

International Union of Pharmacology. LXII. The NR1H and NR1I Receptors: Constitutive Androstane Receptor, Pregnane X Receptor, Farnesoid X Receptor α , Farnesoid X Receptor β , Liver X Receptor α , Liver X Receptor β , and Vitamin D Receptor

DAVID D. MOORE, SHIGEAKI KATO, WEN XIE, DAVID J. MANGELSDORF, DANIEL R. SCHMIDT, RUI XIAO, AND STEVEN A. KLIEWER

Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas (D.D.M., R.X.); The Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan (S.K.); Center for Pharmacogenetics, University of Pittsburgh, Pittsburgh, Pennsylvania (W.X.); Howard Hughes Medical Institute, Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas (D.J.M., D.R.S.); and Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas (D.J.M., D.R.S., S.A.K.)

Abstract—The nuclear receptors of the NR1H and NR1I subgroups include the constitutive androstane receptor, pregnane X receptor, farnesoid X receptors, liver X receptors, and vitamin D receptor. The newly emerging functions of these related receptors are un-

der the control of metabolic pathways, including metabolism of xenobiotics, bile acids, cholesterol, and calcium. This review summarizes results of structural, pharmacologic, and genetic studies of these receptors.

Introduction

The 48 members of the nuclear hormone receptor superfamily can be divided into approximately equal-sized groups of conventional receptors with known ligands and orphan receptors that lack them (Willson and Moore, 2002). The conventional receptors can be further subdivided into comparably sized subgroups of classic receptors, whose ligands were well known before their cDNAs were cloned, and new receptors that are often termed “adopted orphans.” The majority of the new receptors are in the NR1H¹ and NR1I subfamilies.

Address correspondence to: Dr. David D. Moore, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030. E-mail: moore@bcm.tmc.edu

The authors are supported by National Institutes of Health Grants DK067158 (S.A.K.), DK62434 (D.D.M., D.J.M.), ES012479, and CA107011 (W.X.), the Robert A. Welch Foundation (S.A.K. and D.J.M.), and the Howard Hughes Medical Institute (D.J.M.). D.J.M. is an investigator of the Howard Hughes Medical Institute.

¹ Abbreviations: NR, nuclear receptor; RXR, retinoid X receptor; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; FXR, farnesoid X receptor; PXR, pregnane X receptor; CAR, constitutive androstane receptor; VDR, vitamin D receptor; SREBP, sterol regulatory element binding protein; SHP, small heterodimer partner; eCH, 24(S),25-epoxycholesterol; AF, activation function; LBD, ligand-binding domain; 1,25(OH)₂D₃, 1,25-dihydroxyvitamin D₃; CITCO, 6-(4-chlorophenyl)imidazo[2,1-b](1,3)thiazole-5-carbaldehyde-O-3,4-dichlorobenzyl)oxime; TCPOBOP, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene; PCN, pregnenolone-16 α -carbonitrile.

Article, publication date, and citation information can be found at <http://pharmrev.aspetjournals.org>.

doi:10.1124/pr.58.4.6.

An intriguing functional theme has developed for the new receptors as a series of RXR heterodimer partners, first the PPARs and then the LXRs (NR1H2 and NR1H3), FXR (NR1H4), PXR (NR1I2), and CAR (NR1I3), have emerged as key regulators of metabolism (Lu et al., 2001; Willson and Moore, 2002; Francis et al., 2003; Shulman and Mangelsdorf, 2005). The PPARs, receptors for fatty acids and the clinically important antidiabetic thiazolidinediones (PPAR γ) and antihyperlipidemic fibrates (PPAR α), are described elsewhere. A full analysis of the metabolic regulatory roles of the NR1 receptors is outside the scope of this brief review, but the endogenous ligands, primary functions, and sites of expression of the these receptors are summarized in Table 1.

The LXRs are receptors for oxysterols, oxidized cholesterol derivatives that accumulate when cholesterol levels are elevated. LXR α drives cholesterol catabolism in the liver, whereas LXR β activates reverse cholesterol transport from the periphery to the liver (Tontonoz and Mangelsdorf, 2003). The bile acid receptor FXR functions as the major regulator of bile acid homeostasis (Lu et al., 2001). This includes direct activation of pathways that repress bile acid biosynthesis and also induce bile acid export from the liver. The xenobiotic receptors CAR and PXR mediate a chemical defense response to potentially toxic foreign compounds and also toxic endogenous compounds by increasing the capacity of the liver and other tissues to metabolize and clear them (Willson and Kliewer, 2002). The vitamin D receptor (VDR) (NR1I1) is the final member of the NR1I subgroup and the only one

TABLE 1
Endogenous ligands and primary biologic activities of NR1 subgroup receptors

NR1H1 is the insect ecdysone receptor.

Receptor	Major Sites of Expression	Endogenous Ligand/Activator	Primary Function
LXR α (NR1H3)	Liver, intestine, fat, lung, macrophage	Oxysterols	Cholesterol homeostasis
LXR β (NR1H2)	Broadly expressed	Oxysterols	Cholesterol homeostasis
FXR (NR1H4)	Liver, intestine, kidney	Bile acids	Bile acid homeostasis
VDR (NR1I1)	Intestine, thyroid, kidney	1,25(OH) $_2$ D $_3$	Calcium homeostasis
CAR (NR1I2)	Liver, intestine, choroid plexus	Bile acids, ^a bilirubin ^a	Detoxification
PXR (NR1I3)	Liver, intestine	Bile acids	Detoxification

^a Elevated levels of bile acids and bilirubin activate CAR indirectly via induction of nuclear translocation, not by functioning directly as agonists.

that had been characterized before the isolation of its cDNA. VDR is primarily associated with calcium homeostasis, not lipid metabolism, but it has recently been identified as an additional bile acid receptor (Makishima et al., 2002).

It should be emphasized that the NR1H and NR1I receptors do not function in isolation but cooperate to coordinate inter-related metabolic responses and also that each has additional important functions. For example, LXR α activation in liver increases not only cholesterol efflux but also triglyceride production by inducing expression of the lipogenic transcription factor SREBP-1c and its target genes (Joseph et al., 2002a). This is consistent with coordinate release of both cholesterol and triglycerides from the liver in lipoproteins. FXR activation regulates cholesterol and triglyceride metabolism in the opposite direction of LXR α , inhibiting both cholesterol conversion to bile acids and triglyceride production (Lu et al., 2001; Claudel et al., 2003). The LXR and FXR responses share some key target genes, such as cholesterol 7 α -hydroxylase, CYP7A1, and SREBP-1c, but are mechanistically quite distinct, with LXR directly activating both, at least in rodents, whereas FXR acts indirectly via induction of the repressor SHP (NR0B2).

Characterization of these new receptors has also revealed novel links among metabolic pathways and between these pathways and other responses. Thus, recent results show that LXR agonists can have unexpected but potentially beneficial effects on glucose metabolism by both down-regulating expression of gluconeogenic target genes in liver and increasing expression of genes involved in glucose uptake in the periphery (Laffitte et al., 2003). More broadly, LXRs (Joseph et al., 2003) have been found to have anti-inflammatory effects. VDR also has a substantial impact on immune function (DeLuca and Cantorna, 2001), although some of the effects may be secondary consequences of alterations in calcium homeostasis (Mathieu et al., 2001).

Structures

LXR α and β

Structures have been solved for LXR β bound to the natural agonist 24(S),25-epoxycholesterol (eCH) and the

synthetic agonist T0901317 (Hoerer et al., 2003; Williams et al., 2003). The ligands are retained in the pocket primarily through hydrophobic interactions that orient the A ring of eCH toward helix 1 and the D ring and epoxide tail toward the C-terminal end of helix 10. Distinctive features include a long helix 1 and a relatively large ligand-binding pocket ($\sim 800 \text{ \AA}^3$) compared with the classic steroid hormone receptors. Both eCH and T0901317 stabilize the AF-2 helix in the active configuration through a histidine-tryptophan switch that involves hydrogen bonds between the ligand and the His-435 imidazole ring, which in turn makes an edge to face interaction with the Tyr-487 on the inner surface of the AF-2 helix. LBD structures have been determined for LXR α bound to the synthetic agonist T0901317 and GW3987 and are very similar to that of LXR β bound to T0901317 (Svensson et al., 2003). All of the amino acids that line the ligand-binding pocket, including the histidine trigger and the AF-2 tryptophan, are conserved in the two LXR isoforms, so the mechanism of ligand activation seems to be identical.

FXR α

Structures have been solved for FXR α bound to the agonist bile acids 3-deoxychenodeoxycholic acid and 6-ethyl-chenodeoxycholic acid and the synthetic agonist fexaramine (Downes et al., 2003; Mi et al., 2003). Unlike all other steroid-nuclear receptor interactions, the bile acids occupy the $\sim 700 \text{ \AA}^3$ ligand-binding pocket with their A rings facing the AF-2 helix. The A rings activate a histidine-tryptophan switch that stabilizes the AF-2 helix in the active configuration. Agonist-bound FXR α can interact simultaneously with two LXXLL coactivator motifs: one occupies the primary coactivator binding groove, whereas the other binds to an adjacent site in an antiparallel manner. This second binding site enhances the binding affinity of the coactivator.

VDR

The first reported VDR structure was for an LBD derivative of the human receptor (VDR Δ) in which a 50-amino acid segment between helices 1 and 3 was removed, based on secondary structure prediction programs suggesting that this region was disordered (Rochel et al., 2000). VDR Δ was crystallized bound to

1,25(OH)₂D₃. The ligand-binding pocket is ~700 Å³ with vitamin D occupying ~60% of this volume. Vitamin D is oriented with its A ring toward the C terminus of helix 5 and its 25-hydroxyl group close to helices 7 and 11. The interaction between vitamin D and VDR involves both hydrophobic and electrostatic interactions. The AF-2 helix is in the agonist conformation and makes two direct Van der Waals contacts with a vitamin D methyl group. The AF-2 helix position is further stabilized by two polar interactions and several hydrophobic contacts. Recently, the structure of the intact zebrafish LBD was solved in complex with 1,25(OH)₂D₃ and an SRC1 peptide (Ciesielski et al., 2004). The region deleted in VDRΔ was not visible in the electron density map, reflecting its disorder. The binding pocket is identical and makes the same interactions with the ligand seen in the original VDRΔ structure.

CAR

The structure of the CAR LBD has been solved in complex with the agonists 5β-pregnanedione, CITCO, and TCPOBOP and the inverse agonist androstenol (Shan et al., 2004; Suino et al., 2004; Xu et al., 2004). The structures suggest that the constitutive activity of CAR results from several features including a short helix preceding the AF-2 helix, helix 12, which combines with a salt bridge between C terminus of helix 12 and helix 3 to stabilize the AF-2 helix in the active conformation. The CAR LBD is stabilized further by an extended helix 2 that makes contacts with helix 3. The CAR LBD contains a well-formed ligand-binding pocket of ~600 Å³ but lacks the sequence motifs that allow the flexible expansion of the PXR pocket. A single residue difference in the C-terminal region of the mouse versus human CAR is proposed to account for the strong species selectivity for some agonists. The CAR-androstenol complex shows that this inverse agonist sterically interferes with the positioning of the AF-2 helix, preventing CAR from interacting with either coactivators or co-repressors.

PXR

Like VDR, PXR contains an ~60 amino acid region between helix 1 and helix 3. However, in PXR this insert creates an extended five-stranded antiparallel β-sheet and a 13- to 20-amino acid stretch of disordered residues adjacent to the ligand-binding pocket (Watkins et al., 2001). These features generate a ligand-binding pocket with an apo volume of ~1300 Å³ that can adjust its shape to accommodate ligands of distinct size and structure. Twenty-eight amino acid side chains line the pocket of PXR, of which eight are polar and capable of forming hydrogen bonds with ligands. All ligands examined to date, including the cholesterol-lowering drug SR12813, the antibiotic rifampin, and the St. John's wort constituent hyperforin, form a combination of

hydrophobic and polar interactions with PXR ligand-binding pocket residues (Watkins et al., 2001, 2003a,b; Chrencik et al., 2005).

Endogenous Ligands

LXRα and β

The endogenous ligands of the LXRs are a series of oxidized derivatives of cholesterol termed "oxysterols" (Janowski et al., 1996, 1999). Arguments for oxysterols as physiologic agonists for LXRs include their ability to activate the receptors at concentrations comparable with their endogenous levels, the fact that the natural stereoisomers are more active than synthetic variants, and the clear cholesterol-related phenotypes of LXR-null mice. Potential LXR agonists include 24(S),25-epoxycholesterol, which is generated from the cholesterol precursor squalene and is relatively abundant in the liver; 22(R)-hydroxycholesterol, which is a transient intermediate in steroid hormone synthesis; 24(S)-hydroxycholesterol, which is present in the brain; and 27-hydroxycholesterol which is found in macrophages. The two LXR isoforms are very closely related and the endogenous and synthetic agonists characterized to date activate both.

FXRα

It is now well established that FXRα functions as a bile acid receptor. It can be activated by a very wide range of bile acids, including the primary products cholic acid and chenodeoxycholic acid, and their secondary glycine and taurine conjugates (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999). The affinities are not equivalent, however, and it seems likely that distinct bile acids may have somewhat different functional effects on FXRα and also the other NRs that they activate, including VDR, PXR, and CAR. Bile acids are produced from cholesterol via a complex series of enzymatic steps that are organized into two main pathways. The initial and rate-limiting step in the classic or neutral pathway is catalyzed by cholesterol 7α-hydroxylase, CYP7A1. Expression of this key enzyme is powerfully repressed when bile acid levels are too high by a nuclear receptor cascade in which the activated FXRα induces expression of the orphan receptor SHP, which in turn shuts off the activity of another orphan receptor, liver receptor homolog-1, which is essential for CYP7A1 promoter activity (Shulman and Mangelsdorf, 2005).

