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Cytosolic phospholipase $A_2\alpha$: A tale of two functions

New roles for sphingolipids such as ceramide, ceramide-1-phosphate (C1P) and sphingosine-1-phosphate continue to emerge. My research, for example, has implicated C1P as a major regulator of eicosanoid synthesis, and despite the importance of eicosanoids in the inflammatory process, the regulation of eicosanoid synthesis proximal to the activation of Group IVA phospholipase A_2 ($cPLA_2\alpha$) is still an enigma. In this regard, my laboratory demonstrated that C1P is a direct and required lipid co-factor for $cPLA_2\alpha$ activation in cellular models. In further studies, the interaction site for C1P was localized to the calcium-lipid binding domain (C2 domain) of the enzyme allowing for the genetic ablation of the site *in vivo* via the generation of a $cPLA_2\alpha$ knock-in (KI) mouse. In this lecture, the characterization of this new mouse model in comparison to the full genetic ablation of the enzyme will be presented. Specifically, the loss of the C1P/$cPLA_2\alpha$ interaction induced a class-switch in the production specific eicosanoids and specialized lipid mediators driving both sepsis resistance and accelerated wound repair. In further mechanistic studies, C1P was found to modulate the substrate specificity of $cPLA_2\alpha$ explaining the "class switch" as to bioactive lipid mediators observed in the $cPLA_2\alpha$ KI mouse. Overall, these observations led to two new findings: 1) C1P is a pro-inflammatory signaling molecule that directs $cPLA_2\alpha$ in the utilization of primarily phospholipids with sn-2 arachidonic acid, while simultaneously blocking the utilization of phospholipids with sn-2 docosahexaenoic acid; and 2) $cPLA_2\alpha$ has previously overlooked functions in the resolution of inflammation and immune responses.

Biography

Charles E Chalfant has received his PhD from the University of South Florida, College of Medicine and was an NRSA Post-doctoral Fellow at both Duke Medical Center and the Medical University of South Carolina under Dr. Yusuf Hannun. He is currently a GS-15 Research Career Scientist at the Richmond VAMC. He is also a Tenured Professor and Vice Chair of the Department of Biochemistry and Molecular Biology at Virginia Commonwealth University (VCU), School of Medicine. He currently holds the Paul M Corman, MD Endowed Chair in Cancer Research for the VCU Massey Cancer Center and has published more than 100 papers in reputed journals.

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