MINIREVIEW

The Emerging Role of Nuclear Receptor RORα and Its Crosstalk with LXR in Xeno- and Endobiotic Gene Regulation

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Retinoid-related orphan receptors (RORs), including the α, β and γ isoforms (NR1F1–3), are orphan nuclear receptors that have been implicated in tissue development, immune responses, and circadian rhythm. Although RORα and RORγ have been shown to be expressed in the liver, the hepatic function of these two RORs remains unknown. We have recently shown that loss of RORα and/or RORγ can positively or negatively influence the expression of multiple Phase I and Phase II drug metabolizing enzymes and transporters in the liver. Among ROR responsive genes, we identified oxysterol 7α-hydroxylase (Cyp7b1), which plays a critical role in the homeostasis of cholesterol, as a RORα target gene. We showed that RORα is both necessary and sufficient for Cyp7b1 activation. Studies of mice deficient of RORα or liver X receptors (LXRs) revealed an interesting and potentially important functional crosstalk between RORα and LXR. The respective activation of LXR target genes and ROR target genes in RORα null mice and LXR null mice led to our hypothesis that these two receptors are mutually suppressive *in vivo*. LXRs have been shown to regulate a battery of metabolic genes. We conclude that RORs participate in the xeno- and endobiotic regulatory network by regulating gene expression directly or through crosstalk with LXR, which may have broad implications in metabolic homeostasis. Exp Biol Med 233:1191–1201, 2008

Key words: nuclear receptor; gene regulation; metabolism

Introduction

Nuclear steroid hormone receptors were first cloned in the middle 1980s, and they have since been established as ligand-dependent transcriptional factors. This subsequently led to the identification of many so-called "orphan nuclear receptors" based on their homology to the traditional steroid hormone receptors (1). Genomic studies have indicated that there are 48 and 50 nuclear receptor genes in rodents and humans, respectively. Most, if not all, nuclear receptors contain a N-terminal DNA binding domain (DBD) and a C-terminal ligand binding domain (LBD) (Fig. 1A). Nuclear receptors often regulate gene expression by binding, as homodimers, retinoid X receptor (RXR) heterodimers or as monomers, to their responsive elements present in target gene promoters (Fig. 1B).

The nuclear receptor superfamily has been shown to be involved in numerous biological processes, ranging from development to reproduction, metabolism, cell proliferation, differentiation and apoptosis (2). Due to their physiological significance, many of the nuclear receptors have been explored as therapeutic targets for various diseases, a development that has been facilitated by major advances in the identification and characterization of receptor agonists and antagonists. Although the ligands of some nuclear receptors remain unknown and some receptors might be true "orphan receptors", the function of these orphan receptors

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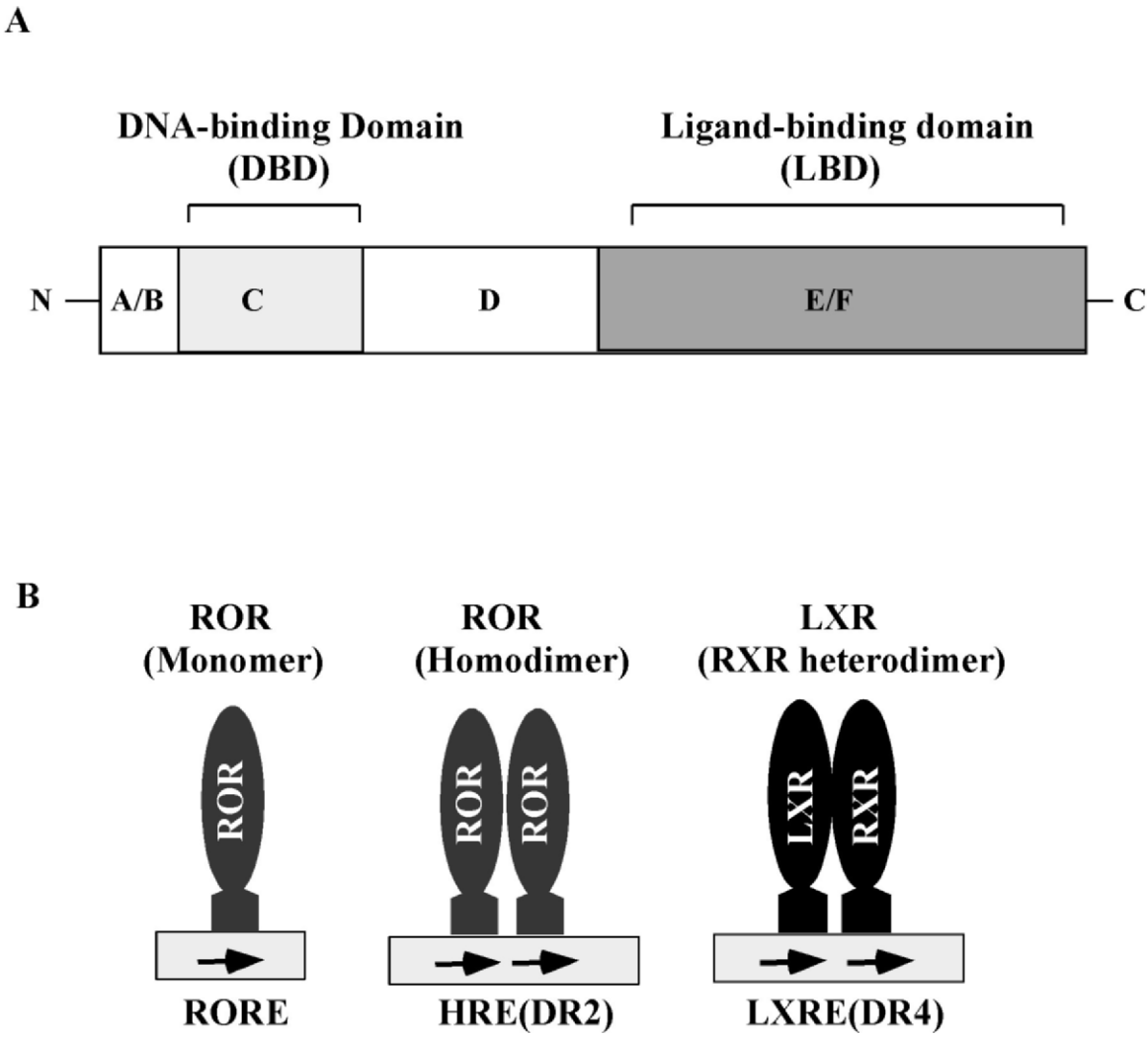

