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REVIEW

Molecular Mechanisms of Latent Inflammation in Metabolic Syndrome. Possible Role of Sirtuins and Peroxisome Proliferator-Activated Receptor Type γ

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Abstract—The problem of metabolic syndrome is one of the most important in medicine today. The main hazard of metabolic syndrome is development of latent inflammation in adipose tissue, which promotes atherosclerosis, non-alcoholic fatty liver disease, myocarditis, and a number of other illnesses. Therefore, understanding of molecular mechanisms of latent inflammation in adipose tissue is very important for treatment of metabolic syndrome. Three main components that arise during hypertrophy and hyperplasia of adipocytes underlie such inflammation: endoplasmic reticulum stress, oxidative stress, and hypoxia. Each of these components mediates activation in different ways of the key factor of inflammation – NF-κB. For metabolic syndrome therapy, it is suggested to influence a number of inflammatory signaling components by activating other cell factors to suppress development of inflammation. Such potential factors are peroxisome proliferator-activated receptors type γ that suppress transcription factor NF-κB through direct contact or via kinase of a NF-κB inhibitor (IKK), and also the antiinflammatory transcription factor AP-1. Other possible targets are type 3 NAD^+-dependent histone deacetylases (sirtuins). There are mutually antagonistic relationships between NF-κB and sirtuin type 1 that prevent development of inflammation in metabolic syndrome. Moreover, sirtuin type 1 inhibits the antiinflammatory transcription factor AP-1. Study of the influence of these factors on the relationship between macrophages and adipocytes, macrophages, and adipose tissue-derived stromal cells can help to understand mechanisms of signaling and development of latent inflammation in metabolic syndrome.

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Obesity is one of the most crucial public health problems in the modern world. Experts of the World Health Organization (WHO) have even assigned this disease a metaphoric name – "pandemic of the XXI century". According to a statistical report of WHO regarding health of the Earth's population in 2014, from 20 to 40% of the population suffer from obesity. In some countries (Tonga, Marshall Islands, Nauru) this number is over 50%. Recently, problem of childhood obesity was brought to the forefront. During last 12 years, the number of children with obesity has increased by 50%, and this tendency remains by now [1]. Thus, at present, the problem of this disease is highly relevant.

Obesity is dangerous because it can cause a large number of comorbidities. The first interest in such "clusterization" of diseases emerged as long ago as in the 1920s in the USSR when G. F. Lang revealed a link between obesity and arterial hypertension (AH), disorders of carbohydrate metabolism, and gout [2]. Then, in 1926 A. L. Myasnikov and D. M. Grotel noted a connection between presence in patients of hypercholesterolemia, hyper-

Abbreviations: AH, arterial hypertension; ATSC, adipose tissue-derived stromal cells; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; HIF, hypoxia-induced factor; IKK, NF-κB inhibitor kinase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein type 1; MMPs, matrix metalloproteinases; NAM, nicotinamide; NMN, nicotinamide mononucleotide; PGC-1α, PPARγ coactivator type 1α; PHD, prolyl-hydroxylase domains; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle; T2D, type 2 diabetes; TLR, Toll-like receptors; TNFα, tumor necrosis factor α; UCP-2, uncoupling protein type 2; UPR, unfolded protein response; VHL, von Hippel–Lindau protein.

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uricemia, AH, and obesity [3]. However, these complexes of disorders were first denoted as a single disease in the West in the middle of XX century: in 1966, J. Camus denoted a complex of gout, type 2 diabetes, and hyperlipidemia as "metabolic trisyndrome" [4-6]. In 1968, H. Mehmert introduced a concept of the "abundance syndrome" [2]. In 1988, G. M. Reaven introduced a concept of "syndrome X" that included a complex of hyperinsulinemia, disorder of glucose tolerance, hyperglyceridemia, low cholesterol in high density lipoprotein fraction, and AH [2]. However, the term "metabolic syndrome" only appeared in 1981, when M. Hanefeld and W. Leonardt proposed to call in such way cases of combination of different metabolic disorders. The term "deadly quartet" introduced by J. Kaplan in 1989 is also worth noting. This is one of the most dangerous types of metabolic syndrome. It implies a combination of such metabolic disorders as disorder of glucose tolerance, hypertriglyceridemia, obesity, and AH. In addition to determining this type of metabolic syndrome, the importance of this work consists in the fact that abdominal obesity as an important part of the metabolic syndrome was first declared there [2, 7]. At the same time, the metabolic syndrome is not always associated with obesity. In particular, a "European" variant of metabolic syndrome includes hyperinsulinemia, AH, hyperlipidemia, and disorder of glucose tolerance or type 2 diabetes (T2D). However, variants with composition hyperinsulinemia, AH, and hyperlipidemia are possible [2, 8].

Classic metabolic syndrome is a complex of abdominal obesity, hyperinsulinemia, hyperlipidemia, AH, and disorder of glucose tolerance or T2D [2]. When considering emergence of metabolic syndrome from the physiological and biochemical points of view, this complex of diseases appears to be logical. Where is the logical connection between the components of this complex of disorders?

