A Critical Role of Platelet Glycoprotein Ibα in Arterial Remodeling

Mark L. Kahn

The canonical role of platelets is hemostasis in which they function as highly specialized cells designed to plug holes in the blood vascular system. To accomplish this task, platelets have evolved unique molecular tools that enable them to function in the vascular environment, such as the GPIbα receptor complex that mediates platelet adhesion to the vessel wall in the face of high shear forces and stringent activation pathways that trigger adhesive interactions mediated by integrin receptors. It is becoming apparent that platelets may also use these specialized molecular tools to perform vascular tasks other than plugging holes and preventing blood loss. Some of these more recently defined roles seem to be variants of their canonical role, for example, lymphovenous hemostasis that controls the flow of lymph into the blood circulation, and inflammatory hemostasis that prevents bleeding at sites of extremely high vascular permeability. Others seem to be truly nonhemostatic, for example, platelet adhesion to leukocytes to facilitate their passage across blood vessel wall at sites of inflammation. Common to these noncanonical platelet roles is the use of unique molecular mechanisms that allow platelets to respond to stimuli in the vascular environment that may be physical (eg, shear), cellular (eg, blood versus lymphatic endothelium), or molecular (eg, platelet activators such as thrombin, ADP).

How do these new findings impact our understanding of platelet participation in nonhemostatic vascular responses? As observed in prior studies of platelet participation in inflammatory responses (eg, after vessel exposure to tumor necrosis factor alpha-α or during lymphocyte extravasation in the high endothelial venule4), an important aspect of the platelet role in collateral growth is to facilitate leukocyte extravasation at specific vascular sites through adhesive interactions. In inflammatory settings, this is accomplished by a subset of circulating platelets that are activated and express the adhesive ligand P-selectin.3,4 Thus, it will be important to determine whether platelet participation in arterial remodeling/collateral vessel formation also requires platelet activation and P-selectin expression. Unlike previous studies, Chandraratne et al5 specifically implicate the shear-responsive adhesive receptor GPIbα in collateral vessel formation. The precise stimuli that drive the remodeling of small arteries to larger collateral vessels are as yet unknown, but one candidate is the rise in perfusion pressure and vascular shear forces to which these vessels are exposed after arterial ligation. Thus, changes in hemodynamic forces in potential collateral vessels may stimulate endothelial von Willebrand’s factor release and transient platelet adhesion through GPIbα, allowing platelets to bridge the vessel wall and circulating leukocytes that need to extravasate to drive vessel remodeling (Figure). In this manner, the molecular specialization developed to generate shear-resistant platelet thrombi may serve a second role in shear-dependent vascular remodeling.

These new findings raise numerous questions on the role of platelets in the vascular remodeling that underlies collateral vessel formation. Is platelet activation required? If so, what is the activating stimulus in an otherwise healthy vessel with intact endothelium? Significantly, the authors observe both platelet and leukocyte adhesion to venules and arterioles in the region of the ligated artery, events that are also GPIbα-dependent. It is not likely that arterial ligation would directly alter venous hemodynamics, raising the question of how adjacent venules become involved in this process. Collateral arteries arise gradually in human limbs and hearts in response to chronic tissue ischemia (eg, as native arteries become occluded by atherosclerosis). It is possible that ischemia in the tissues fed by the ligated or diseased artery results in changes
in the venous blood drained from those tissues that alter the downstream venous endothelium to stimulate the platelet and leukocyte adhesion observed by Chandraratne et al.5 Future studies extending the insights of this study will address these questions and perhaps reveal new strategies to drive collateral vessel formation in patients with ischemic vascular diseases.

Disclosures

None.

References


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