Coagulation Factor Interaction with Platelets

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Since the initial observation that bleeding is stopped by a platelet plug, it has been clear that platelets play an important role in hemostasis. Patients with very low platelet counts (thrombocytopenia) or with dysfunctional platelets have a bleeding diathesis. With the further observation that the platelet plug becomes interwoven with fibrin, it has become clear that platelets interact with the coagulation proteins. In a review article in this issue of the journal,1 Heemskerk et al. have summarized current information about the mechanisms by which platelets become activated. They have also examined current data on the interaction of coagulation factors with activated platelets. The purpose of this commentary is to highlight an area in which experts have differences of opinion: the question of whether platelets possess non-lipid binding proteins or receptors that bind procoagulant factors and coordinate assembly of the coagulation complexes.

Heemskerk et al. have examined the mechanisms that lead to platelet activation with a particular emphasis on the changes that occur in phospholipid composition on the outer leaflet of the platelet membrane. The data cited in the review by Heemskerk et al. provides compelling evidence that changes in platelet membrane phospholipid composition are necessary for functional interaction of coagulation factors with platelets. The authors take the view that exposure of specific phospholipids on the outer leaflet of platelets is both necessary and sufficient to account for platelet procoagulant activity. To support this view, they cite work showing: that mutations of coagulation proteins which interfere with platelet binding also interfere with binding to phospholipid membranes; that blocking prothrombin binding to EPR1, in platelet prothrombinase assembly [references in Heemskerk et al. (1)].

By contrast, a number of workers have seen differences between platelets and phospholipid surfaces in their interactions with coagulation factors. This has led some researchers, including ourselves, to conclude that exposure of specific anionic lipids on the outer leaflet of activated platelets is necessary but not sufficient to account for platelet procoagulant activity. This conclusion is based in part on the work that has shown that binding of some coagulation factors to platelets is qualitatively different from their binding to lipid vesicles. For example, factor VIIIa binding to platelets does not appear to be competed by factor Va (2, 3). Also, factor IX binds to platelets with a Kd of 5 nM (4, 5) compared to a Kd of greater than 500 nM for binding to lipid vesicles with similar phosphatidylycerine content (6). It is noteworthy that when the Glα domain of factor IXa is removed proteolytically, the Kd for des-Gla factor IXa binding to platelets is reduced only slightly (7) whereas binding to lipid vesicles is virtually abolished (6). This work and other data [see references in previous reviews (8, 9)] provide strong evidence to question the assumption that alterations in the exposure of platelet membrane lipids are sufficient to account for all the features of platelet procoagulant activity and suggest that non-lipid receptors or binding proteins are involved in the regulation of platelet procoagulant properties.

Ultimately, however, an understanding of the relative contribution of lipid components and non-lipid components to platelet activity awaits purification and characterization of the non-lipid moieties.

References