The first step in the development of the classic metabolic syndrome is abdominal obesity. Pathological process starts from a little thing – excessively rich in calories nutrition. As a result, adipocyte hypertrophy and activation of adipocyte differentiation occur [9]. For hypertrophy, significant rearrangement of the extracellular matrix is necessary to create a spatial niche for adipocytes to increase in size. Different proteases participate in this process, in particular, cathepsin K that contributes to degradation of type I and type II collagens. It also cleaves a key protein of the extracellular matrix – fibronectin [10]. Expression of cathepsin K in obesity is greatly increased; it was also demonstrated that it might stimulate differentiation of human pre-adipocytes [11]. Besides, an important cathepsin K target is SPARC – an extracellular matrix protein modulating cell interaction with the extracellular matrix. Decrease in its concentration is associated with hyperplasia and adipocyte hypertrophy as well as with decrease in concentration of type I collagen [10]. Second, an important part of remodeling of adipose tissue extracellular matrix in adipocyte hypertrophy is secretion of matrix metalloproteinases (MMPs) and their inhibitors (tissue-specific metalloproteinase inhibitors); increase in concentration of tissue-specific type 1 metalloproteinase inhibitor is observed in adipocyte hypertrophy. It is associated with adipogenesis, while decrease in activity of MMP-2 and MMP-9 precedes adipocyte differentiation [10].

Adipocyte hypertrophy and an increase in their number in adipose tissue initiate a chain of disorders. First, it is the development of chronic latent inflammation in adipose tissue. Reasons for development of inflammation may be hypoxia [12], endoplasmic reticulum stress [13], and oxidative stress [14]. Let us consider in more detail the occurrence of inflammation in adipose tissue in each case.

Occurrence of hypoxia during the development of adipocyte hypertrophy is mediated by several factors: (i) increase in adipose tissue volume is not accompanied by an increase in cardiac output and blood flow velocity; (ii) increase in blood inflow to adipose tissue after a meal that is observed in people without obesity, is absent in obesity; (iii) hypertrophied adipocytes may be up to 200 μm in diameter, which exceeds the normal oxygen diffusion distance [15]; (iv) enlarged adipose tissue cells can compress blood vessels and prevent access of oxygen to local adipose tissue areas. Hypoxia is one of the causes of the constitutive inflammation in hypertrophied adipose tissue as it was convincingly shown in a number of papers [12, 15-17]. A connection was found between hypoxia and inflammation at the level of signaling cascades, including these in adipose tissue. Let us consider the metabolic pathways that bring together hypoxia and inflammation in adipose tissue.

Transcription factor HIF-1 (hypoxia inducible factor) is the main element of the cell protection against hypoxic conditions. It is a heterodimeric DNA-binding complex of two proteins possessing a helix–loop–helix domain. The HIF-1β subunit is constitutively expressed, while expression of HIF-1α is inducible and depends on hypoxic conditions. After association, the HIF-1α–HIF-1β complex binds to a pentanucleotide consensus DNA sequence (RCGTG) in a specific region of a target gene [18]. Stability of HIF-1α and its activity are largely dependent on oxygen content in the medium. Under normoxia conditions, only one proline residue of HIF-1α is hydroxylated. In this state, the factor is recognized by the β-subunit of the von Hippel–Lindau protein (VHL), which recruits an ubiquitin ligase and thus promotes degradation of the protein by proteasomes. Hypoxia sensitivity of HIF is mediated by prolyl-hydroxylase domain proteins (PHD proteins) whose activity requires molecular oxygen. Under oxygen deficiency, PHD proteins are unable to hydroxylate the regulatory proline residue in the HIF-1α molecule. Thus, HIF-1α is not cleaved by the proteasome, and HIF-1α associates with HIF-1β;

this complex binds to the consensus DNA sequence and regulates expression of "hypoxia" genes [19]. The influence of hypoxia on inflammatory signaling was noted in numerous reports [20-22]. The main example is close interactions between the hypoxic signaling that involves HIF and the inflammatory signaling mediated by NF-κB. One of the target genes whose expression is activated upon HIF-complex binding to the consensus sequence is the *NF-κB* gene; as a result, the inflammatory process is activated. PHD-proteins and HIF-inhibiting factors that negatively regulate activity of HIF-complex are able to inhibit IKKb-complex and to impede activation of NF-κB [23]. This indicates a direct contribution of hypoxic conditions in obesity to development of the inflammatory component of metabolic syndrome.

