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Ablation of the ceramide-1-phosphate interaction with group IVA cytosolic phospholipase A_2 induces enhanced wound regenerations

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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$_2$α) is still an enigma. In this regard, my laboratory demonstrated that C1P is a direct and required lipid co-factor for cPLA2α activation in cellular models. In further studies, one 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$_2$α 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$_2$α interaction induced a class-switch in the production specific eicosanoids and specialized lipid mediators driving accelerated wound repair and regeneration, both in acute and chronic murine models. Cellular studies demonstrated that loss of this lipid, protein interaction led to enhanced dermal fibroblast and neutrophil migration, which was mimicked *in vivo*. In further mechanistic studies, C1P was found to modulate the substrate specificity of cPLA$_2$α in opposition to another lipid mediator of the enzyme, PIP2, explaining the class switch as to bioactive lipid mediators observed in the cPLA$_2$α KI mouse. Using lipidomic analyses, these specific lipid fingerprints were linked to human wound healing outcomes, which suggests that modulation of specific lipid mediators could be explored to promote wound healing and regeneration in a number of contexts

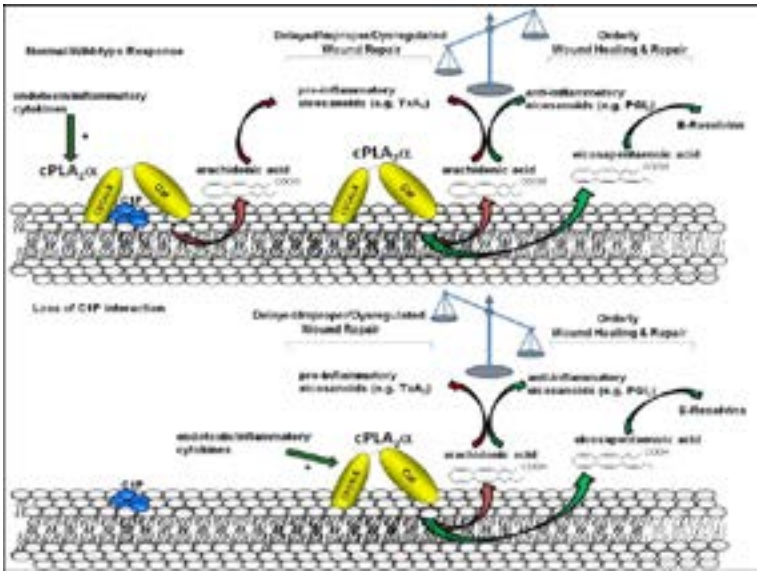

Figure 1.*The current mechanistic hypothesis, "shifting function hypothesis, to explain the loss of pro-inflammatory lipid mediators and concomitant increase in pro-resolution lipid mediators in response to loss of the C1P/cPLA$_2$α interaction.*

Recent Publications:

1. Hoeferlin L A, Huynh Q K, Mietla J A, Sell S A, Tucker J, Chalfant C E and Wijesinghe D S (2015) The Lipid Portion of Activated Platelet-Rich Plasma Significantly Contributes to Its Wound Healing Properties. Advance in Wound Care

(New Rochelle) 4(2):100-109.

2. Mietla J A, Hoeferlin L A, Diegelmann R F, Boise L H, Chalfant C E (2014) Ceramide kinase is required for a normal eicosanoid response and the subsequent orderly migration of fibroblasts. Journal of Lipid Research 55(7):1298-1309.
3. Wijesinghe D S and Chalfant C E (2013) Systems-Level Lipid Analysis Methodologies for Qualitative and Quantitative Investigation of Lipid Signaling Events During Wound Healing. Advance in Wound Care (New Rochelle) 2(9):538-548.
4. Daniel Contaifer Jr, Daniel E Carl, Urszula Osinska Warncke, Erika J Martin, Bassem M Mohammed, Benjamin Van Tassell1, Donald F Brophy, Charles E Chalfant and Dayanjan S Wijesinghe (2017) Unsupervised analysis of combined lipid and coagulation data reveal coagulopathy subtypes among dialysis patients. Journal of Lipid Research 58(3):586-599
5. Dhall S, Do D, Garcia M, Wijesinghe D S, Brandon A, Kim J, Sanchez A, Lyubovitsky J, Gallagher S, Nothnagel E A, Chalfant C E, Patel R P, Schiller N, Martins-Green M (2014) A novel model of chronic wounds: importance of redox imbalance and biofilm-forming bacteria for establishment of chronicity. PLoS One 9(10): e109848.

Biography

Charles Chalfant received his PhD from the University of South Florida, College of Medicine and was an NRSA Postdoctoral fellow at both Duke Medical Center and The Medical University of South Carolina under Dr Yusuf Hannun. He is currently a GS15 Research Career Scientist with the Richmond Veterans Administration Medical Center. He is also a Tenured Professor and Vice Chair of the Department of Biochemistry and Molecular Biology at Virginia Commonwealth University, 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 peer-reviewed manuscripts. The Chalfant laboratory has more than 20 years of experience in Lipid Biology, Cell Signaling, and RNA Splicing.

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