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Liver X Receptor: Crosstalk Node for the Signaling of Lipid Metabolism, Carbohydrate Metabolism, and Innate Immunity

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Abstract

Liver X Receptor- α (LXR α , also known as NR1H3) and LXR β (NR1H2) are members of the nuclear receptor superfamily of ligand-activated transcription factors, a superfamily which includes the more widely known glucocorticoid receptor, estrogen receptor, thyroid receptor, and peroxisome proliferator-activated receptors. The LXRs are activated by physiologic sterol ligands (e.g., oxysterols) and by synthetic agonists. In recent years, our understanding of the importance of LXRs has expanded across several fields of (patho-)physiology. Perhaps best known from a sizeable literature as homeostatic ‘cholesterol sensors’ that drive transcriptional programs promoting cellular cholesterol efflux, ‘reverse cholesterol transport,’ and bile acid synthesis, more recent roles for LXRs in glucose homeostasis, atherosclerosis, and innate immunity have also been identified. These discoveries complement an emerging literature that continues to draw surprisingly intimate connections between host metabolism and host defense. The present review will discuss the roles of LXR in the signaling of metabolism and innate immunity, and the potential for synthetic LXR agonists as novel therapeutics in dyslipidemia, atherosclerosis, disordered glucose metabolism, and inflammation.

Keywords

Liver X Receptor; Innate Immunity; Cholesterol; Inflammation

Introduction

The Liver X Receptors-(LXRs) α and β (NR1H3, NR1H2) are members of the nuclear receptor hormone superfamily, a superfamily of 48 mammalian ligand-activated transcription factors which includes the perhaps more widely known glucocorticoid receptor (GR), estrogen receptor, and peroxisome proliferator-activated receptors (PPARs). Like other nuclear receptors, the LXRs have a highly conserved zinc-finger DNA-binding domain, and a less conserved ligand-binding domain. LXRs bind as obligate heterodimers with the retinoid X receptor (RXR; NR2B1) to a direct repeat four (DR-4)-type target DNA sequence (the LXR response element, LXRE), which is composed of two hexanucleotide sequences separated by four bases (Fig. 1).

Originally cloned as orphan receptors, it is now known that the LXRs have multiple endogenous ligands, several of which are oxysterol metabolites that have been demonstrated to be effective at physiological concentrations (e.g., 22(R)-hydroxycholesterol, see Table I). Of interest, however, the LXR/RXR heterodimer is permissive in that it can be activated by

ligands for either LXR or RXR. A small number of endogenous LXR antagonists (e.g., 5 α ,6 α -epoxycholesterol-3-sulfate, see Table I) and natural exogenous agonists have also been described, suggesting the potential for complex regulation of LXR activation. The pharmaceutical industry has succeeded in the development of a number of synthetic LXR agonists (e.g., TO-901317, GW3965) that have now been used by several independent groups in both *in vitro* and *in vivo* models, and have aided in identification of LXR target genes (Table II). It is thought that LXRs normally bind to the LXRE in a complex with corepressors such as silencing mediator of retinoic acid and thyroid hormone receptor (SMRT)[1] and nuclear receptor corepressor (N-CoR)[2], and that target gene transcription is disinhibited when binding of ligands to LXR induces a conformation change favoring coactivator-for-corepressor exchange (Fig. 1). In other instances, LXRs are also thought to suppress transcription of non-LXRE-bearing genes through a process known as trans-repression. LXR α and LXR β are highly related, sharing ~77% amino acid homology in both their DNA- and ligand-binding domains. The tissue distribution of expression of the two LXR subforms differs, however, as LXR β is fairly ubiquitously expressed while LXR α is predominantly restricted to tissues known to play important roles in lipid metabolism (e.g., liver, macrophages, intestine, adipose tissue). Of interest, as discussed further below, several important molecular differences between LXR α and LXR β have also been identified, including their nuclear localization [3], regulation [4, 5], and functional roles [6].

