Surgical Diseases of the Pancreas and Biliary Tree

Savio George Barreto
John A. Windsor
Editors

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Foreword

This multiauthored text is a valuable addition to the literature regarding pancreatobiliary surgery. The chapter authors and the editors are principally Asian and well recognized for their specific expertise. Their contributions are encyclopedic, extensively referenced, and up-to-date. The illustrations are pertinent to the text, of high quality, and many are in color. The overall tone of the book is clinical, with emphasis on preoperative and postoperative management. Areas of controversy are presented, and even-handed discussions offered. In a particularly useful feature, many of the contributors highlight areas necessitating future evidence-based data to resolve existing controversies.

The initial chapters on Anatomy and Physiology of the Pancreas and Biliary Tree are outstanding and can easily serve as authoritative references for house officers studying for in-service and qualifying examinations. While each of the 17 chapters comprising this book is informative and could stand alone as state-of-the-art reviews and contributions to surgical knowledge, they vary in value as guidelines for clinical management, a frequent complication of multiauthored texts. Particularly noteworthy from this clinician's standpoint were the excellent chapters on Choledochal Cysts, Mucinous Tumors of the Pancreas, Pancreatic Neuroendocrine Tumors, and Hilar Cholangiocarcinoma.

For each of the remaining chapters, any concerns that I had were minor, and truth be told, often reflected my personal biases or practice patterns. As an example, in Chap. 4, Table 4.1, statin drugs should probably be added to the list of pathogenic agents for gallstone formation. In the chapter covering External Biliary Fistula, I would have liked to have seen a discussion of the "Law of Fistulas," a useful concept for clinical management. The chapter on Portal Biliopathy was extremely interesting since it is rarely covered in texts, but the timing of surgical intervention was less clear. The chapter on Acute Pancreatitis was encyclopedic and quite current, but the emphasis on classification of severity provides me an opportunity to express one of my favorite biases. I believe that we have spent an inordinate amount of time and effort on classification systems for the severity of acute pancreatitis. The rationale has been to identify those patients that may require more intensive therapy. While determination of severity is intrinsically worthwhile, since we do not have a proven specific therapy for acute pancreatitis, other than enthusiastic fluid replacement and supportive monitoring in an intensive setting, the seemingly never-ending fine-tuning attempts to classify severity seem to be a largely wasted effort, as severe

acute pancreatitis is easily recognized by experienced clinicians. In my opinion, the efforts spent on the unnecessary polishing of severity classifications would be much better spent on the prevention or amelioration of the cytokine cascade of acute pancreatitis that is responsible for its severity. It is perhaps past time to return our efforts to the cause and prevention of severe acute pancreatitis, rather than to its classification.

Since benign biliary strictures are quite common in chronic pancreatitis, indications for intervention are important. Aside from the clear indication of jaundice due to benign intrapancreatic stricture, we have found that a persistent elevation of alkaline phosphatase predates the development of biliary cirrhosis and reliably indicates the need for biliary bypass.

Recently, Chey and co-workers have described a new functioning pancreatic islet cell tumor, a primary secretinoma, as an additional cause of the watery diarrhea syndrome, increasing the complexity and distribution of pancreatic neuroendocrine tumours (P-NETs).

Adding to the excellent chapter on Pancreatic Cancer, we have found that thoracoscopic splanchnicectomy is a valuable tool for controlling intractable pain from terminal pancreatic cancer. Although nerve interruption procedures are often subject to recurrence, perhaps due to central plasticity of the pain response, life expectancy for metastatic pancreatic adenocarcinoma is often less than the onset of post-neurectomy pain recurrence. Moreover, some patients desire mental clarity for their remaining time of life and wish to avoid narcotic obtundation.

The final chapter on ERAS (enhanced recovery after surgery) is a valuable concept, and not often applied to pancreatobiliary surgery. This seems to be a fruitful area for evidence-based study by future workers and students.

In summary, there is much to learn from this book, and the authors are to be congratulated for the value that they offer to readers.

4 April 2018

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Preface

Diseases of the pancreas and biliary tree are amongst the most common abdominal conditions around the world, and they continue to fascinate and frustrate. Covering a wide range of inflammatory and neoplastic diseases they are responsible for considerable patient suffering. They also represent substantial work for generalists and specialists, including general surgeons, HBP surgeons, gastroenterologists, radiologists, intensivists, general practitioners, nursing staff and allied health workers.

The care of these patients is challenging and changing, not just because of the diseases themselves, but because of the need to remain current in the face of new knowledge, evidence and approaches to management. We have assembled an experienced team of authors who are here to help. All experts in their field, they have provided chapters that address these challenges with an erudite and evidence-based approach. The chapters are also practical, taking a step-by-step approach to real-world issues in patient care. All those providing care to patients with these diseases will find value in these pages.

We are sincerely grateful to the individual authors who have contributed to this book. They have been excellent to work with and responsive to the demands of both editors and publishers. And, as expected, we have gained new knowledge and perspectives, which has made this an enriching experience for us. This project would not have been possible without the sterling support of Dr. Naren Aggarwal and Mr. Kumar Athiappan from Springer through the entire process of bringing you this book.

The diseases of the pancreas and biliary tree continue to be our primary clinical and research interests and we hope you will be inspired to provide the very best of care for your patients, as you read and apply all that is contained here.

Gurgaon, India — Savio George Barreto
Auckland, New Zealand — John A. Windsor

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About the Editors

Savio George Barreto is a Gastrointestinal and Hepato-Pancreato-Biliary (GI & HPB) surgeon and researcher. He completed his undergraduate and postgraduate surgical degrees at Goa Medical College and Hospital, where he also trained in Internal Medicine and General Surgery. He completed his fellowship in GI & HPB Surgical Oncology at the Tata Memorial Hospital in Mumbai and his training in GI and Liver Transplant Surgery at Flinders Medical Centre and the Royal Adelaide Hospital, South Australia. After serving a year as the Chief Surgical Resident at Modbury Hospital, South Australia, Dr. Barreto returned to India. His career includes appointments as Consultant Surgical Oncologist at the Department of GI & HPB Surgical Oncology, Tata Memorial Centre, Mumbai, India, and as Consultant Surgeon at the Department of GI Surgery, GI Oncology and Bariatric Surgery, Medanta—The Medicity. He is currently a Senior Lecturer at the College of Medicine and Public Health, Flinders University, South Australia.

