The role of an endogenous inhibitor of calcineurin in the regulation of glucose homeostasis and islet function

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Calcineurin (CaN) is a protein phosphatase important in the regulation of transcription and protein phosphorylation. The CaN/NFAT transcription pathway regulates pancreatic β-cell growth and insulin secretion. We are investigating the effect of a gene known to endogenously inhibit CaN and its possible role in the pathogenesis of type 2 diabetes. Expression of our gene of interest increased 2.5 fold ($p<0.05$) when islets were exposed *in vitro* to 16.7 mM glucose for 6 days. Transgenic mice (Tg) with a universal over-expression of this gene were used for this study. In Tg islets, genes such as those mutated in hereditary forms of monogenic type 2 diabetes (MODY) and others that regulate β-cell survival, proliferation and insulin production are downregulated. *In vivo* studies show that Tg mice develop diabetes characterized by increased fasting blood glucose levels of 5.8 ± 0.3 mmol/L at 60 days old compared to 4.2 ± 0.2 mmol/L in wild-type mice ($n=9$, $p<0.05$) and this hyperglycemia worsens with age. Immunohistochemical analysis of pancreatic islets reveals that Tg mice develop a 70% reduction in islet area at 100 days ($n=4$) while no change is observed at 40 days. Tg mice also show poorer glucose tolerance, these changes are not due to differences in body weight or insulin resistance. Our findings highlight a novel role of this endogenous inhibitor of calcineurin in regulating glucose homeostasis, expression of major β-cell regulatory genes and islet growth. As this gene is also up-regulated by chronic hyperglycemia, our findings suggest that it may be involved in the β-cell failure and hypoinsulinemia characteristic of type 2 diabetes.