With the development of mice deficient in LXR α and LXR β several years ago [7, 8], our understanding of the fundamental role of LXRs in biology has grown greatly. The LXRs are now known to be cellular sensors of both cholesterol (i.e., oxysterols) [9] and glucose [10], to be central regulators of both lipid and carbohydrate metabolism, and to exert both nuclear receptor class effects and unique effects upon gene expression [11]. More recent work has demonstrated the important regulatory role of LXRs in inflammation/innate immunity, and has thereby begun to clarify novel areas of integration between host metabolism and host defense. This mini-review will focus on recent advances in our understanding of the role of LXRs in physiology and disease. Emphasis will be placed upon advancements in our understanding of how LXR mediates crosstalk between host metabolism and host defense, and upon issues relating to the potential targeting of the LXRs in the treatment of human disease. For further information, the reader is directed to recent comprehensive reviews on LXR biology and pharmacology [12–16].

Role of LXR in cholesterol and fatty acid metabolism

LXR regulates cholesterol metabolism at both the cellular level (i.e., cholesterol efflux) and whole-organism level (i.e., bile synthesis, intestinal absorption, catabolism), in which capacities its overall function is to reduce cellular and organism cholesterol load. Thus, LXR and its target genes (Table II) are critical regulators of ‘reverse cholesterol transport,’ the process by which cholesterol is transported via HDL particles from peripheral cells to the liver for excretion into bile and from there into feces. The first evidence for this concept was provided by the development of LXR α ^{-/-} mice, which were found to develop marked hepatic accumulation of cholesterol esters on a high-cholesterol diet due to insufficient induction of the target gene Cyp7a1, a P450 enzyme which regulates the rate-limiting step in the classical pathway of bile acid synthesis [8]. Subsequent work demonstrating that LXR β ^{-/-} mice do not have an obvious hepatic phenotype indicated important tissue-specific differences between the LXR subforms *in vivo* [7].

It has since been shown that treatment of animals with synthetic LXR agonists increases HDL levels and cholesterol excretion [17], and that this promotion by LXR agonists of reverse cholesterol transport from peripheral macrophage to feces can be directly traced *in vivo* [18]. It is thought that LXR-dependent promotion of reverse cholesterol transport is

driven in large part by the ATP-binding cassette (ABC) superfamily of membrane transporters, in particular by the LXR target genes ABCA1 [17, 19–21], ABCG5, ABCG8 [22, 23], and ABCG1 [24–26], which efflux cholesterol out of the cell. LXRs further complement cholesterol pump upregulation by upregulating a number of apolipoprotein cholesterol acceptors, including apoE [27] and apoC [28]. The critical importance of ABCA1 to cellular cholesterol efflux from peripheral cells is underscored by the fact that cholesterol efflux from Tangier disease fibroblasts, in which ABCA1 is inactivated by mutation, is insensitive to LXR agonists [21]. ABCA1 has been reported to be antiatherogenic *in vivo* [29, 30], although its influence upon atherosclerosis appears to be complex and tissue-specific [31–33]. Interestingly, ABCG1 and ABCG5, which have been described to require heterodimerization with each other for proper apical cell surface location [34], serve at multiple checkpoints in the regulation of bodily cholesterol levels, since their location in enterocytes is thought to explain the decrease in enteric absorption of cholesterol observed with LXR agonists [17], while their location in the liver is thought responsible for proper efflux of cholesterol into the bile [34, 35]. The complex role of ABCG1 in whole body cholesterol homeostasis has been demonstrated by the development of ABCG1^{-/-} mice, which have hepatocyte and macrophage cholesterol accumulation, but normal plasma lipids, on a high-cholesterol diet [36]. Reports on the role of ABCG1 in atherogenesis have been mixed [37–39]. This notwithstanding, it has been shown that macrophage LXR deficiency promotes atherosclerosis *in vivo* [40], and that treatment of mice with LXR agonists is antiatherogenic [41, 42].

