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Review

Liver X receptors and immune regulation

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Abstract

Recent studies suggest that homeostasis of lipid metabolism is crucial for the function of various immune cells. Oxygenated derivatives of cholesterol (oxysterols) are well-known regulators of lipid metabolism and have diverse functions, such as inhibition of cholesterol synthesis, efflux of intracellular cholesterol, synthesis of cholesterol esters, and activation of liver X receptors (LXRs). In this review, we introduce novel roles of the oxysterol receptors LXRs in the immune system, including regulation of inflammatory responses, T cell expansion, immunoglobulin production, and antitumor responses. We also discuss lipid-mediated signaling as a potential target for treatment of immune diseases.

Keywords: adaptive immunity; innate immunity; liver X receptor; oxysterol.

Introduction

Oxygenated derivatives of cholesterol (oxysterols), such as 7-α-hydroxycholesterol, 7-ketocholesterol, 24S-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, and 22R-hydroxycholesterol, are produced from cholesterol through auto-oxidation (1). In addition, enzymatic processes have been reported to occur during oxysterol production. For example, cholesterol 7-α-hydroxylase converts cholesterol to 7-α-hydroxycholesterol. The enzymes 24S-hydroxylase, 25-hydroxylase, and 27-hydroxylase contribute to biosynthesis of 24S-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol, respectively, starting with cholesterol (2, 3). However, oxysterols are present in very low concentrations in plasma, and for that reason, it has been difficult to investigate their biological functions *in vivo* for many years. In the 1990s, Mangelsdorf and colleagues employed an *in vitro* binding assay to reveal that oxysterols are ligands for the liver X nuclear receptor (LXR) (4, 5). Currently, 25-hydroxycholesterol, 27-hydroxycholesterol, 22R-hydroxycholesterol, and 24S, 25-epoxycholesterol are thought to be naturally occurring ligands bound by LXR.

LXRα (NR1H3) and β (NR1H2) were identified from a liver cDNA library in 1994 and 1995. Further studies demonstrated that LXRα expression is restricted to liver, lung, spleen, adipose tissue, kidney, intestine, and adrenal glands. In contrast, LXRβ expression is ubiquitous. As summarized in Table 1, murine leukocytes (excluding macrophages) predominantly express LXRβ but not LXRα (6, 7); however, human CD4 T cells and B cells express both LXRα and LXRβ (Table 1) (8, 9). This discrepancy can be explained by an autoregulatory loop involving LXRα: namely, promoter of the human LXRα gene, but not of the murine LXRα gene, has an LXRα binding region, and binding of LXRα to its own promoter induces transcription of the gene (10).

Recently, Chen et al. used triple-knockout mice deficient in cholesterol 24S-hydroxylase, 25-hydroxylase, and 27-hydroxylase to show that these naturally occurring oxysterols act as ligands for LXR *in vivo* (11). Interestingly, recent studies of LXR-null mice demonstrated that LXR activation via oxysterols plays a role in regulating the innate and adaptive immune responses. Mice lacking LXRs exhibit defective clearance of intracellular bacteria and apoptotic cells (12–14), age-dependent lymphoid hyperplasia, and systemic autoimmune diseases (6, 12), as well as increased antitumor responses (15). In addition to LXR activation, however, oxysterols have LXR-independent biological functions, such as inhibition of HMG CoA reductase (16–18) and synthesis of cholesterol esters (19–22). In the following section, we will discuss how oxysterols contribute to the regulation of the immune response.

Roles of LXR activation for macrophage functions in innate and adaptive immunity

Macrophages play a crucial role in innate immunity against bacterial infection. Joseph et al. reported that activation of LXR in macrophages with a synthetic ligand represses the expression of proinflammatory genes such as interleukin (IL)-6, IL-1β, COX-2, and iNOS in response to bacterial

Table 1 LXR expression in immune cells.

	LXRα	LXRβ
T cells (6)	±	+
B cells (6)	±	+
Macrophage (6)	+ +	+ +
Mast cells (7)	±	+
Human $CD4^+$ T cells (8)	+	+
Human B cells (9)	+	+

infection or lipopolysaccharide (LPS) stimulation, indicating a link between LXR signaling and inflammatory responses (23). This LXR-dependent repression of proinflammatory gene expression in macrophages is mediated through the suppression mechanism known as transrepression (24, 25). In contrast to these findings, upon LPS stimulation in the absence of synthetic LXR ligands, the levels of proinflammatory gene expression induced in $LXR\alpha\beta^{+/+}$ and $LXR\alpha\beta^{-/-}$ macrophages were comparable (23). These results suggest that basal LXR activation via endogenous oxysterols in macrophages is insufficient to repress inflammatory responses against pathogens. Nevertheless, $LXR\alpha^{-/-}$ but not $LXR\beta^{-/-}$ mice show high susceptibility to the intracellular pathogen *Listeria monocytogenes* (LM) (14). This susceptibility is due to the fact that $LXR\alpha^{-/-}$ macrophages fail to express the scavenger receptor SPα/AIM, which protects LM-infected macrophages from apoptosis and promotes the killing of LM cells. These findings indicate distinct functions for LXR isoforms in macrophage antimicrobial activity and apoptosis.