Barreto secured his Doctor of Philosophy degree from Flinders University for his work on the neuropeptide galanin and its antagonists, their effects on pancreatic exocrine secretion, and their role in acute pancreatitis. His interests focus on the basic science and surgical aspects of acute pancreatitis, pancreatic, gastric, and gallbladder cancer. He has published a carcinogenesis model in gallbladder cancer to aid in understanding the development of the cancer and to further therapy-directed research. He, along with Professor John Windsor, has proposed the first evidence-based definition of early gastric cancer. Dr. Barreto has authored more than 150 clinical and basic science research papers as well as book chapters on GI and HPB-related topics and has been invited to lecture on his work all over the world. He serves on the Indian Council of Medical Research Task Force groups for the development of guidelines for the management of gastric, pancreatic, and neuroendocrine cancers for India.

John A. Windsor grew up in the Indian Himalayas, completed his surgical training in Auckland and his specialist HBP training in Edinburgh. He is currently an HBP and Upper GI Surgeon at the Auckland City and Mercy Hospitals. He holds a personal chair in surgery, is Director of Surgical Research and Assistant Director of the national MedTech Centre of Research Excellence. For over 30 years he has been active in promoting research and education, especially in the training of surgeon

scientists. His surgical interests include the management of acute and chronic pancreatitis, pancreatic cancer, and gastro-esophageal reflux and cancer. His research interests include the pathophysiology of acute pancreatitis, the role of toxic mesenteric lymph in critical illness, and the mapping and modulation of gastric electrical activity. He has published over 380 peer-reviewed manuscripts and has an H-index of 60, over 200 invited lectures, and 8 visiting professorships to his credit. He has been Secretary General of the International Hepato-Pancreato-Biliary Association and Chair Section of Academic Surgery at the RACS. He has been awarded the Gluckman Medal for distinguished research contributions to the University of Auckland, the Sir Louis Barnett Medal for distinguished contributions to the RACS, and elected a Fellow of the American Surgical Association and the Royal Society of New Zealand.

Anatomy of the Pancreas and Biliary Tree

1

Constantinos P. Zambirinis and Peter J. Allen

1.1 Pancreas

The pancreas derives its name from the Greek words *παν* (*whole*) and *κρέας* (*flesh*), due to its fleshy consistency as well as the absence of bones or ligaments [1]. The pancreas has a complex microscopic structure and functions as both an exocrine and an endocrine organ. The exocrine component, which is responsible for the digestive functions of the pancreas, represents the bulk of the organ's mass (approximately 98%). The exocrine component is composed of an intricate network of blind sacs (acini) that produce an array of digestive enzymes and form small ductules that interconnect to form larger ducts of progressively increasing caliber, ultimately leading to the main pancreatic duct. This acinar network is supported by loose connective tissue that contains blood vessels, nerves, and pancreatic stellate cells. Interspersed within the exocrine gland are the pancreatic islets of Langerhans, which constitute the endocrine component of the pancreas. The islets of Langerhans are clusters of β, α, δ, PP, and ε cells (in decreasing order of abundance), which are responsible for the production of the hormones insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin, respectively.

1.1.1 Embryology

The developmental biology of the pancreas has attracted the interest of the scientific community not only because of the complexity of the pancreatic structure but also because of the multiple diseases that result from developmental aberrations of this organ. Although significant progress has been made with the recent advances of

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molecular biology that enable lineage tracing of the different cell types, many aspects of pancreatic development remain unclear.

The pancreas originates from the foregut as two separate primordia suspended in the mesentery. These separate components fuse to form the final organ that rests in the retroperitoneum (Fig. 1.1). Near the end of the fourth week of gestation, a mesenchymal condensation is formed dorsal to the primitive foregut, at the level of the future duodenum. This in turn induces the underlying foregut endodermal lining to form the dorsal pancreatic bud (Fig. 1.2). Specifically, mesenchymal fibroblast growth factor 2 (*FGF2*) and activin relieve the inhibition imposed on the foregut

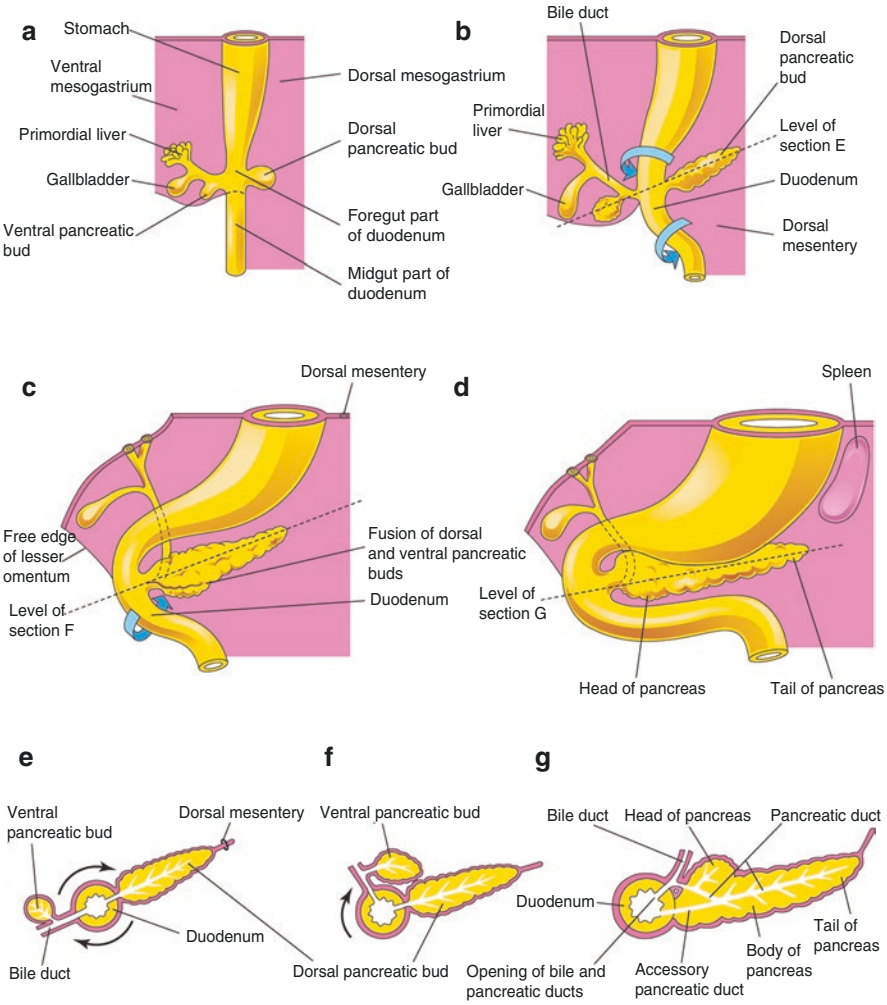

Fig. 1.1 Embryologic development of the pancreas. (**a–d**) Successive stages in the development of the pancreas from the fifth to eighth week. (**e–g**) Diagrammatic transverse sections through the duodenum and developing pancreas. Growth and rotation *(arrows)* of the duodenum bring the ventral pancreatic bud toward the dorsal bud, and the two buds subsequently fuse (Reproduced with permission from Moore et al., "*The developing human: Clinically oriented embryology*", 10th edition. Copyright Elsevier/Saunders 2015)

