Abstract Submission

3. Platelets

ECTH-209

Mathematical model of platelet response to collagen-related peptide activation suggests a role for PNX-1 in GPVI-induced platelet activation.

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Background: GPVI is the major collagen receptor on platelets. It has been reported that defects in platelet GPVI signaling might be a cause for cardiovascular system disorders, e.g. GP6 gene polymorphism has been demonstrated to be associated with an increased risk of myocardial infarction (Croft *et al.* Circulation. 2001., Takagi *et al.* Atherosclerosis. 2002). Two isoforms of GPVI could be defined by five linked polymorphisms: S219P, K237E, T249A, Q317L and H322N. Haplotype-related functional differences in GPVI reduce Fyn/Lyn binding, decrease the rate and the degree of Syk phosphorylation (Trifiro *et al.* Blood. 2009). According to recent data, another possible mechanism involved in GPVI signaling pathway is based on Pannexin-1, a transmembrane anion channel for ATP. Theoretically, extracellular ATP can activate platelets through P2X1 receptors, thus leading to secondary platelet activation (Taylor *et al.*, Thromb Haemost. 2014).

Aims: To determine molecular mechanisms responsible for variability in GPVI induced platelet activation.

Methods: Activity of GPVI receptors in donors was evaluated by polymorphism sequencing. A COPASI software computational model of platelet activation via GPVI, P2Y1, P2X1 and PNX1 receptors was constructed. It described receptors ligation and receptor-induced signalosome assembly. Continuous flow cytometry was used to observe cytosolic calcium response to collagen related peptide (CRP) and ADP stimulation.

Results: Variability in CRP-evoked platelet calcium response has been demonstrated for healthy donors by continuous flow cytometry. To investigate the contribution of various mechanisms to discrepancy between healthy individuals, a computational model of platelet GPVI signaling was constructed. The contribution of the PNX1 and P2X1 signaling pathways to GPVI induced platelet activation was considered. Based on model prediction, we suggest that differences among healthy donors could be explained by varying PNX1-P2X1 activity. However, other signaling pathway contribution could not be definitely excluded. Furthermore, model has also confirmed that discrepancy among the donors could be eliminated in case of ADP stimuli.

Summary/Conclusion: The first comprehensive analysis of the variability of CRP induced platelet activation in healthy donors has been performed. Using computational modeling approach, we suggested that the calcium response variation among different donors could be explained by the PNX1-P2X1 link after GPVI activation. This pathway became irrelevant in the presence of ADP, which corresponded with experimental data. The presence or absence of polymorphism was shown to be a minor contributor in the signaling process. In general, it could be speculated that the GPVI pathway signaling variability is originated from the contribution of P2X1-PANX1 pathway in combination with GP6 gene polymorphisms.