Another reason for the development of constitutive inflammation in adipose tissue in metabolic syndrome can be endoplasmic reticulum stress (ERS). ERS occurs due to overload of the ER system that includes various chaperones (BiP, GRP78, calnexin/calreticulin system) and that is responsible for protein folding [24]. Such overload occurs when biosynthetic activity exceeds the functional capacity of the ER, which is a natural consequence of hypercaloric diet. As a result, inactive and chemically aggressive prone-to-aggregation proteins are accumulated in the ER lumen. Protein misfolding that leads to improper conformation that allows abnormal interaction with cellular components is also dangerous for the cell. The main strategy to overcome this situation is a so-called unfolded protein response (UPR). The first stage of UPR is an adapted decrease in biosynthetic activity. Three proteins (ATF6, PERK, and IRE1) participate in the correction mechanism [25]. First, PERK represses total protein synthesis, and IRE1 degrades mRNAs encoding secretory proteins. Second, additional chaperones are synthesized to increase the folding productivity. This process displays close interaction between nucleus and ER, when the above-mentioned PERK provides a "green corridor" for synthetic activity of the chaperone genes, but not for others. ATF6 also promotes an increase in the synthetic activity of a number of chaperone genes (BiP, GRP78, calnexin/calreticulin system) [24].

If measures taken by cell against ERS are inefficient, UPR factors participate in the apoptosis signaling. Let us show the variety of roles of the UPR factors, for example IRE1α, in apoptosis. This protein can inactivate apoptosis kinase ASK through transcription factor TRAF6. In addition, association between TRAF2 and IRE1α allows activation of caspase 12 [26]. IRE1α is also able to activate transcription factor NF-κB through TRAF2 and to affect directly the inflammatory processes via the main inflammatory signaling molecule.

And, finally, a third reason for occurrence of inflammation in metabolic syndrome is oxidative stress. Oxidative stress accompanies numerous diseases: atherogenic pathological processes, cardiovascular diseases, diabetes, and obesity. In the case of obesity, systemic oxidative stress occurs that stimulates non-physiological production of adipokines, which promotes development and stabilization of metabolic syndrome in patients. It was demonstrated that concentration of numerous oxidative stress markers (C-reactive protein, etc.) depends on body mass index and triglyceride levels in patients with metabolic syndrome [27].

Occurrence of oxidative stress in cells in response to hypercaloric diet is, first, due to active work of mitochondria and oxidative systems of the cell that are forced to process the excessive amount of food. So, in glucose metabolism (in the TCA cycle), generation of electron donors, such as NADH and $FADH_2$, occurs; increase in $NADH/NAD^+$ and $FADH_2/FAD^+$ ratios during increase in glucose input promotes superoxide generation. In case of excessive input of free fatty acids, a similar effect develops, when during fatty acid β-oxidation and oxidation of the acyl-CoA derivatives of fatty acids in the TCA cycle, a large number of electron donors are accumulated in the cell [27]. Oxidative stress in adipose tissue can also occur due to active secretion of proinflammatory cytokines, for example, secretion of TNFα promotes generation of superoxide anion radical [28]. Other possible reasons are formation of superoxide anion radicals during an increase in oxygen uptake by the cardiovascular system in obesity, production of reactive oxygen species (ROS) owing to activity of TNFα that is synthesized during cell damage, and high fat diet [29]. Thus, oxidative stress also facilitates expression of proinflammatory cytokines, and it stimulates their production itself, or proinflammatory cytokines promote development of oxidative stress, which indicates positive feedback in this process.

In adipose tissue inflammation, not only metabolic factors (ERS, hypoxia, oxidative stress), but also exogenous ones (composition of diet, in particular) are important. It was shown that high fat diet facilitates inflammation development directly (activation of cyclooxygenase 2 expression) and leads to oncological diseases in the digestive tract [30]. Gut microbiota also plays an important role in development of systemic inflammatory response. It was shown that microbiota of mice kept on a high lipid diet promoted mobilization of transcription factor NF-κB and expression of inflammatory factors [31]. Some studies have revealed certain representatives of the intestinal microflora (e.g. genus *Oscillibacter*) that appear on consumption of high lipid food, and this can enhance the inflammatory process [32]. Intake of carbohydrates is also a significant factor: low carbohydrate diet reduces the inflammatory response and is associated with the production of short-chain fatty acids (e.g. butyrate) [33] that, in addition, enhance the secretion of angiopoietin-like protein 4, thereby reducing lipoprotein lipase activity and increasing lipolysis in adipose tissue [32].

High-calorie diet stimulating the release of insulin into the bloodstream is directly associated with chronic

inflammation in adipose tissue, as the expression MCP-1 (monocyte chemoattractant protein-1) is insulin-dependent [34]. Expression of MCP-1 and other proinflammatory cytokines in adipose tissue contributes to the attraction of macrophages into the tissue and the development of inflammation.

It is known that macrophages in adipose tissue mainly have one of two functional phenotypes – M1 or M2. These phenotypes have different functions, transition stimuli, gene expression profiles, and, as a result, respond differently to external signals [35]. Resident macrophages of adipose tissue mainly have M2 phenotype (alternatively activated or antiinflammatory macrophages) and play an important role in tissue homeostasis. Latent inflammation in adipose tissue is caused by the attraction of M1 phenotype macrophages (classically activated, or proinflammatory macrophages) and by the polarization of resident macrophages in adipose tissue toward the M1 phenotype. The biochemistry of interaction between macrophages and adipocytes is an important moment in the formation of insulin resistance in obesity. It was shown that its development was stimulated exactly by inflammatory signals of M1-macrophages [36], and the inhibition of the inflammatory signaling disrupts this link [36, 37].

