Platelet Dream Plays a Critical Role During Thrombogenesis in Mice

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Downstream regulatory element antagonist modulator (DREAM), a transcriptional repressor, is known to modulate pain. Using intravital microscopy with DREAM-null mice and their bone marrow chimeras, we demonstrated that hematopoietic and endothelial cell DREAM are required for platelet thrombus formation following arteriolar injury. DREAM deletion also prolonged tail bleeding times. In vitro flow chamber assays and in vivo adoptive transfer experiments indicated the importance of platelet DREAM in thrombogenesis. We found that deletion of platelet DREAM does not alter ultrastructural features but significantly impaired aggregation and ATP secretion induced by collagen-related peptide (CRP), ADP, or A23187, but not thrombin or U46619. Biochemical studies showed that platelet DREAM is required for phosphoinositide 3-kinase (PI3K) activation induced by GPVI-, A23187-, or integrin-mediated signaling. Studies using DREAM-null platelets and isoform-specific PI3K inhibitors revealed that platelet DREAM positively regulates granule secretion, Ca2+ mobilization, and aggregation induced by CRP or A23187 through PI3K class Iβ (PI3K-Iβ) activity. Genetic and pharmacological studies in megakaryoblastic MEG-01 cells showed that DREAM regulates A23187-induced Ca2+ mobilization and that the regulatory function of DREAM requires Ca2+ binding and PI3K-Iβ activity. Taken together, we have identified platelet DREAM as a novel regulator of PI3K-Iβ activity during thrombus formation.

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