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RETRAINING REVIEW

Development of the human pancreas and its vasculature — An integrated review covering anatomical, embryological, histological, and molecular aspects

Brandon Michael Henry, Bendik Skinningsrud, Karolina Saganiak, Przemysław A. Pękala, Jerzy A. Walocha, Krzysztof A. Tomaszewski*

Department of Anatomy, Jagiellonian University Medical College, Kraków, Poland

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ABSTRACT

Objectives: The aim of this study was to provide a comprehensive overview of the clinically relevant anatomical and histological aspects of the development of the human pancreas, with emphasis on the vascularization of the gland.
Methods: A comprehensive search on the relevant aspects of pancreatic biology was performed through the main electronic databases up to August 2017. Data from all relevant articles was gathered, analyzed and included in this narrative review.
Results: This review outlines the main topics on embryology, anatomy, histology, and molecular biology of the microcirculation of the human pancreas. The first part describes in detail the development of the pancreas synthesizing anatomical knowledge with findings of novel molecular studies. The second and third parts give information on the organization of arterial and venous pancreatic circulation. The final part summarizes the most important findings concerning pancreatic microcirculation. All parts taken together create a comprehensive and up-to-date description of the development and organization of the blood supply to the human pancreas.
Conclusions: Detailed knowledge on the physiological development of the pancreas and anatomy of its blood supply play a key role in understanding the pathophysiology of various pancreatic disorders and is crucial for developing novel therapies for pancreatic disorders.

Contents

* Corresponding author at: Department of Anatomy, Jagiellonian University Medical College, 12 Kopernika St, 31-034 Krakow, Poland.
E-mail address: krtomaszewski@gmail.com (K.A. Tomaszewski).

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1. Introduction

The pancreas of an adult human has an average volume of 72 cm^3 (parenchyma — 44 cm^3, fat — 28 cm^3) (Saisho et al., 2007), measures 12–20 cm in length, 3–5 cm in height, and 1–3 cm in width (Quinlan 1991). The shape of the pancreas is elongated, resembling a hook or a hammer. Macroscopically, it can be divided into four parts — the head, neck, body, and tail. The pancreas is a secondarily retroperitoneal organ located on the posterior wall of the abdominal cavity (Fig. 1). The head of the pancreas is surrounded by the duodenum, the neck is located near the superior mesenteric vessels, the body lies behind the posterior wall of the stomach, and the tail extends to the hilum of the spleen (Van Hoe and Claikens, 1999). The pancreas, in contrast to most glands in the human body, does not have a distinct fibrous capsule (Van Hoe and Claikens, 1999).

The pancreatic duct (duct of Wirsung) originates in the tail of the gland, runs across the entire organ, and connects with the common bile duct. This union is called the hepatopancreatic ampulla (ampulla of Vater), and it is located on the major duodenal papilla. A patent accessory pancreatic duct (duct of Santorini) may be present in 41–52.5% of the population (Prasanna et al., 2015). This duct most often drains to the duodenum via the minor duodenal papilla or, in 30% of cases, to the pancreatic duct (Van Hoe and Claikens, 1999).

The pancreas is a complex gland composed of both endocrine and exocrine parts. The enzyme-producing exocrine cells that form acini are conical in shape and arranged around a central lumen. The lobules of the pancreas consist of the acini which are separated by connective tissue containing capillaries. The intercalated ducts connect the acini to the intralobular ducts, which drain to the interlobular ducts. The proximal part of this duct system is lined with simple squamous epithelium; the distal part is lined with simple cuboidal epithelium. The larger interlobular ducts and the main ducts are lined with columnar epithelium and contain mucous-producing cells (Dubois, 1999).

The pancreas consists of two parts integrated into one anatomical structure. The exocrine component of the pancreas secretes the pancreatic juice (approx. 1200–1500 ml per day (Hall and Guyton, 2010)) that contains water, bicarbonate ions (determining its alkaline reaction) and a variety of enzymes, including trypsinogen, chymotrypsinogen, carboxypeptidases, elastase, lipase, phospholipase A, amylase, DNAse and RNAse (Bernard, 1999). The pancreatic juice is excreted to the duodenum via the pancreatic duct(s).

The endocrine component consists of five types of cells producing at least five types of hormones: alpha cells secrete glucagon, beta cells secrete insulin, delta cells secrete somatostatin, PP (gamma) cells secrete pancreatic polypeptide, and epsilon cells secrete ghrelin. The secreted hormones are transported via the bloodstream to their destined organs and tissues (Dubois, 1999). The small clusters of endocrine cells were first described by Langerhans (1869). Today, the endocrine part of the pancreas is customarily called the islets of Langerhans (Zimmermann, 1927). The majority of islets are spherical; however, they may also be flat or elongated. They range in diameter from 50 to 500 μm, and islets measuring 100–200 μm contribute to the bulk of the volume (Buchwald et al., 2009). The greatest number of islets can be found in the body and the tail of the pancreas. There are about 1 million islets in the pancreas of a human, which accounts for 1–2% of the pancreas mass (Tomita, 2002).

The aim of this review is to provide a comprehensive overview of the anatomical and histological aspects of the development of the human pancreas, with emphasis on the vascularization of the gland.

