Platelets and Thrombin Generation
Dougal M. Monroe, Maureen Hoffman, Harold R. Roberts

**Abstract**—This review examines the evidence that platelets play a major role in localizing and controlling the burst of thrombin generation leading to fibrin clot formation. From the first functional description of platelets, it has been recognized that platelets supply factors that support the activation of prothrombin. Studies have demonstrated that on activation, the amount of one specific lipid, phosphatidylserine, is significantly increased on the outer leaflet of platelet membranes. When it was found that phosphatidylserine containing lipid extracts could be substituted for platelets in clotting assays, this suggested the possibility that changes in platelet lipid composition were necessary and sufficient to account for platelet surface thrombin generation. Because a growing body of data suggest that platelet-binding proteins provide much of the specificity for platelet thrombin generation, we review in this report data suggesting that changes in lipid composition are necessary but not sufficient to account for platelet surface regulation of thrombin generation. Also, we review data suggesting that platelets from different individuals differ in their capacity to generate thrombin, whereas platelets from a single subject support thrombin generation in a reproducible manner. Individual differences in platelet thrombin generation might be accounted for by differences in platelet-binding proteins. *(Arterioscler Thromb Vasc Biol. 2002;22:1381-1389.)*

**Key Words:** platelets ■ thrombin ■ lipids ■ phosphatidylserine ■ coagulation

In the 1880s, Bizzozero¹ and Hayem,² working independently, wrote about a blood particle, previously observed by others as a colorless corpuscle smaller than red or white cells, that they called a hematoblast or platelet. Bizzozero wrote that accumulation of this cell might account for the 1875 observation of Zahn³ that bleeding from an injury to a blood vessel was initially blocked by a white thrombus. These studies showed that fibrin was associated with these cells and led them to conclude that platelets supplied a factor that was required for coagulation.¹² Subsequently, a number of investigators demonstrated that the rate of clotting and prothrombin conversion to thrombin was decreased in platelet-poor plasma and increased as a function of platelet number.⁴–⁶

**See Cover**

The initial studies of clotting assays relied on patient platelets in the platelet-rich plasma as the surface for thrombin generation. This led to considerable variability in the results from patient to patient.⁶ To provide an assay reagent that gave more reproducible results, platelet-poor plasma was clotted with phospholipid.⁷ Assay reproducibility was also enhanced by the addition of suspensions of diatomaceous earth to activate clotting.⁸ This modified assay gave reproducible clotting values and was valuable for the diagnosis of bleeding disorders as well as for establishing the relationships between the coagulation proteins. But as a result, the use of lipids as a substitute for platelets became widespread.

In studies involving how lipids influence coagulation assays, it was observed that there was a correlation between the amount of a specific lipid, phosphatidylserine, and the ability of a lipid surface to promote thrombin generation.⁹ Other studies looking at platelet activation showed that circulating unactivated platelets had low levels of phosphatidylserine on the outer leaflet of their membranes.¹⁰ However, when platelets were activated, the amount of phosphatidylserine on the outer leaflets increased dramatically from ~2% of the phospholipid content to as much as 12%.¹¹,¹² Resting platelets do not significantly promote factor X or prothrombin activation.¹³ Even on activated platelets, procoagulant activity is lost on treatment with phospholipases that cleave the head groups from phosphatidylserine.¹⁴ Because there was an obvious correlation between the observation that activated platelets express phosphatidylserine and the observation that phosphatidylserine in purified lipids is required for thrombin generation, it was concluded by many that phosphatidylserine exposure provided the primary mechanism for regulating coagulation reactions and thrombin generation.¹⁰

