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Review

Role of nuclear receptors for bile acid metabolism, bile secretion, cholestasis, and gallstone disease ☆

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ABSTRACT

Nuclear receptors (NRs) play a key role in the transcriptional control of critical steps of hepatobiliary transport and phase I/II metabolism of endo- and xenobiotics such as bile acids and drugs. Apart from these metabolic roles, NRs may also play a key role in the control of hepatic inflammation. Hereditary and acquired alterations of NRs contribute to our understanding of the pathogenesis of cholestasis and gallstone disease. Moreover, NRs may represent attractive drug targets for these disorders. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. Farnesoid X receptor and other nuclear bile acid receptors

Bile acids (BA) not only serve as physicochemical detergents for lipid digestion and absorption but also have a broad spectrum of signaling properties regulating lipid and glucose homeostasis, thermogenesis, and liver regeneration, and have immunomodulatory effects [1–4]. Moreover, bile acids are potentially cytotoxic and their concentration needs to be tightly controlled. This is achieved through transcriptional programs modulating bile acid homeostasis and activated through bile acid-activated nuclear receptors.

The farnesoid X receptor (FXR; NR1H4) belongs to the nuclear receptor super-family of transcription factors and was originally found to be activated by farnesol derivatives [5,6] but later identified as a bile acid-activated nuclear receptor [7–9]. In rodents, but not in human, a second FXR gene was subsequently identified, activated by lanosterol, and called FXRβ [10]. After bile acid binding to the ligand binding domain localized in the C terminal part of the protein (Fig. 1), the DNA binding domain can bind specific FXR response elements (FXRE) that are usually, but not only, inverted repeat 1 (IR-1) [5,6,11–16] (Fig. 1). FXR can bind DNA as heterodimer with the retinoid X receptor alpha (RXRα; NR2B1) even if monomeric sites were also found [11–14]. In addition, the FXR locus shows two alternative promoters and one internal splicing site, therefore generating four isoforms [17,18]. Later, the analysis of FXR-deficient mice revealed the key role played by FXR in bile synthesis, secretion, and detoxification [19–24]. However, other nuclear receptors were subsequently identified as additional bile acids sensors.

Hence, the pregnane X receptor (PXR; NR1I2) was found to be activated by lithocholic acid (LCA) [25,26] and shown to regulate genes involved in synthesis, transport, and detoxification of bile acids, therefore protecting liver from bile toxicity [27]. Interestingly, LCA activated also the vitamin D receptor (VDR; NR1I1) in the intestine and liver [28] and thus participated in bile metabolism control [29], without inducing hypercalcemia [30]. Nevertheless, bile acids do not always bind to and activate nuclear receptors. The constitutive androstane receptor (CAR; NR1I3) is not activated by bile acids but is required to control BA detoxification and transport [31–34]. Furthermore, liver X receptor alpha (LXRα; NR1H3) was found to be activated by cholestenoic acid, a bile acid derivative from the acidic pathway, [35] and cholanoic acid methyl esters [36]. Taken together, redundant nuclear receptors evolved in a network to sense and tightly control bile homeostasis to prevent cellular damage.

2. General principles of bile secretion

Bile secretion represents the exocrine function of the liver and is accomplished by hepatocytes and bile duct epithelial cells (cholangiocytes) [37]. Bile has several important physiological functions including lipid digestion and absorption, elimination of various endo-

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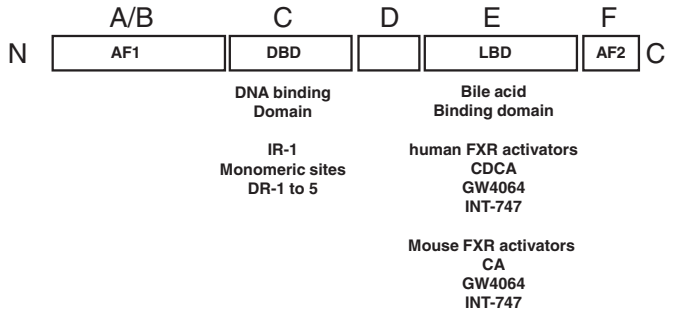

Fig. 1. Structural organization of the nuclear receptor FXR. FXR is a nuclear receptor and contains 5 domains. The A/B domain, or AF-1 domain, is a ligand independent transactivation domain. The C domain, or DNA binding domain (DBD), contains 2 zinc fingers interacting with a specific DNA response element. The D domain, or hinge region, is a structural domain modulating the receptor activity after phosphorylation of key amino acids. The E domain, or ligand binding domain (LBD), binds to natural bile acids (CDCA for human FXR and CA for mouse XR) or pharmaceutical ligands such as GW4064 or INT-747. The F, domain or AF-2 domain, mediates interactions with cofactors after receptor activation. DBD indicates DNA binding domain; LBD, ligand binding domain; N, N terminus; C, C terminus.

and xenobiotics, as well as antibacterial and immunological properties in the intestine [38].

Excretion of bile acids, the major fraction of organic solutes in bile, is mediated by ATP-binding cassette (ABC) transporters for bile acids and non-bile acid organic anions at the canalicular membrane of hepatocytes and represents the rate limiting step in bile formation [39]. Bile acids promote canalicular excretion of phospholipids and cholesterol for subsequent formation of mixed biliary micelles and osmotically drag water *via* aquaporins and tight junctions [40]. Canalicular excretion of reduced glutathione and bicarbonate accounts for the major components of the "bile acid-independent" fraction of bile flow [41]. "Canalicular bile" is further modified by secretory and absorptive processes along the bile ductules and ducts ("ductal bile" secretion) [42–44].