The problem of macrophage polarization in adipose tissue is extremely important in the development of obesity in general and of metabolic syndrome in particular. The polarization process is tightly controlled; it is based on a network of signaling pathways, transcription factors, and epigenetic mechanisms. The canonical signaling cascade IRF/STAT activated by IFNs and TLRs (Toll-like receptors) shifts macrophage phenotype toward M1 state (via the transcription factor STAT1), while interleukins IL-4 and IL-13 shift the phenotype toward M2 state (via transcription factor STAT6) [38]. Each macrophage phenotype has its own expression profile, which is initiated in response to the action of transcription factors. For M1-macrophages, activation receptors are TLRs and interferon receptors that mobilize the transcription factors IRF-3, IRF-5, and STAT1, as well as proinflammatory transcription factor NF-κB. Activation of M2-macrophages occurs with the participation of interleukin receptors IL4, IL10, and IL4/IL13 that trigger work of transcription factors STAT3, STAT6, KLF4, PPARγ, and PPARδ. The general scheme of signal transduction mediating the expression of specific macrophage polarization proteins is shown in Fig. 1.

Expression of mannose receptor type I (CD206) is one of the examples of such regulation [39]. Activation of the IL4/IL13 receptor results in the mobilization of transcription factor STAT6, which in turn stimulates expression of factor KLF4, thereby activating CD206 expression.

The most interesting point in the study of intracellular signaling in latent inflammation in metabolic syndrome is overlapping and interactions between signaling pathways to form signaling networks. The main element

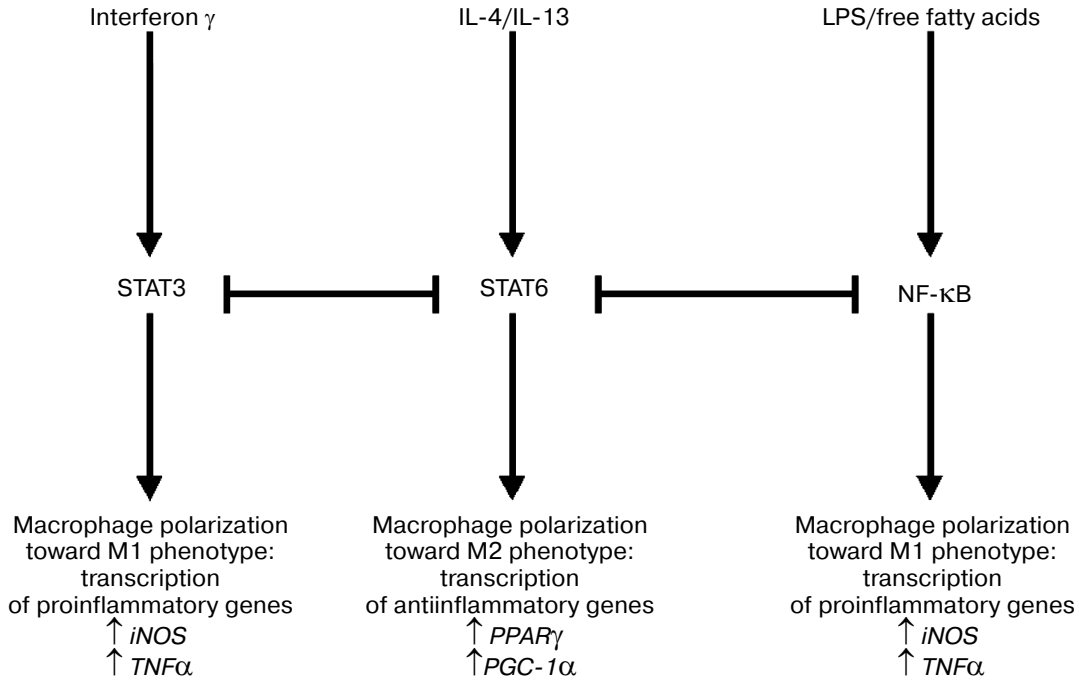

Fig. 1. Scheme of the main interactions of transcription factors that are activated in macrophages of different polarity. Abbreviations: iNOS, inducible NO-synthase; TNFα, tumor necrosis factor α; PPARγ, peroxisome proliferator-activated receptor γ; PGC1α, PPARγ coactivator 1α. According to [34] with modifications.

