

A Novel Role for $\alpha\text{IIb}\beta\text{3}$ in the Development of Procoagulant Platelets via Phosphatidylserine (PS) Exposure

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Platelets play a vital role in hemostasis, a critical physiological response to prevent bleeding from vascular injury. Activated platelets can be divided into two distinct subpopulations: proaggregatory and procoagulant. At the site of vessel injury, proaggregatory platelets promote platelet aggregation by releasing platelet activators through outside-in signaling of activated integrin $\alpha\text{IIb}\beta\text{3}$ and mediating platelet-platelet interactions via fibrinogen-binding to $\alpha\text{IIb}\beta\text{3}$. Concurrently, procoagulant platelets promote thrombin and fibrin generation by exposing phosphatidylserine (PS), which facilitates interactions with coagulation factors to stabilize the platelet plug through fibrin cross-linking. Finally, $\alpha\text{IIb}\beta\text{3}$ signaling triggers clot retraction, thus further stabilizing the thrombus. While the role of $\alpha\text{IIb}\beta\text{3}$ has long been established in platelet aggregation and clot retraction, no studies have demonstrated its role in coagulation and procoagulant platelet development. As such, it is reasonable to hypothesize that it may also be involved in the development of procoagulant platelets via PS exposure consequently facilitating coagulation. Through iSIM microscopy and flow cytometry, the present study demonstrates that inhibiting $\alpha\text{IIb}\beta\text{3}$ with the monoclonal antibody antagonist 28H7Fab results in delayed PS exposure, which may be attributed to the inhibition of the procoagulant subpopulation and the existence of another PS-externalizing platelet subpopulation: apoptotic platelets. Moreover, these results were exclusive to the Fab fragment (28H7Fab) and not the whole antibody (28H7) suggesting different mechanisms of action for these $\alpha\text{IIb}\beta\text{3}$ antagonists. Collectively, these experiments demonstrate a crucial role for $\alpha\text{IIb}\beta\text{3}$ in the PS exposure of procoagulant platelets.

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