Pancreatic beta cell dysfunction in response to chronic hyperglycemia is partially mediated by transcriptional downregulation of Gli-similar 3 (Glis3)

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Gli-similar 3 (Glis3) is a Krüppel-like zinc finger protein that plays critical roles in development and in the maintenance of normal physiological functions in a variety of tissues. In humans, GLIS3 deficiency has been linked to a rare syndrome characterized by neonatal diabetes, hypothyroidism, and polycystic kidney disease. In addition, genome-wide association studies (GWAS) have implicated Glis3 as a risk locus for the development of diabetes. While Glis3 is known to play important roles in the specification of endocrine cell fates during pancreatic development, its role in the mature beta cell and the mechanism by which Glis3 dysfunction results in type 2 diabetes remains unclear. We have characterized a rat pancreatic hybridoma cell line (BRIN BD11) that secretes insulin in response to physiologically normal glucose levels but has greatly diminished expression of *Glis3*. The cell line exhibited significantly decreased levels of known Glis3 target genes, *Ins2* and *Ccnd2* in addition to the insulin activator, *MafA*. We investigated the effects of stable Glis3 overexpression on BRIN-BD11 cells and found that *Ins2* and *Ccnd2* levels were increased in the presence of exogenous Glis3. Interestingly, while chronic exposure of beta cells to high levels of glucose results reduced expression of *Ins1/2* and *MafA*, we found that BRIN BD11 cells were relatively protected from the effects of glucotoxicity and exogenous Glis3 expression partially rescued the phenotype. Collectively, these data suggest that BRIN BD11 cells may be a useful model for the study of beta cell dysfunction preceding the onset of type 2 diabetes.