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REVIEWS

Interaction between Endocrine and Exocrine Pancreas

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Abstract—The pancreas plays a key role in the endocrine system of animals, as well as in the digestion and absorption of nutrients. The exocrine and endocrine portions of the pancreas are structurally separated from each other, however, multiple studies suggest the anatomical and functional unity between them. While previously, the interactions of these two portions received less attention, nowadays the pancreas is considered as a single organ consisting of functionally interlinked components, which coordinates endocrine and exocrine responses. The review addresses the latest data indicating the functional relationship and reciprocal influence of the endocrine and exocrine pancreatic portions. In addition, we consider the impact of SARS-CoV-2 infection on pancreatic function.

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INTRODUCTION

The pancreas is an organ located in the left upper quadrant of the abdomen behind the stomach and divided into a head, body and tail. Releasing various digestive enzymes and hormones, the pancreas regulates macronutrient digestion and thus metabolism and energy homeostasis. It is responsible for converting the food, we consume, into energy for our cells.

The pancreas performs two major functions: exocrine, responsible for digestion, and endocrine, regulating blood sugar levels in particular. Insulin, glucagon, somatostatin, and amylin are the main pancreatic hormones that affect blood glucose levels. The mechanism of glucagon action is due to its binding to glucagon receptors on liver cells, which upregulates Gs protein-mediated adenylate cyclase activity and increases cAMP production. As a result, catabolism of glycogen, deposited in the liver (glycogenolysis), intensifies. Glucagon is an external signal for hepatocytes to release glucose into blood due to glycogen breakdown (glycogenolysis) or its synthesis from other substances (gluconeogenesis). Thus, glucagon, stimulating glycogen breakdown in the liver, contributes to maintaining blood glucose at a constant level. The metabolic function of amylin is to inhibit elevations of plasma glucose levels. Thus, amylin acts as a synergistic partner of insulin, as both hormones are co-secreted by pancreatic β-cells in

response to food intake. The overall effect is to slow down the rate of blood glucose elevation after a meal. This is accomplished by inhibiting digestive secretion of gastric acid and pancreatic enzymes, as well as bile release, and, as a consequence, by reducing food intake. Somatostatin is an inhibitory hormone, which, specifically, inhibits insulin and glucagon secretion. Somatostatin inhibits absorption in the gastrointestinal tract; thus, its function is to prolong the time for nutrients, including glucose, to enter the bloodstream.

The main function of insulin is to regulate carbohydrate metabolism, specifically, glucose utilization in the organism. Insulin increases plasma membrane permeability for glucose and other macronutrients, activates key glycolytic enzymes, stimulates glycogen synthesis from glucose in the liver and muscles, and increases the synthesis of fats and proteins. In addition, insulin inhibits the activity of enzymes that break down glycogen and fats, i.e., in addition to its anabolic action, insulin also exerts an anti-catabolic effect. The human organism requires quite a narrow range of blood glucose levels. The normal range of blood glucose concentrations is 70–130 mg/dL (3.9–7.1 mmol/L). The endocrine pancreatic hormones are predominantly responsible for the regulation of blood glucose levels by adjusting the balance through negative feedback.

The exocrine portion of the pancreas accounts for more than 90% of its total volume. It consists of the acini, which represent clusters of cells secreting such exocrine pancreatic enzymes as lipases, proteases and amylases, and a system of intercalated ducts that transport these enzymes to the proximal duodenum to help split fats, proteins and carbohydrates for their subsequent absorption. The hormones glucagon, insulin, and somatostatin are secreted into the bloodstream by the islets of Langerhans (α-, β-, and δ-cells, respectively) and provide the endocrine function of the pancreas [1]. Pancreatic polypeptide (PP), secreted by PP-cells, and ghrelin, which is produced by epsilon cells (ε-cells), are also produced by the pancreatic islets of Langerhans [1]. Exocrine pancreatic secretion is strictly controlled by the neuroendocrine system, which is anatomically and physiologically connected to the exocrine portion of the pancreas [2].

Most of pancreatic research has been focused on the endocrine system, which is motivated by the need to find methods to treat such a disease as diabetes mellitus. However, in recent years, there has been a growing number of studies dedicated to the functioning of the exocrine pancreatic portion. These studies emphasize the critical role of acinar and ductal cells in pancreatic pathology but also help understand how cells of the exocrine pancreas can serve as a source for the formation of β-cells in the islets of Langerhans [3].

