The Role of FXR in Disorders of Bile Acid Homeostasis

As ligands for the nuclear receptor FXR, bile acids regulate their own synthesis, transport, and conjugation, thus protecting against bile acid toxicity. Recently, the role of genetic variants in FXR itself, FXR target genes, and regulators of FXR in the pathophysiology of the liver and intestine has become increasingly evident.

Members of the nuclear receptor superfamily of transcription factors are the chief regulators of a wide variety of important metabolic pathways (28). Their ability to sense and respond to changes in intracellular metabolic environment is largely due to the fact that the transactivation potential of most nuclear receptors is crucially dependent on small lipophilic ligands, such as bile acids, fatty acids, lipophilic vitamins, and steroidal hormones. Binding of agonistic or antagonistic ligands leads to allostatic changes in the ligand-binding domains of nuclear receptors, thus resulting in alterations in the interactions of nuclear receptors with their coactivators and corepressors, and consequently affecting transcriptional rates of target genes (89). Most nuclear receptors bind to their DNA response elements as either hetero- or homodimers, and their consensus DNA-binding motifs typically contain two hexameric half sites. These hexameric motifs, the consensus sequence for which is AGGTCA, can be arranged as direct (DB), inverted (IB), or reverted (RB) repeats, separated by a variable and receptor-specific number of base pairs.

The suggested role of altered nuclear receptor activity in several metabolic diseases, together with the potential of modulating their activity with specific ligands, has made them attractive targets for pharmacological intervention in these diseases (29). Given that most nuclear receptors are involved in regulating a variety of metabolic processes, and accordingly have multiple target genes, the major challenge will be to achieve functional selectivity by therapeutic ligands, only affecting a desired subset of downstream target genes in specific tissue targets.

The Nuclear Receptor for Bile Acids, FXR

The farnesoid X receptor (FXR, also known as the bile acid receptor or BAR; gene symbol NR1H4) is a member of the nuclear receptor family of transcription factors. FXR functions as the chief sensor of intracellular levels of bile acids (the end products of cholesterol catabolism) and the main executor of bile acid-induced transcriptional programmes. Bile acids directly interact with the ligand-binding domain of FXR and enhance or antagonize the transactivation function of FXR. In accordance with its function as the bile acid receptor, FXR is most abundantly expressed in the tissues commonly exposed to bile acids in normal physiology: liver, intestine, and kidneys (25). Along the intestinal tract, higher FXR levels can be found in the ileal epithelium, the main site of intestine-specific bile acid absorption, than in the epithelium of proximal small intestine or the colon (39). The preferred DNA-binding sequence for FXR within its target promoters is typically a variant of the so-called "inverted repeat-1" motif (IR-1; inverted hexameric AGGTCA-like repeat separated by one base pair) (57), to which FXR binds as a heterodimer with the nuclear retinoid X receptor (RXR). Although in lower mammals there are two FXR genes, Nr1h4 (encoding Fxr) and Nr1h5 (encoding Parx), the latter gene product employing lanosterols as its ligands, in humans and other primates the homolog of Parx is a pseudogene (76). Thus, in this review, focusing on the properties and function of this nuclear receptor in humans, we use the phrase FXR/Fxr to refer to FXR/Fxr4.

Four isoforms of FXR, termed FXR1–4, can be translated from the single NR1H4 gene in humans, generated by both alternative promoter usage and by alternative splicing (37, 109). FXR1 and FXR2, the most abundant FXR isoforms in the human liver, differ from FXR3 and FXR4 at the N terminus, since the mRNAs for these two isoform pairs are transcribed independently from separate promoters. In addition, the isoforms FXR3 and FXR4 contain an additional stretch of four amino acids, MTYG, due to a differential splicing event at the end of exon 5. All four FXR isoforms harbor identical ligand-binding domains but may exhibit different coactivator recruitment, DNA-binding, or RXR heterodimerization properties. In the context of at least a subset of target genes, the FXR isoforms appear to exhibit differential DNA-binding and transcriptional activities (4, 109), although in the context of most FXR target genes this remains to be comprehensively studied.

