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Review

Principles of hepatic organic anion transporter regulation during cholestasis, inflammation and liver regeneration

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Abstract

Hepatic uptake and biliary excretion of organic anions (e.g., bile acids and bilirubin) is mediated by hepatobiliary transport systems. Defects in transporter expression and function can cause or maintain cholestasis and jaundice. Recruitment of alternative export transporters in coordination with phase I and II detoxifying pathways provides alternative pathways to counteract accumulation of potentially toxic biliary constituents in cholestasis. The genes encoding for organic anion uptake (*NTCP*, *OATPs*), canalicular export (*BSEP*, *MRP2*) and alternative basolateral export (MRP3, MRP4) in liver are regulated by a complex interacting network of hepatocyte nuclear factors (HNF1, 3, 4) and nuclear (orphan) receptors (e.g., FXR, PXR, CAR, RAR, LRH-1, SHP, GR). Bile acids, proinflammatory cytokines, hormones and drugs mediate causative and adaptive transporter changes at a transcriptional level by interacting with these nuclear factors and receptors. Unraveling the underlying regulatory mechanisms may therefore not only allow a better understanding of the molecular pathophysiology of cholestatic liver diseases but should also identify potential pharmacological strategies targeting these regulatory networks. This review is focused on general principles of transcriptional basolateral and canalicular transporter regulation in inflammation-induced cholestasis, ethinylestradiol- and pregnancy-associated cholestasis, obstructive cholestasis and liver regeneration. Moreover, the potential therapeutic role of nuclear receptor agonists for the management of liver diseases is highlighted.
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Keywords: Cholestasis; Liver regeneration; Endotoxin; Cytokines; Nuclear (orphan) receptor; Hepatocyte-enriched transcription factor

1. Introduction

The field of hepatobiliary transport has greatly advanced since cloning of the major transport systems for bile acids and other organic anions at the end of the last century. The discovery of bile acids, bilirubin and a broad range of xenobiotics as specific ligands for nuclear (orphan) receptors and the assignment of their regulatory role to individual hepatobiliary transporter genes has given way to an area of extensive research over the past years. Subsequently, a rapidly growing number of publications have been dealing with regulatory mechanisms of hepatobiliary transporter gene expression in health and disease. The transcriptional regulation of hepatic organic anion transporters by liver-enriched hepatocyte nuclear factors and ligand-activated nuclear receptors is key for understanding the molecular mechanisms of cholestasis. Moreover, transporter changes at a transcriptional level may represent potential targets for

Abbreviations: ABC, ATP-binding cassette; CAR (NR1I3), constitutive androstane receptor; CBDL, common bile duct ligation; Cyp, cytochrome p450; FXR (NR1H4), farnesoid X receptor/bile acid receptor; HNF, Hepatocyte nuclear factor; IL-1β, interleukin 1 beta; LPS, lipopolysaccharide; Mdr, multidrug resistance gene; Mrp, multidrug resistance-associated protein; Ntcp (Slc10a1), Na^+/taurocholate cotransporter; Oatp (Slc21a), organic anion transporter; Ost, organic solute transporter; PPARα (NR1C1), peroxisome proliferator activated receptor alpha; PPARγ (NR1C3), peroxisome proliferator activated receptor gamma; PXR (NR1I2), pregnane X receptor; RARα (NR1B1), retinoic acid receptor; RXRα (NR2B1), retinoid X receptor; SHP (NR0B2), short heterodimer partner; TNFα, tumor necrosis factor alpha

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therapy. The aim of this article is to give a comprehensive overview on the transcriptional mechanisms of hepatic organic anion transporter regulation in liver disease and their potential therapeutic implications.

2. Physiology and pathophysiology of hepatobiliary transport

Hepatobiliary transport systems are essential for normal bile formation and hepatic elimination of various endo- and xenobiotics including bile acids, bilirubin, cholesterol phospholipids, hormones, drugs and toxins [1–5]. The liver comprises specific uptake and export systems for these substrates. Progress over the past decade has resulted in the molecular identification of most relevant transport systems involved in normal bile formation and transport in intestine and kidney [1–5] (Table 1).

2.1. Basolateral organic anion uptake

Hepatic uptake of bile acids is mediated by a high-affinity Na^+-dependent bile salt transporter Ntcp/NTCP (*Slc10a1/SLC10A1*) and a family of multispecific organic anion transporters (*Oatps/OATPs; Slc21a/SLC21A*) that mediate Na^+-independent uptake of mostly amphipathic organic compounds, including conjugated and unconjugated bile acids, bromosulphophthalein and bilirubin. Na^+-independent bile acid uptake is quantitatively less important than Na^+-dependent uptake and is largely mediated by facilitated exchange with intracellular anions (e.g., GSH, HCO_3^-). The transport characteristics of Oatp1 (*Slc21a1*, new nomenclature Oatp1a1), Oatp2 (*Slc21a5*, new nomenclature Oatp1a4) and Oatp4 (*Slc21a10*, new nomenclature Oatp1b2*)* can account for the bulk of Na^+-independent bile acid uptake in rat liver. In humans, three liver specific OATPs (OATP1, also called OATP-A (*SLC21A3*) or new nomenclature OATP1A2; OATP2, also called OATP-C (*SLC21A6*) or new nomenclature OATP1B1; and OATP8(*SLC21A8*) or new nomenclature OATP1B3) transport bile acids. In order to avoid confusions it is important to keep in mind that the numbering of human OATPs does not indicate that these transporters are human orthologues of the rodent Oatp with the same number (Table 1) [6]. In addition to these uptake systems, the basolateral membrane also contains efflux pumps. Mrp3/ MRP3 (*Abcc3/ABCC3*) and Mrp4/MRP4 (*Abcc4/ABCC4*) are normally expressed at very low levels in hepatocytes, but are upregulated in cholestasis which may explain the shift towards renal excretion of bile acids in patients with chronic, longstanding cholestasis [7–14]. Members of the Oatp/OATP family also remain candidates for bile acid efflux at the basolateral membrane, since Oatp1 and 2 are able to operate as bi-directional exchangers. Recently the heteromeric organic solute transporter Ostα–Ostβ, was identified as an ileal basolateral bile acid export system [15]. In contrast to mouse Ost α/β which was detected only in mouse kidney and intestine, mirroring Asbt's horizontal gradient with highest expression in the distal gastrointestinal tract, analysis of human OSTα/β also showed high expression in liver [15,16].

2.2. Canalicular and ductular transport: bile-salt dependent and bile salt-independent bile flow

Bile is primarily formed by canalicular excretion of bile acids and non-bile acid organic anions via ATP-binding cassette (ABC) transporters, followed by modification of canalicular bile by the bile duct epithelium. Canalicular excretion accounts for ~75% of daily bile production in man and represents the rate limiting step of bile secretion. Most canalicular transport proteins for biliary organic anion and lipid secretion are ATP-binding cassette (ABC) proteins such as the multidrug resistance (MDR) P-glycoproteins (ABC-B subfamily) or the multidrug-resistance proteins (MRP) (ABC-C subfamily) [1]. As such, the canalicular membrane contains a bile salt export pump (Bsep/BSEP; *Abcb11/ABCB11*) for monovalent bile acids, a conjugate export pump (Mrp2/MRP2, *Abcc2/ABCC2*) for divalent bile acids and various other amphipathic conjugates, including bilirubin diglucuronide and GSH (a major determinant of bile acid-independent canalicular bile flow), a multidrug export pump (Mdr1/MDR1, *Abcb1/ABCB1*) for bulky amphipathic organic cations (e.g., various drugs), a phospholipid flippase (Mdr2 in rodents/MDR3 in humans; *Abcb4/ABCB4*) for phosphatidylcholine translocation, a ABC-G two half transporter (ABCG5 and 8) for sitosterol and cholesterol, a P-type ATPase (Fic1/FIC1; ATP8B1) mutated in hereditary cholestasis whose substrate/function is still unknown and a Cl^-/HCO_3^- exchanger (AE2; SLC4A2) for HCO_3^- excretion which is the only functionally relevant ATP-independent transport system at the canalicular membrane. The vectorial excretion of bile salts into bile by the export pump BSEP represents the major driving force for bile flow ("bile salt-dependent" bile flow). Canalicular excretion of reduced glutathione (GSH) conjugate export pump MRP2 and bicarbonate (HCO_3^-) by the Cl^-/HCO_3^- exchanger AE2 constitute the major components of the "bile salt-independent" fraction of bile flow. However, HCO_3^- secretion occurs mainly at the level of bile duct epithelial cells (cholangiocytes), in response to stimulation by hormones and neuropeptides. Both hepatocellular and ductular secretion establish an osmotic gradient that in turn drives passive transcellular presumably aquaporin-mediated transcellular movement of water. Final modification of bile in the gallbladder is mainly the result of active transport of Cl^- and HCO_3^-, and the passive aquaporin-mediated transport of water into bile [17]. The quantity of "ductular/ductal bile" varies from as little as 5% in rats to as much as 25–40% of secretion in man.

2.3. Cholehepatic shunting and enterohepatic circulation

Many biliary compounds (e.g., bile acids) secreted into bile undergo an enterohepatic circulation, i.e., are reabsorbed in the intestine, taken-up again by the liver and secreted into bile. Organic biliary constituents including bile salts are reabsorbed with high efficiency after reaching the small intestine and recirculate via the portal blood back to the liver. Apical bile salt uptake of conjugated bile salts in the terminal ileum is mediated by the ileal bile salt transporter Isbt/ISBT (*SLC10A2*) also known as the apical sodium-dependent bile salt transporter (Asbt/ASBT) [1,4]. The Na^+-independent bile salt transporter Oatp3 (*Slc21a7*) is predominantly located to the apical surface of jejunal epithelial cells but its relative

Table 1
Nomenclature, hepatocellular localization, function and substrates of major hepatobiliary transport systems

Gene	Function	Substrates
Basolateral membrane		
NTCP/Ntcp (*SLC10A1/Slc10a1*) Na^+/taurocholate cotransporter	Main transporter for Na+-dependent bile acid uptake from portal blood into hepatocyte	Conjugated and unconjugated bile acids with highest affinity for conjugated di- and trihydroxy bile acids; estrogen conjugates (e.g., estrone-3-sulfate), BSP, DHEAS, thyroid hormones, drugs covalently bound to taurocholate (e.g., chlorambucil)
OATP1A2, OATP-A (*SLCO1A2; SLC21A3*) Organic anion transporting protein	Multispecific organic anion transporter for Na^+-independent uptake of bile acids and a broad range of other organic anions and cations; minor contribution to overall bile acid uptake	Conjugated and unconjugated bile acids, estrogen conjugates, DHEAS, BSP; neutral steroids such as ouabain, thyroid hormones, the opioid receptor antagonists D-penicillamine-enkephaline and deltorphine II, the antihistamine fexofenadine, organic cations such as ADP-ajmalium, rocuronium and n-methylquinine
OATP1B1, OATP-C (formerly LST-1) (*SLCO1B1; SLC21A6*) Organic anion transporting protein	Multispecific organic anion transporter for Na^+-independent uptake of bile acids and a broad range of other organic anions; most important OATP for bile acid uptake	Similar to OATP1A2: conjugated and unconjugated bile acids, additionally bilirubin monoglucuronide and unconjugated bilirubin, LTC_4, prostaglandin E_2, thromboxane B_2, pravastatin, rifampin
OATP1B3, OATP-8 (*SLCO1B3; SLC21A8*) Organic anion transporting protein	Multispecific organic anion transporter for Na^+-independent uptake of bile acids and a broad range of other organic anions; role of bile acid transport controversial	Conjugated bile acids; bilirubin monoglucuronide, BSP, DHEAS, cholecystokinine, estrogen conjugates, thyroid hormones, D-penicillamine-enkephaline, n-methylquinine, ouabain, digoxin, rifampin
Oatp1a1, Oatp1 (*Slco1a1; Slc21a1*) Organic anion transporting protein	Multispecific organic anion transporter for Na^+-independent uptake of bile acids and a broad Range of other organic anions; most important Oatp for bile acid uptake in rodent liver	Similar to OATP1A2: conjugated and unconjugated bile acids; bilirubin monoglucuronide, but not unconjugated bilirubin; thyroid hormones, BSP, LTC_4, steroid hormones such as aldosterone, dexamethasone and cortisol; angiotensin-converting enzyme inhibitors (enalapril, temocaprilat), pravastatin, the magnetic resonance imaging contrast agent gadoxetate
Oatp1a4, Oatp2 (*Slco1a4; Slc21a5*) Organic anion transporting protein	Multispecific organic anion transporter for Na^+-independent uptake of bile acids and other organic anions with predominant location in pericentral hepatocytes; less important for bile acid uptake than Oatp1a1	Similar to Oatp1a1: Conjugated and unconjugated bile acids; high-affinity transport of digoxin; bilirubin monoglucuronide (note that BSP and LTC_4 are no substrates)
Oatp1b2, Oatp4 (formerly Lst-1) (*Slco1b2; Slc21a10*) Organic anion transporting protein	Multispecific organic anion transporter for Multispecific organic anion transporter for Na^+-independent uptake of bile acids and a broad range of other organic anions; Oatp1b2 is the full-length isoform of rat liver specific transporter 1 (Lst-1)	Bile acids, DHEAS, LCT_4; prostaglandin E_2, BSP; estrogen conjugates, thyroid hormones, cholecystokinin, gadoxetate, toxins (e.g., microcystin)
MRP3/Mrp3 (ABCC3/Abcc3) Multidrug resistance-associated protein	ATP-dependent efflux of biliary constituents; potential implications for removal of accumulating bile acids in cholestasis	Divalent bile acids (e.g., sulfo-TLCA, sulfo-TCDCA), monovalent bile acids; methotrexate, acetaminophen glucoronide, $E_2$17G, several other glucuronides and glutathione conjungates of endogenous and exogenous compounds
MRP4/Mrp4 (ABCC4/Abcc4) Multidrug resistance-associated protein	ATP-dependent cotransport of GSH and divalent bile acids into portal blood; potential implications for removal of accumulating bile acids in cholestasis	Divalent sulfated and monovalent bile acids; estrogen sulfates, DHEAS, cyclic nucleotides, methotrexate
OSTα/OSTβ Organic solute carrier	Na^+-independent bile salt transport system; expressed in hepatocytes, basolateral counterpart of apical Asbt in intestine and kidney	Bile acids, digoxin, DHEAS, estrone 3-sulfate, prostaglandin E_2
Canalicular membrane		
BSEP/Bsep formerly SPGP/Spgp (ABCB11/Abcb11) Bile salt export pump	ATP-dependent transport of monovalent bile acids into bile; major determinant of bile salt dependent bile flow	Monovalent and divalent bile acids; low affinity for certain drugs (taxol, vinblastine, pravastatin)
MRP2/Mrp2 (ABCC2/Abcc2; cMOAT) Multidrug resistance-associated protein	ATP-dependent transport of organic anions into bile; major determinant of bile salt independent bile flow by GSH transport	Divalent bile acids, but not monovalent bile acids; GSH, bilirubin mono/diglucuronide, LTC_4, several other organic anions most of which are divalent amphipathic conjugates with glutathione, glucuronate and sulfate
MDR1/Mdr1a/1b (ABCB1/Abcb1) Multidrug resistance- protein	Bile excretion of bulky organic cations; important role in drug resistance	Multiple organic cations and other hydrophobic compounds and hydrogen bond acceptors including protoporphyrin and several drugs
MDR3/Mdr2 (ABCB4/Abcb4) Multidrug resistance-protein	Phospholipid flippase, which mediates the translocation of phosphatidylcholine from the inner to the outer leaflet of the canalicular membrane	Phosphatidylcholine, porphyrins, digoxin, paclitaxel, vinblastine
FIC1/Fic1 (ATP8B1/ATP8b1) familiar intrahepatic cholestasis 1 protein	ATP-dependent aminophospholipid translocase; function not yet defined; Mutations cause PFIC1 and BRIC1	Unclear, possibly (hydrophobic) bile acids

