Activation of LXRα Prevents Bile Acid Toxicity and Cholestasis in Female Mice

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Liver X receptors (LXRs) have been identified as sterol sensors that regulate cholesterol and lipid homeostasis and macrophage functions. In this study, we found that LXRs also affect sensitivity to bile acid toxicity and cholestasis. Activation of LXRs in transgenic mice confers a female-specific resistance to lithocholic acid (LCA)–induced hepatotoxicity and bile duct ligation (BDL)–induced cholestasis. This resistance was also seen in wild-type female mice treated with the synthetic LXR ligand TO1317. In contrast, LXR double knockout (DKO) mice deficient in both the α and β isoforms exhibited heightened cholestatic sensitivity. LCA and BDL resistance in transgenic mice was associated with increased expression of bile acid–detoxifying sulfotransferase 2A (Sult2a) and selected bile acid transporters, whereas basal expression of these gene products was reduced in the LXR DKO mice. Promoter analysis showed that the mouse Sult2a9 gene is a transcriptional target of LXRs. Activation of LXRs also suppresses expression of oxysterol 7α-hydroxylase (Cyp7b1), which may lead to increased levels of LXR-activating oxysterols. Conclusion: We propose that LXRs have evolved to have the dual functions of maintaining cholesterol and bile acid homeostasis by increasing cholesterol catabolism and, at the same time, preventing toxicity from bile acid accumulation. (Hepatology 2007;45:422-432.)

T
he liver X receptors LXRα (NR1H3) and LXRβ (NR1H2) belong to the nuclear hormone receptor superfamily of transcription factors. LXRα is highly expressed in the liver and is also found in adipose tissue, intestines, kidneys, and macrophages, whereas LXRβ expression is detectable in most tissues.1,2 LXRs were defined as sterol sensors, as they can be activated by cholesterol-derived oxysterols, such as 24(S),25-epoxy-cholesterol, 24(S)-hydroxycholesterol, and 22(R)-hydroxycholesterol. Several other LXR agonists, including the synthetic T0901317 (TO1317), have also been described.3

LXRs were first shown to exert their overall antiatherosclerotic effect by increasing hepatic cholesterol catabolism and inhibiting cholesterologenesis.1,2,4 In rodents, LXRα increases cholesterol catabolism by inducing cholesterol 7α-hydroxylase (Cyp7a1), a rate-limiting enzyme that catalyzes the conversion of cholesterol to bile acids.5 Interestingly, the LXR induction of CYP7A1 does not seem to occur in humans.6,7 Despite the beneficial functions of bile acids, their excess accumulation is harmful and may lead to hepatotoxicity and cholestasis.8 Orphan nuclear receptors, such as the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), the farnesoid X receptor (FXR), and small heterodimerization partner (SHP), have been shown to prevent bile acid toxicity and cholestasis through various mechanisms9-15 (for a review see refs. 16-18). However, it is not known whether LXRs also play a role in bile acid toxicity and cholestasis.

In the intestine, LXRs increase the expression of the ATP-binding cassette (ABC) superfamily of transporters,
resulting in efflux of cholesterol from enterocytes and blockade of intestinal dietary cholesterol absorption.\textsuperscript{19} In macrophages, LXRs promote reverse cholesterol transport by up-regulating ABC transporters and apolipoproteins E, C-I, C-IV, and C-II.\textsuperscript{4} In addition, LXRs inhibit macrophage inflammatory responses and affect antimicrobial responses.\textsuperscript{20-22} Despite the promise of LXRs as antiatherosclerotic targets, they have also been linked to negative prolipogenic effects. LXR activation increases plasma triglyceride levels through transcriptional activation of Srebp-1c, a transcription factor known to regulate the expression of a battery of lipogenic enzymes.\textsuperscript{3,23-26}

In this study, we showed that activation of LXR prevents bile acid toxicity and cholestasis, a phenotype associated with LXR-mediated regulation of bile acid–detoxifying enzymes and transporters. LXRs also inhibit expression of oxyysterol 7α-hydroxylase (Cyp7b1), which may increase the levels of LXR-activating oxysterols. We propose that LXRs have dual functions of promoting cholesterol catabolism and preventing cholestasis from excess bile acid accumulation.