Figure 1. General signaling of nuclear receptors. (A) General domain structure of a nuclear receptor. (B) Nuclear receptors can regulate gene expression by binding to the hormone response element (HRE) as homodimers, RXR heterodimers, or monomers. ROR and LXR are used as examples. RORE, ROR response element.

can still be revealed by the creation and characterization of gene knockout mice. This review will focus on the novel function of the orphan receptor RORα in xeno- and endobiotic gene regulation.

Orphan Nuclear Receptor RORα Retinoid-related orphan receptors (RORs) are members of the nuclear receptors that include three isoforms: RORα (NR1F1), RORβ (NR1F2) and RORγ (NR1F3) (3). Each ROR isoform has a distinct pattern of tissue distribution (4). RORα is expressed in many tissues, including cerebellar Purkinje cells, liver, thymus, skeletal muscle, skin, lung and kidney (5, 6). RORβ exhibits a more restricted pattern of expression and is expressed in several regions of the central nervous system, retina, and pineal gland. RORγ is most highly expressed in thymus but also detectable in many other tissues, including liver, kidney and muscle (3, 7, 8). The functional ligands of RORs remain elusive. It was reported that cholesterol and its sulfonated derivatives might function as RORα ligands (9). Other ligands suggested to bind to RORα are melatonin (10) and thiazolidinediones (11). To our knowledge, none of these have been established as functional ligands for RORα. Evidence has been provided indicating that certain retinoids, including all-trans retinoic acid, can function as partial antagonists for RORβ and RORγ (12).

RORs bind either as monomers to the ROR-response elements (RORE) within the target gene promoter regions. ROREs are composed of 6-bp A/T-rich region immediately preceding a consensus AGGTCA motif (8, 13). However, RORα has been demonstrated to be able to bind as a homodimer to direct repeats of the consensus AGGTCA motif separated by two base pairs (DR2) (14). Like many other nuclear receptors, RORs are composed of a N-terminal DBD and a LBD located at the C-terminal. ROR isoforms

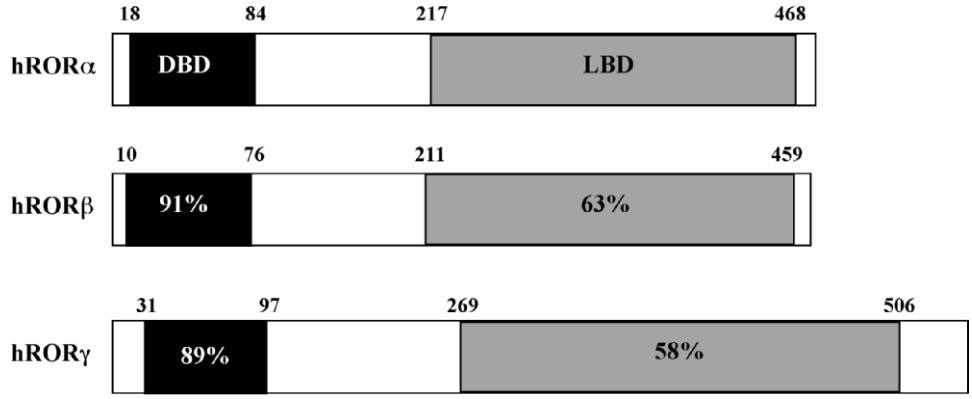

Figure 2. Comparison of the homology among three ROR isoforms. Percentages indicate amino acid identities in the DNA-binding domain (DBD) and ligand-binding domain (LBD) compared to RORα. The positions of amino acids are also labeled.

share a highly conserved DBD but they are more diverse in their LBDs (Fig. 2). The transcriptional activities of RORs are negatively and positively regulated through the recruitment of nuclear receptor co-repressors and co-activators, respectively. It has been reported that co-repressors (N-CoR, RIP140 and SMRT) and co-activator (GRIP, PBP, SRC1, CBP and PGC1α) can interact with RORα (14–18). It was proposed that cell-specific interactions with specific co-regulators may contribute to the molecular mechanism for distinct physiological functions of RORα (14).