2. Development of the glandule

Development of the pancreas is similar to that of other glands. First, the duct appears, and then cells implant around it and create lobules. The endodermal epithelium of the duodenum gives rise to the endo- and exocrine parts of the pancreas. The germs of the glandule grow from the duodenum as two buds, ventral and dorsal, at the turn of the second and third gestational week, when the embryo length is about 3–4 mm (Russu and Vaida, 1959). Some authors state that there are two separate ventral buds: right and left (Kamisawa et al., 2001). The right ventral bud, which is located between the duodenum and the bud of the common bile duct, endures, while the left ventral does not develop and gradually disappears. The dorsal bud is larger and located higher than the above-mentioned ventral buds. It develops towards the spine and settles between laminas of the dorsal mesentery of the duodenum and the stomach, creating the superior part of the head, whole body and tail of the pancreas (Van Hoe and Claikens, 1999).

The rotation of the stomach and the duodenum during embryogenesis cause a shift of the ventral bud to the dorsal direction, and from the right to the left side of the embryo (Fig. 2). In the end, the ventral bud is located under and behind the dorsal bud. It creates the inferior part of the head, and the uncinate process of the pancreas. Each bud has its own independent duct (Tadokoro et al., 2011). Then, during the 7th week of gestation, the two buds fuse tightly (Rizzo et al., 1995). Part of the duct of the dorsal bud in the duodenal segment undergoes atrophy, while the remaining part of the duct, with the duct of the ventral bud, forms the pancreatic duct which communicates with the duodenum via the major duodenal papilla (Fig. 3A). If the duodenal segment of the dorsal bud duct does not regress, it makes a short canal called the accessory pancreatic duct, which has an independent meatus via the minor duodenal papilla (Russu and Vaida, 1959).

However, when the two buds do not fuse, a pancreas divisum occurs — which is the most common congenital variant of pancreatic development, affecting about 10% of the population and 3%–7% of patients undergoing ERCP (Lehman and Sherman, 1998; Mortelé et al., 2006). In pancreas divisum, the duct of the dorsal bud remains and drains the majority of the pancreas via the minor duodenal papilla, while the ventral duct drains the inferior portion of the head via the major papilla (Klein and Affronti, 2004) (Fig. 3B). Although the majority of individuals with pancreas divisum are asymptomatic, there are several conditions linked to this pancreatic anomaly, including acute recurrent pancreatitis, chronic pancreatitis and pancreatic-type pain (Klein and Affronti, 2004). A possible pathophysiological explanation could be that some patients with pancreas divisum have a stenotic minor papilla and develop an outflow obstruction with resulting pancreatitis (Klein and Affronti, 2004).

In the second and third gestational month, parenchyma of the pancreas differentiates (Pan and Brissova, 2014). From the main pancreatic ducts bud the secondary ducts, and from these, smaller ducts form around which the endodermal cells implant, creating the pancreatic lobules. In the third gestational month, the glandule divides into the endo- and exocrine parts. Small groups of cells organized in stands separate from the pancreatic ducts (Zhou et al., 2001). Then, dense capillaries and connective tissue surround the strands creating the future islets of Langerhans (Pan and Brissova, 2014). The islets are located in the part originating from the ventral pancreatic bud, mainly in the body and the tail of the pancreas (Wang et al., 2013).

During development, the pancreas changes its location from the intraperitoneal to secondarily retroperitoneal (except for the tail, which is placed in the splenorenal ligament). The proximity of the pancreatic bud to the stomach and duodenum results in a possible appearance of the heterotopic pancreatic tissue in the gastrointesti-

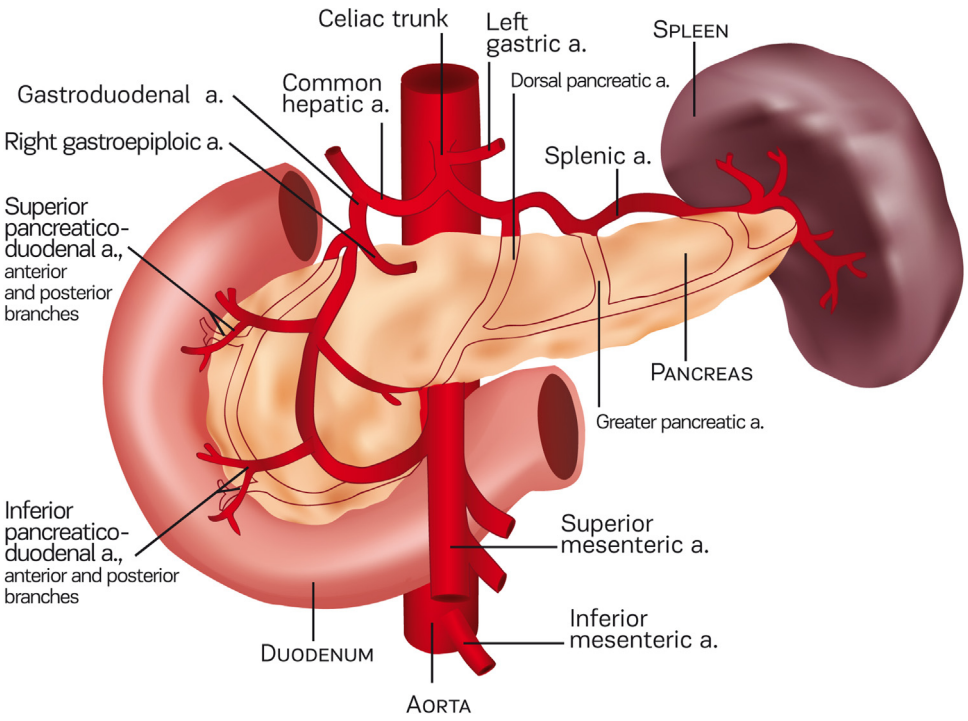

Fig. 1. Gross anatomy of the pancreas.

