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HISTOLOGY OF THE ENDOCRINE PANCREAS: MODERN APPROACHES TO THE ISLETS OF LANGERHANS AND THEIR HORMONE-PRODUCING CELLS

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Abstract: This article presents modern perspectives on the histology of the endocrine portion of the pancreas and the hormone-producing cell types of the Langerhans islets. The pancreas consists of exocrine and endocrine components, which are closely interconnected (crosstalk) and form a complex functional system. During embryonic development, both components originate from a common source, and in some cases, cells retain the ability to transdifferentiate into one another. The endocrine portion is organized into Langerhans islets composed of α, β, D, D1, and PP cells, each synthesizing specific hormones and regulating one another through paracrine signaling.

The article highlights diseases associated with dysfunction of endocrine cells, particularly type 1 and type 2 diabetes, somatostatinoma, and vasoactive intestinal peptide–producing tumors. Globally, diabetes affects 11.1% of the population. It is also noted that long-standing type 2 diabetes may impair β-cell function and potentially contribute to the development of pancreatic cancer (pancreatic adenocarcinoma).

Recent studies have demonstrated that extracellular matrix (ECM) proteins — nidogen-1 (NID1) and decorin (DCN) — reduce β-cell death under hypoxic conditions and help preserve their hormone-producing capacity during transplantation of donor Langerhans islets. In addition, CRISPR-Cas9, RNA-seq, and in vitro 3D models are being used to investigate intercellular interactions and regenerative potential. These approaches offer promising new strategies in endocrine histology, diabetes research, and cellular transplantation.

Keywords: pancreas, endocrine, exocrine, insulin, glucagon, crosstalk, Islets of Langerhans.

Introduction

The endocrine portion of the pancreas is organized into the Langerhans islets, which consist of α, β, D, D1, and PP cells. These cells produce hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide, which regulate glucose homeostasis, energy balance, and digestive processes.

Through paracrine intercellular signaling, these cells coordinate their functions; dysfunction of this regulatory system can lead to the development of disorders such as diabetes and pancreatic adenocarcinoma. Therefore, investigating the structure and function of Langerhans islet cells holds significant importance in endocrine histology and diabetology.

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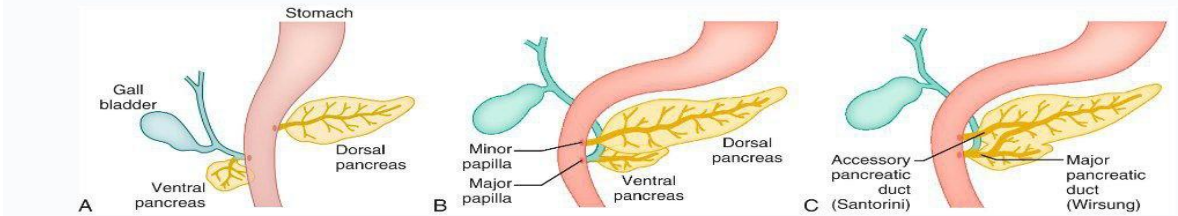
Main body

The pancreas is composed of two major histological components: the exocrine and endocrine parts. These two systems are closely interconnected and operate as a complex functional unit through coordinated crosstalk. During embryonic development, both parts originate from a common source—the endoderm of the duodenum—appearing as the ventral and dorsal buds (the tip-trunk domain [1]) at the end of the 4th week. This developmental process is initiated by the Pdx1 gene and regulated by additional genes such as Ptf1a and Ngn3. In adults, impairment of Pdx1 gene function leads to the development of diabetes mellitus.

Interestingly, although they arise from the same embryonic origin, the cells of the exocrine and endocrine regions retain a certain degree of plasticity; for example, insulin-producing cells of the exocrine pancreas can transdifferentiate into endocrine cells.



The fundamental cellular unit of the exocrine pancreas is the acinar cell, which secretes digestive enzymes.
The endocrine portion consists of clusters of cells known as the Islets of Langerhans, whose principal structural and functional unit is the insulin-producing insulocyte. These islets produce several hormones, including the well-known insulin.

The heterogeneity of islet cells was first demonstrated by Lane in 1907, who identified and classified α and β cells, although their precise functions were not yet known. The role of α cells became clearer in 1923 when Kim and Murlin discovered glucagon. In 1931, a third type of cell, the D (gamma) cell, was identified, and its hormone somatostatin was later described in the 1970s–1980s. In 1968, PP cells—producers of pancreatic polypeptide—were recognized during the isolation of insulin from the chicken pancreas [3].

The Islets of Langerhans are composed of five major cell types: **α, β, D, D1**, and **PP** cells.

β cells (basophilic), located centrally in the islet (70–75% of total), synthesize insulin. Their secretory granules are alcohol-soluble and approximately 275 nm in diameter. Dysfunction of these cells leads to type 1 and type 2 diabetes mellitus. In prolonged type 2 diabetes, β-cell impairment may progress and contribute to the development of pancreatic adenocarcinoma [4].

