hypertension) in the TACE+TKI+ICIs group was significantly higher than that in TACE+TKI and TACE groups (28% vs 17.1% vs 6.7%, P=0.024), and secondly, the morbidity of rash and pruritus in the TACE+TKI+ICIs group was apparently higher than that in the TACE+TKI group (P<0.05). Multivariate analysis showed that ECOG-PS 2 (HR=2.064, 95%CI 1.335-3.191, P=0.001), Hepatitis B virus (HR=2.539, 95%CI 1.291-4.993, P=0.007), AFP ≥ 400 ng/ml (HR= 1.72, 95%CI Frontiers in Oncology frontiersin.org 011.12-2.643, P=0.013), neutrophil-lymphocyte ratio (NLR) ≥ 2.195 (HR=1.669, 95% CI 1.073-2.597, P=0.023) were independent risk factors for OS in uHCC patients. So, TACE+TKI+ICIs therapy can prolong the OS and improve the prognosis of patients effectively, with a well-characterized safety profile.

P140

Mechanism of improvement of non-alcoholic fatty liver disease by silibinin in db/db mice

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Background and Aims: To investigate the effect of Silibinin capsules on non-alcoholic fatty liver disease (NAFLD)in *db/db* mice and the underlying mechanism of its regulation and maintenance of glucose and lipid metabolism homeostasis by possible targeting of the FGF21-Adiponectin axis.

Methods: In the *in vivo* experiment, 8-week-old male diabetic *db/db* mice and normoglycemic *db/m* mice were included. The total metabolism, glucose metabolism, hepatic lipid metabolism, energy metabolism, inflammation and oxidative stress were monitored. In the *in vitro* experiment, the mouse hepatic cell line AML12 was selected and lipid droplets in hepatocytes were observed by oil red O staining. Mitochondrial oxygen consumption and electron leakage during oxidative phosphorylation were measured by Oxygraph-2k.

Results: The weight gain and increase in total and visceral adipose tissue volume in *db/db* mice were inhibited following treatment with silibinin. Silibinin improved central obesity phenotype, activated the expression of phosphorylated AKT, improved glucose tolerance and insulin sensitivity, up-regulated the expression of FAs β-oxidation-related genes, down-regulated the expression of lipogenesis-related genes to attenuate hepatic lipid accumulation,improved the activity of mitochondrial complex II, reversed the decrease in ATP/ADP and ATP/AMP ratios, alleviated the inflammation and oxidative stress, improved FGF21 sensitivity, up-regulated the expression of adiponectin, activated p-AMPK and inhibited the mTOR-S6 signaling pathway.

Conclusion: This study demonstrated that silibinin could improve central obesity, NAFLD, glucose tolerance and insulin sensitivity in *db/db* mice. The mechanism underlying the attenuated hepatic lipid accumulation and insulin resistance by silibinin was likely related to the promotion of FAs β-oxidation-related genes, inhibition of lipogenesis-related genes, improvement of the mitochondrial respiratory chain, alleviation of oxidative stress injury, and regulation of the FGF21-adiponectin-mTOR-S6 pathway.

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Risk assessment and preoperative prediction of microvascular invasion in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common and highly lethal tumors worldwide. Microvascular invasion (MVI) is a significant risk factor for recurrence and poor prognosis after surgical resection for HCC patients. However, MVI can only be diagnosed by immunohistochemical and pathological analysis of postoperative specimens at present. Therefore, accurately predict the status of MVI preoperatively which is crucial for clinicians to select treatment modalities and improve patient overall survival (OS). Currently, plenty of studies have focused on highly accurate methods for preoperative prediction of MVI status and promising progress has been made. Many predictors have been identified in serology and liquid biopsies and are clinically accessible with high objectivity and accuracy, and it would be a valuable effort to predict this biological behavior of MVI at the level of genes and their expression. Moreover, the accuracy of radiomics prediction is significantly higher than that of single imaging features, especially deep learning (DL) automatically extracts a large amount of information from images for analysis and diagnosis, which greatly improves the accuracy of prediction. This article reviews the various predictors and risk factors for preoperative assessment occurrence of MVI and provides a guide for the conduct of subsequent studies.

Fibrosis

P143

3,4-dihydroxyl-phenyl lactic acid ameliorates cardiac fibrosis and cardiac hypertrophy induced by pressure overload

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Background: More than half of patients with heart failure were associated with hypertensive heart disease. However, there is a lack of effective treatments for blocking cardiac fibrosis after cardiac hypertrophy. Our previous study showed 3,4-dihydroxyl-phenyl lactic acid (DLA) was able to attenuate cardiac structure and function injury after I/R. Besides. QiShenYiQi pills, in which DLA is one of main ingredients, alleviated pressure overload-induced cardiac hypertrophy and fibrosis. However, whether DLA could inhibit pressure overload-induced remains unclear.
Method: In the present study, pressure overload-induced cardiac hypertrophy was established in mouse by imposing transverse aortic constriction (TAC) for 4 weeks. DLA (10/30/60 mg/kg/day) was administrated orally. Studies were conducted to assess the effect of DLA on cardiac function, cardiac hypertrophy, cardiac fibrosis and TGF-β1/Smad signaling.
Results: DLA remarkably ameliorated TAC induced cardiac dysfunction, increased EF and FS, decreased HW/BW and HW/TL. DLA treatment reduced cardiac hypertrophy and collagen deposition both in the interstitial and perivascular area of heart tissues as shown by HE and Masson trichrome staining. Western blotting showed that DLA inhibited a-SMA, Collagen 1 and Collagen 3 protein levels, and Smad 3 phosphorylation. Immunofluorescence staining showed reduced that DLA significantly inhibited nuclear translocation of p-Smad 3.
Conclusion: The results showed that DLA inhibited pressure-induced myocardial fibrosis and cardiac hypertrophy, which was probably mediated through inhibition of TGF-β signaling.

COVID-19

P144

Endothelial dysfunction in long-COVID depression: The hub of the abnormal neurovascular-immunity cell communication network

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Background: A significant proportion of individuals experience persistent neurological and neuropsychiatric symptoms following COVID-19, which constitute a major aspect of the post-acute COVID-19 syndrome, commonly referred to as long-COVID. These acute and chronic symptoms of long-COVID include cognitive impairments, depression, and anxiety. However, it remains unclear whether these symptoms share a common mechanism with major depressive disorder (MDD), and whether prolonged symptom presence increases susceptibility to MDD.
Methods: To investigate the relationship between long-COVID depression and MDD, four human single cell/nuclear RNA-sequencing datasets were analyzed. These included MDD prefrontal cortex, COVID-19 infected prefrontal cortex, COVID-19 infected peripheral blood mononuclear cells (PBMCs), and healthy prefrontal cortex controls. The aim of this analysis was to identify the mechanisms underlying MDD in brain injury caused by COVID-19.
Results: Following quality control procedures, known markers were used to annotate the cell types in the single cell/nuclear RNA-seq dataset. Our analysis focused on the cells comprising the neurovascular units (NVU), including neurons, endothelial cells, astrocytes, and pericytes. The NVU is considered the minimum functional unit of the brain and is involved in its normal functioning. Our findings indicate that neuroinflammation plays a dominant role in the six main known ways that COVID-19 causes brain injury. Following COVID-19 infection, all cells in the NVU displayed inflammatory characteristics. In comparison to the NVU of healthy controls, the communication mechanism between the NVU, which is responsible for maintaining energy metabolism, homeostasis, and tissue repair, was significantly altered. Interestingly, similar changes were observed in MDD when compared to healthy controls. Dysfunction in cell communication networks is a crucial mechanism underlying depression, which may explain the occurrence of depression following COVID-19 infection.
To investigate how inflammation in COVID-19 causes the appearance of NVU in the normal brain, which is similar to the cell communication network in MDD, we traced the evolutionary trajectory of NVU cells that progressed with COVID-19 infection. We found that the earliest pathological changes occur in endothelial cells, which change the normal cell communication in NVU, particularly the communication mechanisms related to energy metabolism, homeostasis maintenance, and tissue repair. Numerous studies have shown that endothelial cell injuries in COVID-19 are caused by the adhesion of excessively activated peripheral immune cells. Therefore, we further calculated the interactive relationship between PBMCs and brain endothelial cells. The cells that interact with endothelial cells include lymphocytes (CD8+ T cells and natural killer cells) and myeloid cells (macrophages, neutrophils, and monocytes). Activated CD8+ T cells can output injury signal ligands (IL1-β, TNF-α, and IL6) to endothelial cells through cell adhesion. When the receptors on the endothelial cell surface (IL1RA, TNFRSF1A, and IL6ST) combine with the above ligands, they mediate a strong inflammatory response, causing endothelial dysfunction.
Conclusion: Endothelial cells serve as the central connection hub between NVU and immune cells. Following COVID-19 infection, the activated $CD8^+$ T cells in peripheral blood secrete proinflammatory factors such as IL1-β, TNF-α, and IL-6, which damage endothelial cells. Endothelial cell dysfunction leads to changes in the communication network of NVU cells similar to those observed in MDD. In the brain of individuals with long-COVID, overactivation of immune cells in peripheral blood causes overall changes in the NVU through endothelial cells, resulting in symptoms related to depression.

New Concepts and Technology

P145

Clinical outcomes of retrievable inferior vena cava filters for venous thromboembolic diseases

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Aim: To identify literature evidence assessing retrievable inferior vena cava filter (rIVCF) for venous thromboembolic diseases.
Methods: A systematic literature search was conducted to identify relevant references from the mainstay English and Chinese bibliographic databases (search period: January 2003 to October 2019).
Results: 80 original studies with 11,413 patients were included in this review. The success rates of deploying the six types of rIVCFs ranged from 98.4 to 100.0%. Denali had the highest retrieval success rate (95.4-97.6%). The incidence rates of fracture and perforation associated with retrieving the six rIVCFs were less than 2%.
Conclusion: The approved rIVCF had comparable clinical profiles, except that Denali was easier to be retrieved than other rIVCF.
Keywords: complication; meta-analysis; pulmonary embolism; retrievable inferior vena cava filter; venous thromboembolic diseases.

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Quantitative and Noninvasive Detection of SAH-related MiRNA in Cerebrospinal Fluids in Vivo Using SERS Sensor Based on Acupuncture-based Technology

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Quantitative analysis of microRNAs (miRNAs) in a noninvasive manner is of vital importance for disease diagnosis and prognosis evaluation. However, conventional strategies for realizing accurate, simple, and sensitive detection of target molecules are still a challenge, especially for miRNAs due to their low abundance and susceptibility in the complex biological environment. Here, a novel surface-enhanced Raman scattering (SERS) strategy was established for quantitative detection and monitoring of miRNA-21-5p (miR-21-5p) in living cells and in vivo cerebrospinal fluid (CSF) by applying hairpin DNA (hpDNA)-conjugated gold nanostars (GNSs) SERS probes combined with acupuncture-based technology. This strategy enabled ultrasensitive exploration toward miR-21-5p in a wide range from 1 fM to 100 pM in cell lysates. Moreover, SERS analysis facilitated the detection and long-term monitoring for in vivo miR-21-5p noninvasively. This developed strategy promises to offer a powerful method for the analysis of multiple biomolecules in single cells and living bodies.

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Diverse Effect of Virtual Reality Visual Perceptual Plastic Training in Glaucoma Patients of Different Age and Different Severity

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Objective: To investigate whether the effect of virtual reality visual perceptual plastic training on changing inner retinal structures and lifting macular function are affected by age or disease severity in glaucoma patients.
Methods: 27 glaucoma patients with well-controlled intraocular pressure were divided into three groups according to ages and the severities of visual field defect. The changes of peripapillary retinal nerve fiber layer (pRNFL), macular ganglion cell-inner layer (mGCIPL) thickness and mean macular sensitivity (mMS) were compared between glaucoma patients in each group after 3 months of virtual reality visual perceptual plastic training, and the correlation between retinal structures and macular function were analyzed.
Results: After 3 months of visual perceptual plastic training, the mean value of mGCIPL ($Z = -2.834$, $P < 0.05$) and minimum value of mGCIPL ($Z = -2.781$, $P < 0.05$) were significantly increased in the young group. The mMS improved after receiving visual perceptual plastic training in the middle-aged group ($Z = -2.411$, $P = 0.016$). For the group of VFI ≥ 80% and the group of MD > -6.00 dB whose visual field were mildly damaged, the mMS value was significantly improved ($Z = -2.163$, $P < 0.05$; $Z = -2.371$, $P < 0.05$); however, in the groups (VFI < 50% or MD < -12.00 dB) with the most severe visual field damage, the mean value of mGCIPL was improved significantly ($Z = -2.023$, $P < 0.05$; $Z = -2.692$, $P < 0.05$). In addition, there was a low negative correlation between age and thickenings in the mean value of mGCIPL as well as the minimum value of mGCIPL after virtual reality visual perceptual plastic training ($r = -0.345$, $P < 0.05$; $r = -0.315$, $P < 0.05$).
Conclusion: Under the condition of well-controlled intraocular pressures, young patients as well as those with severe visual field defects had retinal structure improvement after receiving visual training. Macular function was improved in middle-aged patients as well as in patients with mild visual field defects but elderly patients responded poorly to the visual training.

