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Biliary epithelium: A neuroendocrine compartment in cholestatic liver disease

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Summary Hepatic fibrosis is characterized by abnormal accumulation of extracellular matrix (ECM) that can lead to ductopenia, cirrhosis, and even malignant transformation. In this review, we examine cholestatic liver diseases characterized by extensive biliary fibrosis such as primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), polycystic liver disease (PLD), and MDR2$^{-/-}$ and BDL mouse models. Following biliary injury, cholangiocytes, the epithelial cells that line the bile ducts, become reactive and adopt a neuroendocrine phenotype in which they secrete and respond to neurohormones and neuropeptides in an autocrine and paracrine fashion. Emerging evidence indicates that cholangiocytes influence and respond to changes in the ECM and stromal cells in the microenvironment. For example, activated myofibroblasts and hepatic stellate cells are major drivers of collagen deposition and biliary fibrosis. Additionally, the liver is richly innervated with adrenergic, cholinergic, and peptidergic fibers that release

Abbreviations: α, 7nAChRAlpha7 nicotinic acetylcholine receptor; α, -CGRPAlpha-calcitonin gene-related peptide; AT, 1/2Angiotensin 1/2 receptor; AVP, Arginine vasopressin; BDL, Bile duct ligation; CLR, Calcitonin-like receptor; CNS, Central nervous system; cAMP, Cyclic adenosine monophosphate; CREBc, AMP response element binding protein; EMT, Epithelial to mesenchymal transition; ECM, Extracellular matrix; FXR, Farnesoid X receptor; FAK, Focal adhesion kinases; TGR5G, protein-coupled bile acid receptor; HSC, Hepatic stellate cells; H1/H2, Histamine 1/2 receptors; MMP, Matrix metalloproteinases; MDR2, Multidrug resistance protein 2; M3 R, Muscarinic acetylcholine receptor 3; NPY, Neuropeptide Y; PBP, Peribiliary plexus; PLD, Polycystic liver disease; PKA, Protein kinase A; PSC, Primary sclerosing cholangitis; PBC, Primary biliary cholangitis; RAS, Renin-angiotensin-aldosterone; AANAT, Serotonin N-acetyltransferase; SP, Substance P; TIMPS, Tissue inhibitors of proteinases; TGF-β, Transforming growth factor-beta; VEGF, Vascular endothelial growth factor; Wnt, Wingless.

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neurohormones and peptides to maintain homeostasis and can be deranged in disease states. This review summarizes how cholangiocytes interact with their surrounding environment, with particular focus on how autonomic and sensory regulation affects fibrotic pathophysiology. Published by Elsevier Masson SAS.

Introduction

Cholangiocytes are specialized epithelial cells lining the intra and extrahepatic bile ducts that function to modify bile composition through water and electrolyte secretion and absorption and to detoxify xenobiotics. Bile is initially secreted by the apical surface of hepatocytes into specialized interstitial spaces called bile canaliculi that are sealed by tight junctions. Bile flows towards the portal tracts where it first enters the small intrahepatic biliary tree lined with ''small'' cholangiocytes (~8 μm) at the Canals of Herring. The biliary tree becomes progressively larger to form large intrahepatic bile ducts, lined by ''large'' cholangiocytes (~15 μm), and ultimately extrahepatic bile ducts empties bile into the duodenum [1,2]. Large and small cholangiocytes, lining large and small bile ducts, respectively, exhibit distinct morphological, functional, and proliferative features that vary based on the disease state [1—3].

Disease targeting cholangiocytes, termed cholangiopathies, lead to cholestasis, increased biliary pressure, biliary fibrosis, and chronic inflammation that can trigger cirrhosis or malignant transformation [4]. Cholestasis refers to the accumulation of bile in hepatic tissue following intrahepatic or extrahepatic biliary obstruction. Extrahepatic obstruction can be caused by gallstones, pancreatic ductal adenocarcinoma, strictures, or cholangiocarcinoma, whereas intrahepatic biliary diseases include primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and polycystic liver disease (PLD) [5]. Cholangiopathies are commonly characterized by four main stages of disease. Disease progression begins with portal hepatitis and inflammation with bile duct destruction. This is followed by periportal hepatitis and biliary proliferation, which can progress to fibrous septa or bridging necrosis in the liver and eventually stage four, cirrhosis [6]. During late stages of disease, the balance between proliferation and cholangiocyte death is disturbed, leading to ductopenia and further biliary fibrosis [7]. However chronic inflammation can also induce cholangiocyte hyperplasia resulting in an increased risk for malignant transformation, especially in primary sclerosing cholangitis [4]. Symptoms of cholangiopathies are reflective of the cholestatic process and eventual loss of liver function including fatigue, pruritus, portal hypertension and xanthomas [6]. Current treatment options are limited to ursodeoxycholic acid supplementation, providing the best improvement in PBC patients [7].

Cirrhosis is end-stage, irreversible liver scarring and the leading cause of liver failure for which the current mainstay of treatment is liver transplant. There is about an 80% mortality rate without transplant once full hepatic failure ensues [5,8]. Major consequences of cirrhosis include portal hypertension and its effects such as ascites, variceal bleeding, hepatic encephalopathy and renal failure [9]. Liver fibrosis or scar formation is characterized by abnormal accumulation of extracellular matrix and further progression to cirrhosis involves diffuse scarring with dense fibrous septations around regenerating hepatocytes [5]. The onset of liver fibrosis begins with injury or insult to either the hepatic parenchyma or the biliary epithelium, as seen in cholestatic disease. In the face of chronic injury hepatocyte regeneration is no longer sufficient and ductular proliferation of intrahepatic bile ducts takes place. An increased population of cholangiocytes accumulates at the border of the bile ducts and hepatic parenchyma, contributing to the progression of liver fibrosis through the recruitment of fibrogenic cells [5,7]. The etiology of injury plays a role in the cirrhotic pattern, with biliary fibrosis inducing toxic bile acid accumulation that leads to inflammation and activation of cholangiocytes and myofibroblasts that cause a portal—portal fibrotic picture [9].

The aim of this paper is to summarize the new and current research on the proliferative, neuroendocrine and secretory effects of cholangiocytes during cholestatic liver injury and the role they may play in initiating liver fibrosis.

Pathobiology of liver fibrosis

Microenvironment

The anatomical features and the microenvironment surrounding cholangiocytes play an important role in its pathophysiology. Bile ductules are formed by 4—5 ~8 μm diameter cuboidal-shaped small cholangiocytes [1,3], whereas large, columnar-shaped cholangiocytes (~15 μm diameter), make up the increasingly larger bile ducts [1,3]. The apical side of cholangiocytes facing the lumen possess single, primary cilia that is used to both sense the composition of passing bile and to physically help push bile along [5]. Additionally, cholangiocytes are linked by tight junctions to prevent backflow of water, solutes, and/or toxins. The epithelial barrier can become leaky over the course of injury and lead to the regurgitation of toxic substances back into the hepatic parenchyma.

Cholangiocytes sense and respond to their surrounding microenvironment to maintain homeostasis. Biliary epithelium sits atop a basement membrane that separates it from a matrix of proteoglycans and fibrous proteins produced and maintained by portal mesenchymal and fibroblast cells [10]. Proteoglycan fibers hold a large amount of water taking on a gel-like consistency that gives tissue the ability to withstand compressive forces. In addition, they also store signaling ligands for TGF-β and Wingless (Wnt) pathways that are released following injury or changes in the microenvironment such as mechanical stress or proteolytic cleavage [11]. In contrast, fibrous proteins are more rigid and provide

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