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Oxygenase 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) and cyclooxygenase-1 (COX-1) may play a significant role in regulating the degree and stability of platelet reactivity. Although COX-1 has been well studied, the disparate and cooperative roles of 12-LOX and COX-1 in regulation of the platelet remain unclear. Using both inhibitors of oxygenases as well as their metabolites, we investigated the mechanisms by which these enzymes regulate platelet function, thrombosis and hemostasis. To assess the role of each oxygenase in platelet activation and thrombosis, granule secretion and integrin activation were measured by flow cytometry and confirmed by aggregation and Rap1 activation in the presence or absence of their eicosanoid metabolites. Inhibiting 12-LOX resulted in a complete inhibition of dense granule secretion and repression of platelet activation and is PAR4 and collagen specific while inhibition of COX-1 attenuates aggregation for PAR1. Addition of metabolites for alternate fatty acids (ω-3 and 6), resulted in differing levels of inhibition of agonist-mediated platelet activation, giving support to fatty acid metabolism other than AA as mechanism to negatively regulate platelet activity while AA metabolism appears to act as a positive regulator of platelet function. Understanding the role of these oxygenases and their metabolites in platelets will enable us to delineate its contribution in regulation of platelet reactivity as well as determine which biomarkers of oxygenase metabolism are good indicators of potential oncoming thrombotic events 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.

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