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Protein prenylation in glucose-induced insulin secretion

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Abstract

Insulin secretion from the pancreatic beta-cell is regulated principally by the ambient concentration of glucose. However, the molecular and cellular mechanisms underlying the stimulus-secretion coupling of glucose-stimulated insulin secretion [GSIS] remain only partially understood. Emerging evidence from multiple laboratories suggests key regulatory roles for GTP-binding proteins [G-proteins] in the cascade of events leading to GSIS. This class of signaling proteins undergoes a series of requisite post-translational lipidation [e.g., prenylation] by a group of enzymes referred as prenyltransferases. A growing body of evidence suggests that prenylation promotes targeting of modified proteins to respective membranous sites for optimal interaction with their effector proteins. At least 3 classes of prenyltransferases have been identified thus far. The farnesyl transferase [FTase] catalyzes incorporation of 15-carbon farnesyl group into Ras subfamily of G-proteins [e.g., H-Ras] and nuclear lamins [e.g., lamin B]. Geranylgeranyl transferases [GGTases] mediate incorporation of 20-carbon geranyl geranyl groups into substrate proteins. Among GGTases, GGTase-I lipidates G-proteins such as Cdc42, Rac1, and Rho whereas GGTase-II modifies Rab GTPases. Lastly, both FTase and GGTases are heterodimeric in nature comprising of alpha- and beta-subunits. Interestingly, FTase and GGTase-I share a common alpha-subunit, but variable beta-subunits. However, the alpha- and beta-subunits of GGTase-II are distinct from GGTase-I. Data from our laboratory have demonstrated expression of FTase, GGTase-I and GGTase-II subunits in clonal beta-cells [INS 832/13 cells], normal rodent islets and human islets. Pharmacological inhibition of FTase [FTI-277] or GGTase-I [GGTI-2147] markedly attenuated GSIS. siRNA-mediated knockdown of individual subunits of FTase and GGTase also reduced GSIS significantly. Furthermore, a dominant negative mutant of the common alpha subunit of FTase/GGTase also inhibited GSIS suggesting that activation of FTase/GGTase is critical for GSIS to occur. In support of these observations, we also observed that both FTase and GGTase activities are increased significantly by glucose in INS832/13 cells. Lastly, siRNA-mediated knockdown of the alpha- or beta-subunit of GGTase-II also resulted in a marked attenuation of GSIS in isolated beta-cells. Together, our data indicate novel regulatory roles for protein farnesylation and geranylgeranylation in GSIS. Potential alterations in the functional alteration of these enzymes in beta-cell models of glucolipotoxicity and diabetes 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.