Many biliary compounds such as bile acids undergo an enterohepatic circulation, where they are reabsorbed in the intestine, taken up again by the liver, and re-secreted into the bile. This reduces the fecal loss of bile acids to only 3%–5% per day and minimizes the need for replacement by *de novo* bile acid synthesis [39,40,45]. Systemic bile acids, which escape the enterohepatic circulation, are filtered and excreted into urine and again reabsorbed by transporters in the proximal convoluted tubule [45,46]. Bile acids may also undergo "cholehepatic shunting" from the bile duct lumen, *via* cholangiocytes and the periductular capillary plexus back to hepatocytes [47]. This pathway may play a role as escape route under cholestatic conditions with bile stasis in obstructed ducts [46].

3. Regulation of bile acid synthesis

Bile acids are enzymatically formed in the liver from cholesterol [48]. Cholesterol 7α-hydroxylase (CYP7A1) is the rate limiting enzyme of bile acid biosynthesis and is mainly regulated at the transcriptional level in a feed-forward fashion by cholesterol and through a negative feedback pathway by bile acids [49,50]. The feed-forward regulation only exists in rodents. In rodents, the cholesterol sensor LXRα directly mediates feed-forward regulation of CYP7A1 *via* a bile acid response element (BARE I) in the CYP7A1 promoter resulting in increased bile acid synthesis [51,52]. Rev-erbα indirectly represses CYP7A1 in mouse by regulating cholesterol synthesis and therefore oxysterol disposal to activate LXR (Fig. 2) [53]. Since Rev-erbα requires LXR for regulation of CYP7A1, this pathway only operates in rodents but not in humans. In addition, this mechanism provides the molecular basis for the circadian rhythm of CYP7A1 [54–56]. FXR has a central role in regulating the feedback repression of bile acid synthesis [60,50,57,58]. As such, bile acid-activated FXR represses human and rodent CYP7A1 gene transcription by induction of the nuclear repressor SHP (Fig. 2). In line, CYP7A1 expression is increased in SHP knockout animals [59]. SHP was suggested to negatively interact with fetoprotein transcription factor (FTF/NR5A1, also known as liver receptor homolog-1, LRH-1), which binds to the bile acid response element (BARE) in the proximal CYP7A1 promoter region together with HNF4α [61,62]. A similar mechanism has been proposed for regulation of CYP8B1 [61,63,64], which determines the relative hydrophobicity of the bile pool. However, recent studies question the role of LRH-1 in the feedback regulation of CYP7A1 (Fig. 2) [65,66].

Several FXR- and SHP-independent mechanisms for regulation of CYP7A1 transcription have also been identified. Bile acids can not only directly decrease HNF4α promoter activity and gene expression [67] but also impair HNF4α-mediated activation of the CYP7A1 promoter by blocking the recruitment of co-activators, such as peroxisome proliferator activated receptor gamma co-activator (PGC-1α) and cAMP response element binding protein-binding protein (CBP) to HNF4α [68]. PPARα reduces CYP7A1 transcription *via* reduced HNF4α binding, which might contribute to the increased risk of gallstone formation after treatment with fibrates (PPARα activators) [69–75]. In addition, bile acid-stimulated cytokine release from macrophages can decrease CYP7A1 transcription *via* activation of the c-Jun terminal kinase (JNK) pathway and reduction of HNF4α binding in primary rat hepatocytes and HepG2 cells [76,77].

In addition to liver, the terminal ileum also profoundly impacts on human and rodent CYP7A1 gene regulation. FXR-induced mouse ileal fibroblast growth factor 15 (FGF15) [78] signals to the liver, where it binds to FGFR4, a widely distributed receptor with tyrosine kinase activity [79] and represses CYP7A1 through a JNK-dependent pathway [78]. The human ortholog FGF19 has recently been shown to be expressed in both intestine and liver—in contrast to the ileal specific expression of mouse FGF15—where it is also regulated by FXR [80,81]. The interactions between FGF19 and FGFR4 are mediated *via* the membrane bound protein βKlotho [82], which allows a tissue specific fine-tuning of the ligand–receptor interaction [83–85]. Experiments with liver and ileum specific FXR-deficient mice suggest that the ileal route of CYP7A1 repression *via* the FGF15 pathway dominates over hepatic negative feedback pathways [20] and involves SHP [78], indicating that a functional gut–liver signaling may be a prerequisite for bile acid homeostasis. In addition, patients with bile acid malabsorption (e.g., in Crohn's disease or short bowel syndrome) may suffer from excessive fecal bile acid excretion and subsequently bile acid-induced diarrhea and steatorrhea due to the interrupted ileal negative feedback regulation of bile acid synthesis. Recently, in a portion of patients suffering from idiopathic bile acid malabsorption, many of which are commonly sub-categorized as the diarrhea-type of irritable bowel syndrome, low levels of serum FGF19 have been found [86]. This suggests that reduced FGF19 levels may be the primary cause for excessive bile acid synthesis that exceeds the normal capacity for ileal reabsorption, producing bile acid diarrhea. Thus, FXR agonists or FGF19 itself could be used therapeutically to interrupt the cycle of excessive bile acid production in patients with bile acid malabsorption [86,87].