P148

Binocular visual perceptual function in patients with glaucoma in comparison with normal controls

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Purpose: The aim of this study is to explore the changes in binocular visual perceptual function in glaucoma patients at different stages and the comparative analysis of functional defect with normal groups, and to extend the correlation analysis to binocular visual acuity difference at the level of visual quality.
Methods: 56 glaucoma patients and 54 normal people were recruited into the study. They underwent perceptual eye position, random dot static 0^{th}-order stereopsis (fine stereopsis), random dot dynamic 1^{st}-order stereopsis (motor stereopsis), and large-scale static 2^{nd}-order stereopsis (coarse stereopsis) examinations.
Results: There was no significant difference in horizontal perception eye position between the two groups ($p=0.825$), and the vertical perception eye position in the glaucoma group was larger than that in the normal control group ($p<0.001$). The proportion and severity of impaired fine stereopsis and motor stereopsis were higher in the glaucoma subjects than in the normal controls ($P<0.001$). With the progress of glaucoma, there was a significant difference between moderate glaucoma (MG) and advanced glaucoma (AG) in terms of fine stereopsis ($p=0.046$), and there was a significant difference between AG and early glaucoma (EG) in terms of motor stereopsis ($p=0.043$). All subjects were divided into two groups of ≤0.2 and >0.2 according to the binocular visual acuity difference, and it was found that there was no significant difference between the normal control group with binocular visual acuity difference <0.2 and the glaucoma group in all three classes of stereopsis, while the subjects with binocular visual acuity difference >0.2 in the glaucoma group had more severe impairment in the three orders of stereopsis ($P<0.05$). The visual function defects of fine stereopsis, motor stereopsis and coarse stereopsis were correlated with the poor binocular vision of patients.
Conclusion: The pathogenesis of glaucoma is complicated and already has a serious impact on the primary visual cortex of patients, so the sensitivity of the higher functions of both eyes in glaucoma can be further explored through perceptual examinations.

P149

The effect of microcirculation on prediction of delayed extubation

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Introduction: The ability of microcirculation to identify in patients with delayed extubation after cardiac surgery is unclear. The objective was to evaluate the early recognition ability of sublingual microcirculation in patients with delayed extubation after cardiac surgery.

Methods: This was a prospective, observational study. Adult patients undergoing selective cardiac surgery were enrolled in this study. The patients' general characteristic was recorded, including age, sex, surgical information, hemodynamic, etc. The microcirculation images of three different parts of the sublingual were recorded at the first hour(H1), the sixth hour (H6) and 8:00 at the next day (D2) after the patients' arrival in ICU. Each image was analyzed and relevant indicators (including total vascular density (TVD), perfusion vascular density (PVD), perfusion vascular ratio (PPV), and heterogeneity index (HI)) were recorded. Outcomes such as duration of mechanical ventilation time were followed up. Delayed extubation was defined as mechanical ventilation >48 hours, or extubation and intubation within 48 hours. Microcirculation's Power (MCP) was established as a novel index, which is calculated from the logistic regression. Independent sample t test was used to compare the two groups, and area under ROC curve (AUC) was used to evaluate the diagnostic value.

Results: A total of 40 patients were included in this study. There were 27 males (67.5%) with the average age 63.4 years. The median of mechanical ventilation time was 20.13 hours (IQR 18.35-25.71 hours), and the rest characteristic was shown in TABLE 1. 6(15%) patients were included in the delayed extubation group, while 34(85%) patients were included in the non-delayed extubation group. As the results of hemodynamics and microcirculation was shown in Table 2. As shown in FIGURE 1. the AUC of MFI in H1 group was 0.568, 95%CI 0.331-0.840, and the cut-off value was 1.96, which the sensitivity was 58.8% and the specificity was 66.7%. The AUC of the HI in H1 group was 0.600, 95%CI 0.369-0.832, and the cut-off value was 0.578, which the sensitivity was 35.3% and the specificity was 100%. After simplifying the correlation coefficient according to the logistic regression, the MCP is equal to 2*TVD-2.5*PVD+0.5*PPV+MFI-HI IN H1 group. The lower the MCP score, the worse the microcirculation and the higher the risk of delayed extubation. The AUC of the MCP was 0.750, 95%CI 0.571-0.929, and the cut-off value was 42; at this point the sensitivity was 50% and the specificity was 100%.

Conclusions: Sublingual microcirculation monitoring in patients after cardiac surgery is helpful for early identification of patients with delayed extubation.

P150

Exploring the global perfusion characteristics of microcirculation based on local vascular information by mathematical model

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Background: Early fluid resuscitation can reduce organ dysfunction in sepsis patients by improving tissue perfusion. However, persistent microcirculatory dysfunction after resuscitation may worsen outcome. Monitoring the functional status of the microcirculation is crucial to evaluate the effectiveness of resuscitation. In practice, only few vessels in microcirculation network can be observed and it is inaccessible to capture the data of entire microcirculatory network for assessing tissue perfusion. Moreover, it lacks effective quantitative indices for global perfusion status. To address these problems, this study established an analytical model for estimating the global perfusion characteristics of the microcirculation based on local vascular information.

Methods & Materials: The development of the model involves the following steps. (1) Train a generative adversarial network to obtain a pre-trained model for generating vessel bifurcations. (2) Use transfer learning algorithm to retrain the pre-trained model with the collected local vessel bifurcations and obtain a customized model for generating specific vessel bifurcations. (3) Generate venous vascular tree based on the customized model. (4) Assign initial blood flow values to the generated vascular tree based on the information of the collected vessel bifurcations. (5) Construct arterial vascular tree using the reverse parallel method and merge the arterial and venous vascular trees to form vascular network. (6) Optimize the vascular network structure and blood flow distribution using a structure adaptive model. Ultimately, indices of blood flow multifractal spectrum and fractal dimension were produced to estimate the blood flow perfusion. The model was validated by experimental data of mesenteric microcirculatory networks on three rats (provided by Medicine Center Charité, Germany). Assessed by blood flow multifractal spectrum and fractal dimension, the blood flow results produced by the proposed model were compared with the experimental data.

Results: In this study, three groups of venous vessel bifurcations (each with ten bifurcations) were randomly selected from the rat mesenteric microcirculatory networks as the collected local vessel bifurcations. And five complete vascular networks based on each group of collected vascular bifurcation data were generated and assessed. The results show that the height, the width of the blood flow multifractal spectrum and the blood flow fractal dimension for the generated microcirculatory networks based on each group of collected data are: (1) 0.86±0.02, 0.88±0.07, 0.68±0.03, (2) 0.88±0.02, 0.88±0.03, 0.69±0.03, (3) 0.83±0.02, 0.93±0.07, 0.61±0.03. These values are close to the experimental data of blood flow distribution (i.e., multifractal spectrum height of 0.79, width of 1.02 and fractal dimension of 0.52). Moreover, the model facilitated the estimation of the distribution of blood flow velocity and the distribution of blood pressure against diameter, which are both in accordance with the empirical data of real vascular network.

Conclusion: This study proposed a model capable of generating a microcirculatory network using only a small number of collected vessel bifurcations and it yielded blood flow distribution which is comparable to actual conditions. By this model, it is possible to estimate the global perfusion characteristics of microcirculation through local vascular information.

Ocular Fundus Microcirculation

P151

Alteration of intestinal microbiota is associated with diabetic retinopathy and its severity: samples collected from southeast coast Chinese

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Background: Current approaches for the therapy of diabetic retinopathy (DR), which was one of leading causes of visual impairment, have their limitations. Animal experiments revealed that restructuring of intestinal microbiota can prevent retinopathy. Our study aimed to explore the relationship between intestinal microbiota and DR among patients in the southeast coast of China, and provide clues for novel ways to prevention and treatment methods of DR.

Methods: The fecal samples of non-diabetics (Group C) and diabetics (Group DM), including 15 samples with DR (Group DR) and 15 samples without DR (Group D), were analyzed by 16S rRNA sequencing. Intestinal microbiota compositions were compared between Group C and Group DM, Group DR and Group D, as well as patients with proliferative diabetic retinopathy (PDR) (Group PDR, N=8) and patients without PDR (Group NPDR, N=7).Spearman correlation analyses were

performed to explore the associations between intestinal microbiota and clinical indicators.

Results: The alpha and beta diversity did not differ significantly between Group DR and Group D as well as Group PDR and Group NPDR. At the family level,*Fusobacteriaceae*, *Desulfovibrionaceae and Pseudomonadaceae*were significantly increased in Group DR than in Group D (P<0.05, respectively).At the genera level,*Fusobacterium*,*Pseudomonas*, and *Adlercreutzia* were increased in Group DR than Group D while *Senegalimassilia* was decreased (P<0.05, respectively). *Pseudomonas* was negatively correlated with NK cell count (r=-0.39, P=0.03).Further, the abundance of genera *Eubacterium*(P<0.01),*Peptococcus*, *Desulfovibrio*,*Acetanaerobacterium* and*Negativibacillus* (P<0.05, respectively) were higher in Group PDR compared to Group NPDR, while *Pseudomonas*, *Alloprevotella* and *Tyzzerella* (P<0.05, respectively)were lower.*Acetanaerobacterium* and *Desulfovibrio* were positively correlated with fasting insulin (r=0.53 and 0.61, respectively, P<0.05), when *Negativibacillus* was negatively correlated with B cell count (r=-0.67, P<0.01).

Conclusion: Our findings indicated that the alteration of gut microbiota was associated with DR and its severity among patients in the southeast coast of China,probably by multiple mechanisms such as producing short-chain fatty acids, influencing permeability of blood vessels, affecting levels of VCAM-1, HIF-1, B cell and insulin. Modulating gut microbiota composition might be a novel strategy for prevention of DR,particularly PDR in population above.

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Investigation into the AMD fundus microcirculation features by deep learning model

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Background: Deep learning has been widely applied in clinic for aiding the prediction and treatment of age-related macular degeneration (AMD). However, the activity of choroidal microcirculation in AMD lacks comprehensive investigation. This study aims to develop a deep learning based transformer model to examine the spatial distribution characteristics and perfusion patterns activity of choroidal neovascularization (CNV) by optical coherence tomography angiography (OCTA) images. Furthermore, the interpretability of the model's outcome is explored in light of the morphological characteristic of microcirculation in CNV.

Methods and Materials: The study employed the Vision Transformer (ViT) model to obtain the attention weight distribution feature and utilized fractal dimension analysis to gain the vascular space density characteristics of choroidal microcirculation. A total of 462 OCTA images of 176 patients with typical AMD were recruited by the Eye Center at the Second Affiliated Hospital of Zhejiang University, including 300 active CNV images and 162 inactive CNV images. The CNV activity was classified by 3 experienced ophthalmologists. The image dataset is divided into training sets, validation sets and test sets in an 8:1:1 ratio. Based on this dataset, the ViT model was trained to harvest the best model parameters. The attention weight layers were extracted from the model to reflect the intensity of different regions on the image that affect the model outcome. The weight layers were superimposed onto the original OCTA images to create visual heat maps of the model's attention weight distribution. Thereby, the distribution of attention weights in vascular and non-vascular regions is quantified. Fractal dimension analysis was performed on the original OCTA images to identify the vessel density distribution and space-filling properties of the choroidal vessels. By comprehensive examination of the attention weight heat map and the fractal dimension analysis results, the relationship between the attention weight distribution and the degree of vascular space abundance was explored.

Results: The attention distribution heat maps of different CNV activities and the corresponding fractal dimension pictures are shown in Figure 3. The model exhibits diverse attention distribution patterns for images with varying CNV activities. Specifically, for active CNV the attention weights are concentrated on blood vessels, and the concentration increases with higher vascular density. Conversely, for inactive CNV, the attention weights are mainly distributed outside blood vessel region, and less attention is paid to vascular information. Figure 4 shows the statistical results of attention weights ratio inside and outside the vascular region, reflecting the distinct focus of the model for varying CNV activity. It exhibits that active CNV has significant higher ratio of attention weight than inactive CNV, with 0.8306 vs. 0.3867.

The findings demonstrate that micro vessels in inactive CNV exhibit a filamentous morphology with mature vascular branches and fewer anastomoses. However, when CNV transitioned from an inactive to active state, significant alterations in microcirculation were observed, including the emergence of a rich capillary network and an increase in blood vessel density and anastomoses. The deep learning model was responsive to the changes in the morphological aspects of the micro vessel network and generated distinct attention distribution patterns matching the variations.

Conclusion: It can be concluded that OCTA associated with deep learning model has the capacity to identify the structural characteristics of fundus microcirculation and may have the potential to uncover physiological and pathological insights into CNV.

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Retinal fluid is associated with cytokines of aqueous humor in the intraocular microvascular inflammation

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As the aging of population in many countries, age-related degenerative diseases pose significant socio-economic challenges (Mitchell et al., 2018). One of the major degenerative diseases affecting the quality of life is age-related macular degeneration (AMD), affecting 8.7% of the global population (Wong et al., 2014). This study aimed to explain the biological role played by cytokines of aqueous humor in the intraocular microvascular inflammation, the association between the cytokines and retinal morphological changes, and the possible role of inflammatory cytokines in the pathogenesis of AMD by quantitatively analyze the association between cytokine concentrations of aqueous humor and retinal fluid volume based on optical coherence tomography (OCT).