VDR

In contrast with the recent linkage of the other NR1 receptors with their ligands, the active ligand for the VDR has long been known to be 1,25(OH)₂D₃, and both its production and the mechanisms that control its levels are well defined (DeLuca, 1986). 7-Dehydrocholesterol is a vitamin D precursor that is synthesized from cholesterol and is converted into vitamin D₃ by UV light in the skin. Of course, vitamin D is also a nutrient present in

the diet as both vitamin D₂ (ergocalciferol) from plants and vitamin D₃ (cholecalciferol) from animals. The active hormonal 1,25(OH)₂D₃ is generated by sequential enzymatic steps. The initial step in the liver is dependent on cholesterol 27-hydroxylase, CYP27, which produces 25(OH)D₃. 25-Hydroxyvitamin D-1 α -hydroxylase (1 α -hydroxylase, CYP27B1) generates the active hormonal form in the kidney.

Levels of 1,25(OH)₂D₃ are tightly regulated to maintain calcium homeostasis. VDR plays a central role in this process by both repressing expression of the proximal activator, 1 α -hydroxylase, and inducing expression of the inactivating enzyme CYP24, which produces 1,24,25-trihydroxyvitamin D₃.

Based on their discovery that hydrophobic bile acids are also potent VDR agonists, Makishima et al. (2002) proposed that VDR has an additional function in the protection against the toxic and carcinogenic effects of these endobiotics in the gut.

PXR and CAR

These two related receptors are most commonly considered to respond to a wide range of potentially toxic foreign compounds, or xenobiotics. However, they can also be activated by a number of potentially toxic endogenous compounds (endobiotics). For PXR, bile acids, particularly more hydrophobic and toxic examples, such as lithocholic acid, function as direct agonists (Staudinger et al., 2001; Xie et al., 2001). PXR activation by elevated concentrations of such bile acids results in induction of cytochrome P450 enzymes that hydroxylate them and thereby decrease their toxicity. Murine PXR can also be activated by oxysterol precursors of bile acids (Goodwin et al., 2003).

CAR has both direct and indirect mechanisms of activation based on either conventional agonist binding or a still poorly characterized pathway of induced nuclear translocation (Swales and Negishi, 2004; Qatanani and Moore, 2005). In the latter case, the constitutive transactivation function of CAR results in induction of expression of appropriate target genes. There are no known endogenous agonists that directly activate CAR in physiologic pathways. The first CAR ligands identified were the endogenous androgen metabolites, androstanol and androstenol, which are inverse agonists that can block the constitutive activity of CAR (Forman et al., 1998), but this requires micromolar concentrations that are far above those reached in vivo. CAR can be activated indirectly by high concentrations of both bile acids (Zhang et al., 2004) and bilirubin (Huang et al., 2003). Both of these pathways result in detoxification and induced clearance of these endogenous toxins. For both CAR and PXR, normal physiologic concentrations of these endobiotics cannot effectively activate the receptors. Instead, both function to protect against the consequences of pathologically elevated levels.

Synthetic Ligands and Selective Modulators

LXR α and β

The majority of the studies of the effects of synthetic LXR agonists have been carried out with a single compound, T0901317, which activates both isoforms (Schultz et al., 2000). A number of effects have been reported for T0901317, primarily in mouse models, but the best characterized is an increase in reverse cholesterol transport. In this process, LXR activation in macrophages induces expression of the ATP-binding cassette transporters ABCA1 and G1 and increases transport of cholesterol to the acceptor apolipoprotein A1. The result is inhibition of atherogenesis in mouse models (Tangirala et al., 2002; Levin et al., 2005), and a similar beneficial effect has been described for another LXR pan-agonist, GW3965 (Joseph et al., 2002b).

Although LXR activation has desirable effects on reverse cholesterol transport and other potentially desirable effects, it also increases serum triglycerides in mouse models. This increase is believed to be related to the induction of SREBP-1c in the liver and is also thought to be primarily an LXR α function, raising the possibility that an LXR β -specific agonist could retain many of the beneficial effects without the undesirable triglyceride effect.

FXR α

FXR α responds to bile acids at their physiologic concentrations, in the range of 10 to 100 μ M (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999). This is a much lower affinity than that of classic steroid and thyroid hormone receptors and is associated with decreased specificity, which allows responses to structurally diverse conjugated and unconjugated bile acids. However, it also means that FXR α is a relatively non-specific receptor that can respond to a wide range of additional compounds. It is therefore relatively easy to identify novel modulators of FXR α activity, but the large majority of studies on synthetic FXR α ligands have focused on a single compound, GW4064. This potent FXR α agonist binds with high affinity and apparently good specificity, although its spectrum of effects on other potential targets remains to be established. More limited studies have been carried out with another synthetic agonist, fexaramine, and the synthetic bile acid derivative 6- α -ethyl-chenodeoxycholic acid. Like the LXRs, FXR α is a current target for the development of therapeutic agents. The effects of GW4064 and some other agonists in animal models provide support for potential applications in lowering triglycerides (Maloney et al., 2000) and protecting against liver damage in cholestasis (Liu et al., 2003) and cholesterol gallstone disease (Moschetta et al., 2004).

Consistent with the apparent flexibility of FXR α , other ligands seem to have more selective modulatory effects. The naturally occurring phytosteroids *E*- and

Z-guggulsterone were initially described as FXR α antagonists (Urizar et al., 2002) but may be selective modulators with different effects on different targets (Cui et al., 2003), and the synthetic ligand AGN34 reportedly also functions as an agonist or antagonist in different gene contexts (Dussault et al., 2003).

VDR

1,25(OH) $_2$ D $_3$ itself provides a simple means for VDR activation and is clinically used in treatment of osteoporosis, psoriasis, and secondary hyperparathyroidism. However, the undesirable hypercalcemic effects of higher doses complicate these and a wide range of additional potential therapeutic applications in diverse areas that include immunology and cancer. In marked contrast with the other NR1I receptors CAR and PXR, VDR is a highly specific receptor. Thus, substantial effort has been directed to developing selective, noncalcemic 1,25(OH) $_2$ D $_3$ analogs (Nagpal et al., 2005). Although progress has been made, this problem has not been solved, and clinical use of selective VDR agonists is not yet widespread.

PXR and CAR

These two receptors are unique among the NRs in that they are specifically designed to be nonspecific (Willson and Kliewer, 2002). They are not activated by specific hormones but instead can recognize and respond to an enormous range of relatively small, hydrophobic exogenous compounds. Direct binding of such compounds is the dominant mechanism of activation of PXR, which has a larger and more flexible ligand-binding pocket. PXR can be activated by an unknown fraction of the total number of relatively hydrophobic organic molecules with molecular masses roughly <1000 Da. Although the likelihood that a particular compound is a PXR agonist may be small, the enormity of this chemical space means that the number of such compounds is essentially unlimited. As noted above, CAR has a more restricted ligand-binding pocket and has a much more limited range of direct agonist ligands. However, this restriction is complemented by the indirect translocation mechanism in hepatocytes, which can be triggered by elevated levels of a very wide range of structurally unrelated compounds. These two receptors function together to regulate common target genes to promote xenobiotic detoxification, and their distinct mechanisms of activation are thought to facilitate response to an especially diverse range of xenobiotic stimuli.

Another unusual aspect of ligand binding by PXR and CAR is the high divergence of their ligand-binding domains between species, which leads to quite different ligand profiles. Thus, the antibiotic rifampicin is a potent agonist for human PXR but does not bind the rodent receptor (Lehmann et al., 1998). Similarly, the human CAR agonist CITCO is inactive against murine CAR (Maglich et al., 2003). As expected, "humanized" trans-

genic mouse strains expressing the human PXR or CAR instead of the endogenous receptor respond only to appropriate human agonists (Xie et al., 2000; Huang et al., 2004). The agonists most commonly used in studies of mouse PXR and CAR are PCN and TCPOBOP, respectively. Nuclear translocation of both human and mouse CAR can be induced by the widely used CAR activator phenobarbital.

Antagonists of PXR have not been well characterized. As noted above, however, the first murine CAR ligands identified are inverse agonists (Forman et al., 1998). More recently, the antifungal agent clotrimazole (Moore et al., 2000) and the anti-nausea agent meclizine (Huang et al., 2004) have been identified as human CAR inverse agonists. The functional divergence between species is highlighted by the fact that meclizine is a potent agonist for mouse CAR (Huang et al., 2004).

Genetics

LXR α and β

The genetics of the LXR isoforms in humans remains unexplored, with no hereditary diseases associated with LXR defects and not even any published reports on LXR gene polymorphisms. In mice, however, both the individual and the double LXR gene knockouts have been well studied. Loss of LXR α function results in a defect in cholesterol elimination, with the LXR α ^{-/-} livers accumulating much greater amounts of cholesterol than wild-type livers when the mice were challenged with a high cholesterol diet (Peet et al., 1998). The loss of LXR β does not result in a similar defect, but the combined loss of both isoforms exacerbates the cholesterol elimination defect of the LXR α ^{-/-} mice (Laffitte et al., 2001).

The role of LXR isoforms in reverse cholesterol transport was confirmed in mice with selective loss of both isoforms in macrophages, which was accomplished by transplant of double knockout bone marrow into irradiated hosts. In atherogenic models, animals receiving the mutant cells developed much more atherosclerosis than those transplanted with wild-type cells and were also resistant to the antiatherogenic effect of the LXR agonist T0901317 (Tangirala et al., 2002; Levin et al., 2005). Atherogenesis is associated with inflammation, and similar transplants also revealed direct functions for LXRs in inhibiting expression of proinflammatory genes and activating innate immunity (Joseph et al., 2003, 2004).

The other major role of LXR isoforms is in lipid homeostasis as evidenced by resistance to diet-induced obesity seen in LXR double knockout mice (Kalaany et al., 2005). This phenotype is due to loss of hepatic triglyceride synthesis and the uncoupled burning of dietary fat in the periphery.

FXR α and β

The mouse genome encodes two FXR types, FXR α and FXR β (Otte et al., 2003). Remarkably, human FXR β is a

pseudogene, with numerous nucleotide changes that preclude expression of the intact protein. Essentially nothing is known about the function of mouse FXR β . A further complication is that the conserved FXR α (generally termed FXR) gene encodes four protein products (Zhang et al., 2003). Because of differential promoter usage, FXR α 3 and FXR α 4 have 37 additional N-terminal amino acids that are not present in FXR α 1 and FXR α 2. Because of differential splicing, FXR α 1 and FXR α 3 have an additional four amino acids in the hinge region that are not present in FXR α 2 and FXR α 4. There is evidence for functional differences between these very similar proteins, but their potentially distinct physiologic roles remain to be determined.

As with the LXRs, human genetics of FXR α is in its infancy. However, loss of FXR α function in mice results in profound defects in bile acid metabolism, notably a failure to suppress their production in response to elevated bile acid levels (Sinal et al., 2000). The FXR α -deficient mice also have defects in cholesterol homeostasis (Lambert et al., 2003) and accumulate lipids in the liver and in circulation (Sinal et al., 2000). Recent results indicate that the elevated liver and serum lipids result in insulin resistance (Cariou et al., 2006; Ma et al., 2006; Zhang et al., 2006).

VDR

The vitamin D receptor was the first NR gene for which human mutations were identified (Hughes et al., 1988) and remains the only member of the NR1 subgroup for which clear loss of function mutations have been characterized. Disruption of VDR function due to either VDR gene mutation or the absence of the 1,25(OH) $_2$ D $_3$ ligand leads to rickets (Kato et al., 2002). The disease has a number of manifestations associated with dysregulation of calcium homeostasis, including muscle weakness, growth retardation, and bone deformity, along with secondary hyperparathyroidism and aminoaciduria. Some patients come to medical attention because of convulsions or tetany. VDR mutations are the molecular basis for vitamin D-dependent rickets type II, which is also known as hypocalcemic vitamin D-resistant rickets. Patients with vitamin D-dependent rickets type II have elevated circulating levels of 1,25(OH) $_2$ D $_3$, and because of the receptor defect, physiologic doses of 1,25(OH) $_2$ D $_3$ are unable to resolve the disease in its most severe forms. Less severe forms associated with decreased rather than absent receptor functions can be treated with elevated levels of 1,25(OH) $_2$ D $_3$.

VDR knockout mice have been generated by multiple groups (Li et al., 1997; Yoshizawa et al., 1997; Van Cromphaut et al., 2001; Zeitz et al., 2003). These mice are relatively normal until weaning but show a wide range of phenotypes also observed in vitamin D deficiency. Thus, the knockouts fail to thrive and show alopecia, infertility, hypocalcemia, and severely impaired bone formation. Female mice have uterine hypoplasia

and impaired folliculogenesis. VDR-null animals generally die before 4 months of age. Remarkably, however, the pathologic impact of the loss of VDR function is substantially ameliorated by feeding diets rich in calcium, phosphate, and lactose (Amling et al., 1999), indicating that many of these effects are due to dysregulation of mineral homeostasis.

PXR and CAR

Polymorphisms that may have functional effects have been identified for both PXR and CAR (Koyano et al., 2004; Ikeda et al., 2005; Lamba et al., 2005) but genetic variation in humans has not yet been associated with specific phenotypes. Mouse knockouts for PXR (Xie et al., 2000) or CAR (Wei et al., 2000) show the expected deficits in specific xenobiotic induction of drug metabolism and are also sensitive to elevated levels of endobiotic stress. Neither the single knockouts nor the double knockout exhibit obvious phenotypes under basal circumstances, indicating that these receptors function primarily to respond to chemical stresses.