FXR functions typically as an agonist-dependent transcriptional coactivator of its direct target genes. Numerous transcriptional coactivators recruited to agonist-bound FXR, mediating its transcriptional function, have been proposed (reviewed in Ref. 29). FXR can also negatively regulate transcription of specific target genes in an agonist-dependent manner. Although there is evidence from the studies on the human apoAⅠ promoter that the transcriptional binding of FXR to different nuclear receptors and putative genes can influence nuclear receptors (88). The SHP2 protein has been identified as an atypical nuclear receptor, which can interact with the transcriptional activity of other nuclear receptors, including FXR, belonging to the NR1H family (20). SHP2 may also interact with other nuclear receptors and the transcriptional activity of FXR is controlled by the nuclear receptor SHP2 (50). In humans, FXR has two alternative splice variants, FXR1 and FXR2, which are expressed in different tissues (21).

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human apolipoprotein A-I and apolipoprotein C-III promoters that this may be achieved through direct binding by FXR to negative bile acid response elements (11, 13), more often FXR downregulates target genes via an indirect mechanism involving another nuclear receptor, small heterodimer partner (SHP) (88). The SHP (NR1BE2) gene is directly transactivated by FXR in response to FXR ligands and encodes an atypical nuclear receptor, lacking the DNA-binding domain. However, SHP does contain the dimerization domain and a putative ligand-binding domain. SHP can directly interact with target promoters (50, 61), both. No endogenous or exogenous ligands for SHP have been confirmed to exist. However, a synthetic retinoid termed CD437/AHPN was recently shown to both directly interact with SHP and enhance the recruitment of a corepressor complex (21), although it is not yet clear whether the interaction with this compound is in fact mediated by the putative ligand-binding pocket of SHP.

**FXR Ligands: Bile Acids and Beyond**

Nuclear receptors, for which no ligands have yet been identified, have been termed “orphan nuclear receptors.” The first attempt to rescue FXR from the orphanage (i.e., to find its ligand) was made in 1995, when farnesol metabolites were suggested as candidates to be such FXR ligands; however, these compounds only activate FXR at concentrations clearly exceeding physiological conditions and do not appear to act as bona fide direct ligands for FXR (25, 107). FXR was finally identified, by 10.220.33.4 on July 20, 2017 http://physiologyonline.physiology.org/ Downloaded from

Besides naturally existing FXR ligands, an intense interest in designing pharmaceutically effective synthetic FXR agonists and antagonists has developed over the last few years. In rodent models, some of these have already shown promising hepatoprotective qualities in rat models, the synthetic agonist GW4064 (67) provides hepatoprotection against intra- and extrathoracic cholestasis (64) and a semi-synthetic bile acid derivative 6-ethyl chenodeoxycholic acid (6-ECDC) protects against liver fibrosis (24). When evaluating the therapeutic efficiency of FXR agonists in rodent models, one should bear in mind that there appears to be a certain degree of species dependence in the ligand-specificity of FXR/Fxr: for example, although the mouse Fxr is less sensitive to activation by androsterone than the human variant (101). It has been reported to function as an agonistic ligand for FXR (84). Prevalently, farnesol has been shown to be responsible for hypercholesterolemia and increased risk of coronary heart disease associated with high intake of unfiltrated coffee (92, 93, 102), and it is possible that this association is dependent on the ability of farnesol to activate FXR. For example, application of farnesol decreased the expression of the rate-limiting enzyme cholesterol to bile acids and thus impaired elimination of cholesterol from the body. Besides naturally existing FXR ligands, an intense interest in designing pharmaceutically effective synthetic FXR agonists and antagonists has developed over the last few years. In rodent models, some of these have already shown promising hepatoprotective qualities in rat models, the synthetic agonist GW4064 (67) provides hepatoprotection against intra- and extrathoracic cholestasis (64) and a semi-synthetic bile acid derivative 6-ethyl chenodeoxycholic acid (6-ECDC) protects against liver fibrosis (24). When evaluating the therapeutic efficiency of FXR agonists in rodent models, one should bear in mind that there appears to be a certain degree of species dependence in the ligand-specificity of FXR/Fxr: for example, although the mouse Fxr is less sensitive to activation by androsterone than the human variant (101). It has been reported to function as an agonistic FXR ligand (15). Traditionally, oysteroids have been considered to be ligands for another member of the nuclear receptor family, the liver X receptor (LXr), which is an important regulator of cholesterol transport and metabolism. Employing shared ligands may reflect interaction of these two nuclear receptors involved in cholesterol homeostasis. Another physiological FXR ligand was shown to be androsterone, a testosterone metabolite (101). It was suggested that androsterone induces an overlapping but distinct subset of FXR target genes from CDCA, indicating ligand-dependent target gene specificity as previously shown in a study employing synthetic FXR ligands (16).

