Platelets as immune cells in sensing bacterial infection

av

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Abstract

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Platelets are mostly known for their role in haemostasis where they prevent bleeding, however, they are also involved in the immune system and express a broad repertoire of immune cell features such as toll-like receptors (TLRs), FcγRIIA, inflammatory mediators and microbicidal activities. These characteristics make it possible for platelets to recognize pathogens and engage other immune cells for enhanced bacterial clearance and inflammatory response. *Porphyromonas gingivalis* is a key-pathogen in periodontitis, which is an inflammatory oral disease considered to be associated with atherosclerosis.

The major aim of this thesis was to elucidate the role of platelets in sensing bacterial infection and their part in mediating inflammation. We found that platelets are activated via TLR2/1 and FcγRIIA upon adhesion to immobilized receptor-ligands, and that this process was dependent on src/Syk-signalling as well as of activation of P2X1 and P2Y12. Furthermore, TLR2/1-mediated platelet activation led to secretion of the inflammatory mediators RANTES, MIF, PAI-1, IL-7 and PF4, which were degraded by gingipains of *P. gingivalis*. *P. gingivalis*-induced platelet-activation involved increased $[Ca^{++}]_i$, aggregation and release of RANTES and TGF-β. In addition, *P. gingivalis* triggered platelet activation via TLR2- and PAR-receptors, and we could conclude that gingipains were of importance for the ability of the bacteria to induce platelet activation. *P. gingivalis* was also found to induce ROS- and enzyme-mediated lipid peroxidation in whole blood and PRP, respectively. Analysis of clinical samples revealed initial sustained antioxidant levels and temporary decreased lipid peroxidation in patients with periodontitis, indicative of a pre-activated defence mechanism. Taken together, these results strongly suggest platelets as sensors of bacterial infection and as mediators in inflammation, and as a possible linker between periodontal and cardiovascular disease.

Keywords: Platelets, infection, TLR2/1, *Porphyromonas gingivalis*, inflammatory mediators, lipid peroxidation

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