(continued on next page)

Table 1 (*continued*)

Gene	Function	Substrates
ABCG5/8/Abcg5/8	"Two-half transporters", which mediate the sterol and cholesterol transport into bile; mutations cause sitosterolemia	Sitosterol, cholesterol
BCRP/Bcrp (ABCG2/Abcg2) Breast cancer related protein	Mediates cellular extrusion of sulphated conjugates	Sulfoconjugated organic anions such as estrone 3-sulfate, $E_2$17G, folic acid, protopophyrine IX, methotrexate
AE2/Ae2 (SLC4A2) Anion exchanger 2	Mediates bicarbonate transport into bile in exchange for Cl^- and contributes to bile salt independent bile flow	HCO_3^-
Aquaporins (AQPs) AQPs 0, 1, 4, 5, 8, 9 and 11	Integral membrane channel proteins that facilitate rapid passive movement of water	

Abbreviations used in this table: BSP, bromosulphthalein; CA, cholic acid; DHEAS, dehydroepiandrosteronsulfat; $E_2$17G, estradiol-17β-glucuronide; GCA, glycocholic acid; GLCA, glyco-lithocholic acid; GSH, glutathione; LCA, lithocholic acid; LTC_4, leukotriene C_4; TCA, tauro-cholic acid; TCDCA, tauro-chenodeoxycholic acid; TDCA, tauro-deoxycholic acid; TLCA, tauro-lithocholic acid; TUDCA, tauro-ursodeoxycholic acid; UDCA, ursodeoxycholic acid.

importance for intestinal bile salt uptake compared with Isbt remains to be determined [1,4]. Potential candidates for basolateral bile salt efflux from enterocytes include t-Asbt (truncated Asbt, which can function as an anion exchanger) identified in rat ileum, the recently identified OST/Ostα-OST/Ostβ and Mrp3/MRP3, which have both been identified in rat and human small intestine [1,4,18].

Additional "cycles" include a cholehepatic cycle of bile acids between bile duct epithelial cells (cholangiocytes) and hepatocytes, and reabsorption from proximal renal tubules preventing the loss of glomerularly filtered bile acids into urine. Bile salts may also undergo "cholehepatic shunting" from the bile duct lumen, via cholangiocytes and the periductular capillary plexus. Bile salt reabsorption by cholangiocytes is mediated by Isbt/ISBT, also called Asbt/ASBT (*SLC10A2*) and may contribute in part to the conservation of bile salts and the generation of a hypercholeretic bile flow [1,4]. After uptake, bile salts are effluxed via the basolateral membrane of cholangiocytes into the peribiliary plexus by Mrp3/MR3, which has been identified in cholangiocytes and gallbladder epithelium of rats and humans [1,4]. Although this pathway probably plays a minor role under normal physiological conditions, cholehepatic shunting of bile salts may become an important escape route for bile salts under cholestatic conditions when the bile duct epithelium proliferates. Under pathologic, cholestatic conditions with disruption of the enterohepatic circulation, these pathways may be "alternatively" used by biliary compounds normally not excreted into urine. Bile formation not only depends on the proper function of these transport systems, but also on an intact cytoskeleton required for the movement of vesicles and bile canalicular contractions, cell junctions that seal off the bile canaliculi and maintain cell polarity, and signal transduction cascades that regulate and coordinate these processes [1–5].

Cholestasis may result either from a functional defect in bile formation at the level of the hepatocyte or from an impairment in bile secretion and flow at the bile duct level [2,3,19,20]. Reduced expression and function of transport systems play an important role in the pathogenesis of cholestasis. In addition to transporter changes, other mechanisms such as altered cell polarity, disruption of cell-to-cell junctions and cytoskeletal changes may be involved [2,4,19]. Transport defects may be hereditary due to genetic defects or acquired as a result of cholestatic injury. While transporter changes in hereditary cholestasis are primary, most alterations in acquired cholestasis are secondary. Decreased expression of transport systems may at least in part explain the impairment of transport function resulting in or maintaining cholestasis [2–4,19–21]. However, not all of the encountered changes in transporter expression are 'pro-cholestatic' and 'negative' from a teleological point of view. While some of these alterations contribute to cholestasis, other changes may represent compensatory ('anti-cholestatic') defense recations which provide alternative excretory routes for accumulating cholephiles in cholestasis. Generally, cholestasis is associated with a disruption of the normal enterohepatic and nephrohepatic circulation, with an increased cholehepatic shunting (reabsorbing toxic, stagnant bile acids from the obstructed ducts in post-canalicular forms of cholestasis) and an increased basolateral efflux of biliary compounds from liver followed by their renal elimination. These transporter changes may be assisted by metabolic changes of phase I and II enzyme systems (e.g., cytochrome P450 enzymes, sulfotransferases, glucuronyltransferases) involved in the detoxification of bile acids and other biliary compounds which make them less toxic and better substrates for alternative elimination pathways. Therefore, the changes encountered in cholestasis represent a mixture of pro-cholestatic and anti-cholestatic/adaptive alterations of transport and enzyme systems.

Rodent models of hereditary and acquired cholestasis have proven very useful to study the role of transport systems in the pathogenesis of cholestasis. *Mdr2 (Abcb4)* knockout mice develop a sclerosing cholangitis as a result of toxic, phospholipid-deficient bile which contains free, non-micellar bile acids [22,23]. *Bsep (Abcb11)* knockout mice [24] develop a much milder cholestasis than their human counterparts (PFIC 2) which may be due to differences in bile acid composition and the existence of additional canalicular bile salt transport systems in mice [24,25]. Most of our knowledge on acquired alterations of transport systems during cholestasis is based on experimental animal models which mimic to some extent specific clinical conditions [2–4,19–21,26]. Examples include rodent models with administration of endotoxin (experimental model for inflammatory cholestasis), ethinylestradiol (oral contraceptive-induced cholestasis/cholestasis of pregnancy), alpha-naphthylisocyanate (vanishing bile duct syndrome) and common bile duct ligation (extrahepatic biliary obstruction) [26]. *Mdr2*$^{-/-}$ may represent an excellent model to study the pathophysiology of chronic cholangiopathies including PSC

Table 2
Nuclear receptors, ligands and target transporter genes

Nuclear receptor	Ligands	Target transporter gene
RXR (*NR2B1*) Retinoid X receptor	9-cis retinoic acid; rexinoids	Obligate heterodimeric partner for class II NR, multiple target genes;
RAR (*NR1B1*) Retinoic acid receptor	Trans-retinoic acid	*Ntcp, Mrp2, ASBT, Mrp3/MRP3*
FXR (*NR1H4*) Farnesoid X receptor	Hydrophobic bile acids such as CDCA, DCA, CA, LCA, GW4064	*Bsep/BSEP, Mrp2/MRP2; OATP1B1, OATP1B3, I-BABP, Ostα/β, OSTα/β, Asbt, Mdr2/MDR3 (also: Shp/SHP)*
SHP (*NR0B2*) Short heterodimer partner 1	None, transcriptionally activated by FXR	*Ntcp ,OATP1B1*
PXR/SXR (*NR1I2*) Pregnane (Steroid) X receptor	LCA and metabolites, DCA, CA , UDCA?, rifampicin (human), PCN (rodent), hyperforin, dexamethasone, statins	*Mrp2/MRP2, Mrp3/MRP3, Oatp2, MDR1 (also: phase / and II enzymes, e.g., Cyp3a/CYP3A, Sult2a)*
CAR (*NR1I3*) Constitutive androstane receptor	Androstenol (antagonist), phenobarbital, TCPOBOP, bilirubin	*Mrp2/MRP2, Mrp3/MRP3, Mrp4/MRP4, (also: phase / and II enzymes, e.g., Cyp2b/CYP2B, Sult2a, Ugt1a1/UGT1A1)*
VDR (*NR1I1*) Vitamin D receptor	Vitamin D, LCA metabolites	*Asbt, Mrp3 (also: phase/and II enzymes, e.g., Cyp3a/CYP3A, Sult2a/SULT2A)*
LRH-1/FTF (*NR5A2*) Liver receptor homolog-1; α1-fetoprotein transcription factor	None, bile acids and TNFα result in upregulation of Lrh-1 mRNA	*MRP3, Shp, Asbt*
PPARα (*NR1C1*) Peroxisome proliferator activator α	Fatty acids, statins, fibrates, DHEAS, prostaglandins, etc.	*Asbt/ASBT, Mdr2*
LXR (*NR1H3*) Liver X receptor	Oxysterols	*Abcg5/8/ABCG5/8*
GR (*NR3C1*)	Glucocorticoids	*ASBT, Ntcp/NTCP*
HNF1α (*TCF1*) Hepatocyte nuclear factor 1 alpha	–	*Ntcp, Oatp1, Oatp2, Oatp4, Oatp1B1, Oatp1A3, Asbt*
HNF3β (*FOXA2*) Hepatocyte nuclear factor 3 beta	–	*Ntcp, Mdr2*
HNF4α (NR2A1) Hepatocyte nuclear factor 4 alpha	–	*Ntcp, Oatp1, Bsep, Mdr2 OATP1B1*

Abbreviations used in this table: CA, cholic acid; DHEAS, dehydroepiandrosteronsulfat; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GW4064, specific synthetic FXR ligand; LCA, lithocholic acid; PCN, pregnenolone-16α-carbonitrile; TCPOBOP, 1,4-bis-[2-(3,5-dichlorpyridyloxy)]benzene; UDCA, ursodeoxycholic acid.

[22,23,27]. In addition, intraductal 2,4,6-trinitrobenzenesulfonic acid injection into the partially ligated bile duct may induce sclerosing cholangitis in rats as another animal model for PSC [28,29].

Several monogenetic, hereditary cholestatic syndromes such as progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis (BRIC), Dubin–Johnson syndrome and liver involvement in cystic fibrosis now can be attributed to specific mutations of individual hepatobiliary transporter genes [30–32]. Mutations of the canalicular transporters FIC1, BSEP and MDR3 account for the phenotypic expression of PFIC-1, 2 and 3, respectively. Functionally less significant mutations cause a more benign phenotype and may be associated with BRIC 1 (FIC1) and 2 (BSEP) [33–35]. Hereditary MDR3 defects are also involved in intrahepatic and gallbladder cholesterol gallstone formation and the pathogenesis of cholestasis of pregnancy [30,31]. Reduced MDR3 levels have also been found in oriental patients with intrahepatic bile duct stones, suggesting a role for heterozygotes with MDR3 defects in the pathogenesis of this syndrome. Dubin–Johnson Syndrome, a cause of hereditary conjugated hyperbilirubinemia and defects in the excretion of a variety of amphipathic organic anions, is caused by hereditary MRP2 defects [31]. Sometimes hereditary and acquired factors causing cholestasis can overlap, since incomplete or heterozygous transport defects/mutations may predispose to acquired cholestatic liver injury (e.g., subtypes of intrahepatic cholestasis of pregnancy, drug-induced cholestasis) [31]. Acquired, secondary downregulation of the nuclear bile acid receptor FXR may contribute to cholestasis in PFIC1 (FIC1 disease) [36,37]. Transporter polymorphisms of the main hepatobiliary export systems do not appear to play a major role in the pathogenesis of PBC and PSC [38], although their role as disease-modifier genes remains to be elucidated.