4. Regulation of phase I and II bile acid metabolism

Phase I hydroxylation and phase II conjugation renders bile acids more hydrophilic, less toxic, and better amenable for urinary excretion, which can become the favorable elimination route for bile acids accumulating under cholestatic conditions [88,89]; CYP3A4 and the rodent homolog CYP3A11 are the main cytochrome P450 enzymes for bile acid metabolism [90,91]. Expression of CYP3A4 is positively regulated by a battery of transcription factors including PXR [25,26], VDR [92], CAR [93], and FXR [94] (Fig. 2). Administration of ligands for these receptors such as xenobiotics, drugs but also bile acids can induce CYP3A4 expression and phase I detoxification

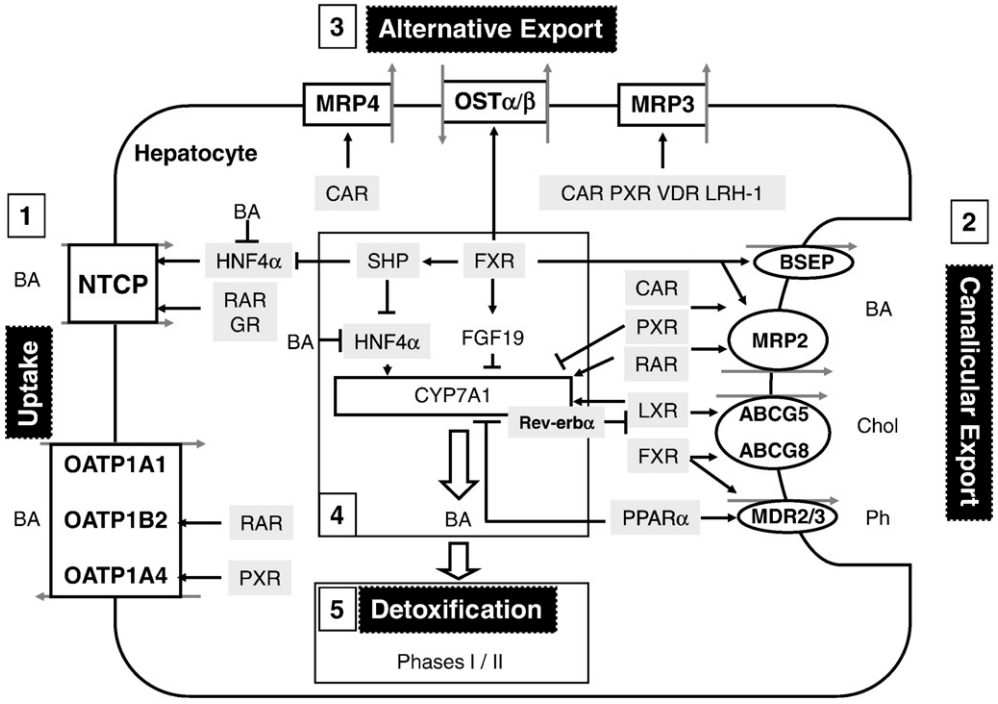

Fig. 2. Role of nuclear receptors in the transcriptional regulation of hepatocellular bile acid metabolism and transport. Schematic representation of a "model hepatocyte" with key enzymes of bile acid synthesis and metabolism, as well as critical transport systems in the basolateral/sinusoidal membrane (uptake and alternative export) and canalicular/apical membrane. 1) Uptake: HNF4α is indirectly the common master regulator of basolateral Na^+-dependent (NTCP) and Na^+-independent (rodent OATP1A1, 1A4, 1B2, human OATP1B1) bile acid uptake systems. HNF4α in turn may be under the negative control of the FXR–SHP pathway or directly inhibited by bile acids. NTCP is under direct positive control of GR and RAR but is regulated in a species specific manner (see text for details). RAR and PXR are additionally involved in the regulation of the rodents OATP1B2 and OATP1A4, respectively. 2) Canalicular excretion: All canalicular transporters involved in bile formation are positively regulated by FXR—the canalicular bile acid transporter BSEP, the phospholipid floppase MDR3 in humans (MDR2 in rodents), the cholesterol transporters ABCG5 and ABCG8, and MRP2 that shares a common response element with PXR and CAR. In addition, the RARα/RXRα heterodimer positively regulates MRP2 and PPARα up-regulates MDR2. 3) Alternative export: Except OSTα/β which is regulated by FXR, alternative export systems are independent of FXR. CAR positively regulates both MRP3 and MRP4, while PXR, VDR, and LRH-1 regulate MRP3 expression. 4) Synthesis: The bile acid-activated FXR–SHP pathway down-regulates CYP7A1 *via* negative impact on the binding of the positive regulatory transcription factors HNF4α. In addition, bile acids and PXR can directly inhibit HNF4α binding to the CYP7A1 promoter. FGF15 in mouse/FGF19 in human, derived from ileal enterocytes (rodent not shown) and hepatocytes (human), strongly represses mouse and human CYP7A1 transcription (see text for details). Rev-erbα, by controlling oxysterol synthesis that generates activators of LXR, indirectly controls the mouse CYP7A1 expression. LXR up-regulates mouse CYP7A1 but not human CYP7A1 gene expression. 5) Detoxification: Since bile acid synthesis and detoxification take place in pericentral hepatocytes, it was represented in boxes.

reactions [91]. Thus, bile acids—being both activators and substrates of CYP3A4—can initiate a feed-forward mechanism limiting hepatocellular bile acid burden and damage from toxic bile acids.

