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Review Article

Development of human pancreas

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Abstract

Pancreas is an exocrine and endocrine organ. Exocrine portion secretes digestive fluid. Endocrine portion secreting insulin and glucagon etc. Pancreas developed from dorsal and ventral pancreatic buds, which arise from either side of distal foregut. When duodenum rotates to right, ventral pancreatic bud(VPB) rotates posterior along with common bile duct(CBD) and finally lies below and behind the dorsal pancreatic bud(DPB). In humans, DPB forms major part and VPB forms inferior part of head and uncinate process of pancreas. Main duct (Duct of Wirsung) is derived from whole of ventral pancreatic duct(VPD) and distal part of dorsal pancreatic duct(DPD). Main duct joins with CBD and it perforated posteromedial side of second part of duodenum at major duodenal papilla. Occasionally accessory duct might originate from proximal part of DPD and open into minor papilla. Sometimes two buds do not fuse and lead to pancreatic divisum. Abnormal rotation and fusion of buds might lead to annular pancreas. A few endodermal pancreatic evaginations may remain and migrate in bowel wall and form accessory(heterotopic) pancreas. Islets originating from DPB have more insulin synthesis. Neck, body and tail of pancreas is supplied by coeliac trunk. Derivatives of right VPB are supplied by branches of superior mesenteric artery. During rotation of VPB, superior mesenteric vessels(SMV) were engaged in between DPB and VPB. Lastly, SMV is located posterior to neck but it is anterior to uncinate process of pancreas. Detailed study of development of exocrine and endocrine portions is required for successful management of pathology of the pancreas

Keywords

Dorsal and ventral pancreatic buds, exocrine and endocrine pancreas. Islets of Langerhans.

Introduction

The pancreas is an exocrine and endocrine organ and it is located in the retroperitoneal position at the vertebrae level of L1 and L2 in the abdomen. It consists of head, neck, body, tail and an uncinate process. The head of pancreas lies within the bend of the duodenum and pancreatic duct joins with the common bile duct and the hepatopancreatic duct to perforate the posteromedial side of the second part of duodenum at the major duodenal papilla (Ampulla of Vater). The three main purposes of pancreas are to produce enzymes for digestion, to produce the bicarbonate to counterbalance the gastric acid, and to produce insulin in order to signal cells to initiate taking the nutrients.

The exocrine pancreatic tissue comprises of acinar cells, which secretes the digestive fluid. The mature duct cells energetically secret the bicarbonate and mucins (1). Valuation of bicarbonate concentration is the gold standard assessment method for the exocrine pancreatic function (2). The endocrine portion consists of separate islets of Langerhans, which are composed of dissimilar distinct cell types. They are glucagon secreting alpha (α) cells, insulin and amylin secreting beta (β) cells, somatostatin producing delta(δ) cells, ghrelin producing epsilon (ε) cells and pancreatic polypeptide secreting gamma cells (PP or F cells). (3) The loss of insulin production by the islets of Langerhans is the symbol for type 1 diabetes mellitus (4). Close collaboration between endocrine and vascular cells controls hormone discharge and maintains glucose homeostasis (1).

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Development of pancreas

The pancreas originates from the endoderm of distal foregut region. The exocrine and endocrine cells are derived from the common endodermal population of cells that also give rise to the liver, gallbladder, and part of the small intestine (5).

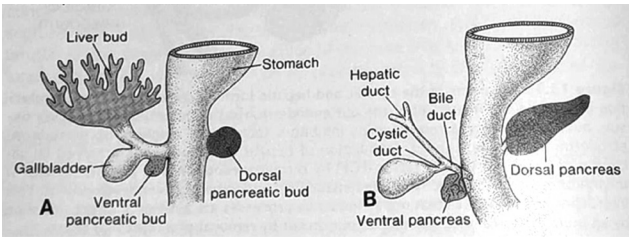
Development of exocrine part of pancreas: Formation of pancreatic buds and duct system:

The pancreas developed from dorsal and ventral pancreatic buds, which arise from both side of the distal foregut endoderm (3). The two buds originate from the endoderm lining of the primitive duodenum (6). Pancreatic growth was started by the condensation of mesenchyme over the endoderm which gives origin of the dorsal pancreatic bud just preceding to 26th day of gestation. The ventral pancreatic bud is formed subsequently (7). The ventral pancreatic bud is developed from the common hepatic diverticulum at the early embryonic stage (5). The remaining cranial part of hepatic diverticulum forms the liver and gallbladder buds at the 6th week of gestational life and the both dorsal and ventral pancreatic buds fused at the 7th week of gestational life (fig1,2) (8).