In daily clinical practice, acquired forms of cholestasis are more relevant. Clinically, bland (e.g., drug or hormone-induced) versus inflammatory hepatocellular cholestasis must be distinguished from vanishing bile duct syndromes involving microscopic small interlobular bile ducts (e.g., primary biliary cirrhosis, PBC) and biliary obstruction at the level of large, macroscopically visible ducts (e.g., primary sclerosing cholangitis, PSC). Generally, the acquired changes in transporter expression in human cholestatic liver diseases are consistent with concepts derived from the findings in experimental animal models of cholestasis [21,26]. Transcriptional mechanisms appear to be less relevant in humans compared to rodents [12,39]. For example, in contrast to the dramatic reduction of Mrp2 mRNA levels in endotoxin-treated rats [40], MRP2 mRNA levels remained unchanged in humans, indicating species differences in its regulation [12]. This is further supported by reduced MRP2 protein but unchanged MRP2 mRNA in the duodenum of patients with obstructive cholestasis and findings obtained with endotoxin- and cytokine-challenged human liver slices [41,42].

In addition to transporter changes, changes in membrane fluidity, ultrastructural changes of the cytoskeleton and tethering proteins (e.g., radixin), cellular (tight) junctions, and alterations of cell signalling (e.g., protein kinase C), may also contribute to hepatocellular cholestasis [2,5,43,44].

3. Principal levels of hepatobiliary transporter gene regulation

Hepatobiliary transport systems are intensively regulated at a transcriptional and posttranscriptional level to meet physiologic demands and variations. Liver-enriched transcriptions factors (e.g., hepatocyte nuclear factors, HNF) and nuclear (orphan) receptors (NR) play a key role in the transcriptional regulation of hepatobiliary transport systems [1,4,5,45] (Table 2). Members of the HNF family are important for constitutive gene expression, while nuclear (orphan) receptors rather represent inducers of gene expression responsible for gene regulation in response to bile acid accumulation or certain xenosensors. Binding of biliary constituents (e.g., bile acids, bilirubin), lipid products (e.g., oxysterols) and xenobiotics (e.g., drugs) to NR facilitate the positive feed-forward and negative feed-back regulation of hepatic transport and phase I/II metabolism of these compounds under physiological and pathological conditions [45].

Many alterations in bile acid transport and metabolism in cholestasis can now be interpreted as NR-mediated action since biliary compounds retained during cholestasis can act as NR ligands and would be predicted to alter expression of respective target genes encoding for transporters and enzymes [1,4,5,45]. Depending on the cause of cholestasis, effects of cytokines, bile acids, hormones or drugs may dominate the picture. However, the extrapolation of physiologic or in vitro NR effects to pathologic (e.g., cholestatic) conditions is complicated by the fact, that NR themselves undergo marked changes in their expression and function during cholestasis and inflammation (see below) [1,3,26]. Thus, the expression patterns observed in cholestasis are the cumulative result of direct alterations of NR by the injury (e.g., proinflammatory cytokines) and accumulation of biliary constituents secondary to cholestasis (e.g., bile acids, bilirubin). In addition to transcriptional transporter changes, posttranscriptional events (affecting mRNA processing, steady-state mRNA stability, translational efficacy) and/or posttranslational changes such as impaired targeting and sorting, transporter redistribution, enhanced transporter protein degradation (e.g., via lysosomal or ubiquitin–proteasome pathway), direct protein modifications (e.g., (de-) phosphorylation, (de-) glycosylation), changes in membrane fluidity or cis-/trans-inhibition of transport systems by cholestatic agents (e.g., drugs) can also play an important role in the pathogenesis of cholestasis [1–5].

4. General principles of transcriptional hepatic organic anion transporter regulation

The transcriptional regulation of hepatic organic anion transporters comprises a complex interacting network of (ligand-activated) nuclear (orphan) receptors (FXR, PXR, VDR, CAR, RXR, RAR, LRH-1, PPARα, Shp) as well as liver enriched hepatocyte nuclear factors (HNF1, HNF3, HNF4) [1,45,46] (Table 2; Fig. 1). Binding of nuclear receptor agonists or antagonists can directly translate physiological and pathophysiological requirements into alterations of gene expression [1,45,46]. These effects can be additionally modulated by transcriptional and posttranscriptional regulation of the transcription factor itself [47–51]. Release of co-repressors and recruitment of distinct co-activators is another critical step in mediating nuclear receptor function [52]. So far, three nuclear receptors (NR), the farnesoid X receptor FXR (NR1H4), the pregnane X receptor PXR (NR1I2) and the vitamin D receptor VDR (NR1I1), have been shown to bind a distinct

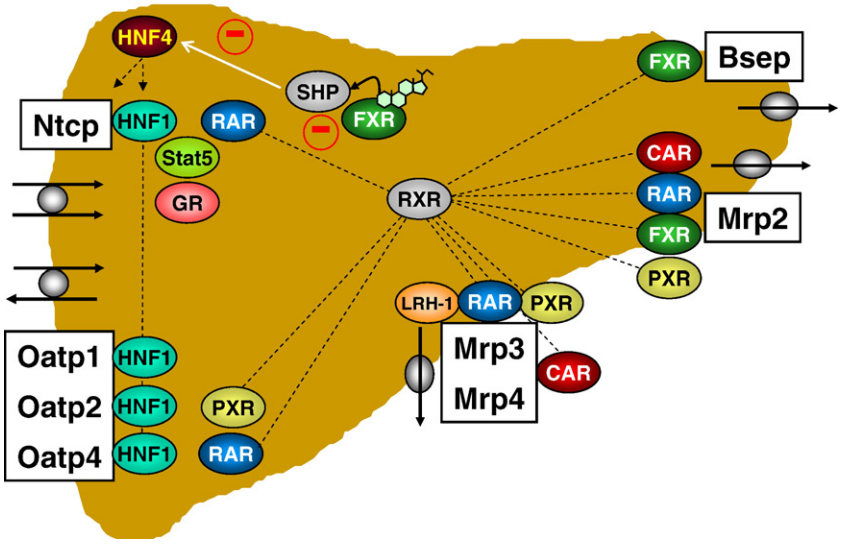

Fig. 1. General principles of transcriptional hepatic organic anion transporter regulation in rat liver. Class II nuclear receptors heterodimerizing with RXR as obligate partner and liver enriched transcription factors mediate the transcriptional regulation of hepatobiliary transporter systems. Hepatocyte nuclear factor HNF1α, which is under positive feedback control of HNF4α is the common master regulator of basolateral Na^+-dependent (Ntcp) and Na^+-independent (Oatp1, 2, 4 (Oatp1a1, 1a4, 1b2)) bile acid uptake systems. HNF4α in turn may be under negative control of the bile acid induced FXR-SHP pathway. *Ntcp* is also under direct control of Stat5 and the glucocorticoid receptor. Please note, species differences in *Ntcp* regulation (see text for details). FXR positively regulates the canalicular bile acid transporters *Bsep* and, sharing a common response element with PXR and CAR also *Mrp2*. PXR regulates basolateral *Oatp2* (Oatp1a4) and potentially *Mrp3*, while CAR regulates both basolateral *Mrp3* and *Mrp4*. The RARα: RXRα heterodimer again positively regulates *Ntcp*, probably *Oatp4* (Oatp1b2) and also *Mrp2*, while negatively regulating *Mrp3*. LRH-1 induces *Mrp3* expression.

spectrum of hydrophobic bile acids as ligands [53–58]. The constitutive androstane receptor CAR (NR1I3) is activated by bilirubin [59], but a role for bile acid sensing has been postulated [60]. All of them belong to class II nuclear receptors, that typically form heterodimers with the retinoid X receptor alpha RXRα (NR2B1) in order to mediate binding to distinct DNA response elements in respective promoter regions defined by different canonical hexamer sequences [61]. In addition, the liver X receptor alpha LXRα (NR1H3) was reported to be activated by 6α-hydroxy bile acids, a hydroxylation product formed by CYP3A4 [62].

The best defined nuclear receptor for bile acids, FXR, is critically involved in regulation of genes whose products mediate hepatocellular bile acid uptake via Na^+-dependent (NTCP) and Na^+-independent (OATP2 (OATP1B1), OATP8 (OATP1B3) [63,64] mechanisms, canalicular excretion of monovalent (BSEP)/divalent bile acids (MRP2) and bilirubin (MRP2) and the rate limiting step of bile acid formation (via CYP7A1). FXR is abundantly expressed in tissues belonging to the enterohepatic circulation (hepatocytes, cholangiocytes and enterocytes), the kidney and adrenal cortex [65]. Moreover, this receptor is also expressed in a variety of non classical bile acid target tissues such as vasculature and vasuclare smooth muscle cells [66]. FXR is activated by bile acids in the rank order of potency: chenodeoxycholic acid (CDCA)>deoxycholic acid (DCA)=lithocholic acid (LCA)>cholic acid (CA) [55]. However, more detailed studies have demonstrated that only CDCA is a full FXR agonist, while DCA, CA and ursodeoxycholic acid (UDCA) are partial FXR agonists regulating target genes in a gene-selective manner [67]. LCA even acts as a partial FXR antagonist in vitro [68]. β-muricholic acid (β-MCA), a hydrophilic bile acid species and predominant bile acid in rodents has not been shown to activate FXR so far [55]. Results in $FXR^{-/-}$ mice indicate that *Bsep* is a direct target of FXR since Bsep baseline expression levels as well as *Bsep* induction upon CA feeding is diminished in this animal model [69]. The human and rodent *BSEP* gene contain an inverted repeat (IR-1) element in their promotor regions that directly bind to the FXR:RXR heterodimer upon activation by bile acids, resulting in enhanced transactivation of the *BSEP* gene [69–73]. Thereby FXR is able to directly regulate hepatocellular bile acid homeostasis by inducing BSEP, the main bile acid export pump. In contrast, LCA reduces *BSEP* expression in cell culture via FXR antagonistic activity [68], proving another explanation for the cholestatic effects of the toxic LCA (for Review [74]). The *MRP2* promotor can also be directly transactivated by FXR agonists through a unusual, common ER-8 response element for FXR, PXR and CAR [72]. However, $FXR^{-/-}$ did not show decreased *Mrp2* baseline expression or impaired induction after bile acid loading, supporting redundant regulatory mechanism for this transporter [49,72,75]. The phospholipid flippase MDR3 in the canalicular membrane of hepatocytes and OATP8 (OATP1B3), involved in basolateral bile acid uptake in human hepatocytes are also, directly transactivated by FXR through IR-1 elements in their promoter regions [63,76]. Recently, the human *OSTα* and *OSTβ* genes were identified to be transactivated by FXR [77].

In addition to these direct, positive regulatory FXR effects as an inducer of gene expression, FXR indirectly negatively regulates gene expression via induction of small heterodimer partner (SHP (NR1I0)) [69,78,79]. The human and rodent *SHP* promotor regions contain FXR response elements [78]. SHP is a true "orphan" receptor since it has no ligands. Moreover, SHP lacks a DNA binding domain but still contains a receptor interacting and repressor domain [80]. SHP mediates its repressive effects on nuclear receptor-mediated transactivation either via competition with coactivators or via heterodimerization with other nuclear receptors thereby blocking their ability to activate transcription [78,79,81]. Since the *Ntcp* promotor does not contain an FXR:RXRα binding element, FXR-dependent repression of *Ntcp* by bile acids is mediated indirectly, at least in part, via SHP. The rat *Ntcp* promotor is activated by several positive regulating elements including HNF-1α, the RARα:RXRα heterodimer as well as the signal transducer and transactivator 5 (Stat 5) [82,83]. Stat5 mediates induction of rat *Ntcp* by prolactin and growth hormone [82,84]. In addition, another liver enriched transcription factor, the divergent homeobox gene *Hex*, was reported to transactivate the rat *Ntcp* promotor via a response element located in the upstream region of the minimal promotor [85]. Bile acid-dependent SHP induction has been shown to interfere with RXRα:RARα activation of the *Ntcp* promoter, thus, reducing *Ntcp* gene expression [86]. On the other hand, SHP also inhibits HNF4α transactivation [81]. Considering the fact that HNF4 may positively regulate HNF1α [87], bile acid-induced FXR/SHP-dependent downregulation of *Ntcp* could also be envisioned by such a pathway. Recently, an HNF4 binding site in the rat *Ntcp* promotor overlapping with the RXRα:RARα response element has been identified, indicating that SHP may also repress rat *Ntcp* via reduced HNF4 activity [46,88]. However, HNF4, HNF1 and RXRα:RARα were previously shown to bind to and activate only the rat minimal *Ntcp* promotor but not the human and murine promoter [88] although recent evidence suggests a more distal HNF4 element in both rodent promoters [89]. The only common motif in all three species in the minimal promoter was HNF-3β, suggesting that there might be relevant differences in regulating the *NTCP/Ntcp* gene between species [88,90]. HNF3β might have a negative regulatory function since HNF3β transgenic mice have reduced Ntcp levels [91]. On the other hand HNF-3β might result in transactivation of Hex, which is predicted to stimulate rat Ntcp expression [92]. To add more complexity, SHP has recently also been shown to suppress the glucocorticoid receptor (GCR)-mediated transactivation of the human *NTCP* promotor [46]. Reduced Ntcp mRNA levels after CA feeding in $Shp^{-/-}$ mice indicate that additional Shp-independent pathways must exist which mediate bile acid triggered downregulation of *Ntcp* [93]. Such potential pathways could include bile acid-induced, JNK-dependent phosphorylation of RXRα leading to reduced DNA binding of the RXRα:RARα heterodimer in the *Ntcp* promotor [94,95]. On the other hand, activated c-Jun might also enhance *SHP* transcription via an AP-1 binding site in the rodent and human *SHP* promoter [94]. Moreover, SHP-independent repression of HNF4 by bile acids involving a yet unidentified posttranscriptional mechanism has also been described [88,96–98]. Bile acids and FXR also negatively regulate OATP1B1, the main Na^+-independent bile acid uptake transporter in human. *OATP1B1* is suppressed by FXR involving a cascade including FXR-SHP activation, SHP-HNF4 interaction and subsequent inhibition of

the HNF4 transactivating effect on HNF1 [46,98]. Since the *OATP1B1* promotor contains a HNF1 binding site the regulatory cascade may involve bile acid-dependent suppression of HNF1 via decreased activation of HNF4 by SHP dependent and/or SHP independent mechanisms [98,99].

