Liver X Receptors as potential therapeutic targets in atherosclerosis

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Abstract

Purpose: Atherosclerosis is the primary independent risk factor of cardiovascular disease, and Liver X Receptor (LXRα and LXRβ) activation may play an anti-atherosclerosis effect. In this article, we summarize the current state of knowledge of the roles of LXRs in physiology and homeostasis as well as the links between LXR action and atherosclerosis, and discuss the potential therapeutic effects of LXR agonists.

Source: A MEDLINE database search was performed to identify relevant articles using the keywords “liver X receptors”, “LXRs”, and “atherosclerosis”. Additional papers were identified by a manual research of the references from the key articles.

Principle findings: Both LXR isoforms promote reverse cholesterol transport (RCT) and have anti-inflammatory activity. LXRα is the predominant receptor in the liver regulating triglyceride synthesis. The antiatherosclerotic ability of LXRs makes them attractive targets for drugs for the treatment of cardiovascular disease. However, LXR activation induces lipogenesis and hypertriglyceridemia. The first-generation synthetic ligands of LXR increase hepatic lipogenesis and plasma triglyceride levels. New LXR ligands need to be designed without undesirable side effects.

Conclusion: LXR β-selective agonists and LXR modulators, which act as agonists in macrophages and induce cholesterol efflux while they are antagonists of lipogenesis in the liver, are two critical and attractive approaches to treat atherosclerosis and cardiovascular diseases.

List of Abbreviations

LXRs Liver X Receptors
LDL-C Low-Density Lipoprotein Cholesterol
HDL-C High-Density Lipoprotein Cholesterol
AF Activation Function
RXRs Retinoid X Receptors
DRs Direct Repeats
LXREs LXR-responsive Elements
N-CoR Nuclear Receptor Corepressor
SMRT Silencing Mediator of Retinoic Acid and Thyroid Hormone Receptor
HDACs Histone Deacetylases
SRC-1 Steroid Receptor Coactivator 1
NF-κB Nuclear Factor κB
PPARs Peroxisome Proliferator-Activated Receptors
SREBR Sterol Regulatory Element-Binding Protein
HMG-CoA Hydroxy-Methyl-Glutaryl Coenzyme A
FPP Farnesyl Diphosphate
SQS Squalene Synthase
ABC ATP-Binding Cassette Transports
NPC1L1 Niemann-Pick C1-Like 1
RCT Reverse Cholesterol Transport
PLTP Phospholipid Transfer Protein
Cardiovascular disease is the leading cause of death and illness in developed and some developing countries. It has become the most widespread health problem worldwide, and atherosclerosis is the primary independent risk factor. Atherosclerosis is a chronic progressive disease characterized by the accumulation of lipids and fibrous elements in large arteries. Subsequently, the arterial wall gradually thickens to form an atherosclerotic plaque, which may rupture abruptly, resulting in myocardial infarction and stroke. Most notable risk factors include high levels of serum low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C). Statins are highly effective lipid-lowering agents which can lower LDL-C by 24-61%. However, many patients still experience adverse coronary events despite statin therapy, leading to the search for additional therapeutic intervention.

Members of the nuclear hormone receptor superfamily play a critical role in metabolism, some of which can exert beneficial pleiotropic effects to reduce atherosclerosis and its complications. In particular, liver x receptors (LXRs) have been linked directly to the regulation of biochemical pathways involved in lipid homeostasis and inflammation. LXRs function as cholesterol sensors and regulators of an array of genes associated with cholesterol synthesis, absorption, efflux and excretion, controlling whole body cholesterol homeostasis. They may also modulate inflammatory and proliferative responses in vascular cells and prevent the development of atherosclerosis. Nevertheless, synthetic LXR agonists may induce lipogenesis and then increase plasma triglyceride concentration and hepatic steatosis, considered an atherogenesis factor. It has been reported that LXR agonists can attenuate the development of atherosclerosis in spite of a potentially adverse lipogenic effect in mouse models. In this review, we summarize the biological roles of LXRs, the links between LXR action and atherosclerosis, and discuss the potential therapeutic effects of LXR agonists.

