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 steroid hormones. Binding of agonistic or antagonistic ligands leads to allosteric 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 (DR), inverted (IR), or everted (ER) 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 tissues.

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 intestinal 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, Nfhl (encoding Barx) and Nfhb5 (encoding Parx), the latter gene product encoding 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/Fxr.

Four isoforms of FXR, termed FXRα1–4, can be translated from the single NR1H4 gene in humans, generated by both alternative promoter usage and by alternative splicing (37, 109). FXRα1 and FXRβ2, the most abundant FXR isoforms in the human liver, differ from FXRα3 and FXRα4 at the NH2 terminus, since the mRNAs for these two isoform pairs are transcribed from separate promoters. In addition, the isoforms FXRα1 and FXRα2 contain an additional stretch of four amino acids, MYTG, 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 posttranslational modifications (i.e., to form complexes and undergo heterodimerization properties). In the context of at least a subset of target genes, the FXR isoforms appear to exhibit differential DNA-binding and transcription activation properties (8, 109), although in the context of most FXR target genes this remains to be comprehensively studied.

FXR functions typically as an agonist-dependent transcriptional activator of its direct target genes. Numerous transcriptional coactivators recruited to agonist-bound FXR, mediating its transactivation function, have been proposed (reviewed in Ref. 20). 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 agonist affinity of FXR for bile acids as well as binding by FXR itself to other promoters that FXR, like other nuclear receptors, binds to typical nuclear receptor target promoters (88). The SHP protein, which is involved in the nuclear receptor family, belongs to the same superfamily as FXR (20). SHP may interact with transcriptional regulators of nuclear receptor target promoters (50) and may negatively regulate FXR, FXR ligands, and nuclear receptor activity (21), although the mechanism of this action is not fully elucidated.

SHP, used in the human isoforms FXRα1–4, contains an additional stretch of four amino acids, MYTG, 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 posttranslational modifications. In the context of at least a subset of target genes, the FXR isoforms appear to exhibit differential DNA-binding and transcription activation properties, although in the context of most FXR target genes this remains to be comprehensively studied.

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human apolipoprotein A-1 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 (NR0B2) 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 activate FXR at concentrations clearly exceeding physiological FXR ligand concentrations (66, 79, 99). Out of the two most important bile acids directly interact with its ligand-binding domain, leading to enhanced transactivation and coactivator recruitment (66, 79, 99). Out of the two most important bile acids in humans, more hydrophobic chenodeoxycholic acid (CDCA) is clearly a more potent FXR activator than the hydrophilic cholic acid (6-ECDCA) protects against liver fibrosis (24). When evaluating the therapeutic efficiency of these synthetic bile acid derivatives, it is of interest in designing pharmaceutically effective synthetic FXR ligands (18). Since the identification of bile acids as FXR ligands, several other endogenous and naturally occurring compounds have been suggested or shown to act as direct FXR ligands. For example, the oxysterol 22(OH) hydroxycholesterol, an intermediate in bile acid and stereo hormone synthesis, has been suggested to be such an agonistic FXR ligand (15). Traditionally, oxysterols 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 selectivity as previously shown in a study employing synthetic FXR ligands (40).

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 cholestatic associated with neonatal parenteral nutrition employing soy-derived lipid emulsions (9). 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). Previously, cafestol had been shown 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 pharmacologically 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 GW40046 (67) provides hepatoprotection against intra- and extrahepatic cholestasis (64) and a semi-synthetic bile acid derivative 6-ethyl chenodeoxycholic acid (6-ECDCA) 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 responsive to CDCA than the human FXR ortholog (14), it has been reported to be more sensitive to activation by androsterone than the human variant (101). Also, concerning experimental rat models, it is worth noting that, unlike humans, rats do not have a gall bladder, and certain regulatory aspects of bile acid homeostasis may thus be fundamentally different in the two species.
Table 1. Hepatic genes discussed in the review, the FXR-dependence of their expression, and their functions