Spectral-domain OCT (SD-OCT) images and aqueous humor samples were collected from 20 AMD patients' three clinical visits. Retinal fluid volume in OCT was automatically quantified using deep learning--Deeplabv3+. Eighteen cytokines were detected in aqueous humor using the Luminex technology. OCT fluid volume measurements were correlated with changes in aqueous humor cytokine levels using Pearson's correlation coefficient (PCC).

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Serum Disease-Specific IgG Fc Glycosylation as potential biomarkers for Nonproliferative Diabetic Retinopathy Using Mass Spectrometry

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Objective: To explore the potential of serum DSIgG glycosylation as a biomarker for the diagnosis of nonproliferative diabetic retinopathy (NPDR).

Methods: A total of 387 consecutive diabetic patients presenting in an eye clinic without proliferative diabetic retinopathy (DR) were included

and divided into those with nondiabetic retinopathy (NDR) (n=181) and NPDR (n=206) groups. Serum was collected from all patients for DSIgG separation. The enriched glycopeptides of the tryptic digests of DSIgG were detected using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Patients were randomly divided into discovery and validation sets (1:1). The differences in glycopeptide ratios between the groups were compared by using Student's t test or the Mann–Whitney U test. The predictive ability of the model was assessed using the area under the receiver operating characteristic curve (AUC).
Results: DSIgG1 G1FN/G0FN, G2N/G2, G2FN/G2N and DSIgG2 G1F/G0F, G1FN/G0FN, G2N/G1N, G2S/G2 were significantly different between NDR and NPDR patients ($p<0.05$) in both the discovery and validation sets. The prediction model that was built comprising the seven glycopeptide ratios showed good NPDR prediction performance with an AUC of 0.85 in the discovery set and 0.87 in the validation set.
Conclusion: DSIgG Fc N-glycosylation ratios were associated with NPDR and can be used as potential biomarkers for the early diagnosis of DR.

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Effectiveness of aflibercept in the treatment of neovascular age-related macular degeneration of eyes and related prognostic factors influencing the drug efficacy

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Purpose: This study aimed to evaluate the effectiveness of aflibercept in the treatment of neovascular age-related macular degeneration and analyze the factors influencing the drug efficacy and improvement in vision.
Methods: This was a retrospective analysis. From July 2019 to July 2021, thirty-three eyes of patients with neovascular age-related macular degeneration (nAMD) were followed for 6 months. Initially, all patients received three monthly intravitreal injections of 0.05 mL of aflibercept (2 mg) followed by a pro re nata(PRN) regimen. We documented the patient's age, sex, best-corrected visual acuity (BCVA), and the times of injections. Besides, at baseline, 1, 2, 3, and 6 months, the data on the variables such as central retinal thickness (CRT), subretinal hyperreflective material (SHRM), ellipsoid zone (IS/OS), and outer membrane (ELM) using optical coherence tomography (OCT) were obtained. Fundus photography was carried out to check for macular hemorrhage.
Results: During the follow-up period, the BCVA and CRT at 1, 2, 3, and 6 months were significantly improved than the baseline respectively ($P<0.05$). CNV type II, the existence of ELM discontinuity, and the presence of scarring and SHRM were associated with worse BCVA. Additionally, eyes without ELM discontinuity, SHRM, and scarring were associated with the improvement of 3- or 6-month BCVA. The CNV type II, presence of SHRM, and ELM discontinuity were strongly associated with scarring.
Conclusion: These results suggested that intravitreal aflibercept was safe and effective in the treatment of neovascular age-related macular degeneration. Factors such as ELM continuity, scarring, and SHRM influenced the improvement in visual acuity, and scarring was associated with the CNV type,ELM integrity, and SHRM.
Keywords: Aflibercept**;** neovascular age-related macular degeneration; macular hemorrhage; ellipsoid zone; subretinal hyperreflective material

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Efficacy and Safety of Intravitreal Injection of Conbercept for Moderate to Severe Nonproliferative Diabetic Retinopathy

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Purpose: To evaluate the efficacy and safety of intravitreal injection of conbercept (IVC) for moderate to severe nonproliferative diabetic retinopathy (NPDR) with or without diabetic macular edema.
Methods: This longitudinal retrospective study enrolled 22 patients (31 eyes) with moderate to severe NPDR and a Diabetic Retinopathy Severity Scale (DRSS) score of 43–53 treated in October 2018–January 2022 at the Department of Ophthalmology, First Affiliated Hospital of Kunming Medical University. The patients underwent three monthly IVC treatments, followed by a pro re nata regimen (3+PRN), and a 1-year follow-up period. Outcomes included best-corrected visual acuity (BCVA), intraocular pressure, central macular thickness (CMT), area of hard exudute (HE), and DRSS scores. The DRSS scores were compared using the Wilcoxon rank-sum test before and after treatment. Systemic and ocular adverse events were recorded to evaluate safety.
Results: From baseline to last follow-up, the mean BCVA increased from 0.39 ± 0.41 to 0.22 ± 0.19 logMAR. The mean CMT decreased from 313.32 ± 65.82 to 286.64 ± 70.82 μm. At 12 months, DRSS scores regressed ≥ 1 stage in 26 eyes (83.87%), ≥ 2 stages in 19 eyes (61.29%), ≥3 stages in 5 eyes (16.13%), and remained unchanged in 3 eyes (9.68%). In 13 of 23 eyes (56.52%) with DME, the mean area of HE decreased significantly from baseline. No serious systemic adverse events were observed.
Conclusions: IVC is effective and safe for treating moderate to severe NPDR, resulting in a robust regression of DRSS scores.

Bone Microcirculation

P157

Effect and Mechanism of Kunling Wan to Improve Osteoporosis and Fat Accumulation in Ovariectomized Female Mice

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Background: Postmenopausal osteoporosis with increased body fat is a major disease that threatens the health of middle-aged and elderly women in China and consumes medical finance. After menopause, reduced estrogen can affect the activity of mTOR, and the differentiation of mesenchymal stem cells to osteogenesis is decreased and adipogenic differentiation is increased, leading to the occurrence of osteoporosis. Osteoporosis and fat accumulation after menopause are associated with low estrogen levels. Kun-ling Wan (KLW) is a compound Chinese medicine preparation for the treatment of infertility and polycystic ovary syndrome associated with low estrogen. However, whether it can improve postmenopausal osteoporosis and fat accumulation is still unclear. In this study, we studied the effect of KLW on osteoporosis and fat accumulation in ovariectomized mice and its mechanism, so as to provide scientific basis for the application of KLW in the prevention and treatment of osteoporosis and fat accumulation in postmenopausal women.
Methods: Healthy female C57BL/6J mice aged 6-8 weeks were treated with sham surgery and bilateral ovariectomy (OVX), respectively, and reared with a high-fat diet after surgery. OVX mice were randomly divided into model group (M group), estradiol group (E_2 group), psoralen group (PSO group), asperosaponin VI group (ASP group), low-dose Kun-Ling Wan group (LKLW group) and high-dose Kun-Ling Wan group (HKLW group). The SHAM group was given the same amount of normal saline daily. After 28 days of administration, microCT was used to detect the density and morphology of femoral trabecular bone. The content and distribution of body fat and the fat content in femoral bone marrow of mice were observed by MRI system. The lipid droplets in the femur were observed by HE staining. The metabolic changes of mice within 24 h were detected. Oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) were used to detect glucose metabolism in mice.
Results: Compared with SHAM group, femoral bone mineral density of mice in M group was significantly decreased, bone marrow fat content increased, the number and volume of fat droplets increased,

and bone mineral density and bone trabecular structure of mice in E2 group, PSO group, ASP group, LKLW group and HKLW group were significantly improved compared with those in M group, and the increased bone marrow fat content was inhibited by high dose KLW. The body fat percentage of mice in group M was significantly increased, and the fat was mostly distributed in the abdominal cavity and subcutaneous, while the energy consumption and activity of mice were significantly decreased. KLW significantly inhibited the increase of body fat percentage induced by OVX, and high dose KLW significantly inhibited the decrease of energy consumption and activity in mice.

Conclusions: This study demonstrated that KLW can improve the decreased bone trabecular density, structural changes, increased bone marrow fat content and fat accumulation induced by OVX in mice. The effects of KLW are related to the promotion of osteogenic differentiation of mesenchymal stem cells, inhibition of adipogenic differentiation, inhibit mTOR and downstream S6K phosphorylation, and increase of energy consumption and activity in mice.

Ischemia and Reperfusion Injury

P158

Co-expression network between placenta tissues and trophoblast organoids highlights ARRDC3 as a diagnostic biomarker supporting the response to hypoxic microenvironment in preeclampsia

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Background: Preeclampsia is a multisystemic but unpredictable disease with few effective preventive and therapeutic options available in clinic. This dilemma makes the identification of biomarker to be urgently needed, and a better understanding of the pathogenesis of preeclampsia is critical important to fulfill this purpose. There is a pathological hypoxic microenvironment in patients with preeclampsia, and insufficient oxygen supply caused by the microcirculation disorder is commonly implicated in the development of preeclamptic placenta. Investigating the hypoxic adaptation and the key events on trophoblasts transcriptome is helpful to identify the potential biomarker underlying the function and regulatory mechanism of trophoblasts at the maternal-fetal interface.

Despite their importance, it has been poorly unraveled for the molecular mechanisms underlying pathological hypoxia caused by ischemia in preeclampsia, mostly due to the lack of appropriate cellular model systems. However, over the past few years major progress has been made by establishing selfrenewing 3dimensional organoids from human trophoblasts and placental tissues opening the path for detailed molecular investigations. Herein, we performed a comprehensive co-expression analysis to identify the potential biomarker driven by hypoxic microenvironment based on the intersected transcriptional data from placental tissue and 3dimensional organoids.

Methods: A group of full transcriptome data were assessed from extracted RNA of trophoblast cell line BeWo which was cultured in a 3-dimensional condition for a week time to form organoids, and consequently exposed in normoxia or hypoxia. Another group of preeclampsia-based transcriptional data in placental tissues were downloaded from gene expression omnibus (GEO) database. The limma R package was used to screen differentially expressed genes (DEGs) intersected by the data of tissues and organoids. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment were performed to investigate the bioinformatic functions and molecular interactions of DEGs. Based on least absolute shrinkage and selection operator (LASSO) and SVEM-RFE analysis, a gene signature for diagnosis of preeclampsia was established. Receiver operating curves were further conduced for diagnostic and Pearson's correlation of screened gene and clinicopathological characteristics.

Results: A total of 602 DEGs were assessed between the BeWo derived organoids cultured in normoxia and hypoxia, while 3142 DEGs between normal and preeclamptic placenta tissue were obtained. The hypoxia-related pathways were enriched by GO and KEGG analysis based on the intersected DEGs from transcriptome of tissues and organoids. 16 DEGs were obtained after the intersected screening, which were closely associated with hypoxia response. Two critical modules and five hub genes were highly related to the diagnosis of preeclampsia based on the results of LASSO and SVEM-RFE analysis. The five hub genes, namely, ARRDC3, BACH1, DUSP1, PLIN2, and TXNRD1, held diagnostic capabilities with area under the curve at 0.753, 0.834, 0.797, 0.805, and 0.761, respectively. A ceRNA network revealed a complex regulatory network based on the 5-DEGs signature. The further analysis indicated the genes involved in the signature might be enriched in preeclampsia by participating in the regulation of energy expenditure, lipid deposition, angiogenesis, and other biological process related to the pathogenesis of preeclampsia. The analysis of the clinicopathological features revealed that ARRDC3 was closely correlated with characteristics and diagnosis. Of note, the diagnostic capacity of ARRDC3 can be further confirmed by another independent data set GSE14281. Furthermore, a transcription factor analysis showed ARRDC3 was the downstream of HIF2a, and its expression might be under the control of HIF2a in hypoxic microenvironment.

Conclusion: In conclusion, the present research developed a diagnostic potency of ARRDC3 which might work as a novel diagnostic marker for preeclampsia. Our data support the importance of hypoxia in the pathogenesis of preeclampsia and highlight more details should be deciphered in the link between hypoxia, ischimia, and preeclampsia.

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The effects of different solutions on oxygen carrying/releasing capacity, ATP and acidity/basicity of stored red blood cells (SRBCs)

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Objective: Oxygen can be released from the stored red blood cells (SRBCs) and permeate through the extremely thin capillary wall to reach the tissue cells to ensure the normal metabolism of the tissue cells when SRBCs carrying oxygen have passed through microcirculation. Changes of SRBCs during storage affect oxygen carrying/releasing capacity which in turn cause changes in microcirculation. Currently, there are few studies on SRBCs in different solution and the ability of RBCs to carry/release oxygen during storage is ignored. This study aims to explore the effects of different solutions on the oxygen carrying/releasing capacity and ATP of SRBCs. Based on the advantages and characteristics of the solutions, one of the solutions was selected to explore the effects of the pH of the solutions on the acidity/basicity of SRBCs.

Methods: The whole blood was filtered through disposable white blood cell filter, and the plasma was removed by centrifugation. The stored red blood cells were mixed with each preservation solution (mannitol-adenine-phosphate solution (MAP), additive solution-1(AS-1), additive solution-3(AS-3), additive solution-7(AS-7), saline-adenine-glucose-mannitol additive solution (SAGM)) with a ratio of 4:1 (stored red blood cells (SRBCs): preservation solution). The NS group was used as the control. P_{50}, ATP, hemolysis rate and bacterial growth were measured on day 0, 1, 3, 7 and 14 of storage. Based on the above results, a superior solution was selected to explore the effects of the pH of the solutions on SRBCs by measuring indicators representing the acidity/basicity (pH, alkali excess (BE), HCO_3^-, and lactic acid (Lac)).

