The formation of a hemostatic thrombus during the vessel wall injury is a highly regulated event which ensures that a blood clot is sufficiently stable but not overly robust to cause thrombus propagation. We have previously identified a proteolytic anti-adhesive process which prevents accumulation of platelets and leukocytes on the surface of fibrin clots. It depends on activation of plasminogen by the plasmin activation system assembled on transiently adherent blood cells. This is followed by plasmin generation and decomposition of the fibrin surface resulting in cell detachment under flow. However, platelets also contain high concentrations of PAI-1, which is secreted during clot formation. Therefore, it is uncertain whether the proteolytic anti-adhesive mechanism is functional when circulating platelets encounter platelet-rich fibrin clots. Here, we show that while fibrinolytic activity of tPA- and uPA-bearing platelets incorporated inside clots was completely inhibited, platelets bound to the surface of clots retained their ability to activate plasminogen and degrade fibrin. Moreover, when platelets and uPA-expressing U937 monocytic cells were both included in fibrin clots, platelets completely suppressed fibrinolytic activity of U937 cells. In contrast, proteolytic activity of U937 cells attached to platelet-rich fibrin clots was not affected. By contrast with platelets incorporated into clots and releasing substantial amounts of PAI-1, no PAI-1 was secreted from platelets adherent to the surface of fibrin. Finally, α2-antiplasmin did not interfere with plasminogen activation occurring at the interface between fibrin and attached cells. These results suggest that platelets inside the clot, via release of PAI-1, block fibrinolysis aiding in thrombus stability, while platelets transiently contacting the surface of fibrin clots are profibrinolytic thus enabling the anti-adhesive mechanism.

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