Materials and Methods

Mouse Models. To create the FABP-VP-LXRα transgene, VP-LXRα cDNA was placed downstream of the rat fatty acid–binding protein (Fabp) gene promoter.\textsuperscript{27} Microinjection to produce the transgenic mice was performed at the University of Pittsburgh Transgenic Core Facility. The LXR double knockout (DKO) mice were described previously.\textsuperscript{2} C57BL/6J background transgenic mice were created by backcrossing to C57BL/6J mice for 7-8 generations. All other transgenic and knockout mice used in this study have a mixed background of C57BL/6J and 129/SvImJ. The use of mice in this study was in compliance with all relevant federal guidelines and institutional policies.

Animal Drug Treatment, Histological Evaluation, and Plasma and Urine Chemistry. Lithocholic acid (LCA) gavage treatment,\textsuperscript{10} bile duct ligation,\textsuperscript{28} and double-blinded liver histology analysis were performed as previously described. In the LCA and bile duct ligation (BDL) models, when necessary, daily gavage of TO1317 (50 mg/kg body weight) 30 minutes before being hydrodynamically transfected with the pCMX-HA-LXRα or pCMX-HA control plasmid. The liver transfaction and ChIP assays were performed as described previously.\textsuperscript{31} The primers used were: for Sult2a9/IR0, 5’- TTC GTAATGAACGCTTCG-3’ and 5’- CTGGAGTAATGCTTTGCGTT-3’. In the sulfotransferase assay, the PCR products of Sult2a9 and Srebp-1c are 169 and 141 bp, respectively.

Northern Blot Analysis and Real-Time PCR. Northern hybridization using \textsuperscript{32}P-dCTP-labeled cDNA probes was carried out as described.\textsuperscript{10} The Sult2a9 cDNA probe was described previously,\textsuperscript{10} and the Cyp7b1 cDNA probe was cloned by RT-PCR from the mouse liver RNA. When necessary, the signals were quantified with NIH Image software. Real-time PCR using predesigned Assay-On-Demand TaqMan reagents or SYBR Green–based assays was performed with the ABI 7300 Real-Time PCR System. Sequences for the real-time PCR oligonucleotides are available on request.

Sulfotransferase Assay. The sulfotransferase assay

DNA-Binding Analysis and Transient Transfections. EMSA using receptor proteins prepared with the TNT \textit{in vitro} transcription and translation system (Promega) was performed as previously described.\textsuperscript{10} The oligonucleotides used were: Sult2a9/IR0, 5’-TTTGG GGTAATGAACGCTTCG-3’; and Sult2a9/IR0 mut, 5’- TTTGGGGGTTGACCGAATTTGGCG-3’. CV-1 and HepG2 cell transfection methods were described previously.\textsuperscript{10,29,30} All the synthetic tk and natural Sult2a9 promoter reporter constructs and their mutant variants have been described previously.\textsuperscript{10} CV-1 cells were chosen as LXR-naive cells, whereas HepG2 cells were chosen for the responsiveness of the natural Sult2a9 promoter. When necessary, cells were treated with drugs in media containing 10% charcoal-stripped serum for 24 hours prior to the luciferase assay. Transfection efficiency was normalized against β-gal activity from the cotransfected CMX-β-gal vector.

Primary Human Hepatocytes and Drug Treatment. Primary human hepatocyte cultures prepared by the collagenase perfusion method were kindly provided by Dr. Steve Strom through the Liver Tissue Procurement and Distribution System (LTPADS).\textsuperscript{29} Cells were maintained in hepatocyte maintenance medium from Cambrex Bio Science (Walkersville, MA) and incubated overnight. Cells were then treated with appropriate drugs for 24 hours prior to RNA harvesting.

Chromatin Immunoprecipitation (ChIP) Assay. Four-week-old wild-type female mice received an intraperitoneal injection of DMSO or TO1317 (50 mg/kg body weight) 30 minutes before being hydrodynamically transfected with the pCMX-HA-LXRα or pCMX-HA control plasmid. The liver transfaction and ChIP assays were performed as described previously.\textsuperscript{31} The primers used were: for Sult2a9/IR0, 5’- TGAAAAATTGTGACCAACGGAG -3’ and 5’- CCATTGGAATGGTCTCTGATGA-3’; for Srebp-1e/IR4: 5’- CTCTTTTCCGGGATGTGTT-3’ and 5’- GGTTTCTCCCGGTGCTCTT-3’. The PCR products of Sult2a9 and Srebp-1c are 169 and 141 bp, respectively.
was carried out using \[^{35}S\]3’-phosphoadenosine 5’-phosphosulfate (PAPS; PerkinElmer) as described. In brief, 5 μg/mL of total liver cytosolic extract was used with 2 μM LCA or \(p\)-nitrophenol (pNP) substrate. After the reactions, free \[^{35}S\]PAPS was removed by extraction with ethyl acetate. Then a scintillation counter was used to count the aqueous phase for radioactivity. At least 3 pairs of mice were used for each SULT assay, and each reaction was run 3 times.

