A Review of Pancreatic Islet Cell Types and their Hormone Biomarkers

In 1869, Paul Langerhans first described cells found in the pancreas that would later be named in his honor, the Islets of Langerhans. Pancreatic islets function as a micro-organ with tightly coordinated signaling between the different cell types. This network allows the islets to respond to changes in blood glucose and to intra-islet signals in a rapid and sensitive manner. Each islet contains 1,000 to 3,000 cells, including alpha, beta, delta, epsilon, and pancreatic polypeptide (PP) cells. Every cell type releases a specific hormone in response to signals. Islets of Langerhans have been much studied in the context of diabetes because the hormones they produce and secrete are involved in the regulation of glucose homeostasis. Understanding the effects of the different hormones generated by each islet cell type and monitoring hormone levels are key elements in the fight against diabetes.[15]

Pancreatic Islet

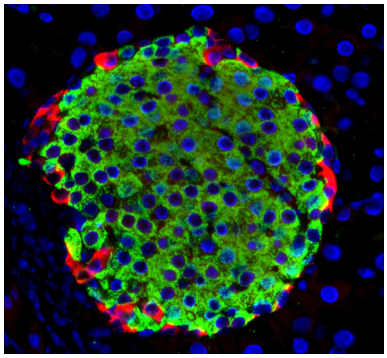


Figure 1: Immunofluorescent staining of a pancreatic islet cell network.

Alpha Cells and Glucagon

Alpha cells comprise 15 - 20% of islet cells in humans and produce the hormone glucagon. Glucagon is processed from a larger precursor molecule that can be processed in different ways, yielding different protein products. These final products are determined by the cell type and the cleavage enzymes found in those cells. In the alpha cell, glucagon is the final product, whereas in intestinal L cells, preproglucagon is processed into the incretins glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2). There have been some reports which suggest that GLP-1 may also be produced by alpha cells.[1,3,4,15]

Glucagon Secretion and its Actions

Glucagon is the counter hormone to insulin and is typically secreted in a fasted state. Under fasting conditions, the elevated glucagon plasma levels are sensed by the liver which then converts glycogen, the storage form of glucose, back into glucose. This glucose is released into circulation where it can be used as fuel by the body. Glucagon is also responsible for the uptake of amino acids by the liver and the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver where it is converted into glucose.[1,4]

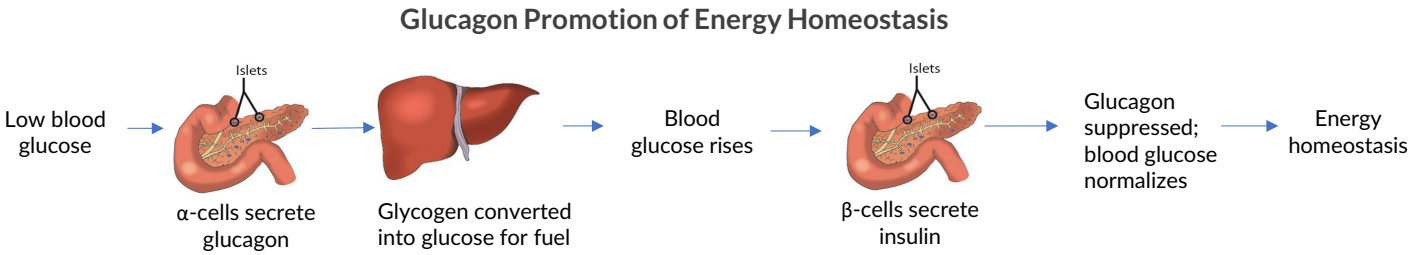


Figure 2: Glucagon promotes energy homeostasis by converting glycogen stored in the liver into glucose during fasting. When blood sugar levels rise, insulin from beta cells suppresses glucagon production from alpha cells.

Glucagon and Diabetes

Glucagon plays a role in the pathophysiology of diabetes. In both type 1 (T1D) and type 2 diabetes (T2D), alpha cells have demonstrated elevated glucagon secretion, an enhanced response to amino acids and ineffective suppression during states of high glucose.[1,4]

Glucagon Regulation

Glucagon regulation occurs through intrinsic alpha cell mechanisms and paracrine mechanisms. The hormone is expressed when glucose levels drop during hypoglycemia and it is suppressed during hyperglycemia. Its secretion is inhibited by insulin, as well as two other beta cell components, gamma aminobutyric acid (GABA) and serotonin. Two gut hormones, GLP-1 and gastric inhibitory polypeptide (GIP), have been proposed as negative regulators of glucagon secretion. In addition, studies suggest that GLP-1 is produced in alpha cells and suppresses glucagon secretion through an indirect mechanism involving somatostatin, produced in neighboring delta cells.[1,2,3,4,9]