In addition to their role in regulation of cholesterol metabolism, the LXRs are pivotal regulators of fatty acid metabolism. LXR agonists induce triglyceride accumulation in the liver and in plasma [43, 44], an effect which is thought to stem from their upregulation of sterol regulatory element binding protein (SREBP)-1c [44, 45] and fatty acid synthase [43], as well as other intermediary targets, such as acyl-CoA carboxylase and stearyl-CoA desaturase. As discussed below, avoidance of hypertriglyceridemia will be a critically important goal in possible future development of LXR agonists for human therapeutics. Finally, on a more global scale, it has been shown that LXRs also regulate the balance between fat storage and oxidation, and thereby the obesity phenotype, through complex effects on intermediary metabolism [46]. In further support of this idea, early studies have suggested possible clinical associations for LXR in human obesity [47].

Role of LXR in carbohydrate metabolism

The LXRs have also been shown to regulate carbohydrate metabolism at multiple levels. Of interest, synthetic LXR agonists have been shown to improve glucose tolerance in rodent models of diabetes [48, 49]. This is thought to occur through coordinate suppression of the hepatic gluconeogenesis at the transcriptional level (e.g., downregulation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase), and enhancement of glucose uptake in adipose tissue through upregulation of the insulin-sensitive glucose transporter, GLUT4 [50]. Regarding the former mechanism, it has also been suggested that the antidiabetic actions of LXR agonists may be mediated in part through downregulation of hepatic GR [51]. Regarding the latter, it has been shown that LXR activation reduces blood glucose in ob/ob mice through both increased peripheral glucose uptake and metabolism [52], and that LXR agonists reduce TNF α -induced insulin resistance in adipocytes through downregulation of protein tyrosine phosphatase-1B [53].

Additional work has demonstrated a role for LXR not only in insulin effect, but also in insulin production. For example, an important role for LXR β has been demonstrated in insulin secretion from beta cells [54] through an SREBP-1-regulated mechanism [55]. It has also been found that LXR α ^{-/-}/ β ^{-/-} mice have reduced plasma insulin and C-peptide levels

[56], and has been confirmed that LXR activation stimulates insulin secretion from pancreatic beta cells [57]. Recent exciting work has indicated that LXR is itself a cellular glucose sensor, as glucose binds LXR and stimulates its transcriptional activity [10]. This may provide further insight on a recent report that glucose induces the translocation of LXR α from cytoplasm to nucleus in rat pancreatic beta cells [58]. The demonstration that LXR-dependent cholesterol homeostasis genes are upregulated in liver and intestine of fasted mice re-fed with a glucose diet [10] provides yet another intriguing demonstration of how LXR integrates glucose and fatty acid metabolism. Finally, yet additional reports have suggested a more complex role for the role of LXR in beta cells, and perhaps even a role for LXR in diabetes pathogenesis, insofar as LXR upregulation in the islets of diabetic rodents may promote beta cell apoptosis [59], and treatment of insulin-secreting cells with a combination of LXR and RXR agonists promotes their apoptosis [60].