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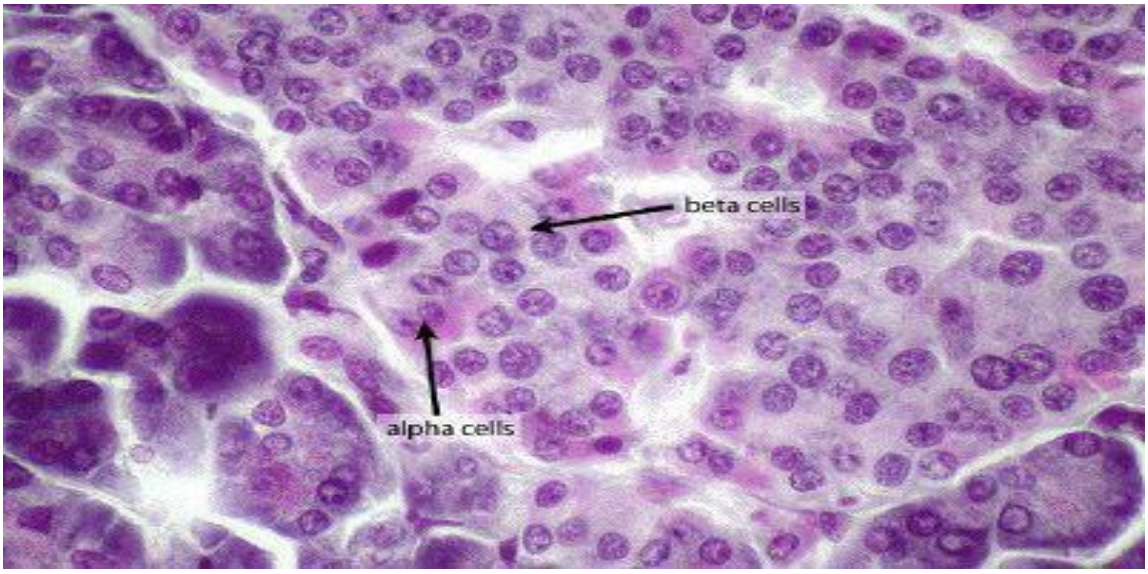
α cells, located peripherally, secrete glucagon, which acts as the physiological antagonist of insulin. These cells measure 15–25 μm in diameter, and their granules are water-soluble but alcohol-insoluble.



D cells produce somatostatin, which inhibits the activity of both α and β cells, thereby maintaining hormonal balance and preventing excessive islet activity.

D1 cells, which are relatively rare, secrete vasoactive intestinal peptide (VIP). VIP enhances the activity of α and β cells and counteracts the actions of D cells.

PP cells secrete pancreatic polypeptide and are more abundant in the caudal region of the pancreas. Their hormone regulates gallbladder contraction and exocrine pancreatic secretion, and indirectly influences appetite and energy expenditure by acting on central hunger–satiety pathways. Altered PP levels are observed in obesity, anorexia, and pancreatic tumors.
Recent studies highlight the continuous paracrine communication among islet cells. For example, α cells stimulate β-cell activity via glucagon; D cells suppress α and β cells via somatostatin; PP cells modulate these interactions at a broader systemic level. Gene regulators such as Pdx1, NKX6, and NEUROD1 tightly control the differentiation and function of these cell types.
Immunohistochemical markers used to identify each islet cell population include:
β cells — insulin, Pdx1;
α cells — glucagon, ARX;
D cells — somatostatin, SST;
PP cells — pancreatic polypeptide, PPY.
The complex interactions within the islets hold significant clinical importance. Disorders such as postprandial hyperglycemia, somatostatinoma, VIPoma, and both type 1 and type 2 diabetes arise from disruptions in this regulatory network. Diabetes mellitus, affecting 11.1% of the world's population [5], is the most prevalent pathology.

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Type 2 diabetes additionally has a strong hereditary predisposition.
In efforts to treat diabetes, numerous studies focus on islet transplantation. However, challenges remain—most notably early post-transplant hypoxia, which compromises β-cell function and induces apoptosis.

Extracellular matrix (ECM) proteins—specifically nidogen-1 (NID1) and decorin (DCN)—have been shown to reduce β-cell loss and preserve hormone secretion in hypoxic environments. Recent studies demonstrate that donor islets treated with NID1 and DCN maintain insulin-producing capacity by:

- enhancing glycolytic gene activity and cellular energy production
- reducing DNA fragmentation and hypoxia-induced apoptosis
- improving β-cell recovery and overall transplantation outcomes

Thus, ECM proteins represent a promising strategy for protecting transplanted islets and sustaining long-term function in endocrine histology and diabetes therapy [6].

Modern methodologies such as CRISPR-Cas9 gene editing, RNA-seq profiling, and 3D in vitro islet models are widely employed to study cell–cell interactions and regenerative potential within islets.

Currently, the pancreas is increasingly viewed as a highly integrated micro-organ system. Islet cells are surrounded by dense networks of interstitial capillaries, nerve fibers, and a vascular supply originating from the dorsal aorta, highlighting the organ's complex and dynamic microenvironment.

Conclusion

The endocrine portion of the pancreas, represented by the islets of Langerhans, is composed of five major cell types that regulate the body's glucose levels and overall energy balance through the secretion of hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide. Paracrine signaling and genetic mechanisms coordinate the functions of these cells.
Dysfunction of the islets of Langerhans can lead to diabetes, pancreatic adenocarcinoma, and other endocrine pathologies. Modern research — including donor islet transplantation supported by ECM proteins, as well as the use of CRISPR-Cas9 and 3D in vitro models to study intercellular interactions — provides new and promising strategies for advancing endocrine histology and diabetes therapy.

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