

Title: Importance of Ca^{2+}-Independent Phosphoplipase $A_2\beta$-Derived Lipids to Type 1 Diabetes Development

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Type 1 diabetes (T1D) is a consequence of pancreatic islet β-cell destruction, due to apoptosis. Our lab is investigating underlying mechanisms that contribute to β-cell loss and we identified a prominent role for the group VIA Ca^{2+}-independent phosphoplipase $A_2\beta$ ($iPLA_2\beta$) in this process. The cytosolic $iPLA_2\beta$ catalyzes hydrolysis of the *sn*-2 sbstituent from membrane phopsholipids. The islet β-cell membranes are enriched in arachidonate-containing phospholipids and activation of $iPLA_2\beta$ in the β-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 ant-inflammatory and anti-apoptotic. Inhibition, knockdown, or knockout of $iPLA_2\beta$ significantly reduces β-cell apopotosis due to ER stress or proinflammatory cytokines. Further, during the development of autoimmune T1D, expression and activity of $iPLA_2\beta$ increases and this is associated with generation of proinflammatory and apoptotic lipid signals. Consistent with this, we find that with selective inhibition of $iPLA_2\beta$ in the spontaneously diabetes-prone non-obese diabetic (NOD) mouse, there is a significant reduction in islet infiltration by leukocytes, preservation of β-cell mass, and a dramatic amelioration of T1D. We further find that $iPLA_2\beta$ inhibition markedly reduces immune responses. These observations provide strong evidence for contribution of $iPLA_2\beta$-derived lipids to T1D development. Our on-going investigations reveal that activation of $iPLA_2\beta$ 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

Dr. Ramanadham was awarded his PhD from the Department of Pharmacology at Texas Tech University Health Sciences Center in 1985. He thesis project 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 singnaling to type 1 diabetes development. He has nearly 100 publications, serves on Journal Editorial Boards, and as a grant reviewer for both National and Intenational Diabetes Foundations. He is currently a Professor in the Department of Cell, Developmental, and Integrative Biology, and a Senior Scientist in the Comprehesive Diabetes Center at UAB.

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