Results: The hemolysis rate increased gradually during storage which did not exceed the national standard requirements (Quality requirements and standards for whole blood and component blood) (except NS group) and the hemolysis rate of AS-3 group was significantly lower than the other groups (p<0.01); There was no bacterial growth in all groups; ATP decreased gradually, and AS-3 group was significantly higher than the other groups (p<0.01); There was a significant positive correlation between ATP and phosphate content in solution (r=0.737, p<0.001), and a significant negative correlation between ATP and hemolysis rate (r=-0.7245, p<0.001).

P_{50} gradually decreased, AS-7 group was significantly higher than NS group and AS-3 group (p<0.01) on day 0, 1, 3 and 7 of storage, while AS-3 group was significantly higher than NS group on day 14 (p<0.05). Based on the above results, a superior solution (AS-7) was selected to further explore the effects of the pH of the solutions on the acidity/basicity of SRBCs. The results showed that pH, BE and HCO_3^- gradually decreased during storage and were significantly higher than AS-7 (pH=5.8) at AS-7 (pH=8.5) (p<0.01) on day 0, 1, 3, 7 of storage, while significantly higher than AS-7 (pH=8.5) at AS-7 (pH=5.8) (p<0.01) on day 14. Lac gradually increased during storage and was higher than AS-7 (pH=5.8) at AS-7 (pH=8.5) on day 0 (p<0.01), 1 (p<0.01), 3 (p<0.05) and 7 (p<0.05) of storage.

***Conclusions*:** Phosphate content positively affects ATP levels in SRBCs and high ATP content can improve the hemolysis of SRBCs. Alkaline solution is beneficial for maintaining the oxygen carrying/releasing capacity of SRBCs. The extracellular acidity/basicity of SRBCs is not affected by the pH of the solutions.

Keywords: stored red blood cells, solution, oxygen carrying/releasing capacity, ATP, pH.

P160

Naotaifang formula alleviates cerebral ischemia/reperfusion injury via attenuating ferroptosis and necroptosis

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Background: Ischemic stroke are the neurological disease with a high incidence of death, disability and recurrence worldwide. Cerebral ischemia/reperfusion injury (CI/RI), the common pathological link, is caused by blood recanalization therapy in ischemic stroke. Naotaifang formula (NTF), a traditional Chinese medicinal prescription, has been reported the clinical effectiveness in ischemic stroke.

Aims: This study aims to establish the middle cerebral artery occlusion/ /reperfusion (MCAO/R) rat model to investigate the evolution law of ferroptosis and necroptosis in CI/RI and to reveal the potential therapeutic targets of NTF.

Methods: First, we verified the evolution law of ferroptosis and necroptosis by assessing pro-ferroptotic and pro-necroptotic changes after different reperfusion time in cortex of MCAO/R rats, along with cerebral blood, pathological change, protein and related factors. Then male rats were divided randomly into Sham, MCAO/R, different concentrations of NTF (9g/kg, 18g/kg, 27g/kg) groups. The effects of NTF on CI/RI were detected by the modified neurological severity score, TTC staining, and other staining. We conducted western blotting, immunohistochemistry and immunofluorescence analyzes of proteins.

Results: The cerebral blood flow value of rats during MCAO was significantly lower than that at baseline, and gradually increased with the extension of reperfusion time, which was significantly higher than that during MCAO. The Zea longa score and infarct volume were the lowest in the Sham group, and the two indexes in the MCAO/R group were higher than that in the Sham group, and these were the highest in the MCAO/ R-24H group, which was significantly higher than that in the Sham group and MCAO/R-2H group. In the Sham group, the number of Nissl bodies was the highest. With the increase of reperfusion time, the number of Nissl bodies was decreased gradually, and reached the turning point at MCAO/R-24H. With the extension of reperfusion time, the contents of factors related to pro-ferroptosis were increased, the levels of factors or proteins related to inhibiting ferroptosis were decreased, and the expression of proteins related to pro-necroptosis were upregulated. Moreover, these changes were reversed after MCAO/R-24H. Therefore, MCAO rats after reperfusion 24h were selected as the model group for NTF pretreatment in vivo experiment. It was found that MCAO/R rats in NTF pre-administration group showed significantly reduced Zea longa scores, Evans Blue content infarction volume, and Nissl bodies, and improved nerve cell morphology with dose-dependent. Except that, NTF pre-administration could down-regulate the protein expression, positive cell rate or mean fluorescence intensity of MLKL and P-MLKL. Besides, NTF pre-administration inhibited the positive cell rate of Prussian blue staining and decreased the contents of GSSG, total iron, ferrous iron, and promoted the expression of GSH and GPX4 protein, as well as the mean fluorescence intensity of GPX4. And the regulation of factors related to ferroptosis and necroptosis by NTF pre-administration is related to the dose of NTF.

Conclusions: The study demonstrated that cell death was occurred in nerve cells suffered CI/RI, and the degree of ferroptosis and necroptosis was gradually aggravated with the addition of reperfusion time, and the degree of these two-cell death gradually was alleviated after 24h reperfusion. NTF attenuated ferroptosis and necroptosis in a dose-dependent manner and played a neuroprotective effect in CI/RI.

P161

Naotaifang Formula ameliorates cerebral ischemia-reperfusion injury by attenuating ferroptosis and m6A demethylases via FTO/ALKBH5/GPX4 signaling pathway

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Background and Aims: Cerebral ischemia-reperfusion injury (CIRI) is a complex pathophysiological process involving multiple factors such as N6-methyladenosine (m6A) which becomes the footstone of rehabilitation after ischemic stroke. As a novel Chinese medicine formula, Naotaifang (NTF) was proven to exhibit a neuroprotective effect against CIRI by alleviating ferroptosis. This study aims to explore the physiological and pathological roles of NTF-targeted m6A and ferroptosis after CIRI.

Methods: The pharmacodynamics of the formula was evaluated by establishing rat model of middle cerebral artery occlusion/reperfusion. *In vivo* experiments, the therapeutic effect of NTF was performed using TTC, HE and Nissl staining. Regional cerebral blood flow (rCBF) was measured the brain blood flow and the morris water maze test was used to investigate rats' learning and memory ability. Dot blot analysis for measuring global m6A modification of RNA. And *in vitro* experiments, we also used Perls staining and colorimetric assay kit to quantify the iron content of cortex. Immunohistochemistry, immunofluorescence and western blot were used to detect the corresponding protein.

Results: Our research showed that pretreatment with NTF improved neurological function and inhibited CIRI. *In vivo* experiments, we confirmed that NTF increased cerebral blood flow, improved neural function, and reduced iron content and level of m6A demethylation via up-regulating the expression of fat mass and obesity-associated protein (FTO) and glutathione peroxidase 4 (GPX4), down-regulating ALKB homolog 5 RNA demethylase (ALKBH5) levels in CIRI rats. The *in vitro* experimental results revealed that NTF alleviated OGD/R-induced SH-SY5Y cell injury. Further experiments demonstrated that the protective role of NTF was achieved by regulating m6A demethylation to reduce ferroptosis in OGD/R.

Conclusions: Taken together, our study systematically revealed the potential therapeutic effects of NTF against CIRI via the FTO/ALKBH5/GPX4 signaling pathway.

L-Cardiac Microcirculation

P162

Correlation Analysis of Tongue Diagnosis and Cardiovascular and Renal Functions in Chronic Heart Failure Patients

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Background: Tongue diagnosis is a characteristic and unique method for diagnosing disease in traditional Chinese medicine (TCM). TCM practitioners observe and evaluate tongue features for syndrome differentiation. However, evidence-based study on the reliability of using tongue diagnosis as a diagnostic method for chronic heart failure patients is seldom reported. In the present study, we conducted a large-scale clinical trial to investigate the tongue characteristics of chronic heart failure patients and investigate the correlation between the tongue feature and cardiovascular functions for the potential use of tongue imaging as a diagnostic indicator.
Methods: This study included 653 chronic heart failure patients recruited from 25 hospitals in Mainland China, with inclusion criteria including a reduced ejection fraction (i.e., LVEF ≤ 40%) and serum NT-proBNP ≥ 450 pg/ml and an established documented diagnosis of heart failure for at least three months according to "Chinese Heart Failure Diagnosis and Treatment Guideline" that issued by the Chinese Medical Association, Cardiovascular Branch. The clinical data, including blood tests and clinical manifestations, were acquired using an evidence-based TCM Syndrome Differentiation Questionnaire for Heart Failure, and corresponding tongue images of the heart failure patients were taken for the study. All tongue images were acquired by a standardized image acquisition device and centrally analyzed by a team of four TCM practitioners with 3 to more than 30 years of clinical experience, with a 2-stages decision workflow.
Results: Most heart failure patients are cataloged as *TCM Blood Stasis Syndrome* presented with dim/purple/bluish-purple tongues with ecchymosis/petechiae as a typical clinical manifestation. The heart failure patients also had the characteristic fissured tongue, teeth-mark tongue, and tongue with thick tongue fur. There were high incidences of tongue tip ecchymosis, which might provide clinical evidence on the external reflection of the cardiovascular function condition. Importantly, serum NT-proBNP and creatinine levels were correlated with the characteristic tongue ecchymosis, providing a cue of the tongue imaging changes reflecting the status of cardiovascular functions and renal functions in heart failure patients.
Conclusion: Tongue diagnosis could be a useful indicator for chronic heart failure patients' cardiovascular and renal functions.

P163

Extracellular vesicle-derived circCEBPZOS attenuates postmyocardial infarction remodeling by promoting angiogenesis via the miR-1178-3p/ PDPK1 axis

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Emerging studies indicate that extracellular vesicles (EVs) and their inner circular RNAs (circRNAs), play key roles in the gene regulatory network and cardiovascular repair. How- ever, our understanding of EV-derived circRNAs in cardiac remodeling after myocardial infarction (MI) remains limited. Here we show that the level of circCEBPZOS is down- regulated in serum EVs of patients with the adverse cardiac remodeling compared with those without post-MI remodeling or normal subjects. Loss-of-function approaches in vitro establish that circCEBPZOS robustly promote angiogenesis. Overexpression of circCEBPZOS in mice attenuates MI-induced left ventricular dysfunction, accompanied by a larger func- tional capillary network at the border zone. Further exploration of the downstream target gene indicates that circCEBPZOS acts as a competing endogenous RNA by directly binding to miR-1178-3p and thereby inducing transcription of its target gene phosphoinositide- dependent kinase-1 (PDPK1). Together, our results reveal that circCEBPZOS attenuates detrimental post-MI remodeling via the miR-1178-3p/PDPK1 axis, which facilitates revascu- larization, ultimately improving the cardiac function.

P164

Exacerbated post-infarct pathological myocardial remodelling in diabetes is associated with impaired autophagy and aggravated NLRP3 inflammasome activation

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Background: Diabetes mellitus (DM) patients surviving myocardial infarction (MI) have substantially higher mortality due to the more frequent development of subsequent pathological myocardial remodelling and concomitant functional deteriora- tion. This study investigates the molecular pathways underlying accelerated cardiac remodelling in a well-established mouse model of diabetes exposed to MI.
Methods and Results: Myocardial infarction in DM mice was established by ligating the left anterior descending coronary artery. Cardiac function was assessed by echocardiography. Myocardial hypertrophy and cardiac fibrosis were determined histologically 6 weeks post-MI or sham operation. Autophagy, the NLRP3 inflammasome, and caspase-1 were evaluated by western blotting or immunofluorescence. Echocardiographic imaging revealed significantly increased left ventricular dilation in parallel with increased mortality after MI in DM mice (53.33%) compared with control mice (26.67%, $P < 0.05$). Immunoblotting, electron microscopy, and immunofluorescence staining for LC3 and p62 indicated impaired au- tophagy in DM + MI mice compared with control mice ($P < 0.05$). Furthermore, defective autophagy was associated with increased NLRP3 inflammasome and caspase-1 hyperactivation in DM + MI mouse cardiomyocytes ($P < 0.05$). Consistent with NLRP3 inflammasome and caspase-I hyperactivation, cardiomyocyte death and IL-1β and IL-18 secretion were increased in DM + MI mice ($P < 0.05$). Importantly, the autophagy inducer and the NLRP3 inhibitor attenuated the cardiac remodelling of DM mice after MI.
Conclusion: In summary, our results indicate that DM aggravates cardiac remodelling after MI through defective autophagy and associated exaggerated NLRP3 inflammasome activation, proinflammatory cytokine secretion, suggesting that restoring autophagy and inhibiting NLRP3 inflammasome activation may serve as novel targets for the prevention and treatment of post-infarct remodelling in DM.