**Cascade Model of Coagulation**
Coagulation, as shown in Figure 1, has often been represented as 2 somewhat independent pathways that converge to a common pathway, with thrombin generation as the end point of the reactions. This model represents an evolution of the initial models of coagulation based on a cascade or waterfall model.
Figure 1. Cascade model of coagulation. This scheme is a modification of previously proposed models and reflects the components tested for in the prothrombin time assay (extrinsic pathway) and the activated partial thromboplastin time assay (intrinsic pathway). The intrinsic pathway consists of HK, factor XII, prekallikrein (PK), factor XI, factor IX, factor VIII, factor X, factor V, and prothrombin (II), which is converted to thrombin (IIa). The activated form of these factors is indicated by adding the letter “a” as a suffix (eg, IXa). The extrinsic pathway consists of TF, factor VII, factor X, factor V, and II. Reactions requiring a phospholipid surface are indicated by lipid.

hypothesis. These models give a good representation of the processes observed in clinical coagulation laboratory tests. The prothrombin time measures the factors of the so-called extrinsic pathway, and activated partial thromboplastin time measures factors in the intrinsic pathway. Although this model reflects some of the interactions of the proteins, it has inadequacies as a model of the in vivo hemostatic processes. For example, deficiencies of factor XII, high molecular weight kininogen (HK), or prekallikrein do not cause clinical bleeding. Furthermore, others have shown that under normal circumstances, hemostasis is initiated by tissue factor (TF). In addition, if the intrinsic and extrinsic pathways are essentially separate, then activation of factor X by the extrinsic pathway should compensate for a lack of factor VIII or IX. However, factors VIII and IX are clearly essential for hemostasis, because their absence results in the bleeding seen in hemophilia, and this bleeding is not compensated by the intact extrinsic system. Interestingly, factor XI deficiency results in a bleeding disorder that has significant variability between patients and is significantly milder than bleeding in patients with hemophilia A or B lacking factors VIII or IX, respectively.

It has long been established that coagulation reactions do not occur physiologically in solution but are localized to a surface. The critical advantage to evolving such a mechanism is that the reactions are confined to a specific site of injury rather than being completely disseminated. Implicit in the view of coagulation shown in Figure 1 is the assumption that the level and amount of coagulation factors drive and regulate coagulation and that the surfaces are essentially passive agents. Also, implicit in the view of coagulation shown in Figure 1 is that the role of cells is primarily to provide a lipid-rich surface for coagulation complex assembly and that all surfaces with similar lipid composition are essentially identical. This supposition is contradicted by a number of studies, including those showing that endothelial cells, which are not considered procoagulant, nonetheless express significant levels of phosphatidylserine on their surface. This phosphatidylserine is important for maintaining the anticoagulant activity of endothelium by enhancing thrombomodulin activity.

A direct comparison of platelets and phospholipids has shown that platelets have complex coagulant activities that are not completely mimicked by phospholipids. Also, a careful analysis of the kinetics of platelet activity was not consistent with the kinetics seen on lipid surfaces. This and other recent evidence suggests that platelet protein components provide virtually all of the specific sites and control mechanisms that determine the expression of procoagulant activity and subsequent thrombin generation.

Cell-Based Model of Coagulation

A useful model to describe coagulation is shown in Figure 2. This model is derived in part from experiments that use cells such as monocytes or fibroblasts as a source of TF (rather than relipidated TF) and activated platelets as a surface for thrombin generation. In this model, coagulation occurs in 3 overlapping phases: initiation, priming, and propagation. During the process of hemostasis, a break in the vessel wall brings plasma into contact with TF-bearing cells. This TF may be derived entirely from extravascular sources, such as fibroblasts, or may in part be derived from encrypted sources in blood through a CD62 (P-selectin)/CD15 (P-selectin glycoprotein ligand 1)–mediated mechanism. Factor VII binds to TF and is rapidly activated by coagulation proteases and by noncoagulation proteases, depending on the cellular location of the TF. The factor VIIa/TF complex activates factor X and factor IX (Figure 2). The activated forms of these 2 proteins, even though activated at the same site, play very different and distinct roles in subsequent coagulation reactions. Factor Xa can activate plasma factor V on the TF cell (as can other cellular proteases). If factor Xa diffuses from the protected environment of the cell surface from which it was activated, it can be rapidly inhibited by the TF pathway inhibitor or antithrombin. However, the factor Xa that remains on the TF cell surface can combine with factor Va to produce small amounts of thrombin. This thrombin, although not sufficient to cleave fibrinogen throughout a wound, nonetheless plays a critical role in amplifying the initial thrombin signal, as shown in Figure 2. The initial factor VIIa/TF complex is subsequently inhibited by the action of the TF pathway inhibitor in complex with factor Xa.

