A Novel Role for αIIbβ3 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 αIIbβ3 and mediating platelet-platelet interactions via fibrinogen-binding to αIIbβ3. 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, αIIbβ3 signaling triggers clot retraction, thus further stabilizing the thrombus. While the role of αIIbβ3 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 αIIbβ3 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 αIIbβ3 antagonists. Collectively, these experiments demonstrate a crucial role for αIIbB3 in the PS exposure of procoagulant platelets.