Structural similarities and differences between the human and the mouse pancreas

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Mice remain the most studied animal model in pancreas research. Since the findings of this research are typically extrapolated to humans, it is important to understand both similarities and differences between the 2 species. Beside the apparent difference in size and macroscopic organization of the organ in the 2 species, there are a number of less evident and only recently described differences in organization of the acinar and ductal exocrine tissue, as well as in the distribution, composition, and architecture of the endocrine islets of Langerhans. Furthermore, the differences in arterial, venous, and lymphatic vessels, as well as innervation are potentially important. In this article, the structure of the human and the mouse pancreas, together with the similarities and differences between them are reviewed in detail in the light of conceivable repercussions for basic research and clinical application.

Introduction

Due to the clinical importance of diabetes, pancreatitis, endocrine tumors and pancreatic cancer, the structure of the exocrine and endocrine pancreas has been studied extensively. However, since the studies in humans are inherently limited to scarce samples at intermittent and often unpredictable intervals, animal models have largely subdued the research field, among which the mouse model is used most often. While the gross anatomical similarities and differences between the 2 species are well established, a large part of our knowledge on cellular architecture in humans is rooted in studies conducted on rodents, especially on mice. Our knowledge of pancreas structure is growing constantly and with it the translation of this knowledge into research and clinical practice. Thus, it is becoming increasingly important to conceive differences between the human and the mouse pancreas and understand the limitations stemming from them.

With the exception of a few articles1–5 and book chapters6,7 that cover some aspects of the human and the mouse pancreas in a comparative way, there is, to the best of our knowledge, no single article or book chapter that would systematically and exhaustively deal with this important topic. Thus, the aim of our review is to survey the similarities and differences between the mouse and the human pancreas by appreciating latest discoveries in the field and pointing out issues of special importance for the clinical and research use.

First, the gross anatomy of the human and the mouse pancreas will be outlined. This section could be particularly valuable to researchers with a background in human medicine, starting to use mice as a model organism for pancreas research, and vice versa, to researchers trained in animal biology and beginning to work with human specimens. Next, we describe in detail the exocrine and endocrine part of the human and the mouse pancreas at the tissue level. This section shall help dismiss some commonly encountered textbook misconceptions about pancreas histology, for example the one regarding microarchitecture of the human islet of Langerhans (islet). The final sections on blood perfusion, lymphatics, and innervation are intended for surgeons and researchers dealing with the pancreas in situ and studying the role of neurotransmitters and neuropeptides in pancreas biology.

Macroscopic Anatomy of the Pancreas

The human pancreas1 is a well-defined solitary organ. Macroscopically, it can be divided into 3 major parts: the head, the body, and the tail.8 There are no clear-cut borders between these parts. Generally, the left border of the superior mesenteric artery (SMA) is considered the border between the head and the body, whereas the midpoint of the body and tail combined is considered the border between the body and the tail.9 Some authors distinguish a fourth and a fifth part, both of which are more generally parts of the head; the uncinate process located beneath the SMA, and the neck or isthmus, a thinned part situated over the SMA.8,9 The head of the pancreas is a C-shaped part aligned with the upper curvature of duodenum. The flat narrow body of the pancreas is located underneath the stomach extending almost horizontally in the medial plane. It crosses with the superior mesenteric artery and vein, abdominal aorta, inferior vena cava, and portal vein. The tail of the pancreas touches the hilum of the spleen. The gland is 14–18 cm long, 2–9 cm wide and 2–3 cm thick, weighing 50–100g.8,10–12 The pancreas is surrounded by a fibrous capsule from which connective tissue septa extend into the gland dividing its parenchyma into distinct lobes and lobules...
Mesenchyme accounts for approximately 15–25% of total pancreas volume (TPV) and contains numerous fat cells. In mice, on the other hand, the pancreas is not as well defined as in humans but is rather diffusely distributed within the mesentery of the proximal small intestine in a dendritic manner. Macroscopically, 3 major parts can be distinguished: the duodenal, the splenic, and the gastric lobe (Fig. 1). The largest lobe that makes up over a half of TPV is the splenic lobe (SL). It extends horizontally between the duodenum and the spleen and is homologous to the body and the tail of the human pancreas. The duodenal lobe is invested in the mesentery surrounding the duodenum and is homologous to the head of the human pancreas. The third and the smallest macroscopically distinguishable lobe is the gastric lobe (GL). It can be viewed as a large part of the splenic lobe from which it develops during ontogeny and it was suggested that the GL is homologous to the pyramidal process also named the ear or auricle of the human pancreas. This is a highly variable part of pancreas existing in approximately half of adult humans at the inferior margin of the transition of the head to the body and protruding toward the stomach (Fig. 1).

The main lobes of the mouse pancreas are often separated by patches of adipose, connective, and lymphatic tissue. Therefore, special attention needs to be paid to entirely remove the pancreas and precisely determine its mass.

**Microscopic Anatomy of the Exocrine Pancreas**

Together with the aforementioned mesenchyme, the exocrine pancreas amounts to 96–99% of TPV. Each lobe of pancreas consists of several smaller lobes called lobules. Their size is proportional to the size of the organism. In humans, lobules measure 1–10 mm in diameter, whereas in mice they are 0.5–1.5 mm in diameter. In humans, the demarcations between lobules are incomplete and the whole parenchyma is a continuous unit. Each anatomical lobule is a single glandular lobule receiving one major duct. Arteries, however, do not run in parallel with ducts and the number of arteries per one glandular lobule is 2–9. In other words, each glandular lobule consists of a few vascular or primary lobules, each of which receives a single artery. Each pancreatic lobule is composed of structures called acini. An acinus is a cluster of pyramidal acinar cells forming a dome-like structure that funnels secretions from apical poles of acinar cells into the lumen of what is called an intercalate duct. The intercalated ducts drain into intralobular ducts (located within lobules) and these, while exiting lobules, drain into larger diameter interlobular ducts (located between lobules). The latter in turn converge into the main pancreatic duct (also called the duct of Wirsung) that extends along the whole pancreatic gland in humans. The ducts entering the lobules are mostly second- or third-order branches of the main pancreatic duct. The main pancreatic duct then empties into the duodenum adjacent to the entrance of the common bile duct. The most distal parts of both ducts form the so called hepatopancreatic ampulla (ampulla of Vater). The ampulla opens into the duodenum via the major duodenal papilla (papilla of Vater). As a variety, the human pancreas may have one accessory duct also called the duct of Santorini that is a remnant of the distal part of the