In the priming phase (Figure 2), the small amount of initial thrombin binds to platelets that have adhered to extravascular matrix components at the site of injury mediated in part by the binding of von Willebrand factor to collagen. The process of binding to matrix proteins, especially collagen, partially activates platelets and also localizes them near a site of TF exposure. Thrombin enhances platelet activation via protease-activated receptor (PAR) mechanisms. There appears to be a synergy between the collagen activation of platelets and the thrombin activation of platelets, such that dual stimulation by those 2 agonists results in platelet activity higher than that...
Thrombin cleaves the partially activated factor V to a fully active form. In addition, thrombin activates factor XI bound to the platelet surface. The result of this stage is a primed activated platelet that rapidly binds the cofactors Va and VIIIa as well as factor Xa.

In the propagation phase (Figure 2C), the factor IXa/VIIIa complex assembles when factor IXa reaches the platelet surface. The initial factor IXa formed by the factor VIIa/TF complex can diffuse to the platelet surface, because factor IXa is not rapidly inhibited by antithrombin or other plasma protease inhibitors. Additionally, platelet surface factor Xa can then provide additional factor IXa directly on the platelet surface. Factor X is recruited to the activated platelet surface and is activated by the factor IXa/VIIIa complex. This allows factor Xa to move directly into a protected complex with factor Va, where (in the presence of prothrombin) factor Xa is protected from the TF pathway inhibitor and antithrombin, even in the presence of heparin. Platelet surface factor Xa/Va complexes generate a burst of thrombin sufficient to form a stable hemostatic fibrin clot.

This model of coagulation provides a rational explanation for the bleeding tendency in hemophilia. The TF pathway is intact in hemophilic patients so that the initiation and amplification steps occur. This leads to normal platelet activation and may account for the tendency of hemophiliacs to stop bleeding as a result of initial platelet plug formation. This also accounts for the normal bleeding time characteristic of hemophilia. However, severe delayed bleeding occurs in hemophilia because there is deficient platelet-dependent factor Xa and thrombin generation throughout the platelet plug. Factor Xa generated by the factor VIIa/TF complex cannot diffuse to the platelet surface without being inhibited. The only factor Xa that can be incorporated efficiently into prothrombinase complexes is that formed on the platelet surface by the factor IXa/VIIIa complex, leading to a decrease in platelet-surface thrombin generation and ineffective clot formation.

Role of Platelet Lipids
Exposure of phosphatidylserine as platelets become activated is necessary for platelet procoagulant activity and is regulated by active transport mechanisms, including a flip-flop mechanism in which phosphatidylserine from the inner leaflet becomes exposed on the outer leaflet of the activated platelet surface. Bleeding has been observed in individuals who have defects in this flip-flop mechanism, as seen in Scott syndrome. This defect is also seen in a canine model with a platelet procoagulant defect. Although initial work has indicated that the most significant role of phosphatidylserine in membranes is to bind the γ-carboxyglutamic acid (Gla) residues in coagulation proteins in a calcium-dependent fashion, recent studies have indicated that the phosphatidylserine head group may instead bind factor Xa at a non-Gla site to act as an allosteric regulator that turns on coagulation by enhancing prothrombin cleavage.

Exposure of phosphatidylserine on the outer leaflet of platelets is necessary for platelet procoagulant activity, and data support the idea that this exposure is sufficient to
account for the procoagulant nature of activated platelets (for review, see Heemskerk et al\(^9\)). However, there is increasing evidence that specific binding sites on platelets regulate formation of the coagulation complexes.\(^{24–26}\) This conclusion is based in part on our own studies of differences in factor IXa/VIIa and factor Xa/Va activity on platelets from different normal individuals.\(^69\) These studies examined platelets from different subjects and showed differences between normal individuals in phosphatidylserine expression even when their platelets were activated in the same way. Although there were differences in the generation of factor Xa and thrombin between individuals, there was no correlation between levels of phosphatidylserine expression and generation of factor Xa or thrombin, as shown in Figure 3. These data support the concept that factors other than phosphatidylserine are necessary for platelet-dependent thrombin generation.

