ABSTRACT

Gαz: An intra-islet signaling hub fundamental for Type 1 Diabetes pathophysiology

In Type 1 Diabetes (T1D), autoimmune destruction of the insulin-producing beta-cells of the pancreatic islet causes extreme hyperglycemia. If insulin is not administered, catastrophic organ failure leads to death. Yet, injectable insulin will never fully mimic the body's natural insulin secretory profile . New strategies for T1D treatment are desperately needed. The alpha-subunit of the heterotrimeric Gz protein, Gαz, has previously been identified as a tonic inhibitor of the conversion of cellular adenosine tri-phosphate into the cell signaling molecule, cyclic AMP. Cyclic AMP is a known stimulator of beta-cell insulin secretion, proliferation, and survival. Utilizing the non-obese diabetic (NOD) mouse strain as a T1D model, I showed systemic loss of Gαz protects from hyperglycemia. Pancreatic islets from mice lacking Gαz secrete more insulin in response to glucose and display increased expression of markers of beta-cell proliferation and survival. While Gαz tissue expression is relatively limited, it has been observed in other insulin-responsive cells, including the brain, immune cells, and other islet cells. To test the importance of loss of beta-cell Gαz in the T1D protection phenotype, I created a NOD mouse lacking Gαz only in beta-cells. These mice were partially protected from developing T1D. We noted that mice that lost Gαz throughout the body or specifically in beta-cells have similar toxic immune cell expression and function as our T1D control mice, suggesting in Gαz is not present in immune cells. My current data suggests Gαz loss in non-beta-cell islet cells may alter the expression of islet hormones having known effects on the beta -cell. In sum, my work not only highlights the importance of intra-islet cell-cell communication in regulating blood glucose levels, but also identifies the Gαz signaling pathway as a potential new target for the preservation of beta-cell function, proliferation, and survival in the face of autoimmune insult.