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Cross-talk of inhibitory and stimulatory signalling pathways of human platelets

Ulrich Walter* and Stepan Gambaryan

Address: Institute of Clinical Biochemistry and Pathobiochemistry, University Clinic of Würzburg, Würzburg, Germany

Email: Ulrich Walter* - uwalter@klin-biochem.uni-wuerzburg.de

* Corresponding author

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The major (but not only) roles of the hemostatic system are to maintain blood in a fluid state under physiologic conditions and to seal a vessel wall defect in order to prevent blood loss. Pathologically, bleeding or thrombosis may occur if the hemostatic stimulus is unregulated, either at the level of stimulatory or inhibitory pathways. The balance of stimulatory and inhibitory pathways is also well established for platelets. These specialized adhesive cells play a key role in normal and pathological hemostasis through their ability to rapidly adhere to subendothelial matrix proteins and to other activated platelets. Such platelet functions are strongly inhibited by endothelium-derived prostacyclin and NO and their cAMP/PKA- and cGMP/PKG-regulated pathways including kinase targets such as VASP, IRAG, LASP and others [1]. It is also well established that both stimulatory and inhibitory platelet pathways interact at various levels representing significant functional cross-talk. Recently, we re-addressed one of the controversially discussed pathways, the platelets NOS system. We discovered that human and murine platelets do not express functional NOS proteins and that platelet soluble guanylyl cyclase (sGC) is NOS-independently activated by von Willebrand factor (VWF) which may represent a new mechanism of feedback inhibition [2]. The underlying mechanisms are currently studied using a recently established quantitative phosphoproteomic approach. Initial data will be presented. As long-term goal, it is hoped that such studies will establish new diagnostic and therapeutic approaches with respect to platelet function and dysfunction, especially in the area of NO/cGMP signalling.

References

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