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**Figure 1.** Macroscopic anatomy of the human and the mouse pancreas. (A) Human pancreas consists of the head, the body, and the tail. (B) Mouse pancreas has 3 lobes that are less well defined: the duodenal, the gastric, and the splenic lobe. Note the 10-fold difference in linear dimension (which accounts for the 1000-fold difference in the size of the organ as well as the organism). The color coding indicates homologous parts.
main duct of dorsal pancreas present during the development of the
intestinal tract. In up to 3% of people undergoing endoscopic
retrograde cholangiopancreatography, the so-called anomalous
pancreato-biliary junction can be found, where the pancreatic duct
crosses the common bile duct a few centimeters outside the
duodenal wall. In these people, the incidence of gallbladder and bile duct carcinoma is increased, possibly due to reflux and stasis of a mixture of bile and pancreatic juice in the bile duct and gallbladder.

The mouse pancreas, on the other hand, displays a quite
different ductal anatomy. A large interlobular duct drains each of
the 3 lobes. The splenic and the gastric duct merge and join with
the common bile duct well before the common pancreatic/bile
duct enters the wall of the duodenum. In 70% of animals, the
point where the common splenic/gastric duct joins the bile duct is proximal to the point where the duodenal duct joins with
the common pancreatic/bile duct (Fig. 1). Accessory small ducts
can individually empty into the bile duct or directly into the
duodenum.

When injecting enzymes into the ductal tree for isolation of
islets or agarose for preparation of tissue slices, it should be kept in mind that – depending on the point of injection, possible clamping and anatomical variations – a variable permeation of the excretory system with the injected substance might be expected. Due to anatomical differences, the techniques developed for preparation of rodent isolated
islets and tissue slices are not directly applicable on human pancreas.

In humans, impaction of a gall stone at the level of ampulla
is a specific cause of pancreatitis. More than a century ago, Opie proposed that due to the impaction, a common channel
between the pancreatic and the common bile duct is created
that the entry of bile into the pancreatic excretory system
triggers the inflammation. Duct ligation and injection of bile into the ductal system of mice are used in studying the pathophysiology of pancreatitis, however this approach is questionable in mice where a common pancreatic/bile duct is present normally.

Microscopic Anatomy of the Endocrine Pancreas

The remaining 1–4% of TPV comprise endocrine microor-
gans called islets of Langerhans. They are of circular to oval to highly irregular cross-sections and are composed of a few
to several thousand endocrine cells. In addition to islets, single
endocrine cells can be found scattered throughout the acinar and ductal tissue. The islet size distributions are similar in
humans and mice. At least 5 types of polypeptide-hor-
mone-secreting endocrine cells can be found in islets. Most
numerous are the beta cells that synthesize and secrete insulin.
Beta cells make up 50–70% and 60–80% of cells in islets in
humans and mice, respectively. Alpha cells, contributing
20–40% and 10–20% of the total number of cells in human and
mice, respectively, secrete glucagon. Thus, in mice the ratio
between beta and alpha cells is higher than in humans. Delta
cells and PP cells releasing somatostatin and pancreatic polypeptide, respectively, are the least frequent cell type and present
less than 10% of cells in humans and less than 5% of cells in mice. However, in the posterior head of the human pancreas which is a vestige of the ventral pancreas
anlage, the proportion of PP cells among endocrine cells is
around 70%. Finally, the hormone ghrelin is released from epsilon cells which present less than 1% of cells.

Beside a relative lack of insulin and a relative surplus of glucagon, changes in concentrations of other islet hormones have been described in type 2 diabetes mellitus.

Until recently, the spatial organization of cells within the islet,
i.e. their microarchitecture, was believed to be markedly different
in the 2 species. In mice, islets were reported to be composed of a
mantle containing mainly non-beta cells and a core containing
practically exclusively beta cells. In humans, on the other hand, in addition to the mantle-core pattern, other patterns were reported. Insulin positive cells were shown to arrange in clusters, in a ribbon-like pattern, or to be dispersed throughout the islet in a rather unorganized manner.

More recently, it was proposed that the human islet cells form
trilaminar plates composed of 2 layers of alpha cells surrounding
a single layer of beta cells. This sandwich is supposed to contain
pits surrounded by alpha cells and protruding along the vessels
into the beta cell middle plate. Finally, the whole sandwich is believed to be folded into a U- or O-shaped islet. This organization conceivably promotes heterologous contacts between alpha and beta cells but still allows for a functional con-
tinuum between beta cells in the middle layer. In mice, on the other hand, homologous contacts between alpha cells in the
mantle and between beta cells in the core predominate. There is evidence that alpha cells stimulate beta cell function and it
is tempting to speculate that the specialized architecture of
human islets could at least partially explain their greater sensitiv-
ity to glucose compared with mouse islets.