The induction of drug metabolism is an undesirable drug side effect because the activation of this process by one therapeutic agent can dramatically alter the biologic activity of others that are coadministered. The divergence of the xenobiotic receptor ligand binding domains means that such drug-drug interactions relevant to humans cannot be reliably studied in standard rodent models. As noted above, however, lines of "humanized" mice expressing the human receptors instead of their mouse counterparts can be used to identify such effects (Xie et al., 2000; Zhang et al., 2002).

Tables 2 through 8 summarize the functions, biologic activities, structural properties, and ligands of these receptors.

REFERENCES

- Amling M, Priemel M, Holzmann T, Chapin K, Rueger JM, Baron R, and Demay MB (1999) Rescue of the skeletal phenotype of vitamin D receptor-ablated mice in the setting of normal mineral ion homeostasis: formal histomorphometric and biomechanical analyses. *Endocrinology* **140**:4982–4987.
- Cariou B, van Harmelen K, Duran-Sandoval D, van Dijk TH, Grefhorst A, Abdelkarim M, Caron S, Torpier G, Fruchart JC, Gonzalez FJ, et al. (2006) The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice. *J Biol Chem* **281**:11039–11049.
- Chrencik JE, Orans J, Moore LB, Xue Y, Peng L, Collins JL, Wisely GB, Lambert MH, Kliever SA, and Redinbo MR (2005) Structural disorder in the complex of human pregnane X receptor and the macrolide antibiotic rifampicin. *Mol Endocrinol* **19**:1125–1134.
- Ciesielski F, Rochel N, Mitschler A, Kouzmenko A, and Moras D (2004) Structural investigation of the ligand binding domain of the zebrafish VDR in complexes with 1 α ,25(OH) $_2$ D $_3$ and Gemini: purification, crystallization and preliminary X-ray diffraction analysis. *J Steroid Biochem Mol Biol* **89**:50–55.
- Claudel T, Inoue Y, Barbier O, Duran-Sandoval D, Kosykh V, Fruchart J, Fruchart JC, Gonzalez FJ, and Staels B (2003) Farnesoid X receptor agonists suppress hepatic apolipoprotein CIII expression. *Gastroenterology* **125**:544–555.
- Cui J, Huang L, Zhao A, Lew JL, Yu J, Sahoo S, Meinke PT, Royo I, Pelaez F, and Wright SD (2003) Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. *J Biol Chem* **278**:10214–10220.
- DeLuca HF (1986) The metabolism and functions of vitamin D. *Adv Exp Med Biol* **196**:361–375.
- DeLuca HF and Cantorna MT (2001) Vitamin D: its role and uses in immunology. *FASEB J* **15**:2579–2585.
- Downes M, Verdecia MA, Roecker AJ, Hughes R, Hogenesch JB, Kast-Woelbern HR, Bowman ME, Ferrer JL, Anisfeld AM, Edwards PA, et al. (2003) A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR. *Mol Cell* **11**:1079–10792.
- Dussault I, Beard R, Lin M, Hollister K, Chen J, Xiao JH, Chandraratna R, and

- Forman BM (2003) Identification of gene-selective modulators of the bile acid receptor FXR. *J Biol Chem* **278**:7027–7033.
- Forman BM, Tzamelis I, Choi HS, Chen J, Simha D, Seol W, Evans RM, and Moore DD (1998) Androstane metabolites bind to and deactivate the nuclear receptor CAR- β . *Nature (Lond)* **395**:612–615.
- Francis GA, Fayard E, Picard F, and Auwerx J (2003) Nuclear receptors and the control of metabolism. *Annu Rev Physiol* **65**:261–311.
- Goodwin B, Gauthier KC, Umetani M, Watson MA, Lochansky MI, Collins JL, Leitersdorf E, Mangelsdorf DJ, Kliewer SA, and Repa JJ (2003) Identification of bile acid precursors as endogenous ligands for the nuclear xenobiotic pregnane X receptor. *Proc Natl Acad Sci USA* **100**:223–228.
- Hoerer S, Schmid A, Heckel A, Budzinski RM, and Nar H (2003) Crystal structure of the human liver X receptor β ligand-binding domain in complex with a synthetic agonist. *J Mol Biol* **334**:853–861.
- Huang W, Zhang J, Chua SS, Qatanani M, Han Y, Granata R, and Moore DD (2003) Induction of bilirubin clearance by the constitutive androstane receptor (CAR). *Proc Natl Acad Sci USA* **100**:4156–4161.
- Huang W, Zhang J, Wei P, Schrader WT, and Moore DD (2004) Meclizine is an agonist ligand for mouse constitutive androstane receptor (CAR) and an inverse agonist for human CAR. *Mol Endocrinol* **18**:2402–2408.
- Hughes MR, Malloy PJ, Kieback DG, Kesterson RA, Pike JW, Feldman D, and O'Malley BW (1988) Point mutations in the human vitamin D receptor gene associated with hypocalcemic rickets. *Science (Wash DC)* **242**:1702–1705.
- Ikeda S, Kurose K, Jinno H, Sai K, Ozawa S, Hasegawa R, Komamura K, Kotake T, Morishita H, Kamakura S, et al. (2005) Functional analysis of four naturally occurring variants of human constitutive androstane receptor. *Mol Genet Metab* **86**:314–319.
- Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ, and Mangelsdorf DJ (1999) Structural requirements of ligands for the oxysterol liver X receptors LXR α and LXR β . *Proc Natl Acad Sci USA* **96**:266–271.
- Janowski BA, Willy PJ, Devi TR, Falck JR, and Mangelsdorf DJ (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR- α . *Nature (Lond)* **383**:728–731.
- Joseph SB, Bradley MN, Castrillo A, Bruhn KW, Mak PA, Pei L, Hogenesch J, O'Connell RM, Cheng G, Saez E, et al. (2004) LXR-dependent gene expression is important for macrophage survival and the innate immune response. *Cell* **119**:299–309.
- Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, and Tontonoz P (2003) Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat Med* **9**:213–219.
- Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, and Tontonoz P (2002a) Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem* **277**:11019–11025.
- Joseph SB, McKilligin E, Pei L, Watson MA, Collins AR, Laffitte BA, Chen M, Noh G, Goodman J, Hagger GN, et al. (2002b) Synthetic LXR ligand inhibits the development of atherosclerosis in mice. *Proc Natl Acad Sci USA* **99**:7604–7609.
- Kalaany NY, Gauthier KC, Zavacki AM, Mammen PP, Kitazume T, Peterson JA, Horton JD, Garry DJ, Bianco AC, and Mangelsdorf DJ (2005) LXRs regulate the balance between fat storage and oxidation. *Cell Metab* **1**:231–244.
- Kato S, Yoshizawa T, Kitanaka S, Murayama A, and Takeyama K (2002) Molecular genetics of vitamin D-dependent hereditary rickets. *Horm Res* **57**:73–78.
- Koyano S, Kurose K, Saito Y, Ozawa S, Hasegawa R, Komamura K, Ueno K, Kamakura S, Kitakaze M, Nakajima T, et al. (2004) Functional characterization of four naturally occurring variants of human pregnane X receptor (PXR): one variant causes dramatic loss of both DNA binding activity and the transactivation of the CYP3A4 promoter/enhancer region. *Drug Metab Dispos* **32**:149–154.
- Laffitte BA, Chao LC, Li J, Walczak R, Hummasti S, Joseph SB, Castrillo A, Wilpitz DC, Mangelsdorf DJ, Collins JL, et al. (2003) Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. *Proc Natl Acad Sci USA* **100**:5419–5424.
- Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, and Tontonoz P (2001) LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. *Proc Natl Acad Sci USA* **98**:5071–5076.
- Lamba J, Lamba V, and Schuetz E (2005) Genetic variants of PXR (NR112) and CAR (NR113) and their implications in drug metabolism and pharmacogenetics. *Curr Drug Metab* **6**:369–383.
- Lambert G, Amar MJ, Guo G, Brewer HB Jr, Gonzalez FJ, and Sinal CJ (2003) The farnesoid X-receptor is an essential regulator of cholesterol homeostasis. *J Biol Chem* **278**:2563–2570.
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, and Kliewer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* **102**:1016–1023.
- Levin N, Bischoff ED, Daige CL, Thomas D, Vu CT, Heyman RA, Tangirala RK, and Schulman IG (2005) Macrophage liver X receptor is required for antiatherogenic activity of LXR agonists. *Arterioscler Thromb Vasc Biol* **25**:135–142.
- Li YC, Pirro AE, Amling M, Delling G, Baron R, Bronson R, and Demay MB (1997) Targeted ablation of the vitamin D receptor: an animal model of vitamin D-dependent rickets type II with alopecia. *Proc Natl Acad Sci USA* **94**:9831–9835.
- Liu Y, Binz J, Numerick MJ, Dennis S, Luo G, Desai B, MacKenzie KI, Mansfield TA, Kliewer SA, Goodwin B, et al. (2003) Hepatoprotection by the farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis. *J Clin Invest* **112**:1678–1687.
- Lu TT, Repa JJ, and Mangelsdorf DJ (2001) Orphan nuclear receptors as eLIXRs and FiXeRs of sterol metabolism. *J Biol Chem* **276**:37735–37738.
- Ma K, Saha PK, Chan L, and Moore DD (2006) Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest* **116**:1102–1109.
- Maglich JM, Parks DJ, Moore LB, Collins JL, Goodwin B, Billin AN, Stoltz CA, Kliewer SA, Lambert MH, Willson TM, et al. (2003) Identification of a novel human CAR agonist and its use in the identification of CAR target genes. *J Biol Chem* **278**:2237–2242.
- Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, and Mangelsdorf DJ (2002) Vitamin D receptor as an intestinal bile acid sensor. *Science (Wash DC)* **296**:1313–1316.
- Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, and Shan B (1999) Identification of a nuclear receptor for bile acids. *Science (Wash DC)* **284**:1362–1365.
- Maloney PR, Parks DJ, Haffner CD, Fivush AM, Chandra G, Plunket KD, Creech KL, Moore LB, Wilson JG, Lewis MC, et al. (2000) Identification of a chemical tool for the orphan nuclear receptor FXR. *J Med Chem* **43**:2971–2974.
- Mathieu C, Van Etten E, Gysemans C, Decallonne B, Kato S, Laureys J, Depovere J, Valckx D, Verstuyf A, and Bouillon R (2001) In vitro and in vivo analysis of the immune system of vitamin D receptor knockout mice. *J Bone Miner Res* **16**:2057–2065.
- Mi LZ, Devarakonda S, Harp JM, Han Q, Pellicciari R, Willson TM, Khorasanizadeh S, and Rastinejad F (2003) Structural basis for bile acid binding and activation of the nuclear receptor FXR. *Mol Cell* **11**:1093–1100.
- Moore LB, Parks DJ, Jones SA, Bledsoe RK, Consler TG, Stimmel JB, Goodwin B, Liddle C, Blanchard SG, Willson TM, et al. (2000) Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands. *J Biol Chem* **275**:15122–15127.
- Moschetta A, Bookout AL, and Mangelsdorf DJ (2004) Prevention of cholesterol gallstone disease by FXR agonists in a mouse model. *Nat Med* **10**:1352–1358.
- Nagpal S, Na S, and Rathnachalam R (2005) Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* **26**:662–687.
- Otte K, Kranz H, Kober I, Thompson P, Hoefler M, Haubold B, Voss H, Kaiser C, Albers M, et al. (2003) Identification of farnesoid X receptor beta as a novel mammalian nuclear receptor sensing lanosterol. *Mol Cell Biol* **23**:864–872.
- Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, et al. (1999) Bile acids: natural ligands for an orphan nuclear receptor. *Science (Wash DC)* **284**:1365–1368.
- Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, and Mangelsdorf DJ (1998) Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR α . *Cell* **93**:693–704.
- Qatanani M and Moore DD (2005) CAR, the continuously advancing receptor, in drug metabolism and disease. *Curr Drug Metab* **6**:329–339.
- Rochel N, Wurtz JM, Mitschler A, Klaholz B, and Moras D (2000) The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. *Mol Cell* **5**:173–179.
- Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, et al. (2000) Role of LXRs in control of lipogenesis. *Genes Dev* **14**:2831–2838.
- Shan L, Vincent J, Brunzelle JS, Dussault I, Lin M, Ianculescu I, Sherman MA, Forman BM, and Fernandez EJ (2004) Structure of the murine constitutive androstane receptor complexed to androstenol: a molecular basis for inverse agonism. *Mol Cell* **16**:907–917.
- Shulman AI and Mangelsdorf DJ (2005) Retinoid X receptor heterodimers in the metabolic syndrome. *N Engl J Med* **353**:604–615.
- Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, and Gonzalez FJ (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102**:731–744.
- Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, LaTour A, Liu Y, Klaassen CD, Brown KK, Reinhard J, et al. (2001) The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *Proc Natl Acad Sci USA* **98**:3369–3374.
- Suino K, Peng L, Reynolds R, Li Y, Cha JY, Repa JJ, Kliewer SA, and Xu HE (2004) The nuclear xenobiotic receptor CAR; structural determinants of constitutive activation and heterodimerization. *Mol Cell* **16**:893–905.
- Svensson S, Ostberg T, Jacobsson M, Norstrom C, Stefanos K, Hallen D, Johansson IC, Zachrisson K, Ogg D, and Jendeborg L (2003) Crystal structure of the heterodimeric complex of LXR α and RXR β ligand-binding domains in a fully agonistic conformation. *EMBO (Eur Mol Biol Organ) J* **22**:4625–4633.
- Swales K and Negishi M (2004) CAR, driving into the future. *Mol Endocrinol* **18**:1589–1598.
- Tangirala RK, Bischoff ED, Joseph SB, Wagner BL, Walczak R, Laffitte BA, Daige CL, Thomas D, Heyman RA, Mangelsdorf DJ, et al. (2002) Identification of macrophage liver X receptors as inhibitors of atherosclerosis. *Proc Natl Acad Sci USA* **99**:11896–11901.
- Tontonoz P and Mangelsdorf DJ (2003) Liver X receptor signaling pathways in cardiovascular disease. *Mol Endocrinol* **17**:985–993.
- Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, and Moore DD (2002) A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science (Wash DC)* **296**:1703–1706.
- Van Cromphaut SJ, Dewerchin M, Hoenderop JG, Stockmans I, Van Herck E, Kato S, Bindels RJ, Collen D, Carmeliet P, Bouillon R, et al. (2001) Duodenal calcium absorption in vitamin D receptor-knockout mice: functional and molecular aspects. *Proc Natl Acad Sci USA* **98**:13324–13329.
- Wang H, Chen J, Hollister K, Sowers LC, and Forman BM (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Mol Cell* **3**:543–553.
- Watkins RE, Davis-Searles PR, Lambert MH, and Redinbo MR (2003a) Coactivator binding promotes the specific interaction between ligand and the pregnane X receptor. *J Mol Biol* **331**:815–828.
- Watkins RE, Maglich JM, Moore LB, Wisely GB, Noble SM, Davis-Searles PR, Lambert MH, Kliewer SA, and Redinbo MR (2003b) 2.1 A crystal structure of human PXR in complex with the St. John's wort compound hyperforin. *Biochemistry* **42**:1430–1438.
- Watkins RE, Wisely GB, Moore LB, Collins JL, Lambert MH, Williams SP, Willson TM, Kliewer SA, and Redinbo MR (2001) The human nuclear xenobiotic receptor PXR: structural determinants of directed promiscuity. *Science (Wash DC)* **292**:2329–2333.