Liver X Receptors

Molecular Structure and Distribution of LXRs

The liver x receptors (LXRα and LXRβ) are ligand-dependent transcriptional factors, belonging to the nuclear hormone receptor superfamily. Their structure consists of: an N-terminal region containing a ligand-independent activation function (AF-1), a central DNA-binding domain containing two zinc fingers, a hydrophobic C-terminal ligand domain which mediates ligand recognition and receptor dimerization, and a ligand-dependent transcriptional activation function (AF-2). LXRα and LXRβ share a lever of cDNA homology of about 63%, but differ in distribution. LXRα is highly expressed in liver (hence its name), and at lower levels in the intestine, macrophages, kidney and other organs, while LXRβ is expressed ubiquitously.

Transcriptional Activities of LXRs

LXRs function as heterodimers with the 9-cis retinoid x receptors (RXRs), then bind to specific DNA sequences consisting of direct repeats (DRs) of the core sequence AGGTCA separated by 4 nucleotides (DR-
4), also known as LXR-responsive elements (LXREs) within the promoters of target genes.\(^6\) The heterodimer can be activated by either ligand of LXR and RXR. Experiments with N-terminal nuclear localization sequences mutant RXR confirmed that RXR may dominate the nuclear import of the LXR/ LXR\(\alpha\) heterodimer, whereas LXR\(\beta\) dominates the nuclear import of the LXR/ LXR\(\beta\) heterodimer.\(^{14}\) LXRs regulate gene expression by at least via three different types of transcriptional activities (Fig 1). First, in the absence of ligands, LXR/RXR heterodimer can bind to target genes and actively repress transcription via the recruitment of corepressor complexes, including nuclear receptor corepressor (N-CoR), silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) and histone deacetylases (HDACs). Second, binding of a ligand induces a conformational change in the protein, which leads to displacement of corepressors and results in the recruitment of coactivator proteins, such as steroid receptor coactivator 1 (SRC-1), then promotes transcription. Third, ligand activation of LXRs can inhibit the activities of other signal-dependent transcription factors which don’t contain LXREs, such as nuclear factor \(\kappa B\) (NF-\(\kappa B\)). This activity, considered trans-repression, contributes to the anti-inflammatory ability of LXRs.\(^{1,6,15}\)

**Ligands of LXRs**

Putative endogenous ligands of LXRs are oxidized cholesterol derivatives (oxysterols). However, free cholesterol and cholesterol ester have no effects. The most important natural activators are 22(R)-hydroxycholesterol, 20(S)-hydroxycholesterol, and 24(S),25-epoxycholesterol. In addition, D-glucose and D-glucose-6-phosphate have been identified as physiological agonists of both LXR isoforms.\(^{14}\) Most endogenous LXR ligands identified so far activate both LXR\(\alpha\) and LXR\(\beta\) except 25-diepoxycholesterol and 6\(\alpha\)-hydroxy bile acids, which are somewhat selective for LXR\(\alpha\). A number of pharmacological LXR ligands have also been synthesized.\(^{12,14,16}\)
Regulation of LXRα

The expression of LXRα is regulated by nuclear receptors, especially the peroxisome proliferator-activated receptors (PPARs) and LXRα itself. In primary human macrophages, PPARs activation induces LXRα, but not LXRβ. Accordingly, oxidized low-density lipoproteins, which include agonists of PPARs, have been found to increase LXRα expression.\textsuperscript{17,18} Several studies have demonstrated the existence of an auto-up-regulatory loop controlling the expression of LXRα, but not LXRβ. Interestingly, LXRα auto-up-regulation appeared to be limited to human cell types, and did not occur in murine macrophages or preadipocytes. This feature may be important during lipid loading of human macrophages, when LXRα is dramatically up-regulated and becomes the predominant LXR isoform, in contrast to the situation in resting macrophages.\textsuperscript{4,19}

LXRs and Lipid Metabolism

LXRs and Cholesterol Metabolism

Cholesterol is a critical component of cell membranes and is the substrate for steroid hormone and bile acid synthesis. Cholesterol homeostasis is mainly maintained by balancing endogenous cholesterol synthesis, intestinal cholesterol absorption and reverse cholesterol transport with excretion of biliary cholesterol and bile acids (Fig 2). Because elevated cholesterol levels may relate to the development of atherosclerosis and cardiovascular diseases, so maintaining cholesterol homeostasis is very crucial.\textsuperscript{20,22,23}

