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Emerging roles of bile acids in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma

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Bile acids (BAs) are cholesterol-derived molecules that are produced in the liver, secreted into the duodenum, absorbed by the small intestine and recycled back to the liver [1]. BAs regulate cholesterol metabolism, promote bile secretion, and emulsify and facilitate the digestion and absorption of dietary fats; in addition, there is growing evidence that BAs also act as endocrine cell signaling mediators that activate nuclear or membrane-localized receptors to trigger specific signaling pathways and regulate various biological processes, including immunity [2, 3]. Findings from studies in patients and cell or mouse models support the notion that BAs are critical regulators of the development of liver diseases, including chronic hepatitis B (CHB) [4], liver cirrhosis (LC) [5], and hepatocellular carcinoma (HCC) [6]. Here, we discuss the emerging roles of BAs in the progression of CHB, LC, and HCC.

THE ROLE OF BAS IN CHRONIC HEPATITIS

Chronic hepatitis leads to cirrhosis and liver cancer, which are the final stages of the liver disease process. Hepatitis B virus (HBV) infection is one of the most common causes of chronic viral hepatitis, especially in developing countries. It was reported that HBV infection alters the expression profiles of BA metabolism genes [7], suggesting that HBV infection alters BA metabolism. Comparison of the BA profiles of CHB patients and healthy controls (HCs) using liquid chromatography tandem mass spectrometry (LC–MS/MS) revealed that CHB patients have significantly higher serum levels of conjugated Bas, including taurocholic acid (TCA), taurodeoxycholic acid, glycocholic acid, glycochenodeoxycholic acid, and glycodeoxycholic acid, than HCs, but there is not a significant difference in unconjugated BA levels [4]. Among conjugated BAs, TCA is the most increased in CHB patients compared with HCs [4]. In these patients, TCA upregulates the expression of programmed death-1 (PD1) in $CD8^+$ T cells and downregulates the expression of NKG2D in natural killer (NK) cells, impairing the effector functions of $CD8^+$ T and NK cells, which in turn promotes HBV replication [4]. Furthermore, serum BAs, particularly TCA, inhibit the response of CHB patients to interferon-alpha therapy by impairing $CD8^+$ T-cell and NK cell functions [4]. It is worth noting that only one BA, ursodeoxycholic acid (UDCA), is detected at lower levels in CHB patients [4]. Recently, UDCA-mediated downregulation of angiotensin converting enzyme 2 by suppressing farnesoid X receptor (FXR) signaling was found to reduce susceptibility to SARS-CoV-2 infection in vitro, in vivo, and in human lungs and livers perfused ex situ [8]. FXR, a liver-enriched nuclear receptor that is also a known BA receptor, plays a pivotal role in the regulation of the HBV transcriptional program by binding to both EnhI and EnhII via the nuclear receptor-response element [9]. UDCA, an FXR antagonist [1], may inhibit HBV replication by suppressing FXR signaling. UDCA also exerts cytoprotective effects in hepatocytes, and treatment with UDCA can improve serum liver biochemistry [10]. These findings suggest that UDCA can inhibit HBV replication and improve liver function and may be a good treatment for CHB.

In summary, the abnormal accumulation of BAs, especially TCA, promotes HBV replication by impairing the effector functions of $CD8^+$ T and NK cells in CHB patients (Fig. 1A). Using UDCA in combination with existing first-line drugs could be a promising clinical strategy for achieving a more desirable therapy endpoint for patients with CHB.

THE ROLE OF BAS IN LIVER CIRRHOSIS

Cirrhosis, which is the late stage of progressive hepatic disease, is a significant cause of mortality worldwide. A targeted metabolomics approach in which LC–MS/MS was used to characterize the BA profiles in LC patients and HCs revealed that serum levels of glycocholic acid, glycochenodeoxycholic acid, TCA, taurochenodeoxycholic acid, and glycoursodeoxycholic acid are significantly higher in hepatitis B-induced LC patients than in HCs and are associated with pathological progression [5]. Among BAs, TCA was the most increased in LC patients compared with HCs [5]. Activation of hepatic stellate cells (HSCs), the key step in the progression of various chronic liver diseases to cirrhosis, is mediated by TCA via the sphingosine 1-phosphate receptor 2/yes-associated protein/p38 mitogen-activated protein kinase signaling pathways, which might be therapeutically relevant for targeting liver fibrosis [11]. It was reported that oral administration of UDCA in mice reduces the overall BA pool and sharply decreases the percentage of TCA from ~32% to only 2.99% [12]. Moreover, UDCA was found to alleviate liver fibrosis in bile duct ligation mice and to promote liver regeneration in partial hepatectomy mice [13]. These findings suggest that UDCA may reverse the effect of TCA on HSC activation by reducing TCA levels and thereby alleviating liver fibrosis.