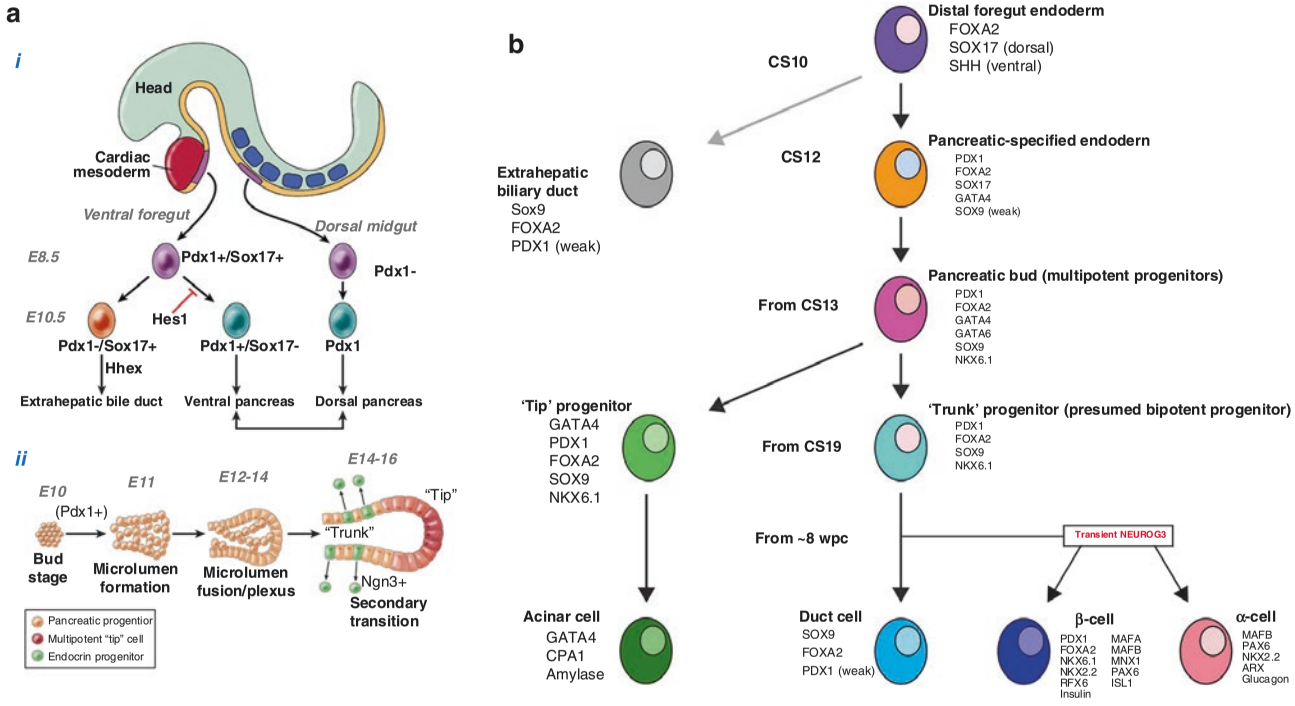

Fig. 1.2 Cellular and molecular interactions defining mammalian pancreas development. (**a**) Regulation of pancreas development in the mouse. Pancreatic specification begins with signals derived from the mesenchyme, with serial expression of different transcription factors (***i***). The "tip-trunk" model explains the intricate microarchitecture of the pancreas (***ii***). From [2]. (**b**) Transcription factors and other key markers that identify different cell types and stages during early pancreas specification and subsequent lineage commitment in humans (based on immunohistochemical studies). Only dorsal pancreas specification is shown for simplicity (markers for the extrahepatic biliary duct are in gray). CS, Carnegie stage; wpc, weeks postconception (Reproduced with permission from [16])

endoderm by sonic hedgehog (*SHH*) signaling, therefore enabling differentiation into the pancreatic primordium. The latter results from epithelial expression of the transcription factors pancreatic and duodenal homeobox 1 (*PDX1*) immediately followed by pancreas-specific transcription factor 1a (*PTF1A*) [2]. The importance of these transcription factors in pancreatic development is underscored by the fact that mutations in either gene lead to *pancreatic agenesis*. Both PDX1 and PTF1A have been exploited in various genetically engineered mouse models of pancreatic diseases, especially in mouse models of pancreatic cancer [3]. Furthermore, uncoordinated expression of pancreas-licensing signals can facilitate the development of *ectopic pancreatic tissue*—most commonly found in the mucosa of the stomach, duodenum, jejunum, or ileal diverticulum (of Meckel)—that may lead to atypical gastrointestinal symptoms (e.g., bleeding or even cancer).

At the microscopic level, pancreatic development follows a process of branching morphogenesis. The inner cells of the growing pancreatic buds that lack contact with the surrounding tissues form microlumens (Fig. 1.2a). Adjacent microlumens subsequently fuse to form duct-like structures, while the epithelial lining is separated into proximal "trunk" and distal "tip" regions. The cells at the trunk regions will develop into cells with ductal and endocrine function. The cells of the tip region initially remain multipotent, but after progressive branching and elongation, the distal tip cells commit to the acinar lineage and will have exocrine function. Complex expression patterns of multiple transcription factors regulate the fate of each cell to give rise to the different lineages found in the adult pancreas (Fig. 1.2b).

Pancreatic parenchymal cells proliferate early in gestation resulting in an increase in the volume of the developing gland. The dorsal bud grows earlier than the ventral bud, taking a progressively oblong shape. The rotation of the stomach and duodenum influences the anatomy and orientation of the pancreatic primordia (Fig. 1.1). The ventral pancreatic bud follows the rotation of the duodenum, moving first to the right and then to its final dorsal position (Fig. 1.1). The two buds normally fuse in the retroperitoneum to form a single organ. The ventral bud eventually lies posterior to the superior mesenteric vessels, posterior and inferior to the dorsal pancreatic bud, giving rise to the bulk of the uncinate process and the inferior portion of the head of the pancreas. The rest of the head of the pancreas, the neck, body, and tail, are all derived from the dorsal bud.