- Wei P, Zhang J, Egan-Hafley M, Liang S, and Moore DD (2000) The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature (Lond)* **407**:920–923.
- Williams S, Bledsoe RK, Collins JL, Boggs S, Lambert MH, Miller AB, Moore J, McKee DD, Moore L, Nichols J, et al. (2003) X-ray crystal structure of the liver X receptor β ligand binding domain: regulation by a histidine-tryptophan switch. *J Biol Chem* **278**:27138–27143.
- Willson TM and Kliewer SA (2002) PXR, CAR and drug metabolism. *Nat Rev Drug Discov* **1**:259–266.
- Willson TM and Moore JT (2002) Minireview: genomics versus orphan nuclear receptors—a half-time report. *Mol Endocrinol* **16**:1135–1144.
- Xie W, Barwick JL, Downes M, Blumberg B, Simon CM, Nelson MC, Neuschwander-Tetri BA, Brunt EM, Guzelian PS, and Evans RM (2000) Humanized xenobiotic response in mice expressing nuclear receptor SXR. *Nature (Lond)* **406**:435–439.
- Xie W, Radomska-Pandya A, Shi Y, Simon CM, Nelson MC, Ong ES, Waxman DJ, and Evans RM (2001) An essential role for nuclear receptors SXR/PXR in detoxification of cholestatic bile acids. *Proc Natl Acad Sci USA* **98**:3375–3380.
- Xu RX, Lambert MH, Wisely BB, Warren EN, Weinert EE, Waitt GM, Williams JD, Collins JL, Moore LB, Willson TM, et al. (2004) A structural basis for constitutive activity in the human CAR/RXR α heterodimer. *Mol Cell* **16**:919–928.
- Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, Kawakami T, Arioka K, Sato H, Uchiyama Y, et al. (1997) Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. *Nat Genet* **16**:391–396.
- Zeitl U, Weber K, Soegiarto DW, Wolf E, Balling R, and Erben RG (2003) Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J* **17**:509–511.
- Zhang J, Huang W, Chua SS, Wei P, and Moore DD (2002) Modulation of acetaminophen-induced hepatotoxicity by the xenobiotic receptor CAR. *Science (Wash DC)* **298**:422–424.
- Zhang J, Huang W, Qatanani M, Evans RM, and Moore DD (2004) The constitutive androstane receptor and pregnane X receptor function coordinately to prevent bile acid-induced hepatotoxicity. *J Biol Chem* **279**:49517–49522.
- Zhang Y, Kast-Woelber HR, and Edwards PA (2003) Natural structural variants of the nuclear receptor farnesoid X receptor affect transcriptional activation. *J Biol Chem* **278**:104–110.
- Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, and Edwards PA (2006) Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proc Natl Acad Sci USA* **103**:1006–1011.

TABLE 2
CAR

Receptor Nomenclature	NR1I3
Receptor code	4.10.1.XE:1:I3
Other names	MB67
Molecular information	Hs: 348aa, Q14994, chr. 1q23.3 ¹ Rn: 358aa, Q9QUS1, chr. 13q24 Mm: 358aa, Q3V008, chr. 1 H3 ²
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AGGTCA (DR4, DR5, palindrome) ^{1,3-5}
Partners	
Agonists	TCPOBOP (20 nM),* meclizine (25 nM), CITCO (49 nM), pregnanedione (670 nM) [EC ₅₀] ^{14,6-8}
Antagonists	Androstanol (400 nM), androstenol (400 nM), meclizine (69 nM), clotrimazole (690 nM) [IC ₅₀] ^{6,8,9}
Coactivator	NCOA1, PPARBP, PGC-1 ⁹⁻¹¹
Corepressor	
Biologically important isoforms	CAR1 (Mm): main isoform in mouse ² ; CAR2 (Mm): truncated form, lacking C-terminal sequence ²
Tissue distribution	Liver, low levels in the kidney, intestine, stomach {Hs, Mm} [Northern blot, Q-PCR, immunohistology] ^{1,2,12,13}
Functional assay	Liver hepatomegaly after PB or TCPOBOP treatment (Mm) ^{14,15} ; drug clearance: recovery from zoxazolamine-induced paralysis (Mm) ¹⁵ ; acetaminophen liver toxicity (Mm) ¹⁵
Main target genes	Activated: cytochrome P450 genes {Hs, Mm, Rn}, ¹⁶ <i>Mdm2</i> {Mm}, ¹⁴ <i>MRP2</i> {Mm} ⁵
Mutant phenotype	Impaired drug metabolism induced by specific xenobiotics; resistance to chronic xenobiotic stress-induced liver tumorigenesis {Mm} [knockout] ^{14,15} ; responsive to human CAR ligands {Mm} [human CAR transgenic with CAR knockout background] ¹⁷
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; PPARBP, PPAR-binding protein; Q-PCR, quantitative polymerase chain reaction; PB, phenobarbital.

* Radioligand.

1. Baes M, Gulick T, Choi HS, Martinoli MG, Simha D, and Moore DD (1994) A new orphan member of the nuclear hormone receptor superfamily that interacts with subset of retinoic acid response elements. *Mol Cell Biol* **14**:1544–1552.

2. Choi HS, Chung M, Tzamei I, Simha D, Lee YK, Seol W, and Moore DD (1997) Differential transactivation by two isoforms of the orphan nuclear hormone receptor CAR. *J Biol Chem* **272**:23565–23571.

3. Frank C, Gonzalez MM, Oinonen C, Dunlop TW, and Carlberg C (2003) Characterization of DNA complexes formed by the nuclear receptor constitutive androstane receptor. *J Biol Chem* **278**:43299–43310.

4. Tzamei I, Pissios P, Schuetz EG, and Moore DD (2000) The xenobiotic compound 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene is an agonist ligand for the nuclear receptor CAR. *Mol Cell Biol* **20**:2951–2958.

5. Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliewer S, Willson TM, and Edwards PA (2002) Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* **277**:2908–2915.

6. Huang W, Zhang J, Wei P, Schrader WT, and Moore DD (2004) Meclizine is an agonist ligand for mouse constitutive androstane receptor (CAR) and an inverse agonist for human CAR. *Mol Endocrinol* **18**:2402–2408.

7. Maglich JM, Parks DJ, Moore LB, Collins JL, Goodwin B, Billin AN, Stoltz CA, Kliewer SA, Lambert MH, Willson TM, et al. (2003) Identification of a novel human constitutive androstane receptor (CAR) agonist and its use in the identification of CAR target genes. *J Biol Chem* **278**:17277–17283.

8. Moore LB, Parks DJ, Jones SA, Bledsoe RK, Consler TG, Stimmel JB, Goodwin B, Liddle C, Blanchard SG, Willson TM, et al. (2000) Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands. *J Biol Chem* **275**:15122–15127.

9. Forman BM, Tzamei I, Choi HS, Chen J, Simha D, Seol W, Evans RM, and Moore DD (1998) Androstane metabolites bind to and deactivate the nuclear receptor CAR-β. *Nature* **395**:612–615.

10. Jia Y, Guo GL, Surapureddi S, Sarkar J, Qi C, Guo D, Xia J, Kashireddi P, Yu S, Cho YW, et al. (2005) Transcription coactivator peroxisome proliferator-activated receptor-binding protein/mediator 1 deficiency abrogates acetaminophen hepatotoxicity. *Proc Natl Acad Sci USA* **102**:12531–12536.

11. Shiraki T, Sakai N, Kanaya E, and Jingami H (2003) Activation of orphan nuclear constitutive androstane receptor requires subnuclear targeting by peroxisome proliferator-activated receptor γ coactivator-1α: a possible link between xenobiotic response and nutritional state. *J Biol Chem* **278**:11344–11350.

12. Nishimura M, Naito S, and Yokoi T (2004) Tissue-specific mRNA expression profiles of human nuclear receptor subfamilies. *Drug Metab Pharmacokinet* **19**:135–149.

13. Wei P, Zhang J, Dowhan DH, Han Y, and Moore DD (2002) Specific and overlapping functions of the nuclear hormone receptors CAR and PXR in xenobiotic response. *Pharmacogenomics J* **2**:117–126.

14. Huang W, Zhang J, Washington M, Liu J, Parant JM, Lozano G, and Moore DD (2005) Xenobiotic stress induces hepatomegaly and liver tumors via the nuclear receptor constitutive androstane receptor. *Mol Endocrinol* **19**:1646–1653.

15. Wei P, Zhang J, Egan-Hafley M, Liang S, and Moore DD (2000) The nuclear receptor CAR mediates specific xenobiotic induction of drug metabolism. *Nature (Lond)* **407**:920–923.

16. Honkakoski P, Sueyoshi T, and Negishi M (2003) Drug-activated nuclear receptors CAR and PXR. *Ann Med* **35**:172–182.

17. Zhang J, Huang W, Chua SS, Wei P, and Moore DD (2002) Modulation of acetaminophen-induced hepatotoxicity by the xenobiotic receptor CAR. *Science* **298**:422–424, 2002.

TABLE 3
PXR

Receptor Nomenclature	NR1I2
Receptor code	4.10.1.XE:1:I2
Other names	ONR1, BXR, PAR, PRR, PXR, SAR, PAR1, PAR2, PARq
Molecular information	Hs: 434aa, O75469, chr. 3q12-q13.3 ¹⁻³ Rn: 431aa, Q9R1A7, chr. 11q21 ⁴ Mm: 431aa, O54915, chr. 16 B3 ³
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	AGGTCA (DR-3, ER6, DR-4, ER8, IR0, PBRE) ^{3,5-11}
Partners	PIT1 (physical): cellular localization ¹²
Agonists	Hyperforin (27 nM), SR12813 (200 nM), pregnenolone-16 α -carbonitrile (300 nM), (+)-S20 (0.4 μ M), dexamethasone (0.8 μ M), schisandrins A and B (1.25–2 μ M), rifampicin (0.8–3 μ M), 5 β -cholestane-3 α ,7 α ,12 α -triol (3–5 μ M), taxol (5 μ M) [EC ₅₀] ¹³⁻²⁰ ; lithocholic acid (9–15 μ M)* [IC ₅₀] ¹¹ ; vitamin K ²¹
Antagonists	Ecteinascidin 743 (3 nM)[IC ₅₀] ¹⁸
Coactivators	NCOA1, NRIP1, PGC-1, FOXO1, GRIP1 ^{3,22-25}
Corepressors	SHP, NCOR2 ^{18,26,27}
Biologically important isoforms	PXR1 {Hs}: main isoform ^{1,2,5} ; PXR2 {Hs}: has a different 5'-UTR and encodes a single full-length product with an N-terminal extension not found in other isoforms; PXR3 {Hs}: has a different 5'-UTR and encodes an isoform lacking 39 N-terminal and 37 internal amino acids compared with PXR2—the reading frame is maintained, and it uses a non-AUG translation initiation codon
Tissue distribution	Liver, intestine, kidney, lung {Hs, Mm} [Northern blot, Q-PCR, immunohistology] ^{1-5,13}
Functional assays	Drug clearance by the liver following tribromoethanol-induced anaesthesia or zoxazolamine-induced paralysis {Mm} ²⁸ ; measurement of bile acid liver toxicity after PXR activation {Mm} ^{13,29} ; bilirubin and corticosterone clearance {Mm} ³⁰ ; warfarin clearance from the liver by PXR-activating Chinese herb wu wei zi (<i>Schisandra chinensis</i> Baill) and gan cao (<i>Glycyrrhiza uralensis</i> Fisch) {Rn} ²⁰
Main target genes	Activated: cytochrome P450 genes {Hs, Mm, Rn}, ^{1-3,10,11,18,28,31} <i>OATP2</i> {Mm, Rn}, ³² <i>MRP2</i> {Hs, Mm}, ⁷ <i>UGT1A1</i> {Mm}, ³⁰ <i>SULT2A</i> {Mm}, ⁸ <i>MDR1</i> {Mm}, ⁶ <i>ALAS-1</i> {Mm} ³³
Mutant phenotype	Impaired drug metabolism induced by specific xenobiotics, such as loss of CYP3A11 inducibility in response to PCN and dexamethasone—sensitivity to bile acid-induced toxicity {Mm} [knockout] ^{15,28,29} ; acquired responsiveness to human-specific ligands such as rifampicin, loss of responsiveness to rodent-specific ligands, such as PCN {Mm} [hPXR transgenic mice and hPXR transgenic with PXR knockout background] ²⁸ ; increased bilirubin and cortisone clearance, increased detoxification of bile acids, increased protection against xenobiotic toxicants, such as zoxazolamine and tribromoethanol {Mm} [transgenes of a constitutively activated hPXR into the liver] ²⁸⁻³⁰
Human disease	Breast cancer: levels of PXR mRNA in ER-positive tumors are significantly lower than those observed in ER-negative tumors ³⁴ ; a significant positive correlation was detected between SXR/hPXR labeling index and both the histologic grade and the lymph node status of the carcinomas ³⁵

aa, amino acids; chr., chromosome; HRE, hormone response element; PAR, proliferator-activated receptor; UTR, untranslated region; Q-PCR, quantitative polymerase chain reaction; h, human; ER, estrogen receptor; BXR, benzoate X receptor; PBRE, phenobarbital response element.