**Statistical Analysis.** Experiments presented were repeated at least three times with at least 4 samples per group. The unpaired Student t test or the Mann-Whitney U test was used to calculate statistical differences.

**Results**

**Activation of LXR Prevents Bile Acid Toxicity and Cholestasis.** We recently created transgenic mice expressing activated LXRα (VP-LXRα) in the liver and intestine under the control of the rat fatty acid-binding protein (FABP) gene promoter (Fig. 1A). \(^{27}\) Created by fusing the VP16 activation domain of the herpes simplex virus to the amino terminal of mouse LXRα, VP-LXRα shares the same DNA-binding specificity as its wild-type counterpart (Fig. 1B), and cotransfection with VP-LXRα activated the LXR responsive reporter gene in the absence of an agonist (Fig. 1C). Northern blot analysis showed the transgene was expressed in the liver and in all segments of the small intestine (Fig. 1D), tissues known to express the endogenous LXRs. Expression of several known LXR-responsive lipogenic enzyme genes was induced in the transgenic mice as expected (Fig. 1E).

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<th>Table 1. LCA-induced Histological Liver Damage in Mice of Indicated Genotypes</th>
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<td><strong>Females</strong></td>
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* Mice of C57BL/6J background. All other mice are of a C57BL/6J and 129/SvlmJ mixed background. Histological liver damage is defined as the appearance of necrotic foci. WT, wild-type; TG, VP-LXRα transgenic; TO, TO1317; DKO, LXR double knockout.
treated mice. The same pattern of histological changes can be seen in the BDL model (Fig. 2L-R). BDL toxicity was so severe in the LXR DKO females that the experiments had to be terminated 2 days early to prevent the loss of animals. The hepatotoxicity was supported by plasma bile acid accumulation and increased liver enzyme activity (Table 2). Although the phenotypes of the LCA and BDL models agree with each other, the magnitude of alterations in serum chemistry is somewhat different. Moreover, unlike their BDL-treated counterparts, all LXR DKO mice survived the regular 4-day LCA regimen.

**Molecular Mechanisms by Which LXR Regulates Bile Acid and Cholestatic Sensitivity.** Regulation of hepatic drug-metabolizing/-detoxifying enzymes and transporters is known to influence cholestasis. These include phase I Cyp3a, phase II Sult2a, and the membrane transporters bile salt export pump (Bsep), Na\(^+\)/taurocholate cotransport protein (Ntcp), solute carrier family 21A6 (Slc21a6), organic anion-transporting polypeptide 1 (Oatp1), and multidrug resistance–associated protein 4 (Mrp4). Expression of these genes with and without LCA or BDL challenges was profiled by Northern blot analysis and real-time PCR. The most notable change in the untreated transgenic mice was marked up-regulation of Sult2a9 in the livers of both females and males, although females have higher basal expression of this gene, as reported. Interestingly, LCA treatment abolished induction of Sult2a9 in transgenic males, but this induction was sustained in transgenic females (Fig. 3A), providing a plausible explanation for the female-specific protection. Expression of the transgene was sustained in the LCA-treated transgenic males (Fig. 3A), so nonexpression of the transgene cannot account for the loss of Sult2a9 induction in this genotype. Interestingly, expression of the transgene was increased in LCA-treated females (Fig. 3A), the mechanism of which is unknown. Expression of mRNA of the endogenous Fabp gene in the transgenic mice did not change regardless of LCA treatment (data not shown), suggesting Fabp promoter activity is not affected by LCA. Whether induction of transgene expression in LCA-treated females contributed to the sustained Sult2a9 induction is also unclear. In wild-type females, LCA treatment suppressed the basal expression of Sult2a9, which may account for the high cholestatic sensitivity of these mice. The regulation of Sult2a9 was confirmed by real-time PCR and extended to the BDL model (Fig. 3B) and to LXR DKO mice (Fig. 3C). Basal expression of Sult2a9 in the sham-treated LXR DKO females decreased by approximately 60% compared to that in their wild-type counterparts, suggesting LXRs are critical for maintaining the basal expression of this Sult isoform.