The above idea finds further support in recent studies demon-
strating that human-type islets can be found in mice in states char-
acterized by an increased demand for insulin, such as inflammation, obesity, diabetes, and pregnancy. This suggests that the pattern of cell distribution in larger mammals, for example humans, may in addition to the increased number of islets (see below) provide a part of the functional compensation for the
increased demand for insulin due to larger body mass. However,
only a small number of alpha cells are found in the islet core in the
domestic pig with a body mass similar to humans. Moreover, in some mammals considerably larger than humans, for example the white whale and the african elephant, the mantle-type
islets seem to prevail. On the other hand, in some mammals considerably smaller than humans, for example the fruit bat and the guinea pig, the human-type islets were described, as reviewed recently. Thus, it seems difficult to relate islet architecture to increased body size only and other factors that
might influence islet architecture, such as the diet or circula-
dian patterns, are worth exploring with regard to their effect
on islet architecture in the future.
Finally, it was shown that in both mice and humans, the architecture of islets is size-dependent, with smaller islets (<100 μm in diameter) being of the mantle-type and larger islets displaying the more complex organization. Noteworthy, at present, different types of islets are defined based on distribution of different types of cells within islets. Including other morphological features, such as innervation and vascularization, might reveal additional similarities and differences between islets and help us get a clearer picture. To sum up, some human islets may possess architectural characteristics of typical mouse islets and vice versa.

The relationship with the size of the organism observed for the size of the exocrine lobules does not hold true in the case of the islets. Namely, the range of observed islet sizes is similar in mice and humans (and also other species), with the upper boundary at around 500–700 μm in diameter. It seems that there is an upper limit of size that is optimal for function. There is a proportionately larger number of islets in species with larger body mass, such that despite the fairly constant islet size, a virtually linear dependence exists between the total islet number and body mass across species. The mouse pancreas contains approximately 1000–5000 and the human pancreas approximately 1.000.000–15.000.000 islets, a ratio that equals the ratio between masses of the 2 organisms. The total mass of islets in a normal human pancreas is estimated at 1–8 mg. Within species, a linear relationship between beta cell mass and body mass was described in humans younger than 20 y of age, as well as a linear relationship between beta cell mass and body mass index in adults. In mice, there is a linear relationship between beta cell mass and body mass.

In mice, the distribution of islets and the beta cell mass in different lobes seems to be rather heterogeneous. For the most frequently used strain of mice C57BL/6, the number of islets per unit of volume is the highest in the gastric lobe, followed by the duodenal and the splenic lobe, with volume densities in the first 2 being 75% and 20% higher than in the latter, respectively. However, the islets in the GL are the smallest and the proportion of beta cells they contribute to the total beta cell volume (12%) is the same as is the proportion of GL volume in the TPV (12%). On the other hand, islets in the DL together contain a disproportionately high volume of beta cells (40%) with regard to the volume that the DL contributes to TPV (≤3%). From this, it can be easily deduced that with regard to its volume (55% of TPV), the SL contributes the least part of beta cell volume (48%). Other distributions were reported for other strains.

In experimental models of diabetes and in investigations of gene effects on islet development, the differences between lobes must be kept in mind. In the human pancreas, the density of islets per unit volume was recently reported to be similar in the head and the body, but approximately 2-fold higher in the tail. Earlier studies, however, detected a more continuous increase in the density of islet volume per volume of total pancreatic tissue from the head to the tail, with 2%, 3%, and 4% endocrine cells per volume of total pancreatic tissue in the head, the body, and the tail, respectively. Although it was reported that there are a larger number of smaller islets in the head and a smaller number of larger islets in the tail, the cellular composition and microarchitecture of the islets were shown to be more constant throughout the pancreas in humans than in mice, with the exception of the posterior head containing islets rich in PP-secreting gamma cells and poor in alpha and beta cells.

In human isolated islets, no regional differences in glucose stimulated insulin secretion could be detected. In patients with type 2 diabetes, the head region of the pancreas and in particular larger islets within the head seem to suffer the most pronounced beta cell loss. Type 2 diabetes mellitus is a major risk factor for pancreatic cancer, together with smoking and obesity, and interestingly, it most often arises in the head of the pancreas where it also displays lower malignancy in comparison with the body and tail. It remains to be investigated whether there is a common factor underlying both susceptibilities of the head region.

In mice, the islets are mostly interlobular in position, and less likely intralobular than in humans (Fig. 2). In the latter case, they are usually located on the edge of lobules. A possible explanation for this difference is that in larger animals, such as humans, the larger lobules ontogenetically emerge by fusion of originally smaller lobules and that this way, originally interlobularly positioned islets become enveloped with acinar tissue, thereby changing their position from inter- to intralobular. Merkwitz et al. have recently proposed an alternative explanation. Islets originate from progenitor cells within the epithelium of the developing ductal system and appear very early during the development of the ductal system. The first islets to develop remain close to the most proximal ducts, i.e., interlobular. Islets that develop later, i.e. from more distal branches of the ductal system, acquire an intralobular position. Within each species, there is probably a centrifugal temporal pattern of an increasing proportion of intralobular islets. Intraspecies differences between islets may arise from the fact that the shift is not complete, and the interspecies differences may result from different time points during ontogeny at which this shift comes to a halt.

Changes in Pancreas Anatomy During Ontogenesis

The process of ontogenesis is a source of differences in the structure of pancreas within a single species. To critically evaluate similarities and differences between 2 different species, it is desirable to compare specimens at equivalent ontogenetic stages. An important caveat in the foregoing discussion about differences in islet architecture is the fact that unfortunately, in some seminal studies the age of mice or human donors or both was not specified, while in the studies that specified the age, considering the expected lifespan for humans and mice, human
donors (n=9 studies; average age=53 years, i.e., >60% of lifespan) were relatively older than mice (n=4 studies; average age=16 weeks, i.e., <20% of lifespan). Thus, could some of the differences presented above as interspecies differences be due to our biased review of samples at different ontogenetic stages? Additionally, how does the microscopic structure of pancreas change in the course of a lifetime? A few recent studies involving younger human donors and older mice may provide some starting points to address these questions.

