Review

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Bile acid transporters and regulatory nuclear receptors in the liver and beyond

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Summary

Bile acid (BA) transporters are critical for maintenance of the enterohepatic BA circulation where BAs exert their multiple physiological functions including stimulation of bile flow, intestinal absorption of lipophilic nutrients, solubilization and excretion of cholesterol, as well as antimicrobial and metabolic effects. Tight regulation of BA transporters via nuclear receptors is necessary to maintain proper BA homeostasis. Hereditary and acquired defects of BA transporters are involved in the pathogenesis of several hepatobiliary disorders including cholestasis, gallstones, fatty liver disease and liver cancer, but also play a role in intestinal and metabolic disorders beyond the liver. Thus, pharmacological modification of BA transporters and their regulatory nuclear receptors opens novel treatment strategies for a wide range of disorders.

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Abbreviations: 6-ECDCA, 6-ethylchenodeoxycholic acid; AE2, anion exchanger 2; ABCG5/8, cholesterol efflux pump, ATP-binding cassette, subfamily G, member 5/8; BA, bile acid; AMPK, AMP activated protein kinase; BCRP (ABCG2), breast cancer resistance protein, ATP-binding cassette, subfamily G, member 2; BRIC, benign recurrent intrahepatic cholestasis; BSEP (ABCB11), bile salt export pump; CAR (NR1I3), constitutive androstane receptor; EGFR, epidermal growth factor receptor; FGF15/19, fibroblast growth factor 15/19; FXR (NR1H4), farnesoid X receptor/bile acid receptor; GLP-1, glucagon like peptide 1; GR (NR3C1), glucocorticoid receptor; HCC, hepatocellular carcinoma; HNF1α, hepatocyte nuclear factor 1 alpha; HNF4α (NR2A1), hepatocyte nuclear factor 4 alpha; IBABP (FABP6, ILBP), intestinal bile acid-binding protein, fatty acid-binding protein 6; ICP, intrahepatic cholestasis of pregnancy; IL6, interleukin 6; LCA, lithocholic acid; LRH-1 (NR5A2), liver receptor homolog-1; LXRα (NR1H3), liver X receptor alpha; MDR1 (ABCB1), *p*-glycoprotein, ATP-binding cassette, subfamily B, member 1; Mdr2/MDR3 (ABCB4), multidrug resistance protein 2 (rodents)/3 (human); MRP2 (ABCC2), multidrug resistance-associated protein 2, ATP-binding cassette, subfamily C, member 2; MRP3 (ABCC3), multidrug resistance-associated protein 3, ATP-binding cassette, subfamily C, member 3; MRP4 (ABCC4), multidrug resistance-associated protein 4, ATP-binding cassette, subfamily C, member 4; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; norUDCA, norursodeoxycholic acid; NR, nuclear receptor; NTCP (SLC10A1), sodium/taurocholate cotransporting polypeptide, solute carrier family 10, member 1; OATP1A2 (SLCO1A2, OATP1, OATP-A, SLC21A3), solute carrier organic anion transporter family, member 1A2; OATP1B1 (SLCO1B1, OATP2, OATP-C, SLC21A6), solute carrier organic anion transporter family, member 1B1; OATP1B3 (SLCO1B3, OATP8, SLC21A8), solute carrier organic anion transporter family, member 1B3; OSTαβ, organic solute transporter alpha/beta; PBC, primary biliary cirrhosis; PFIC, progressive familial intrahepatic cholestasis; PH, partial hepatectomy; PPARα (NR1C1), peroxisome proliferator-activated receptor alpha; PPARγ (NR1C3), peroxisome proliferator-activated receptor gamma; PSC, primary sclerosing cholangitis; PXR (NR1I2), pregnane X receptor; RARα (NR1B1), retinoic acid receptor alpha; RXRα (NR2B1), retinoid X receptor alpha; SHP (NR0B2), short heterodimer partner; SRC2, p160 steroid receptor coactivator; TGR5, G protein-coupled bile acid receptor; TNFα, tumor necrosis factor α; TPN, total parenteral nutrition; UDCA, ursodeoxycholic acid; VDR (NR1I1), vitamin D receptor. Please note that for the convenience of better readability and clarity, abbreviations for transporters and nuclear receptors were capitalized throughout this article when symbols were identical for human and rodents.

