Sirt6 Regulates Insulin Secretion from the Pancreatic Beta Cells

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Sirt6 is an NAD-dependent histone deacetylase, which is involved in multiple biological processes, including aging, DNA repair, and metabolism; however, it is unclear what its functions in pancreatic beta-cells are. The beta cells play an essential role in metabolic regulation by secreting insulin in response to an elevated glucose concentration in the circulation. To examine the role of Sirt6 in beta cells, we initially used adenovirus-mediated shRNA to knock down the Sirt6 gene expression in a mouse pancreatic beta cell line - MIN6. Knockdown of the Sirt6 gene significantly reduced glucose-stimulated insulin secretion. To further validate this phenotype in vivo, we generated pancreatic beta-cell-specific Sirt6 knockout mice (bKO) using mouse genetic approach. Indeed, the bKO mice showed remarkable impairment in both first and second phases of insulin secretion in response to a glucose load. While morphometric analyses did not reveal significant difference in islet area between wild-type and bKO mice, biochemical analysis of ATP concentrations showed a 22% decrease in bKO mouse islets relative to control wild-type islets after glucose stimulation. To assess mitochondrial function in Sirt6-deficient beta cells, we also performed Seahorse bioenergetics assays in MIN6 cells after the Sirt6 gene was knocked down. Glucose oxidation in mitochondria was decreased 20-30% in Sirt6-knockdown MIN6 cells as compared to the control cells. Since calcium signaling is critical to insulin secretion, we also measured intracellular calcium concentrations using a fluorescent imaging approach. The results showed a significant decrease in cytoplasmic calcium in the bKO islets as compared to the wild-type controls. Overall, our data demonstrate that Sirt6 plays a critical role in the regulation of pancreatic insulin secretion.

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