The graph theory of pathology in diabetic islets

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***Short Abstract* — Blood glucose homeostasis is 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 a correct cellular arrangement is necessary for normal function. However, rigorously defining the correct islet cytoarchitecture is difficult since it varies between species and, in humans, with respect to islet size. Here, we utilized graphs to capture the architecture of individual human pancreatic islets over a large dataset (~15,000 islets) in an unbiased fashion. We quantified morphological changes observed with Type 2 diabetes (T2D) using measures from graph theory. We modeled graph mutation processes due to endocrine cell death and replication to find rates that leave observed islet cytoarchitectural parameters invariant, and compared these rates 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. Type 2 diabetes (T2D) is characterized by lack of glucose homeostasis and β-cell mass loss [1]. For normal insulin secretion, these endocrine cells need functional patterns of cell-cell contacts [2]. Defining the correct anatomical arrangement is difficult since normal cellular architecture varies among species and, in humans, varies by size of the islet [3]. For example, small human islets display an inner core of β cells surrounded by α cells, whereas α cells intermingle with β cells in large human islets. Recent studies showed that α-cell locations observed in human islets are not random, but instead create a characteristic structure [4]. This structure is dynamic since cellular replication and death affect the cytoarchitecture. Moreover with T2D, morphological changes (e.g. decrease in β-cell mass, cellular hypertrophy, and amyloid plaque formations [4]) and physiological changes (e.g. an early-on increase in β-cell replication followed by an increase in β-cell death) 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 replication and death on these graphs.

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II. Methods

Data from high resolution large-scale automated imaging of islets in human cadaveric pancreas sections [3] 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 an unbiased, comprehensive capture of their characteristic structure. The graphs were quantified using measures, such as average degree (the average number of edges per node) and components. We examined architectural changes under different cellular replication and death scenarios. We numerically modeled stochastic processes simulating cellular replication and death to find combinations of rates that leave the quantitative graph-theoretical measures of islet cytoarchitecture invariant. We compared the rates that leave normal islet architecture invariant to those associated with T2D islets.

III. Results

We found that T2D islets have a higher average degree than control islets. Furthermore, large control islets have more components but fewer cells per component than large T2D islets. Preliminary results indicate that cell death is sensitive to a cell's degree in maintaining cytoarchitectural homeostasis.

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. The higher average degree of T2D islets is surprising. We speculate that the increase in demand for insulin secretion in T2D can only be met by β cells that have a higher average degree compared to control. This may result in the death of less connected β cells and the elimination of components that have lower average degree, leaving only islets with higher average degree.

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