**Platelet-Binding Proteins Important for the Priming Step**

Although the clotting factors bind to platelets, not all this binding transduces a signal to the platelet. Therefore, some of the high-affinity binding sites for coagulation factors on platelets do not fit the classic definition of receptors and in this review will be referred to as binding proteins (Figure 4).

The small amount of thrombin generated in the initiation step is critical in the development of the procoagulant response.\(^{45,47}\) In the absence of a protected environment, thrombin is inhibited by plasma levels of antithrombin with a half-life of \(<1\) minute. Unactivated platelets appear to contain at least 3 binding proteins for thrombin. One is a site on the glycoprotein (GP) Ib-IX-V complex that binds to thrombin through the heparin-binding site (thrombin anion-binding exosite 2).\(^70\) The second site is one of the PARs, PAR1.\(^71\) PAR1 binds to thrombin through the extended substrate-binding site and anion-binding exosite 1. After this 7-transmembrane-domain protein is cleaved by thrombin, the new PAR amino terminus is a tethered ligand that binds to another site on the same or neighboring PAR and triggers a signaling cascade.\(^71\) Some signaling also occurs through PAR4, but this signal appears to be mainly associated with platelet aggregation rather than the development of platelet procoagulant activity.\(^72\) The binding of thrombin to the GP Ib-IX-V complex significantly enhances the ability of thrombin to cleave PAR1 and catalyze platelet activation.\(^73\) The binding of thrombin to the GP Ib-IX-V complex may also signal platelet activation through a fibrin-dependent mechanism.\(^74\) Also, one group has tentatively identified a thrombin-binding site that is thought to be independent of the 2 sites mentioned above.\(^75\)

Unactivated factor VIII circulates in association with von Willebrand factor and can bind to platelets through the von Willebrand factor–binding site on the GP Ib-IX-V complex.\(^76\) Previous studies have shown that platelets potentiate thrombin activation of factor VIII.\(^77\) This potentiation is maximal when von Willebrand factor is present.\(^78\) We speculate that binding to the GP Ib-IX-V complex brings factor VIII/von Willebrand factor into proximity with thrombin and allows for efficient activation of factor VIII and release of the factor VIIIa from von Willebrand factor to the platelet surface.

Factor XI shows saturable, specific, reversible binding to platelets with a \(K_d\) of \(\approx 10\ \text{nmol/L}\).\(^79\) This binding is mediated through a cluster of residues on the third apple domain of factor XI\(^80,81\) and occurs even in the absence of HK.\(^82\) Baglia and Walsh\(^82\) have shown that HK or prothrombin can enhance the binding of factor XI to platelets. Factor XI bound to the platelet surface is efficiently activated by thrombin,\(^48,82\) which appears to be the physiological activator.\(^69\) One recent
study suggests that the binding site on platelets is on the GP Ib subunit of the GP Ib-IX-V complex.

Platelet-Binding Proteins Important for the Propagation Phase

Factor Va can bind tightly to lipids, and lipid-binding may account for most or all of the procoagulant activity of factor Va on platelets. Other studies suggest that there may be a factor Va–binding protein on platelets. These studies show the following: (1) the kinetics of prothrombin activation are different on platelets and lipids; (2) factor Va can displace factor V from platelets, whereas factor V cannot completely displace factor Va; (3) platelets from 1 patient appear to be deficient in factor Va binding; and (4) a monoclonal antibody can block factor Va binding to platelets but does not block binding to lipid vesicles. Studies of factor Va binding to platelets are complicated by the presence of factor V(a) in platelet α granules so that, at present, the data are not compelling for a platelet-binding protein for factor Va.

