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Review

Chronic cholestatic liver diseases: Clues from histopathology for pathogenesis

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ABSTRACT

Chronic cholestatic liver diseases include fibrosing cholangiopathies such as primary biliary cirrhosis or primary sclerosing cholangitis. These and related cholangiopathies clearly display pathologies associated with (auto)immunologic processes. As the cholangiocyte's apical membrane is exposed to the toxic actions of the bile fluid, the interaction of bile with cholangiocytes and the biliary tree in general must be considered to completely understand the pathogenesis of cholangiopathies. While the molecular processes involved in the hepatocellular formation of bile are well understood in both normal and pathophysiologic conditions, those in the bile ducts of normal liver and in livers with cholangiopathies lag behind. This survey highlights key mechanisms known to date that are important for the formation of bile by hepatocytes and its modification by the biliary tree. It also delineates the clinical pathophysiologic findings for cholangiopathies and puts them in perspective with current experimental models to reveal the pathogenesis of cholangiopathies and develop novel therapeutic approaches.

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1. Introduction

The liver as a key organ is involved in the synthesis of plasma proteins, in energy homeostasis, in protecting the body from potentially harmful xenobiotics, and in metabolism and the elimination of xenobiotics and bile formation. Bile is needed to digest fat and absorb lipids and fat-soluble vitamins from the intestine (Hofmann, 2009; Hofmann and Hagey, 2008). It is also the main vehicle for the elimination of poorly water-soluble compounds from the liver into the gut. Undisturbed and ongoing bile formation so is a pivotal process for our body. The functional unit for bile formation starts with the hepatocytes and extends over canaliculi to bile ductules and bile ducts. Canaliculi, bile ductules and bile ducts are frequently referred to as the "biliary tree", whereby hepatocytes could be considered the leaves, bile canaliculi the slimmest branches, bile ducts the branches, and the choledochal duct the trunk.

Bile is composed of bile salts, lipids consisting of phosphatidylcholine and cholesterol, organic anions such as conjugates of bilirubin and xenobiotics, glutathione and small ions like sodium, chloride and bicarbonate (Esteller, 2008). Primary (or canalicular) bile is formed by hepatocytes and thereafter modified by bile ductules and ducts. Hepatic bile flow is the sum of bile salt-dependent bile flow, being driven by canalicular secretion of bile salts and of bile salt-independent bile flow mediated by canalicular secretion of other organic anions and by contributions from cholangiocytes in the bile duct (Trauner and Boyer, 2003).

2. Physiology of hepatocellular bile formation

Hepatocytes synthesize the bile salts in multiple steps from cholesterol and finally conjugate them to taurine or glycine (Russell, 2009). After synthesis, the latter are mixed with bile salts entering from the portal blood plasma and are secreted via the canalicular membrane into the canaliculi. Animal experiments have provided evidence that bile canaliculi may be able to contract to extrude their content (Watanabe et al., 1991). This contraction is paralleled by a reorganization of the canalicular and subcanalicular cytoskeleton (Tsukada and Phillips, 1993). From the canaliculi, bile salts travel down the biliary tree to empty into the small intestine. Along the small intestine, more than 90% of bile salts are absorbed and transported back to the liver by the portal circulation. In the liver, they are taken up from the sinusoids into the hepatocytes and secreted again into the canaliculi (Dawson et al., 2009). The roundtrip the bile salts take from the intestine to the liver and back is known as the enterohepatic circulation. Canalicular bile formation is an isoosmotic process driven by canalicular solute secretion, which is passively followed by water (Trauner and Boyer, 2003). Water reaches the canaliculi in a paracellular route via tight junctions (TJ) and across hepatocytes, facilitated by aquaporins (Masyuk and LaRusso, 2006). Any disturbance in the bile flow is a pathophysiologic process called cholestasis.

Most bile salts are imported from the sinusoidal blood plasma into hepatocytes in a sodium-dependent and to a lesser extent in a sodium-independent manner (Meier and Stieger, 2002; Stieger, 2011). Hepatocellular uptake of conjugated bile salts depends on the sodium taurocholate cotransporting polypeptide (NTCP, *SLC10A1*), which is expressed in the basolateral plasma membrane of hepatocytes (Dawson et al., 2009; Stieger, 2011) (Fig. 1). NTCP is an electrogenic transporter (Weinman, 1997) that moves bile salts together with two sodium ions, utilizing both the inside negative membrane potential (Boyer et al., 1992) and the sodium-gradient over the basolateral membrane for the uptake of bile salts (Hagenbuch and Meier, 1996). Consequently, NTCP can import bile salts into hepatocytes against a concentration gradient. Sodium-independent uptake of bile salts into hepatocytes depends on organic anion transporting polypeptides (OATPs) of which OATP1B1 (*SLCO1B1*), OATP1B3 (*SLCO1B3*) and OATP2B1 (*SLCO2B1*) are expressed in the basolateral membrane of hepatocytes (Fig. 1). OATP2B1 does not act as a bile salt transporter (Hagenbuch and Meier, 2004; Meier and Stieger, 2002; Roth et al., 2012). *In vivo*, OATPs have a preference for unconjugated bile acids (Meier et al., 1997), as was recently supported by studies with genetically modified mice (van de Steeg et al., 2010). In addition, OATPs transport the metabolic end-product bilirubin (Briz et al., 2003; Cui et al., 2001; Konig et al., 2000; van de Steeg et al., 2010) and many widely prescribed drugs (Hagenbuch and Dawson, 2004; Hagenbuch and Gui, 2008; Konig, 2011).

How bile salts reach the canalicular plasma membrane after their uptake is not known in detail, but it is likely that cytoplasmic binding proteins are involved (Stieger, 2011). To exit at the canalicular plasma membrane, bile salts have to overcome a steep concentration gradient, which is mediated by the ATP-binding cassette (ABC) transporter super family member bile salt export pump BSEP (*ABCB11*) (Stieger, 2009, 2011; Stieger and Higgins, 2007) (Fig. 1). The canalicular export of bile salts represents the rate limiting step for bile salt transport across hepatocytes (Meier and Stieger, 2002; Reichen and Paumgartner, 1976) and is subject to extensive regulation (Stieger, 2011).

Quantitatively, the biliary phospholipids consist almost entirely of phosphatidylcholine. Its secretion into canalicular bile requires the ABC transporter multidrug resistance protein 3 (MDR3, *ABCB4*) (Oude Elferink and Paulusma, 2007)

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