* Radioligand.

- Bertilsson G, Heidrich J, Svensson K, Asman M, Jendeborg L, Sydow-Backman M, Ohlsson R, Postlind H, Blomquist P, and Berkenstam A (1998) Identification of a human nuclear receptor defines a new signaling pathway for CYP3A induction. *Proc Natl Acad Sci USA* **95**:12208–12213.
- Blumberg B, Sabbagh W Jr, Juguilon H, Bolado J Jr, van Meter CM, Ong ES and Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev* **12**:3195–3205.
- Kliwer SA, Moore JT, Wade L, Staudinger JL, Watson MA, Jones SA, McKee DD, Oliver BB, Willson TM, Zetterstrom RH, et al. (1998) An orphan nuclear receptor activated by pregnanes defines a novel steroid signaling pathway. *Cell* **92**:73–82.
- Zhang H, LeCluyse E, Liu L, Hu M, Matoney L, Zhu W, and Yan B (1999) Rat pregnane X receptor: molecular cloning, tissue distribution, and xenobiotic regulation. *Arch Biochem Biophys* **368**:14–22.
- Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, and Kliwer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* **102**:1016–1023.
- Geick A, Eichelbaum M, and Burk O (2001) Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. *J Biol Chem* **276**:14581–14587.
- Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliwer S, Willson TM, and Edwards PA (2002) Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* **277**:2908–2915.
- Sonoda J, Xie W, Rosenfeld JM, Barwick JL, Guzelian PS, and Evans RM (2002) Regulation of a xenobiotic sulfonation cascade by nuclear pregnane X receptor (PXR). *Proc Natl Acad Sci USA* **99**:13801–13806.
- Xie W, Barwick JL, Simon CM, Pierce AM, Safe S, Blumberg B, Guzelian PS, and Evans RM (2000) Reciprocal activation of xenobiotic response genes by nuclear receptors SXR/PXR and CAR. *Genes Dev* **14**:3014–3023.
- Goodwin B, Moore L B, Stoltz CM, McKee DD, and Kliwer SA (2001) Regulation of the human CYP2B6 gene by the nuclear pregnane X receptor. *Mol Pharmacol* **60**:427–431.
- Ferguson SS, Chen Y, LeCluyse EL, Negishi M, and Goldstein JA (2005) Human CYP2C8 is transcriptionally regulated by the nuclear receptors constitutive androstane receptor, pregnane X receptor, glucocorticoid receptor, and hepatic nuclear factor 4 α . *Mol Pharmacol* **68**:747–757.
- Gonzalez MM and Carlberg C (2002) Cross-repression, a functional consequence of the physical interaction of non-liganded nuclear receptors and POU domain transcription factors. *J Biol Chem* **277**:18501–18509.
- Jones SA, Moore LB, Shenk JL, Wisely GB, Hamilton GA, McKee DD, Tomkinson NC, LeCluyse EL, Lambert MH, Willson TM, et al. (2000) The pregnane X receptor: a promiscuous xenobiotic receptor that has diverged during evolution. *Mol Endocrinol* **14**:27–39.
- Moore LB, Goodwin B, Jones SA, Wisely GB, Serabjit-Singh CJ, Willson TM, Collins JL, and Kliwer SA (2000) St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc Natl Acad Sci USA* **97**:7500–7502.

15. Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, MacKenzie KI, LaTour A, Liu Y, Klaassen CD, Brown KK, Reinhard J, et al. (2001) The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *Proc Natl Acad Sci USA* **98**:3369–3374.
16. Dussault I, Yoo HD, Lin M, Wang E, Fan M, Batta AK, Salen G, Erickson SK, and Forman BM (2003) Identification of an endogenous ligand that activates pregnane X receptor-mediated sterol clearance. *Proc Natl Acad Sci USA* **100**:833–838.
17. Goodwin B, Gauthier KC, Umetani M, Watson MA, Lochansky MI, Collins JL, Leitersdorf E, Mangelsdorf DJ, Kliewer SA, and Repa JJ (2003) Identification of bile acid precursors as endogenous ligands for the nuclear xenobiotic pregnane X receptor. *Proc Natl Acad Sci USA* **100**:223–228.
18. Synold TW, Dussault I, and Forman BM (2001) The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. *Nat Med* **7**:584–590.
19. Mu Y, Stephenson CRJ, Kendall C, Saini SPS, Toma D, Cai H, Strom S, Day BW, Wipf P, and Xie W (2005) A PXR agonist with unique species-dependent stereoselectivity and its implications in drug development. *Mol Pharmacol* **68**:403–413.
20. Mu Y, Zhang J, Zhang S, Zhou HH, Toma D, Ren S, Huang L, Yaramus M, Baum A, Venkataramanan R, and Xie W (2006) Traditional Chinese medicines wu wei Zi (*Schisandra chinensis* Baill) and gan cao (*Glycyrrhiza uralensis* Fisch) activate pregnane X receptor and increase warfarin clearance in rats. *J Pharmacol Exp Ther* **316**:1369–1377.
21. Tabb MM, Sun A, Zhou C, Grun F, Errandi J, Romero K, Pham H, Inoue S, Mallick S, Lin M, et al. (2003) Vitamin K2 regulation of bone homeostasis is mediated by the steroid and xenobiotic receptor SXR. *J Biol Chem* **278**:43919–43927.
22. Cavailles V, Dauvois S, L'Horset F, Lopez G, Hoare S, Kushner PJ, and Parker MG (1995) Nuclear factor RIP140 modulates transcriptional activation by the estrogen receptor. *EMBO (Eur Mol Biol Organ) J* **14**:3741–3751.
23. Bhalla S, Ozalp C, Fang S, Xiang L, and Kemper JK (2004) Ligand-activated pregnane X receptor interferes with HNF-4 signaling by targeting a common coactivator PGC-1 α : functional implications in hepatic cholesterol and glucose metabolism. *J Biol Chem* **279**:45139–45147.
24. Kodama S, Koike C, Negishi M, and Yamamoto Y (2004) Nuclear receptors CAR and PXR cross talk with FOXO1 to regulate genes that encode drug-metabolizing and gluconeogenic enzymes. *Mol Cell Biol* **24**:7931–7940.
25. Sugatani J, Nishitani S, Yamakawa K, Yoshinari K, Sueyoshi T, Negishi M, and Miwa M (2005) Transcriptional regulation of human UGT1A1 gene expression: activated glucocorticoid receptor enhances constitutive androstane receptor/pregnane X receptor-mediated UDP-glucuronosyltransferase 1A1 regulation with glucocorticoid receptor-interacting protein 1. *Mol Pharmacol* **67**:845–855.
26. Ourlin JC, Lasserre F, Pineau T, Fabre JM, Sa-Cunha A, Maurel P, Vilarejo MJ, and Pascussi JM (2003) The small heterodimer partner interacts with the pregnane X receptor and represses its transcriptional activity. *Mol Endocrinol* **17**:1693–1703.
27. Takeshita A, Taguchi M, Koibuchi N, and Ozawa Y (2002) Putative role of the orphan nuclear receptor SXR (steroid and xenobiotic receptor) in the mechanism of CYP3A4 inhibition by xenobiotics. *J Biol Chem* **277**:32453–32458.
28. Xie W, Barwick JL, Downes M, Blumberg B, Simon CM, Nelson MC, Neuschwander-Tetri BA, Brunt EM, Guzelian PS, and Evans RM (2000) Humanized xenobiotic response in mice expressing nuclear receptor SXR. *Nature (Lond)* **406**:435–439.
29. Xie W, Radomska-Pandya A, Shi Y, Simon CM, Nelson MC, Ong ES, Waxman DJ, and Evans RM (2001) An essential role for nuclear receptors SXR/PXR in detoxification of cholestatic bile acids. *Proc Natl Acad Sci USA* **98**:3375–3380.
30. Xie W, Yeuh MF, Radomska-Pandya A, Saini SP, Negishi Y, Bottroff BS, Cabrera GY, Tukey RH, and Evans RM (2003) Control of steroid, heme, and carcinogen metabolism by nuclear pregnane X receptor and constitutive androstane receptor. *Proc Natl Acad Sci USA* **100**:4150–4155.
31. Chen Y, Kissling G, Negishi M, and Goldstein JA (2005) The nuclear receptors constitutive androstane receptor and pregnane X receptor cross-talk with hepatic nuclear factor 4 α to synergistically activate the human CYP2C9 promoter. *J Pharmacol Exp Ther* **314**:1125–1133.
32. Guo GL, Staudinger J, Ogura K, and Klaassen CD (2002) Induction of rat organic anion transporting polypeptide 2 by pregnenolone-16 α -carbonitrile is via interaction with pregnane X receptor. *Mol Pharmacol* **61**:832–839.
33. Fraser DJ, Zumsteg A, and Meyer UA (2003) Nuclear receptors constitutive androstane receptor and pregnane X receptor activate a drug-responsive enhancer of the murine 5-aminolevulinic acid synthase gene. *J Biol Chem* **278**:39392–39401.
34. Dotzlaw H, Leygue E, Watson P and Murphy LC (1999) The human orphan receptor PXR messenger RNA is expressed in both normal and neoplastic breast tissue. *Clin Cancer Res* **5**:2103–2107.
35. Miki Y, Suzuki T, Kitada K, Yabuki N, Shibuya R, Moriya T, Ishida T, Ohuchi N, Blumberg B, and Sasano H (2006) Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. *Cancer Res* **66**:535–542.

TABLE 4
FXR

Receptor Nomenclature	NR1H4
Receptor code	4.10.1:BA:1:H4
Other names	BAR, HRR1, RIP14
Molecular information	Hs: 486aa, Q96R11, chr. 12q23.1 Rn: 469aa, Q62735, chr. 7q13 ¹ Mm: 488aa, Q60641, chr. 10 C2 ²
DNA binding	
Structure	RXR partner
HRE core sequence	AGTTCAntGAACT
Partners	
Agonists	GW4064 (15 nM), fexaramine (250 nM), 22(R)-hydroxycholesterol (>3 μM), lithocholic acid (5 μM), chenodeoxycholic acid (5 μM), cholic acid (>10 μM), deoxycholic acid (100 μM), [EC ₅₀] ^{3–8} Guggulsterone (10 μM) [IC ₅₀] ⁹
Antagonists	
Coactivator	
Corepressor	
Biologically important isoforms	FXRα 1 {Hs, Mm} ^{2,10,11} ; FXRα 2 {Hs, Mm} ^{2,10,11} ; FXRα 3 {Hs, Mm} ^{2,10,11} ; FXRα 4 {Hs, Mm} ^{2,10,11}
Tissue distribution	Liver, small intestine, colon, kidney, adrenal gland {Mm, Rn} [Northern blot, Q-PCR, in situ hybridization] ^{1,2,11}
Functional assay	
Main target genes	Activated: <i>FGF19</i> {Hs}, ¹² <i>FGF15</i> {Mm}, ¹³ <i>SHP</i> {Hs, Rn, Mm}, ^{14,15} <i>BSEP</i> {Hs, Rn, Mm}, ¹⁶ <i>IBABP</i> {Hs, Mm}, ¹⁷ <i>MDR3</i> {Hs}, ¹⁸ <i>Mdr2</i> {Rn, Mm}, ^{19,20} <i>MRP2</i> {Hs, Rn}, ²¹ <i>OATP1B3</i> {Hs}, ²² <i>BACS</i> {Hs, Rn}, ²³ <i>ApoCII</i> {Hs, Mm}, ²⁴ <i>C3</i> {Hs}, ¹³ <i>PDK4</i> {Hs, Rn, Mm}, ²⁵ <i>PLTP</i> {Hs, Mm}, ⁹ <i>PPARα</i> {Hs}, ²⁶ <i>αA-crystallin</i> {Hs}, ²⁷ fibrinogen {Hs}, ²⁸ kininogen {Hs}, ¹⁸ syndecan-1 {Hs}, ⁴ <i>VPAC1</i> {Hs}, ²⁹ <i>OSTα</i> and <i>OSTβ</i> {Hs} ^{30–32} ; repressed: <i>CYP7A1</i> {Hs, Rn, Mm}, ^{14,15} <i>ABAT</i> {Hs, Mm}, ^{33,34} <i>NTCP</i> {Rn, Mm}, ³⁵ <i>APOAI</i> {Hs}, ^{36,37} <i>ApoCIII</i> {Hs, Mm}, ³⁶ hepatic lipase {Hs}, ³⁸ <i>SREBP-1c</i> {Mm}, ³⁹ <i>VLDLR</i> {Hs, Mm} ⁴⁰
Mutant phenotype	Elevated serum bile acids, cholesterol and triglycerides; increased hepatic cholesterol and triglycerides; proatherogenic serum lipoprotein profile; reduced bile acid pools and reduced fecal bile acid secretion {Mm} [knockout] ^{41,42}
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; Q-PCR, quantitative polymerase chain reaction; BAR, bile acid receptor; SHP, small heterodimer partner; BSEP, bile salt export pump; IBABP, ileal bile acid-binding protein; BACS, bile acid-CoA synthetase; PLTP, phospholipid transfer protein; OST, organic solute transporter; ABAT, apical bile acid transporter; NTCP, sodium/taurocholate cotransporting polypeptide; APOAI, apolipoprotein A-I; VLDLR, very-low-density lipoprotein receptor.

- Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, et al. (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. *Cell* **81**:687–693.
- Seol W, Choi HS, and Moore DD (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol* **9**:72–85.
- Deng R, Yang D, Yang J, and Yan B (2006) Oxysterol 22(R)-hydroxycholesterol induces the expression of the bile salt export pump through nuclear receptor farnesoid X receptor but not liver X receptor. *J Pharmacol Exp Ther* **317**:317–325.
- Downes M, Verdecia MA, Roecker AJ, Hughes R, Hogenesch JB, Kast-Woelbern HR, Bowman ME, Ferrer JL, Anisfeld AM, Edwards PA, et al. (2003) A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR. *Mol Cell* **11**:1079–1092.
- Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, and Shan B (1999) Identification of a nuclear receptor for bile acids. *Science (Wash DC)* **284**:1362–1365.
- Maloney PR, Parks DJ, Haffner CD, Fivush AM, Chandra G, Plunket KD, Creech KL, Moore LB, Wilson JG, Lewis MC, et al. (2000) Identification of a chemical tool for the orphan nuclear receptor FXR. *J Med Chem* **43**:2971–2974.
- Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel JB, Willson TM, Zavacki AM, Moore DD, et al. (1999) Bile acids: natural ligands for an orphan nuclear receptor. *Science (Wash DC)* **284**:1365–1368.
- Wang H, Chen J, Hollister K, Sowers LC, and Forman BM (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Mol Cell* **3**:543–553.
- Urizar NL, Liverman AB, Dodds DT, Silva FV, Ormentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, and Moore DD (2002) A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science (Wash DC)* **296**:1703–1706.
- Huber RM, Murphy K, Miao B, Link JR, Cunningham MR, Rugar MJ, Gunyuzlu PL, Haws TF, Kassam A, Powell F, et al. (2002) Generation of multiple farnesoid-X-receptor isoforms through the use of alternative promoters. *Gene* **290**:35–43.
- Zhang Y, Kast-Woelbern HR, and Edwards PA (2003) Natural structural variants of the nuclear receptor farnesoid X receptor affect transcriptional activation. *J Biol Chem* **278**:104–110.
- Holt JA, Luo G, Billin AN, Bisi J, McNeill YY, Kozarsky KF, Donahee M, Wang da Y, Mansfield TA, Kliewer SA, et al. (2003) Definition of a novel growth factor-dependent signal cascade for the suppression of bile acid biosynthesis. *Genes Dev* **17**:1581–1591.
- Li J, Pircher PC, Schulman IG, and Westin SK (2005) Regulation of complement c3 expression by the bile acid receptor FXR. *J Biol Chem* **280**:7427–7434.
- Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, et al. (2000) A regulatory cascade of the nuclear receptors FXR, SHP-1, and LXR-1 represses bile acid biosynthesis. *Mol Cell* **6**:517–526.
- Lu TT, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J, and Mangelsdorf DJ (2000) Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Mol Cell* **6**:507–515.
- Ananthanarayanan M, Li S, Balasubramanian N, Suchy FJ, and Walsh MJ (2004) Ligand-dependent activation of the farnesoid X-receptor directs arginine methylation of histone H3 by CARM1. *J Biol Chem* **279**:54348–54357.
- Grober J, Zaghini I, Fujii H, Jones SA, Kliewer SA, Willson TM, Ono T, and Besnard P (1999) Identification of a bile acid-responsive element in the human ileal bile acid-binding protein gene: involvement of the farnesoid X receptor/9-cis-retinoic acid receptor heterodimer. *J Biol Chem* **274**:29749–29754.
- Cui J, Huang L, Zhao A, Lew JL, Yu J, Sahoo S, Meinke PT, Royo I, Pelaez F, and Wright SD (2003) Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. *J Biol Chem* **278**:10214–10220.
- Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, Luo G, Jones SA, Goodwin B, Richardson JA, et al. (2005) Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab* **2**:217–225.
- Jaye MC, Krawiec JA, Campobasso N, Smallwood A, Qiu C, Lu Q, Kerrigan JJ, De Los Frailes Alvaro M, Laffitte B, Liu WS, et al. (2005) Discovery of substituted maleimides as liver X receptor agonists and determination of a ligand-bound crystal structure. *J Med Chem* **48**:5419–5422.
- Mak PA, Kast-Woelbern HR, Anisfeld AM, and Edwards PA (2002) Identification of PLTP as an LXR target gene and apoE as an FXR target gene reveals overlapping targets for the two nuclear receptors. *J Lipid Res* **43**:2037–2041.
- Jung D, Podvinec M, Meyer UA, Mangelsdorf DJ, Fried M, Meier PJ, and Kullak-Ublick GA (2002) Human organic anion transporting polypeptide 8 promoter is transactivated by the farnesoid X receptor/bile acid receptor. *Gastroenterology* **122**:1954–1966.
- Pircher PC, Kitto JL, Petrowski ML, Tangirala RK, Bischoff ED, Schulman IG, and Westin SK (2003) Farnesoid X receptor regulates bile acid-amino acid conjugation. *J Biol Chem* **278**:27703–27711.

24. Kast HR, Nguyen CM, Sinal CJ, Jones SA, Laffitte BA, Reue K, Gonzalez FJ, Willson TM, and Edwards PA (2001) Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids. *Mol Endocrinol* **15**:1720–1728.
25. Savkur RS, Thomas JS, Bramlett KS, Gao Y, Michael LF, and Burris TP (2005) Ligand-dependent coactivation of the human bile acid receptor FXR by the peroxisome proliferator-activated receptor γ coactivator-1 α . *J Pharmacol Exp Ther* **312**:170–178.
26. Pineda Torra I, Freedman LP, and Garabedian MJ (2004) Identification of DRIP205 as a coactivator for the farnesoid X receptor. *J Biol Chem* **279**:36184–36191.
27. Lee FY, Kast-Woelbern HR, Chang J, Luo G, Jones SA, Fishbein MC, and Edwards PA (2005) α -Crystallin is a target gene of the farnesoid X-activated receptor in human livers. *J Biol Chem* **280**:31792–31800.
28. Anisfeld AM, Kast-Woelbern HR, Lee H, Zhang Y, Lee FY, and Edwards PA (2005) Activation of the nuclear receptor FXR induces fibrinogen expression: a new role for bile acid signaling. *J Lipid Res* **46**:458–468.
29. Chignard N, Mergely M, Barbu V, Finzi L, Tiret E, Paul A, and Housset C (2005) VPAC1 expression is regulated by FXR agonists in the human gallbladder epithelium. *Hepatology* **42**:549–557.
30. Frankenberg T, Rao A, Chen F, Haywood J, Shneider BL, and Dawson PA (2006) Regulation of the mouse organic solute transporter α - β , Ost α -Ost β , by bile acids. *Am J Physiol* **290**:G912–G922.
31. Landrier JF, Eloranta JJ, Vavricka SR, and Kullak-Ublick GA (2006) The nuclear receptor for bile acids, FXR, transactivates the human organic solute transporter- α and - β genes. *Am J Physiol* **290**:G476–G485.
32. Zollner G, Wagner M, Moustafa T, Fickert P, Silbert D, Gumhold J, Fuchsichler A, Halilbasic E, Denk H, Marschall HU, et al. (2006) Coordinated induction of bile acid detoxification and alternative elimination in mice: role of FXR-regulated organic solute transporter α / β in the adaptive response to bile acids. *Am J Physiol* **290**:G923–G932.
33. Dussault I, Beard R, Lin M, Hollister K, Chen J, Xiao JH, Chandraratna R, and Forman BM (2003) Identification of gene-selective modulators of the bile acid receptor FXR. *J Biol Chem* **278**:7027–7033.
34. Neimark E, Chen F, Li X, and Shneider BL (2004) Bile acid-induced negative feedback regulation of the human ileal bile acid transporter. *Hepatology* **40**:149–156.
35. Denson LA, Sturm E, Echevarria W, Zimmerman TL, Makishima M, Mangelsdorf DJ, and Karpen SJ (2001) The orphan nuclear receptor, SHP, mediates bile acid-induced inhibition of the rat bile acid transporter, NTCP. *Gastroenterology* **121**:140–147.
36. Claudel T, Inoue Y, Barbier O, Duran-Sandoval D, Kosykh V, Fruchart J, Fruchart JC, Gonzalez FJ, and Staels B (2003) Farnesoid X receptor agonists suppress hepatic apolipoprotein CIII expression. *Gastroenterology* **125**:544–555.
37. Srivastava RA, Srivastava N, and Averna M (2000) Dietary cholic acid lowers plasma levels of mouse and human apolipoprotein A-I primarily via a transcriptional mechanism. *Eur J Biochem* **267**:4272–4280.
38. Sirvent A, Verhoeven AJ, Jansen H, Kosykh V, Darteil RJ, Hum DW, Fruchart JC, and Staels B (2004) Farnesoid X receptor represses hepatic lipase gene expression. *J Lipid Res* **45**:2110–2115.
39. Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, and Auwerx J (2004) Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. *J Clin Invest* **113**:1408–1418.
40. Sirvent A, Claudel T, Martin G, Brozek J, Kosykh V, Darteil R, Hum DW, Fruchart JC, and Staels B (2004) The farnesoid X receptor induces very low density lipoprotein receptor gene expression. *FEBS Lett* **566**:173–177.
41. Kok T, Hulzebos CV, Wolters H, Havinga R, Agellon LB, Stellaard F, Shan B, Schwarz M, and Kuipers F (2003) Enterohepatic circulation of bile salts in farnesoid X receptor-deficient mice: efficient intestinal bile salt absorption in the absence of ileal bile acid-binding protein. *J Biol Chem* **278**:41930–41937.
42. Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, and Gonzalez FJ (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell* **102**:731–744.

TABLE 5
FXR β

Receptor Nomenclature	NR1H5
Receptor code	4.10.1:BA:1:H5
Other names	
Molecular information	Hs: Mm: 505aa, Q80ST6, chr. 3 F2.2 ¹
DNA binding	
Structure	Heterodimer
HRE core sequence	AGTTCA N TGAAC T (ER2)
Partners	
Agonists	Lanosterol (1 μ M), vitamin D ₃ (10 μ M), cholesten (10 μ M), desmosterol (10 μ M) [EC ₅₀] ¹
Antagonists	
Coactivator	NCOA1 ¹
Corepressor	
Biologically important isoforms	FXR β -isoform 1 {Mm} ¹ ; FXR β -isoform 2 {Mm}: splice variant in exon 8 ¹ ; FXR β -isoform 3 {Mm}: splice variant in exon 10, lacking exon 11 ¹ ; FXR β -isoform 4 {Mm}: splice variants in exon 8 and 10, lacking exon 11 ¹ ; FXR β -isoform 5 {Mm}: splice variant in exon 3 ¹
Tissue distribution	Ubiquitous {Mm} [RT-PCR] ¹
Functional assay	
Main target genes	
Mutant phenotype	
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; RT-PCR, reverse transcriptase-polymerase chain reaction.

1. Otte K, Kranz H, Kober I, Thompson P, Hoefler M, Haubold B, Rimmel B, Voss H, Kaiser C, Albers M, et al. (2003) Identification of farnesoid X receptor β as a novel mammalian nuclear receptor sensing lanosterol. *Mol Cell Biol* **23**:864–872.

TABLE 6
LXR α

Receptor Nomenclature	NR1H3
Receptor code	4.10.1.OXY:1:H3
Other names	LXR-a, RLD-1
Molecular information	Hs: 447aa, Q13133, chr. 11p11.2 ¹ Rn: 445aa, Q62685, chr. 3q24 ² Mm: 445 aa, Q9Z0Y9, chr. 2 E1 ³
DNA binding	
Structure	RXR partner
HRE core sequence	AGGTCANNNNAGGTCA (DR-4)
Partners	RXR (physical, functional): required for transactivation ¹ ; SHP (physical, functional): represses transactivation ⁴ ; LRH-1 (functional): competence factor ⁵
Agonists	Acetyl-podocarpic dimer (1 nM), T0901317 (50 nM), 27-hydroxycholesterol (85 nM), GW3965 (190 nM), 24(S)-hydroxycholesterol (4 μ M), 24(S),25-epoxycholesterol (4 μ M), paxilline (4 μ M), 22(R)-hydroxycholesterol (5 μ M) [EC ₅₀] ⁶⁻¹² ; F(3)methylAA (13 nM) [K _d] ¹³
Antagonists	
Coactivator	NCOA1, p300, TRRAP, GRIP1/TIF2, PGC1a, PGC1b ¹⁴⁻¹⁸
Corepressor	NCOR1, NCOR2 ¹⁹
Biologically important isoforms	
Tissue distribution	Liver, small intestine, kidney, adipose tissue, macrophages, spleen, adrenal gland {Rn} [Northern blot] ¹
Functional assay	
Main target genes	Activated: ABCA1 {Hs}, ^{20,21} ABCG1 {Hs}, ^{22,23} SREBP1c {Hs}, ²⁴ APOC1/IV/II {Hs}, ²⁵ APOE {Hs}, ²⁶ APOD {Hs}, ²⁷ CETP {Hs}, ⁵ LPL {Hs}, ²⁸ PLTP {Hs}, ^{29,30} Cyp7A {Mm}, ¹⁰ FAS {Hs}, ³¹ GLUT4 {Hs} ³²
Mutant phenotype	Inability to tolerate dietary cholesterol; accumulation of hepatic cholesteryl esters resulting in hepatomegaly; increased serum LDL; decreased serum HDL, VLDL, and triglycerides {Mm} [knockout] ^{11,33,34} ; resistant to obesity when challenged with a diet containing high fat and cholesterol {Mm} [knockout] ³⁵
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; TRRAP, transformation/transcription domain-associated protein; APOC, apolipoprotein C; APOE, apolipoprotein E; APOD, apolipoprotein D; CETP, cholesteryl ester transfer protein; LPL, lipoprotein lipase; PLTP, phospholipid transfer protein; FAS, fatty acid synthase.

