Comment on Eliaib et al, page 1129

SERCA: navigating calcium signaling in platelets

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In this issue of Blood, Eliaib et al evaluate the role of sarco-endoplasmic reticulum calcium (Ca\(^{2+}\)) adenosine triphosphatase (ATPase) 3 (SERCA3) in platelet function, and discover an unexpectedly strong link between SERCA3 activity and dense granule secretion.\(^1\)

SERCA3 is perhaps the most enigmatic member of the family, distinguished on the basis of its wide tissue distribution and on being a nonmuscle calcium pump. It has a surprisingly low calcium affinity. For example, the affinity of SERCA2b for calcium is \(K_{1/2} \approx 0.27\) \(\mu\)M, whereas that of SERCA3 is \(K_{1/2} \approx 1.1\) \(\mu\)M.\(^3\) Platelets contain both SERCA2b and SERCA3. Platelet SERCA3 is distributed on intracellular membranes\(^4\) and has a known function in sequestering calcium into membrane compartments. Increased SERCA3 levels are associated with peripheral artery disease in the setting of diabetes.\(^5\) However, the role of SERCA3 in platelet function is poorly understood and its role in thrombus formation has not previously been studied.

Eliaib et al have now evaluated SERCA3\(^{-/-}\) mice to determine the role of SERCA3 in platelet function. The authors demonstrated that although these mice breed normally and were phenotypically indistinguishable from littermates, they had abnormal platelet function. Their bleeding times were prolonged following tail clip and rates of rebleeding were markedly increased. They also displayed impaired thrombus formation in a ferric chloride-induced thrombosis model. SERCA3\(^{-/-}\) platelets demonstrated decreased adhesion to collagen in flow chamber assays and impaired aggregation in response to low concentrations of either collagen or thrombin. Platelet dense granule release, as evidenced by decreased ATP release, and \(\alpha\)-granule secretion were also impaired.

In evaluating the defect in SERCA3\(^{-/-}\) platelet function, the authors noted that the addition of ADP to SERCA3\(^{-/-}\) platelets reversed the defects in aggregation, adhesion, and secretion. Furthermore, the mutant platelets showed absolutely no defect in their ability to aggregate in response to ADP. Studies using a SERCA3-specific inhibitor (2,5-di-\((\text{tert}-\text{butyl})\)-1,4-benzohydroquinone; see figure) reproduced the effects of SERCA deletion on dense granule secretion. An inhibitor of SERCA2b (thapsigargin; see image).
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