LXRs and Cholesterol Synthesis

In LXRα-null mice, expression of the sterol regulatory element-binding protein-2 (SREBR-2), as well as Hydroxy-Methyl-\textit{Glutaryl} Coenzyme A (HMG-CoA) reductase and synthase, farnesyl diphosphate synthase (FPP synthase) and squalene synthase (SQS) were all increased. Smaller increases in the hepatic

![FIGURE 2. Role of LXRs in cholesterol homeostasis](Figure.png)
expression of HMG-CoA reductase, FPP synthase and SQS were also observed in LXRβ-null mice, except SREBP-2. Consistently, the expression of these genes was markedly reduced following the administration of the LXR agonist T0901317 to wild-type mice. Current studies indicate that LXRα is a cholesterol synthesis inhibitor, directly inhibiting the expression of the lanosterol 14α-demethylase and SQS.

**LXRs and Cholesterol Absorption**

Activation of LXRs by LXR agonists can reduce intestinal cholesterol absorption in mice. It appears to be primarily mediated through a transcriptional induction of a heterodimer consisting of two ATP-binding cassette transporters (ABC), ABCG5 and ABCG8, which are LXR target genes. These two proteins are an apical sterol export pump to promote active efflux of cholesterol from enterocytes back into the intestinal lumen for excretion.

Niemann-Pick C1-Like 1 (NPC1L1) protein is a critical for intestinal cholesterol absorption. LXR activators down-regulate NPC1L1 mRNA levels in the human enterocyte cell line Caco-2/TC7. Furthermore, NPC1L1 mRNA levels are decreased in vivo, in duodenum of mice treated with the LXR agonist T0901317. Therefore, LXR activation inhibits intestinal cholesterol absorption.

**LXRs and Reverse Cholesterol Transport**

The RCT system actively transports excess cholesterol from lipid-loaded cells back to the liver for secretion into the bile. LXRs regulate all the major steps of RCT through several potential mechanisms. First, LXRs induce the expression of several ABC transporters in macrophages, including ABCA1, ABCG1 and ABCG4, thus facilitating cholesterol efflux from the cell membrane to its extracellular acceptors, such as apolipoproteins apoA1, apoE and HDL particles. LXR activation induces redistribution of ABCG1 from intracellular sites to the plasma membrane and increases cholesterol mass efflux to HDL. Second, LXRs regulate several apolipoproteins and lipid-modulating enzymes involved in cholesterol efflux and HDL remodeling. Both LXR isoforms promote the expression of the entire ApoE/C-I/C-II/C-IV gene cluster via two LXREs identified in the ApoE promoter. Interestingly, LXRs induce expression of apoE in macrophages and adipocytes, but not in liver. The phospholipid transfer protein (PLTP) transfers phospholipids from HDL to triglyceride-rich lipoproteins. LXR activators can increase the expression and activity of PLTP, promoting HDL synthesis. Cholesterol ester transfer protein (CETP) mediates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins prior to their uptake by the liver. Both LXRα and LXRβ induce the expression of CETP. However, because of both beneficial and deleterious effects of CETP, the potential therapeutic impact of LXR up-regulation of CETP expression should be treated with caution. Lipoprotein lipase (LPL) is the rate-limiting enzyme for the hydrolysis of lipoprotein triglycerides, which can promote the maturation of HDL. It is induced by LXR in the liver and macrophages except adipose tissue. Third, LXRs stimulate the mobilization of cholesterol from intracellular to the plasma membrane, and promote cholesterol efflux to extracellular receptors. Activation of LXR transcription factors may be atheroprotective by a novel mechanism that decreases macrophage receptor-independent, fluid-phase pinocytosis of atherogenic lipoproteins such as LDL, and LXR-mediated decrease in macrophage pinocytosis of HDL may also be atheroprotective by increasing plaque HDL that is available to mediate RCT.