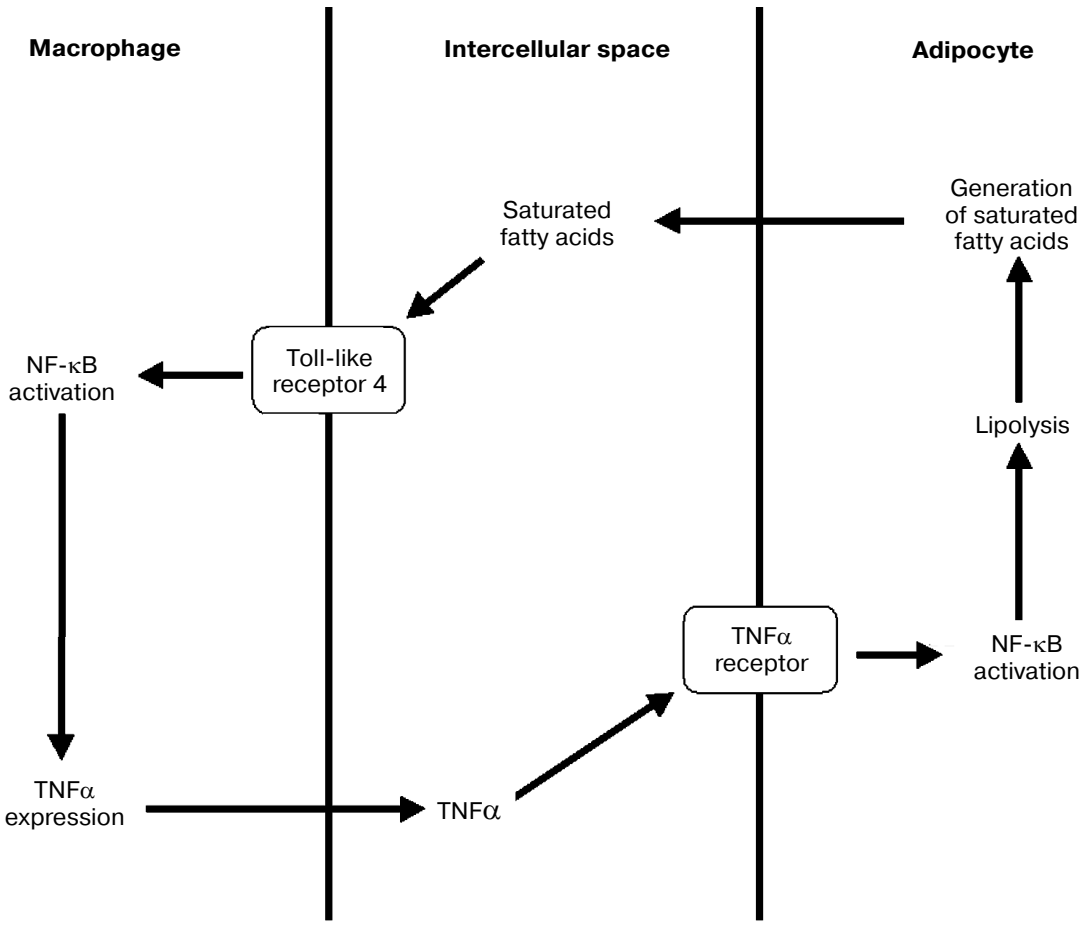

Fig. 2. Scheme of self-sustaining inflammatory cycle between macrophages and adipocytes. According to [37] with modifications.

in the inflammatory process in adipose tissue is a self-sustained cycle with the participation of TNFα and NF-κB [40]. In this situation, interaction between hypertrophied adipocytes and M1-macrophages occurs. TNFα secreted by proinflammatory macrophages interacts with its receptor on the adipocyte membrane and stimulates the hydrolysis of neutral fat to free fatty acids. Free fatty acids along with lipopolysaccharides (LPS) are able to activate TLR4 and transcription factor NF-κB, which triggers expression of a number of proinflammatory genes, including *TNFα*. Here, the inflammatory cycle repeats and it becomes self-sustaining under conditions of high-calorie diet (source of free fatty acids) and adipocyte hypertrophy (source of TNFα in connection with hypoxia, ERS, and oxidative stress) [41] (Fig. 2).

Regarding the role of TLR4 in the development of inflammation in adipose tissue in metabolic syndrome, mobilization of transcription factor IRF3 should be noted, causing expression of IFNβ that autocrinely affects the corresponding receptor and results in STAT1 activation, which in turn initiates transcription of proinflammatory genes in M1-macrophages. A similar effect is caused by the action of IFNγ on macrophages. The existence of antagonistic relationships between transcription factors is also possible. To this end, let us look closer at the process of M2-type polarization of macrophages. Interaction of IL4/IL13 with the corresponding receptor leads to activation of the transcription factor STAT6, which activates transcription factor PPARγ. Mutually antagonistic relationships connect transcription factors NF-κB and STAT6 with transcription factors STAT1 and STAT6. Thus, the "antiinflammatory" transcription factor STAT6 contributes to the inhibition of "proinflammatory" transcription factors STAT1 and NF-κB [38].

A detailed examination of signaling networks of the inflammation process in adipose tissue reveals that it is possible to decrease or even eliminate the inflammation by affecting a number of target molecules. Now, of the above-listed signaling the only proven target for metabolic syndrome therapy (one of its main components – insulin resistance) are thiazolidinediones (troglitazone, pioglitazone, rosiglitazone) that activate transcription factor PPARγ.