Introduction

To exert their unique physiologic functions bile acids (BAs) undergo enterohepatic circulation requiring active transport processes through the liver and digestive tract [1] (Fig. 1). During this tightly regulated cycle, a minor fraction (less than 3–5%) of secreted BAs escapes intestinal reabsorption via feces and needs to be replaced by *de novo* synthesis [1]. Maintenance of the enterohepatic BA circulation is vital for several liver and gastrointestinal functions including bile flow, solubilization and excretion of cholesterol, clearance of toxic molecules, intestinal absorption of lipophilic nutrients, as well as metabolic and antimicrobial effects [2]. Moreover, the enterohepatic circulation efficiently preserves these precious molecules, since BA synthesis from cholesterol involves 17 energy-consuming enzymatic steps [3]. In the body, BAs are mainly present in their conjugated form, which prevents unrestricted diffusion; therefore, BAs must be transported via energy-driven transport systems across the membranes of cells involved in the enterohepatic circulation [4]. BA transporters have different transport affinities for various BA species, but also for other endogenous and exogenous compounds such as drugs and toxins (Table 1). The expression of genes involved in BA homeostasis is tightly controlled by nuclear receptors (NRs) which sense the intracellular concentrations of BAs; in addition, post-transcriptional mechanisms such as insertion/retrieval of transporters into/from the cell membrane regulate the transport capacity via protein kinase C and mitogen-activated protein kinase activation by BAs [5–8]. Together with transcriptional regulation, such post-transcriptional changes fine-tune

transporter expression and activity at the plasma membrane (recently reviewed in [9]). In addition to NRs as intracellular BA sensors, some cells also contain BA receptors at the cell surface including a G-protein coupled receptor (TGR5/M-BAR/GPBAR1) [10] and the epidermal growth factor receptor (EGFR) [11]. Under physiological conditions, these regulatory networks preserve the enterohepatic BA circulation and limit intracellular levels of potentially toxic BAs. Disturbances of this delicate balance may contribute to cholestasis, gallstone disease, malabsorption and intestinal bacterial overgrowth (Fig. 1). By determining the distribution of BAs as signaling molecules with hormonal functions, transporter alterations also play a key role in fatty liver disease, insulin resistance, liver regeneration and cancer (Fig. 1). Modification of transporters and regulatory NRs may be utilized to develop novel therapeutic and preventive pharmacological strategies for these diseases. This review provides a comprehensive summary of the latest advances in understanding the function of hepatobiliary transporters and their key regulatory NRs for BA homeostasis in health and diseases, highlighting the potential clinical and therapeutic implications.

Keypoints

- Hepatic excretion and subsequent enterohepatic circulation of bile acids (BAs) require energy demanding active transport systems in the liver and intestine that are tightly regulated by nuclear receptors (NRs)
- Alterations of hepatobiliary BA transport play a pivotal role in the pathogenesis and pathophysiology of cholestatic liver injury; regulation of BA transporters by NRs may be targeted therapeutically
- Canalicular transporters for cholesterol, BAs and phosphatidylcholine and their regulatory NRs determine the lithogenicity of bile and the risk of gallstone formation
- BAs play a key role in hepatic lipid and glucose homeostasis; disturbances of BA transport with subsequent alterations in BA signaling may contribute to the pathogenesis and pathophysiology of NAFLD
- BAs are required for liver regeneration, but also promote hepatobiliary carcinogenesis; moreover, hepatobiliary transporters may be involved in resistance to chemotherapy
- Already approved (e.g., UDCA, rifampicin) and novel therapeutic agents (e.g., synthetic FXR agonists, norUDCA) exert their beneficial effects in cholestatic liver diseases by modulating BA homeostasis via changes in hepatobiliary transporters and their regulatory pathways

