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Project Summary
Type 2 Diabetes (T2D) is associated with defective β cell insulin secretion and subsequent reductions of β cell mass. Conventionally, apoptosis has been thought of as a major pathway to loss of β cell mass in T2D. However, recent studies using rodent models have shown that dedifferentiation of mature β cells into endocrine progenitor-like cells can also play a role in this process. Nevertheless, it remains unclear whether β cell dedifferentiation is a key pathway in the pathogenesis of β cell dysfunction in human T2D. The constraint stems from the limited ability to assess human T2D islets during disease progression. To address this question, I propose a combinatorial approach of single cell RNA sequencing (scRNA-Seq) using islets from human T2D donors, and computational regulatory network analysis to determine heterogeneity and hierarchy of human islet cells in T2D. In preliminary studies, I demonstrate the presence of unique β cell subpopulations in T2D patients that do not exist in non-diabetic (ND) islets. These T2D-unique subpopulations are reminiscent of β cell dedifferentiation found in rodents.

Thus I propose two aims designed to determine the cellular identities of T2D-unique β cell populations and underlying molecular mechanisms of β cell fate change in T2D. In Aim 1, I will characterize T2Dunique β cell populations by experimental approaches such as RNA-FISH and examine functional differences between these cell populations by GSIS and/or intracellular Ca_{2+} microfluorimetry. In Aim 2, I will determine the molecular mechanisms that lead to the generation of these unique populations from ND β cells by using genetic manipulations of candidate TFs. I will inhibit TFs whose activity is significantly decreased in T2D-unique β populations; and I will perform gain-of-function studies with TFs whose networks are predicted to be increased in T2D-unique β subpopulations.

This work will expand our knowledge of the evolution of β cell failure in T2D using a system-based analysis of human islet cells. Ultimately, I aim to apply information gathered from this work to T2D drug discovery, by targeting key factors that regulate cell fate transition in human T2D.