Each of the two pancreatic buds has its own separate main duct (Fig. 1.1). The duct of the ventral bud lies in continuity with the main bile duct. The two ductal systems normally fuse to become one during the rotation of the duodenum and the pancreas (Figs. 1.1 and 1.3a). The ventral bud forms the proximal main pancreatic duct (of Wirsung), while the duct of the dorsal bud forms the rest of the main pancreatic duct spanning the neck, body, and tail of the gland. The proximal part of the duct of the dorsal bud usually persists as an accessory pancreatic duct (of Santorini) that opens in the minor duodenal papilla (Fig. 1.3a).

Abnormalities in the rotation and/or fusion of the two pancreatic buds may result in anatomical variants. The most common congenital anomaly of the pancreas is *pancreas divisum*. It is due to a failure of fusion of the ventral and dorsal duct system and can be subclassified depending on the extent of communication and the

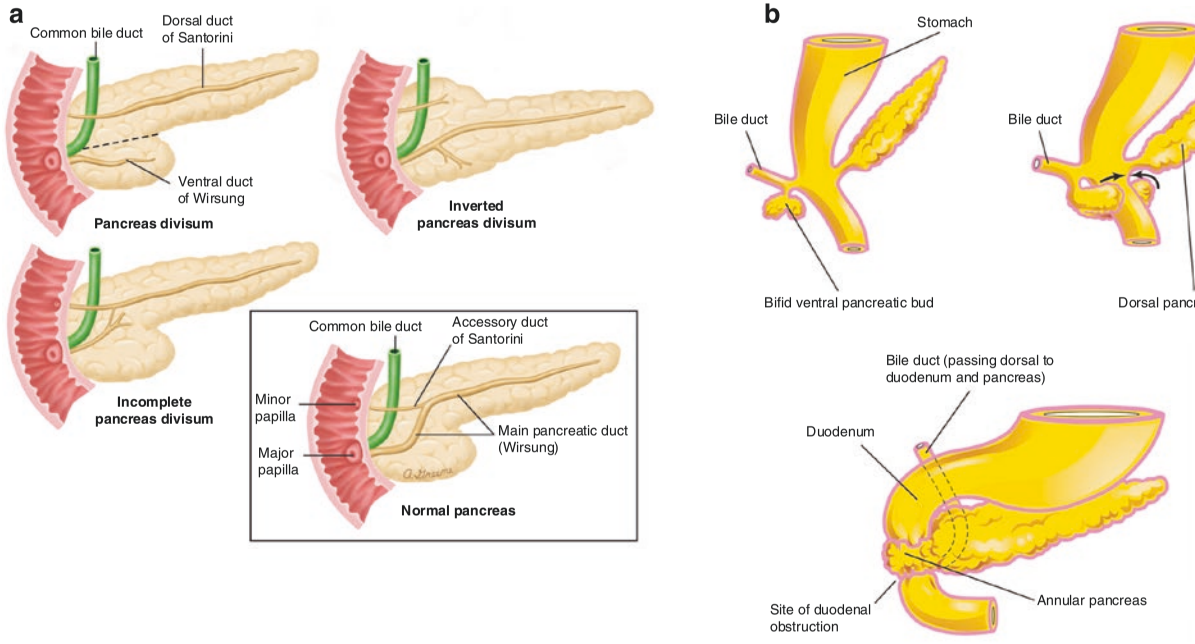

Fig. 1.3 Rotation of the pancreas primordia and its ductal system and related anomalies. (**a**) The rotation of the duodenum brings the two pancreatic buds together. Their ducts, initially separate, usually fuse to form the adult main pancreatic duct that drains into the duodenum. Failure of fusion results in pancreas divisum, whereby the two parts of the pancreas remain distinct to variable extent, each with its own duct [*Source*: UpToDate.com; Graphic 78,995 Version 3.0]. (**b**) Improper rotation of the pancreatic buds may lead to annular pancreas, in which the gland encircles the duodenum. This birth defect produces complete obstruction (atresia) or partial obstruction (stenosis) of the duodenum (Reproduced with permission from Moore et al., "*The developing human: Clinically oriented embryology*", 10th edition. Copyright Elsevier/Saunders 2015)

Table 1.1 Anatomic categorization of congenital pancreatic anomalies and variants

Ventral/dorsal ductal malfusion 1. Pancreas divisum 2. Incomplete pancreas divisum 3. Isolated dorsal segment
Rotation or migration problems 1. Annular pancreas 2. Ectopic pancreas 3. Ectopic papillae
Agenesis or hypoplasia
Ductal duplication
Atypical ductal configuration
Anomalous pancreatobiliary ductal junction
Cystic malformations

location of the two duct systems (Fig. 1.3a). Pancreas divisum is found in approximately 10% of individuals and is usually asymptomatic (in over 95% of individuals); it has been found to be a cause of recurrent acute and chronic pancreatitis. Another rare developmental anomaly is termed *annular pancreas*. In this case the ventral pancreatic bud has a bifid configuration, which leads to the encirclement of the duodenum and which can lead to narrowing of the duodenum (Fig. 1.3b). Approximately half of patients with annular pancreas also have pancreas divisum [4, 5]. Other congenital pancreatic anomalies are shown in Table 1.1.

1.1.2 Surgical Anatomy

In the healthy adult, the pancreas is a soft, retroperitoneal glandular organ, lying transversely and oblique and draped over the vertebral column at the level of L1–L2 vertebrae (Fig. 1.4). The bulk or volume of the pancreas varies and increases during the first 2–3 decades of life but progressively atrophies with aging.

The pancreas is divided into five parts: the head, neck, body, tail, and uncinate process (Fig. 1.4). The neck, head, and uncinate process are encompassed by the C-loop of the duodenum, to the anatomic right of the midline, and are in intimate relationship with the superior mesenteric vessels medially. The body extends laterally to the anatomic left, posterior to the stomach, with the tail terminating in the splenic hilum. The organ is surrounded by a thin capsule that is loosely attached to its surface. Most of the anterior surface of the pancreas is covered with peritoneum, except where it is crossed by the root of the transverse mesocolon, as well as where there is direct contact with the first part of the duodenum and the splenic hilum (Fig. 1.4).

The head of the pancreas is the thickest part of the gland. Anteriorly, it is related to the origin of the transverse mesocolon. Posteriorly, the head is related to the inferior vena cava (IVC), the right gonadal vein near its entrance into the vena cava, and the right crus of the diaphragm. The common bile duct runs either on the posterior surface of the pancreatic head or is embedded within the parenchyma of the gland.