**LXRs and Bile Acid Synthesis, Excretion**

The liver-specific cholesterol 7α-hydroxylase (CYP7A) is the rate-limiting enzyme in the classical pathway of bile acid synthesis, which was identified as the first direct target of LXRs in mice. In rodents, LXRα null mice exhibited massive amounts of choles-
terol in livers, and LXRβ expression was unchanged. However, both wild-type and LXRβ null mice showed only slight increases in hepatic cholesterol levels. All the data suggest that LXRα is the dominant isoform responsible for up-regulation of CYP7A in rodent. Nevertheless, human CYP7A expression is not regulated by LXR in vitro in HepG2 cells, which may explain their susceptibility to the development of hypercholesterolemia on a diet rich in cholesterol.

LXRs may also induce hepatobiliary cholesterol secretion and fecal neutral sterol elimination. So far, the most likely target genes responsible for the LXR-mediated activity are ABCG5 and ABCG8. These proteins form a heterodimer to pump cholesterol into bile, residing in the apical membrane of the hepatocyte.

LXRα and Triglyceride synthesis

In addition to regulation of cholesterol homeostasis, LXR activation also induces the expression of genes involved in lipogenesis in the liver. Schultz et al. showed that oral administration of T0901317 to mice activated the coordinate expression of lipogenesis and increased plasma triglyceride levels. The sterol regulatory element-binding protein-1c (SREBP-1c) in the liver, the major SREBP-1 isoform, is a direct LXR target gene. SREBP-1c can stimulate the transcription of lipogenic genes, including fatty acid synthase (FAS), acetyl-coA carboxylase (ACC) and stearoyl CoA desaturase-1 (SCD-1). Besides, LXR activation can directly induce these lipogenic genes expression. Furthermore, LXRα but not LXRβ is the critical gene to regulate lipogenesis, facilitating the development of highly selective LXR modulators without undesirable lipogenic effects.

LXRs and Inflammation

LXRs suppress an array of inflammatory genes as a result of macrophage activation (Fig 3). Macrophages are essential components for atherosclerosis. They can take up massive OX-LDL and induce the expression of inflammatory genes, leading to lesion initiation and progression. In vitro, LXR activators inhibit the expression of macrophage inflammatory genes, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin (IL-6), IL-β, monocyte chemoattractant protein-1 (MCP-1) and MCP-3, in response to bacterial, tumor necrosis factor-α (TNF-α) or lipopolysaccharide stimulation. Subsequent studies showed that matrix metalloproteinase-9 and tissue factor, which play a critical role in atherosclerotic plaque stability and thrombus formation following plaque rupture, could be suppressed by LXR ligands. Besides, LXR activation can inhibit cytokine-induced osteopontin expression in macrophages, a potential target for pharmacological intervention in atherosclerosis. The repression of inflammatory gene expression by LXR agonist treatment was mitigated in LXRα(-/-), and LXRβ(-/-) compared with wild-type macrophages, but
was completely abolished in LXRα(-/-)LXRβ(-/-) mice, suggesting that both LXR isoforms possess anti-inflammatory activity. In vivo, LXR agonists reduce inflammation in both irritant and allergic contact models of dermatitis. LXR activation can suppress inflammatory genes expression in the aortas of atherosclerotic mice.47

On the other hand, LXR agonists enhance the expression of TNF-α. However, since LXR activation appears not to induce other proinflammatory cytokines involved in the inflammatory immune response, it is possible that specific LXR-mediated stimulation of TNF-α expression may reduce atherosclerotic smooth muscle cells, form cells and infiltrating T cells.

The key mechanism for anti-inflammatory effects of LXRs appears to involve antagonism of NF-κB signaling. NF-κB and these inflammatory genes mentioned above don’t have LXREs in the proximal promoters, so trans-repression of NF-κB by LXR is essential. However, the precise mechanism how LXRs block NF-κB signaling is unknown.9,48

**LXRs and the Immune System**

Current studies have demonstrated that several microbial pathogens could promote foam cell formation and accelerate lesion development, which is associated with LXR-dependent cholesterol metabolism. The innate immune system recognizes conserved motifs found in microbes by so-called pattern recognition receptors, including Toll-Like Receptors (TLR3 and TLR4), which can reduce the expression of LXR target genes. LXR-TLR cross-talk is independent of NF-κB, but mediated by another transcription factor, interferon regulatory factor3, which is also implicated in the interferon response. Recently, it has been demonstrated that 48 h pre-treatment with LXR agonists leads to an increase in TLR4 expression in human macrophages, resulting in increased secretion of cytokines that activate an immune adaptive inflammatory response.49 These findings highly emphasize the ability of LXRs to integrate inflammatory and metabolic signaling.50