LXRs also affect basal and cholestatic responsive expression of bile acid transporters. In vehicle-treated females, expression of the transgene resulted in significant induction of Bsep and suppression of Oatp1. With LCA treatment, the expression of several transporters, including the uptake transporters Ntcp, Slc21a6, and Oatp1, was
significantly suppressed in the wild-type mice but was not in the transgenic mice. The expression of the efflux transporters Bsep and Mrp4 was also significantly higher in the transgenic mice than in the wild-type mice in the presence of LCA (Fig. 3D). The sustained and/or induced expression of transporters in the presence of LCA may have contributed to the LCA resistance in the female transgenic mice. In males, the overall pattern of transporter expression was similar to that observed in females, except that Bsep was suppressed rather than induced in vehicle-treated transgenic mice. In LXR DKO males, both the basal and LCA-responsive expression of all 5 transporters was markedly reduced (Fig. 3E). The combined effects of decreased basal expression of Sult2a9 and bile acid transporters may have contributed to the heightened cholestatic sensitivity in the LXR DKO mice.

Because the VP-LXRα transgene is also targeted to the intestine and intestinal transporters are known to play a role in bile acid homeostasis, we evaluated the expression of several important intestinal bile acid uptake transporters, such as the sodium-dependent bile acid transporter Asbt and organic solute transporter (Ost) α and β.\(^{38,39}\) The transgene had little effect on the expression of these transporters in vehicle-treated mice of either sex. However, with LCA treatment, the expression of all 3 transporters was significantly lower in female transgenic mice than in their wild-type counterparts (Fig. 3F). In males, only the decrease in Asbt was significant. The decreased intestinal transporter expression may lead to decreased reabsorption of bile acid and thus facilitate fecal elimination.

### Activation of LXRα Caused Female-Specific Increase in Urinary Bile Acid Elimination

Consistent with the idea that sulfation increases the solubility and renal secretion of bile acid, the urinary output of bile acids was significantly higher in the female transgenic mice than in their wild-type counterparts throughout the LCA treatment (Fig. 4A). In contrast, there was little difference in the urinary bile acid secretion in the male transgenic mice. These observations are in agreement with the female-specific LCA resistance and lower plasma bile acid levels in the transgenic mice. The increased urinary bile acid output is also consistent with the transgene-dependent induction of Mrp4 (Fig. 3), a cholestatic protective transporter that effluxes sulfonated bile salts to the blood.\(^{35,36}\) Expression of several renal bile acid transporters also was evaluated. As shown in Fig. 4B, the unchallenged transgenic mice had a modest but significant increase in Asbt expression but a decrease in Mrp2 expression. Expression of Mrp4 in females and of all 3 transporters in males was unchanged. Because the transgene was not expressed in the kidney (data not shown), the mechanism for the altered renal transport expression in females is unknown.

### Sult2a9 Is a Transcriptional Target of LXRαs

In addition to its induction in the transgenic mice, Sult2a9 was also induced in wild-type mice treated with TO1317 and 22(\(R\))-hydroxycholesterol (Fig. 5A), and the TO1317 effect was abolished in LXR DKO mice (Fig. 5B). The transgenic mice also exhibited increased hepatic sulfation activity toward LCA and \(p\)-nitrophenol (pNP), two known Sult2a9 substrates,\(^{10}\) in both males (Fig. 5C)
and females (data not shown). To understand the regulatory mechanism, we found that both LXRα/RXR (Fig. 5D) and LXRβ/RXR (Fig. 5E) heterodimers can bind to IR-0 (inverted repeats without a spacing nucleotide) in the Sult2a9 gene promoter, a response element known to bind to CAR,10 PXR,37 and FXR.40 This binding can be efficiently competed with by excess unlabeled wild-type IR-0 or Srebp-1c/DR-4,25 but not by the mutant IR-0.