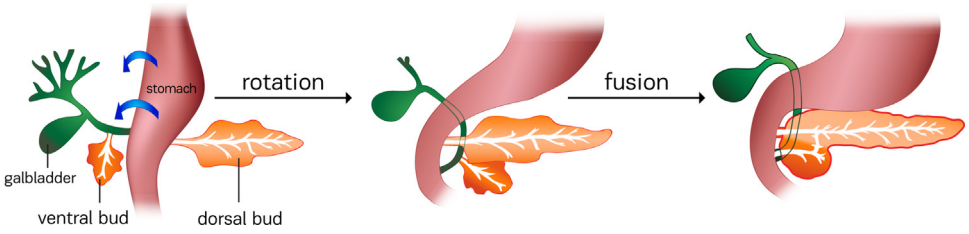

Fig. 2. Development of the pancreas.
The rotation of the stomach and the duodeum leads to a shift of the ventral bud. In the end, the ventral bud is located under and behind the dorsal bud. During the 7th week of gestation, the two buds fuse tightly.

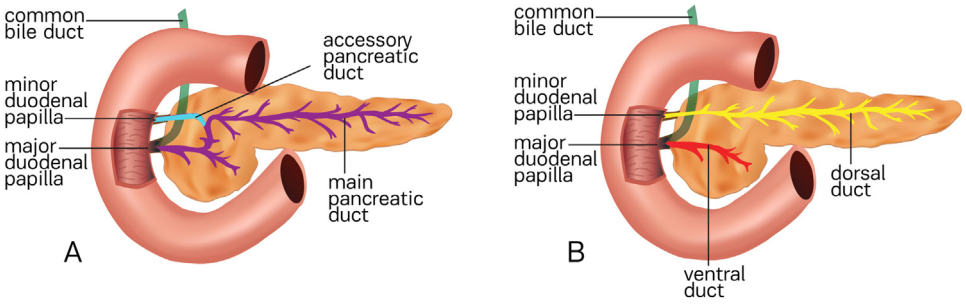

Fig. 3. Anatomy of the pancreatic ducts.
A — normal anatomy (purple: main pancreatic duct, blue: accessory pancreatic duct), B — pancreas divisum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nal tract between the abdominal part of the esophagus and the splenic flexure of the colon. The most common groups of heterotopic pancreatic cells are found in the stomach mucosa and in the Meckel's diverticulum (Yuan et al., 2009).

Changes in the location of the pancreas during its development may lead to pancreatic anomalies. Annular pancreas is a rare congenital anomaly (affecting about 1 out of 12000–15000 liveborn neonates (Lainakis et al., 2005)) where the pancreas forms a ring around the duodenum, impairing intestinal patency. The formation of annular pancreas was first explained by Lecco (1910). If adherence of the ventral pancreatic bud to the duodenum occurs, the subsequent rotation of the ventral bud is abnormal and results in the encirclement of the duodenum (Fig. 4). An alternative explanation was reported by Baldwin: if the left ventral pancreatic bud fails to involute, it may lead to the formation of annular pancreas (Baldwin, 1910). The usual manifestations of annular pancreas include duodenal atresia in neonates (De Ugarte et al., 2006) and duodenal obstruction, pancreatitis, or peptic ulcers in adults, how-

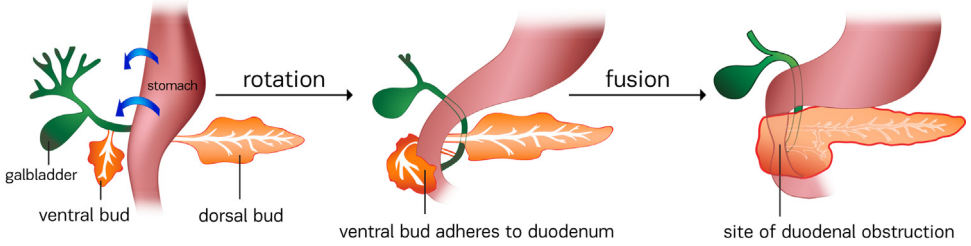

Fig. 4. Formation of the annular pancreas according to Lecco's theory.
If the ventral pancreatic bud adheres to the duodenum, the subsequent rotation results in pancreatic tissue surrounding the duodenum.

ever, obstructive jaundice or malignancy may occur as well (Ji et al., 2015).

In the human pancreas, endocrine cells can be detected around the 7–8th week of gestation. The insulin-expressing cells are the first to appear and they remain the prevailing endocrine cell population during the first trimester (Jennings et al., 2013; Piper et al., 2004; Riedel et al., 2012). Glucagon-expressing cells and somatostatin-expressing cells emerge at 8th week of gestation, while pancreatic polypeptide and ghrelin-expressing cells appear at 9th week (Pan and Brissova, 2014). A study by Riedel et al. (2012) revealed that the endocrine cell population consist of cells that are capable of producing more than a single hormone. With respect to insulin and glucagon, at least three major cell populations can be distinguished: insulin-only cells, glucagon-only cells, and cells that produce both hormones. The cells producing both insulin and glucagon can be observed not only in the fetal pancreas, but also in the adult pancreas. In the fetal pancreas, this cell population is the largest between 11 and 13 weeks and comprises almost 30% of pancreatic cells capable of producing insulin and/or glucagon (Riedel et al., 2012). In the adult pancreas, the population of cells capable of producing both hormones simultaneously is less than 2%. Between 9 and 16 weeks, the prevalence of glucagon-only cells increases, while the insulin-only cell population decreases. Jeon et al. (2009) have suggested that glucagon-positive cells exhibit more proliferative potential, while the insulin-positive cells are less proliferative during this period.