Besides hydroxylation, conjugation of bile acids with sulfate or glucuronidate is an additional mechanism of bile acid detoxification. Dehydroepiandrosterone sulfotransferase (SULT2A1) catalyzes sulfoconjugation of a broad range of endogenous compounds including bile acids, turning their substrates into more water soluble and less toxic products, which are subsequently amenable for renal elimination [95,96]. In humans, bile acid sulfation predominantly occurs under cholestatic conditions as reflected by the appearance of sulfated bile acids in serum and in urine of patients with cholestatic liver diseases [97–99]. Nuclear receptors involved in the positive regulation of SULT2A1 expression include FXR, PXR, VDR, CAR, and PPARα [100–106]. CAR appears to play a central role in regulating bile acid sulfation, since it was proposed to orchestrate bile acid sulfation and subsequent basolateral export *via* CAR-induced over-expression of the basolateral export pump MRP4, which transports steroid sulfates [33,103].

In addition to sulfation, bile acids can also be detoxified through glucuronidation [107,108]. This step is catalyzed by the UDP-glucuronosyltransferases UGT2B4, UGT2B7, and UGT1A3 which again renders bile acids more water soluble and facilitates their renal elimination [13,109,110]. However, hydroxylation at the 6α position is required before glucuronidation in most cases [111,112]. In humans, the combined hydroxylation/glucuronidation detoxification pathway can be stimulated by the PXR ligand rifampicin [113]. Bile acids themselves can induce human UGT2B4 *via* activation of FXR [13]. The UGT2B4 gene promoter contains also a PPAR response element and is activated by the PPARα agonist fenofibrate [109]. Furthermore, UGT2B7 can be repressed by hydrophobic bile acids through a negative FXR response element in the UGT2B7 promoter [14].

5. Regulation of hepatocellular transport

5.1. Basolateral hepatocellular bile acid uptake

Hepatic uptake of bile acids is mediated by an Na^+-dependent bile acid transporter NTCP (SLC10A1) and a family of multi-specific organic anion transporters (OATPs; SLC21A) that mediate Na^+-independent uptake of mostly amphipathic organic compounds, including conjugated or unconjugated bile acids, as well as 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, $HCO3^-$) [39].

Regulation of NTCP by bile acids is complex and differs considerably among humans, mice, and rats [114] The rat NTCP promoter is trans-activated by several positive regulating elements including RARα/RXRα heterodimer as well as the signal transducer and trans-activator 5 (Stat 5) [115] (Fig. 2). Negative feedback inhibition of mouse and rat NTCP is mediated *via* FXR–SHP-dependent and independent mechanisms and limits hepatocellular bile acid uptake [116,117]. Induction of SHP by bile acid-activated FXR interferes with RXRα/RARα mediated activation of the rat NTCP promoter [118]. In addition, SHP reduces NTCP expression *via* a complex pathway

involving repression of HNF4α and HNF1 [67,119]. Potential SHP-independent mechanisms involve activation of the JNK signaling pathway by bile acids [120], which leads to RXRα phosphorylation and subsequently reduced binding of RXRα/RARα to the rat NTCP promoter [121]. In humans, SHP acts mainly by suppressing GR-mediated activation of human NTCP [122], which might account for NTCP down-regulation in cholestatic liver diseases [88,123–125]. Similar to NTCP, repression of the predominant sodium-independent bile acid uptake system in humans, OATP1B1, is also mediated by FXR, involving SHP, HNF4α, and HNF1α [126]. In contrast, OATP1B3, a multi-specific uptake system for organic anions, xenobiotics, and potentially bile acids, is positively trans-activated by FXR [127]. Taken together, bile acids regulate their hepatocellular levels *via* negative feedback regulation of bile acid uptake transporters, which critically involves the bile acid receptor, FXR.

5.2. Canalicular bile acid excretion

Canalicular excretion of bile acids and non-bile acid organic anions *via* ATP-binding cassette (ABC) transporters represents the rate limiting step in bile formation. Monovalent bile acids such as glycine- or taurine-amidates of cholic acid (CA), chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA) are excreted into the bile canaliculus *via* the bile salt export pump BSEP (ABCB11) (Fig. 2) [128,129]. Divalent bile acids with two negative charges such as sulfated tauro- or glycolitho-cholate are transported by multidrug resistance-associated protein MRP2 (ABCC2) (Fig. 2) [130]. MRP2 also mediates the excretion of a broad range of other non-bile acid organic anions, mostly conjugates with glutathione, glucuronidate, and sulfate formed by phase II conjugation in the hepatocyte and of reduced glutathione (GSH) [130–133]. Additional transport systems in the canalicular membrane include a multidrug export pump (MDR1) for amphipathic organic cations [134,135] (e.g., various drugs), a phospholipid floppase (MDR3/MDR2 in rodents) for phosphatidylcholine translocation [136,137], the cholesterol two half-transporters ABCG5/8 for sitosterol and cholesterol export [138–140] (Fig. 2), a P-type ATPase (FIC1; ATP8B1) mutated in hereditary cholestasis [141,142], and an $Cl^-/HCO3^-$ anion exchanger 2 (SLC4A2, AE2) [143,144], all of them involved in bile formation.

Bile acids can promote their own biliary elimination by stimulating both BSEP and MRP2 expression in a feed-forward manner [22,145] (Fig. 2). Human, rat, and mouse BSEP promoters are transcriptionally activated by FXR [146–148] and mouse BSEP baseline-expression largely depends on the presence of FXR and thus is reduced in FXR knockout mice [19,22,149]. A role for VDR in BSEP repression *via* direct VDR–FXR interaction has been postulated *in vitro* [150], but given the rather low levels of VDR expression in hepatocytes [151], a major contribution to negative feedback regulation of BSEP *via* this mechanism appears unlikely.