In addition, mice devoid of both LXRs are more susceptible to microbial infections, developing higher bacterial burdens with accelerated rates of macrophage apoptosis. Valledor48 showed that activation of LXR inhibited macrophage apoptosis in response to apoptotic stimuli and infection. Subsequently, it was found that LXR could induce the expression of the anti-apoptotic gene Api6 (also known as Aim and Spa).51,52 Interestingly, LXRα(-/-) mice but not LXRβ(-/-) mirror the susceptibility of LXRα(-/-)LXRβ(-/-) mice, indicating that LXRα is the major functional isoform in innate immunity. Hence, the study of LXR function in macrophages and other immune cells is unraveling previously unrecognized links between immunity and metabolism.8,49,52

**LXRs and Smooth Muscle Cells**

Proliferation of smooth muscle cells (SMCs) plays an important role in the pathogenesis of the late stage of atherosclerosis. Both LXR isoforms express in primary SMCs (Fig 3). Blaschke et al53 showed that, in human coronary SMCs, LXR activation could inhibit mitogen-induced SMC proliferation by preventing G1 to S phase progression of the cell cycle. Furthermore, the S phase kinase-associated protein 2 (Skp2), which could degrade the cyclin-dependent kinase inhibitor p27Kip1, was identified as the target gene of LXR. Additionally, LXR ligands reduced neointima formation following balloon angioplasty of the rat artery in vivo by increasing p27Kip1 expression.53-55

To repress SMCs proliferation, LXR activation in SMCs can also induce several macrophage LXR target genes expression. It has been reported that LXR activation increases the expression of ABCA1 and ABCG1 in human airway SMCs, promoting cholesterol RCT and reducing the accumulation of intracellular cholesterol. Hence, the antiproliferative effects of LXRs on SMCs are important for prevention of development of atherosclerosis.56

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**LXRs and Atherosclerosis**

Atherosclerosis is a chronic inflammatory state within the arterial wall characterized by alterations in lipid metabolism. As mentioned above, LXRs could regulate cholesterol metabolism as well as suppress inflammatory genes expression and SMCs proliferation, thus it is predicted that LXR activation can prevent the development of atherosclerosis.\(^{57,58}\) Joseph et al\(^{59}\) demonstrated that the synthetic LXR agonist GW3965 led to an approximately 50% reduction in lesion size in both LDLR-deficient and apoE-deficient male mice with a high fat diet, two murine models of atherosclerosis. Terasaka et al\(^{60}\) reported that another LXR agonist T0901317 reduced the lesion area by 70% in LDLR-deficient mice with a high cholesterol diet. The expression of ABCA1 and ABCG1 were increased while the inflammatory genes were inhibited. In contrast, the levels of lipids in plasma were not altered. Furthermore, macrophage-specific loss of LXRs achieved by transplantation of bone marrow from LXR\(\alpha\)(-/-) LXR\(\beta\)(-/-) mice into either apoE(-/-) or LDLR(-/-) mice resulted in an increase in lesion size and aggravated atherosclerosis, mainly through their effect on macrophage cholesterol efflux and the intravascular inflammatory reaction rather than by modulating the lipid profile. Additionally, transplantation of LXR-null bone marrow to LDLR(-/-) mice abolished the antiatherosclerotic effect of T0901317, which indicated that macrophage LXRs are essential for the anti-atherosclerotic effect of LXR agonists.\(^{61,62}\) Current studies demonstrated that LXR agonists led to regression of atherosclerosis in preexisting lesions, contributing to the fact that most humans presenting with signs of cardiovascular disease already had substantial lesion development.\(^{63}\) These findings suggest that LXR activation exerts pleiotropic antiatherosclerotic effects. Meanwhile, it is emphasized that the macrophage LXR pathway is an attractive target for intervention in cardiovascular disease.\(^{63,64}\)

Teupser et al\(^{65}\) showed that transgenic overexpression of LXR\(\alpha\) using a macrophage gene expression construct led to an increase of cholesterol efflux from macrophages, a down-regulation of proinflammatory response, and a reduction of atherosclerosis. Transgenic expression of LXR\(\alpha\) was primarily directed into macrophages, and animals did not show the attendant side-effects usually seen with generalized LXR activation by synthetic LXR agonists, so macrophage overexpression of LXR\(\alpha\) might be useful as a therapeutic principle for the prevention of atherosclerosis.