When duodenum rotates to the right the ventral bud rotates posterior along with the common bile duct and joins with the remaining duct system of pancreas and enters into the duodenum. Finally, ventral bud lies below and behind the dorsal bud. (6) In humans, the dorsal pancreatic bud gives rise to the major part of the pancreas including the upper part of the head, the neck, the body and the tail. The ventral pancreatic bud gives rise to the inferior part of the head and the uncinate process of pancreas. (6,7)

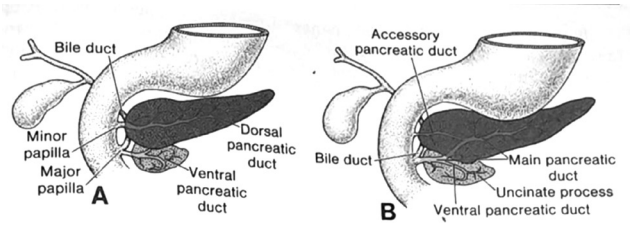
The main duct of pancreas is derived from the whole of the ventral duct and distal part of the dorsal duct. Sometimes the accessory duct might originate from the proximal part of the dorsal duct. In majority of the cases the two ducts fuse and form the single common pancreatic duct, Duct of Wirsung. The accessory duct distal to its union with the main duct became stenosed or obliterated in most. (fig 2. B) (5) The main pancreatic duct opens into the major duodenal papilla. In the condition of existence of accessory duct, it use to open into the minor duodenal papilla. (6)

Figure 1 Stages in the development of pancreas



A. 30 days (approximately 5 mm)
B. B. 35 days (approximately 7 mm), initially ventral pancreatic bud lies close to the liver bud, but later it moves posteriorly around the duodenum towards the dorsal pancreatic bud

Figure 2 Fusion of pancreatic buds



C. Pancreas during the sixth week of development. Ventral pancreatic bud is in close contact with the dorsal pancreatic bud.
D. Fusion of the pancreatic ducts

Abnormal fusion of its ducts would lead to the pancreatic divisum and the presence of a second duct termed as the Duct of Santorini. Duct of Santorini was one of the causes for increased threat for recurrent pancreatitis (5). In this condition, the main duct drains the head and uncinated process but the second duct drains the body and tail of dorsal bud origin. The ductal configuration most commonly (60%) manifests as a bifid configuration with a dominant duct of Wirsung. Less common configurations was absence of duct of Santorini (30%), a dominant duct of Santorini without divisum (1%), and 'ansa pancreatica', in which the duct of Santorini forms a reversed-S shape and connects with a side branch of the duct of Wirsung (9).

Anomalous pancreaticobiliary ductal junction is characterized by fusion of the pancreatic duct and common biliary duct (CBD) outside the duodenal wall, with development of a long common channel. Magnetic resonance cholangiopancreaticography images would disclose variation in passage of pancreatic duct.

The entire development of pancreas was divided into three periods(transitions): In primary transition, the number of multipotent pancreatic progenitor

cells(MPCs) were formed. In secondary transition time, most of the cells are specified to become either endocrine cells, acinar or duct cells and with a small percentage of cells keeping the multipotency. Third transition time, cells within the pancreas become unipotent. However, multipotency cells could be stimulated in adults by injury (5).

During the elongation of the foregut, the developing ventral pancreas, gallbladder and the bile duct rotates posterior to the duodenum and joins the dorsal pancreas in retroperitoneal position (8). The ventral pancreatic duct and common bile duct are connected by their embryonic origins, which results in the adult shape of their shared entrance into the duodenum at the major duodenal papilla (8). The opening of the bile duct in the ventral surface in early stage later due to the rotation of ventral bud, the hepaticopancreatic duct opens into the postero medial aspect of the duodenum.

Annular pancreas

Annular pancreas is a congenital anomaly in which the second part of the duodenum is partially or completely blocked by a loop of pancreatic tissue. The Abnormal turning and fusion of the ventral and dorsal pancreatic buds might lead to annular pancreas (10).

In later gestational life, left ventral anlage vanish in human but it might have persevered and became a part of the mature pancreas in chickens and frogs (8) Therefore the failure of the deterioration of left ventral anlage could lead to the pathological condition known as annular pancreas. The earlier studies documented that the occurrence of annular pancreas was around 0.005% -0.015% (8).

Accessory/Ectopic pancreatic tissue

An ectopic pancreas was an anatomical defect in which pancreatic tissue had grown outside its normal site without vascular or other anatomical contacts to the pancreas. There were several evaginations originating from the wall of the primitive duodenum in early embryo to form the normal pancreas, one or more evaginations might remain in the bowel wall and the movement of this embryonic remnant alongside with the development of the digestive tract might give rise to the accessory or ectopic (heterotopic) pancreatic tissue (11).

The accessory pancreatic tissue might be located from the distal end of esophagus to the tip of the primary intestinal loop (6). The incidence of accessory pancreas tissue in the stomach, duodenum, jejunum as 25-38%, 17-36% and 15-21% respectively. Incidence of ectopic pancreatic tissue in the submucosal layer, muscularis and subserosal layer of stomach was 73%, 17% and 10% respectively (11).