ACINAR AND DUCTAL COMPONENTS OF THE EXOCRINE PANCREAS

The pancreatic acinus consists of pyramidal cells with numerous secretory granules. Connective tissue with blood vessels, lymph, nerves, and excretory ducts isolates the pancreatic acini from each other. The acinar cells secrete a cocktail of digestive enzymes with a small volume of fluid rich in sodium, chlorine and hydrogen ions. Epithelial cells, which line the pancreatic ducts, secrete Cl^- and HCO_3^- ions with a large volume of fluid, making the pH in the duodenal lumen slightly alkaline (up to pH 8.5), thus providing an optimal environment for enzymatic activity [4]. Small intercalated ducts link the acinar lumen to the intralobular ducts within the pancreatic subunits, proceed through the larger interlobular ducts, and eventually flow into the main pancreatic duct, which joins the bile duct to form the common bile duct (Fig. 1). Digestive enzymes, secreted by acinar cells, include more than 10 different proteases, as well as lipases, ribonucleases, amylases and hydrolases. Proteolytic enzymes are released in an inactive form to avoid self-digestion by the pancreas. The cascade of physiological activation starts in the duodenum, where intestinal enteropeptidase converts trypsinogen into an active form of the enzyme, trypsin. Then, trypsin activates other proenzymes [4].

ENDOCRINE PANCREAS

The islets of Langerhans consist of endocrine cell clusters scattered over the exocrine epithelium between the acini and ductal structures. The endocrine cell types have a well-defined spatial arrangement within the islets of Langerhans. This structure is essential for cell–cell communication and hormone secretion. In mice, insulin-secreting β-cells