Findings in HNF1$^{-/-}$ and conditional HNF4$^{-/-}$ mice with reduced *Ntcp, Oatp1 (Oatp1a1)* and *Oatp2 (Oatp1a4)* expression [100,101] indicate a role of HNF1 and HNF4 as central positive regulators of these basolateral bile acid uptake systems responsible for constitutive gene expression. HNF1α also appears to be required for expression of *Oatp4 (Oatp1b2)* [99,102]. Moreover, the genes encoding intestinal and renal Asbt, FXR (containing a HNF1α binding site in its promoter [101]), and the intracellular bile acid binding protein Akr1c2 were found among the downregulated genes in HNF1$^{-/-}$ mice underlining the central role of HNF1α in bile acid homeostasis [101]. While HNF1α is essential for the basal constitutive promoter activity of rat *Ntcp*, so far no HNF1α (as well as HNF4α and RXR:RAR) binding sites have been identified in the human minimal *NTCP* promotor [83,88]. However, the human *OATP2* gene contains an HNF1α binding site in its promotor region [99]. Thus, HNF1α appears to be the master regulator of basolateral Ntcp and Oatp expression. Of interest, HNF1α is also able to negatively regulate its own expression and that of HNF4 by a negative feedback loop [87]. HNF1α expression in turn depends on HNF4α expression and is reduced under conditions of reduced/HNF4α activity [98,103,104].

RAR together with its obligatory binding partner RXRα is at least required for constitutive expression of rat *Ntcp* and binding of this heterodimer to retinoid response elements in the promotor regions of *Ntcp* as well as *Mrp2* positively transactivates these genes [83,105]. Recent reports suggest also a potential positive transactivating role for RXRα:RARα in the promotor regions of Oatp4 (Oatp1b2) [102] and indicate a negative regulation of Mrp3 by RARα:RXRα binding [106]. The latter finding would complement the proposed mechanism of Mrp3 upregulation via TNFα -induced liver receptor homologue-1, LRH-1 (NR5A2) (also known as fetoprotein transcription factor, FTF) [107].

The classical hormone and xenobiotic receptor PXR is also activated by bile acids such as LCA, 3-keto LCA and to lesser extents by DCA and CA [56,58], thus implying a role for PXR not only in xenobiotic defense mechanisms, but also in bile acid metabolism and transporter regulation in addition to FXR. PXR is highly expressed in liver and to lower extents in the intestine and kidney [108] and also forms heterodimers with RXRα upon ligand activation. A unique feature of PXR is its binding affinity for a wide spectrum of diverse ligands and species differences among ligand binding [109,110]. Thus a ligand which is a strong activator of PXR in human may only be a weak activator of rodent PXR, as examplified for rifampicin [111]. However, the DNA binding domain is highly conserved [109]. Ligands of PXR comprise several xenobiotics, including rifampicin, natural steroids or hyperforin, the active compound of St. John's wort [111,112]. The first bile acid transporter shown to be regulated by PXR was Oatp2 (Oatp1a4) [56]. PXR$^{-/-}$ mice have reduced baseline expression of Oatp2 (Oatp1a4) and lack induction upon PXR stimulation via pregnenolone-16α carbonitrile (PCN). Ligand activated PXR was also shown to induce MRP3/Mrp3 expression in human cell lines and in vivo in mice, effects which were not seen in the PXR$^{-/-}$, implying a role for PXR also for Mrp3 [113,114]. A complex regulation was demonstrated for human as well as rodent MRP2/Mrp2, which contains an unusual response element (ER-8) in its promoter, that can be transactivated by either FXR, PXR or CAR [72]. Another link between FXR and PXR is provided by the fact that human and murine PXR is a target for negative regulation of SHP [115]. Thus, it was shown that bile acid-mediated induction of the FXR/SHP pathway mediates repression of the classical PXR target CYP3A4/Cyp3a11 [115]. However, the impact of this pathway for transporter regulation has not been evaluated so far. Moreover, a recent study has identified PXR response elements in the promoter region of SHP in human HepG2 cells [116].

The second xenobiotic nuclear receptor, CAR, which is abundantly expressed in liver and intestine, again forms CAR:RXRα heterodimers but can also bind as CAR monomer to phenobarbital response enhancer modules (PREM) in CAR target genes [117]. Both, PXR and CAR predominantly function as inducers of gene expression and represent so-called "xenosensors". CAR also recognizes structurally diverse compounds and shares overlapping xenobiotic ligands with PXR [112]. However, no binding and activation of CAR by bile acids has directly been shown so far. Interestingly, bilirubin is an activator of human and murine CAR [59]. Similar to PXR, SHP also interacts indirectly with CAR via recruitment of co-repressors or inhibition of co-activators and is thus able to inhibit the transactivation of the classical CAR target gene *CYP2B* [118]. In addition to the effects of CAR on *MRP2/Mrp2* (see above), an induction of human and murine *MRP4/Mrp4* was achieved by treatment with CAR activators [60,114]. This induction was not found in CAR$^{-/-}$ mice. Mrp3 was upregulated in rats and mice after treatment with various CAR activators [114,119]. This role of CAR in mediating ligand-dependent induction of Mrp3 was recently confirmed using CAR$^{-/-}$ mice [120]. This study showed induction of Mrp3 mRNA by lithocholic acid (LCA) in wild-type but not in CAR$^{-/-}$ and PXR/CAR$^{-/-}$, while the induction of Mrp3 was maintained in PXR$^{-/-}$. Oatp2 was regulated inversely to Mrp3 in these receptor knockouts, indicating that CAR may play a major role in Mrp3 induction while PXR is the major regulator of Oatp2. Bile acids might upregulate MRP3 also via LRH-1 since the human *MRP3* promotor contains a binding element for LRH-1 [121]. Since bile acids do not act as LRH-1 ligands [122] another factor mediating bile acid-dependent induction appears to be required [121]. TNFα may be this factor since it upregulates LRH-1 expression in vitro and in vivo [123].

VDR was recently shown to be the third nuclear receptor activated by bile acids, almost exclusively by LCA and its derivates [54]. While so far mainly bile acid detoxifying enzymes such as Cyp3A4/Cyp3a11 and Sult2a1 have been shown to be regulated by VDR, a recent report has identified a VDR response element in the rat *Asbt* gene and its induction by calcitriol [106], indicating that VDR may play also a role in bile acid transporter regulation. Similar to anatagonizing effects of 9-cis retinoic acid on FXR-induced BSEP expression [124], FXR-induced BSEP expression was also inhibited by vitamin D [125].

5. Transporter regulation in inflammation induced cholestasis

Cholestasis frequently occurs as a complication in patients with sepsis and extrahepatic bacterial infections [126,127]. Endotoxin (also termed lipopolysaccharide, LPS) inhibits the transport of organic anions at both the sinusoidal and canalicular membrane of hepatocytes and affects both bile acid-dependent and bile acid-independent fractions of bile flow [128–131]. LPS-induced proinflammatory cytokines include tumor necrosis factor α (TNFα), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which are secreted by macrophages and Kupffer cells shortly upon experimental LPS challenge [132,133], and have been characterized as mediators of reduction in bile flow and organic anion excretion [129,130]. The mechanisms by which LPS-induced proinflammatory cytokines modulate transporter gene expression at the transcriptional level have been intensively studied over the past decade.

Experimental administration of LPS, TNFα, IL-1β or IL-6 reduces expression of several hepatocellular organic anion transport systems at the basolateral or canalicular membrane (Fig. 2). LPS leads to a rapid and marked downregulation of Ntcp mRNA and protein expression to 10–30% in rats which occurs at the transcriptional level as indicated by nuclear run-on studies [134–137]. In human hepatoblastoma-derived HepG2 cells both TNFα and IL-1β down-regulate *NTCP* promoter activity [105]. Similar effects on Ntcp mRNA expression have been observed in mice early after application of either TNFα or IL-1β but not IL-6 [135]. In the pathophysiological context of inflammation-induced cholestasis following LPS-treatment only IL-1β appears to be a major regulator of Ntcp expression in vivo [137]. IL-6 as another regulator of *Ntcp* gene expression only plays a crucial role in downregulation during the later stages of endotoxemia [138]. In addition to Ntcp, a reduction of Oatps, Mrp2 and Bsep is observed [40,102,137,139–143].

Downregulation of *Ntcp* gene expression during inflammation-induced cholestasis is caused by decreased binding activity of the nuclear transcription factors HNF1 and RXR:RAR to the rat *Ntcp* gene promoter [83,105,134]. Alterations in the nuclear availability and binding activity of the two critical transactivators HNF1 and RXR:RAR are induced by the activation of inflammatory intracellular signalling cascades. The function of the RXR:RAR complex during the acute phase response is decreased by different posttranscriptional mechanisms affecting the RXR component [47,95,144,145]. LPS and proinflammatory cytokines including TNFα and IL-1β induce a rapid dose-dependent decline in three distinct RXR mRNAs and proteins (RXR, RXR, and RXR) in hamster liver within hours [47]. Increased RNA degradation is primarily responsible for the repression of RXR, because LPS only marginally reduces RXR transcription [47]. As another mechanism nuclear RXR protein levels rapidly decrease upon LPS, TNFα or IL-1β treatment of hamsters and mice [47,145,146] due to a shift from the nucleus into the cytosolic compartment [145]. In contrast to RXR, the subcellular localization of its heterodimerization partner RAR remains unaffected by LPS but its binding to the promoter is decreased by removal of the heterodimeric partner [145]. LPS-induced stimulation of hepatic Kupffer cells activates several intracellular stress pathways including the mitogen-activated protein kinases, extracellular signal-regulated kinase (ERK), c-Jun-N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) [147]. Of those JNK has been shown to directly phosphorylate RXR [95,148]. Inhibition of the JNK signalling pathway completely prevents IL-1β-mediated suppression of RXR-dependent *Ntcp* gene expression [95]. The parallel time course of JNK activation

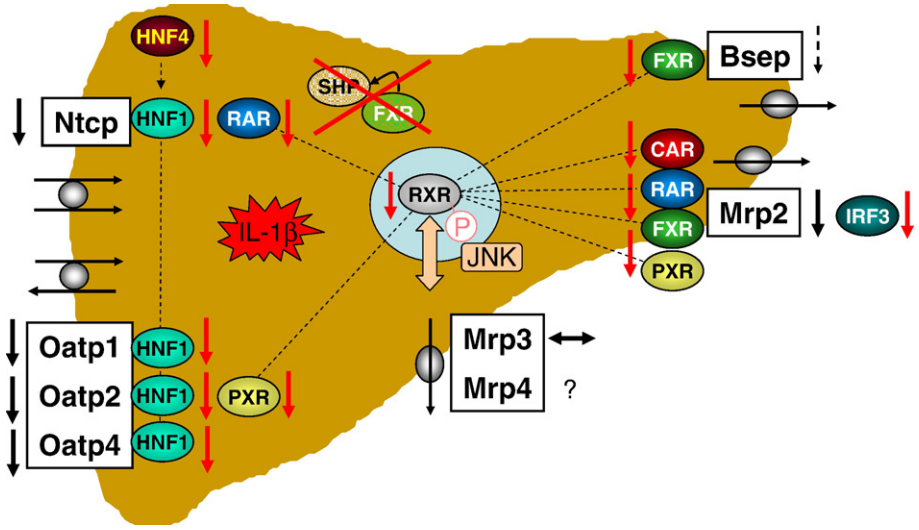

Fig. 2. Transporter regulation in inflammation-induced cholestasis. Endotoxin-mediated signals reduce the expression of several hepatocellular organic anion transport systems at the basolateral or canalicular membrane. Particularly IL-1*β* appears to be the major regulator of *Ntcp* and *Mrp2* expression under the pathophysiological conditions of endotoxemia in vivo. Downregulation of *Ntcp* expression is caused by decreased binding activity of the nuclear transcription factors HNF1α and RXRα:RARα without induction of SHP. The function of the RXRα component is thereby affected by different posttranscriptional mechanisms including RNA degradation, JNK-dependent phosphorylation and a nucleo-cytoplasmic shift. Reduced HNF1α expression may in turn be secondary to reduced HNF4α activity. Downregulation of *Oatps 1, 2*, and *4* (Oatp1a1, 1a4, 1b2) is at least in part mediated by reduced expression and activity of their common regulator HNF1α. Transcriptional control of *Bsep* and *Mrp2* is mediated by a decreased expression of nuclear hormone receptors including FXR, PXR, and CAR. In addition, IRF 3 has recently been identified as a IL-1*β*-dependent regulator of the human *MRP2* promoter.

and increasing cytoplasmic RXR levels led to the hypothesis that LPS-induced activation of JNK results in phosphorylation and possibly further posttranslational modification of RXR, triggering its export from the nucleus to the cytosol [145].