In contrast to BSEP, transcriptional feed-forward regulation of MRP2 involves several overlapping sets of NRs, reflecting the diverse substrate spectrum of MRP2. FXR binds with high affinity to response elements in the human and rodent MRP2 promoters that are also shared with CAR and PXR [152] (Fig. 2). Thus, bile acids, as well as several CAR and PXR ligands, induce human and rodent MRP2 expression [126]. In addition, the rat MRP2 promoter contains a response element for RXRα/RARα, which mediates MRP2 induction by retinoids [153]. FXR also enhances human MDR3 transcription, while PPARα stimulates the expression of rodent MDR2 [154–156]. Collectively, these data indicate that orthograde canalicular bile acid efflux is mainly mediated *via* feed-forward regulation, again involving FXR as the critical key transcription factor.

5.3. Alternative basolateral bile acid export

While bile acids are excreted into canalicular bile under normal conditions, basolateral bile acid transport back into portal blood may represent an alternative elimination route for accumulating hepatic bile acid during cholestasis when canalicular excretion is impaired [157,158]. Alternative basolateral bile acid and bilirubin export is mediated by members of the MRP family (e.g., MRP3 mainly for bilirubin and MRP4 mainly for bile acids) and the heteromeric organic solute transporter (Fig. 2) (OSTα/β) [159–161]. These export systems are normally expressed only at very low levels at the basolateral membrane under normal conditions but can be significantly up-regulated in cholestasis [46,126]. Since MRP3, MRP4, and OSTα/OSTβ can transport sulfated as well as glucuronidated bile acids, the induction of these transporters may explain the shift towards renal excretion of these bile acids as a major route for bile acid elimination in patients with chronic long-standing cholestasis [126]. Induction of both rodent MRP3 and MRP4 is independent of the classical bile acid receptor FXR [22,23,149,162], while PXR and VDR are able to induce human and mouse MRP3 expression [163,164] (Fig. 2). In addition, CAR ligands induce both human and rodent MRP3 and MRP4 [32,33,103,165,166]. FXR induces human OSTα/β through binding to response elements in the respective promoter regions (Fig. 2) [167–169]. Collectively, a complex picture emerges where multiple nuclear receptors (including FXR, PXR, VDR, and CAR) are required for coordination of adaptive basolateral bile acid efflux under bile acid load and cholestatic conditions (Fig. 2).

6. Nuclear receptor regulation of cholangiocellular function

Cholangiocytes account for less than 3%–5% of normal liver cells but play an important role in bile formation [170,171] and contain several transport systems for absorptive and secretory processes [44,172,173]. However, under cholestatic conditions, cholangiocytes can proliferate, thus leading to a considerable expansion of this cell fraction [170,171,174]. Unconjugated bile acids may passively enter cholangiocytes, while amidated bile acids are reabsorbed by the apical sodium-dependent bile acid transporter ASBT, which is also responsible for bile acid uptake in the terminal ileum [175,176]. After uptake, bile acids are effluxed *via* the basolateral membrane of cholangiocytes into the peribiliary plexus not only by OSTα/β but also by MRP3 and potentially by a truncated version of ASBT (tASBT) [159,176–178]. Cholangiocyte bile acid uptake may contribute in part to the conservation of bile acids and the generation of a hypercholeretic bile flow [39,45]. This pathway probably plays a minor role under normal physiological conditions, but “cholehepatic shunting” of bile acids may become an escape route for bile acids 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.

Although the nuclear bile acid receptors FXR and VDR and their heterodimer partner RXR as well as SHP have been found in rodent and human gallbladder and bile duct epithelial cells, their role in regulating cholangiocellular bile formation has so far not been addressed in detail [151,179,180]. Moreover, specific roles of other nuclear receptors, such as PXR, CAR, LRH-1, LXRs, PPARα, PPARγ, GR, as well as HNF4α, which are all expressed in significant amounts, at least in the gallbladder epithelia, remains elusive (for tissue expression profile of nuclear receptors and transcription factors, please visit www.nursa.org/10.1621/datasets.02001). Most of our current knowledge about NR regulation of cholangiocellular transporters such as ASBT, OSTα/β, and MRP3 is derived from extrapolation of studies performed in hepatocytes or ileum.

The data on regulation of ASBT by bile acids are conflicting [181–183] and some of the divergent results can be attributed to species differences [126]. Negative feedback regulation of murine ASBT by bile acids is mediated by FXR *via* SHP-dependent repression of LRH-1 activation of the ASBT promoter [184]. In humans, bile acids exert their negative effects on ASBT *via* an FXR- and SHP-dependent

mechanism upon RXRα/RARα activation of ASBT [185]. Transcription factors, which positively trans-activate human ASBT, include PPARα, GR, RXRα/RARα, and HNF1α [185–187]. Enhanced cholangiocellular ASBT expression may facilitate removal of bile acids from stagnant bile in the biliary lumen during bile duct obstruction in human and rodent. The same applies for the basolateral export systems MRP3 and OSTα/OSTβ, which are also over-expressed under cholestatic conditions [167,177].

In addition to bile acid transporters, cholangiocytes harbor a battery of ion channels and exchangers (including the cystic fibrosis trans-membrane regulator, CFTR, and the anion exchanger, AE2), glucose transporters, and water channels, which modulate bile acid-independent bile flow [188,189]. These processes are, however, mostly regulated at post-transcriptional levels and a direct involvement of NRs in the regulation of these transporter systems seems to be rather the exception (for review, see references 44, 172, and 173). As such, in humans, the AE2 promoter can be trans-activated by the concerted interaction of HNF1 and GR resulting in enhanced transcriptional expression of alternative mRNA isoforms of AE2 and enhanced AE2 activity [190].