Studies by a number of workers have shown that factor Va acts as a binding protein for factor Xa on platelets. There are also studies suggesting that effector cell protease receptor-1 (EPR1) may act as a platelet-binding protein to coordinate factor Xa interaction with factor Va on platelets. Bouchard et al have shown that EPR1 is present on platelets and that an anti-EPR1 antibody inhibited the formation of the factor Xa/Va complex in a dose-dependent and platelet donor–dependent fashion. Furthermore, they showed that formation of the factor Xa/Va complex blocked the binding of this anti-EPR1 antibody. However, these data are contrasted by work that either failed to show the presence of EPR1 mRNA or that showed that EPR1 antigen was present on platelets but did not contribute to the assembly of the prothrombinase complex. Combined, these studies suggest that further work is required to elucidate the role of EPR1 or other binding proteins in factor Xa activity on platelets.

Factor IXa, in the absence of factor VIIIa, binds to activated platelets with a dissociation constant of 2 to 3 nmol/L. This binding is in contrast to the binding of factor IXa to lipids, which has a Kd that depends on the phosphatidylserine content of the lipids but is >500 nmol/L at 12% phosphatidylserine (the composition of activated platelets). When the GlA domain of factor IXa is removed by proteolytic cleavage, the resulting des-Gla factor IXa binds to platelets with a Kd similar to that seen for normal factor IXa. By contrast, des-Gla factor IXa binding to lipids has a Kd of >10 000 nmol/L. Also, the homologous protein factor VIIa binds to activated platelets with a Kd >100 nmol/L, consistent with lipid surface binding. Factor IXa binds to ~500 sites on activated platelets. In the presence of factor VIIIa, the dissociation constant decreases to ~0.6 nmol/L. Unactivated factor IX can bind to ~250 of these sites with the same affinity as factor IXa. Although factor IX binding to platelets is enhanced by factor VIIIa, the affinity of zymogen factor IX for platelets is not altered by factor VIIIa. This saturable, specific, reversible binding is consistent with a platelet-binding protein for factor IXa.

Factor VIIIa binds rapidly (within 90 seconds) to thrombin- or collagen-stimulated platelets and platelet-derived microparticles. Factor VIII binding to microparticles occurred with on and off rates similar to those for the binding of factor VIII to lipid vesicles containing phosphatidylserine and was competed by lipids vesicles containing phosphatidylserine. Factor Va, up to 20 nmol/L, enhanced factor VIII binding to microparticles but inhibited binding at higher concentrations. By contrast, 2 other groups looking at factor VIIIa have shown that it binds to activated but not unactivated platelets, with ~500 sites that have a dissociation constant of ~3 nmol/L. The binding occurs on platelets activated by thrombin or the PAR1 agonist peptide but not on platelets activated by ADP. This binding is blocked by annexin but not by factor V. In these studies, the lack of competition by factor V argues for a protein-mediated binding as opposed to a purely phosphatidylserine-dependent mechanism, although one group has suggested that a specific moiety of phosphatidylserine has sufficient specificity to distinguish between factor Va and factor VIIIa.

Fibrinogen binding to platelets is mediated by the integrin GP Ib-IIIa (αIibβ3). On unactivated platelets, GP Ib-IIIa has little affinity for soluble fibrinogen. Platelet activation leads to activation of GP Ib-IIIa through inside-out signaling, resulting in a significant increase in the affinity for fibrinogen. Platelet fibrinogen binding may be stabilized by covalent attachment of serotonin to fibrinogen. Fibrinogen binding promotes platelet aggregation, presumably by a fibrinogen molecule acting as a bridge between GP Ib-IIIa molecules on different platelets. There also appears to be outside-in signaling by the GP Ib-IIIa complex once fibrinogen is bound. This signaling may alter the procoagulant ability of platelets, because blocking fibrinogen binding with abciximab, a monoclonal antibody directed against GP Ib-IIIa, decreased thrombin generation by 40% to 70%. One group has suggested that prothrombin binding to GP Ib-IIIa may provide a pool of prothrombin for activation by the factor Xa/Va complex and that abciximab may decrease thrombin generation by blocking prothrombin binding.

