Hypoxia-inducible pathway mitigates mitochondrial dysfunction in pancreatic beta cells

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Type 1 diabetes (T1D) is an autoimmune disease characterized by the targeted destruction of insulin-producing beta cells. Although the exact causes of T1D remain unknown, recent evidence points to the role of cellular stress in beta cells provoking the autoimmune reactivity observed in T1D. Beta cells require appropriate glucose metabolism to meet the demand for insulin secretion, and dysregulated glycolysis and mitochondrial oxidative phosphorylation are key features of several disease models of T1D. Furthermore, dysregulation of mitochondrial homeostasis is linked to loss of beta cell function and production of signals that trigger their targeted autoimmune destruction. The transcriptional factor hypoxia-inducible factor-1 (HIF-1) is a master regulator of cellular metabolism, and published research shows the adaptive activation of the HIF-1 pathway in the development of human T1D, as well as its protective role in animal models of T1D. We hypothesize that activation of the HIF-1 pathway protects beta cells against metabolic stress-derived mitochondrial dysfunction. Using single cell transcriptomic from human pancreatic islets exposed to hypoxia, we observed activation of canonical markers of the HIF-1 pathway (*VEGFA*, *PFKP*, *PGK1*, *ENO1*, *ENO2* and *BNIP3*) in beta cells, as well as increased glycolysis and downregulated mitochondrial function. On the other hand, in islets treated with metabolic stressors, we observed upregulation of mitochondrial function, increased endoplasmic reticulum (ER) stress, and unfolded protein response in the beta cell population.
This stress signature was absent in other endocrine cells in the islets, suggesting the induction of a beta cell specific injury in metabolic stress conditions. In order to explore the role of HIF-1 activation in stress response in beta cells, we treated the human beta cell line Endo-CβH1 with Roxadustat, a prolyl hydroxylase inhibitor, at the concentration of 10 μM for 24 hours. Roxadustat treatment upregulated the expression of the glycolytic genes *GLUT1* and *LDHA*, and metabolic activity of Roxadustat-treated cells was increased even in ER and metabolic stress conditions, compared to control. Collectively, we provided first evidence that activation of HIF-1 in pancreatic insulin-producing beta cells skewed cellular metabolism away from error-prone mitochondrial oxidative phosphorylation to glycolysis, harnessing a cytoprotective effect against metabolic stress. In conclusion, by facilitating a shift towards glycolysis, pharmacological HIF-1 activation holds promise for safeguarding pancreatic beta cells against metabolic stress during the early stages of type 1 diabetes.