L-Diabetes and Microcirculation

P165

The effect of novel dimeric peptide GX1 mediated by TGM2 on antiangiogenic activity to diabetic retinopathy

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Objective: Antiangiogenesis plays an important role in preventing and treating diabetes retinopathy and tumor. It has been found that tumor vessels and diabetes retinal neovascularization have some common receptor molecules. GX1 (national patent number ZL200410026137.0) is a small peptide, obtained by using phage in vivo screening technology, which can specifically bind to gastric cancer vascular endothelium and inhibit its angiogenesis through receptor TGM2. After chemical modification, the antiangiogenic activity of dimeric GX1 the retinal neovasculature is significantly enhanced compared to GX1 monomer, but the receptor had not been further determined. This study further explored the expression of TGM2 in oxygen induced retinal neovascularization as well as colocalization with GX1 dimer receptor, and the function of TGM2 in retinal neovascularization. It could provide a new, efficient and specific molecular targeted drug for the treatment of diabetes retinopathy in the future.
Method: An oxygen-induced mouse model of retinopathy (OIR) was constructed, and dimeric GX1 was chemically synthesizing. Immunohistochemistry was used to detect the expression of TGM2 in oxygen induced retinal neovascularization as well as colocalization

with GX1 dimer receptors. Western blotting was performed to detect the expression of TGM2 in retinal endothelial cells. TGM2 siRNA was synthesized and transfected into retinal vascular endothelial cells to observe the effect of TGM2 downregulation on the migration ability of retinal vascular endothelial cells.
Result: (1) TGM2 was highly expressed in the endothelial cells of oxygen induced retinal neovascularization model, and was consistent with the colocalization of dimeric GX1 receptors. The expression of TGM2 was higher in retinal vascular endothelial cells than in retinal pigment epitheliums, which indicated that TGM2 was a receptor for dimeric GX1; (2) TGM2-SiRNA transfection of retinal vascular endothelial cells weakened the migration ability of retinal vascular endothelial cells, which indicated that inhibiting TGM2 can weaken retinal neovascularization (P<0.05).
Conclusion: TGM2 was a receptor of dimeric GX1. Maybe dimeric GX1 inhibit retinal neovascularization through TGM2.

P166

Advanced multifunctional hydrogels for diabetic foot ulcer healing: active substances and biological functions

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Diabetic foot ulcer (DFU) is one of serious complications of diabetes mellitus (DM). Nowadays, most of wound dressings used in clinical practice are still traditional dressings, which are more likely to cause wound dehydration, impaired cell proliferation and bacterial invasion. As an advanced wet dressing, hydrogel has excellent biocompatibility and biodegradability. More importantly, hydrogels can be loaded with substances or treated on their own to play a role. In previous reviews, hydrogels were generally classified by their materials without combination of biological function and pathogenesis. In this review, hydrogels are classified by their active substances such as drugs, cytokines, photosensitizers and biomimetic peptide. Based on this, we summarize and combine the biological functions of hydrogels with the pathogenesis of DFU mainly including oxidative stress, chronic inflammation, cell phenotype change, vasculopathy and infection. We also point out some of the shortcomings of existing researches and hydrogels in order to provide assistance for future researches and clinical application.

P167

Association of first-phase insulin secretion with diabetic vascular complications in type 2 diabetes

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Background: Pancreatic islet dysfunction is one of the consequences of long-term pathology in patients with both type 1 and type 2 diabetes, so the determination of pancreatic islet function is essential for clinicians to diagnose diabetes and formulate subsequent treatment. The results of a large number of existing studies have focused on the relationship between patients' fasting pancreatic islet secretion levels and diabetic complications, while the relationship between stimulated pancreatic islet secretion levels and diabetic complications has not yet been clearly established. In clinical work, according to the patient's pancreatic islet secretory function, we can first judge the patient's pancreatic islet secretion, so this study tries to explore the relationship between pancreatic islet secretory function and type 2 diabetes mellitus macrovascular and microvascular lesions by the combination of pancreatic islet secretory function after arginine stimulation and the patients' carotid, subclavian, coronary, lower limb arteries, and renal function lesions.
Objective: To investigate the relationship between islet secretory function and macrovascular and microvascular lesions in patients with diabetic complications.
Methods: C-peptide levels were obtained from patients at 0, 2, 3, 4, and 5 minutes by the arginine stimulation test, and the corresponding islet one-phase secretory function was calculated. One-way regression analysis of different test results with 0-minute C peptide was performed using ordered multicategorical logistic regression analysis, and normal distribution was expressed as mean±standard deviation, and skewed distribution was expressed as median, upper and lower quartiles, with the significance of P<0.05. The relationship between islet function (2,3,4,5-minute C peptide) and the five lesions was then investigated by multifactorial logistic regression analysis, presented by a forest plot, with OR<1 indicating a protective factor and OR>1 indicating a risk factor.
Results: After adjustment for confounding factors, multifactorial regression analysis of islet function calculated from the level of C-peptide secretion after arginine stimulation showed that the probability of carotid plaque formation, subclavian plaque formation, coronary artery stenosis and occlusion, lower limb artery plaque formation, creatinine elevation and 24-hour urine protein lesions also increased with decreasing islet function.
Conclusion: Decreased pancreatic islet function is a risk factor for carotid plaque formation, subclavian plaque formation, coronary artery stenosis and occlusion, lower extremity artery plaque formation, elevated creatinine and 24-hour urinary protein in patients with type 2 diabetes mellitus.

P168

Liraglutide Accelerates Ischemia-Induced Angiogenesis in a Murine Diabetic Model

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Background: Severe hindlimb ischemia is a chronic disease with poor prognosis that can lead to amputation or even death. This study aimed to assess the therapeutic effect of liraglutide on hind-limb ischemia in type 2 diabetic mice and to elucidate the underlying mechanism.
METHODS AND
Results: Blood flow reperfusion and capillary densities after treatment with liraglutide or vehicle were evaluated in a mouse model of lower-limb ischemia in a normal background or a background of streptozotocin-induced diabetes. The proliferation, migration, and tube formation of human umbilical vein endothelial cells were analyzed in vitro upon treatment with liraglutide under normal-glucose and high-glucose conditions. Levels of phospho-Akt, phospho-endothelial nitric oxide synthase, and phospho-extracellular signal-related kinases 1 and 2 under different conditions in human umbilical vein endothelial cells and in ischemic muscle were determined by western blotting. Liraglutide significantly improved perfusion recovery and capillary density in both nondiabetic and diabetic mice. Liraglutide also promoted, in a concentration-dependent manner, the proliferation, migration, and tube formation of normal glucose– and high glucose–treated human umbilical vein endothelial cells, as well as the phosphorylation of Akt, endothelial nitric oxide synthase, and extracellular signal-related kinases 1 and 2 both in vitro and in vivo. The liraglutide antagonist exendin (9–39) reversed the promoting effects of liraglutide on human umbilical vein endothelial cell functions. Furthermore, exendin (9–39), LY294002, and PD98059 blocked the liraglutide-induced activation of Akt/endothelial nitric oxide synthase and extracellular signal-related kinases 1 and 2 signaling pathways.
CONCLUSIONS: These studies identified a novel role of liraglutide in modulating ischemia-induced angiogenesis, possibly through effects on endothelial cell function and activation of Akt/endothelial

nitric oxide synthase and extracellular signal-related kinases 1 and 2 signaling, and suggested the glucagon-like peptide-1 receptor may be an important therapeutic target in diabetic hind-limb ischemia.

P169

Sex differences in the glycocalyx integrity of the sublingual microvessels in individuals with type 2 diabetes: impact of body fat and LDL-cholesterol

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Background and Aims: Endothelial glycocalyx (EG) is vital for vascular health, and likely plays a role in the development and progression of vascular complications in Type 2 Diabetes (T2D). Previous research has demonstrated associations between EG loss and endothelial dysfunction, kidney disease, and sepsis. Recent developments have allowed estimations of EG integrity by recording images of the red blood cell (RBC) column within the sublingual vasculature and calculating the perfused boundary region (PBR). In health, age and blood pressure are reported to impact EG and PBR, and sex differences have also been reported. This project aimed to explore the associations between PBR and phenotypic markers in T2D, with particular focus on sex and obesity.

Material and Method: Anthropometric data, blood samples, blood pressures (BP) and sublingual images were collected from participants with T2D under standardised conditions, as part of the BEAt-DKD Exeter microvascular study. Glycocheck software was used for PBR analysis, calculated from the 50th and 90th percentile RBC column width, where higher PBR represents poorer EG integrity as RBCs increasingly interact with the vessel wall.

Results: Images were obtained from 112 participants (58% male, mean age: 73.5 range: 58-83 years, BMI: 30.7 ± 5.1kg/m^2, systolic BP: 142.2 ± 16.7, diastolic BP: 75.4 ± 8.9mmHg, diabetes duration: 17.5 ± 8.6 years). PBR was assessed in vessels 5-25µm in diameter (mean PBR: 1.93 ± 0.22µm), and vessel size subcategories of 5-9µm (PBR: 1.07 ± 0.08 µm), 10-19µm (PBR: 2.13 ± 0.24µm), and 20-25µm (PBR: 2.35 ± 0.45µm).

PBR measurements were not associated with age, diabetes duration, blood pressure, BMI, or glycaemic control (HbA1c and fasting glucose). Associations were seen between increased PBR in the smallest microvessels (5-9µm), with higher body fat percentage (BF%) (r=0.25, p=0.01, Pearson's) and higher LDL cholesterol (Rs=0.20, p=0.05, Spearman's).

Differences in total PBR (5-25µm) were non-significant between men and women (1.91, 95% CI [1.86,1.96], vs. 1.96µm [1.88, 2.04], p=0.22). However, when refined to the 5-9µm vessels, women had a larger PBR than men (1.05, 95% CI [1.04,1.07], vs. 1.10 [1.07,1.12]µm, p=0.01). LDL and BF% values were significantly higher in women than men (LDL: 2.28 ± 0.77 vs. 1.97 ± 0.80mmol/L, p=0.01) (BF%: 42.5 ± 6.4 vs. 30.0 ± 6.7%, p<0.001) despite comparable BMIs (women: 30.9 ± 5.5 vs. men: 30.6 ± 4.8kg/m^2, p=0.76), potentially influencing the observed sex difference in PBR. Analysis of covariance showed that when controlling for differences in either BF% (p=0.30) or LDL (p=0.12) the sex discrepancy in PBR was lost, yet it remained when controlling for BMI (p=0.01).

Conclusion: This study has shown that glycocalyx integrity is attenuated in women compared to age matched men with type 2 diabetes. This observed sex difference was explained, at least in part, by the increased LDL and body fat in the women compared to the men, despite comparable BMI. Further research is needed to investigate the relationship between body fat and obesity, cholesterol levels, and the glycocalyx in type 2 diabetes.

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DETECTION OF LOWER LIMBS VASCULAR STENOSES IN PATIENTS WITH DIABETES MELLITUS BY PERFUSION ASSESSMENT USING INCOHERENT OPTICAL FLUCTUATION FLOWMETRY

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Background: Diabetes mellitus is an important cause of hemodynamic impairment in the lower extremities, resulting in both arterial damage and microcirculatory dysfunction.

Aim: To evaluate the ability of a new non-invasive optical technology to assess lower extremity haemodynamics in patients with diabetes mellitus.

Methods: 54 patients with type 2 diabetes mellitus (30 women, 24 men) were included in the study: 26 patients without diabetic foot syndrome (median age 58.5 [56; 63.8] years) and 28 patients with diabetic foot syndrome (64 [56.8; 67.2] years). All patients underwent a perfusion test on the dorsal surface of the foot (d) and on the plantar surface of the big toe (p) using optical incoherent fluctuation flowmetry (IOFF) on the right and left lower limbs against a local heating test (local heating to 42°C). The median baseline perfusion level (BP_d, BP_p) median local thermal hyperemia for each minute of the heat test (LTH_d 1-5 min, LTH_p 1-5 min) as well as the perfusion gain relative to baseline (Delta_d 1-5 min, Delta_p 1-5 min) were analysed.

Results: Of 28 patients with diabetic foot syndrome, 23 had haemodynamically significant stenoses of the lower extremity arteries (degree of stenosis of one of the main arteries of 50% and more). The best diagnostic characteristics in stenoses detection were achieved by the LTH_d 3 min and LTH_p 4 min indices. These indices were able to identify limbs with haemodynamically significant stenoses with AUROC values of 0.887 (0.816, 0.957) and 0.907 (0.849, 0.966), respectively. A model using both indices detected stenoses with a sensitivity of 81.3% and a specificity of 92.3%.

Conclusion: The assessment of perfusion by IOFF not only makes it possible to diagnose microcirculatory disorders, but also to achieve high sensitivity and specificity in the detection of lower extremity arterial stenosis in patients with diabetes.

L-Stroke

P171

Novel function of NMMHC IIA identified by Ruscogenin in blood brain barrier

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Background: Although blood–brain barrier (BBB) compromise is central to the etiology of diverse central nervous system (CNS) disorders, endothelial proteins that control BBB function are poorly defined. Based on previous studies, the underlying mechanisms and function of NMMHC IIA-mediated BBB dysfunction induced by ischemic stroke were still unknown. The aim of this study was to investigate whether NMMHC IIA acts as a executor of the mechanical signal or biological signal regulator in regulating BBB function.

