Abstract citation ID: bvad114.941

Diabetes And Glucose Metabolism

SAT074

Induction Of Insulin Hypersecretion Uncovers Distinctions Between Adaptive And Maladaptive Endoplasmic Reticulum Stress Response In Beta Cells

Gitanjali Roy, Research associate[1], *Karina Rodrigues dos Santos*[1], *Michael B. Kwakye, MSc*[1], *Zhiyong Tan*[2], *Travis S. Johnson, PhD*[1], *and Michael A. Kalwat, PhD*[1]

[1]Indiana Biosciences Research Institute, Indianapolis, IN, USA; [2]Indiana University School of Medicine, Indianapolis, IN, USA

Disclosure: G. Roy: None. **K. Rodrigues dos Santos:** None. **M.B. Kwakye:** None. **Z. Tan:** None. **T.S. Johnson:** None. **M.A. Kalwat:** None.

Pancreatic islet β-cells release insulin to maintain glucose homeostasis. β-cells must translate, package, and secrete large amounts of insulin. During this process the unfolded protein response of the endoplasmic reticulum (UPR^{ER}) is induced to maintain these functions. However, stimuli that force β-cell to secrete insulin at enhanced rates and for prolonged durations risk inducing the terminal UPR^{ER} and eventual apoptosis. In a chemical screen for insulin secretion modulators, we discovered SW016789 which caused hypersecretion of insulin and led to a transient induction of the UPR^{ER}, but not apoptosis. In contrast, SERCA2 ER Ca^{2+} pump inhibitor thapsigargin induces the terminal UPR^{ER}. We hypothesized that SW016789 can be used as a tool compound to discover genes involved in β-cell adaptation to hypersecretion-induced stress. We performed time course transcriptomics in MIN6 β-cells exposed to SW016789 (5 μM) or thapsigargin (100 nM) from 0-24 h. Unbiased analyses using a Dirichlet process Gaussian process (DPGP) method revealed clusters of genes temporally co-regulated and the genes within these clusters were distinct between SW016789 and thapsigargin treatments. In particular, after 6 h of SW016789-induced hypersecretion we found a highly induced cluster of genes (SW cluster 3) enriched in adaptive UPR^{ER} factors (e.g. *Manf*). Conversely, most of the thapsigargin-induced genes clustered at 24 h and were enriched for terminal UPR^{ER} factors (e.g. *Txnip*). Pathway analysis of SW cluster 3 indicated that genes involved in in regulation of mRNA methylation and ER-associated degradation were also induced by SW016789 sooner and with greater amplitude than by thapsigargin, suggesting distinct differences in the handling of protein translation and degradation. From the SW cluster 3 genes we selected proteins known to be ER-associated or secreted and generated stable transgenic or CRISPR knockout MIN6 β-cell lines for each. Our data suggest altered expression of these factors may impair glucose-stimulated insulin secretion responses and alter cell viability in presence or absence of ER stressors including cytokines, thapsigargin, and tunicamycin. In conclusion, we have successfully shown that pharmacological induction of insulin hypersecretion can induce a distinct transcriptional outcome from that of canonically-induced UPR^{ER} and that we can take advantage of this property to discover new β-cell regulatory pathways and targets. We envision this dataset as a resource for the secretory biology and islet biology communities.

Presentation: Saturday, June 17, 2023