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Review

Bile acids and intestinal microbiota in autoimmune cholestatic liver diseases

You Li [a,1], Ruqi Tang [a,1], Patrick S.C. Leung [b], M. Eric Gershwin [b,*], Xiong Ma [a,**]

[a] Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, State Key Laboratory for Oncogenes and Related Genes, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, 145 Middle Shandong Road, Shanghai 200001, China
[b] Division of Rheumatology, Department of Medicine, Allergy and Clinical Immunology, University of California at Davis, Davis, CA, USA

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ABSTRACT

Autoimmune cholestatic liver diseases, including primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), are manifested as an impairment of normal bile flow and excessive accumulation of potentially toxic bile acids. Endogenous bile acids are involved in the pathogenesis and progression of cholestasis. Consequently, chronic cholestasis affects the expression of bile acid transporters and nuclear receptors, and results in liver injury. Several lines of evidence suggest that intestinal microbiota plays an important role in the etiopathogenesis of cholestatic liver diseases by regulating metabolism and immune responses. However, progression of the disease may also affect the composition of gut microbiota, which in turn exacerbates the progression of cholestasis. In addition, the interaction between intestinal microbiota and bile acids is not unidirectional. Bile acids can shape the gut microbiota community, and in turn, intestinal microbes are able to alter bile acid pool. In general, gut microbiota actively communicates with bile acids, and together play an important role in the pathogenesis of PBC and PSC. Targeting the link between bile acids and intestinal microbiota offers exciting new perspectives for the treatment of those cholestatic liver diseases. This review highlights current understanding of the interactions between bile acids and intestinal microbiota and their roles in autoimmune cholestatic liver diseases. Further, we postulate a bile acids-intestinal microbiota-cholestasis triangle in the pathogenesis of autoimmune cholestatic liver diseases and potential therapeutic strategies by targeting this triangle.

Contents

Abbreviations: PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; CYP7A1, cholesterol 7a-hydroxylase; CDCA, chenodeoxycholic acid; CA, cholic acid; LCA, lithocholic acid; DCA, deoxycholic acid; mROS, mitochondrial reactive oxygen species; MPT, mitochondrial permeability transition; AE2, anion exchange 2; BECs, biliary epithelial cells; DCs, dendritic cells; BSEP, bile salt export pump; MRP, multidrug resistance-associated protein; OST, organic solute transporter; ASBT, apical sodium dependent bile acid transporter; NRs, nuclear receptors; FXR, Farnesoid X receptor; SHP, small heterodimer partner; FGF, fibroblast growth factor; NF-κB, nuclear factor-κB; TGR5, transmembrane G protein-coupled receptor 5; UDCA, ursodeoxycholic acid; norUDCA, 24-norUrsodeoxycholic acid; OCA, obeticholic acid; GF Mdr2-/-, germ free multidrug resistance 2 knockout; PAMPs, pathogen-associated molecular patterns; PDC-E2, pyruvate dehydrogenase complex-E2; SCFAs, short-chain fatty acids; PSA, polysaccharide A; FUT2, fucosyltransferase 2; FMT, fecal microbiota transplantation; BSH, bile salt hydrolase; TβMCA, taurine-conjugated β-muricholic acid.

* Correspondence to: M.E. Gershwin, Department of Medicine, Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA.
** Correspondence to: X. Ma, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, 145 Middle Shandong Road, Shanghai 200001, China.
E-mail addresses: megershwin@ucdavis.edu (M.E. Gershwin), maxiongmd@hotmail.com (X. Ma).
[1] YL and RQT joint first co-authorship.

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1. Introduction

In autoimmune cholestatic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), accumulation of specific bile acids in the liver triggers inflammatory responses leading to liver injury [1]. PBC, formerly known as "primary biliary cirrhosis", is characterized by female predominance, genetic predisposition, antimitochondrial antibodies, and immune mediated destruction of intrahepatic small bile ducts leading to cholangitis, fibrosis and potentially cirrhosis [2,3]. PSC is a chronic idiopathic cholestatic liver disease, characterized by ongoing inflammation, destruction, and fibrosis of intrahepatic and extrahepatic bile ducts [4–6]. PSC is strongly associated with inflammatory bowel disease, especially with ulcerative colitis [7]. Nonetheless, PSC differs from classical autoimmune diseases because it is male predominant and is poorly responsive to immunosuppressive treatment [8]. Current evidence suggests that PBC and PSC are heterogeneous, complex disorders with genetic, immunologic and environmental components [6,9–15]. However, the etiology of these diseases remains obscure and effective medical treatments are lacking [16–19]. Patients with end-stage liver disease are offered liver transplantation.