Clearance of apoptotic cells by macrophages is essential for maintenance of the immune system. A-Gonzalez et al. recently showed that basal LXR-mediated signaling in macrophages is necessary for expression of mer receptor tyrosine kinase (Mer) which is crucial for clearance of apoptotic cells via phagocytosis (12). $LXR\alpha\beta^{-/-}$ mice thus exhibit a selective defect in phagocytosis of apoptotic cells and bring about subsequent anomalous proinflammatory responses. Consequently, a breakdown in self-tolerance, production of autoantibodies, and development of autoimmune glomerulonephritis are observed in aging LXR-deficient mice. Figure 1 illustrates the roles of endogenous ligand-mediated LXR activation in macrophage function. In the next section, we introduce the molecular mechanisms responsible for LXR-mediated gene activation and transrepression.

Mechanisms of LXR-mediated gene activation and transrepression

LXRs associate with retinoid X receptor (RXR). These heterodimers bind to specific DNA sequence, termed LXR response element, located in promoter regions of target genes such as ATP-binding cassette transporters. LXR response element consists of direct repeats of hexanucleotide (AGGTCAN4AGGTCA) separated by four nucleotides (26, 27). The heterodimers can be activated by ligands for LXRs or RXR (5). Activated-LXR:RXR heterodimer can act as transcriptional suppressors by co-operating with co-repressor complexes such as nuclear receptor co-repressor (NcoR) and silencing mediator of retinoic acid and thyroid hormone receptors (SMRT). Under inflammatory conditions, the co-repressor complex is degraded via the proteasome pathway in the absence of LXR ligand. In the presence of LXR ligand, LXR is SUMOylated and protects the co-repressor complex from the proteasomal degradation system (28). LXR-mediated stabilization of co-repressor complex results in repression of inflammatory gene expression.

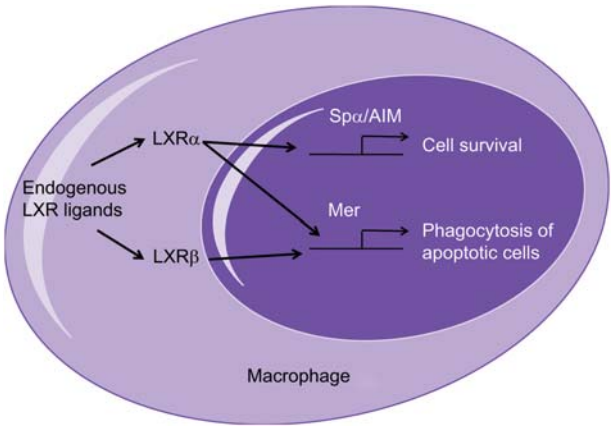

Figure 1 Endogenous ligand-mediated LXR activation in macrophages promotes survival and phagocytosis.
Basal LXR activation via naturally occurring oxysterols is required for the expression of Spα/AIM and Mer in macrophages. LXRβ activation is dispensable for Spα/AIM expression. Spα/AIM promotes cell survival by protecting microbially infected macrophages from apoptosis. Mer is crucial in the clearance of apoptotic cells via phagocytosis.

LXRβ-dependent regulation of murine T cell proliferation in response to antigens

It has been reported that some oxysterols, including 25-hydroxycholesterol effectively inhibit T cell proliferation in response to mitogenic or antigenic stimulation (29–31). However, the reduced proliferative ability of T cells is not fully reversed by the addition of mevalonate, indicating that oxysterol-mediated inhibition of HMG CoA reductase also contributes to the inhibition of T cell proliferation. One recent study employing the synthetic LXR ligand T0901317 demonstrated that ligand-mediated LXR activation reduces T cell proliferation following antigen stimulation (32). Together, these findings raise the possibility that LXR activation regulates the proliferative capacity of lymphocytes. Bensinger and colleagues reported that LXR signaling couples sterol homeostasis to antigen-specific T cell proliferation (6). T cell activation induces expression of the oxysterol-metabolizing enzyme sulfotransferase (SULT)2B1, resulting in repression of LXR signaling leading to cholesterol efflux and upregulation of (sterol regulatory element binding protein) SREBP signaling which induces cholesterol synthesis (Figure 2). SULT2B1 catalyzes the transfer of sulfate groups