Role of LXR in innate immunity and inflammation

A number of studies have described intriguing bidirectional crosstalk between LXR and innate immunity signaling pathways, as summarized in a recent review [61]. Transcriptional profiling of LPS-exposed macrophages revealed reciprocal LXR-dependent regulation of genes involved in lipid metabolism and innate immunity, suggesting that LXR may act as a master switch in coordinated control of these two gene programs [62]. LXR ligands were shown to inhibit the expression of pro-inflammatory genes (i.e., inducible nitric oxide synthase, cyclooxygenase-2, interleukin-6) in response to either bacterial infection or LPS [62], and to inhibit expression of coagulants (i.e., tissue factor) in response to LPS [63], at least in part through inhibition of NF- κ B signaling. Inhibition of NF- κ B by LXR is not thought to involve inhibition of nuclear translocation of NF- κ B, NF- κ B binding to DNA, or degradation of I κ B α [62–64], but perhaps to involve an unidentified effect of LXR in the nucleus. The anti-inflammatory activity of LXR agonists to some extent reflects a class effect of nuclear receptor agonists, since it has been shown quite elegantly that agonists of GR, PPAR γ , and LXR repress overlapping yet distinct transcriptional targets [11]. LXR-dependent repression of cytokine expression is selective insofar as it has been shown that LXR agonists inhibit LPS induction of TNF α , but not IL-1 β nor IL-6 in murine macrophages [63], and LXR α negatively regulates expression of IL-8, IL-4, and CX3CR1 and positively regulates IFN γ expression in human blood mononuclear cells [65]. Conversely, LPS-induced cytokines (i.e., IL-1 β and TNF α) are reported to downregulate expression of LXR α and its coactivators, and to reduce LXRE-driven transcription in HK-2 cells [66]. Additional complex interactions with innate immunity in macrophages are suggested by conflicting reports that LPS either upregulates the LXR target gene ABCA1 through an LXR-independent mechanism [67], or that LPS downregulates ABCA1 [68]. Moreover, one report has even demonstrated that LXR agonists can themselves induce TNF α in human peripheral blood monocytes through a specific LXRE in the TNF α promoter [69].

Confirming a regulatory role for endogenous LXR in *in vivo* responses to pathogen-associated molecular patterns (PAMPs), LXR $\alpha^{-/-}$ / $\beta^{-/-}$ mice were reported to have enhanced cytokine expression in the liver (TNF α , IL-1 β) and plasma (IL-6) following intraperitoneal LPS injection [62]. This suggests that endogenous LXR may serve to dampen innate immunity *in vivo*. Moreover, whereas LXR α expression in the kidney has been reported to be downregulated by LPS *in vivo* [66], a report that LPS induces a late phase of LXR α , but not LXR β gene upregulation in macrophages [5] suggests the possibility that LXR α upregulation may serve as a natural brake upon LPS-induced inflammation in leukocytes. Conversely, TLR3 and TLR4 PAMPs (i.e., lipid A and poly I:C) as well as microbes bearing these PAMPs (i.e., *E. coli* and influenza A) have been reported to antagonize cholesterol efflux in macrophages through IRF3-mediated inhibition of LXR transcriptional activity.

Poly I:C was also shown to inhibit LXR target gene expression *in vivo* [70]. As cholesterol efflux is known to be protective in atherosclerosis, these findings may possibly explain associations that have been reported in the literature between endotoxemia and atherosclerosis [71].

LXR-dependent gene expression has also been reported to play an important role in host defense. Joseph et al. reported that LXR null mice have increased susceptibility to systemic infection with the intracellular Gram-positive bacterium *Listeria monocytogenes* [6]. This was attributed to enhanced macrophage apoptosis due to loss of regulation of the antiapoptotic factor, SP α , an LXR α target gene. Of interest, expression of LXR α in hematopoietic cells was specifically noted to be largely responsible for the anti-*Listerial* host defense phenotype observed in this study, suggesting that important differences exist between the two LXR genes in host defense, and that the tissue localization of LXR expression *in vivo* is critical. Similarly, Valledor et al. reported that combined activation of LXR and RXR protected macrophages from apoptosis caused by infection with *Bacillus anthracis*, *Escherichia coli*, and *Salmonella typhimurium* due to promotion of an anti-apoptotic gene program involving SP α [72]. By contrast, our group has found that treatment of C57BL/6 mice with an LXR agonist impairs host defense in the lung against the extracellular Gram-negative bacterium, *Klebsiella pneumoniae*, likely due to attenuated recruitment of neutrophils to the airspace (unpublished data). Finally, of uncertain significance to host defense, one group has reported that paxilline, a fungal metabolite, is a potent LXR agonist in biochemical and *in vitro* cell-based assays [73]. Taken together, these studies suggest that the role of LXR in host defense may vary with the type of pathogen, and possibly also with the specific effector arm of host defense involved and with the nature of the host compartment that is infected.