Christodoulidis et al., (2007) classified the ectopic pancreas as four types: Type 1 consists of typical pancreatic tissue with acini, ducts and endocrine cells comparable to the normal pancreatic tissue. Type II consists of pancreatic duct only and mentioned as the canalicular variety. Type III consists of acinar tissue only mentioned as exocrine pancreas. Type IV consists of islets cells only mentioned as endocrine pancreas (11). The adenocarcinoma rising from the ectopic pancreas have a healthier prognosis than those arising from the ordinary pancreatic tissue (11).

Formation of endocrine part

Islets of Langerhans were islands of mixed population of endocrine cells that were distributed in the parenchyma of the pancreas and it consists roughly 30% of alpha cells, 60% of beta cells and the remaining 10% of other cells. The central of islet of Langerhans was made of beta cells and encircled by the other types (12). A. Wendt et al., (2020) suggested that the percentage of alpha cells was 65% in human islets and pointed out that alpha and beta cells were mixed all over the islets (13). The total number of islets of Langerhan in a human pancreas has been valued to be between 3.2 and 14. 8 million and most of them have the surface area of between 1000 and 10000 micrometer ^{2} (12). Certain controlling mechanism retains the ideal size of the islets in order to safeguard their functional properties (14) The beta cells vanished by autoimmune destruction in type 1 diabetes (T1D) with the consequent failure to restrain the blood glucose levels but in type 2 diabetes (T2D) was typically characterized by the progressive failure of beta cells to meet the body's demands for insulin (3).

There are functional dissimilarities found between the islets in the head and tail area of the pancreas. Previous studies noted that the islets originating from the dorsal bud has the superior capacity to synthesis and secrete the insulin than the ventral pancreatic bud (12). The thickness of beta cells (core of islet) in the body and tail regions were greater than the head region (14) but its thickness was twofold greater in the tail region of the pancreas. The further investigation revealed that the significant loss of beta cells specially in the head region in the patients of type 2 diabetes and the pancreatic cancer (14).

The blood supply of pancreas

It was believed that the foregut derivatives were supplied

by the branches of the coeliac trunk and similarly the midgut derivatives were supplied by the branches of the superior mesenteric artery. Usually left and right ventral pancreatic anlages and dorsal pancreatic bud were derived from the common site which give rise to the hepatic diverticulum. During the duodenum rotation to the right side and right ventral bud rotates in the posterior direction and comes to lie below and behind the dorsal bud in the left side.

Since the dorsal bud originated from the endothelium of the foregut. The neck, body and tail of the pancreas was purely supplied by the coeliac trunk and the right ventral bud finally shifted to slightly lower level than the left ventral anlage as well as the dorsal bud and its derivatives were supplied by the branches of the superior mesenteric artery.

The relationship between the pancreas and the superior mesenteric artery

In early embryos, the primitive gut was attached with the dorsal and ventral mesentery, where the corresponding pancreatic buds were developed. Later stage, the rotation of the dorsal surface of stomach to the left side spontaneously shifted the dorsal pancreatic bud to the left and it loses the mesentery except at its tail region (leinorenal ligament). Dorsal bud finally lie posterior to the greater omentum, (which is a derivative of the dorsal mesentery). The lesser sac was formed as the result of the rotation of stomach and greater omentum

The ventral mesentery was converted to the lesser omentum and falciform ligament. The lesser omentum provides attachment to the lesser curvature and first part of duodenum to the porta hepatis in liver. The hepatoduodenal ligament was the part of ventral mesentery, which connects the liver and duodenum and usually transmits the main structures like the bile duct, portal vein and hepatic artery. The ventral bud usually has the two anlage left and right ventral anlages, only the right ventral anlages rotates posterior in normal development and finally settled just below and behind the dorsal bud. The same time abdominal aorta was formed by the fusion of the left and right dorsal aorta and abdominal aorta provides the paired and unpaired arteries. Among the unpaired arteries, the superior mesenteric artery was the artery for midgut derivatives. The aorta and inferior vena cava were the retroperitoneal organs in the posterior abdominal wall but superior mesenteric artery (usually origin at inferior border of L1 vertebrae) runs antero inferior direction and enters the mesentery proper to supply the part of small intestine and the 2/3rd of the transverse colon. Superior mesenteric vein joins with the splenic vein behind the neck of pancreas and forms the portal vein. It was interesting to note that during the rotation of right ventral pancreatic bud to the left side, the superior mesenteric vessels(SMV) occupied in between the dorsal and ventral pancreatic buds and thus SMV located posterior to the neck and anterior to the uncinate process of the pancreas.

Conclusions

Understanding the development of pancreas and its clinical correlates are essential and the developmental anomalies might be the cause for pancreatitis and gastric outlet obstruction. The detailed study of the endocrine part of pancreas is much required for the management of diabetes mellitus.

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