<table>
<thead>
<tr>
<th>Gene</th>
<th>FXR Target</th>
<th>Known or Proposed Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSEP</td>
<td>+</td>
<td>Major canalicular bile acid efflux system</td>
</tr>
<tr>
<td>NTCP</td>
<td>-</td>
<td>Major sinusoidal bile acid uptake system</td>
</tr>
<tr>
<td>MDR3</td>
<td>+</td>
<td>Canalicul phospholipid efflux system</td>
</tr>
<tr>
<td>MRP2</td>
<td>+</td>
<td>Canalicular drug and bile acid efflux system</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>+</td>
<td>Sinusoidal drug and bile acid uptake system</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>+</td>
<td>Sinusoidal drug and peptide uptake system</td>
</tr>
<tr>
<td>OSTα/OSTβ</td>
<td>+</td>
<td>Sinusoidal alternative bile acid efflux system</td>
</tr>
<tr>
<td>CYP7A1</td>
<td>-</td>
<td>Bile acid synthesis via cholesterol catabolism</td>
</tr>
<tr>
<td>CYP8B1</td>
<td>-</td>
<td>Bile acid synthesis via cholesterol catabolism</td>
</tr>
<tr>
<td>CYP27A1</td>
<td>-</td>
<td>Bile acid synthesis via cholesterol catabolism</td>
</tr>
<tr>
<td>UGT2B4</td>
<td>+</td>
<td>Glucuronidation of bile acids</td>
</tr>
</tbody>
</table>

For details and references to literature, please see the main text. +, induced by FXR; -, suppressed by FXR.
FXR negatively regulates bile acid uptake systems and bile acid synthesis

The Na⁺-taurocholate cotransporting polypeptide (NTCP) is the predominant transporter responsible for bile acid uptake from portal blood across the basolateral membrane of hepatocytes. In rodent models of cholestasis, expression of the Ntcp mRNA and protein is notably decreased (22, 27, 112). Thus, in addition to enhancing bile acid efflux and decreased NTCP expression (111, 127), bile acids suppress the expression of the major bile acid uptake system in ileal epithelium, the major site of intestinal bile acid absorption. The human NTCP gene is also suppressed by treatment of cultured cells with bile acids (75). Two molecular mechanisms, potentially operational in parallel, have been proposed for this phenomenon: it has been suggested that SHP interferes with RXR-RXR-dependent transactivation (75) or GR-dependent transactivation (19) of the human NTCP promoter. Given that the FXR-SHP pathway also negatively targets GR on the human NTCP promoter, the latter also been suggested to function as a potential alternative bile acid efflux system at the basolateral membrane of human hepatocytes (8). The OSTA and OSTB gene expression can also be induced upon bile acid treatment of biopsy samples derived from the human ileal tissue (58). Physiological support for these in vitro and ex vivo studies is provided by the finding that basolateral uptake of bile acids is increased in ileal and in enterocytes, the cortex is also associated with FXR in ileal epithelium, the major site of intestinal bile acid absorption. The human NTCP gene is also suppressed by treatment of cultured cells with bile acids (75). Two molecular mechanisms, potentially operational in parallel, have been proposed for this phenomenon: it has been suggested that SHP interferes with RXR-RXR-dependent transactivation (75) or GR-dependent transactivation (19) of the human NTCP promoter. Given that the FXR-SHP pathway also negatively targets GR on the human NTCP promoter, the latter
proposed pathway emphasizes the coordinated regulation of the bile salt uptake systems in both human liver and intestine.

In addition to downregulating the expression of bile acid uptake transporters in the liver and the intestine, FXR also represses transcription of three genes coding for bile acid synthesizing enzymes, namely cholesterol-7α-hydroxylase (CYP7A1), sterol-12α-hydroxylase (CYP8B1), and sterol-27-hydroxylase (CYP27A1), in a ligand-dependent manner (reviewed in Ref. 20).

Thus elevated levels of bile acids can suppress their own de novo production through a negative feedback loop. All three CTP promoters contain a negative bile acid response element, which is targeted by the FXR-induced repressor SHP. In the CYP7A1 and CYP8B1 promoters, the targeted DNA-binding transactivators are the monomeric nuclear receptor liver receptor homolog-1 (LRH-1) and homodimeric HNF-4α, which have overlapping DNA-binding motifs on both promoters. In the case of the CYP27A1 gene, the negative bile acid response element contains a DNA-binding site only for HNF-4α but not for LRH-1.

Although SHP-deficient mice exhibit impaired negative feedback regulation of bile acid synthesis, this is not completely abolished, implying that additional or parallel SHP-independent repression pathways may lead to reduced bile acid synthesis (51, 106). One such alternative pathway involving signaling between the liver and the intestine has been proposed: in response to bile acids, FXR directly activates the gene encoding fibroblast growth factor-19 (FGF19; mouse ortholog Fgfr5) in the intestine (33, 38). From the intestine, FGF19/Fgf15 is released to portal blood, and upon reaching the liver it elicits a signaling cascade by binding to the fibroblast growth factor receptor-4 (FGFR4) tyrosine kinase on the surface of hepatocytes. Activated FGFR4 stimulates the intracellular JNK kinase pathway, which eventually suppresses the CYP7A1 promoter in the nucleus. A complex mechanism has been proposed for this downstream effect, according to which JNK signaling induces expression of the transcription factor c-Jun, which via a direct interaction with HNF-4α may block the recruitment of the transcriptional coactivator PGC-1α, thus resulting in suppression of CYP7A1 gene expression (63). It appears that SHP somehow contributes to the FXR-dependent repression of Fgf19/Fgf15, since the effect seems clearly attenuated in SHP-deficient mice (38). The FGF19/Fgf15-mediated endocrine-type loop may explain the previous observations that intestinal administration of bile acids leads to decreased hepatic CYP7A1 expression in rats, whereas intravenous or portal administration does not (73, 78).