The chromatin immunoprecipitation (ChIP) assay was used to demonstrate the recruitment of LXRα to the Sult2a9 promoter. In this experiment, the HA-tagged mouse LXRα or the HA vector control plasmid was transfected into the livers of the wild-type mice with and without TO1317 treatment. The ChIP assay was performed with the use of an anti-HA antibody.31 Treatment with TO1317 resulted in the recruitment of HA-LXRα to the
Sult2a9 promoter (Fig. 5F). ChIP on the Srebp-1c gene promoter was included as the positive control. Consistent with the EMSA and ChIP results, the Sult/IR-0 containing synthetic Sult2a9 promoters (Fig. 5G) and natural Sult2a9 promoters (Fig. 5H) were activated by LXR/H9251 in the presence of TO1317. The promoter activations were abolished when the IR-0 site was mutated (Fig. 5G, H). Expression of SULT2A1, the human homolog of Sult2a9, was induced by TO1317 in primary cultures of human hepatocytes (Fig. 5I), suggesting that the human homolog may also be regulated by LXRs.

**Activation of LXR Suppressed Cyp7b1 Expression.**

LXRs have been shown to activate Cyp7a1 and promote cholesterol catabolism to form bile acids. Cyp7a1 regulation was confirmed in our VP-LXRα transgenic mice (data not shown). Interestingly, the expression of Cyp7b1 was significantly suppressed in both the VP-LXRα transgenic mice (Fig. 6A) and the TO1317-treated wild-type males (Fig. 6B). Moreover, the TO1317 effect was abolished in the LXR DKO mice (Fig. 6B). Our preliminary promoter analysis showed that a 3.5-kb mouse Cyp7b1 promoter was suppressed by LXRα in transient transfection and reporter gene assays (data not shown). Combined loss of LXRα and LXRβ, however, had no effect on the basal expression of Cyp7b1 in both males (Fig. 6B) and females (data not shown). We propose that LXR has dual functions of promoting cholesterol catabolism and preventing bile acid toxicity (Fig. 6C and see Discussion section).

**Discussion**

In this study, we showed a novel function of LXRs in the prevention of LCA toxicity and cholestasis, which is associated with the effect of LXRs on the expression of bile acid–detoxifying genes, such as Sult2a9 and membrane transporters. We have also provided evidence suggesting that Sult is a direct transcriptional target of LXRs. Because Sult2a9 is expressed in the liver but not in the intestine, and many of the evaluated transporters have liver-specific expression patterns, it is likely that the liver is primarily responsible for the phenotypes. However, we cannot exclude that intestine and kidney effects may have also contributed to the phenotypes. It is known that the genetic background of the mice may influence their sensitivity to liver damage. Most results shown were derived from mice with a mixed genetic background. Although the phenotypes of the wild-type and transgenic mice were reproducible in the C57BL/6J background, we cannot exclude that background strain differences may have influenced the results.

Phase I CYP3A enzymes also play a role in bile acid detoxification. Unlike PXR, the cholestatic preventive effect of LXR appears to be independent of Cyp3a11 because expression of Cyp3a11 was not induced but rather was suppressed in the transgenic mice (data not shown). Although the association between Sult2a9 induction and cholestatic resistance in the transgenic mice is strong, and Sult2a9-mediated sulfation may be a prerequisite for subsequent transporter-mediated bile acid elimination, we cannot exclude the possibility that regulation of genes
other than Sult2a9 also may have contributed to the phenotypes. Our results also suggest that although LXR plays a role in the basal expression of xenobiotic genes, its effect on the xeno- or endobiotic responsive expression of detoxifying enzymes and transporters may be more indicative of whether this receptor is protective. We recognize that most gene expression has relied on mRNA detection by Northern blot and real-time PCR analyses. The effort to detect Sult2a9 protein expression was limited by the lack of commercially available antibody that recognizes this mouse Sult isoform.

