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Loss of Glp-1r Signaling in the β-Cell Impairs Adaptive Proliferation and Insulin Secretion

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Type 2 diabetes mellitus is characterized by insulin resistance and loss of pancreatic b-cell mass. b-cells are located in the pancreatic islets and secrete insulin. Though many therapies exist that address insulin resistance and to augment b-cell insulin secretion, there is a critical need to find therapies to preserve b-cell mass in order to decrease the incidence and severity of diabetes. In non-diabetic obesity, an early adaptive response to insulin resistance is increased b-cell proliferation. This compensatory mechanism leads to increased b-cell mass and increased insulin secretion from b-cells. This increase in b-cell mass is seen in as little as 4 days of high fat diet (HFD) feeding in murine models.

A promising therapeutic for the preservation of b-cell mass is glucagon-like peptide-1 receptor (Glp-1r) agonists. The ability of GLP-1 to stimulate b-cell proliferation and inhibit apoptosis is largely based on studies using pharmacologic treatment, but the importance of GLP-1 in b-cell mass regulation in normal physiology or pathophysiology has not been well studied. Notably, GLP-1 is secreted from alpha cells in the local islet environment and this paracrine signaling pathway is important for islet function. The goal of this work is to investigate the contribution of b-cell Glp-1r signaling to b-cell mass regulation in the metabolic stress condition of a one-week HFD. We hypothesize that b-cell Glp-1r signaling is necessary for the compensatory mechanisms needed to maintain glucose homeostasis during metabolic stress conditions and that lack of b-cell Glp-1r will lead to decreased proliferation of b-cells. Understanding the role of β-cell Glp-1r signaling in adaptive b-cell mass expansion will allow for development of new strategies to augment β-cell mass in type 2 diabetes.

We used a newly generated murine model with a b-cell specific knockout of Glp-1r, where the Ins1-Cre knock-in transgene drives recombination in b-cells. Glp-1r fl/fl mice (WT) and Glp-1r fl/fl – Ins1Cre mice (KO) were fed a HFD for one week. There was a trend toward elevated fasting (171+/-29 mg/dl vs 205+/-36 mg/dl, p=0.0475, n=9) and non-fasting blood glucose (195+/-24 mg/dl vs 216+/-40 mg/dl, p=0.0537, n=18) and impaired glucose tolerance in the KO mice. Notably, we found that insulin secretion in response to intraperitoneal glucose is impaired in KO mice. KO mice have a blunted proliferation response to a 1-week HFD stress, as measured by Ki67 mRNA levels (1.5-fold induction of Ki67 in WT vs. 0.6-fold induction in KO, p=0.0167, n=8-10). b-cell proliferation will also be measured by immunofluorescent image analysis of whole pancreas sections. These data suggest there is a critical role for b-cell Glp-1r signaling in the early proliferative response of b-cells in response to metabolic stress.

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