Studies on human islets from the prenatal period to late adulthood provide evidence that human islets probably attain an adult architecture by 2 y after birth. This is accompanied by an increase in beta cell area and mass, as well as beta to alpha cell ratio, predominantly due to a burst of beta cell proliferation, and by an increase in beta to delta cell ratio, due to both beta cell proliferation and a decrease in delta cell mass. The beta cell replication rate is greatest during the first 2 y of age and declines toward adolescence, a pattern similar to the

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**Figure 2.** Microscopic anatomy of the human (A, C, and E) and the mouse (B, D, and F) pancreas. (A and B) Macroscopic anatomy of the human and the mouse pancreas, respectively. (C and D) Magnifying a portion of pancreas reveals larger lobules in humans when compared to mouse, whereas the islets of Langerhans are of fairly comparable size in humans and mice. (E and F) Cell composition and location of the islets of Langerhans within the pancreas are markedly different in the 2 species. Note the more diffusely distributed endocrine cells in humans (E) and the mantle-core pattern in mice (F).
postnatal expansion of beta cells in mice. An increase in islet diameter rather than islet number from the neonatal period is the main mechanism of beta cell expansion, since roughly 10% of beta cell mass increase from birth to adolescence can be ascribed to new islet formation and 90% to an increase in islet size. Importantly, no major quantitative or architectural changes have been described in humans during adolescence. In addition, exocrine pancreas volume increases roughly linearly throughout childhood and adolescence (to 20 y of age). This increase exceeds beta cell expansion, such that a decrease in fractional beta cell area and islet density are observed during this period. During 20 to 60 y of age the exocrine pancreas volume remains stable and then decreases beyond 60 y of age. In contrast, beta cell mass as well as islet structure seem to remain largely constant between 20 and 100 y of age. Thus, fractional beta cell area remains stable between 20 and 60 y of age and increases beyond 60 y of age. Despite the shift toward the adult human-type architecture, it should be stressed that (i) single cells, (ii) pure and mixed clusters, (iii) mantle-type islets, and (iv) hUMAN-type islets can be found in humans beyond 2 y of age. The above 4 patterns overlap with the scheme for prenatal development of islets by Ferner and Robb. Therefore, from the appearance of first endocrine cells (8 weeks prenatally) to 2 y of age, there is a shift to a preponderance of human-type islets, but this shift is not complete. Studies utilizing older mice suggest that the mantle-type islet probably remains the predominant architectural type into old age. In addition, beta cell area, mass, as well as total pancreas mass increase with age, as does the body mass of ad libitum fed mice. The number of islets increases during the first 3–4 weeks and remains stable thereafter. The stability of islets is further supported by the finding that there is a low replication rate in all types of islet cells in 1-year-old mice and that the islet architecture in these mice is of the mantle type. The exocrine tissue expands more slowly than beta cell mass. Consequently, the fractional beta cell area increases with age.

In sum, we believe that the described differences between human and mouse pancreas tissue, especially in islet architecture, are due to true biological interspecies differences. In the following chapters, vascularization and innervation of the pancreas will be covered, for which interspecies differences and ontogenetic changes are less well described. It should be acknowledged that interstrain and interindividual differences might further complicate the situation, but these points are beyond the scope of this paper.

**Major Blood Vessels of the Pancreas**

The pancreas receives approximately 1% of the cardiac output. The arterial blood to the pancreas is derived from the first 2 of the 3 major branches of the abdominal aorta: the celiac and the superior mesenteric artery (Fig. 3). The head of the pancreas is supplied by 2 arcades: an anterior and a posterior. The anterior arcade is formed by the anterior superior pancreaticoduodenal artery (PDA), an indirect branch (via the gastroduodenal artery) of the common hepatic artery, which is the rightmost branch of the celiac artery. The anterior superior PDA anastomoses with pancreatic branches of the splenic artery. The posterior arcade is formed by the posterior superior PDA that is the most proximal branch of the gastroduodenal artery. The anterior and posterior superior PDA Anastomose with the anterior and posterior inferior PDA that both stem from the superior mesenteric artery. The body and the tail of the pancreas (i.e., the dorsal pancreate) are supplied by pancreatic branches of the splenic artery which is the leftmost branch of the celiac artery, and by the dorsal pancreatic artery that branches off near the origin of either celiac, hepatic, or splenic artery. Its right branch anastomoses with the anterior superior PDA whereas its left branch forms the transverse pancreatic artery (also termed the inferior pancreatic artery). The latter runs along the inferior border of the pancreas and usually anastomoses with the pancreatic magna artery, the largest pancreatic branch of the splenic artery in the middle or in the left third of the gland (Fig. 3A).

The venous system of the pancreas drains blood into the portal vein. The venous drainage from the body and the tail of the pancreas is less constant than their arterial supply. In general, the splenic vein collects blood via multiple small branches. The blood from the head of the pancreas is drained in a pattern similar to the arterial system. The anterior venous arcade is formed...
by the anterior superior and inferior pancreaticoduodenal veins (PDV) that both drain into the superior mesenteric vein. Similarly, the posterior arcade is composed of the posterior superior and inferior PDV. The posterior inferior PDV drains blood into the superior mesenteric vein, whereas the posterior superior PDV drains directly into the portal vein (Fig. 3B).\textsuperscript{8,117,118} Numerous anastomoses exist in the venous system that are typically more irregular than those in the arterial system.\textsuperscript{8} In mice, the anatomy of the major arteries and veins supplying and draining the pancreas is largely homologous to the one in humans.\textsuperscript{16,125}

**Microvasculature of the Pancreas**

The smallest intralobular arteries, arterioles, and capillaries are collectively termed the microvascular system of the pancreas.\textsuperscript{126} At the level of the microvasculature, the perfusion of the gland is rather different in humans and mice.