At the 21st week, the proportions of these three cell populations are similar to the composition of an adult pancreas. The same study by Riedel et al. found that in the earlier stages of fetal development, somatostatin and pancreatic polypeptide (PP) can be detected in cells producing insulin and glucagon, however, by 15 weeks, somatostatin-expressing cells and PP-expressing cells were separate, distinct cell populations. The expression of ghrelin was not linked with the production of glucagon or insulin, which could imply that ghrelin-expressing cells arise from a separate cell line (Riedel et al., 2012).

The signaling pathways which regulate human pancreas development are complex (Fig. 5). Jennings et al. (2015) suggest that the transcription factor network of human pancreatic development is similar to that of other mammals. In a human embryo, sonic hedgehog (SHH), as well as pancreatic and duodenal homeobox factor 1 (PDX1) can be detected at approximately the fourth gestational week (Jennings et al., 2015). At the fifth gestational week, the ventral and dorsal pancreatic buds are marked by several transcription factors necessary for pancreatic development: PDX1, GATA binding protein 4 and 6 (of the GATA family) and SOX9 (Piper et al., 2004; Shaw-Smith et al., 2014; Stoffers et al., 1997).

From the eighth gestational week, pancreatic duct cells can be characterized by the presence of SOX9, FOXA2 and PDX1. In the endocrine cells, especially in the developing beta cells, NEUROG3 expression increases. Acinar cells, differentiating from the pancreatic bud cells in a separate cell line, have significant GATA4 levels (Jennings et al., 2015).

Numerous mutations in transcription factors are known to cause permanent neonatal diabetes mellitus (PNDM) (Jennings et al., 2015). The first mutated transcription factor to be identified was PDX1 (pancreatic and duodenal homeobox 1), which is necessary for proper pancreatic development and β-cell maturation (Stoffers et al., 1997). A homozygous point mutation in the PDX1 gene can lead to a frame shift causing agenesis of the pancreas, which results in an exocrine pancreas deficiency and hyperglycemia requiring insulin (Jennings et al., 2015).

Homozygous inactivating mutations in NEUROG3 may also be a cause of neonatal diabetes and congenital diarrhea (Pinney et al., 2011; Rubio-Cabezas et al., 2011; Wang et al., 2006). The protein encoded by this gene, Neurogenin-3, is expressed in endocrine progenitor cells and is important for the development of the pancreas and intestines. Mutations in NEUROG3 cause an arrest in endocrine cell development in pancreas, small intestine and colon, leading to an intestinal failure and malabsorption of all nutrients, except water (Cortina et al., 2007).

Defects in Notch signaling pathway and its effector SOX9 lead mostly to biliary abnormalities, however, exocrine pancreas insufficiency has also been reported (Krantz et al., 1997). Other significant transcription factors that can be affected include PTF1A, in which a mutation results in pancreatic and cerebellar agenesis (Sellick et al., 2004) or GATA6, in which mutations result in hypoplasia or agenesis of pancreas and cardiac malformations (Allen et al., 2011).

3. Development of the arterial circulation

The fetal vascular system develops through two separate mechanism of morphogenesis: vasculogenesis and angiogenesis (Patan, 2000).

Vasculogenesis begins with the emergence of angioblasts from the mesoderm. Angioblasts migrate separately or in small clusters to specific parts of the embryo and the yolk sac (Patan, 2004, 2000). Katsumoto and Kume (2011) reported that the chemokine receptor CXCR4 regulates the migration of blood vessel progenitors. The angioblasts expressing CXCR4 migrate to the pre-pancreatic endodermal region in a chemotactic process, recruited by the CXCL12 ligand expressed by the gut endoderm. After reaching their allocated destinations, the cells adhere to each other, forming embryonic blood vessels (Katsumoto and Kume, 2011). The process of vasculogenesis results in the formation of the primary vascular system of the embryo, consisting of the heart, aorta, common cardinal veins, blood vessels of the yolk sac, primary vessels of the developing organs, and blood cellular components (Cleaver and Dor, 2012). The evolution of this primary vascular system into the mature one involves remodeling of the existing vessels and requires the development of new vessel segments via angiogenesis (Cleaver and Dor, 2012; Katsumoto and Kume, 2011).

