

Investigating the Underlying Mechanisms of Type 1 Diabetes: How Changes in the Extracellular Matrix Affect Pancreatic Islet Function

BY AMIT SELA

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Diabetes is a serious medical condition that causes higher than normal blood sugar levels leading to various symptoms and complications, such as heart disease, chronic kidney disease, and nerve damage. Type 1 diabetes, or insulin-dependent diabetes, is the most severe form of the disease and affects approximately 1.6 million people in the United States today [1]. Over the past decade, knowledge of the pathogenesis and pathophysiology of type 1 diabetes has grown substantially, and technological devices, such as glucose monitors and insulin pumps, have improved to allow patients to better manage the difficulties of living with type 1 diabetes. However, despite these improvements, managing diabetes

remains a challenging, daily task that requires constant vigilance and focus. Thus, the ultimate goal is to discover a biological cure for type 1 diabetes, to relieve people of these burdens and help them return to their normal lives.

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To take steps towards achieving this goal, we must first understand the biological systems that control and affect this disease, and how

they interact with one another. Pancreatic islets, formally known as the islets of Langerhans, are groups of extensively studied endocrine cells in the pancreas that regulate blood glucose via hormone production and secretion. The islets of Langerhans contain four cell types: α -cell, β -cells, δ -cells, and polypeptide-producing cells, which all work together to maintain blood glucose homeostasis [2]. β -cells are the insulin-producing cells within the islets of Langerhans, and in type 1 diabetes, immune cells attack and destroy these insulin-secreting pancreatic β -cells, which leads to insulin deficiency [3]. While the autoimmune contributions to type 1 diabetes have been well characterized, there are still many factors contributing to disease onset

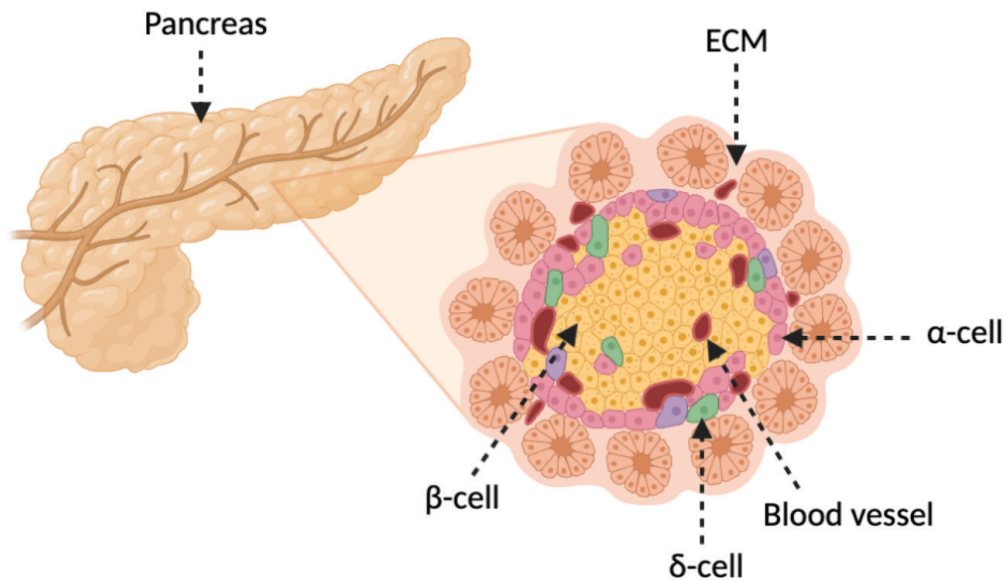


Figure 1 Schematic of the human pancreas and a pancreatic islet. The pancreatic islet consists of various cell types and blood vessels and is surrounded by the ECM (BioRender).

and progression that we need to understand to develop improved therapies.

“Researching factors that influence β -cell function in type 1 diabetes would give us a greater understanding of what to target.”

By researching factors that influence β -cell function in type 1 diabetes, it would give us a greater understanding of what to target and the next steps to take toward finding a cure. The extracellular matrix (ECM) is a specialized protein scaffold that surrounds the islets, and is an important component of the pancreatic microenvironment. The ECM is divided into basement membranes (BM); tight networks of specialized glycoproteins, and interstitial matrix (IM); a thin, looser layer that confers elasticity to tissues due to the presence of fibrillar collagens [4]. As a whole, the ECM regulates β -cell survival and growth, as well as insulin secretion.

