

P027 Role of PI3K isoforms in platelet thrombus formation and procoagulant activity

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Platelet activation results in thrombus formation and stimulation of the coagulation process by surface exposure of phosphatidylserine (PS). In platelets, various phosphoinositide 3-kinase (PI3K) isoforms are expressed, α , β , γ and weakly, δ . While PI3K β and γ have been implicated in platelet aggregation, the function of either isoform in the thrombus-forming process has remained unclear. Here, we studied the roles of PI3K α , β , and γ in these platelet activation processes under physiologically relevant conditions, using human or PI3K deficient murine blood, and using isoform-specific inhibitors. Under flow over collagen, platelet thrombi became unstable and disaggregated rapidly by suppression of PI3K β with TGX221 or of PI3K γ with AS252424, but not by suppression of PI3K α with YM024. In murine blood, absence of PI3K γ but not PI3K α led to formation of unstable thrombi, with multi-platelet emboli leaving. Blocking of PI3K β in addition delayed initial thrombus formation. Procoagulant activity induced by collagen (GPVI) and ADP (P2Y₁₂) was investigated under flow by measuring PS exposure and thrombin generation. This process was greatly reduced by inhibition of PI3K α and β , but not by inhibition or absence of the γ isoform, in both mice and human plasma. Together, the data indicate that PI3K β acts in synergy with PI3K γ in platelet aggregate formation and stability under flow conditions, with each isoform having additive functions. On the contrary, PI3K α and PI3K β , but not PI3K γ , mediate PI3K-dependent regulation of platelet procoagulant activity.