As another major mechanism of *Ntcp* gene downregulation during the acute phase response LPS has also been shown to reduce HNF1 mRNA expression [103,149], nuclear protein levels of HNF1 [149,150] and binding activity of HNF1 [102,134]. Similarly, decreased HNF1 binding activity in mouse liver nuclei has been observed after TNFα or IL-1β treatment [146]. In line with these findings clodronate-induced depletion of Kupffer cells blocks cytokine-mediated *Ntcp* suppression upon endotoxin exposure and the decreased binding activity of RXR:RAR and HNF1 is preserved in clodronate/LPS treated rats [151]. Reduced HNF1 expression may in turn be secondary to reduced HNF4 activity [103,152]. Inflammatory signals induced by LPS, particularly IL-1β, result in a posttranscriptional reduction in HNF4 protein levels in HepG2 cells and rat livers probably caused by degradation via the proteasomal pathway [103]. Recent data indicate that IL-1β inhibits HNF4 promoter activity, protein expression, and its binding to the chromatin via a JNK pathway [153]. In this study a JNK-specific inhibitor blocked IL-1β-inhibition of HNF4 expression and JNK1 was able to phosphorylate HNF4 thereby reducing its DNA binding. However, IL-1β could also affect HNF1-mediated gene transcription in vivo during endotoxemia by interference with chromatin remodeling facilitated by the histone acetyltransferase activity of HNF1 coactivator proteins such as steroid receptor coactivator (SRC)-1 and CREB-binding protein (CBP)/p300 [137,154]. A recent study in the endotoxemic mouse heart demonstrated a decreased expression of SRC-1 and CBP/p300 during the acute phase response [155]. The role of these transcriptional cofactors in mediating gene-specific effects of individual nuclear transcription factors is becoming increasingly recognized [46].

The role for SHP in inflammation-mediated hepatic transporter gene regulation remains controversial [94,105,156]. In contrast to bile-duct ligation, studies in LPS-treated mice demonstrate that LPS-induced cytokines reduce *Ntcp* expression without inducing SHP [156]. In line with these findings, LPS-treatment even decreased SHP mRNA expression in mouse liver [50]. Similarly cytokine-inactivation in obstructive cholestasis rather increases SHP mRNA expression in vivo pointing towards a role for cytokines as SHP suppressors [157]. However, in vitro studies in primary rat hepatocytes have also demonstrated the possibility of c-Jun/AP-1-mediated activation of the SHP promoter via the JNK1-pathway which in turn suppressed cholesterol 7-hydroxylase expression [94].

Expression of the organic anion transporters Oatp1, 2, and 4 (Oatp1a1, 1a4, 1b2) is uniformly decreased in endotoxemia at both mRNA and protein levels [102,137,139–142]. Downregulation of Oatp1 (Oatp1a1) and Oatp2 (Oatp1a4) is also mediated by injection of inflammatory cytokines such as TNFα, IL-1β and IL-6 [138,140]. However, cytokine-inactivation studies in endotoxemic rats indicate that downregulation of the basolateral transporters Oatp1 (Oatp1a1) and Oatp2 (Oatp1a4) does not depend on single cytokines alone and may involve both TNFα- and IL-1β-independent signal transduction pathways [137]. In line with this finding recent data show that reduced Oatp4 (Oatp1b2) expression during LPS-induced cholestasis occurs through toll-like receptor 4 signals independent of inflammatory cytokines such as TNFα, IL-1β or IL-6 [142,158]. The role of toll-like receptor 4 signals in the regulation of organic anion transporters remains to be studied in more detail. Downregulation of Oatps 1, 2, and 4 (Oatp1a1, 1a4, 1b2) during the acute phase response is at least in part mediated by reduced expression and activity of their common regulator HNF1 [102,103, 149,150]. In addition to reduced HNF1 activity, decreased expression of the inducers PXR and CAR during the acute phase response might play a role in the downregulation of Oatp2 (Oatp1a4) [56,58]. As described for RXR:RAR-mediated *Ntcp* expression, posttranscriptional regulation of RXR during the acute phase response by phosphorylation and nuclear export also represents the common denominator for a coordinated downregulation of other nuclear receptor heterodimer target genes [95,145]. LPS also leads to a marked reduction in PXR and CAR mRNA expression, representing another regulatory component [48,144, 159]. Similarly, IL-1β and IL-6 are able to suppress PXR and CAR mRNA [160,161]. Recently, endotoxin and IL-1β in particular have been shown to inhibit CAR-induced *Oatp2* gene expression via induction of nuclear factor (NF) B, which interferes with the enhancer function of the distal glucocorticoid response element in the *CAR* promoter [162]. In regard to downregulation of *Oatp4*, decreased binding activities of several liver-enriched transcription factors including HNF1, RXR:RAR, C/EBP and HNF3, which bind to responsive elements in the proximal promoter region, contribute to a reduction of gene expression [102]. Besides the discussed reduction of HNF1 and HNF4 expression, LPS is also known to suppress HNF3 expression either in cell culture or rat liver [163,164] although the relevance of these findings for transporter regulation remains to be determined. Reduced expression of human NTCP and OATP2 (OATP1B1) have been observed in liver biopsies from patients with inflammation-induced cholestasis [39], but the underlying transcriptional mechanisms in humans remain to be determined.

Reduced canalicular secretion of bile acids and other organic anions during endotoxemia is caused by a concomitant reduction of the canalicular export pumps Bsep and Mrp2 [40,143]. While Bsep mRNA and protein expression is only moderately decreased in inflammation-induced cholestasis upon LPS-treatment by 30% [143], Mrp2 expression is more profoundly reduced to levels as low as 10% of controls [40,136,137,165]. In contrast to TNF, only IL-1β mediates suppression of human and rat *MRP2/Mrp2* promoter activity in HepG2 cells [105,166]. Similarly, IL-1β appears to be the major regulator of Mrp2 expression under the pathophysiological conditions of endotoxemia in vivo because respective anti-cytokine-pretreatment leads to a full preservation of transporter expression [137]. In contrast to the transcriptional downregulation of *Bsep* and *Mrp2* found in LPS-treated rodents in vivo and rat liver slices in vitro, posttranscriptional mechanisms play a more prominent role in the regulation of both human transporter genes. In LPS-treated human liver slices BSEP and MRP2 mRNA levels are unaltered whereas both proteins are virtually absent under these conditions [42]. Similarly, profound reductions in canalicular BSEP and MRP2 staining have been

observed in liver biopsies from patients with inflammation-induced cholestasis [39]. Transporter retrieval from the canalicular membrane has been described as another posttranscriptional mechanism of early and reversible regulation of rodent Mrp2 during endotoxemia [167]. Transcriptional control of the *Bsep* and *Mrp2* genes is mediated by a group of nuclear hormone receptors including FXR, RAR, PXR, and CAR [70–72,105]. As described above in detail, phosphorylation and nuclear export of RXR represents one component of the uniformly decreased transporter gene expression during LPS-induced cholestasis [95,145]. Furthermore, LPS-induced downregulation of Bsep mRNA may be mediated by a suppression of FXR mRNA [50,144]. Either LPS, TNFα or IL-1β significantly decrease FXR mRNA expression and binding activity to the IR-1 response element located in both human and rodent *BSEP/Bsep* promoters [50,70,71].

In addition to reduced FXR- and retinoid-transactivation, decreased activity of PXR and CAR may be important for *Mrp2* repression [48,50,105,123,144,159]. However, cytokine-inactivation experiments in endotoxemic rats which show a fully preserved Mrp2 expression upon anti-IL-1-treatment despite continuously reduced binding to the *Mrp2* promoter ER-8 element and decreased nuclear protein levels of RXR, PXR and CAR raise the question of additional, yet unknown regulators [137]. One IL-1β-dependent regulator has recently identified for the human *MRP2* gene: IL-1β induces down-regulation of the *MRP2* gene by inactivating interferon regulatory factor (IRF) 3 binding to an interferon stimulatory response element (ISRE) in the human promoter sequence [168].

Much less is known about the regulation of the basolateral overflow systems Mrp3 and Mrp4 during inflammatory cholestasis and the limited findings are still contradictory. Either endotoxin or TNF treatment induces a decrease of Mrp3 mRNA expression in mice [140,159] whereas induction of Mrp3 mRNA is found in LPS-treated rats [169]. This difference in gene regulation is not necessarily contradictory, but may rather reflect species differences observed in inflammation-induced transcriptional regulation. The latter finding is confirmed by in vitro studies using HepG2 and HuH7 cells which demonstrate an increased expression of Mrp3 mRNA after cytokine stimulation [123,170]. Furthermore, TNFα increases binding of the transactivator LRH-1 to the *Mrp3* promoter and a subsequent increase in reporter activity [123]. Indirect evidence for a Mrp3 expression stimulating effect of TNFα in vivo is also derived from observations in TNFR-knockout mice during long-term bile duct obstruction [123]. Regulation of the second rescue transporter Mrp4 in endotoxinemia still needs to be determined.

6. Transporter regulation in estradiol induced cholestasis and pregnancy

Pregnancy is associated with significant qualitative and quantitative hormonal changes. Elevated plasma concentrations of estrogens and progesterone contribute to considerable changes in basal expression and regulation of transporters (Fig. 3). Several transport proteins are differentially expressed between genders, and estradiol has been identified as an important modifier. The different concentrations of estradiol between genders are responsible for the significantly reduced basal expression of Ntcp in female rats [171,172]. It is straightforward to hypothesize that pregnancy-associated changes may have a similar mechanism.

During experimental estradiol-induced cholestasis in rats reduced basolateral Ntcp expression parallels Na^+-dependent uptake of bile acids [173]. Although estradiol reduces basal expression of Ntcp in rats, Cao et al. observed no changes in Ntcp expression during pregnancy while finding a significant induction

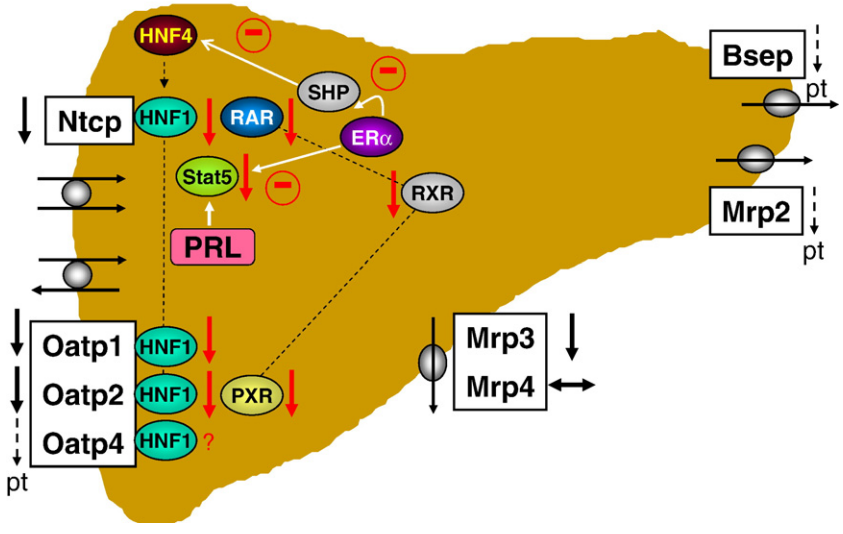

Fig. 3. Transporter regulation in estradiol-induced cholestasis and pregnancy. Several transport proteins are differentially expressed between genders, and estradiol has been identified as an important modifier. *Ntcp* expression is profoundly downregulated, while expression of all *Oatps* is only moderately affected. Estradiol reduces basal expression of *Ntcp* in part by interfering with the upregulating effect of prolactin on Stat5 binding to the *Ntcp* promoter via a signalling cascade involving ERα. Furthermore, estradiol-mediated induction of the nuclear receptor SHP might contribute to the decreased binding activity of HNF1α and RXRα:RARα to the *Ntcp* promoter. Apart from Oatp4 (Oatp1b2), all basolateral anion transporters are transcriptionally downregulated, presumably via reduced activity of HNF1α or PXR. Reduction of Mrp2 and Bsep expression involve posttranscriptional (pt) mechanisms since mRNA levels remain stable after estradiol and throughout pregnancy.

of Ntcp (and Bsep) expression during the early lactation period postpartum [174]. This upregulation could be causally linked to prolactin secretion and subsequent binding of Stat5 to the *Ntcp* promoter [84,175]. Placental lactogen secretion during pregnancy should also elevate Ntcp expression, but the absence of expression changes during pregnancy despite the estradiol and prolactin effects led to the hypothesis that one effect abrogates the other. Subsequently the same group could show that estradiol represses the prolactin effect during pregnancy via a signalling cascade involving ER and Stat5 [176]. Another group demonstrated downregulation of Ntcp in pregnant rats and also found upregulation of Stat5, but downregulation of HNF1 and decreased promoter binding of RXR:RAR as initiating elements, indicating complex transcriptional events [177]. Ethinylestradiol (EE)-mediated induction of the nuclear receptor SHP might either directly or indirectly contribute to the decreased binding activity of HNF1 and RXR:RAR to the *Ntcp* promoter [178]. While Oatp1 (Oatp1a1) remains unchanged in pregnancy and shows no gender difference, Oatp2 (Oatp1a4) is slightly (and not significantly) decreased on protein and mRNA level [172,174,179]. Interestingly, it has been shown that after treatment with EE protein expression of all Oatps (1, 2 and 4) (Oatp1a1, 1a4, 1b2) is moderately reduced in rat liver, while Ntcp protein expression is severely downregulated [173,179]. This expression pattern might contribute to a maintained Na^+-independent bile salt uptake in EE-treated rats [173]. Apart from Oatp4 (Oatp1b2), all basolateral anion transporters were transcriptionally repressed, presumably via HNF1, C/EBP or PXR [179]. This corresponds to results from the estradiol studies and suggests that antagonistic mechanisms in regulation during pregnancy may be valid not only for Ntcp. One such potential antagonistic mechanism could be the estrogen activation of the nuclear receptor CAR [180].