PPARs (peroxisome proliferator-activated receptors) are ligand-activated transcription factors that belong to a nuclear receptor superfamily, which includes steroid

receptor, retinoid, and thyroid hormones. Upon binding to its ligands (hydroxyeicosatetraenoic acid, leukotriene B4), PPAR forms a heterotrimer with the 9-*cis*-retinoic acid receptor and affects transcription of the target genes through interaction with a sequence located in the promoter region of the target genes that includes AGGTCA repeats. These repeats are separated by a single nucleotide or DR-1 sequence (the so-called PPAR-response element, PPRE) [42]. By now, three main PPAR types are known: PPARα, PPARβ/δ, and PPARγ. All the PPAR types have different tissue specificity, ligand specificity, and biological effects [43]. PPARα is expressed in tissues with active metabolism of fatty acids (liver, kidneys, and skeletal muscles). PPARβ/δ is found everywhere, while PPARγ is typical for white and brown adipose tissues. All the PPAR types were found in cells able to penetrate across vessel walls (monocytes, macrophages, endothelial cells) [44]. In general, PPARs play a key role in lipid and glucose metabolisms, adipocyte differentiation; they also participate in the inflammation processes, proliferation, and differentiation of various cells [43].

It is known that PPARs are able to negatively regulate gene expression in a ligand-dependent manner by inhibiting activity of other transcription factors such as NF-κB, AP-1, and NFAT [42]. It is also known that the activity of PPARs depends on the levels of their expression and availability of their ligands, coactivators, and corepressors. Posttranslational modifications of PPARs (phosphorylation, sumoylation) can also regulate their activity [43, 45].

The first identified function of PPARγ was regulation of the promoter of the *FABP4/aP2* gene, which is actively expressed in adipocytes, encoding a protein that binds fatty acids. Later, it was shown that PPARγ controls adipocyte differentiation and it is a key regulator of lipid metabolism. Subsequently, it was demonstrated that PPARγ is expressed not only in adipocytes, but also in other cell types (immune cells, striated myocytes, gastric epithelial cells, osteoblasts, osteoclasts, etc.) [46, 47].

PPARγ, like other nuclear receptors, binds lipophilic ligands and regulates transcription in the activated state. Arachidonic acid metabolites (15-deoxy-$\Delta^{12,14}$-prostaglandin J_2) and unsaturated fatty acid components of oxidized low-density lipoproteins were identified among other endogenous ligands of PPARγ. Some studies revealed that PPARγ could bind not only a single molecule of a specific fatty acid, but also patterns of fatty acids (including two molecules simultaneously). Such ligand binding suggests that PPARγ is not a specific receptor of one fatty acid, but it is an intracellular sensor of a mixture of fatty acids whose ratio can affect physiological processes [46, 48, 49].

PPARγ affects transcription in different ways; typically, it is regulation of gene expression. Nevertheless, PPARγ-mediated ligand-dependent gene repression occurs by means of indirect regulation mechanisms. The full range of these mechanisms is unknown, but at least some of the negative regulatory effects of PPARγ are mediated by protein–protein interactions leading to a phenomenon called transrepression. There are several models that describe this mechanism. According to the most consistent with experimental data model, a protein complex comprising repressors of proinflammatory gene promoters (in particular the gene for inducible NO-synthase) is localized in the nucleus; this repressor complex inhibits transcription in the absence of proinflammatory signals. Removal of the repressor complex by proteasomal ubiquitin-dependent degradation in response to inflammatory signals triggers expression of target genes. Ligand-activated PPARγ is sumoylated, binds to, and stabilizes the inhibitory complex by blocking its proteasomal degradation. Transrepression can also occur through a less direct mechanism (so-called squelching). In this case, ligand-activated PPARγ isolates some coactivator molecules (e.g. CREB-binding proteins) that are only present in cells in limited amounts and could be necessary for functioning of other transcription factors [43, 46].

The mechanisms of regulation of the inflammatory response involving PPARγ are not clear. Using a transient transfection method, it was demonstrated that PPARγ inhibits expression of scavenger-receptors class A, which is induced by NO-synthase and MMP-9 by inhibiting AP-1, STAT, and NF-κB. Similar to PPARα, inhibition of NF-κB-dependent transcription by means of direct interaction with p65 and p50 [46] was demonstrated for PPARγ. It was also shown that PPARγ ligands, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 and other cyclopentane prostaglandins, could inhibit activation of NF-κB through inhibiting IKK activity [50, 51]. A similar effect was found in the case of thiazolidinones (ciglitazone, troglitazone, pioglitazone, rosiglitazone), which are synthetic activators of PPARγ [52].