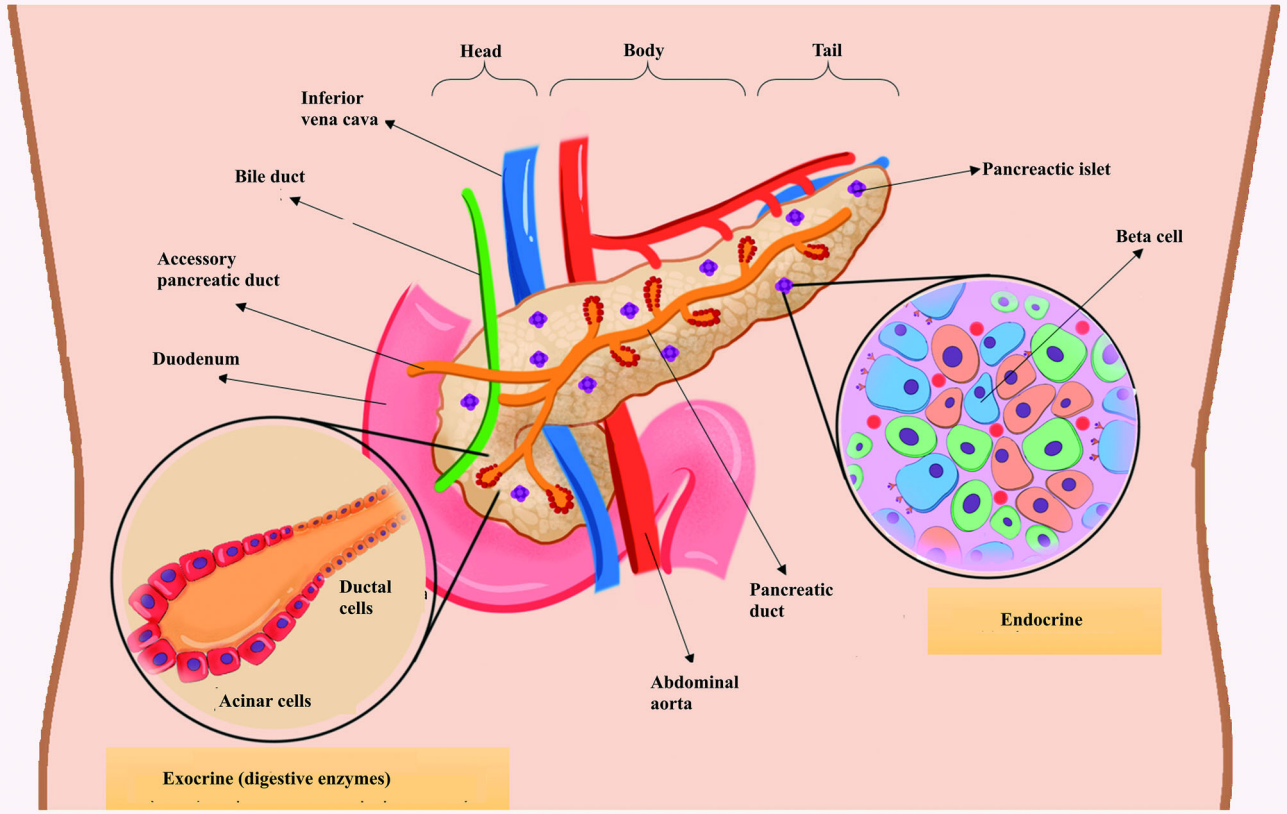

Fig. 1. Pancreatic endocrine and exocrine portions. Exocrine cells secrete digestive enzymes and pancreatic juice into the small intestine, while endocrine cells secrete the hormones insulin and glucagon into the bloodstream to regulate blood sugar levels. This dual function of the pancreas is required to maintain both optimal metabolism and proper digestion in the organism.

account for the bulk of the islet of Langerhans, whereas α-, δ-, and PP-cells make up the periphery of the islet. The insular architecture is more complex in humans and other primates, but it still obeys the general layout in which β-cells are enveloped by α-, δ-, and other endocrine cell types [5]. In humans, the islets contain about 30% glucagon-secreting α-cells and 60% β-cells secreting insulin and amylin, while the remaining 10% fall on somatostatin-secreting δ-cells, γ- or pancreatic polypeptide-producing PP-cells, and ghrelin-producing ε-cells [1].

Glucagon-secreting α-cells are much less studied than insulin-producing β-cells. The fasting state is characterized by the presence of glucagon, a hormone that counteracts insulin. The coordinated regulation of glucagon and insulin secretion is the major mechanism for blood glucose control. The main role of the counter-regulatory response is to prevent hypoglycemia, and it is this response that is hampered in diabetes. In type 2 diabetes mellitus (DM2), α-cells produce more glucagon in response to amino acids and ineffectively inhibit glucagon production due to high plasma glucose levels [6]. The involvement of α-cell functional regulation in the pathophysiology of DM2 is currently under study.

The insulin molecule is formed by two polypeptide chains, A and B, linked together by disulfide bonds and containing 51 amino acid residues. Insulin exerts a significant hypoglycemic effect. This hormone is essential for cellular food assimilation and hence for the organism's survival. One of the key medical achievements of the 20th century was insulin isolation and its effective clinical use in 1923. Insulin, like most other peptide hormones, derives from a precursor molecule, proinsulin, which is then cleaved into three parts: A- and B-chains forming the biologically active insulin molecule, and C-peptide, a connecting or linker peptide that is released at a 1 : 1 molar ratio with insulin. Since insulin and C-peptide are secreted in equal amounts, the measurement of immunoreactive C-peptide release has proven to be

a very valuable independent indicator of the rate of in vivo insulin secretion in humans, especially in diabetic subjects receiving insulin injections. Measuring C-peptide blood levels is used in diabetes to assess insulin production by the pancreas. C-peptide is released concurrently with insulin but has a longer half-life in blood, making it useful indicator of endogenous insulin secretion. This may help distinguish between DM1 and DM2 and assess the necessity for insulin therapy. The islet-associated polypeptide (IAPP, commonly known as amylin) is a 37-amino-acid peptide also secreted by β-cells. IAPP molecules can polymerize under pathological circumstances, yielding massive intrainsular amyloid deposits, which are common in DM2 and insulinoma.

Other cells, found in the islets of Langerhans, are Delta cells (D cells or δ-cells), which secrete somatostatin (formerly known as growth hormone-inhibiting hormone, GHIH, or somatotropin release-inhibiting factor, SRIF), PP-cells, which produce the least studied of the insular hormones pancreatic polypeptide (PP), and ε- or ghrelin-producing cells. Ghrelin was originally isolated from the rat stomach and then found in a certain cell type of the islets of Langerhans. This hormone is believed to play a role in growth hormone release, metabolic regulation, and energy balance of insular cells [7], although its function in these cells is still poorly understood.