Characterizations of ROR null mice have revealed a number of important physiological functions of RORs. RORα$^{-/-}$ mice show an ataxic phenotype similar to that observed in the Staggerer (sg/sg) mutant mice, which carry a natural deletion in the LBD, causing a frame shift and a truncated RORα protein (5, 6). The RORα$^{sg/sg}$ mice exhibit a variety of phenotypes, including, cerebellar degeneration, abnormal circadian behavior, vascular dysfunction, muscular irregularities, osteoporosis, atherosclerosis and altered immune responses, as summarized in Table 1 (19–25). The atherosclerotic phenotype in the RORα$^{sg/sg}$ mice was associated with a marked hypo-α-lipoproteinemia due to a decreased expression of ApoAI, a transcriptional target of RORα in the intestine (26). In the vascular system, RORα is involved in postischemic angiogenesis and differentiation and contractile function of smooth muscle cells (27). The RORα$^{sg/sg}$ mice exhibit more extensive angiogenesis, leading to an increase of inflammatory cytokine production and eNOS protein level (28), suggesting RORα as a potent negative regulator of ischemia-induced angiogenesis. Inflammation is associated with both atherosclerosis and angiogenesis. The RORα$^{sg/sg}$ mice also have a delayed lymphocyte development, which may partially be accounted for by RORα-mediated transcriptional activation of IκBα, the inhibitor of NF-kB (29) and RORα$^{sg/sg}$ mice are less sensitive to autoimmune and allergy-induced inflammation (20, 35). We recognize that the effect of RORα on inflammation is a complex issue. RORα has been shown to

Table 1. Summary of Known Functions of RORα

Physiological function		References
Inflammation:	Anti-inflammation (Suppression of NF-κB activity by activating IκBα)	20, 21, 29
Cerebellar development:	Neuroprotective role during development and aging (Regulating the Purkinje cell protein-2 (Pcp2) genes)	14, 19
Circadian rhythm:	A crucial component of the molecular circadian clock (Regulating the clock gene Bmal1)	22
Angiogenesis:	Inhibit ischemia-induced angiogenesis	27, 28
Skeletal muscle differentiation:	A positive regulator of muscular development (Regulating MyoD and p300)	24
Osteoporosis:	Protection against osteoporosis (Regulating bone sialoglycoprotein and osteocalcin)	23
Smooth muscle differentiation:	Essential role in the differentiation and contractile function of smooth muscle cells	25
Metabolic homeostasis:	Regulation of triglyceride and lipoprotein metabolism and protection against atherosclerosis (Regulating ApoAI and ApoCIII)	26, 85
Drug metabolism:	Positive and negative regulation of Phase I and Phase II drug metabolizing enzymes	58, 61

enhance IkBα expression thereby inhibiting NF-kB (*in vitro* studies), whereas *in vivo* RORα$^{sg/sg}$ mice are less sensitive to autoimmune and allergy-induced inflammation. This may in part be in part related to changes in thymocyte populations.

Among other ROR isoforms, RORβ is believed to be involved in the processing of sensory information, as RORβ$^{-/-}$ mice showed significant phenotypes in circadian behaviors and retinal degeneration (30). RORβ has been reported to regulate the blue opsin gene in cone photoreceptor development (31). RORγ$^{-/-}$ mice lacked all lymph nodes and Peyer's patches, and contained reduced number of thymocytes (17, 32, 33) suggesting that RORγ plays an essential role in lymphoid organogenesis and thymopoiesis. Recent studies have demonstrated an important role for both RORα and RORγ in the differentiation of naïve T cells into Th17 cells (34, 35).

Nuclear Receptors and Xeno- and Endobiotic Metabolism The metabolic homeostasis of foreign chemicals (xenobiotics, including drugs) and endogenous compounds (endobiotics) is essential for the survival of mammals. Xenobiotic metabolism is facilitated by the Phase I and Phase II drug metabolizing enzymes, as well as drug transporters (36, 37). The Phase I reactions include oxidation, reduction, hydrolysis and hydration. The cytochrome P450 (CYP) enzymes play a critical and dominating role in Phase I reactions. Phase II metabolism includes sulfation (mediated by sulfotransferases or SULTs), glucuronidation (mediated by UDP-glucoronosyltransferases or UGTs), or glutathione conjugation (mediated by glutathione *S*-transferases or GSTs). Products generated by Phase I metabolism are generally more polar and can be better substrates for Phase II conjugations. The conjugation by Phase II enzymes results in increased polarity and solubility of xenobiotics and promotes xenobiotic excretion. Drug transporters, which are not the focus of this review, are responsible for the uptake and efflux of parent or biotransformed xenobiotics.

