ADA Presidents' Select Abstract: Glucagon Receptor Antagonism Stimulates Beta-Cell Proliferation in Mouse and Human Islets

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Interrupting glucagon signaling (IGS) elicits robust alpha cell proliferation in an amino acid-dependent manner in mouse and human pancreatic islets. To determine whether IGS triggers beta cell proliferation in mouse and human islets in vivo, we quantified the percentage of Ki67-positive beta cells in adult mouse and human islets after IGS. Wild type (WT) mouse islets transplanted into liver-specific glucagon receptor (GCGR) knockout (LKO) mice exhibited a 4.1-fold increase in beta cell proliferation (WT to LKO: 0.98±0.34%, WT to WT: 0.24±0.19%, P=0.008, n=8). Likewise, treatment of C57BL6 mice with an anti-GCGR monoclonal antibody (GCGR-Ab) elicited a 3.6-fold increase in beta cell proliferation (GCGR-Ab: 1.09±0.21%, control (CTR): 0.30±0.14%, P=0.004, n=10). Given that the cationic amino acid transporter, Slc7a2, is one of the most highly expressed amino acid transporters in pancreatic islets and required for IGS-induced alpha cell proliferation, we assessed GCGR-Ab-induced beta cell proliferation in adult mice with inactivation of Slc7a2. There was a 3.2-fold increase in beta cell proliferation in WT mice treated with GCGR-Ab (GCGR-Ab: 1.45±0.46%, CTR: 0.46±0.15%, P=0.001, n=10). Notably, this effect was absent in Slc7a2 knockout mice (GCGR-Ab: 0.35±0.35%, CTR: 0.41±0.28%, n=10), suggesting that GCGR antagonism induces beta cell proliferation in an amino acid-dependent manner in mice. Furthermore, transplanted human islets from normal donors (ages 10-55, n=8) into immunodeficient mice exhibited a 2.8-fold increase in beta cell proliferation (GCGR-Ab: 0.61±0.60%, CTR: 0.22±0.21%, P=0.05, n=8) following GCGR-Ab treatment. These data indicate that IGS stimulates beta cell proliferation in mouse and human islets and that in mouse islets, this is Slc7a2-dependent.

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