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Review

On the development of the hepatopancreatic ductal system

Alethia Villasenor*, Didier Y.R. Stainier*

Department of Developmental Genetics, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

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ABSTRACT

The hepatopancreatic ductal system is the collection of ducts that connect the liver and pancreas to the digestive tract. The formation of this system is necessary for the transport of exocrine secretions, for the correct assembly of the pancreatobiliary ductal system, and for the overall function of the digestive system. Studies on endoderm organ formation have significantly advanced our understanding of the molecular mechanisms that govern organ induction, organ specification and morphogenesis of the major foregut-derived organs. However, little is known about the mechanisms that control the development of the hepatopancreatic ductal system. Here, we provide a description of the different components of the system, summarize its development from the endoderm to a complex system of tubes, list the pathologies produced by anomalies in its development, as well as the molecules and signaling pathways that are known to be involved in its formation. Finally, we discuss its proposed potential as a multipotent cell reservoir and the unresolved questions in the field.

Contents

Abbreviations: A-P, anteroposterior; APB, anterior pancreatic bud; BA, biliary atresia; CBD, common bile duct; CMV, cytomegalovirus; CD, cystic duct; DE, definitive endoderm; E, embryonic day of gestation; EHB, extrahepatic biliary; EHBA, extrahepatic biliary atresia; EHD, extrahepatic duct; EPD, extrapancreatic duct; HPD, hepatopancreatic ductal; hpf, hours post fertilization; IHD, intrahepatic duct; IPD, intrapancreatic duct; LPM, lateral plate mesoderm; PD, pancreatobiliary ductal sytem; STM, septum transversum mesenchyme; VE, visceral endoderm.

* Corresponding author.
E-mail addresses: alethia.villasenor@mpi-bn.mpg.de (A. Villasenor), didier.stainier@mpi-bn.mpg.de (D.Y.R. Stainier).

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1. Anatomy of the hepatopancreatic ductal system

1.1. Overview of the hepatopancreatic ductal system

The digestive system is composed of the gastrointestinal tract (mouth, pharynx, esophagus, stomach, intestine) and its accessory organs (salivary glands, liver, pancreas and gallbladder). The liver and pancreas provide exocrine secretions necessary for food digestion, which are collected by a network of ducts that acts as a plumbing system, distributing them to the gallbladder for storage or to the digestive tract for food processing.

The hepatopancreatic ductal (HPD) system is part of this ductal network and it includes the ducts that connect the liver, pancreas, and gallbladder to the digestive tract (Fig. 1). The HPD system consists of the extrahepatic duct (EHD), the cystic duct (CD), the common bile duct (CBD) and the extrapancreatic duct (EPD) and together with the intrahepatic bile ducts (IHD's) and the intrapancreatic ducts (IPD's) they form the pancreatobiliary ductal (PD) system [1–3]. The PD system is in charge of transporting the pancreatic digestive enzymes produced by the acini of the pancreas, as well as the bile acid produced by the hepatocytes of the liver into the intestine.

The HPD system is essential for the function of the digestive system. However, little is known about the molecular mechanisms that regulate its formation. This review covers our current understanding of the development of the HPD system by examining studies performed in zebrafish, mouse, and humans.

1.2. Organization of the ductal system

The PD system includes the pancreatic ductal system and the hepatic ductal (aka biliary) system [1]. The biliary system, or biliary tree, establishes the network of ducts that transport the bile produced by the liver to the intestine. It is divided into the extrahepatic biliary (EHB) system and intrahepatic biliary system. The extrahepatic biliary system consists of the EHD, CD and CBD, whereas the intrahepatic biliary system encompasses the IHD's (canals of Hering, ductules, interlobular, septal, area and segmental bile ducts). Hepatocytes organize apically towards bile canaliculi where they secrete bile. Bile then flows towards the canals of Hering, interlobular bile ducts, and the rest of IHD's, which are organized in a hierarchical manner, moving the bile into progressively larger ducts until it reaches the EHD. Once in the EHD, the bile is routed to the intestine or via the CD to the gallbladder for storage [4–10].