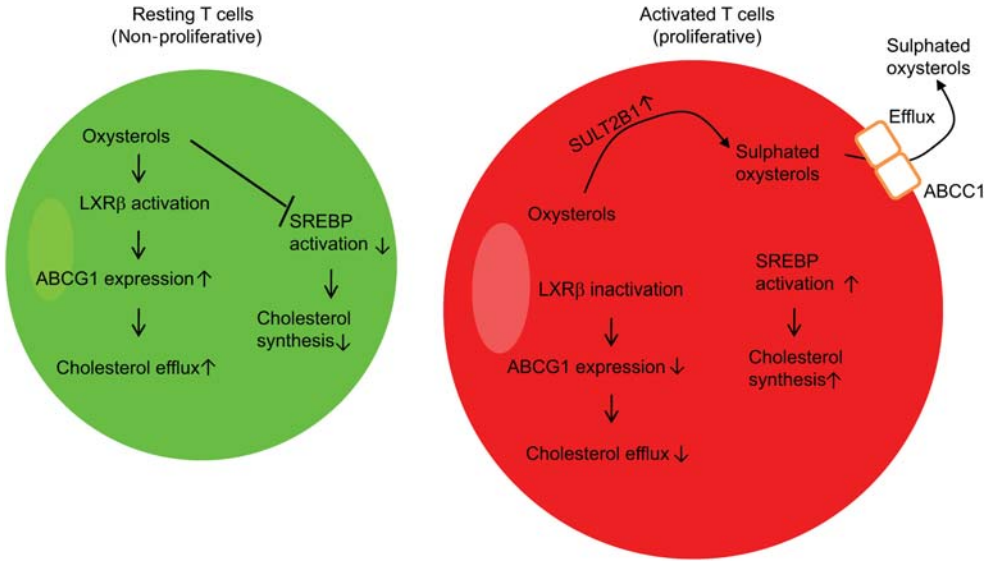

Figure 2 LXR signaling couples sterol homeostasis to T cell proliferation.
In resting T cells, oxysterols suppress intracellular cholesterol levels by activating LXRβ-dependent cholesterol efflux and inhibiting SREBP-dependent cholesterol synthesis. Upon antigen stimulation, expression of SULT2B1, which can inactivate oxysterols, is upregulated. Inactivation of SULT2B1-sensitive oxysterols results in downregulation of cholesterol efflux and upregulation of cholesterol synthesis. ABCG-deficient T cells are unable to proliferate in response to stimulation.

to oxysterols, resulting in inactivation of the oxysterols. The inactivation of oxysterols, in turn, results in downregulation of ABCG1, an LXR-regulated transporter responsible for cholesterol efflux. Downregulation of ABCG1-mediated cholesterol efflux is indispensable for T cell proliferation. Indeed, ABCG1$^{-/-}$ T cells fail to proliferate following mitogenic stimulation. As mentioned in the introduction, murine T cells predominantly express LXRβ. LXRβ$^{-/-}$ mice, therefore, display lymphoid hyperplasia and enhanced responses to antigenic stimulation. Given that (i) murine B cell proliferation in response to antigenic stimulation is reduced in the presence of several synthetic LXR ligands or 22R-hydroxycholesterol (6) and (ii) older LXRαβ$^{-/-}$ mice exhibit a marked increase in the frequency and absolute numbers of CD19^{+}B220^{+} B cells in their spleens and lymph nodes (12), it can be concluded that murine B cell proliferation is regulated by LXR signaling. In contrast, it has been reported that the proliferation of human and murine B cells induced by combined stimulation with anti-CD40 antibody and cytokines is not altered in the presence of T0901317 (9). Further investigations will be required to elucidate the role of LXR activation in B cell proliferation in response to different stimuli.

