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Importance of Ca²⁺-independent phospholipase A₂b-derived lipids to type 1 diabetes development

Type 1 diabetes (T1D) is a consequence of pancreatic islet b-cell destruction, due to apoptosis. Our lab is investigating underlying mechanisms that contribute to b-cell loss and we identified a prominent role for the group VIA Ca²⁺-independent phospholipase A₂b (iPLA₂b) in this process. The cytosolic iPLA₂b catalyzes hydrolysis of the sn-2 substituent from membrane phospholipids. The islet b-cell membranes are enriched in arachidonate-containing phospholipids and activation of iPLA₂b in the b-cells leads to accumulations in arachidonic acid and its various oxidized metabolites (i.e. eicosanoids). The eicosanoids manifest different activities, some of which are proinflammatory and apoptotic and some are anti-inflammatory and anti-apoptotic. Inhibition, knockdown, or knockout of iPLA₂b significantly reduces b-cell apoptosis due to ER stress or proinflammatory cytokines. Further, during the development of autoimmune T1D, expression and activity of iPLA₂b increases and this is associated with generation of proinflammatory and apoptotic lipid signals. Consistent with this, we find that with selective inhibition of iPLA₂b in the spontaneously diabetes-prone non-obese diabetic (NOD) mouse, there is a significant reduction in islet infiltration by leukocytes, preservation of b-cell mass and a dramatic amelioration of T1D. We further found that iPLA₂b inhibition markedly reduces immune responses. These observations provided a strong evidence for contribution of iPLA₂b-derived lipids to T1D development. Our on-going investigations revealed that activation of iPLA₂b triggers molecular mechanisms that favor generation of pro-apoptotic/pro-inflammatory signals and these work in concert to promote T1D development. Our work was supported by the American Diabetes Association, NIH/NIDDK, and the Iacocca Family Foundation.

Biography

Sasanka Ramanadham was awarded his PhD from the Department of Pharmacology at Texas Tech University Health Sciences Center in 1985. His thesis project was focused on cardiovascular complications associated with diabetes. He has continued work in the diabetes area and is now engaged in studies to understand the contribution of lipid signaling to type 1 diabetes development. He has nearly 100 publications, serves on Journal Editorial Boards and as a Grant Reviewer for both national and international Diabetes Foundations. He is currently a Professor in the Department of Cell, Developmental, and Integrative Biology, and a Senior Scientist in the Comprehensive Diabetes Center at UAB.

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