Commentary

Coagulation Factor Interaction with Platelets

Dougald M. Monroe[1], Maureane Hoffman[2]

[1]Center for Thrombosis and Hemostasis, University of North Carolina, Chapel Hill, NC
[2]Durham VA Medical Center and Department of Pathology, Duke University, Durham, NC, USA

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 disfunctional 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 $\alpha_{IIb}\beta_3$ does not reduce the amount of thrombin generated on platelets; and that some workers have not been able to demonstrate a role for the putative factor Xa receptor, 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 phosphatidylserine content (6). It is noteworthy that when the Gla 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 procogulant 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.

Correspondence to: D. M. Monroe, Department of Medicine, University of North Carolina, 932 Mary Ellen Jones Bldg., CB # 7035, Chapel Hill, NC 27599-7035, USA – Tel.: ++919 966 7639; Fax: ++919 966 7639; E-mail: dmonroe@med.unc.edu

References

1. Heemskerk JWM, Bevers EM, Lindhout T. Platelet activation and blood coagulation. Thromb Haemost 2002; 88: 186.
2. Nesheim ME, Pittman DD, Wang JH, Slonosky D, Giles AR, Kaufman RJ. The binding of 35S-labeled recombinant factor VIII to activated and unactivated human platelets. J Biol Chem 1988; 263: 16467-70.
3. Ahmad SS, Scandura JM, Walsh PN. Structural and functional characterization of platelet receptor-mediated factor VIII binding. J Biol Chem 2000; 275: 13071-81.
4. Ahmad SS, Rawala-Sheikh R, Walsh PN. Comparative interactions of factor IX and factor IXa with human platelets. J Biol Chem 1989; 264: 3244-51.
5. Hoffman M, Monroe DM, Roberts HR. Coagulation factor IXa binding to activated platelets and platelet-derived microparticles: a flow cytometric study. Thromb Haemost 1992; 68: 74-8.
6. Jones ME, Griffith MJ, Monroe DM, Roberts HR, Lentz BR. Comparison of lipid binding and kinetic properties of normal, variant, and gamma-carboxyglutamic acid modified human factor IX and factor IXa. Biochemistry 1985; 24: 8064-9.
7. Rawala-Sheikh R, Ahmad SS, Monroe DM, Roberts HR, Walsh PN. Role of gamma-carboxyglutamic acid residues in the binding of factor IXa to platelets and in factor-X activation. Blood 1992; 79: 398-405.
8. Nesheim ME, Furmaniak-Kazmierczak E, Henin C, Côté G. On the existence of platelet receptors for factor V(a) and factor VIII(a). Thromb Haemost 1993; 70: 80-6.
9. Hoffman M, Monroe DM. A cell based model of hemostasis. Thromb Haemost 2001; 85: 958-65.