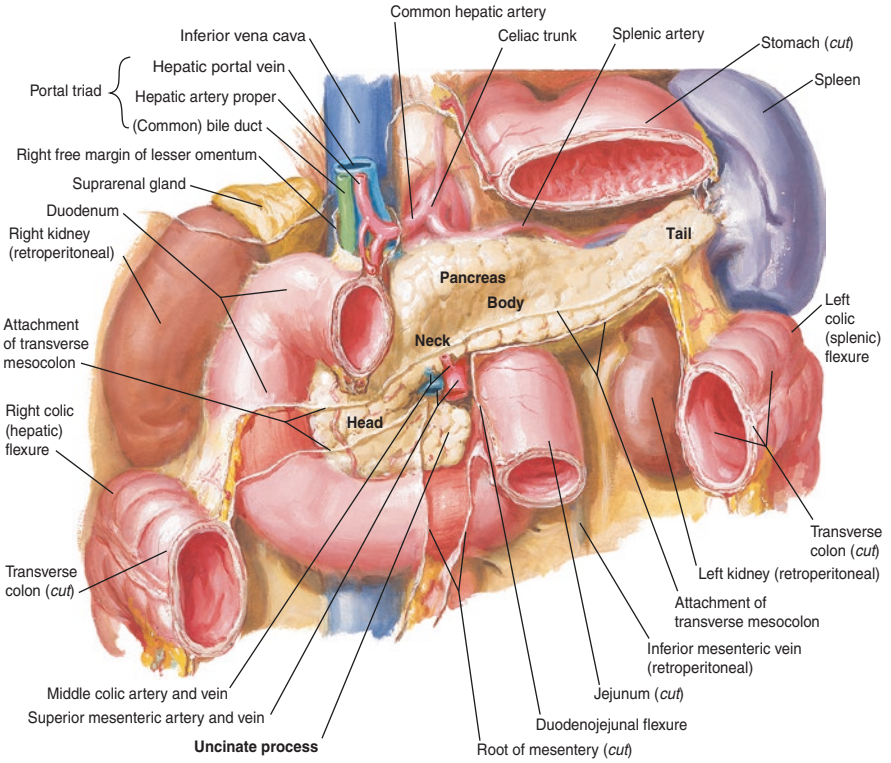

Fig. 1.4 The pancreas in situ [*Source*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders]

The transitional zone between the head and the body of the pancreas is termed the neck. It is defined by its anatomic location anterior to the formation of the portal vein (usually by the confluence of the superior mesenteric and splenic veins). It is approximately 2 cm wide and usually the most anteriorly located portion of the pancreas. Anteriorly the neck is covered by peritoneum and is related to the pylorus superiorly. Its posterior aspect is grooved by the superior mesenteric vein (SMV) and the portal vein (PV).

The anterior body of the pancreas is covered by the peritoneal layer that constitutes part of the posterior wall of the lesser sac (Fig. 1.5a). Toward the inferior border of the pancreas, the peritoneal layer is reflected anteroinferiorly to form the superior leaf of the transverse mesocolon (Fig. 1.5). The posterior surface of the body lies on the fusion fascia of Toldt in the retroperitoneum, the so-called bloodless plane of Treves. The posterior body is related to the abdominal aorta and the origin of the superior mesenteric artery (SMA), the left crus of the diaphragm, the left renal vein, the left kidney, and the left adrenal gland, from right to left (Figs. 1.4 and 1.5a).

The pancreas has important relationships to major blood vessels, of relevance to surgery of the pancreas. The splenic vein runs along the posterior surface of the

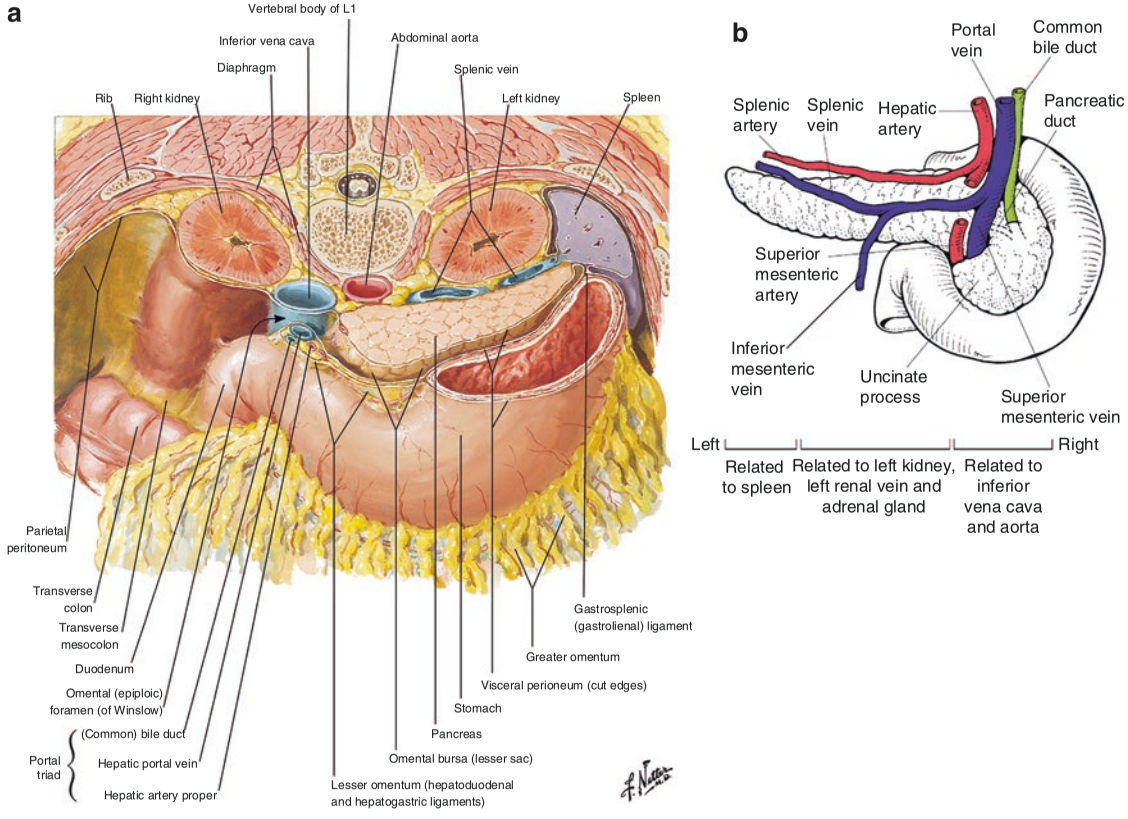

Fig. 1.5 Descriptive anatomy of the pancreas and its relationships to surrounding organs and vascular structures. (**a**) Axial cross-section at the level of L1 vertebral body. The omental bursa or lesser peritoneal sac is evident. Peripancreatic inflammation can lead to obliteration of this potential space by adhesions and complicate pancreatic dissection. (**b**) The posterior relationships of the duodenum and pancreas [*Sources*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders (**a**); Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders (**b**)]

