Editorial

Induction of Platelet-Endothelial Interactions in Postcapillary Venules in Hypercholesterolemia
Critical Role of P-Selectin

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Hypercholesterolemia is well established as a major risk marker for atherosclerosis and resultant cardiovascular disease. Recent studies suggest that platelets are intimately involved not only in thrombosis after plaque rupture, but also in the earliest events in the atherogenic process. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Tailor and Granger establish another potential link between hypercholesterolemia and atherosclerosis by demonstrating that diet-induced hypercholesterolemia promotes P-selectin-dependent platelet-endothelial interactions in postcapillary venules.

See page 675

The adhesive events initiating hemostasis and thrombosis after vessel injury or plaque rupture are now relatively well understood. At shear flow rates relevant to the arterial side of the circulation, initial platelet adhesion involves the coordinated interaction of two platelet adhesion receptors, GP Ib binding to von Willebrand Factor (vWF) and GP VI binding to collagen. These adherent platelets become activated, leading to granule release (reflected in surface expression of the α-granule membrane glycoprotein, P-selectin) and up-regulation of function of the platelet aggregation receptor, the integrin GP IIb-IIIa (αIIbβ3).

In 1995, Wagner and colleagues demonstrated that platelets not only adhered to vessel matrix, but like leukocytes, could also translocate and stably adhere on activated endothelium in vivo. In their seminal study, the mesenteric venules of mice were acutely activated by treatment with calcium ionophore, A23187. Under these conditions, platelet-endothelial interaction occurred with both resting and activated platelets and, like leukocyte rolling, was critically dependent on the activation-dependent surface expression of endothelial P-selectin. However, at very low shear rates (80 to 100 s⁻¹), translocation and adhesion of resting platelets on A23187- or histamine-activated venous endothelium is dependent on endothelial expression of vWF and on platelet GP Ib and is independent of P-selectin.

In mice, both resting and activated platelets have also been shown to translocate and adhere to chronically inflamed endothelium, activated in vivo by tumor necrosis factor (TNF)-α. In this circumstance, resting platelet adhesion is dependent on both endothelial P- and E-selectin and selectin counter-receptors on platelets, GP Ib and PSGL-1. Similarly, in endotoxin-treated rats, immunoneutralization of either endothelial P-selectin or platelet GP Ib abolishes platelet interactions with venular endothelium. In contrast, activated platelet adhesion to TNF-activated venules is mediated by platelet P-selectin and an unknown TNF-inducible P-selectin receptor on endothelium.

Taken together, these various studies establish that different adhesive mechanisms foster platelet-endothelial interactions and point to a key role for P-selectin in this process. P-selectin is also pivotal at different stages in atherogenesis. Fatty streak formation is delayed in mice lacking low-density lipoprotein receptor and fed a cholesterol-rich diet, if P-selectin is also absent. P-selectin also plays a prominent role in the advanced atherosclerosis that develops in ApoE-deficient mice. In this model, absence of P-selectin results in smaller lesions with less macrophage recruitment and smooth muscle infiltration. Both endothelial P-selectin and platelet P-selectin are involved in the attenuation of lesion development in the ApoE-deficient mice, suggesting that endothelial P-selectin as well as P-selectin expressed on platelets bound to endothelium may be involved in macrophage recruitment. More recently, Massberg et al demonstrated platelet adherence to the vascular endothelium of the carotid artery in ApoE-deficient mice even prior to lesion development. Platelet adhesion was dependent on GP Ib and GP Ib-IIIa, coincided with inflammatory gene expression in the endothelium, and preceded leukocyte recruitment into the lesion. Prolonged blockade of platelet adhesion attenuated the early events in the atherogenic process indicating a primary role for platelet-endothelial interaction in the initiation of atherogenesis. This is consistent with a separate, recent report by Theilmayer et al demonstrating endothelial vWF-dependent recruitment of platelets to atherosclerosis-prone sites in rabbits with diet-induced hypercholesterolemia.

