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Hepatology Snapshot:

The heterogeneity of the biliary tree

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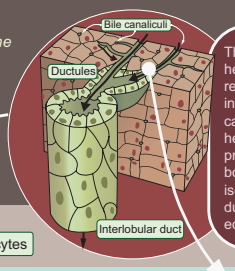
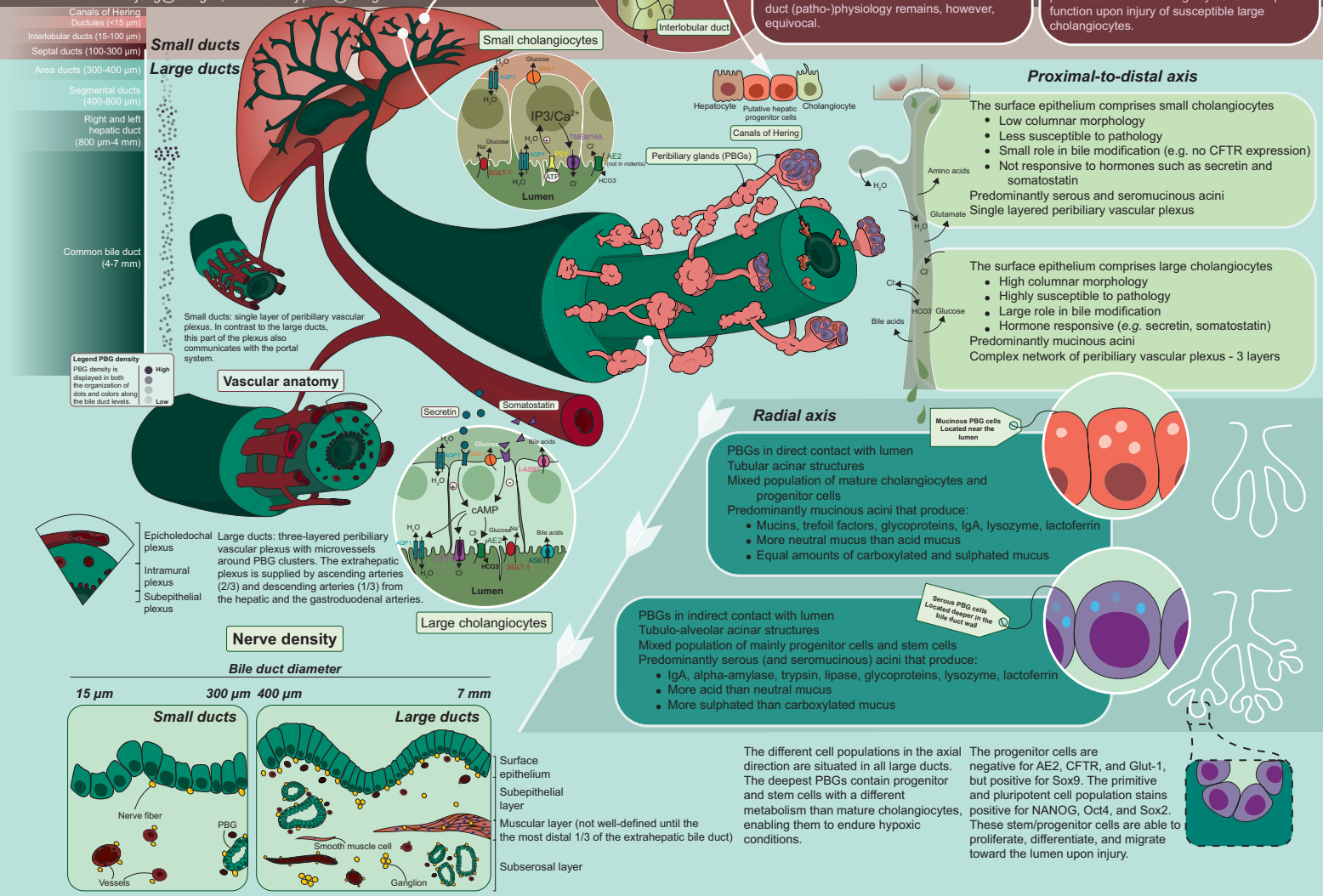


The canals of Hering are populated by both hepatocytes and cholangiocytes. These canals represent the only hepatocyte-cholangiocyte interface in the human body. In addition, the canals of Hering are thought to harbour a hepatic progenitor niche. These liver stem/progenitor cells were able to differentiate into both hepatocytes and cholangiocytes when isolated in vitro. Their exact role in liver and bile duct (patho-)physiology remains, however, equivocal.