gland in a groove of variable depth, sometimes almost entirely embedded within the pancreatic parenchyma (Fig. 1.5). The celiac trunk and its branches emanate along the superior border of the body, with the common hepatic artery running to the right and the splenic artery to the left (Figs. 1.4 and 1.5b). The inferior border of the pancreas is crossed posteriorly by the inferior mesenteric vein (IMV), typically at its confluence with the splenic vein, and it serves as a useful landmark for identification of the former vessel on cross-sectional imaging (Fig. 1.5b).

The tail of the pancreas is the relatively mobile, left-most part of the pancreas that is confined between the layers of the splenorenal ligament together with the splenic artery and the origin of the splenic vein (Figs. 1.4 and 1.5a). It is 1.5–3.5 cm long in adults and may extend variably to the hilum of the spleen in 50% of cases and may extend posterior to vessels in the hilum. This makes the tail of the pancreas vulnerable to injury during splenectomy and needs to be visualized prior to ligating the splenic vessels.

The uncinate process can be considered as a distinct part of the pancreas due to its different embryologic origin and its location extending posterior to the superior mesenteric vessels (Figs. 1.4 and 1.5). It extends in the plane between the superior mesenteric vessels anteriorly and the aorta posteriorly (Fig. 1.5b). Superiorly, it relates to the left renal vein. It lies immediately superior to the third part of the duodenum, such that tumors arising in the uncinate process can compress the former leading to duodenal obstruction (Figs. 1.4 and 1.5b).

The main pancreatic duct of Wirsung begins at the tail of the pancreas and runs through the body roughly midway between the superior and inferior border (Fig. 1.6a). It receives multiple small ductules throughout its course that drain the pancreatic parenchyma, thus increasing progressively in diameter from 1 mm in the tail to 3 mm in the head. It deviates inferiorly and posteriorly in the head as it

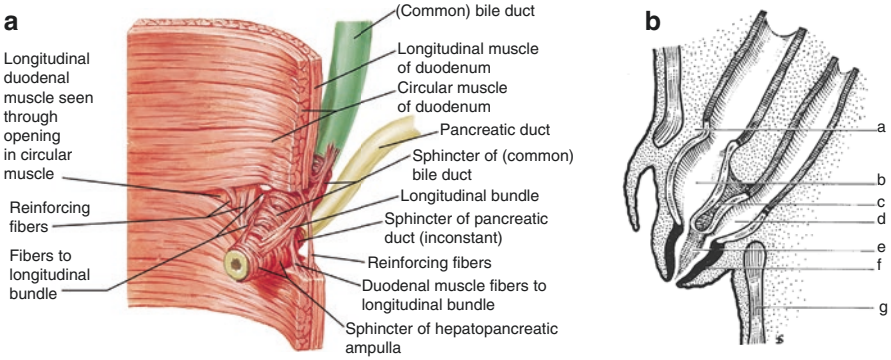

Fig. 1.6 Pancreatic duct and sphincter of Oddi. (**a**) Anatomy of the pancreatic duct at its junction with bile duct within the duodenal wall. (**b**) Schematic representation of the sphincter of Oddi: notch (a); biliary sphincter (b); transampullary septum (c); pancreatic sphincter (d); membranous septum of Boyden (e); common sphincter (f); smooth muscle of duodenal wall (g) [*Sources*: Netter, F.H., Atlas of human anatomy. 6th ed. 2014: Saunders (**a**); Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders (**b**)]

courses toward the main ampulla. The pancreatic duct and bile duct are usually separated by the transampullary septum before joining in a "Y" configuration within the duodenal wall (Fig. 1.6c). The terminal part of the two ducts is surrounded by a complex circular arrangement of smooth muscle fibers known as the sphincter of Oddi (Fig. 1.6b, c). The sphincter of Oddi is anatomically distinct from the muscular layers of the duodenum, and it has a dual function: (a) to regulate flow of biliary and pancreatic secretions into the duodenal lumen and (b) to impede reflux of intestinal content into the pancreatobiliary ductal system.

The accessory duct of Santorini runs superior and parallel to the duct of Wirsung. It drains part of the head of the pancreas into the minor duodenal papilla, roughly 1–2 cm proximal to the ampulla of Vater. The pattern of fusion of the main and accessory ducts is variable and can be entirely separate (pancreas divisum) (see above).

1.1.2.1 Regional Blood Supply and Lymphatic Drainage

The celiac trunk emerges from the aorta immediately after it exits the aortic hiatus of the diaphragm, just superior to the upper border of the pancreatic neck (Fig. 1.4). It runs anteriorly for a very short distance and then typically trifurcates into the left gastric artery (LGA), the splenic artery, and the common hepatic artery (CHA; Figs. 1.4 and 1.7a). The LGA may occasionally arise directly off of the aorta as a separate branch (Fig. 1.4). The splenic artery, the largest of the three celiac branches, runs a tortuous course posterior to the superior border of the pancreas toward the splenic hilum (Fig. 1.4). The splenic artery provides blood supply to the stomach via multiple short gastric arteries as well as via the left gastroepiploic artery in addition to the pancreas and spleen. The CHA initially travels forward and then curves to the right just above the pancreas. It gives rise to the gastroduodenal artery (GDA) and the right gastric artery, after which it becomes the proper hepatic artery. The proper hepatic artery ascends in the hepatoduodenal ligament to the left of the CBD and anterior to the portal vein for a short distance (Fig. 1.5a) and usually divides into left hepatic (LH) and right hepatic (RH) artery (Fig. 1.7a). The LH artery rises vertically toward the base of the umbilical fissure of the liver, giving off one or more branches to the caudate lobe as well as a branch to the quadrate lobe (segment IV) known as the middle hepatic artery. The RH artery usually passes behind the common hepatic duct and enters the hepatocystic triangle on its way to the right liver. It gives off the cystic artery that supplies the gallbladder, as well as branches to the caudate lobe.