There are two major mechanisms of angiogenesis, intussusceptive angiogenesis and sprouting angiogenesis (Carmeliet, 2003; Djonov et al., 2002; Kurz, 2000; Kurz et al., 2003; Patan et al., 2001; Tomanek and Schatteman, 2000), with the latter being the domi-

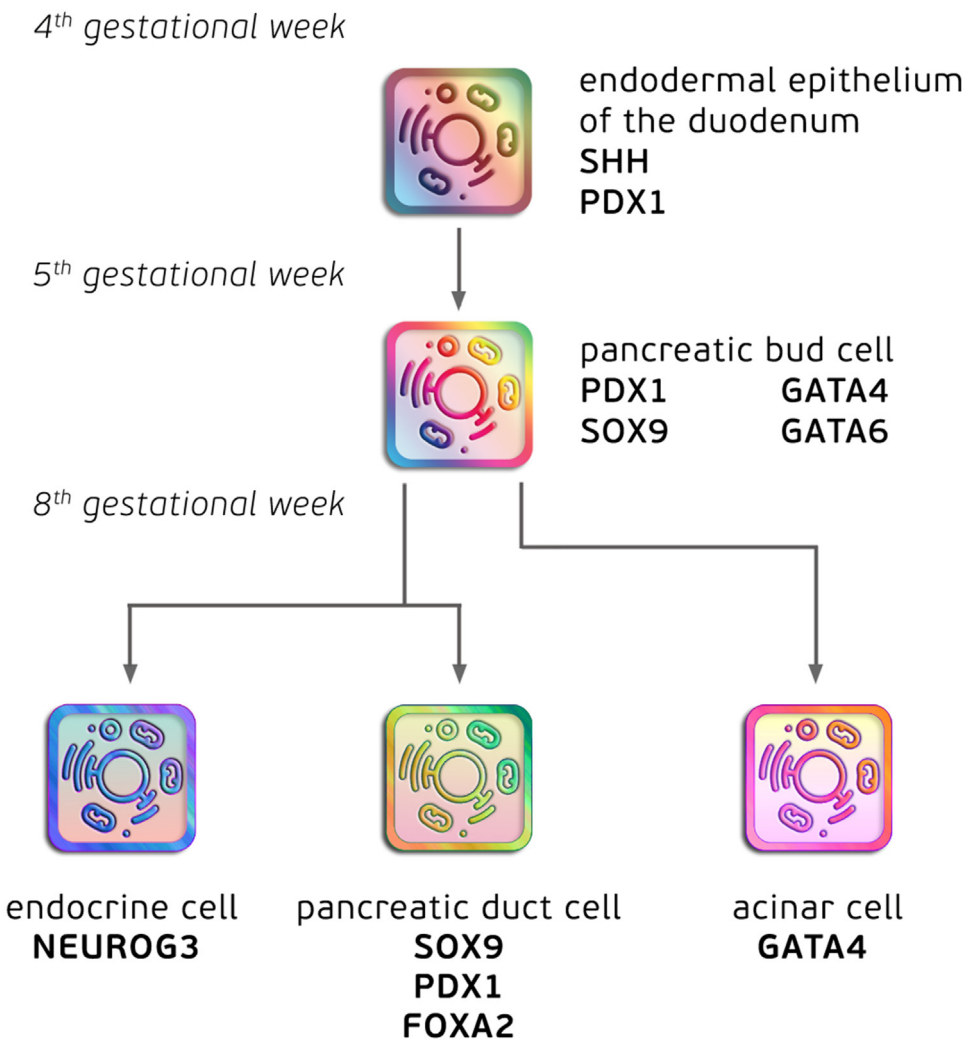

Fig. 5. Major signaling pathways and transcription factors involved in pancreatic development (adapted from Jennings et al., 2013, 2015).

nant process in pancreatic development (Narayanan et al., 2017). During intussusception, the endothelial cells at the opposing walls of a vessel begin to grow into the lumen, splitting a single vessel in two. On the contrary, sprouting angiogenesis starts with the proteolytic degradation of the vascular basement membrane, followed by proliferation and migration of endothelial cells into the connective tissue (Ribatti and Crivellato, 2012). The proliferating endothelium first creates a solid bud, which later develops a lumen and becomes a new capillary. If a budding vessel connects to a pre-existing one, a new route for blood circulation is created, which is stabilized by the cells of the vessel wall, i.e. pericytes (Carmeliet, 2003; Patan, 2000; Tomanek and Schatteman, 2000; Zakrzewicz et al., 2002).

Over the past couple decades, many angiogenic factors have been found, including the family of vascular endothelial growth factor (VEGF) and their specific receptors (VEGFR), fibroblast growth factor (FGF), angiopoietins and their receptors, the family of ephrins (determining the formation of arteries or veins) and others (Adams, 2003; Carmeliet, 2003; Folkman and D'Amore, 1996; Hardikar et al., 2003; Lammert, 2001; Lammert et al., 2003; LeCouter et al., 2001; Sato et al., 2002; Tang et al., 2001; Yancopoulos et al., 2000). Vascular endothelial growth factor A (VEGFA) is one of the most widely described angiogenic factors. VEGFA recruits blood vessels and stimulates vessel ingrowth. Furthermore, it also regulates cell differentiation and pancreas branching via reciprocal signals (Cleaver and Dor, 2012). Pierreux et al. (2010) reported regionalized expression of VEGFA during pancreatic development in mice. VEGFA expression in the pancreatic epithelium can be described as heterogenous: It becomes predominant in trunk (central) cells of the epithelium and decreases in tip cells located at the end of the branched ducts. As a result, the endothelial cells are located in close proximity to the trunk cells of the epithelium (Pierreux et al., 2010). Magenheim et al. (2011) showed that hypervascularization using VEGFA overexpression resulted in reduced branching and growth of the pancreas. This resulted in limited formation of acinar and endocrine cells (Magenheim et al., 2011).