Pancreatic Beta Cells and Alpha Cells

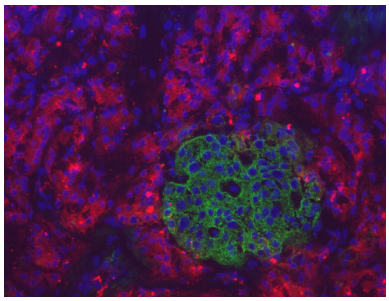


Figure 3:Immunofluorescent staining of a pancreatic islet showing beta and alpha cells.

Beta Cells, Insulin, and C-peptide

The beta cell accounts for 60 - 80% of islet cells in humans and is the most studied of all the islet cell types. The main hormone produced from beta cells is insulin. Insulin is derived from a precursor peptide, proinsulin. Proinsulin is cleaved to form two products, insulin and C-peptide. While insulin is known for its effects in glucose metabolism, C-peptide has no known metabolic effects. C-peptide has a 1:1 stoichiometry with insulin and due to having a longer half-life than insulin, it is often used in the diagnosis of diabetes. C-peptide can aid in endogenous insulin secretion, especially during exogenous insulin treatment. Its measurement also plays a role in distinguishing between T1D and T2D.[2,6,7,15]

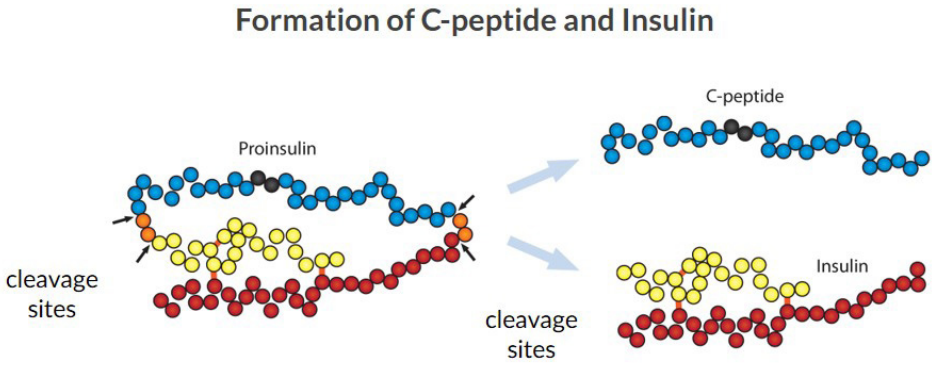


Figure 4: Beta cells secret proinsulin which is then cleaved into insulin and c-peptide.

Insulin, Glucose Regulation, and Diabetes

Insulin is the primary anabolic hormone regulating glucose storage. It is also responsible for increasing both lipid synthesis and storage in the liver. Insulin promotes protein synthesis in various tissues as well. The inability for insulin to act as a glucose regulator is the prime mechanism behind diabetes. In T1D, beta cells are diminished through an autoimmune reaction thereby causing a lack of insulin to regulate glucose. In T2D, insulin is produced by beta cells, but the body is somehow resistant to the secreted insulin and production can decrease in later stages.[5,8]

Insulin Secretion and Regulation

Insulin is made and secreted by beta cells in response to glucose. Its secretion is enhanced by the presence of incretins, such as GLP-1 and GIP. Glucagon is also believed to increase insulin secretion, although it is not known whether the influence is direct or indirect. Somatostatin performs the opposite function, which is to inhibit insulin secretion. Other inhibitors include epinephrine, galanin, ghrelin, and leptin. Urocortin 3 is also secreted by beta cells. Urocortin 3 acts in a paracrine fashion upon neighboring delta cells, leading to the secretion of somatostatin, and thereby creating a feedback loop to decrease insulin production. Decreased production of urocortin 3 is an early sign of pre-diabetes.[1,5,6,9,11]

Delta Cells and Somatostatin

Delta cells account for less than 10% of human islet cells. They secrete somatostatin, a negative regulator of insulin, glucagon, and pancreatic polypeptide under conditions of nutrient stimulation. Delta cells cleave a larger precursor to form the 14 amino acid peptide sequence version of somatostatin. The gastrointestinal (GI) tract also produces somatostatin as a 28 amino acid peptide which appears to be the main circulating form of the hormone. However, kinetic analysis suggests that it is somatostatin from the delta cells, not the circulating form, that acts within the islets.[2,4,10,15]