The peri-islet ECM may provide a critical barrier to islet infiltration; however, the contributions to loss of the peri-islet ECM are not well studied, limiting potential therapies targeted at this critical step in type 1 diabetes.

Extracellular matrix stiffness can influence mitochondrial function [5], which regulates β -cell activity [6].

Mitochondria are highly dynamic organelles that play crucial roles in fundamental cellular processes such as metabolism and the cell cycle. In pancreatic β -cells, mitochondria integrate the metabolism of nutrients into an energy output, leading to insulin release [6]. As such, mitochondrial dysfunction plays a role in β -cell failure and the development of type 1 diabetes [6].

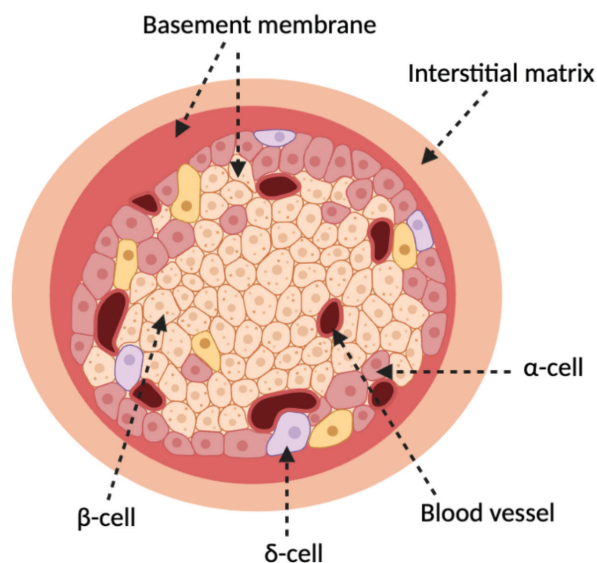


Figure 2 Schematic of pancreatic islet surrounded by the ECM. The BM surrounds blood vessels and encases the islet. The IM appears as a thin layer immediately adjacent to the BM (BioRender).

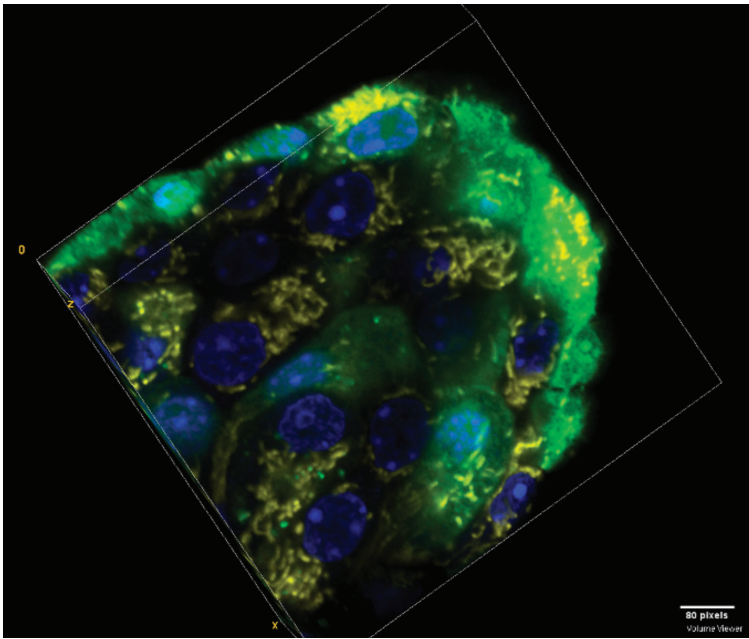


Figure 3 3D image constructed from fluorescence confocal microscopy image of a pancreatic mouse islet. Cell nuclei are blue, β -cells are green, and mitochondria are yellow.

Mitochondria constantly undergo morphological changes, and this morphology of the mitochondria network is largely determined by two opposing processes; fusion and fission. Fusion joins smaller mitochondria to form larger ones

and is characterized by elongated, connected structures [7]. Fission is where smaller mitochondria are separated from larger ones, and it leads to the production of spherical, isolated organelles [7]. By understanding how much

of these two processes occur, we can understand the level of mitochondrial function. My project focuses on investigating the mechanisms of pancreatic β -cell death in type 1 diabetes, with a focus on how changes in the stiffness of the extracellular matrix affect pancreatic islet function and mitochondrial morphology. For this project, isolated mouse islets are encapsulated in biomaterial scaffolds of varying stiffnesses, mimicking the ECM environment. Then, fluorescence confocal microscopy is utilized to visualize and investigate how the varying environmental stiffness influences mitochondrial morphology. A specific aspect of morphology that is calculated is the mitochondrial aspect ratio: the length of the major axis divided by the length of the minor axis. An aspect ratio of 1 is indicative of a circular morphology and mitochondrial fission, while lower values suggest a more elongated shape, correlating to fusion.