The SMA arises from the aorta in an acute angle at the level of L1, about 1 cm distal to the origin of the celiac trunk (Fig. 1.5b). It runs inferiorly, posterior to the neck of the pancreas, the PV, and SMV and anterior to the left renal vein, the uncinate process, and the third part of the duodenum, eventually continuing into the small bowel mesentery to branch off into colic, ileal, and jejunal arteries (Fig. 1.5b). Near its origin it is surrounded by fatty tissue containing lymphatics and nerves which is frequently invaded by pancreatic cancer, a critical determinant of resectability.

The classic anatomy of the arterial blood supply to the liver, biliary tree, and pancreas is found in only approximately 60% of cases. A great degree of variability

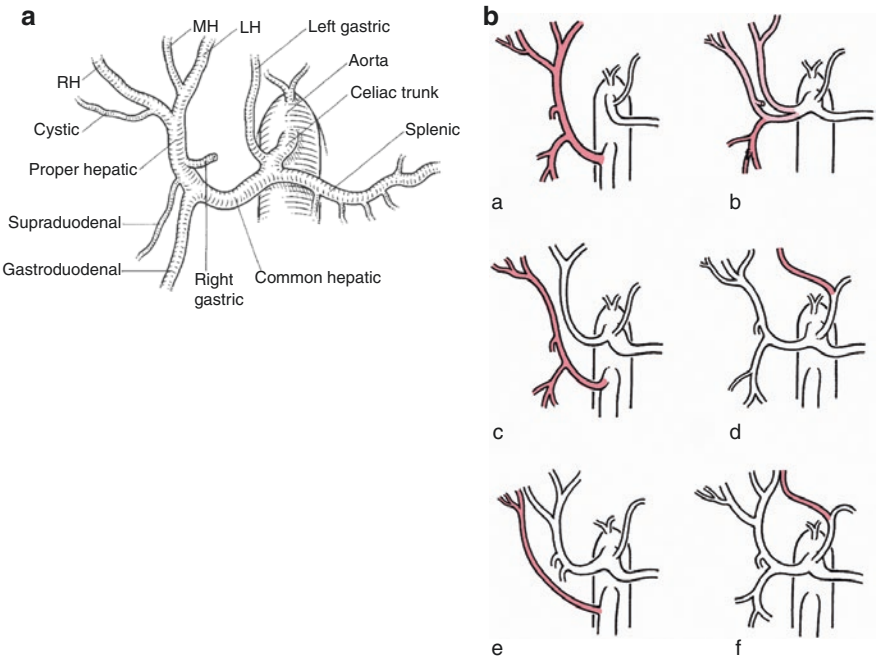

Fig. 1.7 Arterial inflow to the liver, biliary tree, and pancreas. (**a**) Usual anatomy of the celiac trunk. *LH* left hepatic artery, *MH* middle hepatic artery, *RH* right hepatic artery [*Source*: Jarnagin, W.R., et al., Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th ed. 2012, Philadelphia, PA: Saunders]. (**b**) Common anatomic variations of the branches of the celiac trunk

exists, and knowledge of these variations is very important for safe liver and pancreatic surgery (Fig. 1.7b). The CHA may arise from the SMA instead of the celiac trunk (Fig. 1.7b-a), coursing to the right of the portal vein and posterolateral to the CBD. This variation is important because it places the CHA at risk of operative injury during a pancreatoduodenectomy and should be identified preoperatively on imaging studies. The GDA may originate from the right hepatic artery (Fig. 1.7b-b) and may be duplicated. The RH artery arises from the SMA in up to 25% of cases (Fig. 1.7b-c, e) and may, or may not, anastomose with the LH artery. In a similar proportion of cases, the LH artery may be replaced by a branch arising from the left gastric artery (Fig. 1.7b-d) or duplicated (Fig. 1.7b-f). In rare occasions, either of the two hepatic arteries may be derived independently from the celiac trunk.

The pancreas is a richly vascularized organ. Consistent with its embryologic origin from the foregut-midgut junction, the pancreas receives its arterial inflow from branches of the celiac trunk as well as the SMA, which form multiple arcades within and around the gland (Fig. 1.8). The head and uncinate process along with the adjacent duodenum are supplied by two main arterial vessels: the superior pancreaticoduodenal artery (SPDA), a branch of the gastroduodenal artery, and the inferior pancreaticoduodenal artery (IPDA), a branch of the SMA (Fig. 1.8).

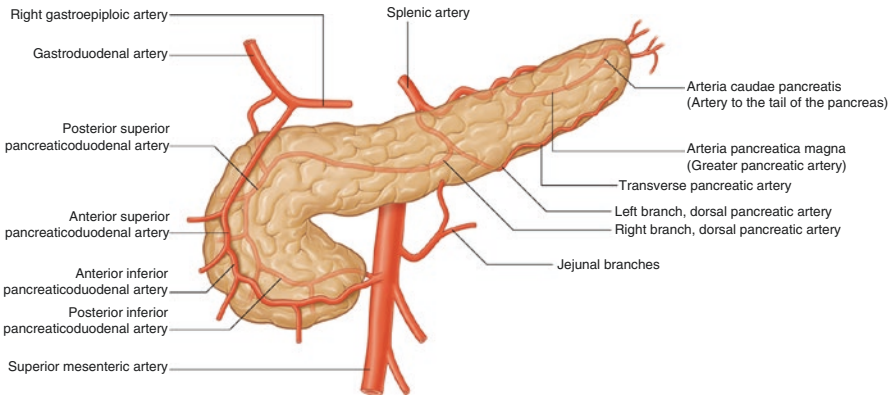

Fig. 1.8 The arteries supplying the pancreas form a rich anastomotic network around and within the gland [*Source*: Standring, S., Gray's Anatomy: the anatomical basis of clinical practice. 41st ed. 2016]

Each of these arteries divides into anterior and posterior branches. The anterior arteries unite to form the anterior (or ventral) pancreaticoduodenal arcade, and the posterior branches may unite in a posterior (dorsal) arcade (Fig. 1.8). The two arcades are connected by multiple small arteries that either run in the pancreaticoduodenal groove or traverse the pancreatic parenchyma. Usually a large branch known as the communicating artery (or middle pancreaticoduodenal arcade) runs between the main and accessory pancreatic ducts to connect the anterior arcade with the SPDA.

The body and tail of the pancreas are supplied by branches of the splenic artery (Fig. 1.8). These arteries enter the substance of the gland at its superior and inferior borders. During pancreatectomy, they should be ligated at the borders of the pancreas prior to transection, to prevent bleeding. Three large branches deserve special attention. The most prominent is the dorsal pancreatic artery, usually originating from the initial 2 cm of the CHA (Fig. 1.8). It supplies multiple small branches and divides into right and left terminal branches. The right runs toward the head to unite with the pancreaticoduodenal arcades, while the left branch courses toward the tail, eventually uniting with the transverse pancreatic artery. The other two named branches are the great pancreatic (*arteria pancreatica magna*) and the artery to the tail of the pancreas (*arteria caudae pancreatis*), both of which may join the transverse pancreatic artery running along the inferior border of the gland.