1. Willy PJ, Umesono K, Ong ES, Evans RM, Heyman RA, and Mangelsdorf DJ (1995) LXR, a nuclear receptor that defines a distinct retinoid response pathway. *Genes Dev* **9**:1033-1045.
2. Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G, and Pfahl M (1994) A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. *Mol Cell Biol* **14**:7025-7035.
3. Alberti S, Steffensen KR, and Gustafsson JA (2000) Structural characterisation of the mouse nuclear oxysterol receptor genes LXR α and LXR β . *Gene* **243**:93-103.
4. Brendel C, Schoonjans K, Botrugno OA, Treuter E, and Auwerx J (2002) The small heterodimer partner interacts with the liver X receptor α and represses its transcriptional activity. *Mol Endocrinol* **16**:2065-2076.
5. Luo Y and Tall AR (2000) Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. *J Clin Invest* **105**:513-520.
6. Bramlett KS, Houck KA, Borchert KM, Dowless MS, Kulanthaiavel P, Zhang Y, Beyer TP, Schmidt R, Thomas JS, Michael LF, et al. (2003) A natural product ligand of the oxysterol receptor, liver X receptor. *J Pharmacol Exp Ther* **307**:291-296.
7. Collins JL, Fivush AM, Watson MA, Galardi CM, Lewis MC, Moore LB, Parks DJ, Wilson JG, Tippin TK, Binz JG, et al. (2002) Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. *J Med Chem* **45**:1963-1966.
8. Fu X, Menke JG, Chen Y, Zhou G, MacNaull KL, Wright SD, Sparrow CP, and Lund EG (2001) 27-Hydroxycholesterol is an endogenous ligand for liver X receptor in cholesterol-loaded cells. *J Biol Chem* **276**:38378-38387.
9. Janowski BA, Willy PJ, Devi TR, Falck JR, and Mangelsdorf DJ (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR α . *Nature (Lond)* **383**:728-731.
10. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA, and Willson TM (1997) Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J Biol Chem* **272**:3137-3140.
11. Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, et al. (2000) Role of LXRs in control of lipogenesis. *Genes Dev* **14**:2831-2838.
12. Sparrow CP, Baffic J, Lam MH, Lund EG, Adams AD, Fu X, Hayes N, Jones AB, Macnaull KL, Ondeyka J, et al. (2002) A potent synthetic LXR agonist is more effective than cholesterol loading at inducing ABCA1 mRNA and stimulating cholesterol efflux. *J Biol Chem* **277**:10021-10027.
12. Menke JG, Macnaull KL, Hayes NS, Baffic J, Chao YS, Elbrecht A, Kelly LJ, Lam MH, Schmidt A, Sahoo S, et al. (2002) A novel liver X receptor agonist establishes species differences in the regulation of cholesterol 7 α -hydroxylase (CYP7a). *Endocrinology* **143**:2548-2558.
14. Huuskonen J, Fielding PE, and Fielding CJ (2004) Role of p160 coactivator complex in the activation of liver X receptor. *Arterioscler Thromb Vasc Biol* **24**:703-708.
15. Lin J, Yang R, Tarr PT, Wu PH, Handschin C, Li S, Yang W, Pei L, Uldry M, Tontonoz P, et al. (2005) Hyperlipidemic effects of dietary saturated fats mediated through PGC-1 β coactivation of SREBP. *Cell* **120**:261-273.
16. Oberkofler H, Schraml E, Krempler F, and Patsch W (2003) Potentiation of liver X receptor transcriptional activity by peroxisome-proliferator-activated receptor gamma co-activator 1 α . *Biochem J* **371**:89-96.
17. Song C, Hiipakka RA, and Liao S (2001) Auto-oxidized cholesterol sulfates are antagonistic ligands of liver X receptors: implications for the development and treatment of atherosclerosis. *Steroids* **66**:473-479.
18. Unno A, Takada I, Takezawa S, Oishi H, Baba A, Shimizu T, Tokita A, Yanagisawa J, and Kato S (2005) TRRAP as a hepatic coactivator of LXR and FXR function. *Biochem Biophys Res Commun* **327**:933-938.
19. Hu X, Li S, Wu J, Xia C, and Lala DS (2003) Liver X receptors interact with corepressors to regulate gene expression. *Mol Endocrinol* **17**:1019-1026.
20. Costet P, Luo Y, Wang N, and Tall AR. (2000) Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J Biol Chem* **275**:28240-28245.
21. Repa JJ, Turely SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, and Mangelsdorf DJ (2000) Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science* **289**:1524-1529.
22. Kennedy MA, Venkateswaran A, Tarr PT, Xenarios I, Kudoh J, Shimizu N, and Edwards PA (2001) Characterization of the human ABCG1 gene: liver X receptor activates an internal promoter that produces a novel transcript encoding an alternative form of the protein. *J Biol Chem* **276**:39438-39447.
23. Venkateswaran A, Repa JJ, Lobaccaro JM, Bronson A, Mangelsdorf DJ, and Edwards PA (2000) Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages: a transcriptional role for specific oxysterols. *J Biol Chem* **275**:14700-14707.
24. Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL, and Mangelsdorf DJ (2000) Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXR α and LXR β . *Genes Dev* **14**:2819-2830.
25. Mak PA, Laffitte BA, Desrumaux C, Joseph SB, Curtiss LK, Mangelsdorf DJ, Tontonoz P and Edwards PA (2002) Regulated expression of the apolipoprotein E/C-I/C-IV/C-II gene cluster in murine and human macrophages: a critical role for nuclear liver X receptors α and β . *J Biol Chem* **277**:31900-31908.
26. Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, and Tontonoz P (2001) LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. *Proc Natl Acad Sci USA* **98**:507-512.

27. Hummasti S, Laffitte BA, Watson MA, Galardi C, Chao LC, Ramamurthy L, Moore JT, and Tontonoz P (2004) Liver X receptors are regulators of adipocyte gene expression but not differentiation: identification of ApoD as a direct target. *J Lipid Res* **45**:616–625.
28. Zhang Y, Repa JJ, Gauthier K, and Mangelsdorf DJ (2001) Regulation of lipoprotein lipase by the oxysterol receptors, LXR α and LXR β . *J Biol Chem* **276**:43018–43024.
29. Cao G, Beyer TP, Yang XP, Schmidt RJ, Zhang Y, Bensch WR, Kauffman RF, Gao H, Ryan TP, Liang Y, et al. (2002) Phospholipid transfer protein is regulated by liver X receptors in vivo. *J Biol Chem* **277**:39561–39565.
30. Laffitte BA, Joseph SB, Chen M, Castrillo A, Repa J, Wilpitz D, Mangelsdorf D, and Tontonoz P (2003) The phospholipid transfer protein gene is a liver X receptor target expressed by macrophages in atherosclerotic lesions. *Mol Cell Biol* **23**:2182–2191.
31. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, and Tontonoz P (2002) Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem* **277**:11019–11025.
32. Dalen KT, Ulven SM, Bamberg K, Gustafsson JA, and Nebb HI (2003) Expression of the insulin-responsive glucose transporter GLUT4 in adipocytes is dependent on liver X receptor α . *J Biol Chem* **278**:48283–48291.
33. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, and Mangelsdorf DJ (1998) Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR α . *Cell* **93**:693–704.
34. Schuster GU, Parini P, Wang L, Alberti S, Steffensen KR, Hansson GK, Angelin B, and Gustafsson JA (2002) Accumulation of foam cells in liver X receptor-deficient mice. *Circulation* **106**:1147–1153.
35. Kalaany NY, Gauthier KC, Zavacki AM, Mammen PP, Kitazume T, Peterson JA, Horton JD, Garry DJ, Bianco AC, and Mangelsdorf DJ (2005) LXRs regulate the balance between fat storage and oxidation. *Cell Metab* **1**:231–244.

TABLE 7
LXR β

Receptor Nomenclature	NR1H2
Receptor code	4.1.1:OXY:1:H2
Other names	LXR-b, UNR, OR-1, NER, NER1, RIP15
Molecular information	Hs: 461aa, P55055, chr. 19q13.3 ¹ Rn: 446aa, Q62755, chr. 1q22 ² Mm: 446aa, Q60644, chr. 7 B3 ³
DNA binding	
Structure	RXR partner
HRE core sequence	AGGTCANNNNAGGTCA (DR-1, DR-4)
Partners	RXR (physical) ³ ; SHP (physical, functional) ⁴
Agonists	Acetyl-podocarpic dimmer (1 nM), GW3965 (30 nM), T0901317 (50 nM), 27-hydroxycholesterol (71 nM), 22(R)-hydroxycholesterol (3 μ M), 24(S)-hydroxycholesterol (3 μ M), 24(S),25-epoxycholesterol (3 μ M),* paxilline (4 μ M), [EC ₅₀] ⁵⁻¹¹ ; F(3)methylAA (7 nM) [K _d] ¹²
Antagonists	
Coactivator	NCOA1, p300 ¹³
Corepressor	NCOR1, NCOR2 ¹⁴
Biologically important isoforms	
Tissue distribution	Ubiquitous {Rn} [Northern blot] ^{2,15}
Functional assay	
Main target genes	Activated: <i>ABCA1</i> {Hs}, ^{16,17} <i>ABCG1</i> {Hs}, ^{18,19} <i>SREBP1c</i> {Hs}, ²⁰ <i>APOC1/IV/II</i> {Hs}, ²¹ <i>APOE</i> {Hs}, ²² <i>CETP</i> {Hs}, ²³ <i>Cyp7A</i> {Mm}, ⁹ <i>FAS</i> {Hs}, ²⁴ <i>GLUT4</i> {Hs} ²⁵
Mutant phenotype	Alterations in adipocyte growth, glucose homeostasis, and β -cell function (normal resistance to dietary cholesterol, unlike the LXR α knockout) {Mm} [knockout] ^{26,27}
Human disease	

aa, amino acids; chr., chromosome; HRE, hormone response element; UNR, ubiquitously expressed nuclear receptor; APOC, apolipoprotein C; APOE, apolipoprotein E; CETP, cholesteryl ester transfer protein; FAS, fatty acid synthase.

* Radioligand.