Although the structure and function of Phase I and Phase II enzymes have been subjects of extensive studies for several decades and it has been known that the expression of many drug metabolizing enzymes is inducible, little is known about the transcriptional regulators that control the production of these enzymes. In the late 90s, the role of nuclear receptors in the transcriptional regulation of drug metabolizing enzymes began to emerge, which was highlighted by the cloning of the xenobiotic receptor pregnane X receptor (PXR) (38–41) and characterization of the constitutive androstane receptor (CAR) as another important xenobiotic nuclear receptor (42, 43). In the past 10 years, considerable advances have been made in establishing nuclear receptors as master regulators of the expression of Phase I and Phase II drug metabolizing enzymes and transporters (Fig. 3) (36, 37).

In addition to PXR and CAR, several other nuclear receptors, such as vitamin D receptor (VDR), hepatic nuclear factor 4α (HNF4α), peroxisome proliferator-activated receptors (PPARs) and farnesoid X receptor (FXR), have also been implicated in the regulation of xenobiotic enzymes and transporters (44–47). More recently, results from our lab have shown that the liver X receptor (LXR), a previously known sterol sensor, can also regulate the expression of Phase II sulfotransferases, such as the bile acid detoxifying hydroxysteroid sulfotransferase Sult2a9/2a1 (48) and the estrogen sulfotransferase (Est/Sult1e1) (49).

It is conceivable that nuclear receptor-mediated regulation of drug metabolizing enzymes has implications in drug metabolism, drug toxicity and drug-drug interactions. Interestingly, the same metabolic enzyme and transporter systems are responsible for the metabolism of numerous endobiotics, such as steroid hormones, bile acids and lipid metabolites (50). Consistent with this notion, studies have implicated nuclear receptor-mediated enzyme and transporter regulation in many pathophysiological conditions by impacting the homeostasis of endobiotics. Examples include the role of PXR and CAR in hyperbilirubinemia (51–53) and cholestasis (41, 54–57), and the role of LXR in cholestasis (48) and estrogen homeostasis (49).

A Potential Role of RORs in Xeno- and Endobiotic Gene Regulation Both RORα and RORγ have been shown to be expressed in the liver (58). However, the hepatic function of these two receptors remains unknown until recently. To determine the role of RORα in the liver, we examined the gene expression profiles in livers of the RORα$^{sg/sg}$, RORγ null and RORα$^{sg/sg}$/RORγ double knockout (DKO) mice by microarray analysis (58). To our surprise, the microarray results suggested that loss of RORα and/or RORγ had a major effect on the expression of multiple drug metabolizing enzymes and transporters (58). The effects of loss of RORα are summarized in Table 2. In the ROR DKO mice, major effects on gene regulation include the activation of Cyp2b9/10, Cyp4a10 and Cyp4a14, Sult1e1/Est and Sult2a9/2a1, and suppression of Cyp7b1, Cyp8b1, Hsd3b4, and Hsd3b5 (58). Interestingly, some genes are selectively controlled by RORα or RORγ, whereas some other genes are affected by both receptors. For example, Hsd3b4 and Hsd3b5, two enzymes involved in the deactivation of steroid hormone, were decreased in both RORα$^{sg/sg}$ and RORγ null mice, whereas the decreases of these genes in ROR DKO mice were more dramatic than those of single knockout mice (58).

Some of the gene regulation observed in the ROR loss of function knockout mouse models have been further supported by studies using ROR gain of function experiments. For example, we showed that overexpression of RORα by transfection in primary mouse hepatocytes or mouse liver *in vivo* suppressed the expression of Sult1e1/Est and Sult2a9/2a1, consistent with the activation of the same genes in the RORα$^{sg/sg}$ mice (58).

To study the mechanism by which RORs affect the expression of CYP genes, we focused on the regulation of oxysterol 7α-hydroxylase (Cyp7b1), an enzyme that plays