Although basal expression of canalicular Mrp2 does not differ between genders in rodents [181,182], hepatic Mrp2 protein expression is reduced in rat liver to about 50% of control animals during pregnancy [183]. This reduction of protein mass is accompanied by a decrease of Mrp2 function as measured by biliary excretion of the classic Mrp2 substrate 2,4-dinitrophenyl-glutathione [183]. Interestingly this appears to involve posttranscriptional mechanisms since Mrp2 mRNA remains stable throughout pregnancy [174]. Comparable changes in Mrp2 expression are also observed after experimental EE treatment in rats where protein levels are decreased to 50% without corresponding changes in mRNA levels [40,143]. As described in other models of cholestasis, estradiol-17β-glucuronide induces endocytosis of Mrp2 from the canalicular membrane [184].

For rat Bsep, in vitro studies support a role of -estradiol in transcriptional downregulation of this gene [185]. One could speculate that estradiol-induced Bsep repression is mediated by reduced FXR binding [67]. Consequently it was demonstrated that after administration of EE Bsep protein expression decreased significantly to about 60% [143], an effect that was reversible by administration of ursodeoxycholate (UDCA) [186]. In contrast, reduction of Bsep-mediated bile acid-dependent bile flow after estradiol-17-glucuronide administration does not primarily represent a gene regulation event but is mechanistically linked to Mrp2-mediated transport of estradiol-17-glucuronide into bile [187,188].

Mrp3 is considered one of the basolateral "overflow"-pumps compensating for impaired canalicular Mrp2. Of note, Mrp3 is downregulated to about 50% of the control expression during pregnancy on protein level, i.e. to the very same extent as Mrp2 [183]. However, Mrp3 mRNA is also downregulated to 50% of normal controls in contrast to unchanged Mrp2 mRNA [183], so that pregnancy cannot be compared to the cholestatic conditions with compensatory induction of basolateral efflux pumps. Effects of pregnancy or experimental estradiol application on Mrp4 expression have not been investigated in detail so far. Studies in mice did not show any changes in Mrp4 expression in contrast to the marked changes of Mrp2 and Mrp3 in pregnancy [189]. In addition, a significant increase of renal Mrp3 and a pronounced downregulation of renal Mrp4 are observed in these pregnant mice, although, the impact of these findings need to be further investigated [189]. Similar to the higher expression of bile acid sulfotransferases in female mice [190] also sulfated bile acid-transporting Mrp4 was higher expressed in livers of female mice [189].

7. Transporter regulation in obstructive cholestasis

Obstructive cholestasis induced by CBDL initiates marked changes in transporter expression in rat liver (Fig. 4). As an important protective regulatory step, the basolateral Na^+-dependent bile acid uptake system, Ntcp, is downregulated to prevent further bile acid uptake by hepatocytes [191–193]. While Oatp1 (Oatp1a1) is also decreased during obstructive cholestasis, maintained Oatp2 (Oatp1a4) and Oatp4 (Oatp1b2) expression ensures continuos elimination of other organic anions into the bile under these conditions and contributes to the progressive nature of obstructive liver damage [192,194,195]. Most prominent is the downregulation of rat Mrp2 to less than 10% of the normal expression after 7 days of CBDL [40]. However, this downregulation does not only prevent biliary excretion of the endogenous substrate bilirubin diglucuronide but also of many exogenous and potentially toxic Mrp2 substrates which can accumulate in the liver. Accumulation of such compounds can decrease glucuronidation in hepatocytes and therefore inhibit metabolism and detoxification [41]. Alternatively, these compounds are effluxed into the sinusoidal blood via basolateral transport systems which are compensatively upregulated (Mrp3 and 4) [8,11,192]. This also comprises bile acids, especially in their metabolized (glucuronidated and sulfated) form, followed by their renal excretion. Interestingly, Mrp2 downregulation during obstructive cholestasis is absent in mice indicating fundamental species differences [196]. Bsep as canalicular bile acid exporter is largely maintained during obstructive cholestasis [143].

It is noteworthy that the mechanisms of *Ntcp* downregulation during obstructive cholestasis are completely different from inflammatory states (such as endotoxin-related cholestasis [137]. Systemic proinflammatory cytokines have no effect on *Ntcp* expression during obstructive cholestasis [157]. Selective inactivation of TNFα and IL-1β is without effects on *Ntcp* expression, clearly demonstrating that downregulation of *Ntcp* in obstructive cholestasis is independent of these cytokines. Rather, accumulation

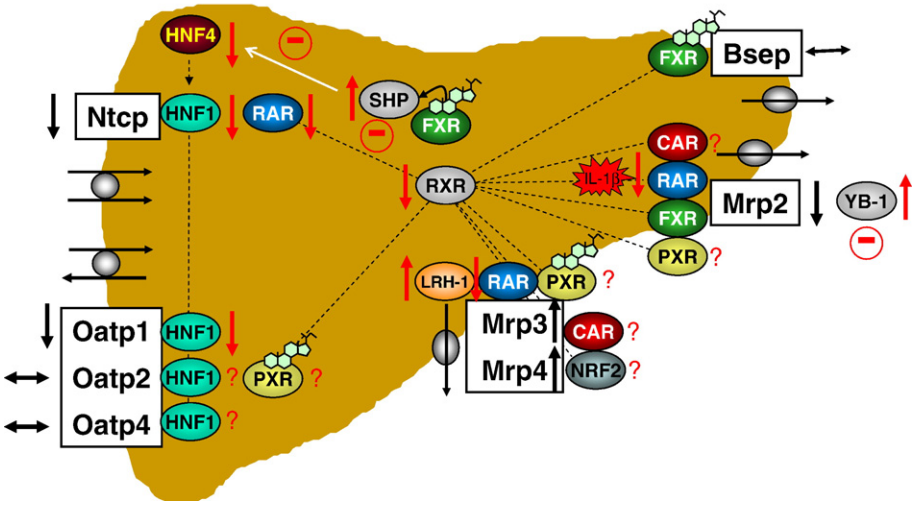

Fig. 4. Transporter regulation in obstructive cholestasis. Obstructive cholestasis induces a marked downregulation of basolateral *Ntcp* and *Oatp1 (Oatp1a1)* expression as an important protective regulation step to prevent further bile acid uptake, while maintained *Oatp2* and *4* (Oatp1a4, 1b2) expression ensures continuos elimination of other organic anions into the bile. Most prominent is the downregulation of canalicular *Mrp2* whereas *Bsep* expression is relatively well preserved. Basolateral overflow systems including *Mrp3* and *4* are compensatorely upregulated during biliary obstruction. Mechanisms of *Ntcp* downregulation during the early stage of obstructive cholestasis in vivo are completely different from inflammatory states since downregulation is mediated without major contribution of cytokines by accumulating bile acids *per se*. Such effects may involve bile acid-dependent suppression of the HNF4α/HNF1α pathway by SHP-dependent and independent mechanisms. In contrast IL-1*β* leads to decreased binding of the RXRα:RARα heterodimer to the *Mrp2* promoter. Reduced binding activity of the Y-box binding protein YB-1 may have additional suppressive effect on Mrp2 expression. During the early obstructive phase a rapid posttranscriptional mechanism adds to Mrp2 downregulation. The mechanism of upregulation of *Mrp3* and *4* has not yet been fully elucidated. Bilirubin induces Mrp3 expression likely by stimulating CAR and may contribute as a regulator during obstructive cholestasis. In addition biliary obstruction leads to enhanced binding of the *Mrp3* transactivator Lrh-1 in a TNF-dependent fashion and decreases the activity of RXRα:RARα which functions as a repressor of *Mrp3*. Hypothetical mechanisms of Mrp4 induction include upregulation via the xenosensors CAR and PXR that have been shown to be activated by bile acids and bilirubin. Recently the transcription factor Nrf2 has been suggested that is another regulator of basolateral Mrp expression.

of bile acids which activate FXR and thus induce SHP may downregulate *Ntcp* [156,157,197]. Alternatively, it has been shown in vitro that bile acids are also capable of inducing SHP via an FXR-independent mechanism: taurocholic acid strongly activates JNK and overexpression of c-Jun in turn results in enhanced *SHP* promoter activity [94] which, in the light of above cited data, may contribute to *Ntcp* repression during obstructive cholestasis. During the first 3 days of CBDL, SHP mRNA expression correlates inversely with Ntcp expression while after 7 days SHP mRNA levels approximate normal values while Ntcp remains repressed [156]. This apparent discrepancy could be attributed to rising levels of proinflammatory cytokines such as TNFα and IL-1β over time [197], since these cytokines are known to inhibit RXRα:RARα activity which is decreased primarily during later stages of biliary obstruction [41,95,105,198]. Moreover, bile acids have been shown to suppress *HNF4*α transcription through SHP-independent mechanisms [96,98], effects which could explain reduction of HNF1α and subsequent *Ntcp* expression despite low SHP levels. Taken together bile acids *per se* accumulating during the early stage of obstructive cholestasis without major contribution of cytokines are the dominant cause for *Ntcp* downregulation after CBDL. Such effects may involve bile acid-dependent suppression of the HNF4α/HNF1α pathway by SHP-dependent and independent mechanisms [98] as a central pathway of *Ntcp* gene regulation. Downregulation of Oatp1 could also be explained via reduced HNF1 [101].

One of the central regulatory elements during obstructive cholestasis is again RXRα. Obstructive cholestasis induces secretion of IL-1β and leads to decreased binding of the RXRα:RARα heterodimer to the *Mrp2* promoter thereby reducing transcription of the rat *Mrp2* gene [105,198]. Although so far only shown for inflammation-induced cholestasis (LPS model), it is likely that also in obstructive cholestasis which is also accompanied by systemic release of proinflammatory cytokines such as TNF and IL-1 [199,200], a rapid decline of RXR levels in the nucleus may play an important role, leaving the other receptors without partner for dimerization [145]. Downregulation of *Mrp2* via the systemic proinflammatory cytokine IL-1β is also observed in the duodenum [41], but interestingly enough not in kidney [198]. This indicates organ-specific regulatory mechanisms beyond the described cascades. Moreover, binding activity of the Y-box binding protein YB-1 is enhanced in obstructive cholestasis and may have additional suppressive effect on *Mrp2* expression [201]. Downregulation of Mrp2 protein expression is much faster than of Mrp2 mRNA expression in liver and intestine [41,198]. This may indicate a rapid posttranscriptional mechanism for *Mrp2* downregulation in the early phase after CBDL (up to 3 days), while the transcriptional effect requires more time. The posttranscriptional mechanisms may comprise translational regulation [202] as well as mechanisms for reducing the half life of the protein, e.g., by removal from the canalicular membrane [203].

Bsep expression during obstructive cholestasis is relatively well preserved compared with other membrane transporters and may lessen the extent of liver injury produced by bile acid retention particularly when cholestasis is prolonged [143]. Induction of Bsep by bile acids via FXR seems to operate as an adaptive mechanism under these conditions by which accumulating bile acids promote their own export into bile [10,69,204].

However, enhancing biliary pressure via stimulation of Bsep in the presence of a complete obstruction may aggravate cholestatic liver injury (bile infarcts) in this situation [23].