7. Role of nuclear receptors for pathogenesis and treatment of cholestasis

Cholestasis may result either from a defect in hepatocellular bile formation or from impairment in bile secretion and flow at the bile duct level [191–194]. Reduced expression and function of transport systems and their regulatory NRs play an important role in the pathogenesis of cholestasis.

Transport defects may be primary due to hereditary genetic defects (e.g., progressive familial intrahepatic cholestasis (PFIC)-1,2, and 3, benign recurrent intrahepatic cholestasis (BRIC)-1,2) or secondary acquired as a result of accumulating cholephiles and pro-inflammatory cytokines which can alter transporter expression *via* modulation of NR signaling [195]. 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 [196–198]. While some of these (e.g., cytokine-mediated) alterations contribute to cholestasis [198], other (e.g., bile acid-induced) changes may represent compensatory ("anti-cholestatic") defense mechanisms which provide alternative excretory routes for accumulating cholephiles in cholestasis.

In addition to transporter defects, polymorphisms in NRs contribute to cholestasis development and outcome. Intrahepatic cholestasis of pregnancy (ICP) is a disorder appearing during the second half of pregnancy and characterized by abnormal liver enzymes, high serum bile acid levels, pruritus, and fetal stress but resolving spontaneously after delivery [199]. FXR polymorphisms [200], perhaps by lowering the expression of downstream targets such as SHP and OATP1B3 [201], were shown to predispose to ICP. Moreover, combined polymorphisms on FXR and BSEP can result in short cholestasis episode early in life and ICP [202]. During ICP, CA levels—a good FXR ligand—are increased and the ratio CA/CDCA was identified as ICP indicator [203–205]. It is therefore plausible that ICP might represent a disease in a population where FXR, or FXR cofactors, and/or FXR target genes polymorphisms contribute to abnormal FXR activation. In line with this hypothesis, FXR was also identified as a candidate gene for the cholesterol gallstone locus Lith7, even if other modifiers are likely to explain the discrepancies between populations [206]. In addition, a deficiency in the P-type adenosine triphosphatase ATP8B1 was identified as the cause of PFIC-1 (also known as Byler's disease) and its more benign variant BRIC-1 (also known as Summerskill syndrome) [141]. ATP8B1 mutations were shown to lower FXR activity in liver [207], intestine [208], and HepG2 cells [209], perhaps by interfering with FXR phosphorylation and translocation into the nucleus [210]. Subsequent localization and expression study established that ATP8B1 is primarily expressed in cholangiocytes [211]. Interestingly, ATP8B1 defects in patients drastically reduce CFTR expression and therefore could impair the cholangiocyte contribution to bile secretion [211]. However, *in vitro* repression of ATP8B1 in rat and human hepatocytes only disrupt the canalicular membrane but does not change FXR expression or activity [212]. Therefore, the low FXR expression and activity found in ATP8B1 mutated patients could be a secondary consequence of the cholestasis. Interestingly, polymorphisms in PXR were also shown to determine the survival of PSC patients [213], while PBC patients were found to display a tendency to have reduced levels of a broad range of NRs (FXR, RXR, SHP, PXR, CAR, HNF1α, and HNF4α) [214].

Under cholestatic conditions, when intrahepatic and systemic bile acid levels rise, an orchestrated adaptive response, which is mainly coordinated by a complex interplay of bile acid and bilirubin-activated NRs (mainly FXR, VDR, PXR, and CAR), attempts to counteract cholestatic liver injury [215]. As a result of this transcriptional program, basolateral bile acid uptake and bile acid synthesis are markedly reduced, while phase I and phase II detoxification and alternative basolateral bile acid export are increased (the reader is referred to several recent in depth reviews on alterations of NR signaling in experimental animal models of cholestasis [126,157,158,198,215–217]). These adaptive modulations in response to cholestasis are not only restricted to the liver but also occur in the intestine, kidney, and bile duct epithelia (for review see references 126 and 158). Bile acid reabsorption in the intestine is adapted to local bile acid load due to altered transporter expression [22,218,219]. In proximal renal tubular cells, bile acid export is induced whereas tubular bile acid reabsorption is reduced resulting in enhanced urinary bile acid excretion [22,24,219,220]. Unfortunately, this armamentarium of intrinsic NR-mediated adaptive responses is apparently too weak in order to fully prevent cholestatic injury.

Several therapeutic strategies are aimed at NRs and their target genes which affect not only "orthograde" biliary excretory routes and bile acid phase I and II detoxification systems but also "retrograde" alternative/basolateral overflow and renal elimination systems. So far, the only approved drug for treatment of cholestatic disorders is a hydrophilic bile acid ursodeoxycholic acid (UDCA) [221]. The effects of UDCA are to most extent mediated by post-transcriptional and therefore non-NR-mediated mechanisms (for reviews, see references 222–224), since UDCA only weakly activates GR [225], FXR [7,9], and possibly PXR non-directly *via* LCA generation after bacterial modification [25,26]. Alternatively, FXR agonists are promising treatment options for cholestasis, and phase II studies (e.g., 6-ECDCA) in PBC showed improvement of biochemical cholestasis parameters, despite itching at higher doses, in patients with incomplete response to UDCA [226]. Since these PBC patients had a combination of 6-ECDCA and UDCA, it will be of interest to determine whether FXR agonists *per se* or the combination of UDCA and FXR agonist at high dose is involved in itching, perhaps by impacting on lysophosphatidic acid metabolism [227]. 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) [228–230]. In addition, FXR agonists also support adaptive reactions of the cholestatic hepatocyte which would be predicted to limit the hepatocellular bile acid burden, such as down-regulation of bile acid import, inducing alternative export (*via* OST), as well as reducing endogenous bile acid synthesis [46,126,198]. In addition, stimulation of the canalicular phospholipid floppase MDR2/MDR3 is predicted to change the intrabiliary bile composition rendering bile less aggressive [154,231]. Since FXR also regulates the expression of several genes involved in xenobiotic detoxification such as SULT2A1 and UGT2B4, highly specific FXR modulators will have to be developed in order to limit drug interactions. However, it is also important to consider that UDCA aggravated bile infarcts by disrupting cholangioles in a mouse model of obstructive cholestasis [145] and that conversely FXR-