Presumably, the cellular architecture of the islets of Langerhans is crucial for the provision of their function. Obesity and diabetes in mice and humans are associated with the structural impairment of these pancreatic subunits [8]. Homeostatic regulation of the islet microenvironment is essential for proper islet cell functioning, especially for insulin secretion. Endocrine, immune and nerve cells, as well as vascular endotheliocytes, play a pivotal role in maintaining islet homeostasis and β-cell function [9].

HOW DO ENDOCRINE AND EXOCRINE PANCREAS INTERACT WITH EACH OTHER?

In many histological studies, both endocrine and exocrine portions of the pancreas were considered as separate entities, disregarding their interrelationship, and is only recently when the mechanisms of interaction between the islets of Langerhans, ducts, and acini have begun to come into focus. Currently, the pancreas is regarded an integrated organ consisting of three functionally related components that coordinate endocrine and exocrine functions [10].

In terms of embryology, both pancreatic portions develop similarly, when epithelial cells invaginate into connective tissue underlying the epithelial membrane. The initial invaginations of the exocrine portion persist as the ducts and acinar system, but the links between the islets and the epithelial membrane disappear. As a result, secretory products of insular tissues are released into the bloodstream as hormones [11]. The islets of Langerhans, once fully developed, are separated from the surrounding acinar tissue by a thin layer of reticular fibers having no connection with the ducts. However, in the human pancreas, small pancreatic ducts and acinar cells have been found in the islets of Langerhans [12].

Moreover, the islet–exocrine interface (IEI), which is the major anatomical and functional region, has been shown to provide cell–cell communication between the endocrine pancreatic islets and exocrine acinar cells. Desmosomes and adhesive junctions have recently been found between insular and acinar cells at IEI [11]. In both experimental animals and patients, it has been found that the loss of cell–cell paracrine communication, as well as fibrosis that leads to extracellular matrix remodeling, can culminate in the dysfunction of the insulin–acinar–ductal–incretin gut–hormone axis, resulting in pancreatic insufficiency and glucagon-like peptide-1 deficiency, which are common in prediabetes and DM2 [11].

Another study has attempted to find out whether the restoration of regulatory effects, mediated by duct-derived epithelial cells in vitro, enhances the long-term function of β-cells. It has been found that the decrease in β-cell mass and insulin secretion, as observed in isolated and human islets co-cultured with duct-derived epithelial cells, was due to the loss of trophic support provided by surrounding pancreatic non-endocrine cells. These findings confirm that ductal epithelial cells fulfill the function of supporting islet viability [13].

Furthermore, ductal and acinar cells have been found to impact on the physiology of endocrine insular cells through the release of cytokines and growth factors [14]. Increased gastrin and TGF-α expression in ductal cells have been shown to play a