The mechanism of Mrp3 and 4 induction has not yet been fully elucidated. Administration of bilirubin alone (just referred to as bilirubin without closer specifications) is sufficient to induce Mrp3 mRNA in Sprague–Dawley rats [192] likely by stimulating CAR [59,114,120] and may also contribute during obstructive cholestasis but obviously represents not the only mechanism for upregulation. Released TNFα induces expression of LRH-1 during obstructive cholestasis, and enhanced LRH-1 binding to the *Mrp3* promoter was followed by upregulated expression of mRNA and protein in cholestatic mice liver [123]. RXR:RAR functions as a suppressor of human and rat *MRP3/Mrp3* expression. Upregulation of MRP3/Mrp3 during obstructive cholestasis occurs when RXR:RAR binding to a DR-2 element in the promoter is diminished [106]. However, differences in *Mrp3* regulation exist between species and even within different mouse strains, since a higher basal expression Mrp3 is not further induced in FVB/129 Ola mice after 3 days of bile duct ligation [205]. PXR has also been implicated in upregulation of Mrp3 in mouse liver and theoretically may be activated in obstructive cholestasis by accumulating, hydrophobic bile acids [49,113]. Biliary obstruction induces a pronounced upregulation of Mrp4 in mouse liver and kidney [10,189] while being downregulated in rat kidney [11]. Upregulation of Mrp4 was even more pronounced in $FXR^{-/-}$ [10] implying an FXR-independent mechanism. The precise (probably species-dependent) mechanisms need to be further studied. Hypothetical mechanisms include upregulation via the xenosensors CAR and PXR that have been shown to be activated by biliary compounds (e.g., bilirubin, bile acids) [59,60,113]. Recently it was suggested that the transcription factor NF-E2-related factor (Nrf2) may be a common regulator of basolateral Mrp expression, since $Nrf2^{-/-}$ did not respond with Mrp1,3,4 and 5 induction after BDL. This finding was accompanied by marked reduction of bile serum acids in these animals, consistent with their role in basolateral bile acid reflux in cholestasis [206]. Lack of Ostβ – and to a lesser degree – Ostα induction in $FXR^{-/-}$ mice undergoing BDL underline the importance of bile acids and FXR in the regulation of Ostα/β [14].

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent the prototypic, chronic cholestatic liver disease in humans. Downregulation of MRP2 was observed in patients with chronic obstructive cholestatic caused by PSC [207]. This strengthens the data from a rat model for PSC, where a sharp decline in Mrp2 protein expression was observed [29]. However, Mrp2 expression is maintained in a mouse model of PSC, while Ntcp and Oatp1 (Oatp1a1) are reduced in this model, suggesting that downregulation of import systems may be the predominant longstanding adaptive mechanism [14]. In analogy to the diverse regulation of Oatps in experimental cholestasis, mRNA expression of OATP-A (OATP1A2) is upregulated in PSC (in contrast to downregulation of OATP2 (OATP1B1) [75]), which has been interpreted as an attempt to facilitate efflux of cholephiles from cholestatic hepatocytes into the sinusoidal blood [208]. Cholestasis associated with PBC may have an "obstructive" component at the small bile duct level as a result of ductopenia in advanced stages of the disease. In early stages, no differences were found in patients compared to healthy controls [39]. With disease progression, however, OATP2 (OATP1B1) and – to a lesser degree – NTCP expression was downregulated in later PBC stages (III and IV), while MRP3 and MDR P-glycoprotein expression was upregulated [75]. Recent data indicate, that MRP4 and OSTα/β are also induced in PBC [209]. Induction of basolateral MRP3, MRP4 and OSTα/β together with downregulation of basolateral uptake systems (NTCP, OATP2 (OATP1B1)) may at least in part explain the appearance of bile acids and conjugated bilirubin in plasma and the shift towards renal excretion. Teleologically these changes may be protective by limiting continuing bile acid overload of cholestatic hepatocytes. Expression of canalicular BSEP and MRP2 even increases in PBC stage III before returning to normal levels in stage IV [75]. Colabeling studies of BSEP and MRP2 with other canalicular markers have revealed a normal canalicular localization pattern on confocal laser scanning microscopy. However, other studies have reported diminished MRP2 expression by either transcriptional [211] or posttranscriptional mechanisms [43]. Taken together, the changes in hepatobiliary transporter expression in PBC represent secondary, adaptive rather than primary, causative changes in chronic cholestasis. Livers from PFIC patients also showed secondary, adaptive transporter changes which were principally comparable with PBC with the interesting exception of MRP3 which was not induced in these livers [212]. Studies in patients with biliary obstruction undergoing percutaneous transhepatic biliary drainage (PTBD) revealed a downregulation of MRP2, BSEP and induction of MRP3 [213]. NTCP mRNA levels were also decreased in patients with extrahepatic biliary atresia and subsequently increased if complete biliary drainage by portoenterostomy (Kasai procedure) was achieved [214], while BSEP expression was relatively well preserved, even in untreated patients [215]. The transcriptional mechanisms underlying the adaptive transporter changes remain to be determined in more detail, although posttranscriptional effects (e.g., enhanced retrieval, degradation) may be more important in human cholestasis. Preliminary data indicate reduced mRNA levels of FXR and its target gene SHP in human inflammatory and obstructive cholestasis [216] as well as in PFIC1 and 2 [217].

8. Transporter regulation during liver regeneration and toxic liver injury

Liver regeneration occurs in response to various forms of hepatocellular injury including viral hepatitis, toxic, or drug-induced liver injury and surgical resection [218,219]. This complex process results in restoration of the original liver mass and maintenance of liver-specific functions but is frequently associated with transient cholestasis. The underlying molecular pathogenesis has been described in two distinct animal models after either partial hepatectomy or toxic zone 3 liver injury induced by carbon tetrachloride (CCl_4) [137,220–223]. While canalicular transporter expression is maintained, a coordinated downregulation of basolateral transport systems might protect replicating liver cells by diminishing the uptake of potentially toxic bile salts, because the remaining liver initially cannot cope with the original bile acid pool (Fig. 5).

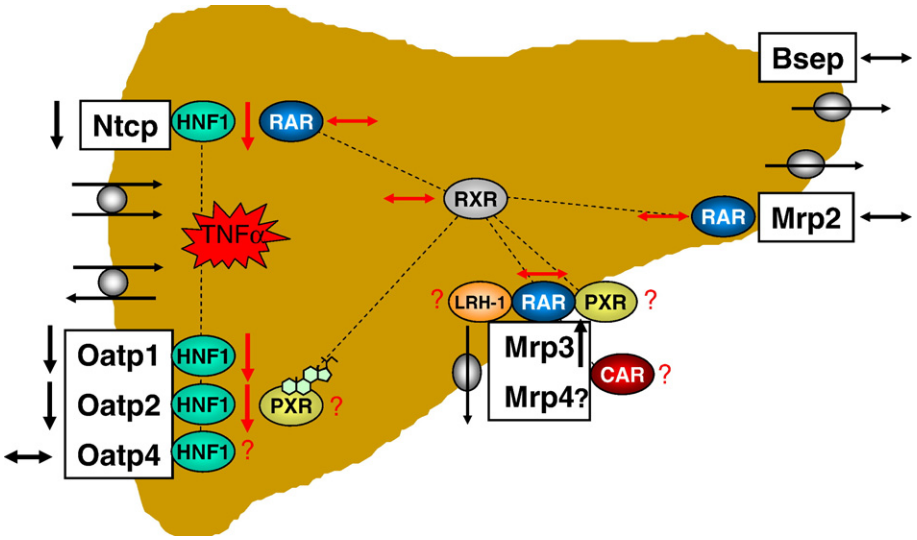

Fig. 5. Transporter regulation during liver regeneration and toxic liver injury. Different forms of liver regeneration induce a coordinated downregulation of basolateral transport systems while canalicular transporter expression is maintained. Toxic liver injury leads to a downregulation of HNF1α binding activity whereas RXRα:RARα binding remains unaffected. TNFα represents the master regulatory cytokine for the HNF1α-dependent reduction of basolateral *Ntcp, Oatp1* and *Oatp2* (Oatp1a1, 1a4) expression during liver regeneration in vivo. The molecular mechanism responsible for *Mrp3* induction after subtotal hepatectomy remains unclear since binding activity of the repressor RXRα:RARα is not significantly altered during liver regeneration and the influence of TNFα signalling on the inducer LRH-1 is controversial.

After partial hepatectomy mRNA and protein expression of the basolateral Ntcp is diminished to 25% and 50%, respectively [220–222]. Likewise Oatp1 (Oatp1a1) and Oatp2 (Oatp1a4) protein declines to 50% but reduction in mRNA expression is less pronounced [221,222]. In contrast to reduced expression of basolateral transporters, the canalicular export pumps Bsep and Mrp2 remain stably expressed or even increased (maximum increase of protein by 50–80%) 24 h after surgery [221,222]. Mrp3 expression remains stable after 70% hepatectomy but protein expression is increased after more extensive 90% resection during the later time course after 72 h [224].

Similar changes in transporter expression have been observed in the CCl_4-model of toxic liver injury [137,223]. Reduced mRNA expression of the basolateral uptake systems Ntcp, Oatp1 (Oatp1a1) and Oatp2 (Oatp1a4) were associated with decreased transcriptional activities in nuclear run-on studies [223]. Downregulation of Ntcp mRNA was significantly correlated to increased ALT levels [223]. Oatp4 (Oatp1b2) expression occurs exclusively at the posttranscriptional level with reduced protein expression in the presence of unchanged mRNA levels [223]. The unchanged expression of the canalicular export pumps Bsep and Mrp2 resembles the results after partial hepatectomy [223].

The molecular mechanisms underlying hepatocellular transporter regulation have been studied in more detail only in toxic liver injury [137,223]. As known for liver regeneration after partial hepatectomy CCl_4-toxic liver injury also leads to a massive induction of TNFα necessary for priming of hepatocytes to enter the regenerative cell cycle [223,225,226]. Cytokine-inactivation studies in CCl_4-treated rats clearly demonstrated that TNFα rather than IL-1β represents the master regulatory cytokine for the basolateral transporter gene expression during liver regeneration [137]. In contrast to IL-1β, TNFα inactivation alone fully prevents downregulation of Ntcp, Oatp1 (Oatp1a1) and Oatp2 (Oatp1a4) mRNA expression.

Toxic liver injury leads to a downregulation of HNF1 and C/EBP DNA binding activity whereas RXR:RAR binding remains unaffected [223]. HNF1 activity can be maintained by anti-TNF treatment whereas IL-1 inactivation exerts only partial effects [137]. The coincidence of maintained basolateral transporter expression in parallel to HNF1 activity in the light of an almost absent expression of these transporters in HNF1 knockout mice strongly favours a TNF-induced HNF1-mediated mechanism of *Ntcp, Oatp1* (*Oatp1a1) and Oatp2 (Oatp1a4)* repression [101,137]. Unchanged nuclear levels of RXR, PXR and CAR by CCl_4-treatment and a suppressed binding activity to a DR-3 consensus site despite cytokine inactivation indicate the possibility of post-translational changes such as phosphorylation during toxic liver injury but exclude these inducers as mediators of Oatp2 (Oatp1a4) downregulation [137].

The hypothesis of TNFα as the central regulator of transporter gene expression during liver regeneration is in line with an unchanged Mrp2 expression after both partial hepatectomy and toxic liver injury. In vitro experiments clearly demonstrated that in contrast to IL-1β, TNFα is unable to affect either *Mrp2* promoter activity or nuclear levels of RXR:RAR [105]. The molecular mechanism responsible for Mrp3 induction after subtotal hepatectomy remains still unclear. Binding activity of the repressor RXR:RAR is not significantly altered during liver regeneration and the influence of the TNF/c-*jun*/AP-1 pathway on LRH-1, a Mrp3 inducer, is still controversial [94,123]. Subsequent studies need to address further details of an adaptive Mrp3 and Mrp4 response during liver regeneration.

9. Potential therapeutic implications

The increasing information on the molecular mechanisms of bile acid transport and metabolism under physiological and

pathophysiological conditions allows a better understanding of empiric treatment strategies (i.e. UDCA, rifampicin (Rifa), Phenobarbital (PB)). More importantly, understanding therapeutic principles of "old" drugs may guide the development of novel, more effective drugs for cholestatic liver diseases.

UDCA improves biochemical and clinical parameters in a variety of human cholestatic syndromes and is considered the first line treatment for PBC and PSC although the effects on survival free of liver transplantation are controversial [227,228]. One proposed mechanism of UDCA action at least in mice includes stimulation of hepatocellular transport mechanism. In naïve mice, UDCA stimulates the expression of canalicular efflux systems (i.e. Mrp2, Bsep) [75,204] for "orthograde" biliary excretion and adaptive basolateral export pumps (i.e. Mrp3, Mrp4) effluxing bile acids back from hepatocytes into to sinusoidal blood [14,75]. Moreover, UDCA stimulates renal (Mrp2, Mrp4) and intestinal (Mrp2, Mrp3) efflux pumps in mice, changes which may coordinately result in increased elimination of potentially toxic biliary constituents [75]. Recent human evidence demonstrates, that the effects of UDCA on canalicular excretion (BSEP) and basolateral alternative efflux (MRP4) are also seen in otherwise healthy non-cholestatic gallstone patients [229]. UDCA enrichment correlated positively with OATP2 (OATP1B1) and MRP2 in PBC patients [75], effects which could at least in part contribute to reduced bilirubin and bile acid levels observed in these patients [227,230]. In addition, UDCA has been shown to stimulate bile acid hydroxylating CYP3A4/Cyp3a11 in human and rodents [231,232] and to downregulate the key enzyme of bile acid synthesis, CYP7A1, at least in vitro [67,233]. Thus, UDCA appears to act on the metabolic level by induction of detoxification pathways and on transporter level by restoring defective transporters and generating alternative overflow-systems for accumulating biliary compounds. Although UDCA has been the focus of research for many years, no definite transcriptional target or nuclear receptor partner of UDCA has been characterized. So far there has been one report suggesting that UDCA activates human PXR in vitro and induces CYP3A4 [232] and another study suggesting that UDCA might be a partial agonist for human FXR by activating BSEP and suppressing CYP7A1 [67]. Results in $FXR^{-/-}$ mice, however imply that UDCA effects are largely independent of FXR [75]. In addition to these transcriptional effects, UDCA also stimulates vesicular exocytosis and insertion of canalicular transport systems into the canalicular membrane in rats, changes which are mediated by activation of Ca^{2+}-dependent protein kinase C and mitogen-activated protein kinases [227,230]. Moreover, UDCA may also directly stimulate canalicular transport function by inducing phosphorylation of ABC transporters [234]. Despite the marked effects of UDCA on ABC transporter expression and function in normal rodents, UDCA-feeding in cholestatic (common bile duct-ligated) mice results only in a mild further induction of hepatic and renal Mrps, while still having a marked stimulatory effect on Bsep expression [196]. Thus, UDCA treatment is not able to significantly enhance the intrinsic adaptive ABC transporter response under cholestatic conditions in mice. Therefore more specific stimulators/inducers of a coordinated detoxification and alternative escape systems are desirable.