The sex-specific effect of LXR on LCA and cholestatic sensitivity is intriguing. In the transgenic mice, the induction of Sult2a9, seen in untreated mice of both sexes, was maintained in females but was lost in LCA-treated males. We reason that the maintenance of Sult2a9 induction in females was a result of the positive regulation of this Sult isoform by LXR. The mechanism for the loss of Sult2a9 induction in LCA-treated transgenic males remains to be determined. Nevertheless, the loss of induction in males may have contributed to the failure of protection. However, the low basal expression and/or loss of inducibility of Sult2a9 may also have a sex-specific effect on cholestatic sensitivity. Although the female wild-type mice have higher basal expression of Sult2a9, they were more sensitive to LCA gavage than their male counterparts. In contrast, in the presence of LCA, although the transgenic males lost their ability to induce expression of Sult2a9,
they were not as sensitive as the LCA-treated wild-type females, whose Sult2a9 expression was suppressed to a comparable level. A more definitive role for Sult2a9 in LXR-mediated cholestatic resistance may be revealed with the future creation of Sult2a9-null mice. Moreover, because the same Sult/IR-0 site can bind to LXR, CAR, PXR, and FXR, the relative contribution of individual receptors in Sult2a9 regulation in vivo is yet to be determined. The transgene alone had no effect on the basal expression of PXR (Fig. 6A) and FXR (data not shown) in either sex. Whether the differential effect of LXR on intestinal uptake transport expression plays a role in the sexual dimorphism of the transgenic phenotype also remains to be determined. Interestingly, both the male and female LXR DKO mice were more sensitive to cholestasis, presumably because of the decreased basal expression of both Sult2a9 and bile acid transporters. The molecular mechanism for this sex specificity remains to be determined. Sex hormones have been implicated in the sex-specific expression of detoxifying enzymes. Estrogens have been shown to affect cholestatic sensitivity. For example, estradiol-17β-glucuronide, an estradiol glucuronidation product, is known to induce acute but reversible inhibition of bile flow in rodents. The human relevance of the sex-specific cholestatic sensitivity observed in our animal models also remains to be established. Ninety percent of those who have primary biliary cirrhosis, an immune-mediated disorder often associated with cholestatic symptoms, are female (for a review, see ref. 46). CYP7A1 is believed to be regulated by LXRs in mice, but not in humans. SULT2A1, the human homolog of Sult2a9, was induced by TO1317 in human hepatocytes, suggesting this regulation may be conserved in humans. However, because TO1317 also activates PXR, it remains to be determined whether the ligand effect is mediated by LXR or PXR.

We initially used VP-LXRα transgenic mice to demonstrate cholestatic protection and Sult2a9 regulation. Ligand-facilitated target gene identification using wild-type or gene knockout mice has been widely used. We consider the use of the VP-fusion receptor transgene to have unique advantages over drug treatment. This is particularly important because we now know that treatments with receptor pan-agonists such as TO1317 and bile acids may affect multiple receptors. Moreover, ligand treatment may have additional transcriptional consequences independent of the presence of the endogenous receptor. For example, Ueda et al identified 168 differentially expressed tags in response to phenobarbital treatment. However, nearly half these tags were similarly affected in the CAR knockout mice. Bypassing the requirement of ligand treatment, the VP fusion of receptors provides a unique strategy to examine the biological consequences of receptor activation and to identify novel target genes. The utility and practicality of this strategy have been demonstrated in published studies on the in vivo roles of PXR, CAR, PPARδ/β, and PPARα. Although the VP fusion receptor of LXR represents a unique tool to genetically dissect gene regulation by LXR, we recognize that LXR expression and/or activity in VP-LXRα mice may be substantially higher than the endogenous LXR activity in response to endogenous li-
glands in normal physiology. However, the limitation of this genetic model does not exclude the potential for pharmacological modulation of LXR activity to be applied to the detoxification of bile acids. It is also important to note that, although the initial observations were made in VP-LXRx transgenic mice, the effect of LXR on bile acid toxicity and cholestasis has been substantiated with the use of LXR DKO mice as well as LXR ligand-treated wild-type mice.

LXR was previously shown to promote cholesterol catabolism to form bile acids by activating Cyp7a1. In this report, we have shown that Cyp7b1, the oxysterol 7α-hydroxylase, was markedly suppressed by LXR activation. The mechanism of Cyp7b1 suppression by LXR remains to be determined. The human CYP7B1 promoter has been shown to be suppressed by SREBP.57 It would be interesting to know whether activation of Srebp by LXR is responsible for Cyp7b1 suppression in rodents. Nevertheless, Cyp7b1 suppression may lead to an accumulation of oxysterols, which is suggested by the phenotypes in the Cyp7b1-null mice.58 Oxysterols are endogenous LXR agonists. We propose that, at least in rodents, LXRs have evolved to have dual functions to maintain cholesterol homeostasis and, at the same time, to prevent toxicity from bile acids. It is also important to note that, although the initial observations were made in VP-LXRx transgenic mice, the effect of LXR on bile acid toxicity and cholestasis has been substantiated with the use of LXR DKO mice as well as LXR ligand-treated wild-type mice.

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References