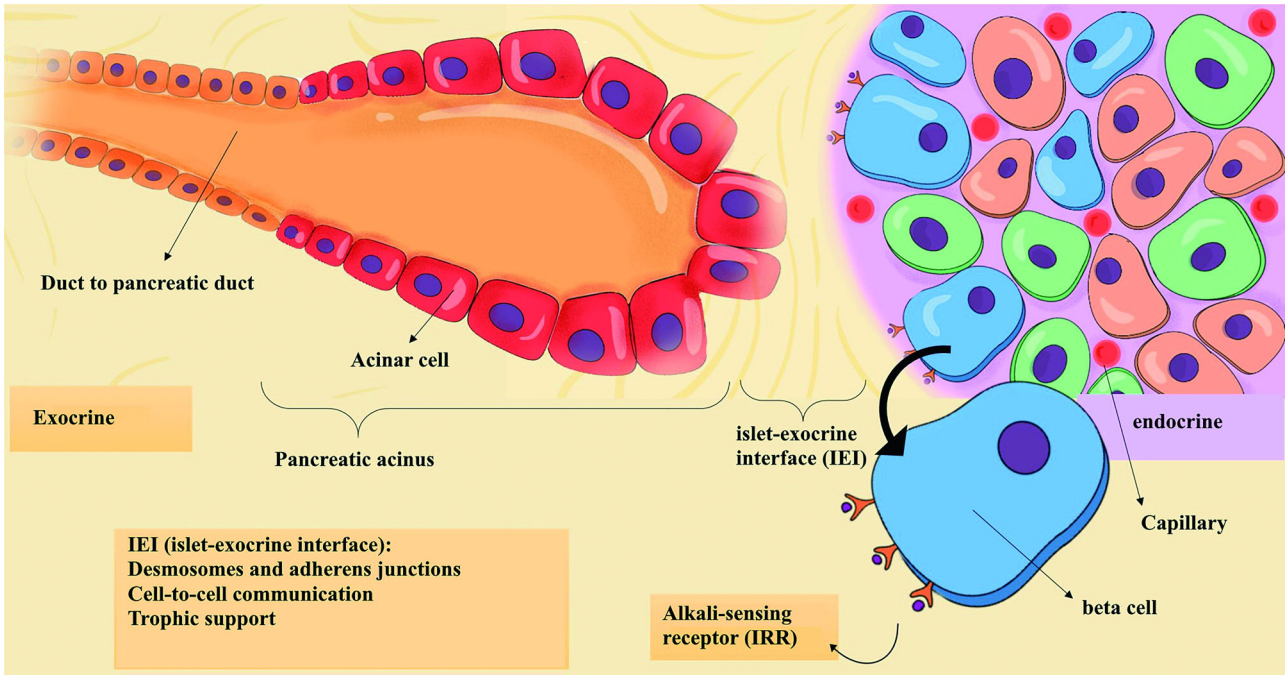

Fig. 2. Mechanisms of interaction between the endocrine insular and exocrine ductal and acinar pancreatic cells. While exocrine cells secrete pancreatic juice and digestive enzymes into the small intestine, endocrine cells release systemic hormones (insulin and glucagon) into the bloodstream. These hormones are vitally important for regulating blood sugar levels. They work in concert with digestive enzymes to ensure proper digestion and absorption of nutrients. The interplay between the two pancreatic portions ensures the regulation of these processes.

role in the proliferation and differentiation of insular cells from progenitor cells residing in the ductal epithelium [15, 16].

As is well known, one of the main functions of the pancreas is to secrete a slightly alkaline (pH 8.0–8.5) juice into the intestinal lumen. By the latest data, the pancreatic ductal system, which contains a slightly alkaline juice, may be linked to endocrine cells of pancreatic islets [17]. It has also been found that the alkaline-sensitive receptor, called insulin receptor-related receptor (IRR), is expressed on the cell surface of pancreatic β-cells. This receptor was discovered as a homolog of the insulin receptor (IR) and was considered an orphan receptor as it does not respond to insulin or other insulin receptor agonists [18]. According to a study conducted on the pancreatic β-cell line MIN6, alkaline activation of IRR may be one of the steps in the feedback between the pancreatic exocrine and endocrine systems. Pancreatic juice alkalinization causes activation of IRR tyrosine kinase, which, in turn, activates intracellular signaling protein IRS-1 and perturbs actin cytoskeleton remodeling in β-cells, which can potentially affect the ability of β-cells to secrete hormones [17] (Fig. 2).

It has also been found that pancreatic endocrine and non-endocrine cells produce β-cells via transdifferentiation, i.e., transformation from another, fully differentiated, cell type. Several research groups have reported ex vivo generation of cells like β-cells from the human acinar tissue using various experimental techniques [19].

PANCREATIC INFECTIONS AND COVID-19 PANDEMIC

As the world has recently gone through the COVID-19 pandemic, it has become an urgent task to find out how this virus affects every organ in our body and what its long-term effects are. As time goes on, there is an increasing number of reports on its systemic effects on the human organism.

Although at first, COVID-19 infection was thought to affect only the upper respiratory tract, it has been later discovered that the virus can affect almost all systems. To penetrate the cell, SARS-CoV-2 binds to

angiotensin-converting enzyme 2 (ACE2), which is a transmembrane protein, and also employs transmembrane serine protease 2 (TMPRSS2) [20, 21]. In addition to the respiratory system, ACE2 has been found in the gastrointestinal tract, kidneys, pancreas, and gallbladder [22, 23]. Although most patients experience respiratory symptoms, such as cough, dyspnea, and shortness of breath, there have been several reports of gastrointestinal symptoms, including diarrhea, nausea, vomiting, and abdominal pain, which may occur even in the absence of respiratory symptoms [24–27].