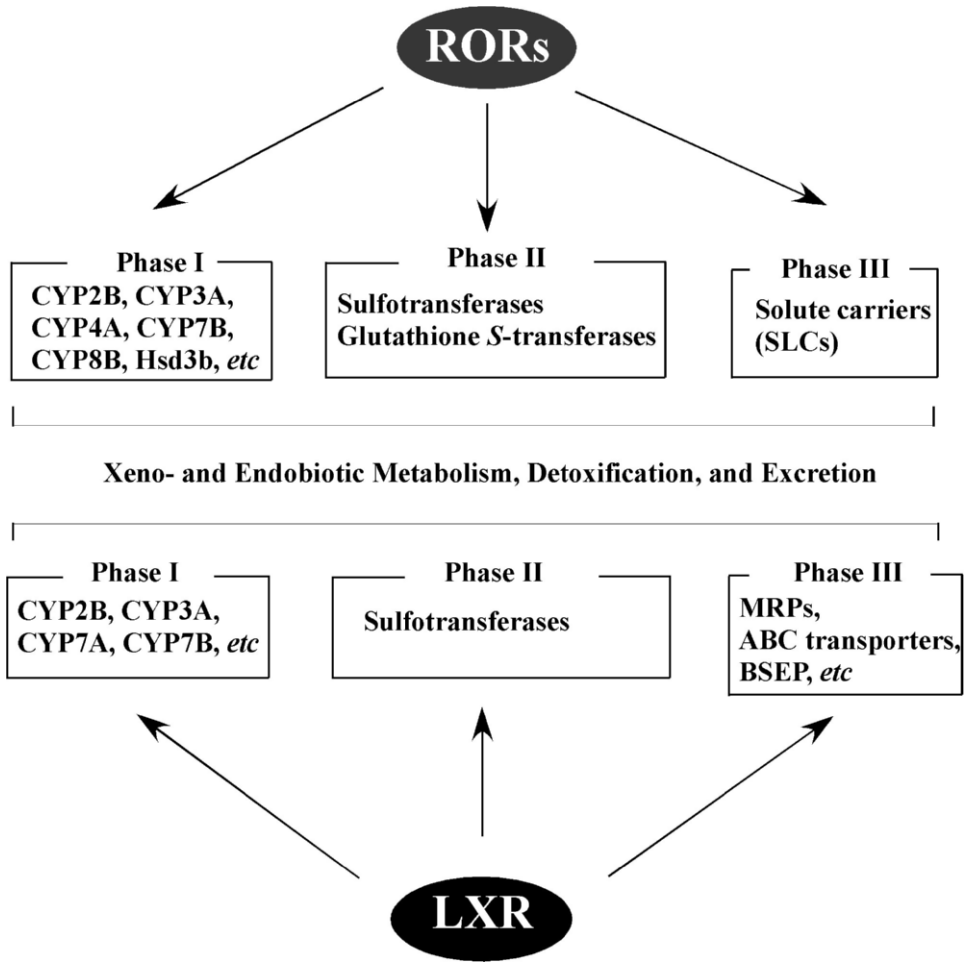

Figure 3. Proposed model of nuclear receptor-mediated regulation of drug metabolizing enzymes and transporters. Activation of nuclear receptor may result in the concerted regulation of Phase I and Phase II enzymes and the "Phase III" drug transporters. ROR and LXR are used as examples.

an important role in the homeostasis of cholesterol, oxysterols and bile acids (59, 60). The expression of Cyp7b1 gene was suppressed in the RORα$^{sg/sg}$ mice (58, 61), suggesting RORα as a positive regulator of Cyp7b1. Promoter analysis established Cyp7b1 as a transcriptional target of RORα and a functional RORE was identified in the Cyp7b1 gene promoter. Moreover, transfection of RORα induced the expression of endogenous Cyp7b1 in the mouse liver. Interestingly, Cyp7b1 regulation appeared to be RORα-specific, as RORγ had little effect, consistent with the notion that RORα, but not RORγ, may play a dominating role in Phase I and Phase II enzyme regulation. Our microarray analysis also suggests that, although loss of RORγ alone affected the expression of some enzymes, the overall effect of RORγ null on metabolic enzyme regulation was not as dramatic as that observed in the RORα null or RORα/RORγ DKO mice (58). The molecular mechanism by which RORs affect the expression of other drug metabolizing enzymes remains to be established.

Although the primary focus of this article is the regulation of xeno- and endobiotic gene expression, it is worthwhile to mention that in addition to the regulation of drug metabolizing enzyme and transporter genes, loss of RORα and/or RORγ also affect the expression of many other genes in the liver (for the complete microarray data, see http://www.ncbi.nlm.nih.gov/geo/ (GEO Series accession number GSE7564)). Moreover, RORα$^{sg/sg}$ mice, but not the RORγ null mice, showed lower plasma triglyceride and cholesterol levels than the control mice. In contrast, RORγ null mice, but not RORα$^{sg/sg}$ mice, exhibited lower blood glucose levels. These results suggested RORα and RORγ may play distinct roles in the regulation of triglyceride and glucose homeostasis, respectively.

