Editorial

Procoagulant Platelets
Further Details but Many More Questions

George L. Dale

Procoagulant platelets are known by several synonyms, including collagen and thrombin–activated platelets,[1] coated platelets,[2] sustained calcium–induced platelet morphology,[3] superactivated platelets,[4] and superplatelets.[5] This assortment of names is confusing to those outside the field and has remained a stubborn problem within the field. However, it is key to recognize that all of these variously named activated platelets share a common pentad of characteristics, mitochondrial depolarization,[6,7] sustained cytoplasmic calcium elevation,[8] surface expression of phosphatidylserine (PS),[1] inactivation of glycoprotein IIb/IIIa receptors,[9] and enhanced retention of several procoagulant proteins, including fibrinogen, factor V, and von Willebrand factor,[2] within a surface cap.[10] This commentary is too brief to detail all the intracellular events associated with the production of procoagulant platelets but suffice it to say that simultaneous engagement of thrombin and collagen receptors is the most common mechanism for their production. Surprisingly, dual agonist activation results in only a fraction of platelets being converted into procoagulant platelets, on average 30% in humans.[11] The remaining 70% of platelets demonstrate traditional activation end points: active fibrinogen receptors, granule release, and little to no exposed PS. The mechanism that bifurcates a platelet population into these 2 distinct products remains unknown.

See accompanying article from the August 2017 issue on page 1503

Procoagulant platelets are an efficient platform for assembly of the prothrombinase complex,[1] an observation that has guided studies examining their physiological significance. Along these lines, Brooks et al[12] identified German Shepherd dogs with an inherited bleeding diathesis resulting from an inability to produce procoagulant platelets. Studies in humans demonstrated that not all individuals make the same level of procoagulant platelets with controls ranging from 15% to 55%.[11] This large range has led to an examination of potential thrombotic consequences in individuals overproducing procoagulant platelets. Prodan et al[13] found an increased risk of recurrent events in ischemic stroke patients with the highest levels of procoagulant platelets. Similarly, Kirkpatrick et al[14] observed that elevated levels of procoagulant platelets identify transient ischemic attack patients at greatest risk for a subsequent stroke.

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The August issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* presents an article by Choo et al[15] examining 2 aspects of procoagulant platelets that add to an understanding of their synthesis and function. As noted, mitochondrial depolarization is essential for procoagulant platelet synthesis, although the details of how this occurs are poorly understood. Choo et al[15] have cleverly examined several mitochondrial changes and observed that disruption of the inner mitochondrial membrane, with either proapoptotic agents or dual agonist stimulation, is critical to the process of PS exposure. However, disruption of the outer mitochondrial membrane and release of cytochrome C, as observed in apoptosis, does not occur in procoagulant platelet formation. Furthermore, the time frame for inner mitochondrial membrane disruption and PS exposure is too slow with proapoptotic signals to be relevant to the formation of procoagulant platelets, lending further support to the argument that classical activation pathways for apoptosis are not linked to procoagulant platelet formation. These authors have also repeated their earlier observation that cyclophilin D, a regulator of the mitochondrial permeability pore, is critical to procoagulant platelet formation,[7] although the signaling events leading to mitochondrial depolarization and subsequent PS exposure are still not clear.

The second observation by Choo et al[15] concerned a report that challenged the pentad of characteristics for procoagulant platelets. Topalov et al[16] observed that high levels of thrombin stimulation produced PS-positive platelets that retained polarized mitochondria and functional GP (glycoprotein) IIb/IIIa receptors, labeling their new class of platelets as integrin-regulated procoagulant platelets. Choo et al observed platelets similar to those of Topalov et al.[16] However, closer examination with confocal microscopy and flow cytometry indicated that the experimental conditions used by Topalov et al resulted in microaggregate formation. Aggregates consisted of one procoagulant platelet and at least one nonprocoagulant platelet, thereby, sharing the characteristics of both classes of activated platelets. In addition, inhibitors of the fibrinogen receptor attenuated the microaggregate population, as well as the integrin-regulated procoagulant platelet population. This series of experiments has 2 important conclusions: first the pentad of characteristics for procoagulant platelets remains valid, and second, the cap of proteins, including fibrinogen, on the surface of procoagulant platelets is functional in binding to normally activated platelets via GP IIb/IIIa interactions. This latter observation may serve as a mechanism whereby procoagulant platelets can be retained within a growing thrombus. Although some have suggested that procoagulant platelets may actually be negative regulators of thrombus growth because they do not propagate the aggregate,[17] this premise contradicts the clinical and large animal data that support a prothrombotic role for procoagulant platelets (Figure).

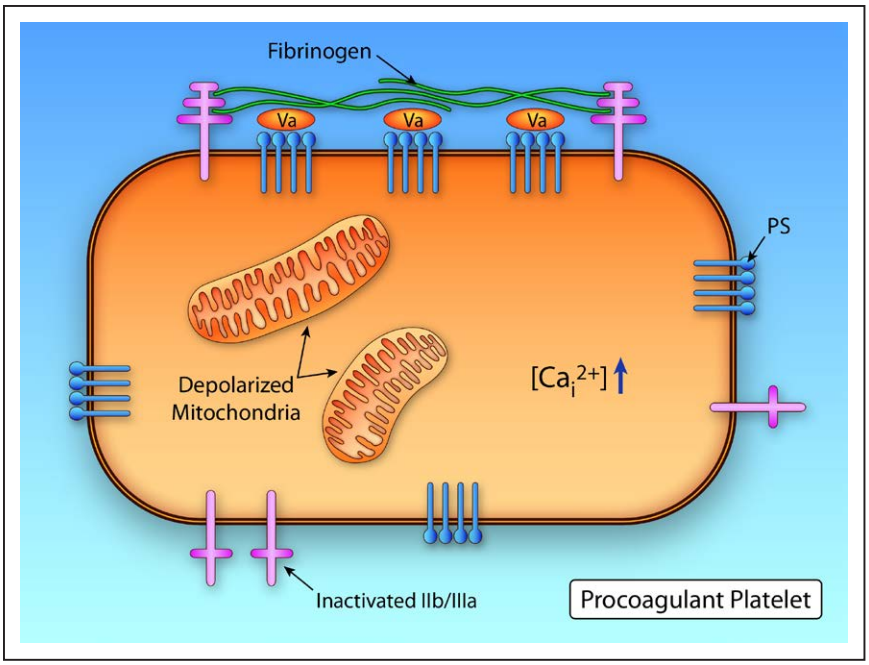

Figure. Unique characteristics of procoagulant platelets, including depolarized mitochondria, sustained elevation of cytoplasmic calcium, enhanced retention of procoagulant proteins (eg, fibrinogen, factor Va) in a cap on the cell surface, inactivation of most fibrinogen receptors (IIb/IIIa), and cell surface expression of phosphatidylserine (PS).

The last 17 years have seen the introduction of procoagulant platelets, an examination of the synthetic steps involved in their formation, and some clarity concerning their physiological function. Future work will hopefully lead to a further understanding of procoagulant platelet synthetic steps, as well as identification of specific antiplatelet medications aimed at the inhibition of either their synthesis or function.

Disclosures

None.

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