Platelets are crucial in supporting coagulation reactions. The classical view is that platelets bind the vitamin K–dependent factors (VII, IX, X, II, protein C, S, and Z) via their gamma carboxyglutamic acid (gla) residues, and in this way localize coagulation factor complexes to the platelet membrane. For binding of gla-containing proteins to the platelet to occur, the platelet needs to be activated after which negatively charged phospholipids, including phosphatidylserine, are translocated from the inner to the outer leaflet of the platelet membrane. Exposure of negatively charged lipids enables a Ca$^{2+}$-dependent interaction of gla-containing proteins with the negatively charged platelet membrane.

See accompanying article on page 1602

In addition to the gla-containing coagulation factors, multiple coagulation factors lacking a gla-domain, including thrombin, factor XI(a), factor XII(a), and high-molecular-weight kininogen interact with platelets, and the interaction of all these proteins has been shown to be (in part) mediated by glycoprotein Ibα (GPIbα). Recent work has demonstrated that also some of the gla-containing coagulation factors, factor VII(a), factor IX(a), and both zymogen and activated protein C interact with GPIbα. These findings indicate that localization of coagulation factors to the platelet surface is much more complicated than anticipated by the model in which the interaction with negatively charged phospholipids was considered required and sufficient for gla-containing proteins to bind to platelets. Indeed, it has been demonstrated that the thrombin-generating capacity of activated platelets from different individuals are not related to the extent of phosphatidylserine exposure, which might indicate that levels of platelet-binding proteins are also determinants of the procoagulant potential of the platelet.

In this issue of Atherosclerosis, Thrombosis, and Vascular Biology, White-Adams and coworkers add more complexity to the platelet-binding mechanisms of coagulation proteins.

In experiments in which they reexamine factor XI binding to platelets, White-Adams and coworkers identify apolipoprotein E receptor 2′ (APOER2′) to be essential for binding of both factor XI and factor Xla to platelets. In experiments examining adhesion of platelets to factor XI under static or flow conditions, the authors make several striking observations: (1) Platelets bind factor XI and Xla in a GPIbα– and APOER2′-dependent manner; (2) Factor XI(a) interaction with platelets activates intracellular signaling events; (3) The platelet binding site of factor XI appears distinct from that of factor Xla as factor Xla but not factor XI binding to platelets is inhibited by dimeric beta2-glycoprotein I; (4) Platelet adhesion to factor Xla depends in part on its proteolytic activity, and the authors suggest that factor Xla may activate one of the protease activated receptors (PARs), resulting in additional platelet activation. Although the identification of a dual receptor system for factor XI on platelets is exciting progress in our understanding of platelet-mediated coagulation, a number of questions remain. A working model based on the data by White-Adams is depicted in panels A and B of the Figure, with question marks at all steps for which experimental evidence is still lacking.

Factor XI is able to interact with a platelet via a dual GPIbα/APOER2′ receptor system, which is in complex in the platelet membrane. Because factor XI is a homodimer, it is not unlikely that one end of the factor XI molecule interacts with GPIbα, whereas the other end binds APOER2′. The interaction of factor XI with the platelet induces intracellular signaling, but it is not known via which receptor, although both GPIbα and APOER2′ are capable of inducing signaling events (panel A in the Figure). When factor XI is activated by thrombin, which can occur on the platelet surface, factor Xla presumably slightly relocates and gains additional signaling properties that are dependent on its active site, which may involve protease-activated receptors, although no experimental data to support this are currently available (panel B in the Figure). The relevance of factor XI(a)-induced signaling events in the context of physiological or pathophysiological thrombus formation is a subject for future studies. Specifically, the question arises whether factor XI(a)-induced signaling events are required, considering the many platelet activation signals elicited during thrombus formation by “traditional” platelet activators including collagen, ADP, thromboxane A2, thrombin, and others.

The use of the dual receptor system GPIbα/APOER2′ is not unique for factor XI(a). A functional role for APOER2′ on platelets was discovered in a search for receptors mediating platelet activation by β2-glycoprotein I/anti-β2-glycoprotein I antibody complexes, which is thought to be the pathogenic trigger of thrombotic events in the antiphospholipid syndrome. Subsequently, it was demonstrated that dimeric β2-glycoprotein I (a genetically engineered model for β2-glycoprotein I/anti β2-glycoprotein I antibody complexes) binds to both APOER2′ and GPIbα on the platelet...
surface, and that signaling via both receptors contributes to platelet activation by this molecule. Furthermore, the authors of the current article showed both GPIbα and GPIbβ to be involved in the interaction of both zymogen and activated protein C on platelets, and also protein C initiated activatory signaling events.

Thus, at least 3 proteins (one of which occurs only in a specific situation, ie, the antiphospholipid syndrome) use the GPIbα/APOER2β and GPIbα combination to bind to platelets, and this receptor combination localizes both pro- and anticoagulant systems at the platelet surface. In addition, at least 5 other coagulation proteins have been shown to interact with GPIbα, and the bulky low-density lipoprotein (LDL) interacts with platelets via APOER2β. Finally, GPIbα facilitates platelet interaction with other cells by binding to P selectin and the leukocyte receptor MAC-1, and GPIbα is essential for von Willebrand factor (VWF)- or thrombospondin (TSP)-mediated platelet adhesion in flowing blood. Needless to say, it is getting crowded around the GPIbα/APOER2β complex (Panel C in the Figure), and the challenge for the future will be to investigate the relative importance of all these interactions.

The significance of platelet receptors (or platelet binding proteins) for localization of coagulation factors to the platelet surface was thoroughly reviewed in ATVB in 2002. The article by White-Adams and coworkers is illustrative for the specific situation, ie, the antiphospholipid syndrome) use the GPIbα/APOER2β combination including coagulation factors (green), a coagulation inhibitor (red), transmembrane proteins (blue), adhesive proteins (orange), and a pathological protein–antibody complex (gray).

References

Factor XI Binding to Platelets: Glycoprotein Ibα Has an Accomplice
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