In addition to endogenous molecules, recent reports have suggested that compounds present in our dietary intake may act as FXR ligands. For example, a soy lipid-derived phytosterol, stigmastanol, has been reported to function as an antagonist of FXR activity, possibly contributing to the cholesterol-lowering effects of soy products. Additionally, a diterpene compound found in coffee beans and present in unfiltered coffee brews, called cafestol, was found to function as an agonistic ligand for FXR (84). Additionally, it has been reported to be responsible for hypercholesterolemia and increased risk of coronary heart disease associated with high intake of unfiltered coffee (92, 93, 102), and it is possible that this association is dependent on the ability of cafestol to activate FXR. For example, application of cafestol decreased the expression of the rate-limiting enzyme cholesterol to bile acids and thus impaired elimination of cholesterol from the body. Besides naturally existing FXR ligands, an intense interest in designing pharmaceutically effective synthetic FXR agonists and antagonists has developed over the last few years. In rodent models, some of these have already shown promising hepatoprotective qualities in rat models, the synthetic agonist GW4064 (67) provides hepatoprotection against intra- and extrathoracic cholestasis (64) and a semi-synthetic bile acid derivative 6-ethyl chenodeoxycholic acid (6-EC) protects against liver fibrosis (24). When evaluating the therapeutic efficiency of FXR agonists in rodent models, one should bear in mind that there appears to be a certain degree of species dependence in the ligand-specificity of FXR/Fxr: for example, although the mouse Fxr is less sensitive to activation by androsterone than the human variant (101). It has been reported to function as an agonistic FXR ligand (15). Traditionally, oysteroids have been considered to be ligands for another member of the nuclear receptor family, the liver X receptor (LXr), which is an important regulator of cholesterol transport and metabolism. Employing shared ligands may reflect interaction of these two nuclear receptors involved in cholesterol homeostasis. Another physiological FXR ligand was shown to be androsterone, a testosterone metabolite (101). It was suggested that androsterone induces an overlapping but distinct subset of FXR target genes from CDCA, indicating ligand-dependent target gene specificity as previously shown in a study employing synthetic FXR ligands (16).

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Therapeutic usage of cholesteric FXR ligands that leads to increased bile flow via the regulatory mechanisms described below may not be advantageous in cholestatic diseases that frequently have an obstructive component: in a mouse study, increased bile flow and biliary pressure in fact aggravated bile infarcts in mice suffering from obstructive cholestasis upon bile duct ligation (23).

**FXR Controls and Fine-Tunes Bile Acid Homeostasis**

Bile acids are the end products of hepatic cholesterol catabolism, thus providing a major pathway of excess cholesterol elimination from the body. Approximately 500 mg of bile acids are synthesized every day in the adult human liver. Enterohepatic cycling of bile acids, mediated by plasma membrane transporters expressed in hepatocytes and enterocytes in a polarized manner, is highly efficient in healthy individuals, with approximately only 5% escaping ileal reabsorption and being lost into feces. Functioning as physiological detergents, bile acids promote absorption of lipophilic nutrients and vitamins in the intestine. Furthermore, bile acids contribute to the solubilization of cholesterol in bile, thus protecting against precipitation of cholesterol crystals and preventing the formation of cholesterol gallstones. Despite these crucially important roles in normal physiology, elevated levels of bile acids, such as observed in cholestatic disease, can be cytotoxic due to their detergent property. To avoid cellular damage, bile acids function as homeostatic regulators and signaling molecules to adjust their own intracellular levels. Bile acids exert their regulatory effects chiefly by acting as FXR ligands, although they can also elicit other signaling pathways, such as those involving a G-protein-coupled receptor TRG5 (48) and the c-Jun NH2-terminal kinase (JNK) (30), which are likely to contribute to the protection against bile acid-induced damage. It is interesting to note that different bile acids have differing affinities to FXR and TGR5 (85), providing one mechanism for the divergent downstream signaling events that they elicit.

In the liver and intestine, the transcriptional events exerted by bile acid-activated FXR lead to increased cellular bile acid efflux and detoxification and decreased bile acid uptake and synthesis, as described below.

