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12-Lipoxygenase Regulation of Platelet-Mediated Hemostasis and Thrombosis

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Platelet activation plays a central role in regulating hemostasis and thrombosis. Following platelet activation, metabolism of phospholipids such as arachidonic acid (AA) by 12-lipoxygenase (12-LOX) may play a significant role in regulating the degree and stability of platelet reactivity. Although 12-LOX has been described as mediating both pro- and anti-thrombotic effects in the platelet, the underlying mechanism for these actions has remained elusive. Using both inhibitors of 12-LOX as well as its metabolites, we investigated the mechanisms by which this enzyme regulates platelet function. To assess the role of 12-LOX in platelet activation and thrombosis, granule secretion and integrin activation were measured by flow cytometry and confirmed by aggregation in the presence or absence of 12-LOX activation or exogenous addition of eicosanoid metabolites. Inhibiting 12-LOX resulted in a complete inhibition of dense granule secretion and repression of platelet activation. Addition of 12-HETE, resulted in a significant increase in dense granule secretion and addition of 12-HETrE, resulted in complete inhibition of thrombin-mediated platelet activation, giving support to DGLA metabolism (the substrate for 12-HETrE) as a negative regulator of platelet activity while AA metabolism appears to act as a positive regulator of platelet function. Understanding the role of 12-LOX and its metabolites in platelets will enable us to delineate its contribution in regulation of platelet reactivity as well as a readily available biomarker indicating the potential for thrombosis and stroke.

Biography

Michael Holinstat is an assistant professor of Medicine at Thomas Jefferson University in Philadelphia. He received his Ph.D. in Pharmacology from the University of Illinois at Chicago and postdoctoral training at Vanderbilt University in the Department of Pharmacology. His research focuses on identifying novel approaches to anti-platelet therapy with a special emphasis on regulation of platelets through the lipoxygenase pathway leading to a number of oxidized fatty acids which may play a central role in regulating unwanted platelet activation. Additionally, the lab studies regulation of platelet signaling through PAR1 and PAR4.