Methods: In this study, selection endothelial-targeted NMMHC IIA conditional knockout (MYH9^{iECKO}) mice to construct in vitro and in vivo model, include middle cerebral artery occlusion/reperfusion (MCAO/R)-injured mice and oxygen-glucose deprivation/ reoxygenation (OGD/R)-injured primary brain microvascular endothelial cells (pBMEC). The effect of NMMHC IIA in BBB was investigated using HE staining, evans blue-labeled albumin (EBA) leakage assays, electron microscopy assays. The integrity of ZO-1, occludin structure at intercellular tight

junction were determined by IF. In order to investigate molecular mechanism of NMMHC IIA involving OGD/R-induced BBB dysfunction in vitro, we used transcriptomics for enrichment analysis.
Results: The results in vivo suggested that MYH9^{iECKO} could significantly could ameliorate histopathological damage, reduce the BBB leakage and improve brain endothelial cell structure. In addition, MYH9^{iECKO} also could up-regulate the expression of ZO-1 and Occludin expressions in brain tissue. In transcriptomics, we selected the LATS1/2/YAP signaling pathway in ischemic stroke-induced mice. Meanwhile, the in vitro results demonstrated that MYH9^{iECKO} could significantly ameliorate the signaling pathway activation.
Conclusions: All these findings indicated that the function of NMMHC IIA protein might be the key target and pivotal link involved in regulating ischemic stroke-induced BBB dysfunction.
Keywords: NMMHC IIA, BBB, Transcriptomics, Ischemic Stroke

L-Shock

P172

The Role of TIPE2 in Dendritic Cell Maturation Dysfunction Induced by Post-Hemorrhagic Shock Mesenteric lymph

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Purpose: Immune dysfunction plays a crucial role in the progression of hemorrhagic shock to septic shock and multiple organ dysfunction syndrome. The reflux of post-hemorrhagic shock mesenteric lymph (PHSML) is a key factor triggering immune dysfunction after hemorrhagic shock. Dendritic cells (DCs) are the professional antigen-presenting cells with the strongest function in the body, which stimulate the proliferation and activation of naive T cells to initiate adaptive immune response. Tumor necrosis factor α induced protein 8 like-2 (TIPE2) maintains immune homeostasis by regulating the function of immune cells through T cell receptor (TCR) or Toll-like receptors (TLR). This study investigated the effect of TIPE2/TLR2 signaling pathway-related molecules on DC maturation dysfunction induced by hemorrhagic shock.
Methods: In vivo experiments, normal C57 mice were randomly assigned to sham surgery group (Sham), hemorrhagic shock group (Shock) and hemorrhagic shock with mesenteric lymph drainage group (Shock+Drainage). Immunomagnetic bead sorting method was used to obtain splenic DCs from mice of each experimental group. In vitro experiments, DCs from normal mice spleen were obtained by immunomagnetic bead sorting method, and stimulated with PHSML. A blank control group was also included. DCs transfected with TIPE2-specific interfering fragments (shRNA) and DCs pretreated with TLR2 blocking antibodies were stimulated with PHSML, respectively. The expression of DC membrane costimulatory molecules CD80, CD86, CD40 and major histocompatibility complex class II (MHC-II) was examined with flow cytometry. The mRNA and protein expression of TIPE2 and TLR2 associated with signaling molecules in DCs were measured with RT-PCR and Western blotting, correspondingly.
Results: Compared with the sham group, hemorrhagic shock significantly increased the expression of CD80 and CD86 on DCs, while significantly decreased the expression of CD40. The expression of CD86 and MHC-II on DCs in the Shock+Drainage group was markedly decreased. In addition, the expression of TLR2, MyD88 and TRAF6 were increased in the Shock group, contrary to the expression of TIPE2. PHSML significantly decreased the expression of CD86, CD40 and MHC-II on DCs. Silencing TIPE2 significantly decreased the expression of CD80 and CD86 on DCs, increased the expression of MHC-II, while there was no significant difference in the expression of CD40 . Inhibition of TLR2 resulted in a significant increase in the expression of CD86, CD40, and MHC-II on DCs.
Conclusion: Following hemorrhagic shock, the aberrant expression of costimulatory molecules and antigen presenting molecules on DC leads to its maturation dysfunction. The low level of TIPE2 expression is involved in PHSML-induced DC maturation dysfunction. Inhibition of TLR2 can alleviate PHSML-induced DC maturation dysfunction.
Keywords: Hemorrhagic shock; PHSML; Dendritic cells; TLR2; TIPE2
Funding: This work was supported by the Science and Technology Research Project of Hebei Higher Education Institutions (No. ZD2020301).

L-Cerebral Microcirculation

P173

Both acute kidney injury and chronic kidney disease sensitize cerebral vasoconstriction through fibroblast growth factor 2 signaling pathway

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Background and Objective: Acute kidney injury (AKI) and chronic kidney disease (CKD) are both independent risk factors for ischemic stroke, but the mechanisms remain unknown. Here, we identify a possible mechanism that can drive brain vessel injury after AKI and CKD.
Methods: We isolated brain microvessels and macrovessels from C57Bl/6 mice with 30 minutes bilateral renal ischemia followed by 24 hours reperfusion or surgical 5/6 nephrectomy fed a 6% sodium chloride diet for three months to test their responses to vasoconstrictors.
Results: We found that after AKI or CKD, brain vessels were sensitized to angiotension II (Ang II). Moreover, after CKD, brain vessels were also sensitized to norepinephrine (NE) and endothelin-1 (ET-1). Upregulation of fibroblast growth factor 2 (FGF2) and FGF binding protein 1 (FGFBP1) expression in both serum and kidney tissue after AKI and CKD suggested a potential contribution to the vascular sensitization. Administration of FGF2 and FGFBP1 proteins to isolated healthy brain vessels mimicked the sensitization to Ang II after both AKI and CKD, and to NE and ET-1 after CKD. Brain vessels in FGF2 signaling pathway gene knockout mice failed to induce brain vascular sensitization. Complementary to this, systemic treatment with the clinically used FGF receptor kinase inhibitor BGJ398 (Infigratinib) reversed the kidney injury-induced brain vascular sensitization.
Conclusion: Therefore, we hypothesized that AKI and CKD can promote the contraction of cerebral arteries by activating FGF2 pathway, reduce cerebral blood flow and ultimately lead to ischemic stroke. The inhibitors of FGF2 pathway maybe beneficial in preventing AKI and CKD-induced brain vessel injury.

L-Ferroptosis

P174

A Ferroptosis-Related Long Noncoding RNA Signature Predicts the Prognosis of Colorectal Cancer Patients

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Ferroptosis, which is an iron-dependent form of regulated cell death, plays an important role in the regulation of colorectal cancer cells. Long non-coding RNA (lncRNA) is a key mediator of regulating ferroptosis. In this study, We obtained the RNA sequencing data of colorectal cancer patients from The Cancer Genome Atlas (TCGA) database. Univariate and multivariate Cox regression analyses were performed to construct a ferroptosis-related lncRNAs signature. Kaplan-Meier analysis, univariate and multivariate Cox regression analyses and receiver operating characteristic (ROC) curve analysis were performed to verify

that the signature is an independent prognostic factor for colorectal cancer patients. Gene set enrichment analysis showed that gene sets are notably enriched in tumor-related pathways. In conclusion, our study constructed an effective prognostic signature for colorectal cancer patients and assist in diagnosis and treatment.

L-Noncoding RNAs

P175

Hypoxia-induced circPLOD2a/b promote migration and invasion of GBM cells via suppressing XIRP1 through binding to HuR

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Background: Glioblastoma (GBM) is the most lethal form of brain tumors in human, and hypoxia is a common microenvironment during tumor progression and metastasis of this disease. Circular RNAs (circRNAs) are identified as regulators in cancers including GBM. However, what roles circRNAs play in GBM under hypoxic condition remains unclear.

Methods: RNA-seq was used to analyze expression profile of circRNAs in U87 cells under normoxia and hypoxia. Two circRNAs spliced from the same parental gene *PLOD2* were named as circPLOD2a and circPLOD2b, whose circular structure and expression pattern were verified by RT-PCR, qRT-PCR, RNase R digesting and Sanger sequencing in GBM cells and clinical specimens. Knockdown and overexpression of circPLOD2a/b in GBM cells were used to investigate the biological functions of circPLOD2a/2b on tumorigenesis. RNA fluorescence in situ hybridization (FISH) assay, RNA-pulldown, mass spectrometry, RNA binding protein immunoprecipitation (RIP) assay, deletion-mapping and rescue experiments were conducted to explore the interaction between circPLOD2a/b, ELAV like RNA binding protein 1 (ELAVL1, HuR), and xin actin binding repeat containing 1 (*XIRP1*).

Results: CircPLOD2a/b were significantly up-regulated in hypoxic GBM cells and directly induced by HIF1a under hypoxia. These two circRNAs also showed higher expression levels in GBM patient tissues compared with non-cancer controls. Knockdown of circPLOD2a/b suppressed the invasion ability of GBM cells *in vitro* while had no effect on cell proliferation. Mechanistically, circPLOD2a/b could competitively bind to RNA binding protein HuR, and inhibit the interaction between HuR and mRNA of downstream gene *XIRP1*, thus suppressing the tumor aggressiveness in GBM through downregulating *XIRP1*.

Conclusions: Hypoxia-induced circPLOD2a/b were identified as key regulators of migration and invasion in GBM cells under hypoxia, which acts as oncogenic circular RNAs to attenuate the interaction between HuR and *XIRP1*. Our study suggests that circPLOD2a/b may be potential therapeutic targets for GBM patients.

L-Aging and Microcirculation

P176

EFFECT Of OLIGOPEPTIDE TO MICROCIRCULATION AS A NUTRITION FOR ANTI AGING & REGENERATION

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Peptide are small proteins And molecule active inside collagen formed from two or more amino acids. Can covers dipeptides, tripeptides , tetrapeptides , and pentapeptide.

Oligopeptide mechanism in cells:

Collagen absorbed by body in form amino acids , tripeptide / dipeptide => then synthesized in fibroblasts => In fibroblasts, collagen tripeptide and dipeptide are translated at the ribosome into the endoplasmic reticulum system (RES) => In RES the peptide chain becomes pro-alpha => Hydration process occurs with co-factor vitamin C (ascorbic acid) => Then the hydroxylysine residue undergoes glycosylation => In the RES, a triple alpha helix is formed => Then procollagen is exocytosed to the Golgi bodies => Procollagen is converted to tropocollagen by procollagen peptidase => Some tropocollagen forms collagen fibrils through covalent cross-linking => Next to form collagen fibers => Collagen then attaches to the cell membrane through several proteins, including fibronectin and integrin.

Smooth microcirculation is very important for the flexibility of blood vessel walls which are influenced by elastin and collagen fibers.

Because oligopeptides in the body's metabolism have an important role in the formation of collagen and elastin.

Stiffness artery especially determined by characteristic elastic intrinsic wall artery . Change structural on wall arteries , in particular decline elastin density with enhancement content collagen , presumed play role main in enhancement stiffness artery related center age.

L-Lymphatic Vessel

P177

12th World Congress of Microcirculation

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In modern neurobiology, sleep is considered as a novel biomarker and a promising therapeutic target for brain diseases [1]. This is due to recent discoveries of the nighttime activation of the Brain's Waste Removal System (BRWS) playing an important role in removal wastes and toxins from the brain and contributing neuroprotection of the central nervous system. In our review we discuss that night stimulation of BWRS might be a breakthrough strategy in a new treatment of Alzheimer's and Parkinson's disease, stroke, brain trauma and oncology [2]. Although this research is in its infancy, however, there are pioneering and promising results suggesting that night transcranial photostimulation (tPBM) stimulates more effectively lymphatic removal of amyloid-beta from the mouse brain than daily tPBM that associated with a greater improvement of the neurological status and recognition memory of animals [3]. In our previous studied, we discovered that tPBM modulates the tone and permeability of the lymphatic endothelium by stimulating the NO formation promoting lymphatic clearance of wastes and toxins from the brain tissues [4]. We also demonstrate that tPBM can also lead to angio- and lymphangiogenesis, which is other mechanism underlying tPBM-mediated stimulation of BWRS [4,5]. Thus, photo-augmentation of BWRS might be a promising therapeutic target for preventing or delaying brain diseases associated with BWRS dysfunction.

Here we present pioneering technology for simultaneous tPBM in humans and sleep monitoring for stimulation of BWRS. The wireless controlled gadget includes a flexible organic LED source that is controlled directly by a sleep tracking device or via mobile application. The design autonomous LED source is capable to provide the required therapeutic dose of light radiation at certain region of patient's head without disturbance of sleeping patient. To minimize patients discomfort advanced materials like flexible organic LEDs was used.

This study was supported by RSF project No.23-75-30001.

L-Monocytes

P178

Calciprotein particles cause pro-inflammatory response in systemic circulation

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Background: Calciprotein particles (CPPs) represent an elegant mineral buffering system responsible for scavenging of excessive

calcium and phosphate ions in the human blood and preventing extraskeletal calcification. However, circulating CPPs are internalised by endothelial cells and may trigger endothelial dysfunction, in particular in patients having concomitant pathologies such as diabetes mellitus and chronic kidney disease. In patients with end-stage renal disease which is accompanied by hyperphosphatemia, a significant proportion of primary CPPs (i.e., amorphous mineralo-organic complexes) undergo conversion to secondary (crystalline) CPPs which are believed to enhance systemic inflammation. Yet, the pathogenic effects of circulating CPPs on the blood cells have not been reported hitherto.