Hepatocellular bile acid transporters and their regulation by nuclear receptors

Basolateral uptake systems in the liver

BAs return to the liver via portal blood (and to a much lesser extent via the hepatic artery) and are efficiently removed during their first passage through the hepatic sinusoids by hepatocellular BA uptake systems [12], involving a sodium-dependent sodium/taurocholate co-transporting polypeptide (NTCP/SLC10A1) and a family of sodium-independent multispecific organic anion transporters (OATPs/SLCOs) [13,14] (Fig. 2; Table 1).

NTCP accounts for the bulk (about 90%) of BA uptake and was the first cloned BA transporter [13]. Its regulation under physiological and pathological conditions is therefore well understood thus serving as a paradigmatic model to understand transporter regulation. NTCP expression is controlled by BAs, hormones such as estrogen and prolactin, as well as pro-inflammatory cytokines (recently reviewed in [15]). In cholestatic patients [16,17] and animal models of cholestasis induced by biliary obstruction, estrogen or endotoxin, NTCP expression is universally reduced (reviewed in [18]). A key repressive mechanism involves activation of the farnesoid X receptor (FXR) through accumulating BAs, which then induces the small heterodimer partner (SHP) as repressor of hepatic nuclear factor 1 alpha and 4 alpha (HNF-1α and HNF-4α, and also interfering with retinoid X receptor (RXR), retinoic acid receptor (RAR) heterodimers in rats, or the glucocorticoid receptor in humans (recently reviewed in [15]), which are all required for normal NTCP expression (Fig. 2, Table 1).

Canalicular export systems

At the canalicular membrane, highly specialized canalicular transporters mediate excretion of the individual components of bile such as BAs, phospholipids and cholesterol [4] (Fig. 2, Table 1). The bile salt export pump (BSEP, ABCB11 or sister of *p*-glycoprotein (Spgp)) is the major canalicular BA efflux system [19]. The relevance of BSEP is emphasized by the severe progressive familial cholestatic syndrome (PFIC2) or benign recurrent intrahepatic cholestasis (BRIC2) resulting from *BSEP* mutations (Table 1). Importantly, the functional implications of BSEP deficiency may be underestimated in knockout mice (Table 1) where BA composition is less toxic than in humans, and BAs can be excreted by other canalicular transporters (Table 1). BSEP expression/activity is tightly controlled at transcriptional and post-transcriptional levels. FXR [20] upregulates BSEP expression (recently reviewed in [21]). While BSEP is downregulated by inflammatory injury and estrogen, it is relatively well preserved in obstructive cholestasis, which may help limit intracellular BA accumulation, although a preserved bile flow may cause bile infarcts in biliary obstruction (recently reviewed in [15]).

The canalicular membrane also contains transport systems mediating excretion of biliary phospholipids (MDR3, Mdr2 in rodents, ABCB4) and cholesterol (two half transporters ABCG5/8 which are tightly coupled with BA excretion [22] (Fig. 2, Table 1). Other canalicular transport systems (Fig. 2, Table 1) are less relevant for BA transport. Multidrug resistance-associated protein 2 (MRP2/ABCC2) mainly excretes bilirubin–glucuronides and glutathione conjugates, but also divalent sulfo-conjugated BAs into the bile (Fig. 2, Table 1) (Table 1). Multidrug resistance protein (MDR1, ABCB1) primarily excretes lipophilic cations including diverse drugs and carcinogens [23], while breast cancer resistance protein (BCRP, ABCG2) facilitates the transport of potentially toxic xenobiotics and food-derived carcinogens [24] (Table 1). Both transporters have also been implicated in BA transport when induced under cholestatic conditions, although this is still disputed in humans.

Alternative basolateral efflux systems in hepatocytes

During hepatocellular BA overload, BAs can also be transported back to the sinusoidal blood to protect the liver and for subse-