In humans, due to their predominant location within the lobules, the islet capillaries lead blood to capillaries surrounding acini, which is named the insulo-acinar portal system.\textsuperscript{25,41,77} Therefore, the blood from the islets is collected in efferent capillaries that exit islets to form a secondary capillary network supplying the acinar cells. Islet vasculature was reported to contain approximately 3-times more smooth muscle cells in humans where smooth muscle cells can be found deep within the islets than in mice where smooth muscle cells are associated only with the feeding arterioles at the islet periphery.\textsuperscript{127}

In mice, due to the mostly interlobular location of islets, their venous blood is collected by interlobular veins forming the so-called insulo-venous system. The less frequent intralobular islets pass blood either to the acinar capillary network or to interlobular veins.\textsuperscript{7,25,26,41} Importantly, via both the insulo-acinar and insulo-venous system, the blood is ultimately passed to the systemic circulation only indirectly after passing the liver.\textsuperscript{116,128}

The insulo-acinar portal system is the anatomical substrate for the influences that the endocrine pancreas may exert upon the exocrine pancreas.\textsuperscript{129}

The islets are highly vascularized and receive approximately 10-times more blood than the exocrine part when expressed per unit weight of tissue (i.e., approximately 15% vs. 85% of total pancreas blood flow).\textsuperscript{130} In both mice and humans, 1–5 arterioles enter each islet (depending on the size of the islet) and divide into fenestrated capillaries that form a dense capillary network resembling the kidney glomeruli.\textsuperscript{82,131} They are 5-times more numerous and bear 10-times more fenestrae than the capillaries in the surrounding acinar tissue. The capillaries possess a basement membrane.\textsuperscript{7} Capillaries have been reported to constitute 7–8% of islet volume.\textsuperscript{132}

Interestingly, in mice it has been shown that the blood may follow a specific microcircular pattern with regard to the cell type.\textsuperscript{128,131,133} Bearing in mind that according to the classical picture of islet microarchitecture, in mice the non-beta cells form a mantle around the core of beta cells, the blood perfusion was suggested to be organized in 3 possible patterns: (i) from periphery to center (blood reaches the non-beta cells first),\textsuperscript{26,134} (ii) from center to periphery (blood reaches beta cells first)\textsuperscript{133} or (iii) from one pole of the islet to the other (no hierarchical perfusion with regard to the cell type)\textsuperscript{133,135} (Fig. 4). The evidence for the described patterns of perfusion was based on structural vascular cast studies. It was recently shown that in mice, 66% of islets have the center-to-periphery pattern and the remaining islets the pole-to-pole flow across the islet.\textsuperscript{133}

There are some indications that the center-to-periphery pattern also prevails in humans, as revealed by functional studies of perfusion.\textsuperscript{136} However, since in humans the cell type distribution seems to be much less orderly, it was suggested that in humans the pattern of perfusion does not follow a clear cell type pattern.\textsuperscript{25,49}

Considering the fact that in human islets, the alpha cell distribution was shown not to be random but that alpha cells form 2 outermost layers flanking a beta cell rich middle layer of a folded trilaminar plate and that endothelial cells were never found in the middle layer, it is possible that in human islets, a hierarchy of perfusion exists, with arterial blood coming in contact with alpha cells first.\textsuperscript{38}

**The Lymphatic System**

The internal lymphatic system

The fine organization of the internal lymphatic system of the pancreas has been described practically exclusively in rodents. The internal lymphatic system of the mouse pancreas starts with blind-beginning intralobular lymphatic vessels that run in the larger intralobular connective tissue septa alongside smallest blood vessels and ducts and at a certain distance from acinar cells.\textsuperscript{137,138} The evidence suggests that in mice, every lobule has many intralobular vessels.\textsuperscript{137} They empty into interlobular vessels running in the connective tissue that separates lobules and also contains the interlobular blood vessels and ducts. Only about 20% of endothelial cells have been found close to acinar cells, 10-times less to ductal cells, and only exceptionally were they found close to endocrine cells of islets.\textsuperscript{138} They have never been
Figure 5. Lymph nodes of the pancreas. (A) Groups of lymph nodes that outline the gland. (B) Groups of nodes at the aorta. 8: hepatic nodes. 9: celiac nodes. 10: splenic and gastrosplenic nodes. 11: suprapancreatic nodes. 12: hepatoduodenal nodes. 13a: superior posterior nodes. 13b: inferior posterior nodes. 14: superior mesenteric nodes. 15: middle colic nodes. 16: paraaortic nodes. 17a: superior anterior nodes. 17b: inferior anterior nodes. 18: infrapancreatic nodes. Red dots on the top and at the bottom of lymph nodes indicate the nodes most frequently involved in carcinoma of the body or the tail, and the head, respectively.

observed within the islets but always at their periphery. Among rodents, contacts were more numerous in mice than in rats, due to the topographical arrangement of mouse islets at the periphery of lobules or within the interlobular connective tissue septa, alongside lymphatic vessels. Extrapolating this conclusion to humans, one could assume that the contact between the internal lymphatic system and islets is more pronounced in mice, due to a higher proportion of interlobular islets. The largest interlobular vessels, sometimes referred to as collecting vessels, reach the surface of the gland and drain into the external lymphatic system of the pancreas. There are no major structural differences between the intra- and interlobular lymphatic vessels. Both are lined by a continuous non-fenestrated endothelium supported by a discontinuous basal lamina, the latter being more prominent at sites where valves protrude into the lumen.