Materials and Methods: Here, we added physiologically relevant doses of either primary CPPs (CPP-P), secondary CPPs (CPP-S), or physiological saline to the blood cells cultured in the pulsatile flow system or to the circulation of Wistar rats, and then assessed which blood cells are capable of internalising CPPs and which cytokines are upregulated in such conditions. Analytical techniques included complete blood count measurements, flow cytometry, confocal microscopy, and dot blotting. In addition, we measured the levels of pro- and anti-inflammatory cytokines in plasma-derived extracellular vesicles (EVs) and EV-depleted plasma to identify the relative contribution of these compartments to CPP-induced systemic inflammation.

Results: Co-incubation of CPP-P or CPP-S with the human blood did not cause alterations of the complete blood count parameters at any of the time points (30 minutes, 2, 4, or 24 hours). Among the blood cells, monocytes were the only cell population internalising CPPs as soon as within 1 hour after their addition to the pulsatile flow system, whereas neutrophils, eosinophils, T cells, B cells, NK cells, platelets, and red blood cells were free from these particles. Co-incubation of CPP-P with the human blood triggered the release of pro-inflammatory cytokines (MIP-1a/1b, SDF-1a/CXCL2, and IL-8), whilst CPP-S enhanced the production of sICAM-1, albeit such response was largely donor-dependent. Intravenous administration of CPP-P to Wistar rats also resulted in a considerable pro-inflammatory response, increasing the production of MIP-1a, MIP-3a, CINC-1, CINC-3, CXCL10, and sICAM-1. Intriguingly, we noticed the concurrent upregulation of several anti-inflammatory cytokines (IL-1Ra, IL-10, and CNTF) that might partially balance the hazardous effects of CPP internalisation. Differential expression of abovementioned pro-inflammatory cytokines upon the co-incubation of human or rat blood with CPP-P was observed both in EV-depleted plasma and EV lysate, suggesting that excessive amounts of pro-inflammatory cytokines synthesised upon the CPP internalisation can be either loaded into the EVs or released into plasma as soluble factors. However, most of the overproduced cytokines freely circulated in plasma rather than were enclosed into the EVs.

Conclusions: CPP-induced systemic inflammatory response in vivo is accompanied by the release of monocyte-derived cytokines (MIP-1a, MIP-3a, CINC-1, CINC-3, and CXCL10) and endothelial-derived cytokines (sICAM-1 and IL-8), in accord with the data on exclusive internalisation of CPPs by these two cell types. Pro-inflammatory response to immature CPPs (CPP-P), which precede mature CPPs (CPP-S) during the artificial synthesis and CPP formation in vivo, was significantly higher that might indicate their easier dissolution and better availability of calcium ions.

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L-Stem Cells

P179

Photomodulation promotes the differentiation of adipose-derived stem cells towards endothelial progenitor cells

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Aim: Adipose-derived stem cells (ASCs) therapies are emerging as a promising approach to therapeutic angiogenesis. Therapeutic persistence and reduced primitive stem cell function following cell delivery remains a critical hurdle for the clinical translation of stem cells in current approaches.

Methods: Cultured ASCs were derived from subcutaneous white adipose tissue isolated from mice fed a normal diet. We conducted high-throughput miRNA sequencing to detect the miRNA profiles of light-activated ASCs-exosomes (Exos) and used dual-luciferase reporter gene assay, specific miRNA inhibitor, and siRNA to analyze the roles of miRNA and target gene in vitro. Flow cytometry was used to determine the characterization of ASCs and endothelial progenitor cells (EPC). ASCs secretomes were analyzed by liquid chromatography tandem mass spectrometry.

Results: Our study demonstrated that photoactivated ASCs increased ASCs-derived EPC. Mass spectrometry revealed that light-treated ASCs conditioned medium retained a more complete pro-angiogenic activity with significant upregulation of angiogenesis related proteins. We further investigated the photoreceptive effect of Opsin3 (Opn3) in light-activated ASCs. Deletion of Opn3 abolished the differentiation of light activation in expression of EPC markers, and the changes of Ca^{2+} influx as well as cAMP levels. Finally, light-activated ASCs-Exos can drive the differentiation of ASC to EPC via miR-3572-5p-mediated targeting of ELVAL1.

Conclusion: Photomodulation is an effective method for generating the functionality of ASCs-Exos which trigger differentiation of ASC to EPC.

P180

TC14012 inhibited tumor cell-induced endothelial necroptosis

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Endothelial necroptosis plays significant roles in mediating tumor cell-transendothelial migration and cancer metastasis. It's still a big challenge to find reliable approaches suppressing endothelial necroptosis and cancer metastasis. The CXCL12-CXCR4/CXCR7 axis remarkably regulates cancer metastasis. TC14012 is an agonist of CXCR7 as well as an antagonist of CXCR4. However, the role of TC14012 on cancer metastasis remains to be defined. Here, we have determined the effects of TC14012 on the transendothelial migration of the tumor cells using the transwell analysis system. And, cell death was also evaluated using EthD-IIIstaining. Finally, the expression and phosphorylation of mixed lineage kinase domain-like protein (MLKL), the key mediator of cell necroptosis, were evaluated using Western blot. The results showed that TC14012, by working on its receptor CXCR7, significantly inhibited transendothelial migration of lung cancer cells, and suppressed endothelial cell death induced by the tumor cells. Inhibiting necroptosis with NEC-1 blunted the inhibitory effects of TC14012 on endothelial cell death and transendothelial migration of tumor cells. Further explorations have demonstrated that TC14012 significantly restrained the phosphorylation of MLKL. Together, these results suggested that TC14012 may serve as an inhibitor of cell necroptosis through inhibiting phosphorylation of MLKL, protruding an important potential of TC14012 in retarding cancer metastasis.

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3	偏头痛中西医结合诊疗指南	中华中医药学会	2023年
4	中国偏头痛中西医结合防治指南(2022年)	中国中西医结合学会神经科专业委员会	2023年
5	偏头痛中医临床实践指南	中国标准化协会	2022年
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- ☑ 与抽动障碍指南一线药物等效，神经精神类不良反应发生率显著低于一线药物
- ☑ III期临床试验研究 *JOURNAL of CHILD PSYCHOLOGY AND PSYCHIATRY* SCI-IF8.982
- ☑ 第一个欧美指南推荐具有强证据的儿童创新中成药

芍 麻 止 痉 颗 粒

国谈医保品种 专注抽动障碍

咨询热线：*800-818-9818　400-618-9818*　天士力医药集团股份有限公司

天士力TASLY

卓效保护 糖网优选

用于2型糖尿病引起的Ⅰ期（轻度）、Ⅱ期（中度）非增殖性糖尿病视网膜病变气滞血瘀证所致的视物昏花、面色晦暗、眼底点片状出血，舌质紫暗或有瘀点瘀斑、脉涩或细涩。

口服。一次20丸 一日3次 疗程24周

咨询热线：

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复方丹参滴丸

国药准字：Z20030139 津药广审（文）第250306-00799号 请按药品说明书或在药师指导下购买和使用 禁忌：尚不明确 不良反应：尚不明确

天士力 TASLY

CCTV 品牌强国工程

中央广播电视总台

刺痛

大便干结

口渴欲饮

多食易饥

消渴清颗粒

提高糖尿病患者生活质量

- 可改善该证所见口渴欲饮、多食易饥、怕热心烦、溲赤或尿多、大便干结、或胸中闷痛、或肢体麻木、刺痛，以及盗汗等症；
- 配合抗糖尿病化学药品用于II型糖尿病属阴虚热盛挟血瘀证的治疗；
- 滋阴清热，活血化瘀。

咨询热线：

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天士力医药集团股份有限公司

消渴清颗粒

国药准字：Z20080034 津药广审(文)第 号 本广告仅供医学药学专业人士阅读 【禁忌】孕妇禁用；有出血倾向者慎用；肝、肾功能不全者慎用。 【不良反应】个别患者发生恶心，呕吐；个别患者在用药期间出现ALT增高。

天士力 TASLY

CCTV. 品牌强国工程

中央广播电视总台

冻干粉针心动力

- 益气复脉、养阴生津
- 冠心病劳累性心绞痛气阴两虚证
- 冠心病所致左心功能不全II、III级气阴两虚证

咨询热线：

800-818-9818　400-618-9818

天津天士力之骄药业有限公司

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有效改善心脏功能

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用于气虚血瘀型胸痹，症见胸闷、胸痛，气短乏力、心悸、面色少华、自汗，舌体胖有齿痕、舌质暗或紫暗或有瘀斑，脉沉或沉弦。 适用于冠心病、心绞痛见上述证候者

咨询热线：

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口服。一次20丸 一日3次 疗程24周

咨询热线：

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国家市场监督管理总局批准

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·海藻囊材　·香港制造

保健功能：本品经动物实验评价，具有增强免疫力的保健功能。
适宜人群：免疫力低下者。
不适宜人群：少年儿童、孕妇、乳母。
本品不能代替药物，适宜人群外的人群不推荐食用本产品

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不适宜人群：少年儿童、孕妇、乳母。
本品不能代替药物，适宜人群外的人群不推荐食用本产品

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广西 河丰药业 有限责任公司
GUANGXI HEFENG PHARMACEUTICAL CO.,LTD

高质量发展50亿红色药企　高质量发展双百红色全产业链

广西河丰药业有限责任公司

企业简介 Company Prfile

广西河丰药业有限责任公司位于东兰县第三开发区,其前身是广西东兰制药厂,始建于1970年,是开国将军韦国清在革命根据地东兰县建立的三大企业之一,是全国较早的、集中草药种植、生产原料药、中西制齐综合性知名制药企业之一,公司拥有小容量注射剂、片剂、胶囊剂、颗粒剂、茶剂、原料药等六个剂型,并通过GMP认证,目前有69个品种获得国药准字批文,其中有35个品规进入全国医保目录,2个国家独家药品(岩黄连注射液和银葛通脉茶),8个原料药;技术力量雄厚,生产设备先进。现有员工300多人,其中高级制药工程师、工程师、助理工程师、技术员及相关的工程技术人员168人。先后获得“高新技术企业”、“广西科技二等奖”、“专精特新”中小企业、“全国工人先锋号”、“广西老字号”、“广西农业产业化重点龙头企业”、“广西五一劳动奖状”、“全市脱贫攻坚先进集体”、“东兰县纳税大户”等二十多奖项及荣誉称号,同时也是河池市重点税源保护单位。拥有专利11项。

2022年我公司在自治区、市、县党委政府及各部门的帮助下创建了广西东兰县天然中药材产业示范区并获评广西农业农村厅评定的五星级中药材产业示范区。我公司以“公司+基地+农户+合作社”经营模式与郭型经营主体及农户利益联结紧密。通过分工协作,联合发展、产业增值明显,农民受益较大。中药材示范种植基地3000亩,基地主要分布在东兰县东兰镇板逢村、乐里村,武篆镇红里村等,种植天冬、百部、岩黄连、肿节风、山乌龟等,年产2.5万吨。至2022年末公司带动农户数达到了1300多户,农户户均年增收2.3万元。

同时，2020年公司成立社会责任部，现安置残疾人就业110多人，解决残疾人就业难，为政府排忧解难。

企业荣誉 Company Honar

企业微信

中国,广西省河池市东兰县第三开发区新城路266号　电话: 0778-6329099
地址邮编:547400　客服电话: 0772-2772797　网址: www.gxhfyy.com

赛斯美®
海博麦布片

赛斯美®Hyzetimibe
——联合降脂治疗的首选

联合他汀，强效降脂，1+1≈8

安全性高，联合他汀不增加不良反应发生率

中国原创、中国人群、中国证据

简明处方

药品信息：

【商品名称】 赛斯美 ®

【通用名称】 海博麦布片

【剂　　型】 片剂

【规　　格】 10mg、20mg

【主要成分】 海博麦布

【适 应 症】 本品作为饮食控制以外的辅助治疗，可单独或与HMG-CoA还原酶抑制剂（他汀类）联合用于治疗原发性（杂合子家族性或非家族性）高胆固醇血症，可降低总胆固醇（TC）、低密度脂蛋白胆固醇（LDL-C）、载脂蛋白B（ApoB）水平。

【用法用量】 患者在接受本品治疗的过程中，应坚持适当的低脂饮食。

口服；本品单独服用推荐剂量为每次10mg或20mg，每天一次；与他汀类联合应用，每次10mg或20mg。空腹或与食物同时服用。

老年患者不需要调整剂量。鉴于本品对儿童、肝肾功能受损患者的影响尚未明确，故不推荐此类患者应用本品。

【禁 忌 证】 对本品任何成份过敏者。活动性肝病，或原因不明的肝酶（ALT/AST/GGT）持续升高的患者。所有HMG-CoA还原酶抑制剂被限制使用于怀孕及哺乳期妇女。当本品与此类药物联合用于有潜在分娩可能性的妇女时，应参考HMG-CoA还原酶抑制剂产品说明书（详见说明书【孕妇及哺乳期妇女用药】）。

【不良反应】 使用本品常见不良反应有乏力、腹部不适、血肌酸磷酸激酶升高、腹胀、腹泻、上腹痛、肝功能异常等。10mg或20mg单独应用造成肝酶升高（ALT/AST/GGT≥正常值上限3倍）发生率1.72%，联合阿托伐他汀造成肝酶升高（ALT/AST/GGT≥正常值上限3倍）发生率2.75%。10mg或20mg单独应用造成肌酸磷酸激酶升高（CPK≥正常值上限10倍）发生率0.40%，联合阿托伐他汀造成肌酸磷酸激酶升高（CPK≥正常值上限10倍）发生率0.27%。

