# Editorial

# Procoagulant Platelets Get Squeezed to Define the Boundaries of the Hemostatic Plug

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Two functionally and phenotypically distinct populations of activated platelets form on platelet stimulation, a proaggregatory (historically called activated) platelet subpopulation and a minority procoagulant platelet subpopulation.[1] The more familiar proaggregatory platelet comprises a large fraction of the primary hemostatic plug. Among the key features of the minority procoagulant platelet subpopulation is its high level of surface phosphatidylserine exposure (which supports coagulation complex assembly) and its decreased adhesivity.[2,3] Perhaps as a consequence of these disparate features, how procoagulant platelets function to regulate hemostasis remains debated.

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Among the topics driving this debate are questions around where and when procoagulant platelets are formed and found in hemostatic thrombi. Procoagulant platelets have been found in discrete patches in vivo and in vitro, on the surface of hemostatic plugs as ballooned platelets in early electron microscopy studies, and even found to be absent depending on the model in which they have been visualized.[4–8] Even when strongly stimulated in vitro, only a fraction of platelets become procoagulant.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Nechipurenko et al[9] define the peripheral distribution of procoagulant platelets within multiple in vivo and in vitro models of thrombosis and hemostasis. In a series of elegant studies, the authors demonstrate that the large majority of procoagulant platelets originate as a subpopulation within the growing thrombus and are subsequently translocated to its surface. Fluorescently labeled procoagulant platelets can be observed moving to the surface, whereas passing by, in the opposite direction, are proaggregatory platelets. A passive model of procoagulant platelet extrusion, in which minimally adhesive procoagulant platelets are squeezed to the periphery by the retracting mass, is demonstrated both theoretically using mathematical modeling, as well as in MYH9 (myosin heavy chain 9)-deficient mice, in which platelet contractile function is markedly impaired. Importantly, the functional consequence of the peripheralization of the procoagulant platelet is demonstrated to be the rapid initiation of fibrin formation at the periphery of the hemostatic plug on procoagulant platelet extrusion (Figure).

These insights point towards a mechanism in which 2 physiochemical features of the procoagulant platelet drive the architecture of the hemostatic plug. The first of these features, the catalytic capability of the procoagulant platelet, has long been known.[10] However, the highly regulated nature of this potent catalytic function has, perhaps, been underappreciated. In the absence of active coagulants, such as components of the tenase or prothrombinase complex, the phosphatidylserine-rich procoagulant platelet surface is at most inert and perhaps even anticoagulant because of the expression of tissue factor pathway inhibitor-α on its surface.[11] The second of these features, the nonaggregatory or nonadhesive nature of the procoagulant platelet, is more recently described.[12–14]

Guided by the findings here, one can now imagine the short and functionally important journey of a procoagulant platelet following its stochastic formation within the nascent hemostatic plug.[15] Newly transformed into a phosphatidylserine-externalizing, but now minimally adhesive, procoagulant platelet, the isolated procoagulant platelet is squeezed to the periphery by its contracting, proaggregatory neighbors. Finally, at the boundary of the hemostatic plug, the procoagulant platelet finds the company of similarly relocated compatriots and its raison d'etre. At the periphery and no longer squeezed, procoagulant platelets identify and define the edge of the hemostatic plug. If peripheralized to a site of active coagulation, as occurs in the presence of exposed tissue factor at a wound's edge,[16] the procoagulant platelet will catalyze a burst of fibrin formation and formation of a fibrin border. However, if peripheralized to a site of minimal active coagulation, such as occurs intravascularly,[17] the extruded procoagulant platelet would instead limit intravascular extension of the hemostatic plug, either by creating a minimally adhesive surface[12,13] or by its removal, dislocation, and subsequent clearance.[18] Thus, working in concert and with distinct physiochemical properties, proaggregatory platelets tightly seal, and procoagulant platelets newly delineate the site of a vascular injury in preparation for the definitive process of wound repair.

## Disclosures

None.

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**(*Arterioscler Thromb Vasc Biol*. 2019;39:5-6. DOI: 10.1161/ATVBAHA.118.312066.)**



***Arterioscler Thromb Vasc Biol* is available at https://www.ahajournals.org/journal/atvb**
**DOI: 10.1161/ATVBAHA.118.312066**

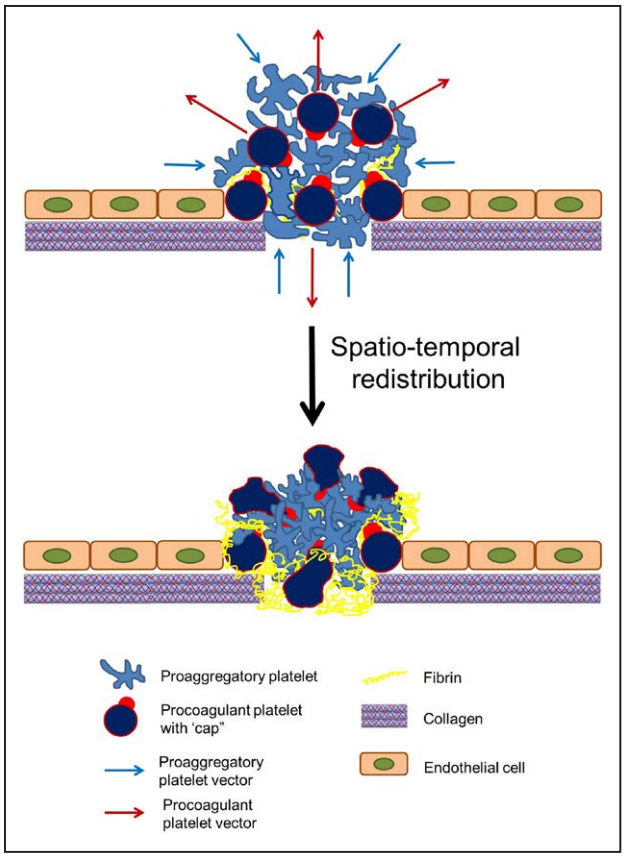


**Figure.** Schematic representation of platelet translocation within the evolving hemostatic plug. After vascular injury, platelets adhere and aggregate at the wound site. A subpopulation of platelets within the hemostatic plug transitions to a procoagulant state. Procoagulant and proaggregatory platelets have opposing vectors of translocation. Clot retraction, driven by platelets with a proaggregatory phenotype, squeezes procoagulant platelets to the periphery where they catalytically amplify tissue factor-initiated coagulation.

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KEY WORDS: Editorials ■ adhesive ■ fibrin ■ hemostasis ■ mice ■ thrombosis