Both insulin and enzymes of the exocrine pancreas are found in the lymph leaving pancreas through the thoracic duct. Insulin enters the lymph by means of leakage from islets to interstitial fluid or directly through lymphatic vessels in close contact with an interlobular islet. The flow of lymph from the pancreas is low compared to blood flow and the concentration of insulin in the lymph is lower than in plasma. Thus, the mass flow of insulin to the systemic circulation via lymph is much less than via portal venous blood (probably less than 1% of total delivery). It should be kept in mind, however, that the insulin entering the bloodstream via lymph does not undergo the first pass metabolism in the liver. Thus, a role for this route cannot be excluded, particularly in hyperinsulinemic states, such as insulinoma. Evidence suggests that inadequate removal of extracellular fluid and pancreatic enzymes from interstitium by the lymphatic overflow system might play an etiological role in pancreatitis, which can in turn further damage the interstitium and lymphatic vessels, initiating a vicious circle.

The external lymphatic system

When the collecting vessels emerge on the surface of the pancreas they drain into the surface network of lymphatic vessels. From here, larger lymphatic vessels transport the lymph to the regional lymph nodes. There are 7 main groups of lymphatic vessels, each associated with a corresponding group of blood vessels: superior vessels (along the splenic blood vessels), inferior vessels (along transverse pancreatic artery), anterosuperior, anteroinferior, posterosuperior, posteroinferior pancreaticoduodenal vessels (along the corresponding arteries), and the gastroduodenal vessels. The first 2 drain the left part of the body and the tail, the latter 5 the right part of the body and the head of the pancreas. Due to its clinical importance in carcinoma, the external system has been studied extensively in humans. However, there exists controversy regarding nomenclature of lymph nodes, with a descriptive and an alternative numerical system. Here we briefly review the most important lymph node groups according to the descriptive system with their corresponding numerical notations in parentheses (Fig. 5). The lymph nodes of the pancreas are organized in 2 major groups. The first group of nodes lies approximately along the outline of the gland. Left to the aorta are the splenic and gastrosplenic nodes situated within and superior to the splenic hilus (10), as well as suprapancreatic (11) and infrapancreatic (18) nodes lying along the splenic and inferior pancreatic artery, respectively. These nodes receive lymph from the body and the tail of the pancreas. To the right of aorta, there are 5 main groups of nodes that drain the head. First, as an extension of the suprapancreatic nodes to the right side there are the hepatic (8) and hepatoduodenal (12) nodes. Along the superior and inferior anterior and posterior pancreaticoduodenal arteries lie the next 4 groups of nodes named the superior anterior (17a), superior posterior (13a), inferior anterior (17b), and inferior posterior (13b) pancreaticoduodenal nodes. The second major group of nodes are associated with abdominal aorta and its trunks, the paraaortic (16), celiac (9), superior mesenteric (14), and the middle colic nodes (15). Nodes 1–7 belong to the perigastric lymph nodes and are believed not to drain the pancreas.

Four out of 5 patients with pancreatic carcinoma display lymph node involvement. Rich anastomoses between lymphatic vessels that promote fluid drainage make predictions about the exact routes of spreading of pancreatic cancer practically impossible. In carcinoma of the body and tail of the pancreas, nodes 8, 11, 16 and 18 are most frequently involved by metastatic spread and only nodes 17 have been spared in all cases. In carcinoma of the head, nodes 13, 17, 14, and 16 are involved most often, and only nodes 10 and 15 have been

137,138 138,139 137,138,140 137,138,141 137,138,142
spared and nodes 11 and 18 have been involved only in cases of cancers extending to the neck or body. It has been demonstrated that the embryological origin of the tissue influences the spread of cancer of the head of the pancreas. Tumors confined to the part of the head stemming from the ventral pancreas spread to nodes around the superior mesenteric artery (14), whereas tumors confined to the part of the head stemming from the dorsal pancreas spread to nodes around the common hepatic artery (8) and in the hepatoduodenal ligament (12).

All of the lymph is eventually drained into the left subclavian vein via cisterna chyli and the thoracic duct.

Data on the internal lymphatic system in humans and the external lymphatic system in mice are lacking. Thus, differences between the lymphatic systems of mice and men are largely unexplored. Given the practical importance of the lymphatic system in pancreatitis and cancer, further research in this field is called for.

**Innervation**

The pancreas is richly innervated by sympathetic, parasympathetic, and afferent fibers. Nerve fibers enter or exit pancreas as neurovascular stalks, follow the blood vessels also within the pancreatic tissue and end or begin close to capillary walls and endocrine cells. They do not form classical synapses with target cells, but have release sites from which they presumably release neurotransmitters into the extracellular space and influence more than one target at a time.

Autonomic nerves are believed to mediate the insulin response during the cephalic phase of feeding as well as to contribute to the increase in glucagon and the decrease in insulin secretion during sympathetic stimulation in animals and humans.

Due to recent advancements in experimental approaches enabling studies of many cells at a time in situ in isolated islets and thick tissue slices as well as in vivo, a clearer picture of the structure and function of the nervous system within pancreas is beginning to emerge, together with differences between mice and humans.

**Sympathetic efferent fibers**

Cell bodies ofpreganglionic sympathetic nerves are located in the lateral horn of the thoracic and the upper lumbar segments of the spinal cord (C8-L3) (Fig. 6). The myelinated axons of these cells project to ganglion cells in the paravertebral sympathetic ganglia. However, some neurons pass the paravertebral ganglia without forming a synapse. These neurons travel via the splanchnic nerves to form synapses within the prevertebral sympathetic ganglia, i.e., the celiac ganglia and the superior mesenteric ganglion. Additionally, intrapancreatic sympathetic ganglia have been reported.