70% of bile is produced by hepatocytes. Bile is collected in the bile canaliculi and flows downstream through a merging network of ducts into the common bile duct. Along the way, cholangiocyte secretion contributes another 30% of the volume of bile. Large cholangiocytes lining the large bile ducts are primarily responsible for secretory and absorptive processes. Small cholangiocytes can adopt this function upon injury of susceptible large cholangiocytes.



Proximal-to-distal axis

The surface epithelium comprises small cholangiocytes
- Low columnar morphology
- Less susceptible to pathology
- Small role in bile modification (e.g. no CFTR expression)
- Not responsive to hormones such as secretin and somatostatin

Predominantly serous and seromucinous acini
Single layered peribiliary vascular plexus

The surface epithelium comprises large cholangiocytes
- High columnar morphology
- Highly susceptible to pathology
- Large role in bile modification
- Hormone responsive (*e.g.* secretin, somatostatin)

Predominantly mucinous acini
Complex network of peribiliary vascular plexus - 3 layers

Radial axis

Mucinous PBG cells Located near the lumen

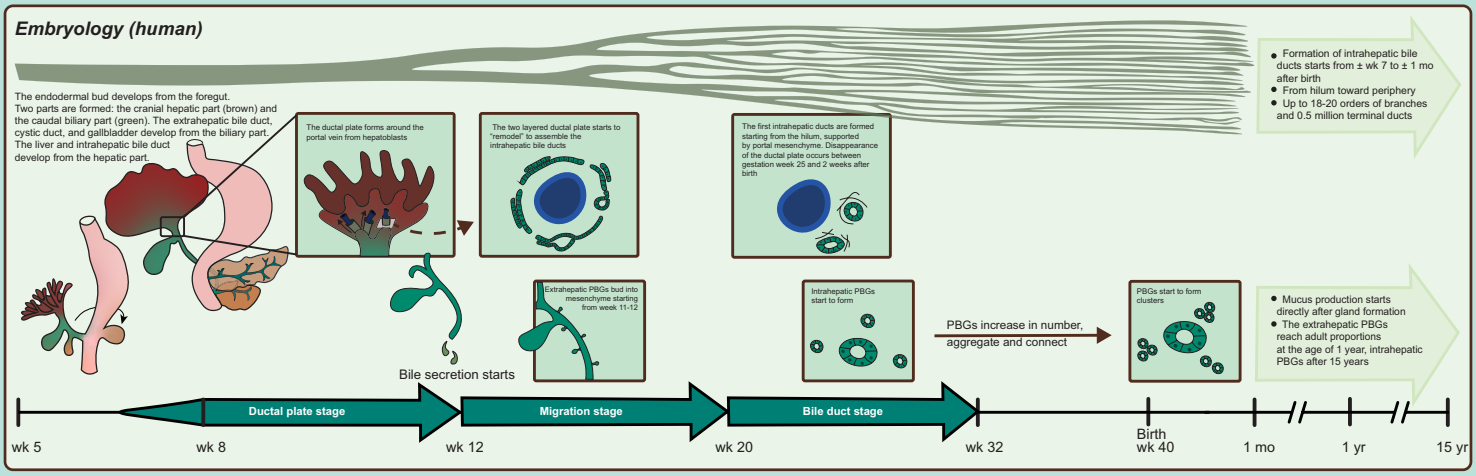
PBGs in direct contact with lumen
Tubular acinar structures
Mixed population of mature cholangiocytes and progenitor cells
Predominantly mucinous acini that produce:
- Mucins, trefoil factors, glycoproteins, IgA, lysozyme, lactoferrin
- More neutral mucus than acid mucus
- Equal amounts of carboxylated and sulphated mucus

Serous PBG cells Located deeper in the bile duct wall

PBGs in indirect contact with lumen
Tubulo-alveolar acinar structures
Mixed population of mainly progenitor cells and stem cells
Predominantly serous (and seromucinous) acini that produce:
- IgA, alpha-amylase, trypsin, lipase, glycoproteins, lysozyme, lactoferrin
- More acid than neutral mucus
- More sulphated than carboxylated mucus

The different cell populations in the axial direction are situated in all large ducts. The deepest PBGs contain progenitor and stem cells with a different metabolism than mature cholangiocytes, enabling them to endure hypoxic conditions.