An elevated level of pancreatic enzyme was found in about 20–30% of hospitalized COVID-19 patients and shown to be associated with a high degree of COVID-19 infection severity and worse clinical outcomes [28–30]. In addition, diabetes mellitus and hyperglycemic stress are currently recognized as risk factors for severe COVID-19 outcomes, including hospitalization and death [31, 32]. COVID-19 is supposed to be associated with a higher risk of first-diagnosed hyperglycemia and diabetes in both adults and children [33–35]. Although the exact mechanisms behind the occurrence of diabetes in people with COVID-19 are unknown, a number of complex interrelated processes are hypothesized to be involved, including stress- and steroid-induced hyperglycemia, direct or indirect impact of SARS-CoV-2 on β-cells [36].

To elucidate the mechanisms of SARS-CoV-2-induced pancreatic dysfunction, several research groups have attempted to localize ACE2 and TMPRSS2 in the pancreas, but the results are still contradictory. In the pancreas, the ACE2 protein has been mainly detected in the ductal and microvascular structures, without obvious expression in β-cells [37, 38]. Other authors have reported pancreatic ACE2 expression in the microcirculatory bed, as well as in human pancreatic islets, predominantly in β-cells [39]. Müller et al. [40] found a strong ACE2 expression in endothelial and ductal cells, as well as its moderate expression in endocrine cells (mainly β-cells). Similarly, TMPRSS2 was detected in the endocrine pancreas and some ducts. However, SARS-CoV-2 penetration into the cell is thought to be mediated not only by ACE2 alone, as not only ACE2-expressing pancreatic cells were positive for viral particles [41]. Neuropilin 1 (NRP1) has been proposed as an alternative receptor for SARS-CoV-2 virus penetration. NRP-1 is a major co-receptor for SARS-CoV-2 penetration into the host cell. It has also been noted that the presence of NRP-1 on the host cell surface facilitates the spread of SARS-CoV-2 infection and may promote viral penetration, among other things, into the brain. Moreover, it appears that the use of NRP-1 or VEGF-A/NRP-1 inhibitors is to be considered as a potential analgesic and antiviral drug therapy. The significance of NRP-1 in SARS-CoV-2 needs to be further investigated to verify its role in coronavirus infection [42].

SARS-CoV-2 has also been demonstrated to replicate in isolated human pancreatic islets, predominantly in β-cells [43], causing subcellular and functional alterations as well as impaired regulation of insulin production and secretion. SARS-CoV-2 has also been detected in pancreatic autopsy specimens (7 out of 9 patients died of COVID-19 complications), while SARS-CoV-2 nucleocapsid protein (NP) staining was detected in β-cells in 4 out of 7 patients [43]. Steenblock et al. [41] also observed SARS-CoV-2 NP in the endocrine and exocrine pancreas of COVID-19 patients and hypothesized that SARS-CoV-2 can cause immune cell infiltration and necroptotic cell death in the islets of Langerhans. It was found that in SARS-CoV-2 infection, β-cells undergo trans-differentiation, leading to decreased insulin and increased glucagon and trypsin expression [44]. Presumably, SARS-CoV-2-induced β-cell trans-differentiation is mediated via the eIF2 pathway.

Studies of long COVID-19 show that even after the acute phase of the disease, survivors have an increased risk of developing diabetes [45], while recovered patients with diabetes are more often to suffer long-term sequelae of COVID-19 compared to those without diabetes [46, 47].

CONCLUSIONS

The pancreas is typically divided into two discrete systems, endocrine and exocrine. The endocrine pancreas consists of the islets of Langerhans, individual endocrine cells and their rudiments, whereas the exocrine pancreas comprises acinar cells and a ductal system. The former secretes a slightly alkaline juice and digestive enzymes into the duodenal lumen, while the latter produces systemic hormones

and releases them into the bloodstream. Meanwhile, recent studies show that these two pancreatic entities have a strong reciprocal relationship with each other [10]. All pancreatic disease specialists need to gain a deeper insight into the function of both pancreatic portions, as well as the anatomical and functional relationships between them, in order to develop new therapies with novel biological targets for treatment, in particular.

AUTHORS' CONTRIBUTION

Writing and editing the manuscript (A.M., E.A.G., O.V.S., T.M., I.E.D.).

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ETHICS APPROVAL

This work contains no experimental human or animal studies.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflict of interest.

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