Procoagulant platelets are known by several synonyms, including collagen and thrombin–activated platelets, coated platelets, sustained calcium–induced platelet morphology, superactivated platelets, and superplatelets. 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, sustained cytoplasmic calcium elevation, surface expression of phosphatidylserine (PS), inactivation of glycoprotein IIb/IIIa receptors, and enhanced retention of several procoagulant proteins, including fibrinogen, factor V, and von Willebrand factor; within a surface cap. 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. The remaining 70% of platelets demonstrate traditional activation results in only a fraction of platelets being converted into procoagulant platelets, on average 30% in humans. The remaining 70% of platelets demonstrate traditional activation pathways for procoagulant platelet formation, although the details of how this occurs are poorly understood. Choo et al 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, although the signaling events leading to mitochondrial depolarization and subsequent PS exposure are still not clear.

The second observation by Choo et al concerned a report that challenged the pentad of characteristics for procoagulant platelets. Topalov et al 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. 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, this premise contradicts the clinical and large animal data that support a prothrombotic role for procoagulant platelets (Figure).
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 inhibition of either their synthesis or function.

Disclosures
None.

References
Procoagulant Platelets: Further Details but Many More Questions
George L. Dale

doi: 10.1161/ATVBAHA.117.309847

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/37/9/1596

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/