**FXR induces bile acid efflux and detoxification machinery**

The ABCB11 gene encoding BSEP, the chief liver canalicular bile salt export pump of the ATP-binding cassette (ABC) transporter family (90), is a target for direct transactivation by FXR (2, 81, 87) (FIGURE 1; Table 1). Thus, in conditions of increased bile acid load in hepatocytes, bile acids enhance their own efflux into bile by activating FXR and consequently increasing BSEP expression. Although BSEP is responsible for the efflux of nonvalent bile acids from hepatocytes into bile, the multidrug resistance-associated protein 2 (MRP2, ABCG2) contributes to the overall canalicular bile acid efflux by exporting divalent and sulphonated or glucuronidated bile acids into bile (reviewed in Ref. 53). Both the human and rodent ABCG2/Abcc2 promoters can be activated by FXR in the presence of bile acids (47). Yet another ABC transporter gene that is transactivated by FXR is ABCB4, encoding MDR3 (35), which is thought to be a flippase for phospholipids within the canalicular membrane of hepatocytes. Via induction of ABCB4 expression, FXR enhances the function of MDR3 in counteracting the toxicity of biliary bile acids by promoting formation of mixed micelles that contain cholesterol, bile acids, and phospholipids in bile canaliculi.

The SLCO1B3 gene encoding a member of the organic anion transporting polypeptide (OATP) family, OSTA/OSTb, is directly transactivated by FXR in a ligand-dependent manner through an IR-1 element (45). SLCO1B3 is an uptake system at the sinusoidal membrane of hepatocytes for numerous drugs and peptides, such as digoxin and cholecystokinin (46, 55). OSTA/OSTb may also transport bile acids in a sodium-independent manner (31), although the extent of its contribution to overall bile acid transport into hepatocytes has not been established. As discussed below, the activity of another liver-specific basolateral uptake system with an overlapping substrate specificity, OATP1b1, is suppressed by FXR-dependent pathways in cholestatic, bile acid-enriched environment (44). Induction of OATP1b1 expression by FXR may serve to maintain sufficient hepatic extraction of organic solutes and xenobiotics in conditions that lead to decreased expression of other basolateral drug uptake transporters, such as OATP1b1 (56).

In an analogous manner to the ABCB11 gene, FXR induces the expression of the two genes encoding the essential heterodimeric bile acid efflux system at the basolateral membrane of ileocytes, OSTA/OSTb (Refs. 58, 59, 82; Table 2). The OSTA/OSTb heterodimer has also been suggested to regulate bile acid homeostasis in humangenomes by inducing the expression of ABCB4, a target for direct transactivation by FXR (2, 81, 87) (FIGURE 1; Table 1). Thus, in conditions of increased bile acid load in hepatocytes, bile acids enhance their own efflux into bile by activating FXR and consequently increasing BSEP expression. Although BSEP is responsible for the efflux of nonvalent bile acids from hepatocytes into bile, the multidrug resistance-associated protein 2 (MRP2, ABCG2) contributes to the overall canalicular bile acid efflux by exporting divalent and sulphonated or glucuronidated bile acids into bile (reviewed in Ref. 53). Both the human and rodent ABCG2/Abcc2 promoters can be activated by FXR in the presence of bile acids (47). Yet another ABC transporter gene that is transactivated by FXR is ABCB4, encoding MDR3 (35), which is thought to be a flippase for phospholipids within the canalicular membrane of hepatocytes. Via induction of ABCB4 expression, FXR enhances the function of MDR3 in counteracting the toxicity of biliary bile acids by promoting formation of mixed micelles that contain cholesterol, bile acids, and phospholipids in bile canaliculi.

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The divergent effects of FXR on bile acid absorption. The primary bile acid transporter (ABCB4) and several other transportersplay a role in bile acid absorption in the liver, intestine, and other tissues. FXR negatively regulates bile acid uptake systems and bile acid synthesis.

**FXR negatively regulates bile acid uptake systems**

- **NTCP** is the predominant transporter responsible for bile acid uptake from portal blood across the basolateral membrane of hepatocytes. FXR negatively regulates NTCP expression in response to bile acids (4).

- **ASBT** belongs to the same family of transporter proteins as NTCP, and is the major bile salt uptake system in enterocytes (5).

- **OATP** family members are involved in the transport of bile acids from the liver to the intestine (6).

**FXR binds to the Fxr response element** (FRE) in the promoter of several genes, including NTCP and ASBT, to regulate their expression (7).

**FXR also regulates the expression of SHP** (8), a negative regulator of bile acid transport (9). SHP induction by FXR is mediated by the binding of FXR to its cognate response element, the Fxr response element (FRE) (10).

