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* Abstracts should clearly indicate the scientific question addressed in the study and its importance, a brief description of methods, objective data to answer the scientific question and conclusions of the study directly supported by the results.

**Targeting P2X1 ion channels increases sepsis-associated coagulopathy through neutrophil hyperresponsiveness**

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ATP-gated P2X1 ion channels contribute to arterial thrombosis by amplifying platelet activation. In the search for novel anti-platelet strategies, targeting P2X1 ion channels is appealing. However, in this study, we found that lack or inhibition of neutrophil P2X1channels enhanced respiratory burst activity *in vitro*.

To study the consequence of P2X1 deficiency on neutrophil function *in vivo*, P2X1-/- mice were used in a model of endotoxin-induced sepsis. Upon injection of lipopolysaccharides (LPS), plasma myeloperoxidase (MPO) concentrations reached higher levels in the P2X1-/- mice and circulating neutrophils expressed higher levels of surface CD11b compared to wild-type mice. Neutrophil relocalization into the lungs of LPS-treated P2X1-/- mice was also significantly augmented, reflecting a higher activation state of P2X1-/- neutrophils under conditions of sepsis. Accordingly, more extensive lipid peroxidation was observed in the liver of LPS-treated P2X1-/- mice, indicative of exaggerated oxidative damage. Concomitantly, the levels of thrombin-antithrombin complexes were higher in the plasma of LPS-treated P2X1-/- mice and thrombocytopenia was worsened as compared to wild type mice. Elevated numbers of microthrombi were found in the lungs of these mice. These observations coincided with a higher susceptibility of P2X1-/- mice to LPS-induced septic shock than wild type animals.

Our results strongly suggest that P2X1 ion channels play a protective role in sepsis by negatively regulating systemic neutrophil activation, thereby limiting oxidative damage, platelet accumulation into the lungs and coagulopathy. Therefore, since antagonists of P2X1 ion channels may not only reduce platelet activation but also target neutrophils, inhibiting these channels in the highly inflammatory environment of severe sepsis or of acute coronary syndromes might be detrimental.