A possible role for LXR activation in immunoglobulin production by B cells

The number of circulating auto-antibodies that recognize nuclear antigens (e.g., double-stranded DNA and histones) is drastically increased in older LXRαβ$^{-/-}$ mice. It seems that the increased number of B cells in LXR-deficient mice can contribute to the excess production of immunoglobulin. However, recent studies have suggested that LXR signaling directly regulates immunoglobulin production in B cells. Chang et al. reported that T0901317 inhibits polyclonal IgG secretion from murine B cells stimulated with homocysteine (33). Moreover, Heine et al. demonstrated that the same synthetic LXR ligand induces the expression of CD23, a low-affinity IgE receptor, in murine B cells and suppresses production of IgE induced by LPS and IL-4 (Figure 3) (9). Together, these findings demonstrate that induced LXR signaling affects immunoglobulin production. Recently, the Russell group addressed the *in vivo* roles of endogenous 25-hydroxycholesterol in immunoglobulin secretion from murine B cells (34). Cholesterol 25-hydroxylase-deficient mice exhibit a marked increase in serum IgA but not IgG1, IgG2b, IgG3, or IgM, demonstrating that 25-hydroxycholesterol negatively regulates IgA production. Treatment of splenic B cells with 25-hydroxycholesterol specifically inhibits IgA class switch recombination in response to costimulation with LPS, IL-5, and TGF-β1 by reducing the expression of activation-induced cytidine deaminase (AID) (Figure 3). Despite these findings, it is unclear whether LXR activation is responsible for 25-hydroxycholesterol-mediated suppression of IgA class switching for a few reasons. First, treatment of B cells with two other LXR-activating oxysterols, 22R-hydroxycholesterol and 24S-hydroxycholesterol, does not suppress IgA class switching (34). Moreover, the synthetic LXR ligand T0901317 fails to repress AID expression or IgA production in murine B cells (9).

In vivo, macrophages are a major source of 25-hydroxycholesterol. Upon LPS stimulation, the expression of choles-

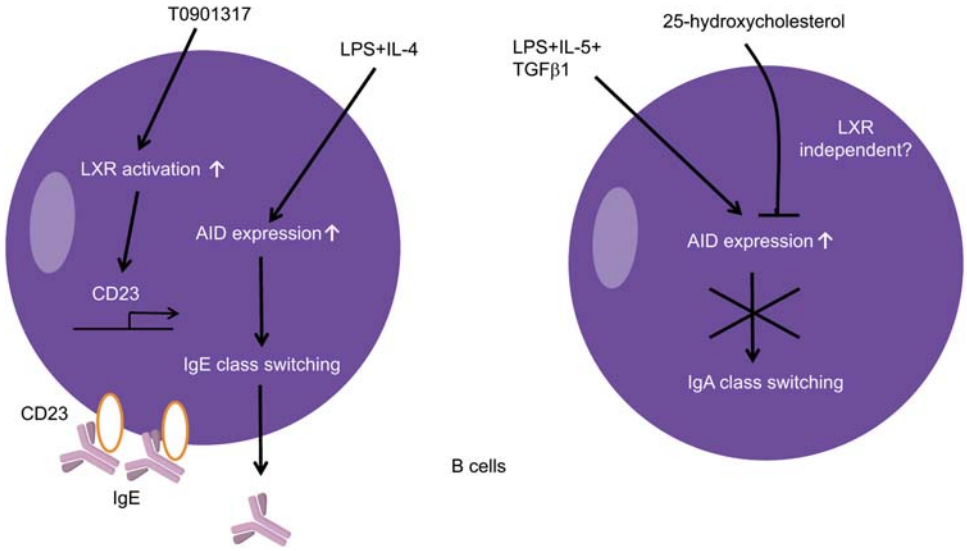

Figure 3 Regulation of immunoglobulin class switching in B cells.
Activation of LXR with synthetic ligands inhibits IgE production from B cells by inducing CD23 expression, whereas LXR activation does not alter AID expression and IgE class switching. In contrast, 25-hydroxycholesterol, a naturally occurring oxysterol, suppresses AID expression and IgA class switching. It is unclear whether LXR activation is involved in 25-hydroxycholesterol-mediated suppression of AID expression.

terol 25-hydroxylase in macrophages is upregulated and newly synthesized 25-hydroxycholesterol is released from the cells (35). Importantly, activation of innate immunity could increase *de novo* synthesis of 25-hydroxycholesterol, which in turn modulates the expression pattern of immunoglobulin isotypes in B cells.

