Von Willebrand factor: a matrix protein that tries to be soluble

Platelet adhesion and aggregation onto vascular wall lesions contribute to the arrest of posttraumatic bleeding but may also cause arterial occlusion leading to complications such as myocardial infarction and stroke (Ruggeri, Nat Med. 2002;8:1227-1234). The interaction between the membrane glycoprotein (GP) Ibα and von Willebrand factor (VWF) is required to support platelet adhesion and aggregation in areas of the vasculature with rapid blood flow, a hemodynamic condition that reaches pathologic extremes at sites of arterial stenosis. VWF is a large multimeric protein assembled from disulfide-linked identical subunits. Endothelial cells secrete VWF as an insoluble constituent of the extracellular matrix or as a soluble plasma component; megakaryocytes package VWF into α granules for release by platelets upon activation. Plasma VWF multimers exceed a mass of 1 x 10 7 Da but may derive from even larger forms that are cleaved by ADAMTS-13, a recently identified metalloproteinase (Levy et al, Nature. 2001;413:488-494). Previous evidence had indicated that plasma VWF multimers can self-associate on a surface exposed to flowing blood (Savage et al, Proc Nat Acad Sci U S A. 2002;99:425-430).

In this issue Shankaran and coworkers (page 2637) extend this concept and show that self-association can also occur with VWF multimers in solution. These new results are presented in the context of studies that, with a remarkable effort to numerical accuracy, contribute to clarify the mechanisms of shear-induced platelet activation, a process that depends on the binding of VWF to GP Ibα and may contribute to pathologic thrombosis. It is generally accepted that the prothrombotic functions of VWF are directly related to multimer size. This and previous studies demonstrate that shear forces generated by flowing blood can cause the noncovalent but relatively stable assembly of very large VWF polymers from plasma multimers and, thus, enhance platelet adhesion and activation. The cleavage by ADAMTS-13 of very large VWF released from endothelial cells, and presumably platelets, may be necessary to limit the size of circulating VWF multimers and reduce the risk of unwarranted platelet activation and aggregation. Indeed, when this mechanism is deficient, thrombotic disorders develop. Size, however, is of the essence for VWF function, and shear-mediated reassembly into larger structures may represent an efficient way to allow locally the presence of molecular species needed for thrombus formation but whose systemic appearance would not be desirable. Through such a mechanism, ultralarge VWF may be made available even where it cannot be released as such by endothelial cells. Reassembled large VWF polymers are probably subjected to size-limiting cleavage by ADAMTS-13, delineating a tightly regulated mechanism that controls the proadhesive properties of VWF through polymer size and may become a contributing cause of arterial thrombosis if unregulated.

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