Mouse Pancreatic Islets Immunofluorescent Staining[15]

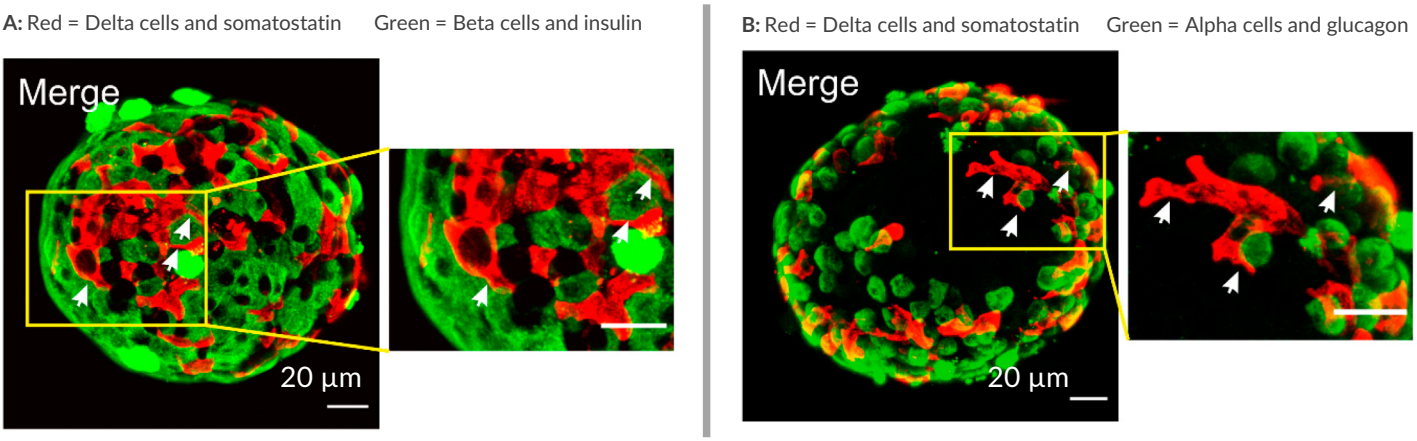


Figure 5: Immunofluorescent staining of mouse islets and hormones shows some differences in morphology between beta, alpha, and delta cells. The staining in image A shows somatostatin from delta cells in red merged with insulin from beta cells in green. While image B shows somatostatin from delta cells in red merged with glucagon from alpha cells in green. Both merges show unique elongated projections protruding from the delta cells which are noted with the white arrows. Images from figure 1 of Gao, et al 2021. Refer to reference 15 for full image.[15]

Delta Cell Somatostatin Secretion and Regulation

Delta cell somatostatin is secreted in response to glucose stimulation. This process requires the peptide urocortin 3, which is produced in beta cells and co-secreted alongside insulin. Urocortin 3's presence stimulates somatostatin release, which then inhibits insulin secretion in a feedback loop. Beta cells produce the neurotransmitter GABA, which also stimulates somatostatin release.[4,9,10,12]

Receptors on Delta Cells

Delta cells are known to express insulin receptors, though the effect of insulin remains unclear. They also express receptors for GLP-1 and GIP, both of which stimulate somatostatin secretion. Ghrelin receptors can also be found in delta cells, where they inhibit insulin release through the somatostatin mechanism.[9,10]

Epsilon Cells and Ghrelin

Epsilon cells represent fewer than 1% of islet cells in humans. They secrete ghrelin, which was first identified as a ligand leading to the secretion of various growth hormones. It also plays a role in modulating appetite. Ghrelin is produced by numerous tissues throughout the body including the GI system and its levels are increased during fasting. The hormone can regulate blood glucose by suppressing insulin release from beta cells. Ghrelin has been found to increase glucagon secretion. Ghrelin secretion has also been shown to be inhibited by glucagon.[11,13,14]

Immunofluorescent Staining of Mouse Pancreatic Islets and Ghrelin[16]

