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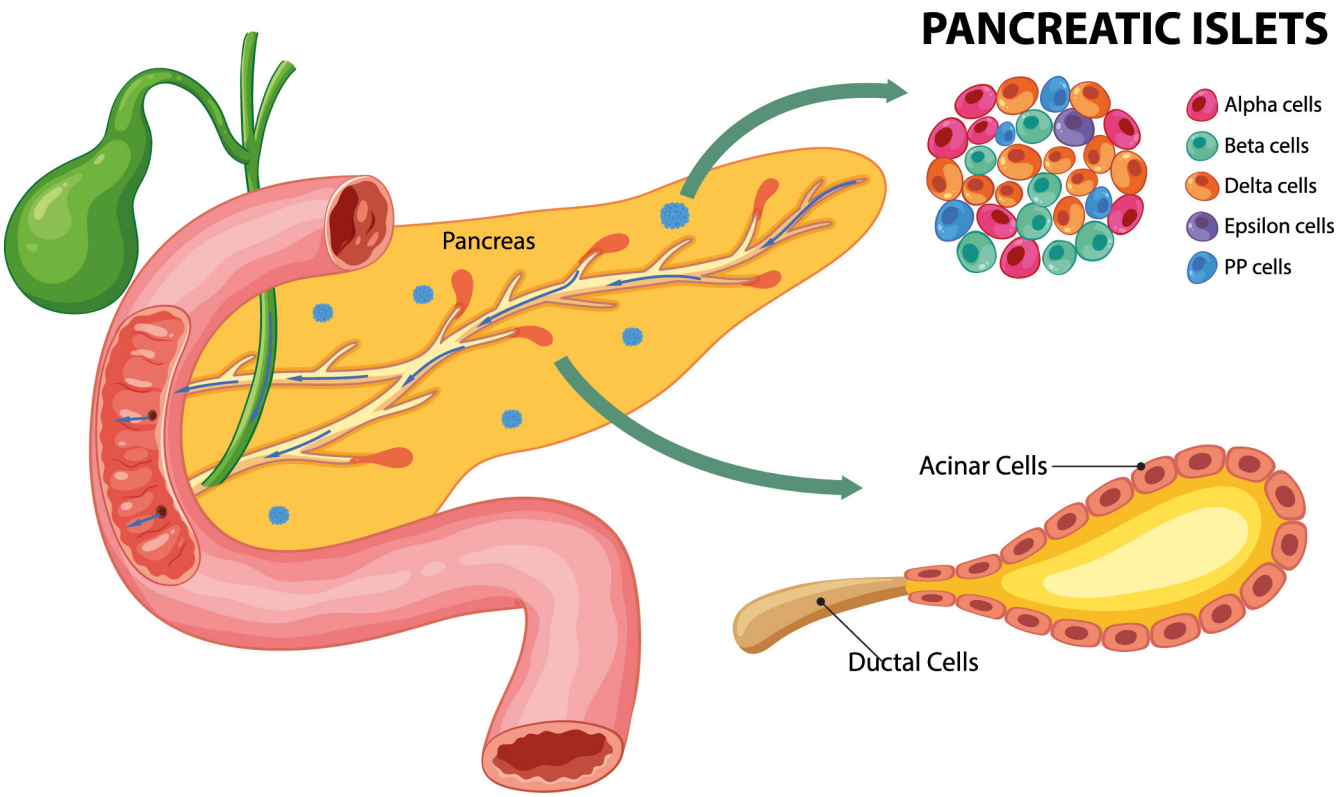

The Role of Pancreatic Alpha Cells in the Pathophysiology of Diabetes

Glucagon is one of the main hormones regulating glucose homeostasis due to its hyperglycemic effect and its opposition to several insulin actions. In experimental animal models such as mice, the islet of Langerhans predominantly consists of pancreatic beta cells, with other cell types making up approximately 20% of the total population. However, the human islet is characterized by a higher proportion of pancreatic alpha cells, comprising 30% up to 45% of the total population. This greater proportion suggests that alpha cells and glucagon secretion play a significant role in the function of the human endocrine pancreas. Nevertheless, although glucagon was discovered more than a century ago, the role of this cell type in diabetes remained unclear for decades.

Indeed, if a search is conducted in a database such as PubMed on published studies about **alpha cells** and their involvement in this condition, these represent a minority compared to those on pancreatic beta cells. Despite the central role that insulin plays in the etiology of diabetes, several factors have hindered a deeper understanding of glucagon-secreting cells. Among these are the lower proportion of alpha cells in commonly used experimental animal models, difficulties in isolating and purifying this cell type, and technical limitations in identifying their functional patterns, which have all been key barriers to alpha cell research.

