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).

See accompanying article on page 589

In the present issue of ATVB, Chandraratne et al describe a new role for platelets and for GPIbα, the platelet-specific receptor that enables cellular adhesion under shear, during the formation of collateral arteries after femoral arterial ligation (a process termed arteriogenesis, although it involves expansion of existing vessels rather than the growth of new ones). Using in vivo microscopy, they observe transient adhesion of platelets to the endothelium of small arteries destined to become collateral vessels shortly after femoral artery ligation and to that of adjacent veins as well. Platelet adhesion is dependent on the function of GPIbα, a receptor that binds endothelial-derived von Willebrand’s factor under high shear forces, and is coincident with firm leukocyte adhesion to the walls of those vessels. Loss of platelet GPIbα reduces leukocyte adhesion and migration across the walls of developing collateral vessels. The formation of platelet-leukocyte complexes is observed in whole blood shortly after femoral artery ligation, and loss of either platelets or GPIbα receptor function impairs the recovery of blood flow that results from collateral vessel expansion. These studies identify a role for platelets and the GPIbα receptor in facilitating the leukocyte migration associated with the expansion of collateral vessels after arterial ligation (Figure).

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- or during lymphocyte extravasation in the high endothelial venule), 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. 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 al specifically implicates the shear-responsive adhesive receptor GPIbα in collateral vessel formation. The precise stimuli that drive the remodeling of small arterioles 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.3 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
A Critical Role of Platelet Glycoprotein Ibα in Arterial Remodeling
Mark L. Kahn

Arterioscler Thromb Vasc Biol. 2015;35:498-499
doi: 10.1161/ATVBAHA.115.305213
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/35/3/498

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/