**FXR-mediated repression of the OATP gene** is mediated by the binding of FXR to its cognate response element, the Fxr response element (FRE) (11).

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Table 2. Intestinal genes discussed in the review, the FXR-dependence of angiogenin, iNOS, FGF19, ASBT, and OST.

<table>
<thead>
<tr>
<th>Gene</th>
<th>FXR Target</th>
<th>Known or Proposed Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSt/HO1</td>
<td>+</td>
<td>Heterodimeric basolateral bile acid efflux system</td>
</tr>
<tr>
<td>ASBT</td>
<td>-</td>
<td>Apical bile acid uptake system</td>
</tr>
<tr>
<td>FGF19</td>
<td>+</td>
<td>Bile acid-inducible growth factor</td>
</tr>
<tr>
<td>iNOS</td>
<td>+</td>
<td>Nitric oxide synthase, anti-microbial</td>
</tr>
<tr>
<td>angiogenin</td>
<td>+</td>
<td>Anti-microbial</td>
</tr>
</tbody>
</table>

For details and references to literature, please see the main text. +, induced by FXR; -, suppressed by FXR.
The reduced expression of FXR (68). The difference between the two studies remains unclear but may simply be due to the different experimental setups. Interestingly, the mRNA expression levels of the FXR target genes SHP and OATP1B3 are significantly reduced in the livers of the heterozygote subject carrying the –1G>T allele, whereas the FXR mRNA expression remained comparable to the wild-type in a cell-free assay and in transfected HEK293 cells. The difference between the two studies remains unclear but may simply be due to the different experimental setups.

In further support of the role for FXR in cholelithiasis, FXR-null mice exhibit the typical characteristics of cholesterol gallstone disease, such as supersaturation of cholesterol in bile, precipitation of cholesterol crystals in the gallbladder, and increased hydrophobicity of bile salts (32, 71). Furthermore, in a gallstone-susceptible FXR wild-type mouse strain, application of the specific FXR ligand GW4064 reduced cholesterol solubility by increasing biliary bile salt and phospholipid concentrations and restoring cholesterol solubility.

It is clear that other regulatory factors are also involved in the development of the undoubtedly multifactorial gallstone disease. In a recent report of a mouse study (7), the winged helix/forkhead transcription factor FoxO1 was shown to be a positive regulator of FXR expression in the liver and in the intestine, thus affecting the amount of cholesterol available for biliary excretion. No significant difference in FXR mRNA levels was reported in liver biopsies obtained from 11 untreated cholesterol cholelithiasis patients when compared with 9 cholesterol gallstone-free subjects (6). However, in this latter study, the allelic status of the NR1H4 gene was not determined in the patients. Although the expression of FXR itself was not altered in this group of gallstone patients, the transcriptional coactivator PGC-1α was significantly less expressed in the livers of patients with cholesterol cholelithiasis when compared with non-gallstone patients. PGC-1α can function as a coactivator of FXR, mediating the activation of FXR target genes (46, 108), and may also enhance the expression of the NR1H4 gene itself via coactivation of the nuclear receptors PPARγ and HNF-α (108). Reduced expression of PGC-1α in gallstone patients could thus lead to decreased expression of both FXR and its target genes BSEP and MDR3, the actions of which help to maintain cholesterol in its soluble form in the bile.

This study the functional activity of the –1G>T variant also appeared to be compromised, the level of transcription and translation efficiency of the variant was evaluated comparable to the wild-type in a cell-free assay and in transfected HEK293 cells. The difference between the two studies remains unclear but may simply be due to the different experimental setups. Interestingly, the mRNA expression levels of the FXR target genes SHP and OATP1B3 are significantly reduced in the livers of the heterozygote subject carrying the –1G>T allele, whereas the FXR mRNA expression remained comparable to the wild-type in a cell-free assay and in transfected HEK293 cells. The difference between the two studies remains unclear but may simply be due to the different experimental setups.