In this issue of Arteriosclerosis, Thrombosis and Vascular Biology, Tailor and Granger establish that hypercholesterolemia also promotes platelet-endothelial interactions, but in this case involving the venules of mice fed a cholesterol-rich diet. Platelets from wild-type mice fed a normal diet were isolated, fluorescently labeled with the fluorochrome, carboxyfluorescein diacetate succinimidyl ester, and reinfused into either wild-type or hypercholesterolemic mice. Platelet interaction with venule endothelium was imaged by intravital microscopy. A statistically significant increase in the number...
of platelets either translocating or stably adhering to the post-capillary venules was observed in the hypercholesterolemic mice after one week on the cholesterol-rich diet. This increased platelet adhesion remained statistically significant during the first 8 weeks of atherogenic diet but returned to baseline at 12 weeks, even though the mice retained similarly elevated total serum cholesterol levels and the vessels under observation had similar wall shear rates throughout the study period. No platelet interactions were seen in adjacent arterioles. Platelet translocation and stable adhesion was attenuated ≈50% when wild-type platelets were infused into hypercholesterolemic P-selectin–deficient mice instead of hypercholesterolemic wild-type mice, indicating at least partial involvement of endothelial P-selectin in these events. In contrast, no platelet translocation or stable adhesion was observed when labeled platelets from P-selectin–deficient mice were transfused into hypercholesterolemic wild-type mice, indicating a critical role for platelet P-selectin in mediating hypercholesterolemia-induced platelet-endothelial interactions.

A number of observations derive from these interesting findings. First, Tailor and Granger establish in their article that their platelet isolation and labeling procedure lead to minimal platelet activation as evaluated by P-selectin surface expression on flow cytometry. However, within five minutes of infusion into hypercholesterolemic wild-type mice, these same platelets translocate and stably adhere to the venules in a process critically dependent on platelet P-selectin. In this regard, Tailor and Granger’s findings are consistent with previous evidence that adhesion of activated platelets to activated endothelium is platelet P-selectin dependent. Their observations thus suggest that rapid platelet activation must occur in the circulation of hypercholesterolemic mice. Although this was not directly established for the infused platelets, endogenous platelets in the hypercholesterolemic mice did have significantly higher surface P-selectin expression. Further investigation is clearly necessary to define the mechanism for platelet activation in hypercholesterolemic mice, and possibly other species, including humans. One potentially relevant recent finding is that a subpopulation of GP Ib is present in platelets in cholesterol-rich rafts and that platelet adhesion and activation increases with the level of membrane cholesterol. It is known that interaction of GP Ib with vWF initiates shear-dependent platelet activation, although other mechanisms for increased platelet hyperreactivity in hypercholesterolemia are possible.

A second intriguing observation warranting further investigation concerns the mechanism for loss of platelet-endothelial interaction after prolonged hypercholesterolemia at 12 weeks. This suggests that a regulatory mechanism must exist to attenuate platelet adhesion to the post-capillary venules. This could conceivably involve lesser platelet activation, increased shedding of platelet P-selectin, or increased shedding or downregulation of the as-yet-undefined, inflammation-dependent P-selectin receptor on endothelium.

Finally, it is interesting to consider the relevance of the induction of platelet-endothelial interactions in postcapillary venules in hypercholesterolemia to vascular inflammation and atherosclerosis. The view that atherosclerosis is associated with endothelial activation is now accepted. P- and E-selectin on activated endothelium and P-selectin on activated platelets are pivotal in mediating leukocyte-endothelial, platelet-endothelial, and platelet-leukocyte interactions. These platelet-dependent interactions may also perpetuate downstream vascular inflammation by stimulating release of various inflammatory and thrombotic mediators. In this regard, it is tempting to speculate that Tailor and Granger’s findings might point to an additional role for platelet P-selectin in augmenting vascular thrombosis and inflammation. As discussed above, their data clearly indicate rapid platelet activation and platelet P-selectin surface expression associated with hypercholesterolemia. Surface-expressed platelet P-selectin is rapidly shed in the circulation, consistent with increased levels of soluble P-selectin in the plasma of individuals with hypercholesterolemia. Increased soluble P-selectin mediates a procoagulant state, potentially exacerbating the thrombotic and inflammatory predisposition associated with hypercholesterolemia.

References


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