The progenitor cells are negative for AE2, CFTR, and Glut-1, but positive for Sox9. The primitive and pluripotent cell population stains positive for NANOG, Oct4, and Sox2. These stem/progenitor cells are able to proliferate, differentiate, and migrate toward the lumen upon injury.



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The biliary tree and the liver are inseparably linked. They complement each other and are generally considered 1 organ. However, the biliary tree has a well-defined identity of its own. Moreover, if you look closely, an astonishing number of structural, functional, and embryological variation is evident within this ductular network.

Grossly, the heterogeneity of the biliary tree can be appreciated along both the proximal-to-distal axis and the radial axis.[1] Hepatocyte bile canaliculi are located at the most proximal end of the biliary tree and transition into the canals of Hering (CoH), which contains progenitor cells and is where cholangiocytes are juxtaposed to hepatocytes. From the CoH, bile flows into the ductules (<15 μm diameter) and through the merging network of ducts (increasing in size from 15 μm to several mm in diameter) into the duodenum (sizes apply to the human bile duct). The cholangiocyte population changes from proximal to distal: generally, the interlobular and septal ducts are lined with small cholangiocytes while the large intrahepatic, segmental, and hepatic ducts and the common bile duct are lined with large cholangiocytes.[2] As bile duct diameter increases, the cytoplasm-to-nucleus ratio increases, cholangiocytes become hormone-responsive, and the involvement of cholangiocytes in bile modification intensifies. The total number of peribiliary glands (PBGs) increases as well as the number of mucus producing PBGs.[3] Distally located cholangiocytes play an increasing role in secretion and absorption. At the same time, the vascular and neural networks merge into a complex network of multiple layers in line with the growing role of the bile ducts in bile modification[4,5] such that the distal end of the bile duct harbors a 3-layered peribiliary vascular plexus surrounding the PBGs. In addition, the bile duct is extrinsically and intrinsically innervated, resembling the gut. Biliary-nerve contacts are rare in the CoH, are more common in the ductules and interlobular ducts, and are part of multiple plexuses moving toward the common bile duct.[5]

Radial axis heterogeneity refers to the epithelial diversity from the lumen toward the deeper PBGs in the bile duct wall. This axis parallels the transition from mucus-producing cells toward serous acini and from mature cholangiocytes toward progenitor/stem cells.[1,3]

The structural diversity in both the proximal-to-distal and radial directions reflects the functional heterogeneity along the biliary tree and its ability to withstand injury. Small cholangiocytes are more resistant to severe damage than large cholangiocytes and are able to proliferate, differentiate, and ultimately replace the large cholangiocytes, as has been shown after bile duct ligation of the rat bile duct.[2] In the radial direction, PBGs harbor endoderm progenitor cells and stem cells that are less susceptible to damage than mature cholangiocytes. This epithelial cell compartment is able to survive in hypoxic conditions, ensuring the regeneration of injured epithelia.[6] Participation of PBGs in bile duct regeneration has been demonstrated in a tissue culture using human extrahepatic bile duct and a mouse model in which lineage tracing was used after chemically induced biliary injury.[6,7]

Finally, the heterogeneity of the biliary tree is underlined by its embryological origins and the existence of distinct small and large duct cholangiopathies. The intrahepatic and extrahepatic bile duct develop from different parts of the ventral foregut at different gestational stages, merging at the level of the hepatic hilum.[8] Considering the embryological, structural, and biological heterogeneity of the bile duct, it should be no surprise that cholangiopathies manifest at specific sites of the biliary tree. For example, primary sclerosing cholangitis affects large ducts whereas primary biliary cholangitis targets small ducts;[9] ischemic cholangiopathies, as would be expected from their exclusively arterial blood supply, are restricted to large bile ducts. Biliary atresia begins in the extrahepatic duct whereas Alagille Syndrome is characterized by paucity of the interlobular ducts.[10] Thus, it is clear that the biliary tree is highly complex and can by no means be considered a “simple” conduit for bile.

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Conflict of interest
The authors of this study have no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions
IEMdJ designed and executed the artwork and wrote the text. MCvdH, RGW, and RJP edited the figure and wrote and edited the text.

Supplementary data
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Author names in bold designate shared co-first authorship

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