deficiency reduced bile infarcts in bile duct ligated mice by lowering bile flow and pressure [149]. Therefore, extra-hepatic cholestasis and/or obstructive cholestasis in human could constitute conditions in which FXR agonists would be detrimental. The same concerns may apply to advanced stages of PBC or PSC with dominant strictures prior to endoscopic management [232].

FXR agonists may also target inflammation and fibrosis [233] helping to counteract the consequences of cholestatic liver injury. Inflammation plays a key role during cholestasis but requires control to limit further liver damage. FXR, like RXR [234], is a negative acute phase gene [235]. Since CYP7A1 and CYP27A1 are also repressed during acute phase [236,237], FXR and its ligands are therefore depleted during endotoxemia. Interestingly, FXR activation in mice counteracted the LPS-induced serum amyloid P component and serum amyloid A3 hepatic gene expression [238], whereas FXR-deficient mice had higher hepatic inflammatory marker expression, such as iNOS, COX-2, or INFγ, after LPS challenge [239]. These data are in line with the observation that FXR-deficient mice displayed prominent hepatic inflammation and subsequently liver tumors [240,241], while FXR agonists attenuated hepatic fibrosis and inflammation in a chronic mouse model of fatty liver [242] and in acute hepatitis [243]. Furthermore, the hepatic re-expression of a constitutively active FXR lowered liver inflammation after LPS challenge, probably by interfering with NFκB signaling [239]. Altogether, FXR agonists may therefore constitute a new treatment in chronic and acute liver inflammation. However, since the acute phase response, by lowering cholesterol catabolism into bile acids and by repressing FXR expression, favors hypertriglyceridemia probably to neutralize bacterial components, viruses, or parasites and to redirect nutrients to immune cells and to injured tissues, a careful evaluation of FXR agonists will be required to not interfere with the beneficial effects of the basic immune response. Finally, FXR agonists *via* SHP and/or PPARγ dependent pathways might be able to inhibit hepatic stellate cells activation and therefore fibrosis [244,245]. However, the relevance of these findings is now highly questionable since FXR-deficiency in several mouse models reduced liver fibrosis and since FXR protein was barely detectable in human hepatic stellate cells and myofibroblasts [246].

In addition, FXR is not the only NR playing an important role in bile acid detoxification, since FXR-deficient mice were shown to better tolerate cholestasis than their wild-type littermates due to constitutive PXR and CAR activation leading to enhanced detoxification [23,149] and urinary excretion of bile acids [24,247].

Therefore, PXR and CAR may represent additional therapeutic targets due to their broad involvement in the regulation of bile acid and bilirubin detoxification enzymes and transporters [31]. In common bile duct ligated mice, a model for obstructive cholestasis, pre-treatment with rodent PXR and CAR ligands led to a significant reduction of elevated serum bilirubin and bile acid levels, which were accompanied by increased levels of polyhydroxylated bile acids in serum and urine [33]. These findings may be explained by a coordinated stimulation of phase I (e.g., CYP2B10, CYP3A11) and phase II (e.g., SULT2A1, UGT1A1) detoxification enzymes together with alternative basolateral overflow systems (e.g., MRP3, MRP4), while classical orthograde bile acid and organic anion transporters (NTCP, OATP1A1, OATP1A2, BSEP) remained unaffected [33]. A study exploring cholic acid toxicity (the major retained bile acid species in cholestasis) in FXR- and PXR-knockout mice revealed that CAR agonists can mitigate bile acid toxicity, even when both classical bile acid receptors are knocked-out, strengthening the fundamental role of CAR in bile acid detoxification [31]. In humans, administration of the "old-fashioned" PXR agonist rifampicin to healthy volunteers significantly induced CYP3A4, UGT1A1, and MRP2 expression, resulting in increased bile acid hydroxylation and reduced serum bilirubin levels [248] which may explain the beneficial effects in treatment of pruritus. A decoction of Yin Chin (*Artemisia capellaris*), which is widely used in Asia for the treatment of neonatal jaundice, contains a powerful CAR agonist, which is capable to sufficiently reduce bilirubin by transactivation of enzymes and transporters of bilirubin metabolism [249].

PPARα agonists such as fibrates showed beneficial effects on biochemical and histological parameters of cholestasis in PBC patients [250]. A potential mode of action of PPARα agonists in rodent cholestasis was linked to the stimulation of the canalicular phospholipid floppase MDR2, thus protecting the bile duct epithelium by counteracting the detergent effects of bile acids *via* enhanced biliary phospholipid excretion [155,251–254]. Moreover, in humans, bile acid glucuronidation *via* UGT2B7 and UGT1A3 is enhanced by PPARα, rendering bile acids more hydrophilic for urinary excretion. Finally, the PPARγ agonist rosiglitazone reversed LPS-mediated down-regulation of hepatic transporters, implying a role for its potential use in inflammation-mediated liver diseases [255].