In the past two decades, however, advances in biocomputation, molecular, genetic, and omics techniques, as well as access to human pancreatic and islet samples, have enabled unprecedented progress in understanding alpha cells under both physiological conditions and in pathologies such as diabetes and obesity. The perception of the alpha cell's role in diabetes has evolved in light of new findings. Moving away from a more "insulin-centric" view of diabetes, Unger and Orci proposed the bihormonal hypothesis of diabetes in the 1970s, supported by their excellent work in the field, and later suggested a **"glucagon-centric"** perspective. It is now widely accepted that alpha cell and glucagon dysfunction contribute to the pathophysiology of diabetes. Recent advancements are reshaping the role of these cells, establishing new perspectives, and driving new lines of research and therapeutic development. In this context, besides glucagon release, alpha cells can secrete incretins such as GLP-1, promoting insulin secretion from neighboring beta cells. On the other hand, the specific capabilities of alpha cells in proliferation, survival, and plasticity are being explored as a strategy to regenerate beta cell mass. These advances are also leading to the design of new drugs or the reevaluation of existing ones aimed at mitigating the effects of alpha cell dysfunction and/or glucagon action in diabetes.

Function of Pancreatic Alpha Cells: like pancreatic beta cells, glucagon-secreting alpha cells act as sensors of plasma glucose. Changes in extracellular glucose levels are efficiently detected by these cells and translated into precisely controlled hormonal secretion. This process involves glucose entry via specific membrane transporters, its metabolism, and the generation of metabolic signals that regulate electrical activity and intracellular calcium signaling, a secondary messenger that stimulates the transport and fusion of secretory granules with the membrane to release insulin from beta cells or glucagon from alpha cells.

However, specific differences exist between the 2 cell types at various levels, such as glucose transport and metabolism, ion channel expression, and other biochemical and physiological characteristics. These differences allow insulin and glucagon release to occur at distinct glucose concentrations. For instance, hyperglycemia stimulates insulin release, while glucagon secretion is favored at low glucose concentrations, establishing one of the primary defenses against hypoglycemia. Alpha cells, however, also respond to other nutrients, such as amino acids and fatty acids, generally increasing glucagon secretion, which makes the regulation of these cells after dietary intake complex. Additionally, other levels of modulation influence alpha cell activity, such as paracrine communication with beta and delta cells, signals from incretins and adipokines, and control from the nervous system. This intricate regulation of alpha cells can be disrupted in pathological conditions or contribute to certain diabetes symptoms, as discussed below.

Actions of Glucagon: the most well-known and studied action of this hormone is the hepatic stimulation of gluconeogenesis and glycogenolysis, thereby increasing hepatic glucose production and its release into the bloodstream. This effect is primarily mediated by glucagon's action on the expression and/or activity of various enzymes involved in hepatic glucose metabolism. Glucagon also regulates lipid metabolism in the liver, and recent studies have demonstrated the existence of a liver-alpha cell communication axis that participates in amino acid metabolism and their plasma levels.

Glucagon actions extend beyond nutrient regulation; it has been shown to modulate various pharmacologically relevant metabolic processes, such as stimulating insulin secretion, controlling food intake, and thermogenesis. Numerous preclinical and clinical studies have provided evidence that glucagon's actions are altered in pathological con- »

CURRENTLY, IT IS WIDELY ACCEPTED THAT ALPHA CELL AND GLUCAGON DYSFUNCTION CONTRIBUTE TO THE PATHOPHYSIOLOGY OF DIABETES

RESEARCH IS ONGOING INTO THE THERAPEUTIC POTENTIAL OF DUAL AND TRIPLE AGONISTS TARGETING THE RECEPTORS OF GLUCAGON, GLP-1, AND/OR GIP

» ditions such as diabetes, obesity, and hepatic steatosis.

Glucagon and Diabetes: several studies indicate that patients with diabetes exhibit **hyperglucagonemia**, either absolute or relative to insulin, thus promoting increased hepatic glucose release and contributing to hyperglycemia. Functional alterations are also observed; notably, alpha cells fail to respond adequately to a decrease in blood glucose, increasing the risk of hypoglycemia, especially in patients with type 1 diabetes and in advanced stages of type 2 diabetes mellitus. Similarly, the suppression of glucagon secretion at high glucose concentrations is inadequate, contributing to postprandial hyperglycemia. Although many of these alterations have been known for decades, recent years have clarified numerous processes and signaling pathways involved in these dysfunctions.

