Interleukin 37 attenuates platelet activation and thrombosis formation

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Aims: Interleukin 37 (IL-37) emerges as a natural suppressor of innate inflammatory and immune responses. Plasma IL-37 is abnormally increased in cardiovascular disease. Pleiotropic effects of IL-37 beyond anti-inflammation have been shown. However, the direct effects of IL-37 on platelet activation and thrombosis remain unclear. This study explored the direct effects of IL-37 on platelet activation and thrombosis.

Methods and results: A negative correlation between plasma IL-37 concentration and platelet aggregation was observed in patients with myocardial infarction. IL-37 directly inhibited ADP, thrombin and collagen induced platelet aggregation and dense granule release (Figure 1A, B). Platelet spreading in immobilized fibrinogen and clot retraction driven by integrin αIIbβ3 mediated out-side in signaling were inhibited by IL-37 concentration-dependently. In vivo thrombosis formation and stability in a FeCl3-injured mesenteric arteriole thrombosis mouse model was also severely suppressed by IL-37. Using co-immunoprecipitation, confocal microscopy and platelet-specific IL-1R8-deficient mice, we found that IL-37 bound to platelet IL-1R8 and IL-18Rα, and silencing of IL-1R8 impaired inhibitory effects of IL-37 on platelet activation. Mechanistic studies revealed that IL-37 combined with IL-1R8 to enhance PTEN activity and inhibited Akt, mitogen-activated protein kinase pathways. Platelet-specific IL-1R8-deficient mice presented impaired thrombosis and hemostasis but had improved cardiac function, reduced infarct size, decreased inflammatory response, and microthrombus after permanent ligation of the left anterior descending coronary. While control mice treated with IL-37 were protected from myocardial injury, IL-1R8-/- mice were not (Figure 1C, D).

Conclusions: IL-37 directly attenuated platelet activation and thrombosis formation by binding to platelet IL-18Rα and IL-1R8 and regulating the downstream signaling pathways, suggesting the potential role of exogenous IL-37 protein to prevent platelet hyperactivity thrombotic complications in patients with low plasma IL-37 levels.
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