LXR and Its Regulation of Xeno- and Endobiotic Genes LXRs, both the α and β isoforms (NR1H2, 3), were cloned and initially defined as sterol sensors that can be activated by the endogenous cholesterol derivative hydroxycholesterols, as well as synthetic LXR agonists, such as T0901317 (TO1317) and GW3965 (62, 63). Upon ligand activation, LXRs regulate gene expression by heterodimerization with the retinoid X receptor (RXR) and subsequent binding of LXR-RXR heterodimers to LXR

Table 2. Summary of Major Regulation of Drug Metabolizing Enzymes in the RORα Null Mice

	Microarray regulation[a]	Confirmed by Northern blot	Confirmed real-time PCR
Phase I enzymes			
Cyp2b9	↑	+	-
Cyp2b10	→	+	-
Cyp2b13	↑	-	-
Cyp2e1	→	-	-
Cyp3a11	→	-	-
Cyp3a25	→	-	-
Cyp4a1	↑	-	+
Cyp4a10	↑	-	+
Cyp7b1	↓	+	+
Cyp8b1	→	-	+
Phase II enzymes			
Sult1e1	↑	+	+
Sult2a1	→	+	+
Sult1d1	→	-	-
Sult1a1	→	-	-
Gstt3	→	-	-
Gstm4	→	-	-
Gsta1	→	-	-
Gstp1	→	-	-
Hsd3b4	↓	+	-
Hsd3b5	↓	+	+

[a] ↑, Up-regulated; ↓, down-regulated; →, no change.

response elements (LXREs) present in target gene promoters. LXRα is highly expressed in the liver and is also found in adipose, intestine, kidney and macrophages, whereas LXRβ is ubiquitously expressed (64, 65).

LXR was first shown to have an anti-atherosclerogenic effect by favoring an overall increase in cholesterol removal, while decreasing endogenous cholesterol synthesis and dietary absorption (65–67). Despite their promises as anti-atherosclerogenic targets, LXRs were linked to pro-lipogenic effects by activating the sterol regulatory element-binding protein-1c (SREBP-1c), a transcriptional factor that regulates the expression of a battery of lipogenic enzymes, including stearoyl CoA desaturase-1 (SCD-1), acetyl CoA carboxylase (ACC), and fatty acid synthase (FAS) (62, 68–70). In macrophages, activation of LXRs results in the efflux of cholesterol via the up-regulation of LXR target genes ABCA1, ABCG1, and ApoE (71). Treatment with LXR agonists in macrophages prevented bacterial or LPS-triggered induction of inflammatory signals. LXR signaling can impact antimicrobial responses by regulating macrophage gene expression and apoptosis (72, 73).

LXRs have been recently shown to regulate drug metabolizing enzymes, including sulfotransferases, suggesting a broader function of LXR beyond being sterol sensors. We have recently reported that LXRs can regulate Sult2a9/2a1 and impact sensitivity to bile acid toxicity and cholestasis (48). Genetic (using VP-LXRα transgene) or pharmacological (using a LXR agonist) activation of LXR in mice conferred a resistance to lithocholic acid (LCA)-induced hepatotoxicity and bile duct ligation (BDL)-induced cholestasis in female mice. In contrast, LXR DKO mice deficient of both the α and β isoforms exhibited heightened cholestatic sensitivity. LXR-mediated cholestatic resistance was associated with an increased expression of Sult2a9/2a1 and several bile acid transporters, whereas the basal expression of these gene products was reduced in the LXR DKO mice. In the same study, promoter analysis established Sult2a9/2a1 as a LXR target gene (48).

In another independent study, we showed that LXR controls estrogen homeostasis by regulating the basal and inducible hepatic expression of estrogen sulfotransferase (Est/Sult1e1), a designated sulfotransferase that catalyzes the sulfonation and deactivation of estrogens (74). Genetic or pharmacological activation of LXR resulted in Est/Sult1e1 induction, which in turn inhibited estrogen-dependent uterine epithelial cell proliferation and gene expression, as well as estrogen-dependent breast cancer growth in a nude mouse model of tumorigenicity. We further established that Est/Sult1e1 is a transcriptional target of LXR and a deletion of the Est/Sult1e1 gene in mice abolished the LXR effect on estrogen deprivation (49).

In addition to its regulation on SULTs, LXR may influence the expression of Phase I and Phase II enzymes other than SULTs. It was reported that loss of both LXR isoforms in mice resulted in an increased basal expression of Cyp3a11 and 2b10 (75). In contrast, activation of LXR resulted in a suppression of Cyp3a11 expression, but had little effect on the expression of Ugt1a1 (48).

A Functional Cross-Talk Between RORα and LXR in the Regulation of Xeno- and Endobiotic Genes The possibility of RORα-LXR crosstalk was initially indicated by the remarkable overlap in the pattern of genes affected in livers from the RORα$^{sg/sg}$ and LXR-activated mice. As mentioned earlier, activation of LXR in mice induced the expression of Est/Sult1e1 and Sult2a9/2a1. In the same LXR-activated mice, the expression of Cyp7b1 was suppressed (48), whereas the expression of CD36, a fatty acid uptake transporter, was induced (76). Remarkably, the same pattern of gene regulation was observed in the RORα$^{sg/sg}$ mice. These results suggest that RORα and LXR may be mutually suppressive *in vivo*.