- Shinar DM, Endo N, Rutledge SJ, Vogel R, Rodan GA, and Schmidt A (1994) NER, a new member of the gene family encoding the human steroid hormone nuclear receptor. *Gene* **147**:273–276.
- Song C, Kokontis JM, Hiiapakka RA, and Liao S (1994) Ubiquitous receptor: a receptor that modulates gene activation by retinoic acid and thyroid hormone receptors. *Proc Natl Acad Sci USA* **91**:10809–10813.
- Seol W, Choi HS, and Moore DD (1995) Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors. *Mol Endocrinol* **9**:72–85.
- Brendel C, Schoonjans K, Botrugno OA, Treuter E, and Auwerx J (2002) The small heterodimer partner interacts with the liver X receptor α and represses its transcriptional activity. *Mol Endocrinol* **16**:2065–2076.
- Bramlett KS, Houck KA, Borchert KM, Dowless MS, Kulanthaivel P, Zhang Y, Beyer TP, Schmidt R, Thomas JS, Michael LF, et al. (2003) A natural product ligand of the oxysterol receptor, liver X receptor. *J Pharmacol Exp Ther* **307**:291–296.
- Collins JL, Fivush AM, Watson MA, Galardi CM, Lewis MC, Moore LB, Parks DJ, Wilson JG, Tippin TK, Binz JG, et al. (2002) Identification of a nonsteroidal liver X receptor agonist through parallel array synthesis of tertiary amines. *J Med Chem* **45**:1963–1966.
- Fu X, Menke JG, Chen Y, Zhou G, MacNaul KL, Wright SD, Sparrow CP, and Lund EG (2001) 27-Hydroxycholesterol is an endogenous ligand for liver X receptor in cholesterol-loaded cells. *J Biol Chem* **276**:38378–38387.
- Janowski BA, Willy PJ, Devi TR, Falck JR, and Mangelsdorf DJ (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR α . *Nature (Lond)* **383**:728–371.
- Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA, et al. (1997) Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. *J Biol Chem* **272**:3137–3140.
- Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, et al. (2000) Role of LXRs in control of lipogenesis. *Genes Dev* **14**:2831–2838.
- Sparrow CP, Baffic J, Lam MH, Lund EG, Adams AD, Fu X, Hayes N, Jones AB, Macnaul KL, Ondeyka J, et al. (2002) A potent synthetic LXR agonist is more effective than cholesterol loading at inducing ABCA1 mRNA and stimulating cholesterol efflux. *J Biol Chem* **277**:10021–10027.
- Menke JG, Macnaul KL, Hayes NS, Baffic J, Chao YS, Elbrecht A, Kelly LJ, Lam MH, Schmidt A, Sahoo S, et al. (2002) A novel liver X receptor agonist establishes species differences in the regulation of cholesterol 7 α -hydroxylase (CYP7 α). *Endocrinology* **143**:2548–2558.
- Huuskonen J, Fielding PE, and Fielding CJ (2004) Role of p160 coactivator complex in the activation of liver X receptor. *Arterioscler Thromb Vasc Biol* **24**:703–708.
- Hu X, Li S, Wu J, Xia C, and Lala DS (2003) Liver X receptors interact with corepressors to regulate gene expression. *Mol Endocrinol* **17**:1019–1026.
- Lu TT, Repa JJ, and Mangelsdorf DJ (2001) Orphan nuclear receptors as elixirs and fixers of sterol metabolism. *J Biol Chem* **276**:37735–37738.
- Costet P, Luo Y, Wang N, and Tall A (2000) Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J Biol Chem* **275**:28240–28245.
- Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, and Mangelsdorf DJ (2000) Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science (Wash DC)* **289**:1524–1529.
- Kennedy MA, Venkateswaran A, Tarr PT, Xenarios I, Kudo H, Shimizu N, and Edwards PA (2001) Characterization of the human ABCG1 gene: liver X receptor activates an internal promoter that produces a novel transcript encoding an alternative form of the protein. *J Biol Chem* **276**:39438–39447.
- Venkateswaran A, Repa JJ, Lobaccaro JM, Bronson A, Mangelsdorf DJ, and Edwards PA (2000) Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages: a transcriptional role for specific oxysterols. *J Biol Chem* **275**:14700–14707.
- Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL, and Mangelsdorf DJ (2000) Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXR α and LXR β . *Genes Dev* **14**:2819–2830.
- Mak PA, Laffitte BA, Desrumaux C, Joseph SB, Curtiss LK, Mangelsdorf DJ, Tontonoz P, and Edwards PA (2002) Regulated expression of the apolipoprotein E/C-I/C-IV/C-II gene cluster in murine and human macrophages: a critical role for nuclear liver X receptors α and β . *J Biol Chem* **277**:31900–31908.
- Laffitte BA, Repa JJ, Joseph SB, Wilpitz DC, Kast HR, Mangelsdorf DJ, and Tontonoz P (2001) LXRs control lipid-inducible expression of the apolipoprotein E gene in macrophages and adipocytes. *Proc Natl Acad Sci USA* **98**:507–512.
- Luo Y and Tall AR (2000) Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element. *J Clin Invest* **105**:513–520.
- Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, and Tontonoz P (2002) Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem* **277**:11019–11025.
- Dalen KT, Ulven SM, Bamberg K, Gustafsson JA, and Nebb HI (2003) Expression of the insulin-responsive glucose transporter GLUT4 in adipocytes is dependent on liver X receptor α . *J Biol Chem* **278**:48283–48291.
- Alberti S, Schuster G, Parini P, Feltkamp D, Diezfalusy U, Rudling M, Angelin B, Bjorkhem I, Pettersson S, and Gustafsson JA (2001) Hepatic cholesterol metabolism and resistance to dietary cholesterol in LXR β -deficient mice. *J Clin Invest* **107**:565–573.
- Gerin I, Dolinsky VW, Shackman JG, Kennedy RT, Chiang SH, Burant CF, Steffensen KR, Gustafsson JA, and MacDougald OA (2005) LXR β is required for adipocyte growth, glucose homeostasis, and β cell function. *J Biol Chem* **280**:23024–23031.

TABLE 8
VDR

Receptor Nomenclature	NR1I1
Receptor code	
Other names	
Molecular information	Hs: 427aa, P11473, chr. 12q13.11 ¹ Rn: 423aa, P13053, chr. 7q36 ² Mm: 422aa, P48281, chr. 15 F1 ³
DNA binding	
Structure	Heterodimer, RXR partner
HRE core sequence	DR-3
Partners	
Agonists	KH1060 (6.5×10^{-11} M), EB1089 (2.7×10^{-10} M), $1\alpha, 25\text{-(OH)}_2\text{D}_3$ (6.2×10^{-10} M),* 25-OHD ₃ (1.2×10^{-9} M), (23S,25R)- $1\alpha, 25\text{-(OH)}_2\text{D}_3\text{-26,23-lactone}$ (3.1×10^{-8} M) [K_d] ⁴⁻⁷ ; 2MD (1×10^{-10} M) [ED ₅₀] ⁸ ; MC903 (131), TV-02 (66), F ₆ - $1\alpha, 25\text{(OH)}_2\text{D}_3$ (45), Gemini [1R,25-dihydroxy-21-(3-hydroxy-3-methylbutyl)vitamin D ₃] (38), OCT (10) [RCI] ^{5,9-13} ; Ro-26-9228 (6.2×10^{-9} M) [IC ₅₀] ¹⁴ ; LG190178 (1.5×10^{-7} M), 3-keto-LCA (2.9×10^{-7} M), LCA (8×10^{-6} M) [K_i] ^{15,16} ; ED-71, 1α -OHD ₂ , 19-nor- $1\alpha, 25\text{(OH)}_2\text{D}_2$ ^{17,18} TEI-9647 (10), ZK159222 (7) [RCI] ^{19,20}
Antagonists	
Coactivator	
Corepressor	
Biologically important isoforms	
Tissue distribution	
Functional assay	
Main target genes	
Mutant phenotype	Knockout mice exhibit typical rachitic features such as hypocalcemia, hyperparathyroidism, impaired bone formation, uterine hypoplasia, growth retardation, and alopecia after weaning; they also have an impaired insulin secretory capacity [Mm] [knockout ²¹⁻²³]
Human disease	Vitamin D-dependent rickets type II ^{24,25}

aa, amino acids; chr., chromosome; HRE, hormone response element; OCT, 22-oxa- $1\alpha, 25\text{-dihydroxyvitamin-D}_3$; LCA, lithocholic acid; RCI, relative competitive index.
* Radioligand.

- Baker AR, McDonnell DP, Hughes M, Crisp TM, Mangelsdorf DJ, Haussler MR, Pike JW, Shine J, and O'Malley BW (1988) Cloning and expression of full-length cDNA encoding human vitamin D receptor. *Proc Natl Acad Sci USA* **85**:3294-3298.
- Burmester JK, Maeda N, and DeLuca HF (1988) Isolation and expression of rat $1,25\text{-dihydroxyvitamin D}_3$ receptor cDNA. *Proc Natl Acad Sci USA* **85**:1005-1009.
- Kamei Y, Kawada T, Fukuwatari T, Ono T, Kato S, and Sugimoto E (1995) Cloning and sequencing of the gene encoding the mouse vitamin D receptor. *Gene* **152**:281-282.
- Wiberg K, Ljunghall S, Binderup L, and Ljunggren O (1995) Studies on two new vitamin D analogs, EB 1089 and KH 1060: effects on bone resorption and osteoclast recruitment in vitro. *Bone* **17**:391-395.
- Bishop JE, Collins ED, Okamura WH, and Norman AW (1994) Profile of ligand specificity of the vitamin D binding protein for $1\alpha, 25\text{-dihydroxyvitamin D}_3$, and its analogs. *J Bone Miner Res* **9**:1277-1288.
- Erben RG, Soegiarto DW, Weber K, Zeitz U, Lieberherr M, Gniadecki R, Möller G, Adamski J, and Balling R (2002) Deletion of deoxyribonucleic acid binding domain of the vitamin D receptor abrogates genomic and nongenomic functions of vitamin D. *Mol Endocrinol* **16**:1524-1537.
- Shiina Y, Abe E, Miyaura C, Tanaka H, Yamada S, Ohmori M, Nakayama K, Takayama H, Matsunaga I, Nishii Y, et al. (1983) Biological activity of 24,24-difluoro- $1\alpha, 25\text{-dihydroxyvitamin D}_3$ and $1\alpha, 25\text{-dihydroxyvitamin D}_3\text{-26,23-lactone}$ in inducing differentiation of human myeloid leukemia cells. *Arch Biochem Biophys* **220**:90-94.
- Sicinski RR, Prahl JM, Smith CM, and DeLuca HF (1998) New $1\alpha, 25\text{-dihydroxy-19-norvitamin D}_3$ compounds of high biological activity: synthesis and biological evaluation of 2-hydroxymethyl, 2-methyl, and 2-methylene analogues. *J Med Chem* **41**:4662-4674.
- Ikeda M, Takahashi K, Dan A, Koyama K, Kubota K, Tanaka T, and Hayashi M Synthesis and biological evaluations of A-ring isomers of 26,26,26,27,27,27-hexafluoro- $1,25\text{-dihydroxyvitamin D}_3$. *Bioorg Med Chem* **8**:2157-2166.
- Weyts FA, Dhawan P, Zhang X, Bishop JE, Uskokovic MR, Ji Y, Studzinski GP, Norman AW, and Christakos S (2004) Novel Gemini analogs of $1\alpha, 25\text{-dihydroxyvitamin D}_3$ with enhanced transcriptional activity. *Biochem Pharmacol* **67**:1327-1336.
- Abe J, Takita Y, Nakano T, Miyaura C, Suda T, and Nishii Y (1989) A synthetic analogue of vitamin D, 22-oxa- $1\alpha, 25\text{-dihydroxyvitamin D}_3$, is a potent modulator of in vivo immunoregulating activity without inducing hypercalcemia in mice. *Endocrinology* **124**:2645-2647.
- Sato K, Nishii Y, Woodiel FN, and Raisz LG (1993) Effects of two new vitamin D₃ derivatives, 22-oxa- $1\alpha, 25\text{-dihydroxyvitamin-D}_3$ (OCT) and 2β -(3-hydroxypropoxy)- $1\alpha, 25\text{-dihydroxyvitamin-D}_3$ (ED-71), on bone metabolism in organ culture. *Bone* **14**:47-51.
- Okano T, Tsugawa N, Masuda S, Takeuchi A, Kobayashi T, and Nishii Y (1989) Protein-binding properties of 22-oxa- $1\alpha, 25\text{-dihydroxyvitamin D}$, a synthetic analogue of $1\alpha, 25\text{-dihydroxyvitamin D}$. *J Nutr Sci Vitaminol (Tokyo)* **35**:529-533.
- Peleg S, Uskokovic M, Ahene A, Vickery B, and Avnur Z (2002) Cellular and molecular events associated with the bone-protecting activity of the noncalcemic vitamin D analog Ro-26-9228 in osteopenic rats. *Endocrinology* **143**:1625-1636.
- Boehm MF, Fitzgerald P, Zou A, Elgort MG, Bischoff ED, Mere L, Mais DE, Bissonnette RP, Heyman RA, Nadzan AM, et al. (2002) Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than $1,25\text{-dihydroxyvitamin D}_3$. *Chem Biol* **6**:265-275.
- Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, and Mangelsdorf DJ (2002) Vitamin D receptor as an intestinal bile acid sensor. *Science (Wash DC)* **296**:1313-1316.
- Miyamoto K, Murayama E, Ochi K, Watanabe H, and Kubodera N (1993) Synthetic studies of vitamin D analogues. XIV. Synthesis and calcium regulating activity of vitamin D₃ analogues bearing a hydroxyalkoxy group at the 2 β -position. *Chem Pharm Bull (Tokyo)* **41**:1111-1113.
- Okano T, Tsugawa N, Masuda S, Takeuchi A, Kobayashi T, Takita Y, and Nishii Y (1989) Regulatory activities of 2 β -(3-hydroxypropoxy)- $1\alpha, 25\text{-dihydroxyvitamin D}_3$, a novel synthetic vitamin D₃ derivative, on calcium metabolism. *Biochem Biophys Res Commun* **163**:1444-1449.
- Miura D, Manabe K, Ozono K, Saito M, Gao Q, Norman AW, and Ishizuka S (1999) Antagonistic action of novel $1\alpha, 25\text{-dihydroxyvitamin D}_3\text{-26, 23-lactone}$ analogs on differentiation of human leukemia cells (HL-60) induced by $1\alpha, 25\text{-dihydroxyvitamin D}_3$. *J Biol Chem* **274**:16392-16399.
- Fujishima T, Kojima Y, Azumaya I, Kittaka A, and Takayama H (2003) Design and synthesis of potent vitamin D receptor antagonists with A-ring modifications: remarkable effects of 2 α -methyl introduction on antagonistic activity. *Bioorg Med Chem* **11**:3621-3631.
- Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, Kawakami T, Arioka K, Sato H, Uchiyama Y, et al. (1997) Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. *Nat Genet* **16**:391-396.
- Li YC, Pirro AE, Amling M, Dellling G, Baron R, Bronson R, and Demay MB (1997) Targeted ablation of the vitamin D receptor: an animal model of vitamin D-dependent rickets type II with alopecia. *Proc Natl Acad Sci USA* **94**:9831-9835.
- Zeitz U, Weber K, Soegiarto DW, Wolf E, Baling R, and Erben RG (2003) Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. *FASEB J* **17**:509-511.
- Hughes MR, Malloy PJ, Kieback DG, Kesterson RA, Pike JW, Feldman D, and O'Malley BW (1988) Point mutations in the human vitamin D receptor associated with hypocalcemic rickets. *Science (Wash DC)* **242**:1702-1705.
- Malloy PJ, Pike JW, and Feldman D (1999) The vitamin D receptor and the syndrome of hereditary $1,25\text{-dihydroxyvitamin D}$ -resistant rickets. *Endocr Rev* **20**:156-188.