**Gene** | **FXR Target** | **Known or Proposed Function**
---|---|---
OST/OSTL | + | Heterodimeric basolateral bile acid efflux system
ASBT | + | Apical bile acid uptake system
FGF19 | + | Bile acid-inducible growth factor
iNOS | + | Nitric oxide synthase, anti-microbial
angiotensin | + | Anti-microbial

For details and references to literature, please see the main text. +, induced by FXR; -, suppressed by FXR.

**FGF19/Fgf15 pathway of repression of bile acid synthesis, since the effect seems clearly attenuated in SHP-deficient mice (38).** This repression of Fgf19/Fgf15-mediated endocrine-type loop may explain the previous observations that intestinal administration of bile acids leads to decreased hepatic CYP7A1 expression in rats, whereas intravenous or portal administration does not (73, 78).

**Genetic Variation in the FXR Gene in Liver and Biliary Diseases**

Genetic variations and polymorphisms in several members of the nuclear receptor family, such as peroxisome proliferator-activated receptors-α and -γ (PPARα, PPARγ; Refs. 70, 91), vitamin D receptor (VDR; Ref. 95), and hepatocyte nuclear factor-4α (HNF-4α; Ref. 105) have been associated with specific metabolic disorders. There are currently approximately 400 genetic single nucleotide polymorphisms (SNPs) or mutations within the NR1H4 gene encoding FGF19/Fgf15 (http://www.ncbi.nlm.nih.gov/snp) and HapMap (http://www.hapmap.org) SNP databases, most of them located in the intronic regions or in regions flanking the FGF19 coding sequence. Only recently have reports been published on associations between genetic variants in the NR1H4 gene and human pathobiology, and these are summarized below.

**Intrahepatic cholestasis of pregnancy**

In the study by van Mil et al. (97), both the coding regions and exon/intron boundaries of the NR1H4 gene were studied in 92 British women of varied ethnic origins, who were suffering from intrahepatic cholestasis of pregnancy (ICP). ICP is a reversible form of a cholestatic disease, which is frequently associated with adverse pregnancy outcomes, such as premature birth, fetal distress, and intra-uterine death. Four heterozygous NR1H4 variants were identified: -1G>T, 1A>G (M1V), 238T>C (W80R), and 518T>C (M173T). The first two FVR variants, -1G>T and 1A>G (M1V), were shown to lead to reduced FXR protein expression and decreased level of transcriptional activation of a FXR-dependent promoter construct in transfected human embryonic kidney HEK293T cells compared with the wild-type FXR. The 518T>C (M173T) variant, harboring an amino acid substitution within the zinc finger DNA-binding domain of FXR, also led to a reduction in the transcriptional activity of FXR in cell-based assays, even if the degree of protein expression, DNA-binding, and heterodimerization with FXR remained apparently unaffected by the change of residues. Another group published simultaneously an independent study on FXR polymorphisms in populations of European, African, Chinese, and Hispanic descent (68). One of the four FXR variants identified in this latter study also contained the -1G>T substitution in the base position adjacent to the translational initiation site. Although in this study the -1G>T variant also appeared in a chi-square and evaluation of linkage disequilibrium between the two SNPs was done, this study likely be due to chance. Interestingly, the target gene NR1H4 was reduced in the case of the -1G>T variant, instead of the polymorphism itself. No other polymorphism was not expression confirmed.

Also in the case of the ABCB4 gene (97), a case-control study of 290 cases and 290 controls, 59 common allelic variants were identified. Their variant was expressed in subjects of British ICP patients, who were suffering from intrahepatic cholestasis of pregnancy. These further investigated the allelic nature of the NR1H4 variants.

Consistent variations of alleles being affected in known FXR variants, like ABCB4, encoding the bile acid exporting protein, with this pathologic condition, have been previously described, as well as the fact that FXR variants are not expressed in ICP patients. Further investigation of genetic variants in such genes would be needed to confirm whether these rare disease-causing alleles or variants in the FXR gene are well conserved.
The acid synthesis
inhibited by the
1,25(OH)2D receptor.