The pancreatic ductal system is a group of interconnected ducts in control of the transport of the pancreatic juice (digestive enzymes, electrolytes, and bicarbonate ions) to the intestine. In a similar fashion as in the liver, acinar cells organize apically towards the ducts, where they secrete pancreatic juice [11]. The pancreatic juice then flows through a hierarchical IPD network, until it reaches the EPD, where it is then transferred to the intestine through the hepatopancreatic ampulla. The EPD connects with the CBD to join the pancreas with the biliary system [2].

Constituents of both the biliary system and the pancreatic ductal system form the HPD system. The HPD system is the collection of tubes that connect the pancreas to the liver, but it does not include the ductal networks of the individual organs (IHD's or IPD's) (Fig. 1). The HPD system is required to distribute to the intestine secretions that aid in digestion and absorption of metabolites as well as to ensure structure and stability of the accessory organs with respect to the digestive tract.

There are some minor differences in the nomenclature used to describe the components of the HPD system across species, probably due to intrinsic morphological differences. In the murine model, the EHD is referred to as the 'right or left hepatic ducts' and the term 'extrahepatic ducts' is applied collectively to the hepatic ducts, CD, and CBD [8]. In humans, the EHD is also named the 'right or left hepatic ducts'. However, humans have an additional extrahepatic duct, the 'common hepatic duct', which emerges from the porta hepatis and brings the right and left hepatic ducts into the CBD. Hence, the EHD in humans includes the hepatic ducts and the common hepatic duct [12,13]. In addition, the EPD is known as the 'pancreatic duct' or the 'duct of Wirsung', the CBD is simply referred to as the 'common duct', and the merging point of the EPD and CBD, before both tubes converge into the Ampulla of Vater, is known as the 'common hepatopancreatic duct' [12,13] (Fig. 1). For convenience to the reader, in this review we do not make a distinction in terminology and the terms EPD, EHD and CBD are applied across species.

1.3. Architecture of the HPD system

The ducts of the biliary system are lined by epithelial cells (cholangiocytes), which differ in size and function depending on their location. Small and cuboidal cholangiocytes reside in the fine canals of Hering. They are highly proliferative and believed to be the progenitors of the large cholangiocytes, which reside in the interlobular ducts and wider IHD's [9,14]. The canals of Hering are lined by a single layer of hepatocytes as well as with cuboidal cholangiocytes [9,15]. As the IHD's progressively increase in diameter, extending to the EHD's, connective tissue accumulates around the ducts and cholangiocytes acquire a columnar shape. The ducts of the HPD system are then lined by columnar epithelial cells and surrounded by large amounts of connective tissue that contains elastic fibers and occasionally smooth muscle fibers. Smooth muscle fibers are mostly found in the CD close to the neck of the gallbladder and in the EHD near the porta hepatis. The HPD system is held together by two layers of hepatoduodenal ligament, serous membranes that extend from the porta hepatis to the duodenum and maintain the structure of the HPD system [16–19].

2. Morphogenesis of the HPD system

The HPD system is derived from the foregut endoderm. The molecular mechanisms guiding endoderm induction and gut morphogenesis are highly conserved between different model organisms, including chicken, frog, mouse, and zebrafish [20–22]. Here, we provide the basis of endoderm formation and patterning in mouse and zebrafish, as well as a detailed description of the anatomical origin of the HPD system and the morphological steps that shape its formation.

2.1. From scattered cells to tube formation

In the mouse embryo, at embryonic day of gestation (E) 6.0, multipotent epiblast cells migrate through the primitive streak, undergo an epithelial-to-mesenchymal transition and emerge as mesodermal or endodermal cells depending on the levels of Nodal exposure [20–22]. Definitive endoderm (DE) cells, expressing