Figure 5. Individual variability in platelet procoagulant function. Figure reprinted from Sumner et al with permission from Elsevier Science. Thrombin generation (IIase activity) and factor Xa generation (Xase activity) were measured as described in the legend for Figure 3. There was no significant correlation between thrombin generation and factor Xa generation. Note that neither the x-axis nor the y-axis goes to zero.
Variability of Platelet Procoagulant Response in Individuals

As early as 1949, Buckwalter et al.6 noted wide variations in the ability of platelets from different individuals to convert prothrombin to thrombin, even when the platelet number was held constant. Subsequently, other workers have noted individual differences in (1) platelet procoagulant activity,91,108 (2) thrombin generation in platelet-rich plasma even when clotting factors were relatively constant,113 and (3) platelet activation triggered by thrombin-receptor–activating peptide.114 Of particular interest is the variability seen in patients with factor XI deficiency.19 Some patients with modest levels of factor XI antigen have severe bleeding symptoms,17 whereas other patients with no detectable antigen lack significant bleeding symptoms.18

Studies looking at the contribution of individual differences in platelet procoagulant function have at least 3 difficulties. One is that the assays are dependent on platelet number.4,6,115 Another difficulty is that all the platelets from an individual may not have an identical function, possibly as a result of differences in platelet age. For example, some workers have seen platelets from a single individual display distinct subpopulations with respect to factor X binding116 or factor V binding,45 although other investigators have not seen these subpopulations.59 And a third difficulty in studying individual differences in platelet procoagulant function is that the results are very dependent on the levels of coagulation factors.117,118 With an awareness of these difficulties, we have investigated the ability of platelets from different individuals to support the conversion of factor X to factor Xa and of prothrombin to thrombin.69 Using platelets isolated from 17 different individuals, we have observed differences in factor IXa/factor VIIIa activation of factor X of up to 3-fold (Figure 5). We have also observed differences in factor Xa/factor Va activation of prothrombin of up to 5-fold (Figure 5). Platelets from the same individuals gave similar results in repeated assays even though there was wide variation between individuals. A number of factors were examined in an attempt to determine a mechanism that would account for this variability. Unexpectedly, as shown in Figure 5, the differences in factor X or prothrombin activation did not correlate with each other; ie, high levels of factor Xa generation did not correlate with high levels of thrombin generation.69 The differences also did not correlate with age, sex, platelet factor Va levels, binding of plasma factor Va, platelet microparticle production, or phosphatidylserine levels (see Figure 3).69

Overall, in a model system of coagulation consisting of purified platelets with a highly controlled concentrations of procoagulant proteins and inhibitors at plasma concentrations, the differences in thrombin generation between normal individuals were significant (Figure 6A). The experiments were designed such that the proteins were tightly controlled, and the platelet number was normalized so that the source of the platelets would be the only variable. The peak level of thrombin for individual 2 is almost half the peak level in individual 1 (Figure 6A). These data, representative of results on a larger population, demonstrate that thrombin generation in this system is dependent on the source of platelets.

By use of this same cell-based model system, the contribution of factor XI to thrombin generation was measured by using platelets from different individuals. Platelets from some normal individuals show a large increase in thrombin generation on adding factor XI (individual 1 of Figure 6), whereas platelets from other normal individuals show very little response to factor XI (individual 2 of Figure 6). These differences reflect real differences between individuals, inasmuch as the results have been shown to be reproducible in repeated experiments over a period of years.48

In conclusion, previous and recent studies show that the platelet surface plays a central role in the promotion and regulation of thrombin generation. This regulation extends beyond the expression of phosphatidylserine on the outer leaflet of the platelets and requires binding proteins and receptors that contribute to promoting and controlling the extent of thrombin generation. Cell-based models of coagulation provide the starting point for examining the mechanisms by which platelets can produce a burst of thrombin in a regulated fashion.

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