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·专题报告·

Platelets in Thrombosis and Atherosclerosis

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Platelets are anucleate cells generated from megakaryocytes in the bone marrow. After being released into the blood, platelets play essential roles in hemostasis and preserving vessel wall integrity. However, the processes of platelet adhesion, activation, and aggregation at the site of vascular injury may also cause vessel occlusion, and lead to thrombotic diseases. The formation of platelet rich thrombi following the rupture of atherosclerotic lesions is a common cause of myocardial and cerebral infarction. In addition to their pivotal roles in thrombosis and hemostasis, platelets also contain significant amounts of P-selectin, CD40/CD40L, TGF-β and other inflammatory factors. Through interaction with endothelial cells, leukocytes and/or progenitor cells and by regulation of the immune response, platelets may also play important roles in the initiation and development of atherosclerotic lesions.

It has been documented for more than 4 decades that fibrinogen is required for platelet aggregation. However, using an intravital microscopy thrombosis model, we found that platelet aggregation and thrombus formation occurred in mice lacking either fibrinogen or both fibrinogen and von Willebrand factor (Fg/VWF$^{-/-}$). We further demonstrated that Fg/VWF-independent platelet aggregation

can be induced in vitro under more physiological conditions (i.e. non-anticoagulated blood) and β3 integrin (GPIIbIIIa) is the platelet receptor required for this mechanism of platelet aggregation. To examine whether plasma fibronectin (pFn) is the alternative β3 integrin ligand mediating this novel platelet aggregation, we generated Fg/VWF/pFn$^{-/-}$ triple knockout mice. Surprisingly, platelet aggregation and thrombus formation in Fg/VWF/pFn$^{-/-}$ mice were not abolished, but were enhanced as compared with Fg/VWF$^{-/-}$ mice. This suggests that other, currently unidentified, β3 integrin ligand(s) exist. Our data demonstrated that pFn plays a dual role (i.e. both supportive and inhibitive) in thrombosis.

Platelet P-selectin (CD62P) is also involved in thrombosis and hemostasis. This selectin family adhesion molecule plays important roles in inflammation and mediates platelet-leukocyte interaction. While it has been reported that VWF affects P-selectin expression on endothelial cells, little information is available regarding regulation of platelet P-selectin expression. We recently found that fibrinogen, by interaction with platelet β3 integrin, promotes platelet P-selectin synthesis. Therefore, plasma fibrinogen contributes to atherothrombosis not only via its direct role in thrombosis, but also by controlling platelet P-selectin expression, which may affect the development of atherosclerotic lesions.

(Edited by LI Xiao-Ling)