Glucocorticoids, which activate GR, may either directly improve cholestasis *via* transactivation of several transporters in human (e.g., ASBT, NTCP, MRP2, AE2, BSEP) and/or indirectly *via* their anti-inflammatory properties [126]. In addition, GR may expand its anti-cholestatic spectrum *via* a response element in the promoter of CAR, thereby activating CAR and CAR-dependent genes [256]. Of interest, UDCA was reported to activate GR [257–260]. Moreover, a combination of UDCA and dexamethasone enhanced transcriptional expression and activity of cholangiocellular AE2 and may thus explain some of the beneficial effects of the combination of UDCA and glucocorticoids in PBC patients with inadequate response to UDCA monotherapy [190].

8. Nuclear receptors in gallstone disease

Gallstones have high prevalence rates of 8%–22% in the Western world as assessed by cross-sectional ultrasound studies [261]. Formation of gallstones may occur if the amounts of cholesterol or bilirubin exceed their solubility (for the development of bilirubin pigment stones, see reference 262). Since biliary cholesterol is kept in solution in vesicles with phospholipids or in mixed micelles with bile acids and phospholipids, the relative composition of bile acids, phospholipids, and cholesterol determines the solubility of cholesterol in bile. Bile becomes supersaturated with cholesterol when the biliary concentration of cholesterol is increased or the concentration of bile acids and phospholipids is decreased [262]. Therefore, it was suggested that enzymes, transporters, and NRs involved in bile acid, phospholipid, and cholesterol metabolism could play a role in cholesterol gallstone formation. As such, patients with MDR3 mutations typically develop cholelithiasis [263–265]. Genetic variants of BSEP and polymorphisms in the key enzyme of bile acid biosynthesis, CYP7A1 are at significantly higher risk for cholesterol gallstone disease [266]. Surprisingly, no association with LXRα and BSEP polymorphisms has been found in symptomatic but otherwise normal gallstone patients [267].

Quantitative trait locus analysis identified FXR, its target gene SHP, and the heterodimer cholesterol exporter ABCG5/ABCG8 as possible determinants of cholesterol gallstone formation in human and susceptible mice [206,268]. Subsequently, FXR knockout mice fed a lithogenic diet were shown to display more supersaturated bile, a *sine qua non* condition for gallstone formation, although gallstone development was not shown in this model [231]. Moschetta et al. [231] subsequently extrapolated that low expression of mouse BSEP and MDR2 could result in an increased cholesterol saturation index and therefore in gallstone formation. *Vice versa*, treatment with a potent FXR agonist prevents bile supersaturation in the susceptible strain, a result which may be due to FXR induction of target genes BSEP and MDR2 with a subsequent increase in the transport of bile acids and phospholipids in the lithogenic bile [231]. Oral administration of the endogenous FXR activator CDCA had been used in the past

to dissolve gallstones in human but was later replaced by the less toxic UDCA. UDCA, however, is a weak FXR activator and suffers from low efficacy, a long treatment period, and a high rate of stone recurrence. Using more potent synthetic FXR agonists could potentially overcome these shortcomings [269]. Nevertheless, it should be emphasized that highly potent FXR agonist may result in a smaller bile acid pool and therefore could impact on the bile composition and saturation index. More importantly, patients with a contracted bile pool also are at higher risk to develop cholesterol gallstones [270–272].

The picture involving FXR in gallstone formation is becoming more complex since mice lacking βKlotho are resistant to gallstone formation [82]. βKlotho knockout mice have markedly increased CYP7A1 levels and consequently enhanced bile acid synthesis rate, which is likely to contribute to gallstone prevention [82]. It has been speculated that, in the terminal ileum, FXR-activated FGF15/19 is requiring βKlotho as co-receptor to be targeted to the corresponding FGFR4 receptor in the liver (see above), finally resulting in repression of CYP7A1 [273]. Absence of βKlotho would be predicted to disrupt the FXR–FGF15/19 mediated gut liver signaling, the most relevant pathway for FXR-dependent CYP7A1 down-regulation [20], leading to increased CYP7A1 levels. Thus, inhibition of βKlotho could improve current (i.e., UDCA) and potential future therapies (i.e., synthetic FXR agonists) for gallstone disease by increasing cholesterol breakdown *via* increasing CYP7A1, which is typically reduced in treatment with FXR agonists.

Obesity and metabolic syndrome are well known risk factors associated with gallstone formation [274,275]. Obese individuals display a higher ratio of cholesterol to phospholipids and bile acids that makes their bile susceptible for gallstone formation. Insulin-resistance [276] and high sucrose consumption [277] are associated with gallstones formation and are preeminent features of the metabolic syndrome. The role of hepatic insulin-resistance was therefore assessed in a mouse model of insulin receptor deficiency in hepatocytes [278]. Activation of FOXO1 in this model leads to induction of ABCG5/ABCG8 gene expression and increased cholesterol secretion into the bile and thus generated gallstones, while FXR negative feedback of bile synthesis was partially lost [278]. Thus, correction of insulin-resistance could contribute to lowering gallstone prevalence in obese subjects.

9. Summary and conclusions

Hereditary and acquired alterations in NR function are keys for understanding the physiology of bile formation and pathophysiological changes leading to cholestasis and gallstone disease. Targeting NRs therefore represents an attractive therapeutic approach for these disorders. As such, several drugs already used to treat cholestatic liver diseases and gallstone diseases modulate NR function. The future should bring well defined and more specific NR ligands for restoring and/or adapting defective NR function in these disorders.

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