Role of liver X receptors in cholesterol efflux and inflammatory signaling (Review)

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Abstract. Liver X receptors (LXRs) are nuclear receptors that play a central role in cholesterol metabolism. When activated, LXRs induce a series of genes that are involved in cholesterol efflux, absorption, transport and excretion. In recent studies, LXRs have also been shown to play an important role in inflammatory signaling. LXR agonists show promise as potential therapeutics, given their anti-atherogenic and anti-inflammatory properties. The function of LXRs in cholesterol efflux and inflammatory signaling make them attractive as therapies for cardiovascular and inflammatory diseases.

Contents

1. Introduction

LXRs were originally considered as 'orphan' nuclear receptors, since their natural ligands were unknown; however, these receptors were 'adopted' following the discovery that metabolites of cholestorol oxysterols bind to and activate these receptors at physiological concentrations. More and more evidence indicates that LXRs function as key modulators of cholesterol metabolism and play an important role in inflammatory signaling. This review focuses on recent advances concerning LXRs in cholesterol efflux and inflammatory signaling in order to explore their use as potential therapies for cardiovascular and inflammatory diseases.

Construction and transcription of LXRs. LXRs have two subtypes: LXRα (nuclear receptor subfamily 1, group H, member 3, NR1H3) and LXRβ (nuclear receptor subfamily 1, group H, member 2, NR1H2). The two LXRs share considerable sequence homology and appear to respond to the same endogenous ligands. Similar to other members of the nuclear receptor family, these proteins contain a zinc finger DNA-binding domain that accommodates specific small lipophilic molecules. Ligand binding triggers a conformational change that promotes interaction with coactivator proteins and facilitates the activation of specific target genes (1,2). However, their tissue distribution differs. LXRα is highly expressed in liver and at lower levels in adrenal glands, intestine, adipose, macrophages, lung and kidney, whereas LXRβ is expressed in all tissues examined. LXRs play a role in the regulation of energy homeostasis; LXRα as well as LXRβ may play a crucial role in the regulation of energy homeostasis. Both LXRα and LXRβ are activated by physiological concentrations of sterol metabolites. Natural ligands that activate LXRs include oxysterol derivatives such as 25-hydroxycholesterol, 27-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S), 25-epoxycholesterol [24(S),25-EC], and 5α,6α-epoxycholesterol [5,6-EC] (3-5). LXRs bind to target DNA sequences in heterodimer complexes with retinoid X receptor (RXR). The LXR/RXR is a so-called permissive heterodimer; in that it can be activated by ligands for either LXR or RXR. The heterodimer binding to LXR-responsive elements (LXREs) in DNA consists of direct repeats (DRs) of the core sequence AGGTCA separated by 4 nucleotides (DR-4). LXR/RXR heterodimer is bound to LXREs in the promoters of target genes and in complex with co-repressors such as silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) and nuclear receptor co-repressor (N-COR). The function of nuclear proteins can be affected by their sequestration in the nucleoli. Mutations in the activation function-2 of LXR, an important protein-protein interaction site in all nuclear receptors, was found to result in exclusion of LXRβ from the nucleolus. In the absence of ligand these co-repressors are maintained and the transcriptional activity of target genes is repressed. Binding of ligand to LXR results in a conformational change that facilitates an exchange of

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co-repressor-complex for coactivator and transcription of target genes (6-8).

2. The role of LXRs in cholesterol efflux

CYP7A1. Cholesterol 7α-hydroxylase (CYP7A1) is a member of the cytochrome P450 family of enzymes and the rate-limiting enzyme in the classical pathway of bile acid synthesis, and is the first direct target of LXRs. CYP7A1 encodes for the rate-limiting step in the conversion of cholesterol to bile acids in the liver. The inability of LXRα$^{-/-}$ mice to induce hepatic CYP7A1 expression results in a diminished ability to metabolize cholesterol to bile acids and the accumulation of cholesterol esters (9). In response to acute cholesterol feeding, CYP7A1 was up-regulated in mice via stimulation of the liver X receptor α (LXRα). However, chronic cholesterol feeding also results in activation of the mitogen-activated protein (MAP) kinases, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK), which leads to suppression of CYP7A1 via activation of JNK and ERK signaling pathways (10,11). The mRNA expression of CYP7A1 and synthesis of bile acids was found to be low in embryonic stages, suggesting that farnesoid X receptor (FXR) might be a key regulator of CYP7A1 gene expression in the chicken embryo. In rabbits, activation of FXR is dominant over activation LXRα in the regulation of CYP7A1. The increased recruitment of LXRα, a CYP7A1 stimulatory pathway and decreased expression of FGF15 and phosphorylated ERK1/2, a CYP7A1 repressive pathway, combined to increase CYP7A1 expression during lactation (12). However, LXR agonists would not be expected to promote bile acid syntheses in humans, since the LXR response element is not conserved in the promoter of the human CYP7A1 gene.