Using endothelin-1 promoter as a model, it was shown that PPARγ inhibits transcriptional activity of factor AP-1 by decreasing its DNA-binding ability. It occurs, presumably, as a result of PPARγ–c-Jun interaction; this was previously shown for PPARα. Activation of AP-1 may also result from affecting activity of JNK kinase [46]. In general, the existence of a number of mechanisms for the regulation of PPARγ confirms again the complexity and multifunctionality of signaling that involves this nuclear receptor. It was redoubled by additional data for a number of tissues (e.g. lung tissue) regarding PPARγ role in restoration of IKK (kinase IκB) activity and stimulation of IκB degradation with recovery of NF-κB function [43].

It would seem that thiazolidinones are perfect anti-inflammatory agents, especially taking into account their positive effect on the relief of insulin resistance and the absence of side effects in the gastrointestinal tract and a side effect of an increase in risk of hyperglycemia. However, for PPARγ activators, formation of peripheral edema and an increase in body mass are typical side

effects [8]. This side effect is natural as PPARγ is one of the master regulators of adipocyte differentiation. Its interaction with another master regulator of adipogenesis, C/EBPα, initiates expression of adipocyte genes *FABP4*, *ADIPOQ*, *LPL*, and many others, which activate the development of peripheral fat. This is why unspecific activation of PPARγ, undoubtedly, promotes relief of inflammation by acting on macrophages, but upon affecting the mesenchymal adipose tissue-derived stromal cells (ATSC), adipocyte development is stimulated leading to obesity [53]. By the example of rosiglitazone, it was shown that thiazolidinones could hold glycemic control within normal values longer than other medicines. However, it was also demonstrated that thiazolidinone compensation of metabolic syndrome lasts for 2-3 years. Then, rise of side effects, such as an increase in peripheral fat mass, edemas, and risk of cardiovascular diseases occurs. In this connection, in 2010 the European Drug Agency prohibited the use of thiazolidinones in metabolic syndrome therapy [8].

In this regard, the question arises of finding molecular targets to relieve latent inflammation and to reduce the risk of comorbidities. One promising type of targets is NAD^+-dependent type 3 histone deacetylases – sirtuins. Seven types of sirtuins have been found in mammalian cells. All the mammalian sirtuins have conserved NAD-binding and catalytic domains but differ in their *N*- and *C*-terminal domains. Sirtuins of different types are varied in substrate specificity and biological functions. They are found in different cell compartments.

One of the important functions of sirtuins is participation in nicotinamide adenine dinucleotide (NAD^+) metabolism. NAD^+ is an important cofactor of the electron transport chain and is involved in many enzyme reactions. Deacetylation reactions with the participation of sirtuins consist of two steps. The first step is the cleavage of NAD^+ to nicotinamide (NAM) and adenosine diphosphate ribose (ADP-ribose), and the second step – transfer of an acetyl group from substrate to the ADP-ribose with generation of O-acetyl-ADP-ribose and deacetylated substrate. Most sirtuins have deacetylase activity, only ADP-ribosyl transferase activity was shown for type 4 sirtuin, while both deacetylase and ADP-ribosyl transferase activities were shown for type 1 and type 6 sirtuins [54].

NAD^+ is necessary for the deacetylation reaction that is catalyzed by sirtuins, as it is one of the substrates, while the deacetylation reaction product NAM inhibits the reaction.

Formed during the reaction, NAM is converted into nicotinamide mononucleotide (NMN) with NMN-transferase. Then, NAD^+ is regenerated by NMN adenyl transferase. Sirtuins were shown to be key regulators of NAD^+ biosynthesis. In particular, NMN adenyl transferase-mediated NAD biosynthesis is controlled by type 1 sirtuin [55].

Because of their participation in many energetic processes in the cell, NAD^+ and NAM are not preferable tools for analysis of sirtuin action. Thus, an extensive search is being performed for pharmacological agents that inhibit or activate protein factors of this class. Resveratrol is the most widely used among sirtuin activators.

Resveratrol is a polyphenolic phytoalexin (3,5,4′-trihydroxy-*trans*-stilbene) present in white and red grape wines [56, 57]. *Cis-trans* isomerizations of resveratrol occur upon the action of ultraviolet light. It was shown that *cis*-resveratrol plays a role in protecting an organism from different pathological processes including cardiovascular and oncological diseases. Much less is known about *cis*-resveratrol activity as antioxidant and antiinflammatory agent, while both these activities are evident for *trans*-resveratrol [56]. A number of reports were published regarding different activities of resveratrol. There is an assumption that resveratrol is a plant analog of hormones, a regulator of epigenetic processes [58], immunomodulator, factor that decreases neurodegenerative processes in aging, apoptosis sensor, etc. An outstanding book by Aggarwal and Shishodia [59] is devoted to the structure and function of resveratrol.

Sirtinol (2-[(2-hydroxynaphthalen-1-yl-methylene)amino]-N-(1-phenethyl)benzamide) is commonly used as a sirtuin inhibitor. This compound is also a useful tool for sirtuin-related studies. Sirtinol mainly inhibits type 1 and type 2 sirtuins. Considering physiological effects of sirtinol, it is worth mentioning that they are very ambiguous: there are data regarding apoptosis induction by application of sirtinol [60] and sirtinol-dependent early aging [61]; however, sirtinol is an efficient antiinflammatory agent, as shown in corresponding studies [62]. In general, there are numerous restrictions for using sirtinol as therapeutic agent, but pharmacological studies focused on synthesis of sirtinol analogs that would have minimal side effects are being carried out.