The pancreas drains into multiple peripancreatic lymph node stations via an extensive lymphatic network. Lymphatic vessels lying within the connective tissue septae of the gland unite to form larger branches that travel along the regional arteries. The lymphatic drainage of the body and tail of pancreas occurs into the nodes of the splenic artery and the inferior pancreatic and the splenic hilar nodes and from there to the celiac and preaortic nodes. The neck and head of the pancreas have a much wider drainage to the nodal stations of all the supplying arteries. Lymph node status is one of the most important prognostic factors of pancreatic cancer which

means that adequate lymphadenectomy and appropriate staging (including number of involved lymph nodes and presence of lymphatic invasion) are very important for appropriate management of these patients.

1.1.2.2 Innervation

The pancreas has a rich autonomic innervation that contributes to the regulation of both the exocrine and the endocrine functions of the gland. Parasympathetic nerve fibers distributed throughout the gland within the interlobular connective tissue transmit impulses to and from the vagus via its hepatic, gastric, and celiac branches. This is integrated with additional feedback from enteric neurons of the stomach and duodenum as well as sympathetic efferent neurons. In addition, sympathetic nerves innervate the intrapancreatic blood vessels and ducts, causing vasoconstriction and inhibiting exocrine secretion. Pain associated with pancreatic diseases is conveyed via visceral afferents of the celiac plexus and thoracic splanchnic nerves to the T6–T12 dorsal root ganglia, thus explaining its poor localization and ill-defined nature. However, in cases of extensive inflammatory or infiltrative processes involving the retroperitoneum, the regional somatic nerves may be involved leading to pain localized to the lower thoracic spine.

1.2 Biliary Tree

The biliary tree comprises of a series of epithelium-lined ductal structures which function as a conduit for bile from where it is produced in the liver to the duodenum. The biliary tree is divided into intrahepatic and extrahepatic portions, with the latter being further subdivided into the extrahepatic bile ducts and the accessory biliary apparatus (gallbladder and cystic duct). An in-depth understanding of the anatomy of the biliary tree and its associated vasculature constitutes an essential knowledge that must be possessed by every upper abdominal surgeon and general surgeon. Cholecystectomy is the most common abdominal procedure performed in developed countries, and biliary injury during this procedure continues to occur.

1.2.1 Embryology

The events leading to the embryologic development of the liver and biliary tree have some similarity to the ones described above for the pancreas. The liver primordium appears in the middle of the third week of gestation as an outgrowth of the endodermal lining at the ventral aspect of the distal foregut. The hepatic progenitor cells, or hepatoblasts, proliferate rapidly and penetrate the basal lamina to expand into the septum transversum—a mesodermal plate separating the pericardial cavity and the future abdominal cavity. As this outgrowth (termed hepatic diverticulum or liver bud) continues to grow into the septum transversum, the connection to the distal foregut becomes progressively narrower, leading to the formation of the bile duct (Fig. 1.1). The part of the septum transversum lying between the liver and the

ventral abdominal wall eventually transforms into the falciform ligament, while the part of it between the liver primordium and the foregut forms the lesser omentum. An evagination at the ventral aspect of the developing bile duct gives rise to the gallbladder and cystic duct. Bile formation commences around the 12th week of gestation.

Bidirectional communication of the endodermal liver primordium with the septum transversum mesenchyme and the overlying cardiac mesoderm is critical for liver specification. The entire gut endoderm has the potential to form liver tissue, but this is suppressed by the action of surrounding tissues, particularly the notochord. Bone morphogenetic proteins (BMPs) originating from the septum transversum enable the endoderm to respond to liver-inducing signals [6]—a phenomenon termed hepatic competence and mediated by expression of forkhead box proteins A (*FOXA*) transcription factors. Next, fibroblast growth factors (FGF) from the cardiac mesoderm disinhibit the liver specification program, which is tonically repressed, leading to liver induction. Vessel-forming endothelial cells also contribute to this process.

The proliferating hepatoblasts give rise to both mature hepatocytes and biliary epithelial cells, while the surrounding mesoderm of the septum transversum forms the stromal cells of the liver (primarily liver sinusoidal endothelial cells, hepatic stellate cells, and Kupffer cells) and its vasculature. Notably, at this stage of embryogenesis, the liver is an important site for hematopoiesis. Portal and hepatic vein radicals begin to form derived from the vitelline veins. The bipotential hepatoblasts initially express genes for adult hepatocytes (*ALB*, *HNF4A*) and biliary epithelial cells (*KRT19*). Subsequently, they downregulate either of the two and commit to the opposite lineage (Fig. 1.9a). This event appears to depend on the proximity of the cells to portal vein tributaries, possibly under the control of signals such as transforming growth factor-β (TGF-β) and Wnt originating in the periportal mesenchyme (Fig. 1.9).

Fig. 1.9 Embryologic development of the liver and biliary tree. (**a**) Model of hepatoblast differentiation into hepatocytes or biliary epithelial cells (BEC). Hepatoblasts are bipotential, which is reflected in expression of both hepatocytes (albumin) and BECs (CK19). Interaction with the periportal mesenchyme promotes differentiation to BECs by expression of BEC-promoting (OC1, OC2, HNF1β) and repression of mature hepatocyte (HNF4 and C/EBP) transcription factors. On the contrary, hepatoblasts not influenced by periportal mesenchyme signals (such as Wnt and TGF-β) undergo differentiation toward mature hepatocytes. Additional signals from the periportal mesenchyme (Notch, EGF, and HGF) facilitate ductal plate remodeling, while other factors (OSM, Dex, HGF, and Wnt) promote hepatocyte maturation (Reproduced with permission from Zorn, A.M., Liver development (October 31, 2008), StemBook, ed. The Stem Cell Research Community, StemBook, https://doi.org/10.3824/stembook.1.25.1, http://www.stembook.org. Copyright 2008 Aaron M. Zorn). (**b**) Formation of bile duct progresses from the hilum to the periphery of the liver. Sections at different stages of maturation are shown, with the least mature at the periphery (ductal plate; section 1) and mature bile ducts near the hilum (section 4). Part of the ductal plate cells form asymmetrical ducts that result in mature bile ducts, while the rest regress (Reproduced with permission from [7])