ABC transporters. The ABC (ATP binding cassette) transporters are critical for the ability of LXRs to enhance efflux to cholesterol acceptors. ABCA1, ABCG1, ABCG5, ABCG8 and ABCG4 of the ABC transporter family are target genes of LXRs.

ABCA1 protein is critical for the efflux of excess cellular cholesterol to Apo acceptors such as ApoA1, the first step in reverse cholesterol transport. ATP-binding cassette protein A1 (ABCA1)-mediated cholesterol efflux is highly regulated at the transcriptional level through the activity of the nuclear receptor LXR. Cells from patients suffering from Tangier disease, which is caused by a mutation in the ABCA1 gene, are defective in their ability to efflux cholesterol. Expression of ABCA1 is strongly induced by natural and synthetic LXR ligands which are attributed to the presence of LXREs in the proximal promoter of the ABCA1 expression. LXRβ directly binds to the C-terminal region of ABCA1 to mediate its post-translational regulation. LXRβ can cause a post-translational response by directly binding to ABCA1, as well as a transcriptional response, to maintain cholesterol homeostasis (13-15). However, Genvigir *et al* found that lipid-lowering drugs down-regulate ABCA1 and ABCG1 mRNA expression in individuals and exhibit differential effects on HepG2 cells. Moreover, they found that the ABCA1 and ABCG1 transcript levels were not correlated directly to LXR mRNA expression in both cell models treated with lipid-lowering drugs (16). LXR/RXR functions as a sensor of cellular cholesterol concentration and mediates cholesterol efflux by inducing the transcription of key cholesterol shuffling vehicles namely, ABCA1 and ApoE. The LXR/RXR-induced up-regulation of ABCA1 and ApoE levels may be the molecular determinants of cholesterol dyshomeostasis (17). ABCG1 has recently been identified as a direct target of LXRs. It is also strongly induced by cholesterol loading of macrophages. ABCG1 is thought to function as a homodimer, although a functional partnership with ABCG4 has also been suggested. Induction of ABCG1 may provide an additional pathway for cholesterol efflux from macrophages or may act in concert with ABCA1. ABCG1 regulates macrophage cholesterol efflux and hence plays a vital role in macrophage foam cell formation. The sequential synergistic role of ABCG1 in promoting cholesterol efflux involves phospholipid-rich nascent HDL particles first generated by the lipidation of ApoA1 by the ABCA1 transporter. The expression of ABCG1 induced by synthetic or natural LXR ligands [TO901317, 22-(R)-hydroxycholesterol] was attenuated by inhibitors of c-Jun N-terminal kinase and phosphoinositide 3-kinase (PI3K). LXR agonists also induced the binding of activator protein-1 (AP-1), a key transcription factor family regulated by JNK, to recognition sequences present in the regulatory regions of the ABCG1 gene (18-20). In *in vitro* experiment assays, ABCG1 was demonstrated to facilitate cholesterol efflux to HDL-2 and HDL-3 particles but not to ApoA1. In *in vitro* experiments, macrophages lacking ABCG1 showed a diminished cholesterol efflux capacity to HDL, while cholesterol efflux to ApoA1 which is mainly mediate by ABCA1 was unchanged. Conjugated linoleic acid isomer trans-9, trans-11 (t9, t11-CLA) is an agonist of LXRα in human macrophages and its effects on macrophage lipid metabolism can be attributed to transcriptional regulations associated with ABCG1 (21,22).

ABCG1 is known to be expressed in numerous cell types and tissues, whereas ABCG4 expression is limited to the central nervous system. ABCG4 is also modestly induced in macrophages by cholesterol loading and LXR ligands and has been reported to promote cholesterol efflux to HDL particles when overexpressed in HEK293 cells (23,24).

Administration of the LXR agonist T0901317 to pregnant mice via their diet led to induced fetal hepatic expression levels of the cholesterol transporter genes Abcg5/g8 and Abca1. ABCG5 and ABCG8 perhaps play a prominent role in the inhibition of intestinal absorption of cholesterol and plant-sterol absorption and cholesterol efflux from hepatocytes into bile. The ABCG5 and ABCG8 proteins form a functional heterodimer that resides in the apical membrane of hepatocytes. ABCG8 has a more profound effect upon biliary cholesterol secretion than sitosterol; ABCG5/G8, unlike ABCA1, together with bile acids should participate in sterol efflux on the apical surface of Caco-2 cells (25). The mutation in either ABCG5 or ABCG8 causes the rare genetic disease sitosterolemia. Patients with this disease exhibit hyperabsorption of cholesterol and plant sterols and show diminished secretion of sterols into bile and hypercholesterolemia and develop premature atherosclerosis (26).