The vasculature of the pancreas during its embryogenesis is strongly associated with the vasculature of the anterior and middle parts of the primitive gut (Villasenor and Cleaver, 2012). Three groups of branches arise from the aorta: ventral splanchnic, lateral splanchnic and dorsal somatic branches. The ventral splanchnic branches form a vertical anastomosis anterior to the aorta, which surrounds the dorsal and ventral aspects of the gut. The celiac trunk is formed from the initial part of the anastomosis, while the superior mesenteric artery is formed from its terminal part. The development of the superior mesenteric artery finishes when the vitelline circulation stops. During embryogenesis, the blood vessels of the gut move caudally: The celiac trunk descends from the level of C_7 to Th_{12}, and the superior mesenteric artery descends from Th_2 to L_1 (Datwyler, 1967).

The pancreas is supplied by branches of the celiac artery and the superior mesenteric artery (Fig. 1). In the classic vasculature of the pancreas, the common hepatic artery arises from the celiac trunk and bifurcates into the proper hepatic artery and gastroduodenal artery. The gastroduodenal artery branches off the right gastroepiploic artery and the superior pancreaticoduodenal artery divides into anterior and posterior branches.

The inferior pancreaticoduodenal artery is the first branch of the superior mesenteric artery and it divides into anterior and posterior branches. The posterior branch anastomoses with the posterior branch of the superior pancreaticoduodenal artery, forming the posterior pancreaticoduodenal arch. The anterior branch of superior pancreaticoduodenal artery runs between the head of pancreas and duodenum, and anastomoses with the anterior branch of inferior pancreaticoduodenal artery, forming the anterior pancreaticoduodenal arch (Bertelli et al., 1997).

The splenic artery gives off multiple branches to the pancreas, as it passes behind the upper border of the gland (Madoff et al., 2005). The major branches are the dorsal pancreatic artery and the greater pancreatic artery, which arises from the middle segment of the splenic artery. The common hepatic artery can also give off small pancreatic branches supplying the head of the pancreas (Fiedor et al., 1989; Marni et al., 1985).

The developmental process of the visceral vessels involves their reduction and relocation resulting in great variability of the blood supply to the gut (Villasenor and Cleaver, 2012). The variations are mostly related to the celiac trunk, less often to the superior mesenteric artery. The diversity of branching patterns of the aforementioned vessels determines the pancreatic blood flow, which affects the endocrine and exocrine function of pancreas. Zhou et al. (2001) suggested that an impaired pattern of insular drainage vessels could be the morphological basis of the pancreatic exocrine pathologic lesion observed in human diabetes. Understanding the developmental process of visceral vessels is essential for successful transplantation of pancreatic islets (Barker et al., 2013).

4. Development of the venous circulation

The venous system develops simultaneously with the arterial system at the end of 3rd gestational week (Azizoglu et al., 2016). The venous blood vessels originate from the vessel network of the embryo and its amniotic sac. Vitelline veins of the yolk sac drain to the sinus venosus. The branches of the umbilical veins in the chorionic villi carry oxygenated blood to the embryo and also drain to the sinus venosus (Benoist et al., 2007). In the embryo, two pairs of common cardinal veins are formed. The anterior cardinal veins drain the cephalic region of the embryo, the posterior cardinal veins drain the body regions below the heart. The anterior and posterior cardinal veins anastomose, forming the common cardinal veins that drain to the sinus venosus (Hikspoors et al., 2017).

The development of the venous system of the pancreas is strictly related to the development of the vitelline veins that drain blood from the capillary network of the yolk sac. Vitelline veins enter the embryo's body and form three transverse anastomoses, resembling a figure of eight. The superior anastomosis lies in the liver, the middle one crosses the duodenum from the back, the inferior one crosses the duodenum from the front (Hikspoors et al., 2017).

During the 2nd gestational month, the anastomoses of the vitelline veins begin to disappear. As a result of these changes, the anastomosis network surrounding the duodenum becomes a single vessel, the hepatic portal vein, which develops from the left vitelline vein (Dubois, 1999). The superior and inferior mesenteric veins and the splenic vein develop from the right vitelline vein. Thus, the portal vein originates from 3 vessels: the superior and inferior mesenteric veins and the splenic vein. In one third of the population, the inferior mesenteric vein drains to the splenic vein (in the vicinity of the developing portal vein), in one third to the superior mesenteric vein, and in the remainder, it drains to the junction of the splenic vein and superior mesenteric vein (Van Hoe and Claikens, 1999). The veins of the pancreas accompany their corresponding arteries and drain to the major vessels i.e. superior mesenteric vein, splenic vein, and portal vein (Calas et al., 1956a, 1956b; Marni et al., 1985; Michels, 1966; Mourad et al., 1994).

5. Microcirculation

As the pancreatic buds grow into the dorsal mesentery of the duodenum and stomach, the capillary plexus forms within the buds' mesenchyme (Cleaver and Dor, 2012). The branches of the plexus enter the buds, forming interlobular arteries, which branch off intralobular arteries (Figs. 6 and 7-I). The arteries are accompanied by their corresponding veins, which do not run parallel with the branching of the pancreatic ducts, and therefore do not form triads (like portal triads in the liver) (Gorczyca et al., 2017). The smaller lobules measuring < 500 μm are usually supplied by only one artery, whereas the bigger lobules (> 500 μm) can be supplied by several arteries, usually 2–5. The intralobular arteries, which arise from the interlobular arteries, typically measure less than 20 μm in diameter and supply the capillary network surrounding the pancreatic parenchyma. In a lobule without a pancreatic islet, the intralobular vessels form a capillary network surrounding the lobule. In a lobule containing islets, one or several intralobular arteries create capillary networks for the islets that connect to interlobular networks (Fig. 7-II). The capillaries drain to the small intralobular veins, then to interlobular veins (Gorczyca et al., 2017, 2010).

