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Vascular endothelium: in defense of blood fluidity.

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Editorial

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These pipes and these conveyances of our blood. . .

Shakespeare
Coriolanus, V, i.

Contrary to the classical view of the vessel wall as simply a passive conduit for blood flow, the vasculature is now recognized to be a dynamic metabolic organ. The endothelial cells that line its intimal surface throughout the circulatory tree, a surface area equivalent to a half dozen tennis courts in an average-sized man (1), occupy a continuous and strategic interface between blood and body. Among the myriad of regulatory roles vascular endothelium subserves, it is the pivotal modulator of blood fluidity and hemostasis.

Under normal circumstances, quiescent endothelial cells present a highly thromboresistant surface to flowing blood. This property is constitutively effected by the elaboration of several mediators that prevent fibrin accumulation, including thrombomodulin, heparinlike substances, tissue factor pathway inhibitor, and tissue plasminogen activator, as well as antiplatelet mediators, including prostacyclin (PGI_2), nitric oxide (NO), and possibly carbon monoxide. The anticoagulant properties of intact endothelium are disrupted at sites of vascular injury by exposure of blood to potent thrombogenic materials in the subendothelium and by the conversion (e.g., by cytokines and proteases) of remaining endothelial cells to a procoagulant surface. The fibrin-promoting and platelet-activating products of perturbed endothelium include tissue factor, plasminogen activator inhibitor, von Willebrand factor, and P-selectin. Thus, blood fluidity and hemostasis can be exquisitely regulated by the balance of anticoagulant and procoagulant properties of endothelial cells, which are coordinately modulated by their relative states of quiescence or activation.

To the platelet inhibitory armamentarium of normal endothelial cells, we must now add ADPase, a membrane-associated ectonucleotidase. ADP, released by platelets and other cells, is an activator of platelets; endothelial ecto-ADPase metabolizes this platelet agonist and thereby maintains platelets in their resting state. The other major platelet inhibitory products of endothelial cells, PGI_2 and NO, are also potent vasodilators. While ADPase does not intrinsically have this property, it can indirectly exert this action by generating vasodilator adenosine. Endothelial cells are equipped with an enzyme chain of ectonucleotidases that sequentially dephosphorylate ATP→ADP→AMP→adenosine at the luminal surface (2). Thus, PGI_2, NO, and ADPase all represent locally active, endothelium-derived platelet inhibitors that are also vasodilators, thereby promoting blood fluidity.

In this issue of *The Journal*, Marcus et al. (3) provide persuasive evidence that endothelial ecto-ADPase is CD39. Functionally, transfection of COS cells with full-length CD39 conferred on them ADPase activity and the ability to inhibit ADP-induced platelet aggregation. CD39, previously identified on the surfaces of B lymphocytes, macrophages, and natural killer cells, as well as endothelial cells, has been postulated to have immunological functions including homotypic adhesion of lymphocytes; however, its role in thromboregulation has not been heretofore suspected.

The physiological relevance of endothelial ADPase, as well as the other endothelium-derived antiplatelet autocoids, may be reasonably challenged. Indeed, while a thrombotic tendency has been clearly linked to mutations of the natural fibrin-inhibitory anticoagulants (e.g., antithrombin and proteins C and S) (4), such clinical correlations have not been found with the endothelium-derived antiplatelet mediators. Specific antiplatelet properties of endothelium may be impaired in a variety of clinical conditions of "endothelial dysfunction," including inhibition of ADPase activity in hyperhomocysteinemia (5). Furthermore, reduced bioavailability of NO was recently associated with arterial thrombosis (6). However, direct causal relationships between PGI_2, NO, or ADPase "deficiency" and thrombosis have been difficult to establish. Furthermore, disruption of the gene encoding the endothelial isoform of NO synthase causes hypertension but no spontaneous thrombosis in the mutant mice (7). Likewise, cyclooxygenase 1 (COX-1) gene disruption causes reduced ex vivo platelet aggregability, but no spontaneous hemostatic abnormalities (8). The results of CD39 knock out are eagerly awaited.

These observations by no means preclude an important physiological role for endothelium-derived platelet inhibitors. Arterial thrombosis, which predominantly involves platelets, generally occurs in the presence of underlying vascular disease and elevated levels of shear stress. Therefore, the importance of endothelium-derived antiplatelet mediators may be recognized only when provoked by these pathophysiological conditions. Indeed, it was recently found that endothelial NO synthase mutant mice develop larger brain infarcts after experimental middle cerebral artery occlusion (9). Both shear stress and cyclic strain, the major hemodynamic forces to which the vessel wall is exposed, stimulate PGI_2 and NO release by endothelial cells (10). Thus, it may be only under pathological hemodynamic conditions that the loss of these protective antiplatelet mediators may result in thrombosis. It will be of particular interest to study the effects of shear and strain on endothelial ADPase expression, since the release and action of adenine nucleotides is significantly modulated by fluid flow conditions around endothelium (11).

The identification of ecto-ADPase as an endothelial thrombomodulator raises other interesting questions. First, what is the relationship between endothelial ADPase (which may ultimately lead to the generation of vasodilator adenosine from extracellular ADP) and endothelial P_2 purinoceptors, which transduce the signals of extracellular ADP (and ATP) to endothelium-dependent vasorelaxation and platelet inhibition by stimulating PGI_2 and NO release (12)? These may be competing activities on the endothelial surface. Alternatively, it could be speculated that endothelial purinoceptors and ADPase act in concert to promote blood fluidity: ADP/ATP-induced PGI_2 and NO production is transduced by P_2 receptors, and excess platelet-activating ADP is degraded by ADPase (and 5′-nucleotidase) to platelet inhibitory and vasodilatory adenosine. Sec-

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ond, what are the functions of endothelial ADPase relative to other ADPases in blood (plasma and those on the surfaces of leukocytes, red cells, and platelets themselves)? Third, in view of the well-documented heterogeneity of vascular endothelial cell responses, what is the role of ADPase in cells other than those derived from human umbilical vein, particularly in microvascular endothelium? Finally, how will the identification of endothelial cell ecto-ADPase as CD39 translate to a novel strategy for antiplatelet therapy in clinical practice?

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