To obtain support for this hypothesis, we examined the mutual suppression between RORα and LXR using the regulation of Cyp7b1 as a model system. Having established RORα as a positive Cyp7b1 regulator and knowing LXR suppresses the expression of Cyp7b1, we hypothesized that LXR may suppress Cyp7b1 gene expression by antagonizing RORα activity. Indeed, we showed that the activation of Cyp7b1 promoter by RORα was suppressed by co-transfection of LXRα, even in the absence of LXR agonists. The inhibitory effect of LXRα was enhanced by the LXR agonist TO1317. The inhibitory effect of LXRα was largely abolished when the RORE was mutated, suggesting that

Table 3. Regulation of LXR Target Genes in Female RORα Null Mice

LXR target genes	Regulation[a]
Est/Sult1e1	↑
Sult2a9/2a1	↑
Cd36	↑
Lpl	↑
Fas	↑
Akr1d1	↑
SR-BI	↑
Cyp7a1	→
Acc-1	↑
ApoE	→
Scd1	→
Srebp-1c	↓

[a] ↑, Up-regulated; ↓, down-regulated; →, no change.

Table 4. Regulation of ROR Target Genes in Female LXR DKO Mice

ROR target genes	Regulation[a]
Bmal1	↑
ApoAI	↑
p21	↑
ApoCIII	→
IKKβ	↑
Rev-erbα	→

[a] ↑, Up-regulated; ↓, down-regulated; →, no change.

the inhibition was mediated by RORα (61). The inhibitory effect of LXR on ROR was also seen when the RORE-containing synthetic reporter genes were used (61). The LXRα activity was reciprocally suppressed by RORα. tk-MTV is a LXR-responsive reporter gene (77). We showed that the activation of tk-MTV by LXRα was inhibited by co-transfection of RORα in a dose-dependent manner.

Our further studies suggest that, at least in cultured cells, the mutual suppression between RORα and LXR may be due to their competition for the nuclear receptor co-activators. RORα is known to interact with nuclear receptor co-activators without an exogenously added ligand (78, 79). We showed that LXRα also exhibited ligand-independent interaction with the nuclear receptor co-activator SRC-1 as confirmed by both mammalian two-hybrid assay and chromatin immunoprecipitation (ChIP) analysis. We hypothesize that the ligand-independent recruitment of co-activator accounts for the constitutive activities of both RORα and LXR, and co-activator competition may represent a plausible mechanism for the mutual suppression of transcriptional activity between these two receptors. However, we cannot exclude the possibility that the "constitutive" activity of RORα may have resulted from the binding of an endogenous ligand to this "orphan receptor".

The potential functional crosstalk between RORα and LXR was further investigated *in vivo*. For this purpose, we measured the expression of LXR target genes and ROR target genes in the RORα$^{sg/sg}$ and LXR DKO mice, respectively. As summarized in Table 3, in female RORα$^{sg/sg}$ mice, in addition to the activation of Est/Sult1e1, Sult2a9/2a1, Cd36 and Cyp7b1, the expression of other LXR target genes, such as lipoprotein lipase (Lpl) (80), aldo-keto reductase 1d1 (Akr1d1) (81), scavenger receptor BI (SR-BI) (82) and acetyl CoA carboxylase 1 (Acc-1), was also significantly induced. However, the expression of Srebp-1c was significantly suppressed, whereas the expression of ApoE, Abcg5 and LXRs was not affected. When the expression of RORα target genes was measured in the LXR DKO mice, we found that the expression of Bmal1 (83), ApoAI (26), p21 (84) and Ikkβ (29) was induced in LXR DKO female mice, but the expression of ApoCIII (85), Reverbα (78) and RORα was not significantly altered as summarized in Table 4. It is interesting to note that the mutual activation of target gene expression in the RORα$^{sg/sg}$ and LXR DKO mice are gene-specific. The mechanism for this selective gene regulation remains to be determined. Crosstalk between RORα and LXR can involve several mechanisms, including competition for co-activators and DNA binding sites. In addition, the promoter context might be a determining factor. The inhibition of RORα-mediated Cyp7b1 activation by LXR appears to involve competition for common co-activators. Repression of LXR target genes by RORα may also be mediated through crosstalk involving adjacent or distant ROREs.

The activation of LXR target genes in the RORα$^{sg/sg}$ mice has its physiological consequences. We showed that RORα$^{sg/sg}$ mice exhibited an increase in hepatic triglyceride accumulation. The expression of Srebp-1c, a LXR target gene, however, was not induced in the RORα$^{sg/sg}$ mice (61). We reason that the hepatic steatotic phenotype in RORα$^{sg/sg}$ mice is most likely accounted by the activation of Cd36, another LXR target gene. Cd36, a fatty acid transporter, facilitates the uptake of free fatty acids from the circulation and their subsequent conversion into triglycerides. We have recently shown that the steatotic effect of both PXR (86) and LXR (76) was associated with the activation of Cd36. Moreover, the steatotic effect of LXR agonists was largely abolished in mice deficient of Cd36 (76). The LXR-ROR crosstalk and its potential implications in physiology are summarized in Figure 4.