The vascular plexuses of the pancreatic ducts are supplied by vessels arising from the interlobular arteries, or rarely from the arteries of the lobule (Fig. 7-III). The plexuses form an internal layer consisting of small capillaries supplied by afferent vessels. The blood from the internal layer drains to the venous network, which comprises the external layer of the plexus (Gorczyca et al., 2017, 2010). The blood from the external layer drains then to the interlobular veins. The described system of vascular plexuses of the ducts is not always easily distinguishable (Aharinejad and Bock, 1992; Ashizawa et al., 1991; Ohtani, 1983). Only a few studies have reported on the microcirculation of the human pancreas (Gorczyca et al., 2017, 2010; Murakami et al., 1994, 1992; Yaginuma et al., 1986, 1981). Murakami et al. (1994, 1992) investigated the pancreas of an adult human using scanning electron microscopy of micro-corrosion casts. Their research revealed the presence of a vascular network consisting of the capillary plexuses of lobules, islets and the extralobular ducts. It was reported that the pancreatic islets are primarily located within the lobules (the so-called intralobular islets), with 1–4 islets in a single lobule (Murakami et al., 1992). Nonetheless, a few islets can be found scattered in the interlobular space or along the interlobular ducts. These extralobular islets receive one or several vessels from the interlobular arteries or occasionally from periductal arteries (Fig. 7-IV). The vessels of the extralobular islets divide into a sinus capillary network joined with interlobular veins or periductal veins (Gorczyca et al., 2017, 2010).

The results of the previous studies indicate that in an adult pancreas, the majority of the islets are located inside the lobules, with each islet supplied by its own arteries and efferent vessels. The efferent vessels of the islets usually anastomose with the capillaries of a lobule; therefore, they can be described as islet-lobular anastomoses (Gorczyca et al., 2010).

There have been recently suggested that there are two populations of islets within a healthy rodent pancreas: (1) a large islet

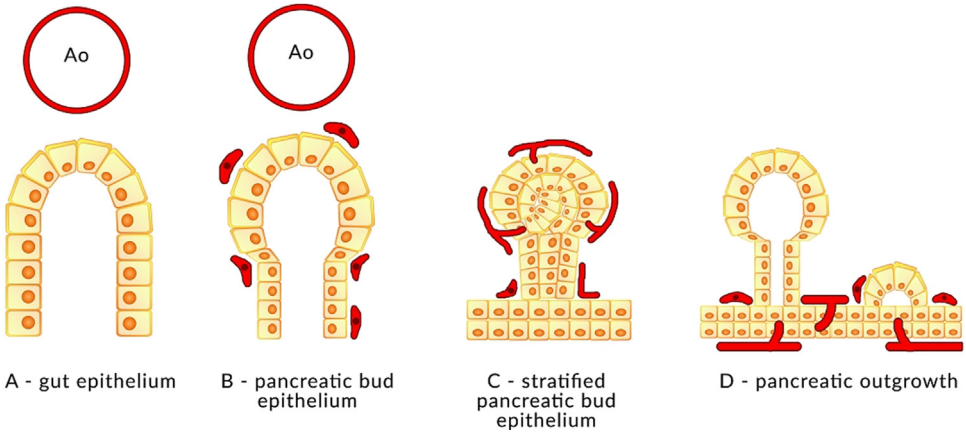

Fig. 6. Formation of the pancreatic blood vessels.
(A) Aorta provides signals supporting cell differentiation, (B) new blood vessels surround the pancreatic bud, (C) blood vessels communicate with bud epithelium, (D) formation of capillary network surrounding the lobule (adapted from Villasenor and Cleaver, 2012).

