The heterogeneity of the biliary tree

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 growth of susceptible large cholangiocytes.

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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. Hebacyte 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. As bile duct diameter increases, the cytoplasm-to-nucleus ratio increases, cholangiocytes become hormone-responsive, and the involvement of cholangiocytes in bile duct proliferation intensifies. The total number of peribiliary glands (PBGs) increases as well as the number of mucus producing PBGs. 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 modification4,5 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.

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. 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. 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.5,7

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. 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; 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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Authors’ contributions
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References
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