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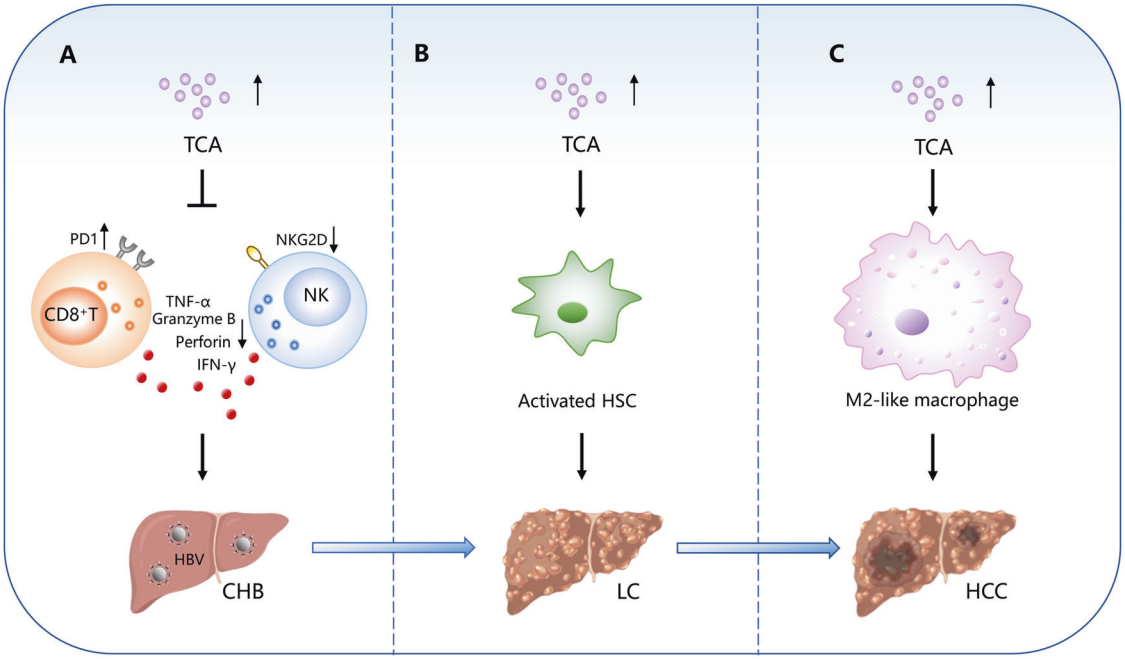

Fig. 1 A model illustrating the role of bile acids in chronic hepatitis B, liver cirrhosis, and hepatocellular carcinoma pathogenesis. **A** Abnormal accumulation of bile acids (BAs), especially taurocholic acid (TCA), promotes HBV replication by impairing $CD8^+$ T and NK cell function in patients with chronic hepatitis B (CHB). **B** TCA-mediated activation of hepatic stellate cells (HSCs) promotes the progression of liver cirrhosis (LC). **C** Abnormal accumulation of BAs (including TCA) in hepatocytes skews macrophage polarization and induces an immunosuppressive tumor microenvironment favorable for hepatocarcinogenesis

In summary, TCA promotes the development of LC via activation of HSCs (Fig. 1B). Treatment with UDCA could be a promising clinical strategy for the treatment of patients with LC.

THE ROLE OF BAS IN HEPATOCELLULAR CARCINOMA

HCC is the most common malignancy of the liver, and it is the third leading cause of cancer mortality worldwide. Integrated proteogenomic analyses of HBV-related HCC revealed dramatic downregulation of most key proteins (transcription factors, enzymes, and transporters) involved in BA metabolism [14]. Quantitative LC–MS/MS analysis revealed that serum levels of TCA are significantly elevated in patients with HCC compared with HCs [6]. Accumulated TCA from hepatocytes can promote M2-like macrophage polarization through FXR activation, creating an immunosuppressive tumor microenvironment that favors the expansion of tumor-initiating cells and tumor growth [6]. Accordingly, high serum TCA levels are positively correlated with increased M2-like tumor-associated macrophages in HCC patient samples [6]. Moreover, cholestyramine, an anion exchange resin that sequesters bile salts, indeed reduces hepatic and serum levels of TCA in mice, which could reshape the tumor microenvironment and exert antitumor effects [6]. This indicates that treatment with other BA sequestrants should be considered for HCC therapy. UDCA, a clinically approved drug used for first-line treatment of primary biliary cholangitis [10], causes the displacement of endogenous toxic BAs in the intestine and liver and an increase in the secretion of BAs from the liver (choleretic effect); it also regulates immune responses and has cytoprotective activities [15]. Thus, UDCA may reverse the effect of TCA on immune evasion and liver tumor growth in HCC patients by displacing TCA.

In summary, abnormal accumulation of BAs, particularly TCA, skews macrophage polarization and creates an immunosuppressive tumor microenvironment favorable for tumor-initiating expansion and tumor growth in HCC (Fig. 1C). Treatment with UDCA alone or in combination with immune checkpoint inhibitors could be a promising clinical strategy for the treatment of patients with HCC.

CONCLUDING REMARKS

BAs have been linked to the development of many types of chronic liver diseases. This highlights the importance of understanding the dual effects of BAs in chronic liver diseases. In addition, BAs contribute to the progression of different chronic liver diseases in different ways, and different BAs have different effects in different chronic liver diseases. TCA is one of the most abundant BAs, and it plays an important role in the progression of CHB, LC, and HCC (Fig. 1). Targeting TCA could be a promising approach for future therapies for chronic liver diseases. UDCA, accounting for approximately 1–3% of BAs and the predominant BA targeted by pharmacotherapy, accelerates BA enterohepatic circulation to prevent the toxic effects of endogenous BAs. Treatment with UDCA alone or with existing first-line drugs is a promising potential clinical strategy for future treatment of patients with CHB, LC, and HCC. Although targeting the BA receptor FXR to treat CHB, LC, and HCC is another potential strategy, finding drugs that target FXR is challenging and will require further exploration.

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AUTHOR CONTRIBUTIONS

ZX and XY drafted and edited the manuscript. QO critically reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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