Conclusions and Perspectives Our recent findings have clearly suggested that RORs can positively or negatively regulate the expression of drug metabolizing enzymes in a gene specific manner. Although RORα regulates the expression of certain drug metabolizing enzymes, it is questionable that RORα is a traditional "xenobiotic receptor." Unlike PXR and CAR that are mostly associated with positive xenobiotic gene regulation,

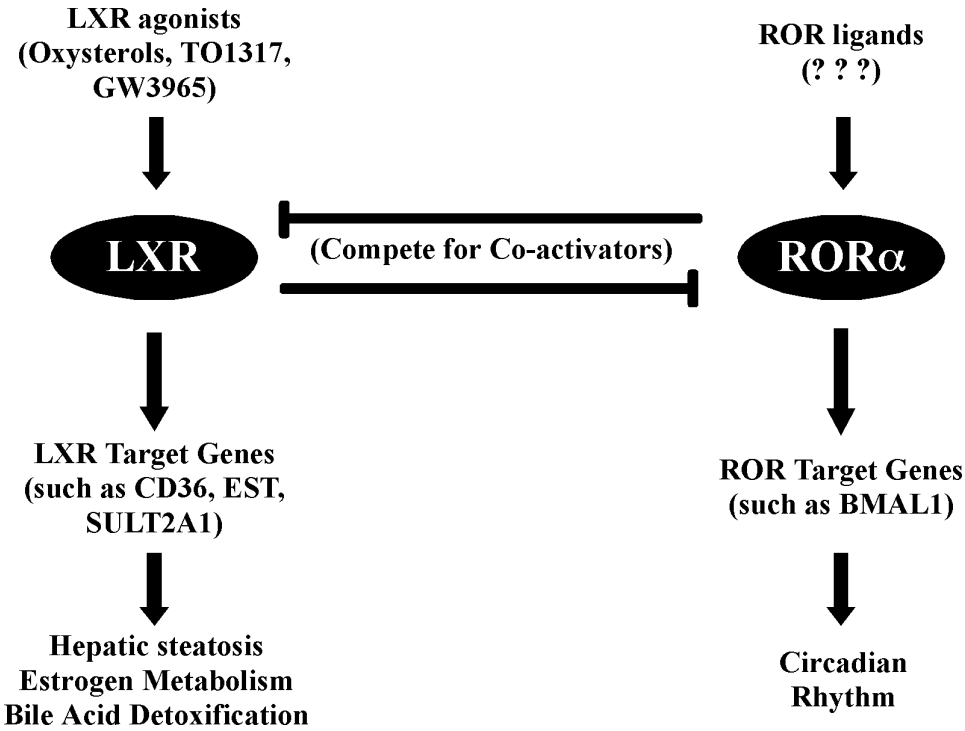

Figure 4. Proposed model of ROR-LXR crosstalk and its potential implications in physiology.

RORα can exert both positive and negative regulation in a gene-specific manner. Another hallmark of xenobiotic receptors is their wide spectrum of xenobiotic ligands. Unlike their xenobiotic receptor counterparts, no physiological ROR agonists have been reported despite efforts from several laboratories (9, 12).

The crosstalk between RORα and LXR is of particular interest. The crosstalk between xenobiotic receptors PXR and CAR has been reported and shown to involve competition for binding to the same DNA response elements and therefore regulation of common target genes (53). Nuclear receptors may also crosstalk in regulating xeno- and endobiotic genes through the presence of multiple nuclear receptor binding sites on the same target gene promoter. For example, we have recently shown that PXR, LXR and PPARγ cooperate to regulate the free fatty acid transporter CD36. In this case, three distinct nuclear receptor response elements, a DR3/PXRE, a DR7/LXRE and a DR1/PPRE, were found to cluster in 500-bp sequences of the mouse Cd36 gene promoter (76). The RORα-LXR crosstalk appears to involve the competition of common co-activators, adding another dimension of complexity to the nuclear receptor-mediated metabolic safety net.

Although the role of RORs in xeno- and endobiotic gene regulation has emerged, there are several outstanding challenges. First, the physiological relevance of ROR-mediated xeno- and endobiotic gene regulation remains to be further defined. For example, the oxysterol levels were increased in mice deficient of Cyp7b1, presumably due to a defect in the conversion of oxysterols to bile acids (87). It would be interesting to know whether the decreased basal expression of Cyp7b1 in the RORα$^{sg/sg}$ mice is associated with accumulation of oxysterols, the endogenous LXR agonists. It is also unknown whether the activation of Sult2a9/2a1 and Est/Sult1e1 in the RORα$^{sg/sg}$ mice will be associated with decreased sensitivity to bile acid toxicity and compromised estrogen responses, respectively. Second, having established Cyp7b1 as a RORα target gene, the molecular mechanism for the activation of Sult2a9/2a1 and Est/Sult1e1 in the RORα$^{sg/sg}$ mice remains to be established. It would be interesting to determine whether RORs exert their effect on Sult2a9/2a1 and Est/Sult1e1 gene expression via crosstalk with LXR. Finally, continued effort should be made to identify or develop functional ROR ligands, which will provide valuable pharmacological tools to dissect the function of RORs.

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