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Lauren M. Bayliss
The University of Texas Rio Grande Valley, lauren.muenchow01@utrgv.edu

Bosma J. Karin
Vanderbilt University

James K. Oeser
Vanderbilt University

Richard M. O'Brien
Vanderbilt University

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Lauren P. Muenchow (University of Texas-Rio Grande Valley School of Medicine), Karin J Bosma, James K. Oeser, and Richard M. O'Brien

Department of Molecular Physiology & Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee

G6PC2 encodes a glucose-6-phosphatase catalytic subunit that is highly expressed in pancreatic islet beta cells. Genome wide association studies (GWAS) have shown that single nucleotide polymorphisms (SNPs) in the *G6PC2* gene are associated with variations in fasting blood glucose (FBG), a parameter linked with risk for type 2 diabetes (T2D). Studies in mice have complemented these GWAS data by showing that deletion of *G6pc2* abolishes islet glucose-6-phosphatase activity and lowers FBG. We hypothesize that G6pc2 forms a substrate cycle with glucokinase that determines the sensitivity of glucose-stimulated insulin secretion (GSIS) to glucose. In support of this hypothesis we have previously shown that deletion of G6pc2 enhances GSIS at sub-maximal glucose concentrations and abolishes glucose cycling in isolated islets. More recently we have demonstrated that deletion of G6pc2 enhances glycolysis in isolated mouse islets, and that high rates of glucose cycling are also detected in human islets. Our broad hypothesis is that the results of these studies will strongly suggest that G6PC2 inhibition should be considered as a novel therapeutic strategy for lowering FBG and thereby preventing T2D. To extend these observations we have developed a novel intact cell assay for G6PC2 activity. This assay relies on the observation that CREB and ChREBP bound to the rat *G6PC1* promoter are highly glucose responsive in the rat islet-derived 832/13 cell line and the fact that endogenous G6PC2 is absent. In the presence of catalytically-dead G6PC2, glucose stimulates *G6PC1*-luciferase fusion gene expression. However, this induction is blunted in the presence of wild type G6PC2. We are using this assay to determine the effect of non-synonymous *G6PC2* SNPs on G6PC2 activity and then examining the association between SNPs that markedly affect G6PC2 activity with their effects on human health as assessed using Vanderbilt's BioVU biobank. These data will reveal whether SNPs in G6PC2 are associated with only altered FBG or whether G6PC2 affects other aspects of human health.