As mentioned above, sirtinol is not a very specific agent, as it inhibits type 1 and type 2 sirtuins. For specific inhibition of different sirtuins, synthetic inhibitors have been produced, for example, Ex-527 (6-chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide) [60]. However, analyzing the side effects and problems in application of pharmacological agents in PPARγ activation [8], it should be mentioned that use of pharmacological agents nonspecifically regulating sirtuin activity is highly unlikely beyond laboratory practice.

The spectrum of biological activity of different sirtuins, as mentioned above, is extremely diverse [55]. One of the most interesting fields of sirtuin investigation is their participation in intracellular signaling that regulates different metabolic processes. Sirtuins also affect inflammatory signaling and signaling in adipocyte/adipogenic differentiation.

One of the key aspects in sirtuin-mediated regulation of inflammation is antagonistic relationships between one

of the central inflammatory cytokines – NF-κB and type 1 sirtuin [63].

It was shown that type 1 sirtuin could interact directly with the ReIA/p65-component of the NF-κB complex [64]. Deacetylation of Lys310 inhibits transcriptional activity of the ReIA/p65 subunit and, therefore, it suppresses the transcription of NF-κB-dependent proinflammatory genes. Furthermore, deacetylation of Lys310 in the ReIA/p65-subunit makes Lys314 and Lys315 residues available for methylation, which further promotes ubiquitinylation and proteasomal degradation of NF-κB. By now, many studies have revealed mechanisms of function of activators and inhibitors of type 1 sirtuin as pharmacological agents that prevent inflammation [65-67].

Another way to affect the inflammatory signaling by type 1 sirtuin is inhibition of AP-1 via deacetylation of its subunits – c-Jun and c-Fos. This process plays a key role in regulating the functions of certain immune cells. For example, activation of type 1 sirtuin in macrophages decreases transcription of the *COX-2* (the gene encoding prostaglandin endoperoxide synthase 2), a typical proinflammatory AP-1-activated gene, while in T-lymphocytes, deacetylation of AP-1 by type 1 sirtuin precedes proliferation [64].

In addition to the influence on NF-κB and AP-1, type 1 sirtuin affects other biologically active molecules inside cells: different transcription factors (FoxP3 – a transcription factor that participates in differentiation and functioning of regulatory T-lymphocytes [64], FOXO-1 [53]), histones, regulatory proteins (UCP-2 (uncoupling protein type 2), p53), and microRNAs (miR34a) [58]. It follows that affecting sirtuins causes much larger physiological impact. This statement is also correct when studying the influence of any regulatory protein on certain cellular process. However, the influence of type 1 sirtuin on the inflammatory process is mainly based not on the acetylation of histones and microRNAs, but on the interaction with the above-mentioned inflammatory transcription factors [63, 64].

As to the influence of sirtuins on adipocyte differentiation and on adipocytes, it is worth noting that there is an indirect regulation of adipocyte gene expression through sirtuins. For example, type 1 and type 2 sirtuins can regulate activity of transcription factor FOXO-1 that inhibits activity of PPARγ. Thus, sirtuins activate lipolysis and inhibit adipogenesis. At the same time, even protein–protein interactions between the sirtuins can affect adipogenesis. Therefore, type 7 sirtuin activates adipogenesis, as it is able to bind to type 1 sirtuin [68].

Analyzing literature data related to a problem of interaction between macrophages and adipocytes and with ATSC, signaling in this process, and its role in metabolic syndrome, suggests that many studies are focused on the problem of signaling in certain cell types. At the same time, many gaps remain, in particular, in signaling and regulation of intercellular interactions of macrophages with adipocytes and with ATSC, and also in the influence on the most important process of macrophage polarization that largely affects development of latent inflammation in adipose tissue in metabolic syndrome, and, hence, development of comorbidities. Therefore, studying the molecular mechanisms of signaling in macrophage polarization and interaction between signaling pathways of macrophages and ATSC, macrophages, and adipocytes, influence of macrophages, and their polarization on the adipocyte differentiation process is a very promising research field. To date, a number of approaches have been developed that correct disturbances of the regeneration process and of adipose tissue function in metabolic syndrome. Regulation using pharmacological agents acting on all cell types nonspecifically was proven not valid by the example of use in therapy of PPARγ ligands. Such approaches are only suitable for primary laboratory studies. Further perspectives in studying the regulation of inflammatory signaling are associated with gene therapeutic approaches (using small interfering RNAs), medical technologies of genome editing (CRISPR-Cas9 system, specific nucleases), and with increase in selectivity of targeted tools. One example of such novel cell-specific tools is development of new macrophage-secreted recombinant one-domain antibody that would specifically bind to TNFα [69].

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