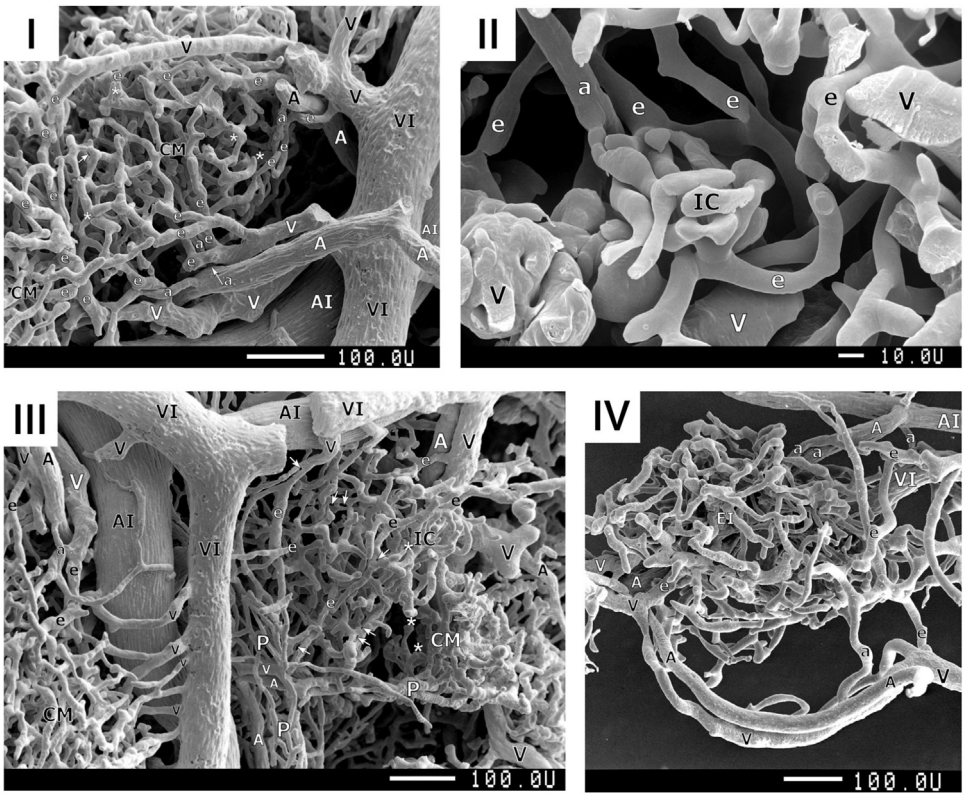

Fig. 7. SEM images of fetal pancreas microcirculation.
A — the intralobular artery, a — afferent branch, AI — the interlobular artery, CM — the lobular plexus, e — efferent branch, EI — extralobular islet, IC — the islet plexus, P — the ductal plexus, V — the intralobular vein, VI — the interlobular vein (main trunk), → — intussusceptive angiogenesis, * — sprouting angiogenesis.

population that contains a dense vascular network, is well blood-perfused and oxygenated, and has a high beta cell proliferation rate and strong secretory function, and (2) a small population of islets representing about 20–25% of all islets within a rate pancreas that are not well perfused or well oxygenated, contain only very few proliferating beta cells and have a low secretory function (In't veld and Lammert, 2015). Islet beta cells metabolize glucose almost exclusively via aerobic glycolysis making them heavily oxygen dependent, partially explaining the correlation between vascular density and islet function (Schuit et al., 1997).

Another study report that highly perfused islets are more susceptible to cell death induced by inflammatory cytokines or hypoxia in vitro (Ullsten et al., 2015). Interestingly, the highly perfused islets were found to be more prone to cell death and fibrosis, despite being better vascularized and oxygenated in the host. These findings indicate that strongly vascularized islets seem to be more susceptible to cell death following islet transplantation, which could be explained by the highly perfused islets being more accessible to inflammatory cytokines and immune cells (In't veld and Lammert, 2015).

Gorczyca et al. reported that at the 18th–25th week of gestation, the structure of the vascular network is similar to that of the adult pancreas and is strongly associated with lobular division of the pancreas. A number of microvascular anastomoses has been reported.

In the specimens studied by Gorczyca et al. (2017, 2010) different lobulo–lobular connections were often found: One type of anastomosis included capillaries running through the interlobular space between the two neighbouring lobules, another one was observed between the efferent branches flowing into the peripherally running interlobular vein. These anastomoses were also described by Murakami et al. (1994, 1992) in their casts of the adult human pancreas. Other microvascular anastomoses confirmed by Gorczyca et al. (2017, 2010) were rare direct connections between the circulations of the islets and the intralobular ducts and also the connections between the islet's capillaries and the lobular plexus (Gorczyca et al., 2017).

Accurate and detailed knowledge regarding the microvascular structure of the human pancreas is clinically significant. Changes in the microvasculature have been found to be an important prognostic factor in pancreatic ductal carcinoma (Lytras et al., 2015). Furthermore, both blood vessels signals and extracellular matrix (ECM) signals are crucial for differentiation of pancreatic stem cells (Cleaver and Dor, 2012). Yet, in vitro-directed differentiation of stem cells faces many limitations, including reduced amounts of stimuli from blood vessels. In a 2008 study by Kroon et al. (2008), in vitro differentiated human embryonic stem cells could secrete insulin in response to various secretagogues, but not to glucose. However, after implantation into mice, the same hES cells generated glucose-responsive, insulin-secreting cells (Kroon et al., 2008). The differences between in vitro and in vivo responses of cells might suggest that microcirculation and blood-borne signaling play an important role in beta cells differentiation (Cleaver and Dor, 2012).

In addition, the role of blood vessels in beta cell regeneration remains undetermined, due to the difficulties of separating blood vessels signals from ECM signals in vivo (Cleaver and Dor, 2012). Pancreatic microcirculation might play an underappreciated role in islet transplantation; during preparation of cadaveric islets for transplantation, many associated capillaries are lost, which results in a delayed revascularization of implanted islets lasting about 1–2 weeks and greatly impairing their survival (Mattsson et al., 2002).

Detailed understanding of the microvascular anastomoses in the human pancreas may be useful in the development and improvement of islets transplantation techniques, in which effective revascularization of transplanted islets can be difficult, yet essential to islet survival and functioning (Brissova and Powers, 2008; Gorczyca et al., 2017; Pepper et al., 2013).

6. Conclusion

This is the first comprehensive review containing information on the biology of the pancreatic microcirculation. Detailed knowledge on the development and anatomy of the human pancreas is essential for all specialists dealing with disorders of this gland. One must remember the significance of various transcription factors which regulate the physiological development of the pancreas and play key roles in the pathophysiology of various pancreatic disorders (i. e. congenital malformations, permanent neonatal diabetes mellitus, etc.). Moreover, detailed anatomical knowledge is crucial for developing new therapies, which target diabetes mellitus, such as islets transplantation.

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