**LXR Agonists for Atherosclerosis**

The antiatherosclerotic ability of LXRs makes them attractive targets for drugs developed for the treatment of cardiovascular disease. The first generation of non-selective synthetic ligands inhibited atherosclerosis in mice, but increased hepatic lipogenesis and plasma triglyceride levels, induction of proinflammatory cytokines such as TNF-\(\alpha\) in macrophages. Bradley et al\(^{66}\) demonstrated that treatment of LXR\(\alpha\)(-/-) Apoe(-/-) mice with synthetic LXR ligand ameliorated the cholesterol overload phenotype and reduces atherosclerosis. Their observations indicated that the pursuit of LXR\(\beta\)-specific agonist ligands for the treatment of atherosclerosis may prove to be fruitful.

The nonsteroidal compounds T0901317 and GW3965 are two common and important agonists of LXRs. Both compounds can increase rate of RCT and improve cholesterol homeostasis in mice. Furthermore, both agonists induce ABCA1 expression to similar extents in the small bowel, but in liver, T0901317 induces FAS and triglyceride generation while GW3965 has limited effects. However, there are other contradictory researches in vivo, so it is not easy to define GW3965 as a selective agonist regulating non-hepatic genes and improving cholesterol metabolism. Therefore, a new LXR ligand is needed without these side effects.\(^{67-69}\)

Designing selective ligands is one possible approach. Both LXR isoforms promote cholesterol RCT
and have anti-inflammatory ability. However, LXRα is the predominant gene in the liver to regulate triglyceride synthesis. Plasma triglyceride levels and the expression of hepatic multiple enzymes of fatty acid synthesis were reduced in LXRα-deficient mice. Administration of a nonselective LXR agonists to LXRα-deficient mice reduces whole-body cholesterol levels and atherosclerosis without causing hepatic steatosis, so LXRβ selective agonists may be the ideal antiatherosclerotic drugs. Nevertheless, the crystal structure of the ligand-binding domains of LXRα and LXRβ indicates that binging pockets are virtually identical, making it difficult to achieve highly selective agonists.

The development of selective estrogen receptor modulators indicates the feasibility to design nuclear receptor ligands that function as agonists in one cell type but as antagonists in others depending on the co-regulator levels present. Therefore, designing LXR modulators that act as agonist in macrophages and induce cholesterol efflux, but which act as antagonists of lipogenesis in the liver, is another critical and attractive approach. Furthermore, the crystal structure of LXR, with a large ligand-binding domain, makes it possible to identify LXR modulators. Two synthetic steroidal LXR agonists, ATI-829 and DMHCA, can be defined as good candidates for drug development by selectively activating, in mice, LXR target genes in certain tissues but not genes involved in liver lipogenesis.

Mice and humans have different gene expressions in response to LXR activation. Genes involved in bile-acid production, innate immune response, and hepatic lipogenesis are regulated differently in mice and humans. Hence, any LXR-associated therapy needs to be tested in animals which are more similar in their metabolic pathways to humans. So far, none have been tested in humans. Attention should be paid to important species-differences with respect to the genes regulated by LXRs.

Conclusion

The versatile antiatherosclerotic effects of LXRs provide possibilities for the development of a novel class of therapeutic drugs to treat atherosclerosis and cardiovascular diseases. However, due to the undesirable effects caused by first-generation LXR agonists, LXRβ-selective agonists and selective LXR modulators need to be developed. Besides, the species-specific LXR regulation should not be ignored. In all, further research on the molecular mechanism of LXR is needed, which may facilitate treatment of clinical cardiovascular disease with more suitable drugs.

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