FXR agonists could overcome the reduction of bile flow in cholestasis via stimulation of BSEP (increasing bile acid-dependent bile flow) and MRP2 (increasing bile acid-independent bile flow) (Fig. 6) [68,72,235]. However, it may be simplistic to treat cholestasis merely by stimulation of bile flow, particularly in the presence of biliary obstruction. For example, application of high, choleretic doses of UDCA (a weak partial FXR agonist) in CBDL mice results in increased biliary pressure with rupture of cholangioles resulting in aggravation of bile infarcts and an increased mortality [23]. Unfortunately, many clinically relevant chronic cholestatic liver diseases such PSC have a significant obstructive component which, however, may evolve slowly (in

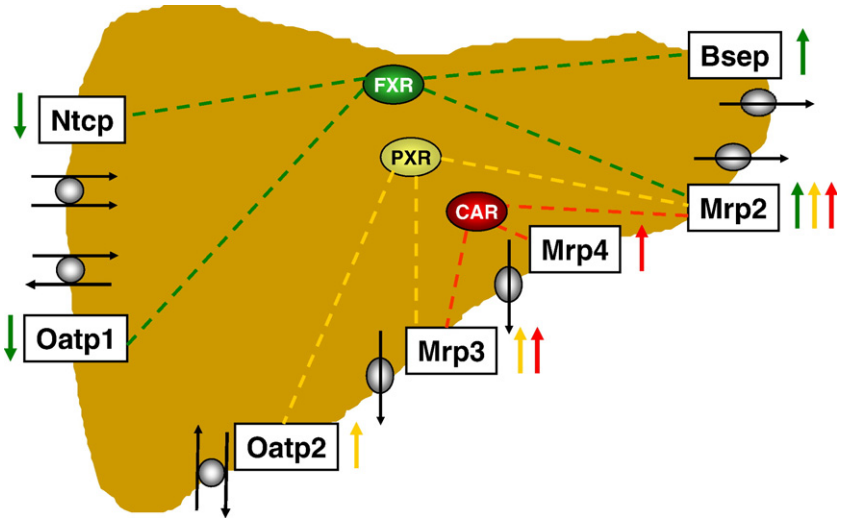

Fig. 6. Nuclear receptors as potential therapeutic targets in cholestatic disorders. FXR agonists should counteract cholestasis by limiting bile acid uptake systems via reduction of Na^+-dependent and the major Na^+-independent transport systems, Ntcp and Oatp1 (Oatp1a1), respectively. Simultaneously, FXR agonists stimulate bile acid-dependent bile flow via induced *Bsep* and bile acid-independent bile flow via induced *Mrp2*. In addition to their multiple effects on detoxification enzymes, PXR agonists mainly stimulate *Oatp2 (Oatp1a4)*, *Mrp2* and potentially *Mrp3*. CAR agonists preferentially induce *Mrp2* and both alternative basolateral export pumps for accumulated bile acids, *Mrp3* and *Mrp4*. Continuous lines and arrows, FXR effects; dotted lines and arrows, PXR effects; broken lines and arrows, CAR effects.

contrast to acute biliary obstruction induced by CBDL) and may permit more time for pharmaceutical intervention. However, FXR agonists may also support some adaptive reactions of the cholestatic hepatocyte which would be predicted to limit the hepatocellular bile acid burden (i.e. downregulation of Ntcp, Oatp1 (Oatp1a1) as well as Cyp7a1 and Cyp8b1 and upregulation of Mrp2 and Bsep [69,75,194,233]. First experiments with synthetic FXR agonists in cholestatic rodent models have been promising. In CBDL rats the FXR agonist GW4064 reduced biochemical and histomorphological markers of liver injury, which was accompanied by induction of Bsep, Mdr2 and Shp mRNA and reduction of Cyp7a1 and Cyp8b1 mRNA levels. [236]. However, serum markers of cholestasis (i.e. alkaline phosphatase, bilirubin and bile acids) were not reduced. In rats treated with ANIT, as a model for intrahepatic cholestasis, GW4064 reduced serum markers of liver injury and cholestasis and improved histology by stimulating transport and metabolic systems [236]. In the LCA rat model of intrahepatic cholestasis, the strong half-synthetic FXR agonist 6α-ethyl-chenodeoxycholic acid (6-ECDCA) reversed impairment of bile flow and improved liver cell necrosis, effects which were not observed after treatment with the strongest endogenous FXR ligand, CDCA [237]. 6-ECDCA also has antifibrotic effects of in vitro and in vivo in rats, suggesting that FXR (via SHP and AP-1) may suppress fibrogenesis in hepatic stellate cells [238]. Improvement and induction of FXR target genes was also observed in ethinyestradiol induced cholestasis after 6-ECDCA treatment in rats [239]. However, the wider therapeutic use of FXR agonists could be jeopardized by interfering FXR functions in lipid homeostasis such as HDL and triglyceride metabolism [235].

PXR and CAR agonists have been used for treatment of human cholestatic disorders and jaundice long before their mode of action was clarified. PXR and CAR may be rational therapeutic targets since – in contrast to FXR – they are not reduced during cholestatic conditions in mice [49,240] (Wagner, Trauner unpublished observations). The human PXR agonist rifampicin was predominantly used for the treatment of pruritus, but in most cases effects on cholestatic parameters in PBC were only minor and drug-related side effects were observed in up to 10% of treated patients [241–243]. The potent rodent PXR ligand PCN was reported to protect against LCA induced liver injury on various levels, effects, which were not seen after treatment of $PXR^{-/-}$ mice. These protective effects may be mediated by induction of Cyp3a11, which is supposed to hydroxylate hydrophobic bile acids [58], induction of Oatp2 (Oatp1a4) and downregulation of Cyp7a1 [56], and induction of bile acid sulfating sulfotransferase (Sult2a1) together with its sulfonyl donor 3′-phosphoadenosine 5′-phosphosulfate synthetase 2 (PAPSS2) [244]. All of these target genes were shown to be directly activated via PXR. In addition, PXR activation might contribute to reduced injury in mice by its effects on bilirubin glucuronidating Ugt1a1 and exporting Mrp2 [72,245]. In common bile duct ligated mice PCN pretreatment led to a significant reduction of serum bile acid levels, which was accompanied by increased relative levels of polyhydroxylated bile acids in serum and urine [114]. Administration of the human PXR agonist rifampicin to healthy human volunteers significantly induced *UGT1A1* and *MRP2* expression which reduced serum bilirubin levels [229]. Moreover, rifampicin potently induced *CYP3A4* expression resulting in increased bile acid hydroxylation [229]. In addition, a recent study reported that PCN has also antifibrotic effects by inhibiting the trans-differentiation of quiescent hepatic stellate cells into a myofibroblast-like phenotype and thereby reducing α-smooth muscle antigen and collagen as fibrotic markers [246]. These effects, however were partially attributed to the proliferative potential of PCN and suggested to act via PXR-dependent and -independent pathways.

Certain traditional Chinese herbs are potent CAR activators and have long been used for treatment of neonatal jaundice [247]. In mice treatment with CAR agonists (TCPOBOP and phenobarbital) drastically reduced serum levels of infused bilirubin via induction of a cascade involving hepatocellular bilirubin uptake (Slc21a5), binding to glutathione-S transferases (Gsta1, Gsta2), glucuronidation of bilirubin (Ugt1a1) and canalicular excretion via Mrp2 [59]. The prototypic CAR agonist phenobarbital is also an “old fashioned” treatment used in several human cholestatic disorders, again predominantly for the treatment of pruritus [248–250]. In PBC, studies using phenobarbital showed partial improvement of cholestasis in selected patients [249,251,252]. CAR agonists were shown to protect against LCA-induced toxicity in mice primarily by induction of Sult2a1/2a9 and PAPSS2 gene expression with subsequent LCA sulfatation rather than induction of Cyp3a11 and hydroxylation [253]. It has also been proposed that sulfation of bile acids via Sult2a1 and subsequent export via sulfated bile acid transporting Mrp4 is controlled by CAR in a coordinated fashion [60,114]. A study exploring cholic acid toxicity in $FXR^{-/-}$ and $PXR^{-/-}$ mice revealed that CAR agonists can mitigate cholic acid toxicity even when both classical bile acid receptors are knocked-out; this may be explained by induction a cascade of bile acid/bilirubin detoxifying enzymes and transporters [49], strengthening the fundamental role of CAR in bile acid detoxification. The use of PXR and CAR double knock-out mice in LCA induced injury underlined the essential role of both nuclear receptors for xenobiotic and bile acid metabolism, since injury was most aggravated in the double knock-out mice [120,254]. In the CBDL model, treatment of mice with CAR agonists reduces serum bilirubin and bile acid levels, the latter via enhanced hydroxylation resulting in a more effective renal clearance [114]. These findings may again be explained by a coordinated stimulation of the orchestra of phase I (Cyp2b10, Cyp3a11) and phase II (Sult2a1, Ugt1a1) detoxification enzymes together with alternative basolateral overflow systems (Mrp3, Mrp4), while classical orthograde bile acid and organic anion transporters (Ntcp, Oatp1, Oatp4, Bsep) remain unaffected [114]. Thus, the use of specific agonists for PXR or CAR for the treatment of human cholestasis may be promising. However one has to keep in mind that these drugs not only detoxify but also can toxify [114,120,255] by interacting with several other endogenous metabolic pathways (e.g., thyroid hormone metabolism pathway [256] or influencing drug metabolism [58]). Another caveat is the liver tumor promoting potential of PB via CAR [257] and the potential role of PXR in the pathogenesis of endometrial cancer [258].

Peroxisome proliferator-activated receptor alpha (PPARα) agonists are also promising therapeutic approaches in human cholestatic liver disease since fibrates or statins showed beneficial

effects on biochemical parameters of cholestasis and/or transaminases in PBC patients [259–262]. A potential mode of action of PPARα agonists in cholestasis could be linked to their potential to stimulate the canalicular phospholipid flippase Mdr2, thus protecting the bile duct epithelium by counteracting the detergent effects of bile acids via enhanced biliary phospholipid excretion with subsequent formation of mixed micelles [263–267]. In addition, repression of CYP7A1 (so far only shown for fibrates [268]), or pleiotropic anti-inflammatory effects may contribute to potential therapeutic effects [269].

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists have originally been introduced as insulin-sensitizing, antidiabetic drugs, but also have broader effects on lipid metabolism, inflammation and fibrosis [270]. As such PPARγ agonists have antifibrotic effects in patients with non-alcoholic steatohepatitis and in vivo and in vitro experimental models of hepatic fibrosis [271,272,272]. PPARγ overexpression led to a significant decrease of collagen type 1A1 and tissue inhibitor of metalloproteinases 2 with subsequent reduction of hydroxyproline in 14d CBDL rats [273]. These antifibrotic effects may be mediated to a certain degree via FXR and SHP [274]. Moreover, rosiglitazone was demonstrated to reverse LPS-mediated downregulation of hepatic transporters implying a role for its potential use in inflammation-mediated liver diseases [275].

Corticosteroids have been used both in acute human cholestasis (steroid-induced normalization of liver function tests or "steroid whitewash" in drug- and inflammation-induced cholestasis) and chronic cholestatic disorders such as PBC (e.g., prednisolone or budesonide) [276–278]. In addition to their anti-inflammatory and immune-modulatory effects, part of their effects could be mediated via transporter and enzyme alterations (possibly by targeting the glucocorticoid receptor, although this has so far only been shown in promoter studies in vitro for intestinal ASBT [279] and NTCP [280]). Corticosteroids induce *Mrp2* and *Bsep* and counteract their downregulation after endotoxin treatment in vitro [167,281]. Recently, omeprazole has been shown to stimulate MRP3 in human liver [282].

In summary nuclear receptors are promising targets for modulating transporter expression (Fig. 6). The future should bring us more gene-selective agonists in order to specifically target subsets of genes and separate "wanted" from "unwanted" effects.

10. Conclusions

Transcriptional regulation of hepatic organic anion transporter regulation is key for understanding the pathophysiology of cholestasis. While some of the changes may contribute to or maintain cholestasis, others (especially with prolonged duration of cholestasis) may be the result of adaptive processes which aim at limiting the extent of the cholestatic liver injury. The underlying molecular mechanisms are complex and our insights are still incomplete since major parts of the puzzle are still missing. The growing information on the transcriptional regulation of hepatobiliary transport systems should lead to the identification of novel therapies. Nuclear receptors and their target genes represent worthwhile therapeutic targets for cholestatic liver diseases.

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