Processes and Mechanisms of Alpha Cell Dysfunction in Diabetes: significant differences exist in the dynamics of alpha and beta pancreatic cell mass and function throughout the natural history of diabetes, in both type 1 and type 2. While beta cell mass decreases significantly during autoimmune diabetes and declines in the late stages of type 2 diabetes, alpha cell mass in both types of diabetes remains relatively well-preserved compared to beta cells—or at least for a longer period—leading to an increased alpha/beta ratio. These alterations may partly contribute to higher plasma glucagon levels. The higher prevalence of alpha vs beta cells in diabetes may be associated with their greater capacity for survival against pro-apoptotic stimuli characteristic of the diabetogenic environment, based on the expression of certain genes and the activation of specific signaling pathways in this cell type. Similarly, it has been shown that some alpha cells possess a higher proliferative capacity, potentially contributing to the maintenance of this cell population.

Functional alterations of the alpha cell in diabetes have been attributed to various factors, ranging from impaired communication with the nervous system and paracrine signals from the beta cell to intrinsic defects of the alpha cells related to loss of glucose sensitivity and its metabolism. Omics techniques and massive data analysis of purified alpha cells from animal models and diabetic patients are enabling deeper insights into the molecular basis of alpha cell dysfunction. In this regard, the genetic and epigenetic regulation specific to alpha cells plays an important role not only in the determination of this cell type during development from pancreatic progenitors but also in enabling, among other attributes, the high plasticity of adult alpha cells in terms of cell identity. In fact, it has been proposed that type 2 diabetes mellitus involves a process of beta cell dedifferentiation, which could also involve cell identity changes toward glucagon-producing cells. In this regard, the existence of cells expressing both insulin and glucagon in the pancreas of type 1 and 2 diabetic patients has been observed. It has been postulated that the presence of these **bihormonal cells** may indicate cell identity changes in diabetogenic conditions. On the other hand, recent studies combining transcriptomic and functional analyses have supported the notion that alpha cell dysfunction in diabetes could be due to a loss of phenotypic maturity, as important changes have been found in genes associated with transcription factors and signaling pathways that regulate both the identity of the alpha cell and glucagon secretion. It has also been proposed that the alteration of the liver-alpha cell communication axis that regulates metabolism and plasma amino acid levels could contribute to some of the clinical manifestations of diabetes. Recent preclinical studies have demonstrated that this axis may be of interest for pharmacological development.

Therapeutic Strategies Based on Pancreatic Alpha Cells and Glucagon Action: numerous studies support the idea that decreasing glucagon secretion or action are beneficial strategies in the context of hyperglucagonemia and diabetes therapy. Different drugs, such as **GLP-1 mimetics** or **sulfonylureas**, can inhibit glucagon secretion. On the other hand, **glucagon receptor antagonism** has proven effective in preclinical diabetes models to block the excessive hepatic signaling of the hormone and, in this way, decrease hyperglycemia. Some of these antagonists are in clinical phases, although due to some undesirable effects, further research is still needed to refine these drugs before clinical approval.

Based on the positive metabolic effects resulting from supra-physiological glucagon »

THE EXISTENCE OF BIHORMONAL CELLS EXPRESSING BOTH INSULIN AND GLUCAGON HAS BEEN OBSERVED IN THE PANCREAS OF PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS

» receptor activation inducing thermogenesis and energy expenditure, as well as inhibition of intake, the therapeutic role of **dual and triple agonists** with activity at glucagon, GLP-1, and/or GIP receptors has also been explored. Based on this combination, the hyperglycemic effects resulting from glucagon receptor activation would be mitigated by the effects generated by the receptors of both incretins. The results obtained in both preclinical models and clinical settings are promising for the treatment of obesity, type 2 diabetes mellitus, and liver disease.

The alpha cell could also serve as a reservoir for beta cell regeneration in diabetic patients. As mentioned earlier, the alpha cell possesses high plasticity, so under certain experimental conditions or through treatment with pharmacological agents that increase GLP-1 activity, alpha cells can undergo **transdifferentiation into beta cells**. There is great interest in understanding the mechanisms associated with this reprogramming to establish efficient protocols that could induce these processes. D

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CONCLUSIONS

The dysfunction of the alpha cell in diabetes and its contribution to the disease is widely accepted. These alterations may contribute to part of the symptoms in these patients, particularly hyperglycemia. In fact, there is great pharmacological interest in modulating glucagon secretion and/or action as a therapeutic tool. Recent findings, mainly with the help of advances in molecular techniques, are enabling a detailed definition of the processes and mechanisms that determine the involvement of the alpha cell in the pathophysiology of diabetes. All of this will allow for the improvement of therapeutic strategies, both in their pharmacological dimension and in optimizing protocols focused on the regeneration of pancreatic beta cells.

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