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Dual roles for 12-Lipoxygenase in regulation of hemostasis and thrombosis

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Abstract

Formation of bioactive lipids by oxygenases is known to play both a protective and pro-thrombotic role in circulation. 12-lipoxygenase (12-LOX) and its oxidized products play an important but unresolved role in regulation of platelet function. 12-LOX oxidation of the fatty acid, dihomo-γ-linolenic acid (DGLA), produces the novel bioactive metabolite 12-hydroxyeicosatetrienoic acid (12(S)-HETrE). Recent work suggests that while 12(S)-HETE (produced from 12-LOX oxidation of AA) is pro-thrombotic to the platelet, 12(S)-HETrE acts in a protective manner in platelets to limit activation. Therefore, we sought to identify the mechanism by which DGLA inhibits platelet activation through 12(S)-HETrE. Delineating the mechanism by which this previously unknown metabolite regulates cellular activity is essential to begin to understand how 12-LOX oxidation of DGLA can potentially lead to regulation of a number of physiological processes including thrombosis. To address these questions, we have employed pharmacological and whole animal studies. Pharmacological intervention has confirmed an integral role of 12-HETrE production through 12-LOX to negatively regulate activity in the platelet. These observations have been confirmed in mice lacking the 12-LOX gene. Further, dietary supplementation of DGLA-enriched chow supports our ex vivo studies exogenously adding DGLA and/or 12-HETrE to attenuate agonist-induced platelet activation. Hence, these studies are the first to begin to elucidate the underlying mechanisms by which omega-3 and 6 fatty acids are protective against cardiovascular disease 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. 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. Dr. Holinstat recently received the Kenneth M. Brinkhous Young Investigator Prize in Thrombosis from the American Heart Association for his work on 12-lipoxygenase in cardiovascular medicine.