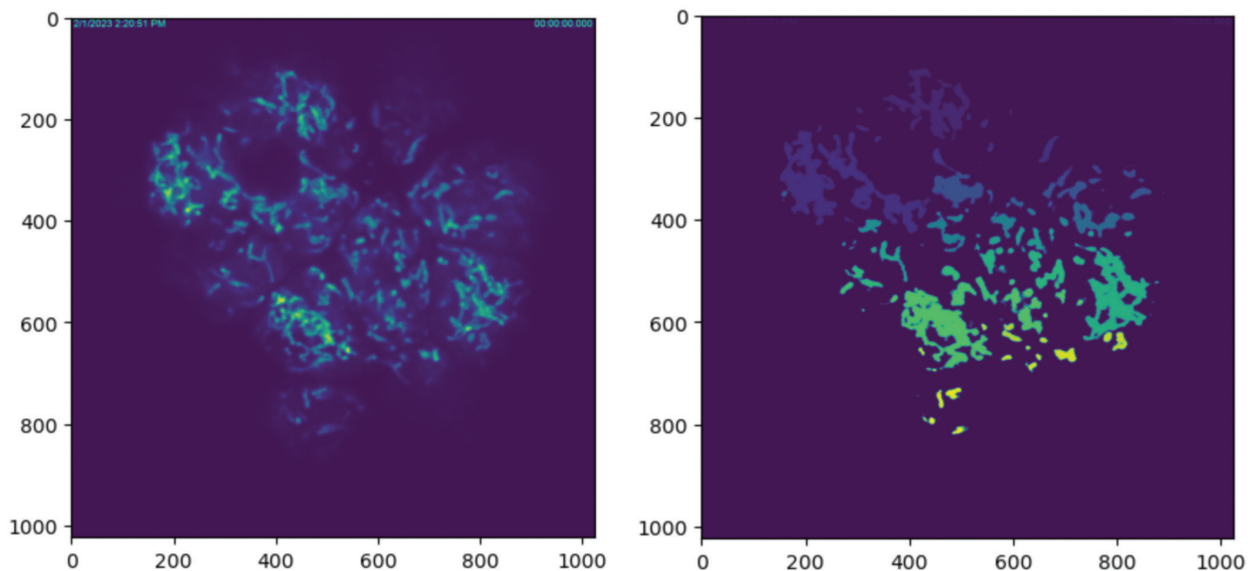


Figure 4 Comparison of an origin fluorescence microscopy image (left) and a thresholded and labeled image (right). Each different colored region represents a mitochondria. Region properties can be used on these regions to determine aspect ratio and fragmentation.

“Understanding changes in the mitochondrial function will help us understand early changes in β -cell function.”

To increase efficiency and accuracy of this process, a more quantitative and computational approach is used. I am creating python code utilizing the SciKit data analysis library; with this image analysis, we are able to isolate and identify the various mitochondria in the image, and then utilize region properties functions to calculate the aspect ratio and fragmentation of the mitochondria. Understanding changes in the mitochondrial function through quantifying the amount of fission and fusion after changes in ECM, as occurs in type 1 diabetes, will help us understand early changes in β -cell function and allow us to find future areas of research to target.

By taking a multidisciplinary approach of working with biomaterials, quantitative microscopy, and computational biology, we are able to work towards understanding the effects of changes in ECM stiffness on mitochondrial shape and size and the fusion versus fission events. The skills I've gained as a Quantitative Biosciences and Engineering student here at the Colorado School of Mines have been greatly

beneficial in allowing me to smoothly communicate between the wet lab and computational aspects of research. As an aspiring MD-PhD, this major is invaluable as it not only allows me to learn core skills and concepts of pure biology, chemistry, and engineering, but also teaches me new skills, such as coding, to push my scientific abilities to the limit, and to make me a better scientist.



Amit Sela is an upcoming junior studying Quantitative Biosciences and Engineering and has been involved in research since her first year at Colorado School of Mines. She currently works as an undergraduate researcher in Dr. Nikki Farnsworth's interdisciplinary research lab, which focuses on developing biomaterials, quantitative optical imaging, and cell biology. In the future, Amit plans to attend either a graduate or medical school to further pursue her interests in medical research.

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