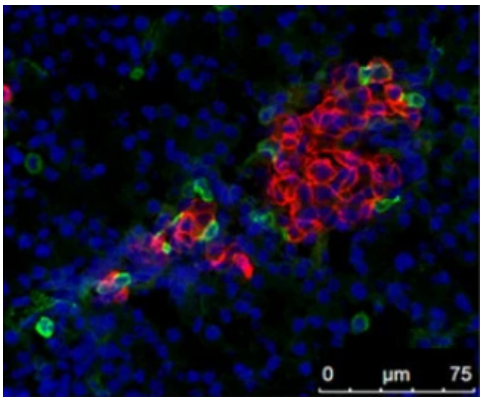


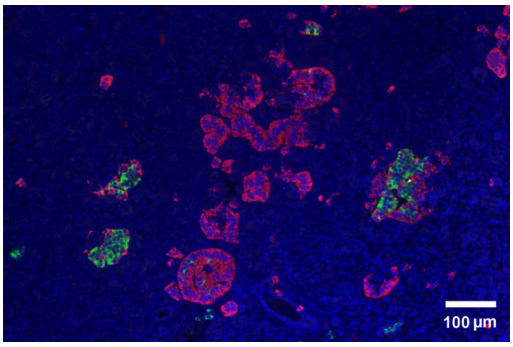
Figure 6: Immunofluorescent staining of wild type mouse pancreatic islets. Cells positive for Ghrelin are stained green while insulin positive cells are in red. Image from figure 2A of Kordowich, et al (2011). Refer to reference 16 for full image.[16]

Pancreatic Polypeptide (PP) Cells

PP cells make up about 1-2% of the islet population. Secretion of pancreatic polypeptide is regulated by vagal and enteric nervous input. It is not responsive to glucose. Pancreatic polypeptide has been shown to be an inhibitor of glucagon during low glucose.[2,4]

Figure 7: PP-cell rich area in human pancreatic islet. Immunofluorescent staining shows PP in red, insulin in green, glucagon in white and nuclei in blue. From figure 3B-a. Wang, et al (2013). Refer to reference 17 for full image.[17]

Human Pancreatic Polypeptide Cells in Islet[17]

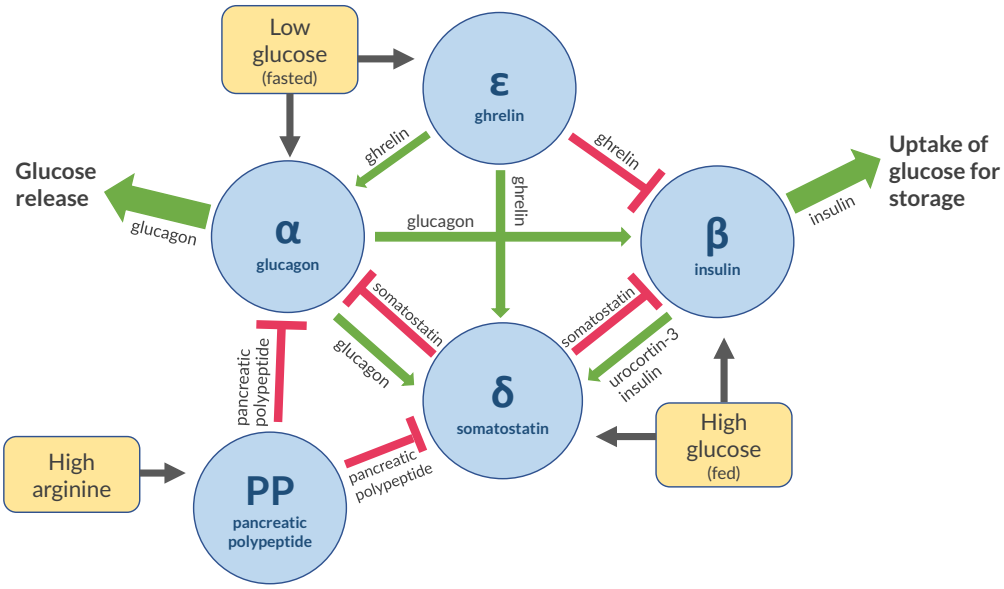


Pancreatic Islets and Diabetes

Pancreatic islets are a complex network of cell types that work to maintain energy homeostasis. The requirement for proper regulation of the numerous islet hormones is vital to prevent diseases such as diabetes. Despite the advances in islet biology research, there is still much more to be discovered. Understanding the production, function, interactions, and loss of the various islet hormones is vital in the fight against diabetes.

Figure 8: The five types of pancreatic islet cells secrete different hormones during fasted and fed states in order to maintain energy homeostasis. Proper regulation of these islet hormones is needed to prevent metabolic diseases such as diabetes.

How Pancreatic Islet Cells Interact to Maintain Energy Homeostasis



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