Apolipoproteins. A subset of apolipoproteins (APOs) such as ApoE, ApoCI, ApoCII, ApoD and ApoCIV may contribute to LXR-driven reverse cholesterol transport and may serve

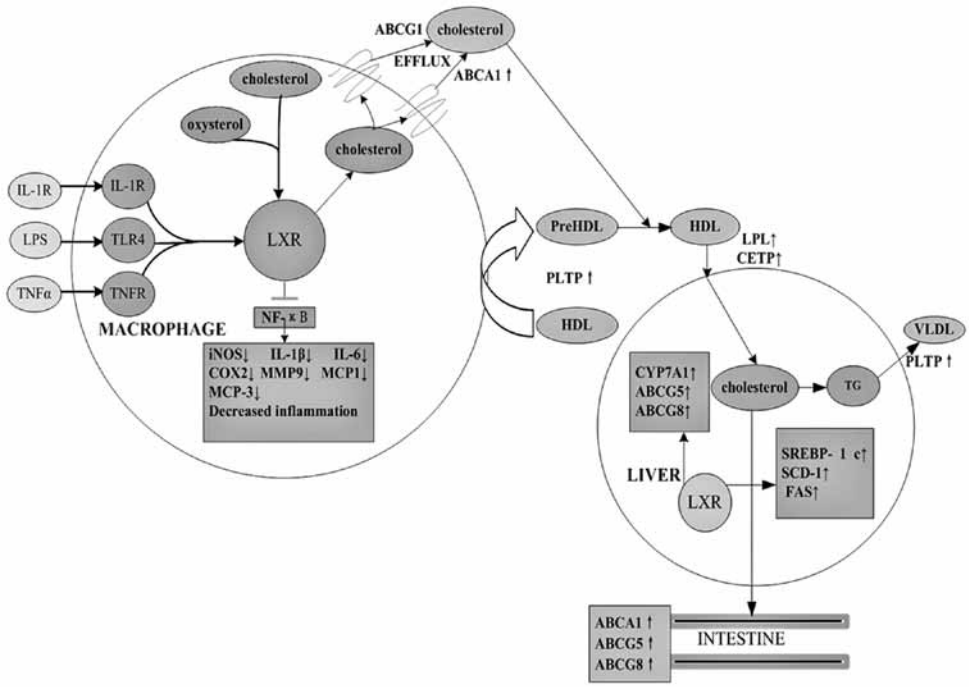

Figure 1. The role of LXR target genes in cholesterol metabolism and inflammatory signaling. As cholesterol-sensing nuclear receptors, LXRs promote cholesterol efflux via regulation of CPY7A1, ABCA1, ABCG1, ABCG4, ABCG5 apolipoproteins, lipoprotein remodeling enzymes and lipogenesis. Following their ligand-induced activation, LXRs inhibit expression of inflammatory genes such as iNOS and COX2, IL-1β, IL-6, IL-8, IL-12, MCP-1, MCP-3, MMP-9 and TNF-α.

as cholesterol acceptors. ApoE is a principal protein component of chylomicron remnants, very low-density lipoproteins. Recognition of ApoE by LDL receptors mediates hepatic uptake of these particles. Hepatic ApoE expression is controlled by a distal enhancer known as the hepatic control region, whereas expression in macrophages and adipocytes is directed by a distinct flanking sequence termed the multiple enhancer (ME) region. ApoE was the first gene shown to be regulated by LXR/RXR heterodimers in a tissue-specific manner. LXR mediates lipid inducible expression of the ApoE gene in adipose tissue and macrophages but not in liver. This differential regulation correlates with the presence of a critical LXR response element in the ME region of the ApoE gene. LXR-regulated ApoE expression by JNK and PI3K/AKT signaling in macrophages of several key genes has been implicated in atherosclerosis (18,27). Mice lacking ApoE exhibit greatly elevated plasma VLDL and intermediate-density lipoprotein cholesterol levels. Interestingly, Apos such as ApoE, ApoCI, ApoCII, ApoD and ApoCIV have been shown to serve as acceptors in ABCA1-mediated cholesterol efflux. The elaboration of these acceptors by macrophages within the arterial wall would be expected to promote cholesterol efflux and reverse cholesterol transport. LXR/RXR-induced up-regulation of ABCA1 and ApoE levels may be the molecular determinants of cholesterol dyshomeostasis (19,28,29).