The fibers projecting from the prevertebral ganglia reach the pancreas either within the mixed autonomic nerves or directly. In humans, the body and the tail of the pancreas are innervated from nerve fibers originating in the celiac plexus and accompanying 2 arteries: the splenic artery around which they form the so called splenic plexus, and the transverse pancreatic artery (Fig. 7). More recently, a nerve that enters the pancreas independently of the celiac ganglion/plexus was described. This nerve winds around the main pancreatic duct rather than following blood vessels. The head of the pancreas receives the majority of nerve fibers.
innervated from the anterior hepatic plexus distributed along
the common hepatic artery, and from the posterior hepatic
plexus at the dorsal aspect of the portal vein, both of which
originate from the celiac plexus. Nerves derived from the
superior mesenteric ganglion follow the inferior PDA and
enter the uncinate process. In mice, distribution of auto-
nomic nerves is largely homologous to the one in
humans, but with nerve densities more equally distrib-
uted among different lobes.

As already mentioned, lymph node involvement is one of the
most important prognostic factors in pancreatobiliary tract carci-
nomas. In general, lymph node metastasis is established by lym-
phatic invasion, however, tumor cells were shown to be able to
spread into the hilum of lymph nodes via neural invasion. The
knowledge of patterns of neural architecture may improve cura-
tive procedures. Moreover, embryological development of the
pancreas served as a useful template for patterns of extrapancre-
atic nerve plexus invasion of pancreatic head carcinoma.

In the exocrine pancreas, the sympathetic axons contact pre-
dominantly the intrapancreatic ganglia, blood vessels, and exo-
crine ducts and inhibit the exocrine secretion indirectly via
inhibiting stimulatory influences from ganglia and via vasocon-
striction diminishing the blood flow. In mice, however, innerva-
tion of the acinar tissue is rather poor.

In the islets in mice, major nerves running along interlobular
arteries branch to form nerve plexuses toward the islets. Sympa-
thetic axons are in contact with alpha cells, but not beta cells
(Fig. 8). Additionally, they innervate vessel smooth muscle cells
and the perivascular space, forming the so called sympathetic neuro-
vascular complex.

In humans, the sympathetic fibers only sparsely contact the endo-
crine cells directly. Rather, they preferentially innervate vascular
smooth muscle cells. The above findings suggest that in addition to
the direct effect on endocrine cells in mice, the sympathetic nervous
control of the endocrine pancreas is indirect, via controlling blood
flow to the islet (similar to the sympathetic influence in the exocrine
pancreas) or by acting on targets distant from the release site (similar
to the communication pathway in the pituitary gland).

Splanchnic nerve stimulation increases the release of glucagon
and inhibits the release of insulin and somatostatin from the pan-
creas. The effects of splanchnic nerve stimulation are rather con-
tradictory for the pancreatic polypeptide. Supporting the
idea that the effects of catecholamines are at least partially mediated via release
into islet blood vessels is the finding
that sympathetic stimulation increases
the concentration of noradrenaline in
the pancreatic vein. Since the pancre-
atic veins drain into the portal system,
this spillover could contribute to the
metabolic effects of catecholamines in
the liver.

Parasympathetic efferent fibers
The preganglionic fibers of the para-
sympathetic limb originate in 2 nuclei
of the medulla oblongata: the dorsal
motor nucleus of vagus and the nucleus
ambiguus (Fig. 6). The efferent
fibers exit medulla as the bulbar outflow
tract, travel mainly along the vagus
nerve and to a smaller extent within the
splanchnic nerves. The efferent fibers
enter the pancreas either directly or
indirectly after traversing the celiac

Figure 7. Macroscopic autonomic innervation of the pancreas. 1: the
splenic plexus accompanying the splenic artery; 2: the plexus accompa-
nying the transverse pancreatic artery; 3: the plexus around the main
pancreatic duct; 4: the anterior hepatic plexus; 5: the posterior hepatic
plexus.

Figure 8. The autonomic innervation of islets of Langerhans. (A) In mice, the postganglionic sympa-
thetic fibers contact ρ cells and smooth muscle cells of the blood vessels, whereas the parasympa-
thetic fibers contact all endocrine cell types. (B) In humans, the islets are sparsely innervated. The
sympathetic and parasympathetic postganglionic fibers preferentially contact vascular smooth muscle
cells and exocrine tissue, respectively.
ganglion without forming a synapse (Fig. 7). In both cases these fibers join the neural plexuses along arteries and intermingle with the sympathetic fibers.\textsuperscript{164} Macroscopic innervation in mice is similar to the one in humans.\textsuperscript{165} The vagal fibers enter the pancreas along the vessels reaching intrapancreatic ganglia that contain 2–30 neurons and are positioned within the interlobular connective tissue, lobules, and islets.\textsuperscript{126,146} Importantly, in addition to the input from parasympathetic preganglionic fibers, neurons within the intrapancreatic ganglia receive input from other pancreatic ganglia, sympathetic fibers, the myenteric plexus, as well as the sensory fibers (see below).\textsuperscript{126}

In the exocrine part of the pancreas, short unmyelinated postganglionic fibers extend from multiple poles of the intrapancreatic ganglia to the acinar and ductal epithelial cells, ductal smooth muscle cells, to vascular plexuses, as well as to other ganglia. Activation of these fibers stimulates secretion from acinar and ductal cells, constriction of ducts, as well as vasodilation.\textsuperscript{126,146} As mentioned above, the scarce innervation of the acinar tissue in mice may imply a major role for hormonal control of exocrine secretion in rodents.\textsuperscript{150}

In the islets, postganglionic axons reach to all types of cells in the mouse (Fig. 8).\textsuperscript{127,146} Recently, it was suggested that the pattern of parasympathetic innervation in humans is different from the one in mice. First, in contrast to mice, only a few parasympathetic axons penetrate the islet in humans and most of the axons terminate in the exocrine tissue.\textsuperscript{127} Second, it was demonstrated recently that human beta and delta cells respond to stimulation with acetylcholine, whereas alpha cells are poorly responsive to acetylcholine.\textsuperscript{172} However, this does not rule out the possibility that human alpha cells might respond to neuropeptides released from parasympathetic fibers.\textsuperscript{146,173} Interestingly, alpha cells themselves are supposed to be the main source of acetylcholine in human islets.\textsuperscript{174} Here, this classical neurotransmitter probably assumes the role of a paracrine signal controlling endocrine, vascular, and immune cells.\textsuperscript{175}