An emerging literature has also begun to identify a role for LXR in regulation of adaptive immunity. It has been shown that human CD4-positive lymphocytes express both LXR α and LXR β , and that LXR activation can reduce Th-1 cytokine expression in these cells [74]. LXR agonists are also reported to interfere with LPS-induced dendritic cell maturation and T-cell stimulatory ability [75]. These studies suggest a broader role for LXR in host defense and in immune-mediated pathogenesis than previously appreciated.

Finally, a potential therapeutic role for LXR agonists has also been reported in non-PAMP-induced *in vivo* models of inflammation. For example, it is reported that LXR agonists ameliorate irritant and allergic contact dermatitis [62, 76], and experimental autoimmune encephalitis [77]. Recent literature has also indicated that the antiinflammatory effects of LXR agonists may be mediated in part through their direct induction of anti-inflammatory target genes, such as arginase II [78]. Gene expression studies suggest that combinatorial therapy of LXR agonists with other nuclear receptor agonists (e.g., glucocorticoids) may provide therapeutic synergy [11], expanding the range of potential opportunities for application of LXR agonists in human disease.

LXR as a potential drug target

The pharmacology of LXR-active compounds has been covered in a recent comprehensive review [16]. Emerging literature suggests a number of potential therapeutic applications for LXR agonists in disease models, including insulin resistance [48, 51, 52], atherosclerosis [40, 79], dyslipidemia [80], and Alzheimer's disease [81, 82]. In several instances, however, it is not yet clear how well animal models will translate to human disease. For example, the LXRE found in the promoter of rodent Cyp7a1, the rate-limiting enzyme in the classical pathway of bile acid synthesis, is not conserved in humans [83]. Perhaps more concerning is the fact that it has been reported that unlike mice, which do not express the LXR target

cholesterol ester transport protein (CETP), hamsters and cynomolgus monkeys (which, like humans, do express CETP) have an increase in serum LDL-cholesterol and no increase in serum HDL-cholesterol with synthetic LXR agonists [84]. The significance of this inter-species difference to human disease is uncertain since CETP inhibitors have recently been reported to increase HDL cholesterol and reduce LDL cholesterol but to have no significant effect on progression of human coronary atherosclerosis [85].

Early literature nevertheless suggests the potential for pharmacologic LXR activation in a number of assorted disorders. The possibility of pharmacologic activation of LXR as a corrective therapy in selected genetic disorders of cholesterol trafficking, such as Niemann Pick type C disease, has been suggested [86, 87]. A possible role for LXR agonists as immunomodulatory adjuvants in the therapy of certain infections has been advanced based on their protection against pathogen-induced macrophage apoptosis [6, 72]. A potential role in therapy of prostate cancer has also been reported [88–90]. Finally, the anti-inflammatory therapeutic potential of LXR agonists has been suggested in animal models of experimental autoimmune encephalomyelitis [77] and dermatitis [62, 76], and it has been suggested that anti-inflammatory synergy may potentially be achieved in combination therapy of LXR agonists with glucocorticoids [11]. A challenge for the pharmaceutical industry in development of LXR agonists for systemic administration will be avoidance of the hepatic lipogenesis and associated plasma hypertriglyceridemia seen with the early series of commercialized compounds, such as TO-901317 [91]. It is expected that more selective and/or partial LXR agonists may succeed in addressing this problem by causing less induction of SREBP1c and/or tissue-selective activity. Miao et al. reported that a tissue- and gene-selective agonist of LXR α increased serum HDL cholesterol without inducing hepatic steatosis or hypertriglyceridemia [92]. Lund et al. recently reported that a nonselective LXR agonist raised HDL cholesterol without causing hepatic steatosis in LXR α -deficient mice [93]. It is also thought that competitive binding of coactivators and corepressors may offer new routes to rational design of partial LXR agonists with tissue-specific activity [94].