Lipoprotein remodeling enzymes. LXR has been shown to influence the expression of several enzymes that act on lipoproteins, including lipoprotein lipase (LPL), cholesterol ester transfer protein (CETP) and the phospholipid transfer protein (PLTP). The functions of these enzymes are complex and likely to be context-dependent. LXR activation induces expression of LPL, which plays a crucial role in binding of modified lipoproteins and may promote the conversion of triglyceride-rich lipoproteins to cholesterol-rich lipoproteins such as LDL. CETP is secreted by the liver and circulates in plasma principally bound to HDL. LXRα has an essential role in the regulation of CETP expression and maintaintence of RCT. Synthetic LXR agonist enhanced plasma CETP activity resulted in non-high density lipoprotein (non-HDL) increase and HDL decrease in cynomolgus monkeys and human CETP transgenic mice (30,31). LXR-mediated induction of human CETP expression is switched on during monocyte-to-macrophage differentiation, is magnified by lipid loading and is selectively lost in inflammatory macrophages. LXRs affect remodeling of ApoB-containing lipoproteins via induction of hepatic expression of CETP, which facilitates the transfer of CE from HDL to ApoB-containing lipoproteins. PLTP has been identified as a modulator of HDL metabolism and may also be involved in reverse cholesterol transport (32). PLTP can also mediate lipid transfer between LDL particles to produce a small pre-β-HDL and a large α-HDL. Expression of a human PLTP transgene in mice increased production of pre-β-HDL and enhanced hepatic uptake and clearance of the cholesterol ester. Increased PLTP expression in the artery wall may serve to generate cholesterol acceptors and therefore contribute to cholesterol efflux.

Lipogenesis. Earliest studies on LXR pointed to an important role in the control of fatty acid as well as cholesterol metabolism. LXRs have been proposed as a glucose sensor affecting LXR-dependent gene expression and *de novo*

lipogenesis (33,34). However, nuclear factor erythroid-2-related factor-2 (Nrf2) activation promoted deacetylation of farnesoid X receptor (FXR) by competing for p300, leading to FXR-dependent induction of the small heterodimer partner (SHP), which was responsible for the repression of LXRα-dependent gene transcription and inhibits LXRα-dependent hepatic lipogenesis (35). Mice lacking LXR were noted to be deficient in the expression of sterol regulatory element binding protein 1c (SREBP-1c), fatty acid synthase (FAS), steroyl coenzyme A desaturase 1 (SCD-1) and acylcoenzyme A carboxylase (ACC). LXRs play an important role in cholesterol synthesis and uptake and the effect of LXR agonists on cholesterol synthesis plays only a minor role in the regulation of cellular sterol homeostasis (36). On one hand, the expression of SREBP-1C and FAS induced by LXR activation promotes the esterification of free cholesterol to fatty acid which is an important mechanism for buffering free cholesterol levels; on the other hand, it is also likely to cause the elevation of plasma and hepatic triglyceride levels.

3. The role of LXRs in inflammatory signaling

LXRs and innate immunity. Recent studies have uncovered a common mechanism by which different microbial pathogens might contribute to foam cell formation and accelerate lesion development and interference with LXR-dependent cholesterol metabolism. The innate immune system recognizes conserved motifs found in microbes through so-called pattern recognition receptors that include the TLR (Toll-like receptor) family of proteins. Activation of TLR3 or TLR4 during viral bacterial infections in macrophages severely compromises the expression of ABCA1, ABCG1, ApoE and other LXR target genes both *in vitro* and *in vivo*. A synthetic liver X receptor (LXR) ligand, TO-901317, was found to restore cholesterol efflux from HIV-infected T lymphocytes and macrophages. TO-901317 potently suppressed HIV-1 replication in both cell types and inhibited HIV-1 replication in *ex vivo* cultured lymphoid tissue and in RAG-hu mice infected *in vivo* (37). Activation of LXR represents a novel lipid-signaling paradigm that alters the inflammatory response of human dendritic cells (DCs), and LXR-positive DCs are present in reactive lymph nodes *in vivo*. Administration of LXR-specific natural or synthetic activators induced target gene expression accompanied by increased expression of DC maturation markers (38). T cell responses were strongly affected in $LXR\alpha^{-/-}LXR\beta^{-/-}$ mice, Treatment of WT mice with the LXR agonists TO901317 and GW3965 resulted in a decrease in the pulmonary bacterial burden and a comparable increase of Th1/Th17 function in the lungs. The dependence of LXR signaling on the neutrophil IL-17 axis may be a novel function for these nuclear receptors in resistance to *M. tuberculosis* infection (39). Consistent with these effects on LXR-dependent gene expression, LXR activation was found to increase reactive oxygen species generation by enhancing the expression of NADPH oxidase subunits. Activation of TLR3 or TLR4 potently inhibits cholesterol efflux from macrophages. TLR3/4-dependent inhibition of LXR is accomplished through activation of the viral response transcription factor IFN regulatory factor 3 (40), however, the mechanism by which this factor blocks LXR action remains to be determined. LXR-TLR crosstalk provides a potential mechanism to explain how microbial infections may interfere with cholesterol metabolism.