【注意事项】 当本品与他汀联合应用时，请同时参考他汀类药物的使用说明书。单独应用本品或与他汀联合应用的研究中，发现有肝酶升高（ALT/AST/G-GT≥正常值上限3倍）。当本品与他汀类联合应用时，建议治疗前进行肝功能检查，同时参照他汀类的产品说明书。本品对轻、中度或重度肝功能不全患者的影响尚不明确，故不推荐此类患者应用本品。在临床研究中，本品未发生肌病和横纹肌溶解症，发生肌痛，严重程度多为轻度。建议所有患者在开始本品的治疗时，应被告知肌病潜在发生的危险性，并被告知要迅速报告任何不明原因的肌痛、触痛或无力。对于CPK≥正常值上限10倍患者需密切监测CPK及相关肌肉骨骼症状，若持续或加重则考虑停用海博麦布和或他汀类药物。如果患者被诊断为或疑似肌病时，应立即停用本品以及正在合用的任何一种他汀类药物。

【特殊人群】 目前尚无本品用于孕妇的充足的和良好对照的临床研究，孕妇应谨慎应用本品。目前本品尚不明确是否经过人类母乳排泌，故不宜用于哺乳期妇女。尚无本品用于18岁以下儿童和青少年患者的安全性和有效性数据。>75岁患者，暂未进行临床研究，建议在医生指导下使用。本品尚未在肝、肾功能不全患者中进行临床研究。

【贮　　藏】 遮光，密封，不超过 25℃保存。

【包　　装】 10mg：铝塑泡罩包装，外加聚酯/铝/聚乙烯药用复合袋，复合袋内加固体药用纸袋装硅胶干燥剂。7片/板，2板/盒；10片/板，2板/盒。
20mg：铝塑泡罩包装，外加聚酯/铝/聚乙烯药用复合袋，复合袋内加固体药用纸袋装硅胶干燥剂。7片/板，2板/盒。

【有 效 期】 24个月

【生产企业】 浙江海正药业股份有限公司

【生产地址】 浙江省台州市椒江区外沙路 46 号

【药品上市许可持有人】 浙江海正药业股份有限公司

【批准文号】 国药准字H20210030，国药准字H20210031

完整处方资料请见药品说明书

【参考文献】 赛斯美®产品说明书（20221118）

本资料仅供医学药学专业人士阅读

参考文献：
1.Rioufol G, et al. Circulation. 2002;106(7):804-8.
2.Sato A, et al. Am J Cardiol. 2010;105(7):930-5.
3.中华医学会心血管病学分会介入心脏病学组 中华心血管病杂志 2016;44(5):382-400
4.Jiang J,et al.Ther Clin Risk Manag.2018 Nov 16;14:2255-2264.
5.Anselm K Gitt,et al.Atherosclerosis.2017 Nov;266:158-166.
6.Mei Zhang,et al.Int J Cardiol.2018 Jun 1;260:196-203.
7.李建军. 中国医学前沿杂志：电子版, 2013(12):5.
8.中国血脂管理指南修订联合专家委员会. 中国循环杂志. 2023 3;38(3)237-270.
9.Visseren FLJ, et al. Rev Esp Cardiol (Engl Ed). 2022 May;75(5) 429.
10.依折麦布片说明书.20180428版.
11.Ruan Z, et al. J Clin Pharmacol. 2014 Oct;54(10)1144-52
12.Liao J, et al. Front Pharmacol. 2021 May 28;12665372.
13.James E Patrick, et al. Drug Metab Dispos . 2002 Apr;30(4):430-7.
14.Data in HISUN
15.海博麦布片说明书. H1.2. 20221118版.
16.Dujovne CA, et al. Am J Cardiol. 2002 Nov 15;90(10):1092-7.
17.Stein E, et al. Am Heart J. 2004 Sep;148(3)447-55.
18.Ballantyne CM, et al. Circulation. 2003 May 20;107(19):2409-15.

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微循环监测与活体成像方案 »

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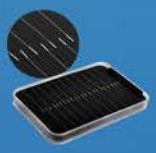

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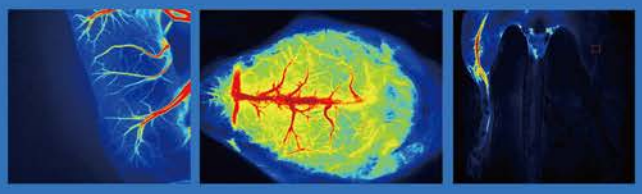
血流灌注监测及成像方案 Step 3



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行为功能和组织病理研究方案 Step 4

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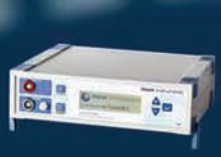
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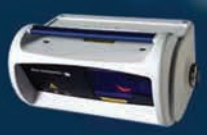
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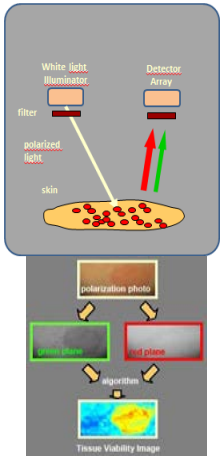
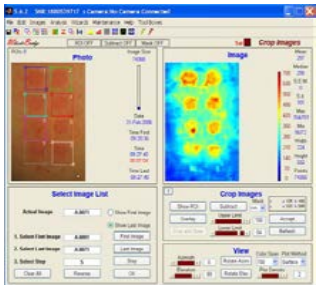
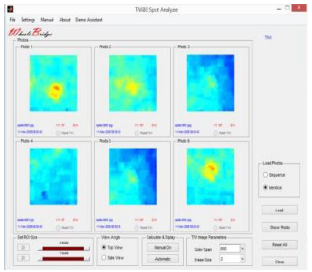
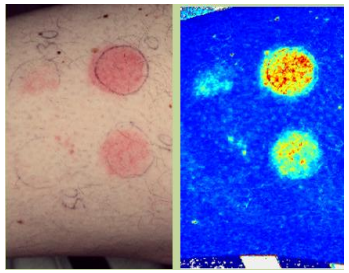
TiVi700 系统通过对用偏振光镜头拍摄的图像进行分析可以绘出皮下平均约 0.5mm 深的局部红血细胞的聚集图像。高性能的软件可以对大量的数据进行快速定量分析，用于代替人用眼睛进行皮肤测试观察的主观判断方法，对局部皮肤的红斑量和苍白度进行独立的定量估算。









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1. 对于护肤品、化妆品的研制和评估，TiVi 700 测试系统是一个理想的产品评估设备。
2. 对皮肤刺激等级分类和斑贴试验，TiVi 700 系统可以用客观的测试数据代替用肉眼观察的皮肤刺激性等级分类标准。
3. 揭示皮肤局部使用化妆品和用药后微血管的反应和变化情况。
4. 在烧伤整形外科中监测皮肤血流灌注量判断皮肤损伤的程度。
5. 监测血流灌注量可以评估疾病所引起的微血管病，用以量化药物治疗的效果。
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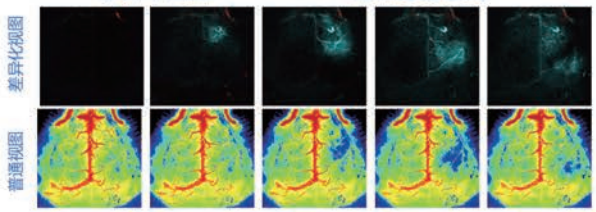

普通视图：可观察血流灌注的空间分布以及缺血区的扩散过程
差异化视图：可清晰观察到缺血区（蓝色区域）的扩散过程
＊ 以上为动态视频的截图，如需观看视频请登录网站。

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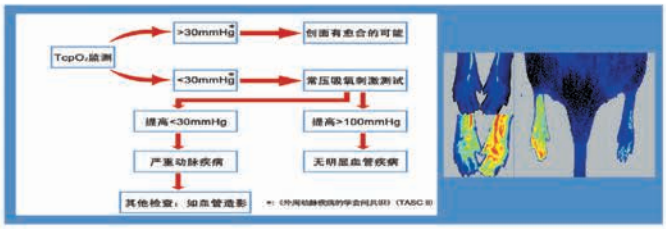

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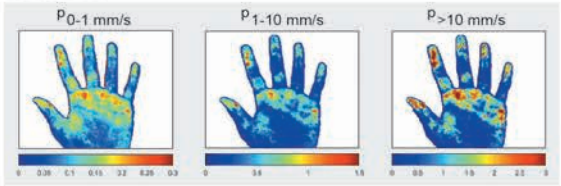

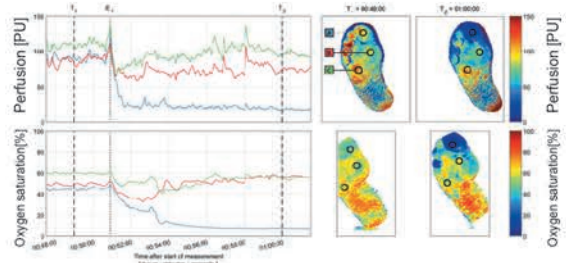

Fig. 3. Case 2. A significant decrease in both perfusion and oxygen saturation following recanalization of the occlusion in the superficial femoral artery and angiography at T_2, indicating localized occlusion in 1st and 4th toe persisting for more than 1 h after the initial onset (outside time-scale of the figure). The patient reported great pain in the 1st toe. A micro-embolisation due to the recanalization was suspected.

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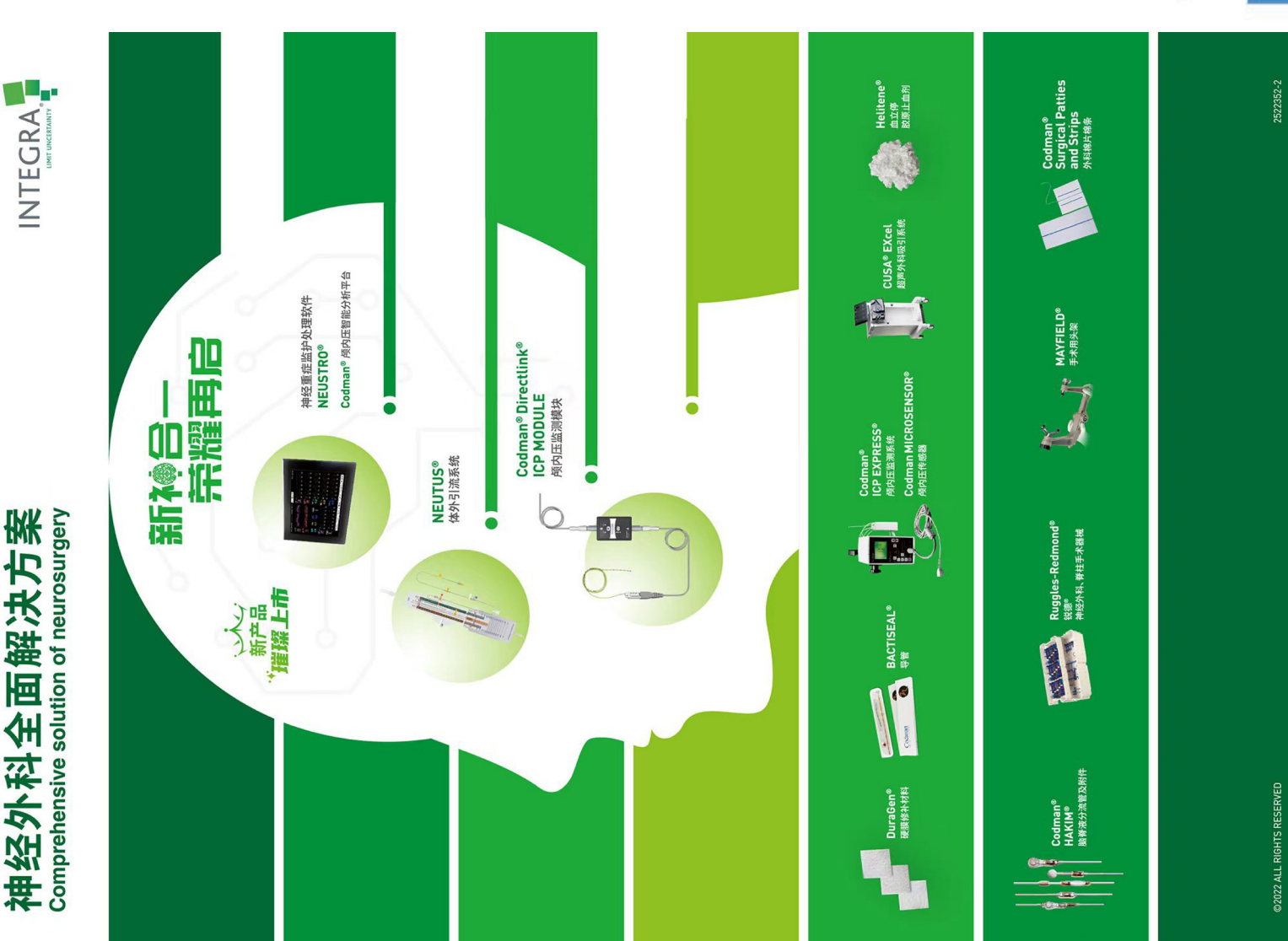

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