In terms of more present-day implications of LXR in human therapeutics, it is worth noting that LXR α is a target gene of PPAR γ , thiazolidinedione agonists of which are currently clinically used to improve insulin resistance in patients with diabetes mellitus. Moreover, CYP27, a P450 enzyme that synthesizes the endogenous LXR agonist 27-hydroxcholesterol, has been reported to be upregulated by PPARs through a PPAR-retinoic acid response element in its promoter [95]. Hence, to what extent clinically used thiazolidinediones are efficacious through direct or indirect induction of LXR α is an interesting question.

New horizons in LXR research

While a comprehensive review of emerging directions in LXR research is well beyond the scope of this mini-review, three exciting areas worthy of mention are genetic epidemiology of LXR, manipulation of endogenous LXR agonists and antagonists, and roles of LXR in signal transduction.

Recently, studies have suggested possible associations between LXR α and LXR β polymorphisms and obesity [47], and LXR β polymorphisms and Alzheimer's disease [96]. The possibility that LXR polymorphisms may influence human disease offers the opportunity for future investigations of the association of LXR genotype with other disorders (e.g., diabetes, atherosclerosis, dyslipidemia, fatty liver), and also offers the potential for pharmacogenomic evaluation of both future LXR agonists and of currently used drugs that influence the LXR pathway (e.g., statins [97], thiazolidinediones [52]). Finally, the potential also exists for correlating LXR genotype and drug responsiveness in the future with the metabolic profile of subjects (e.g., plasma oxysterol levels).

A few studies have reported altered levels of endogenous LXR agonists [98] and/or antagonists [99] in inflammatory disease states in human subjects. We have also recently detected upregulation of a heat-labile endogenous LXR inhibitor in the airspace of rodents exposed to inhaled lipopolysaccharide (unpublished observation). Taken together, such observations suggest that fluxes in LXR-active endogenous metabolites may play a role in disease pathogenesis and perhaps also serve as causative disease biomarkers. Moreover, these studies suggest that manipulation of endogenous LXR-active metabolites may possibly be a novel therapeutic strategy in certain diseases. Both overexpression of an oxysterol catabolic enzyme and deletion of oxysterol synthetic enzymes have been shown to impair induction of LXR target genes by dietary cholesterol *in vivo* [100]. By contrast, it has been shown that upregulation of endogenous LXR agonists [i.e., 24(S),25-epoxycholesterol] by partial inhibition of oxidosqualene:lanosterol cyclase may bear therapeutic promise as it selectively upregulates expression of macrophage LXR-regulated cholesterol efflux genes without stimulating genes linked to fatty acid synthesis [101]. Finally, a report suggests that clinically used statins may impact biology in part through inhibiting the synthesis of endogenous LXR agonists [102].

In addition to the physiological roles for LXR described above, an evolving literature has begun to identify novel means for regulation of LXR by, and effects of LXR upon intracellular signals. It was recently reported that LXR α is phosphorylated at a mitogen-activated protein kinase family consensus target [103]. Protein kinase A has also been reported to phosphorylate LXR α , thereby impairing its DNA binding activity and transcriptional activity [104]. Finally, LXR activation has been reported to promote generation of reactive oxygen species [105], suggesting the potential for complex interactions of LXR with redox-sensitive signaling pathways.

Conclusion

As pivotal regulators of cholesterol, triglyceride, and glucose handling, the LXRs represent an important integration hub among the arms of host metabolism. Through their regulatory effects on pro-inflammatory gene expression, they also marshal bidirectional crosstalk between host metabolism and host defense/inflammation. We are far from understanding the full implications of this crosstalk for human disease. While significant challenges remain, the LXRs represent promising therapeutic targets for both metabolic and inflammatory disease.