LXRs and inflammation. Atherosclerosis is now recognized to be a chronic inflammatory disease as well as a disorder of lipid metabolism. Activation of inflammatory signaling pathways and release of inflammatory mediators are fundamental to the diverse immune functions of macrophages. The microenvironment within the atherosclerotic lesion is pro-inflammatory and results in activation of these same pathways. Studies have demonstrated that excessive inflammation is a risk factor for the promotion of atherogenesis.

Evidence indicates that LXRs not only induce genes involved in cholesterol efflux, but also repress a set of inflammatory genes after bacterial, LPS, TNF-α or IL-1β stimulation. The inflammatory genes include those involved in the generation of bioactive molecules such as iNOS and COX2, IL-6 and IL-1β, the chemokine monocyte chemoattractant protein-1 (MCP-1) and MCP-3 and MMP-9 (38,41). In mature DCs, LXR activation increased the production of inflammatory cytokines IL-12, TNF-α, IL-6 and IL-8 and resulted in an increased capacity to activate $CD4^+$ T cell proliferation upon ligation with TLR4 or TLR3 ligands (42). LXRs centrally control reverse cholesterol transport, but also negatively modulate TLR-mediated inflammatory pathways. LXR ligands repress these genes in macrophages derived from $LXR\alpha^{-/-}$ or $LXR\beta^{-/-}$ mice but are unable to do so in macrophages from $LXR\alpha\beta^{-/-}$ mice, indicating both LXR isoforms possess anti-inflammatory activity. LXR ligands also exhibit a similar repression of tissue factor (TF) and osteopontin, both of which are associated with the development of atherosclerosis. LXR null mice exhibit enhanced responses to inflammatory stimuli, while the LXR ligands can significantly reduce inflammation in a murine model of contact dermatitis. Astrocytic LXRα activation and subsequent release of ApoE by astrocytes is critical for the ability of microglia to remove fibrillar Aβ in response to treatment with TO901317 (43). In addition, treatment of $APOE^{-/-}$ mice with LXR agonists was found to reduce the expression of the inflammatory mediator MMP-9 and tissue factor in atherosclerotic aortas while inducing expression of ABCA1. $LXR\alpha\beta^{-/-}$ mice, challenged with LPS, exhibit an exacerbated systemic inflammatory response and increased hepatic expression of iNOS, TNF-α or IL-1β.

The mechanisms underlying the repression of inflammatory genes by LXRs are poorly understood. LXREs have not been identified in the proximal promoters of the repressed genes, thus may be an indirect mechanism. In addition to the possible competition for transcriptional co-activators, evidence suggests that inhibition of the NF-κB pathway is involved. This inhibition, referred to as transrepression, is thought to underlie anti-inflammatory actions of nuclear receptors such as LXRs. Transrepression of NF-κB by LXR involves a nuclear event. In a recent study of transrepression of the iNOS promoter by peroxisome proliferator activator receptor γ (PPARγ), sumoylation of PPARγ was identified as a possible mechanism involved in this process. Sumoylated PPARγ was suggested to prevent the LPS-dependent exchange of co-repressor for co-activators, thus maintaining the iNOS promoter in a repressed state.

4. Conclusion

On the whole, it is clear that LXRs play an important role in cholesterol metabolism and inflammatory signaling as summarized in Fig. 1. LXR agonists show promise as potential therapeutics, given their anti-atherogenic and anti-inflammatory properties. Future research should continue to define the roles of LXRs in cholesterol metabolism and the inflammatory response in order to identify new compounds which can be designed to avoid the side effects of current drugs, including hypertriglyceridemia and steatosis while conferring beneficial effects on cholesterol metabolism and inflammation. Investigation of LXRs can offer additional potential therapies for cardiovascular and inflammatory diseases.

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