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Phagocyte-like NADPH oxidase mediates islet dysfunction in models of impaired insulin secretion and diabetes: So, is it "druggable"?

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Excessive generation of reactive oxygen species [ROS] is considered central to the development of cellular dysfunction in diabetes. The generation of free radicals is relatively low under physiologic conditions; however, increased levels of circulating glucose, lipids or proinflammatory cytokines promote intracellular accumulation of superoxides, leading to cellular dysregulation. Although mitochondria remain the primary source for free radicals, recent evidence implicates phagocyte-like NADPH oxidase [Nox] as a principal source of extra-mitochondrial ROS. Nox is a highly regulated membrane-associated protein complex that promotes a one-electron reduction of oxygen to superoxide anion involving oxidation of cytosolic NADPH. The Nox holoenzyme consists of membrane and cytosolic components. The membrane-associated catalytic core consists of gp91phox/p22phox, and the cytosolic regulatory core includes p47phox/ p67phox/p40phox/Rac1. Following stimulation, the cytosolic core translocates to the membrane for association with the catalytic core for activation of Nox. To this end, our recent findings suggested that exposure of isolated beta-cells to glucolipotoxic conditions or proinflammatory cytokines results in the activation of cytosolic core of Nox [p47phox phosphorylation and Rac1 activation] culminating in the generation of Nox-derived ROS. Importantly, our data are suggestive of an accelerated Nox signaling cascade in islets derived from animal models of obesity and diabetes [ZDF Rat] and type 2 DM human donors. It is noteworthy that in vitro approaches involving the use of Rac1 inhibitors [NSC23766] appear to halt the progression of mitochondrial defects and loss in beta-cell viability induced by glucolipotoxic conditions and cytokines. Even though these advancements paint a positive picture that inhibitors of Rac1-Nox-ROS signaling pathway could serve as novel therapeutic tools to attenuate islet dysfunction under the duress of glucolipotoxic or cytokine exposure conditions; they could be met with some skepticism given the indispensable nature of Rac1 signaling axis in beta-normal cell function and survival. Potential therapeutic modalities that are being considered to target Nox and prevent intracellular oxidative stress and beta-cell demise will be discussed.

Biography

Anjan Kowluru is Associate Dean and Professor Pharmaceutical Sciences and Medicine at Wayne State University. He also holds Senior Research Career Scientist position at the John D. Dingell VA Medical Center in Detroit. Dr. Kowluru is involved in understanding regulatory roles of small G-proteins in islet function in health and diabetes. He published more than 125 papers and presented 225 papers at various local, regional, national and international meetings. His research is supported by grants from the NIH, the Department of VA and other private foundations including the ADA and the JDRF. He serves [or served] on scientific advisory panels at the NIH, the VA, the ADA and the JDRF. He is currently serving [or served] on the editorial boards of several journals, including Endocrinology, Biochemical Pharmacology, American J. Physiology-Endocrinology and Metabolism, Experimental Diabetes Research and the Journal of Diabetes and Metabolism.

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