Perspectives

In closing, the crosstalk that LXR regulates between lipid/carbohydrate metabolism and innate immunity is unlikely to be a mere coincidence. Multiple examples exist of the striking degree of homology and molecular overlap shared between host lipid metabolism and host defense, including the homology between LPS-binding protein, CETP, and PLTP [106]; the activity that fatty acids, minimally modified LDL, and ceramide have upon TLR4 [107–109]; the uptake of LPS and regulation of its action by SR-BI [110, 111]; the regulation of LPS signaling by ABCA1 [112]; and the regulation of cellular phospholipid efflux by CD14 [113], to name a few. Taken together, such reports reinforce at least three exciting ideas: 1) that primary perturbations of innate immunity and of host lipid/carbohydrate metabolism may both be expected to exert reflexive influences upon the other; 2) that molecules traditionally thought to subserve just host defense or host metabolism functions may possibly represent novel therapeutic targets for the other; and 3) that innate immunity should be construed more broadly than solely in its relation to host defense and inflammation, but should also be accepted as an integral regulator of host metabolism.

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Figure 1. LXR integrates host metabolism and host defense

A theoretical cell, depicted as a macrophage, is shown to illustrate LXR's role in integrating cellular signals and processes. Ligands, such as oxysterols and glucose, bind to LXR in its heterodimeric complex with RXR, and induce its activation via co-activator for co-repressor exchange. LXR target genes (shown in red), including ABCA1, apoE, SREBP-1c, FAS, and GLUT4 are thereby induced, and contribute to cellular cholesterol efflux, lipogenesis, and glucose transport. Pathogen-associated molecular pattern ligands for TLR3 and TLR4 inhibit LXR via IRF3, whereas LXR attenuates pro-inflammatory gene (e.g., cytokine) expression through inhibition of NF-κB. Abbreviations: ABCA1 = ATP-binding cassette transporter A1; Apo = apolipoprotein; ER = endoplasmic reticulum; FAS = fatty acid synthase; GLUT4 = glucose transporter 4; IRF3 = interferon regulatory factor 3; LXR = Liver X Receptor; oxLDL = oxidized low density lipoprotein; RXR = Retinoid X Receptor; SREBP-1c = sterol regulatory element binding protein-1c; TLR = Toll like Receptor.

Table I**LXR Agonists and Antagonists**

LXR Agonists	LXR Antagonists
22(R)-hydroxycholesterol	5 α ,6 α -epoxycholesterol-3-sulfate
24(S)-hydroxycholesterol	7-ketocholesterol-3-sulfate
24(S),25-epoxycholesterol	GGPP
25-hydroxycholesterol	
27-hydroxycholesterol	
Cholestenic acid	
Paxilline	
Glucose	

Abbreviations: GGPP = geranylgeranyl-pyrophosphate

Table II**LXR Target Genes**

Gene	Regulation
Lipid metabolism	
ABCA1	↑
ABCG1/5/8	↑
SCD-1/2	↑
CETP (human)	↑
PLTP	↑
LXRα	↑
Angptl3	↑
LPL	↑
SREBP-1c	↑
SHP	↑
Cyp7α(murine)	↑
FAS	↑
ApoE, ApoC	↑
Carbohydrate metabolism	
PEPCK	↓
GLUT4	↑
Fbp1	↓
G6P	↓

Abbreviations ABCA1 = ATP-binding cassette transporter A1; ABCG = ATP-binding cassette transporter G; Cyp7α = cholesterol 7α-hydroxylase; SCD = stearoyl CoA desaturase; CETP = cholesterol ester transfer protein; PLTP = phospholipid transfer protein; Apo = apolipoprotein; Angptl3 = angiopoietin-like protein 3; LPL = lipoprotein lipase; SREBP = sterol regulatory element binding protein; SHP = short heterodimer partner; FAS = fatty acid synthase; PEPCK = phosphoenolpyruvate carboxykinase; GLUT4 = glucose transporter 4; Fbp1 = fructose biphosphatase 1; G6P = glucose-6-phosphatase. ↑ = upregulated; ↓ = downregulated.