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plasma membrane. Genetic mutations and polymorphisms in the ATP8B1 gene have been associated with familial intrahepatic cholestasis, characterized by low y-glutamyltransferase plasma levels (reviewed in Refs. 41, 96). A disease entity termed progressive familial intrahepatic cholestasis type 1, or PFIC1 (also known as “Byler’s disease”) is the severe form of PFIC-related liver disease, characterized by fat malabsorption, intense pruritus, and frequently leads to the cirrhosis of the liver. The milder form of PFIC-related disease is known benign recurrent intrahepatic cholestasis type 1, or BRIC1. In BRIC1, discrete cholestatic episodes are separated by asymptomatic periods, and BRIC1 does not typically lead to progressive liver injury. PFIC1 and BRIC1 are associated with distinct sets of genetic variants in the ATP8B1 gene, and it could be hypothesized that the severity of the disease may correlate with the degree of corresponding effect in FIC1 function.

In 2004, two groups reported that, in PFIC1 patients, there is a tendency for decreased hepatic and intestinal mRNA levels of FXR and of genes transactivated by FXR (1, 10), implying that FIC1 may influence the expression and/or function of FXR, possibly thus contributing to the pathogenesis of the liver disease. Intriguingly, in a more recent report, it was shown that, whereas the wild-type FIC1 was capable of potent activation of the BSEP promoter, the PFIC1-associated FIC1 variants were inactive, and the BRIC1-associated FIC1 variants activated the BSEP promoter to a moderate degree (26). The authors further hypothesized that the wild-type FIC1 protein induces nuclear localization of FXR through stimulation of a phosphorylation cascade targeting FXR and that FIC1-related disease may be caused by the compromised ability of the associated FIC1 variants to influence FXR localization and function.

FXR-Mediated Indirect Mechanisms Affecting Intestinal Bacterial Growth

It was previously known that bile acids can protect against bacterial overgrowth in the small intestine via their anti-microbial activity, thus helping to maintain the integrity of the intestinal epithelium and to prevent systemic infections caused by bacterial translocation across the mucosal barrier (5, 65). In mice, bile acids exert this protection against intestinal mucosal injury via FXR (38). In wild-type mice, bile duct ligation resulted in a significant increase in the number of intestinal bacteria and led to bacterial invasion of the mucosa. Administration of the synthetic and potent FXR ligand GW4064 alleviated these effects of bile duct ligation in wild-type but not FXR-deficient mice. In gene profiling studies in mice, several candidate GW4064-induced genes were identified that could potentially be involved in the intestinal mucosal defense. Perhaps one of the most notable of these is the gene encoding the inducible nitric oxide synthase (iNOS), given the antimicrobial properties of nitric oxide, as well as its role in epithelial barrier function (74, 98). Another gene identified as GW4064-inducible was the gene encoding angiogenin, which also exerts anti-bacterial effects (34). It may be that agonistic ligands for FXR could be therapeutically useful in patients with reduced bile flow and consequently elevated bacterial growth and invasion across the intestinal mucosa.

Outlook

At present, the physiological significance of FXR function and expression is largely supported by observations in FXR-deficient mice. As crucial as such rodent whole-organism studies are, their results should be interpreted with a certain degree of caution: even slight differences in the complex promoter regions of FXR target genes between species may result in differential transcriptional consequences of FXR activation, and thus differential physiological downstream effects. Furthermore, since FXR-null mice have been devoid of any FXR function throughout their embryonic development and adult life, compensatory mechanisms may have developed. These models may not accurately reflect the situation in human pathologies, where genetic variants of FXR may have altered, but by no means are absent in, function. Increased knowledge of the consequences of genetic variation in the human FXR gene itself, FXR target genes, or potential upstream regulators of FXR such as FIC1, and of association between these genetic events and human pathogenesis should assist us in our understanding of the pathobiology of these diseases and point to new therapeutic targets.

In addition to the bile acid homeostasis in the liver and intestine discussed here, FXR has been identified as a key player in several other metabolic processes, such as glucose and lipid metabolism (12), as well as carcinogenesis (52, 106) and liver cell proliferation (36). Although this has raised much excitement about the potential of modulating FXR activity in pathogenic processes beyond those involving disturbed bile acid homeostasis, this has also highlighted the potential difficulties in achieving tissue, process, and even gene specificity in therapeutic targeting of FXR. Since the range of FXR ligands, endogenous and synthetic, is rapidly increasing, the likelihood of discovering FXR agonists and antagonists that may function in a more specific manner may be increased, and modeling of novel synthetic FXR ligands displaying such specificity may be facilitated.

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48. Konig J, Nies AT, Cui Y, Leier I, Keppler D. The nuclear bile acids receptor FXR is asso-


Bile acids: hepatic synthesis and extrahepatic function

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