Generally, parasympathetic activation is believed to increase the release of insulin, glucagon, somatostatin, as well as the pancreatic polypeptide in various species, although the exact contributions of acetylcholine and neuropeptides to these effects remain to be determined.\textsuperscript{146,148} The pancreatic polypeptide is often used as a specific marker of parasympathetic stimulation of islets, since it is released from the islets only by vagal stimulation. However, as mentioned previously, it is released from a subpopulation of gamma cell-rich islets in the head of the pancreas and thus cannot be regarded as representative of all islets.\textsuperscript{148}

### Afferent fibers

In humans, the islets also contain sympathetic afferent fibers that are sensitive to capsaicin and contain substance P (SP) or calcitonin gene-related product (CGRP) as neurotransmitters. They exit the pancreas within the sympathetic splanchnic nerves and transmit noci- and mechano-receptive sensory information to cell bodies within the dorsal root ganglia and further on to preganglionic sympathetic neurons in the spinal medulla (lateral horn) (Fig. 6).\textsuperscript{126} These fibers innervate the exocrine as well as the endocrine tissue and may play a role in pancreatitis and diabetes mellitus,\textsuperscript{126,148} as well as in pain accompanying pancreatic cancer or pancreatitis.\textsuperscript{149} In mice, similar to humans, these fibers also arise from DRG and exit the pancreas via the splanchnic nerve.\textsuperscript{149,166}

Cell bodies of vagal afferent neurons are located within the nodose ganglia in humans (Fig. 6). Similarly to the sympathetic afferents, these cells are sensitive to capsaicin and contain SP and/or CGRP. They innervate the blood vessels, ducts, acini, and islets. At present, centripetal pathways of these neurons are not known.\textsuperscript{126} In mice, this route is most likely of less importance.\textsuperscript{149,166}

Dorsal root ganglion sympathetic afferent neurons send collaterals to efferent ganglia, representing a neuroanatomical substrate for monosynaptic vegetative reflexes. For example, SP and

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### Table 1. Summary of differences between the mouse and the human pancreas.

| Scale          | Property                           | Mouse                     | Human                         |
|----------------|------------------------------------|---------------------------|-------------------------------|
| Organ          | Anatomical type                    | Diffuse/dendritic, lobular, soft | Solitary, compact, firm       |
| Ducts          | Main duct joins with the bile duct proximal to the entry into duodenum | Main duct joins the bile duct at the point of entry into the duodenum  |
| Tissue         | Diameter of lobules                | 0.5–1.5 mm                | 1–10 mm                       |
|                | Diameter of islets                 | Single cells to 500–700 μm | Single cells to 500–700 μm    |
|                | Number of islets                   | 1,000–5,000               | 1,000,000–15,000,000          |
|                | Location of islets                 | More random, interlobular | Uniform, intralobular         |
|                | Microvascular pattern              | Insulo-venous system prevails, insulo-acinar portal system also present | Insulo-acinar portal system prevails |
| Cells          | Order of perfusion                 | Center-to-periphery (66%), and polar | Most likely polar             |
|                | % of β and α cells                 | Beta cells: 60–80 %       | Alpha cells: 50–70 %          |
|                |                                   | Alpha cells: 10–20 %      | Alpha cells: 20–40 %          |
|                | Microarchitecture of islets        | Mantle islets predominate | Trilaminar islets predominate |
|                | Sympathetic fibers                 | Scarce innervation of exocrine tissue | Rich innervation of exocrine tissue |
|                | Contact with α cells and vascular smooth muscle cells | Contact with vascular smooth muscle cells |
|                | Parasympathetic fibers             | Scarce innervation of exocrine tissue | Contact with vascular smooth muscle cells |
|                |                                   | Contact all types of endocrine cells | Rich innervation of exocrine tissue |
|                |                                   | Contact β and delta cells, possibly α cells | Contact β and delta cells, possibly α cells |
CGRP released at intrapancreatic ganglia inhibit exocrine secretion. Intrapancreatic ganglia are also contacted by vagal afferents.\textsuperscript{126}

The functional studies showing similar systemic effects of the autonomic nerves in mice and humans imply that if structural differences do exist between islets of mice and humans, they are either not great enough to significantly impact the function or are coupled with differences at the level of signaling that, together with the morphological differences, produce a similar physiological response at the systemic level.

Other cells

The islet is sheathed with a capsule that is composed of collagen and glia.\textsuperscript{13} Other cells found throughout islets are the pericytes, macrophages, and dendritic cells.\textsuperscript{13,175-177}

A short summary of the most important similarities and differences

Table 1 summarizes the major hallmark differences and similarities between the mouse and human pancreas tissue.

Conclusions

The morphological differences between human and mouse pancreatic tissue seem to be numerous and call for inclusion of human tissue into basic and applied research. We suggest that in analyzing and reporting interspecies differences, the intra- and interspecies variability both be considered and accounted for whenever this is practically achievable. Future research is also expected to shed new light on interstrain and interindividual differences. A detailed presentation of islet development and structure in the prenatal period is beyond the scope of this paper. Thus, we mainly focused on data relevant for explaining differences in the postnatal period. Additionally, we limited ourselves to structural aspects. The emerging developmental, physiological, and pathophysiological intra- and interspecies differences, such as in gene expression,\textsuperscript{2,106,178-181} in functional phenotypes,\textsuperscript{5,42,64,161,182,183} and in disease progression,\textsuperscript{64,184-187} deserve separate reviews.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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