The liver receives 70% of its blood supply from the portal vein, the direct venous outflow of the intestine. The close relationship between gut and liver is termed the gut-liver axis and has been first linked to liver pathogenesis in 1998 [20]. Various studies suggested that the gut-liver axis plays an important role in the initiation and progression of many autoimmune liver diseases, including PBC and PSC [21,22]. However, the mechanisms underlying the relationship between gut microbiota and cholestatic liver diseases are poorly understood.

This review mainly focuses on the interactions between bile acids and intestinal microbiota affecting cholestasis. We propose the importance of a bile acids-intestinal microbiota-cholestasis triangle in the pathogenesis of autoimmune cholestatic liver diseases as well as the therapeutic potential in targeting this triangle.

2. Bile acids in autoimmune cholestatic liver diseases

Bile acids are the major organic solutes of bile. They act as detergents to facilitate the absorption of dietary lipids and fat-soluble vitamins and maintain cholesterol homeostasis in the body. Bile acids are synthesized in the pericentral hepatocyte, through a series of reactions performed by cytochrome P450s. Cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting enzyme in bile acid synthesis. Most bile acids undergo conjugation with the amino acids taurine and glycine. After draining through the bile ducts into the hepatic duct, bile acids are released into the duodenum at a junction regulated by the sphincter of Oddi [23]. In the intestine, primary bile acids chenodeoxycholic acid (CDCA) and cholic acid (CA) are converted into secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA), respectively. About 95% of bile acids are then reabsorbed by the intestinal epithelium and into hepatocytes through the portal vein system, re-conjugated and re-secreted into the bile fluid, thereby completing the enterohepatic circulation [24]. The cellular and molecular mechanisms involved in the development of cholestatic liver diseases remain elusive. However, excessive intrahepatic accumulation of bile acids and/or their metabolites is thought to play a pivotal role in mediating the hepatic injury of cholestatic diseases [25].

2.1. Role of bile acids in autoimmune cholestatic liver diseases

2.1.1. Cytotoxicity of bile acids

Experimentally, hydrophobic bile acids are known to induce injury to hepatocytes [26], but the mechanisms involved in this toxicity are unclear. When bile acids accumulate in hepatocytes above their physiological concentration range, clinical hepatotoxicity may be observed. Recent literature suggested that bile salts at concentrations of 15–25 μM act as signal molecules; 50–200 μM cause apoptosis; ~200 μM induce pro-inflammatory actions; 200–2000 μM yield necrosis and above 2000 μM bile acids act as detergents [27–30]. Therefore, higher bile acid concentrations may exert cytotoxicity by causing necrosis, which would be the major mechanism of cell death in severe cholestasis. Conversely, in the μM range of supra-physiological bile acid concentrations, apoptosis is supposed to be the predominant mechanism in milder cholestasis [31].

Hydrophobic bile acids can initiate apoptosis through the direct induction of mitochondrial reactive oxygen species (mROS) and subsequent mitochondrial oxidative stress, one of the most important mechanisms contributing to the progression of cholestatic liver diseases. In addition, bile acids also induce the mitochondrial permeability transition (MPT), a critical intracellular trigger of both apoptotic and necrotic forms of cell death in hepatocytes [32]. These two pathways would reduce oxidative phosphorylation, decrease mitochondrial DNA copy number, cause the mitochondrial to swell and collapse, and lead to release of cytochrome c. Cytosolic cytochrome c initiates the activation of caspase 9, leading to a caspase cascade of activated effector caspases and to irreversible hepatocyte death [33]. Apart from mitochondrial oxidative stress, it is also suggested that endoplasmic reticulum stress might be involved in apoptosis caused by bile acids with both the disruption of Ca^{2+} homoeostasis and activation of caspase 12 [34]. The extrinsic pathway is initiated by bile-acid-activated vesicular trafficking from Golgi to the plasma membrane of death receptors Fas and TRAIL-receptor 2 [35]. After death receptor activation and formation of the death-inducing signaling complex, caspase 8 is activated and the pro-apoptotic protein Bid is cleaved and translocated to the mitochondria. Bid opens the MPT pore, releasing cytochrome c, which activates the effector caspases leading to irreversible hepatocyte death.

As for necrosis, hydrophobic bile acids can trigger necrosis by two main mechanisms: oxidative-stress-induced lipid peroxidation and solubilization of the hepatocellular plasma membrane [36]. As stated above, bile acids induce mROS from a mitochondrial origin. Therefore, exposure