Morphology of Pancreatic Islet Cytoarchitecture with Type 2 Diabetes

Deborah A. Striegel[1], Manami Hara[2], Vipul Periwal[3]

***Short Abstract* — Blood glucose levels are maintained by hormones secreted by endocrine cells in pancreatic islets of Langerhans. Cell-cell contacts between these cells regulate the oscillatory production of insulin and glucagon. Thus appropriate cellular arrangement is necessary for normal function. Graph theory provides a framework for quantifying cytoarchitectural features. Here, using large-scale imaging data for ~15,000 islets containing 100,000+ cells in human organ donor pancreata, we show that quantitative graph characteristics differ between control and type 2 diabetic islets. We then modeled islet rearrangement to determine processes that leave observed islet graph measures invariant, and compared these processes between normal and T2D islets.**

***Keywords* — diabetes, pancreatic islets, cytoarchitecture, graphs, β cells**

I. Purpose

PANCREATIC islet cells play a major role in blood glucose homeostasis by secreting a number of hormones: glucagon by α cells, insulin by β cells, and somatostatin by δ cells. For normal insulin secretion, these endocrine cells need functional patterns of cell-cell contacts [1]. Defining the correct anatomical arrangement is difficult since normal cellular architecture varies among species and, in humans, varies by size of the islet [2]. Recent studies showed that α-cell locations observed in human islets are not random, but instead create a characteristic structure [2]. β-cell mass is dynamic due to cell reorganization, death, and replication, in individual islets. Type 2 diabetes (T2D) is characterized by lack of glucose homeostasis and β-cell mass loss [3]. The T2D morphological and physiological changes should have a marked effect on this characteristic structure. Here, we capture the cellular arrangement of each islet by utilizing a graph, use measures from graph theory to quantify islet architecture and changes observed with T2D, and study the effects of β cell reorganization on these graphs.

II. Methods

Data from high resolution large-scale automated imaging of islets in human organ donor pancreas sections [2] was used to first compute graphs consisting of α, β, and/or δ cells as nodes and cell-cell contacts as edges for each individual islet. This allowed for a comprehensive capture of their characteristic structure. The graphs were quantified using measures, such as mean degree (the mean number of edges per node) and components. We examined architectural changes under different rearrangement processes. We numerically modeled stochastic processes simulating cellular reorganization to find degree- and component-specific parameter combinations that leave the quantitative graph-theoretical measures of islet cytoarchitecture invariant. We then compared the parameter combinations that leave normal islet architecture invariant to those associated with T2D islets.

III. Results

We found that T2D islets have a higher mean degree than control islets. Furthermore, large control islets have more components but fewer cells per component than large T2D islets. To maintain an equilibrium population, we found that cells with a large degree and respective component size are removed independent of the placement of newly added cells. Furthermore, if cells are added preferentially to large degree cells then the degree and component-size for removing a cell is increased to maintain equilibrium.

IV. Conclusions

Cell-cell interaction graphs give a new quantitative perspective on islet endocrine cell interactions in the pathophysiology of T2D, and may allow for a better understanding of the changes in islet architecture that accompany diabetes. We speculate that the higher mean degree of T2D islets is due to the increase in demand for insulin secretion in T2D that can only be met by β cells that have a higher mean degree compared to control. This may result in the death of less connected β cells and the elimination of components that have lower than average degree. Large degree cell loss may maintain optimal contact with capillaries for oxygen uptake and glucose sensing.

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[1]Laboratory of Biological Modeling, National Institute of Diabetes Digestive and Kidney Disorders, NIH. E-mail: deborah.striegel@nih.gov

[2]Kovler Diabetes Center, The University of Chicago. Email: mhara@uchicago.edu

[3]Laboratory of Biological Modeling, National Institute of Diabetes Digestive and Kidney Disorders, NIH. E-mail: vipulp@mail.nih.gov

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