In a recent study, the functional activity of the -1G>T variant also appeared to be compromised, the level of trans- 
scription and translation efficiency of the variant was 
evaluated comparable to the wild-type in a cell-free 
assay and in transfected HeLa cells. The difference 
between the two studies remains unclear but may sim-
ply 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 carry-
ing the -1G>T allele, whereas the FXR mRNA expres-
sion was comparable in both groups indicating that this
polymorphism may lead to compromised function but
not expression level of FXR (68).

Also in the above-mentioned report by van Mil et al.
(97), a case-control study of a British cohort (293 ICP 
cases, 290 controls) and a Swedish cohort (49 ICP 
cases, 59 controls) was performed to determine the
allelic frequencies of the NR1H4 variants previously
identified. The variant 238T>C (W80R) was not pres-
ent in subjects of Caucasian origin, and only one
British ICP patient carried the 1A>G (M1V) variant.
Out of the two variants present in both the ICP group
and the control group, -1G>T and 518T>C (M173T),
only the latter exhibited significant associations with
the ICP phenotype in the Swedish group. It is clear that
in such genetic association studies larger cohorts will
be needed to confirm the results and to discover fur-
ther rare disease-associated variants. Furthermore, as
cholestatic diseases may be complex, possibly requir-
ing particular allelic variants in multiple susceptibility
genes, the exact significance of FIC1 in normal physiology is not
known in detail, but it is believed to contribute to the
detergent-resistant properties of the liver canalicular
membrane and at the apical membrane of
enterocytes, in addition to many other tissues (94).

The familial intrahepatic cholestasis-1 (FIC1) protein,
encoded by the
FIC1 gene, is expressed at the liver
and intestinal membranes, and at the apical membrane of
enterocytes, in addition to many other tissues (94).

The expression of FIC1 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 nongallstone patients. PGC-1α can function as a
coactivator of FXR, mediating the activation of FXR tar-
get genes (46, 108), and may also enhance the expres-
sion of the NR1H4 gene itself via coactivation of the
nuclear receptors PPARs 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.

In further support of the role for FXR in cholesterol
metabolism, FXR-null mice exhibit the typical characteris-
tics of cholesterol gallstone disease, such as supersaturation
of cholesterol in bile, precipitation of cholesterol crys-
tals in the gallbladder, and increased hydrophobicity of
bile salts (32, 71). Furthermore, in a gallstone-suscepti-
ble FXR wild-type mouse strain, application of the spe-
cific FXR ligand GW4064 reduced gallstone prevalence
by increasing biliary bile salt and phospholipid concen-
trations and restoring cholesterol solubility.

It is clear that other regulatory factors are also
involved in the development of the undoubtedly mul-
tifactorial gallstone disease. In a recent report of a
mouse study (7), the winged helix/forhead transcription
factor FoxO1 was shown to be a positive regulator
of the genes encoding the heterodimeric cholesterol
efflux system ABCG5/ABCG8 at the canalicular mem-
brane of hepatocytes. Disinhibition of FoxO1 activity may,
in a concerted manner with compromised FXR function, promote
gallstone cholesterol formation.

The FIC1-FXR Connection and
Intrahepatic Cholestasis

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gallstone cholesterol formation.
plasma membrane. Genetic mutations and polymor-
phisms in the ATP8B1 gene have been associated with
familial intrahepatic cholestasis, characterized by low
γ-glutamyltransferase plasma levels (reviewed in Refs.
41, 96). A disease entity termed progressive familial
intrahepatic cholestasis type 1, or PFIC1 (also known as "Bylet’s disease") is the severe form of FC1-related
liver disease, characterized by fat malabsorption,
intense pruritus, and frequently leads to the cirrhosis of
the liver. The milder form of FC1-related disease is
named 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 vari-
ants in the ATP8B1 gene, and it could be hypothesized
that the severity of the disease may correlate with
the degree of corresponding effect in FC1 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 FC1 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
FC1 was capable of potent activation of the BSEP pro-
moter, the PFIC1-associated FC1 variants were inactive,
and the BRIC1-associated FC1 variants activated the
BSEP promoter to a moderate degree (26). The authors
further hypothesized that the wild-type FC1 protein
induces nuclear localization of FXR through stimulation
of a phosphorylation cascade targeting FXR and that
FC1-related disease may be caused by the compo-
mination of the associated FC1 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 pre-
vent systemic infections caused by bacterial transloca-
tion across the mucosal barrier (5, 65). In mice, bile
acids exert this protection against intestinal mucosal
injury via FXR (39). In wild-type mice, bile duct liga-
tion 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 those effects of bile duct
ligation in wild-type but not FXR-deficient mice. In

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...er 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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