LXR activation and dendritic cell-mediated antitumor immune response

Dendritic cells take up antigens and migrate into the draining lymphoid organs, where they prime naïve T cells to become effector T cells. In the case of antitumor immunity, killer T

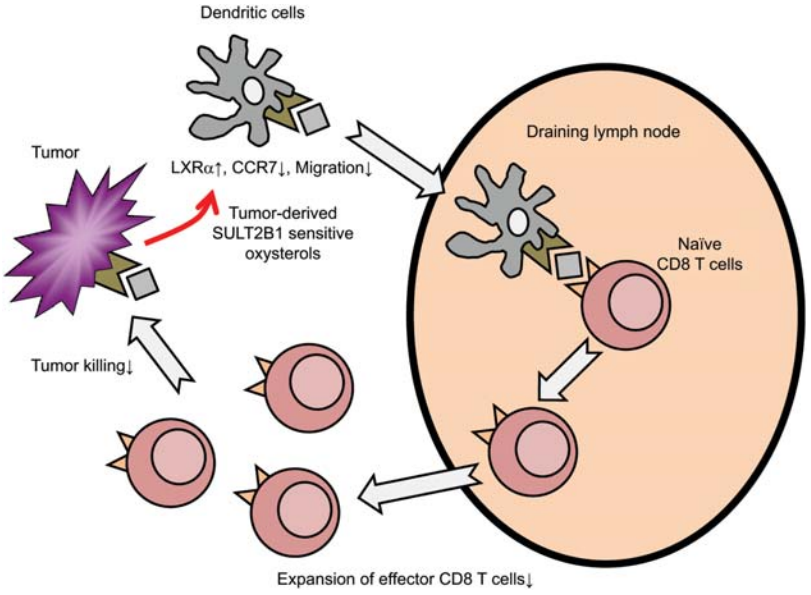

Figure 4 Tumor cells escape from antitumor immune responses by activating LXR signaling.
Tumor cells produce oxysterols that are sensitive to SULT2B1. These oxysterols activate LXRα in dendritic cells. CCR7 expression on dendritic cells is subsequently reduced in an LXRα-dependent manner. Dendritic cells lacking CCR7 fail to migrate into lymphoid organs such as draining lymph nodes, resulting in abrogation of naïve CD8 T cell priming and effector cell expansion.

cells that recognize specific tumor-derived antigens attack their target cells. The migration of dendritic cells requires expression of CC chemokine receptor-7 (CCR7), the lymphoid-homing receptor, on the cell surface (36). Recently, Villablanca et al. showed that tumor cells escape the antitumor immune response by activating LXR signaling in dendritic cells, which results in reduced dendritic cell CCR7 expression (Figure 4) (15). Various tumor cells, including melanoma (14/21; 66%), colon (2/4; 50%), lung (2/5; 40%), and kidney tumors (3/8; 37.5%), produce oxysterols. These tumor-derived oxysterols effectively downregulate CCR7 expression in dendritic cells in an LXRα-dependent manner. Consequently, tumor growth is decreased in chimeric mice transplanted with bone marrow from LXRα-deficient mice. In addition, mice injected with tumor cells expressing SULT2B show reduced tumor growth, suggesting that SULT2B-sensitive oxysterols play an important role in the mechanism of tumor immunoescape.

Expert opinion and outlook

As reviewed above, naturally occurring LXR agonists such as oxysterols are essential for proper regulation of the immune system. We believe that these findings confer novel insights into functional relevance of lipid-mediated signaling and immune responses. We also discuss the potential value of artificial enhancement of LXR activation by oxysterols or synthetic ligands as a therapeutic strategy for treatment of immune diseases. In many animal models, administration of natural or synthetic LXR agonists results in the amelioration of glomerulonephritis (12), allergic dermatitis (23, 37, 38), experimental autoimmune encephalomyelitis (32, 39), and type II collagen-induced arthritis (40) (Table 2). Taken together, these studies raise the possibility that the regulation of LXR activation is a promising therapeutic target for treatment of these immune disorders. With regard to collagen-induced arthritis, however, the opposite conclusion has been reached by other researchers (41). Thus, further studies will be required to assess the therapeutic potential of LXR activation in autoimmune and inflammatory diseases. Additionally, the route of administration is crucial for the clinical application of LXR ligand because systemic administration of LXR ligands causes hypertriglycemia by inducing the expression of lipogenic genes in the liver (42). The discovery of tissue- or cell-type specific LXR ligand [such as YT-32, a small intestine-selective LXR agonist (43)] will therefore prove the importance of LXR ligands as therapeutics. However, recent studies suggest that actions of LXR ligand differ between human and murine inflammatory responses (44, 45). Unlike murine cells, LPS response in human macrophages and mature dendritic cells is enhanced by pretreatment with LXR ligand. In human cells, LXR activation results in enhancement of TLR4 expression and NF-κB signaling. Such species-specific regulation of gene expression is dependent on the presence of the LXR response element on the human TLR4 gene promoter. This element does not present in the promoter of the murine TLR4 gene. These findings clearly indicate complexity of LXR signaling. Thus, we consider that findings obtained from animal models need to be carefully assessed.

Table 2 Inhibitory effects of LXR agonists on immune diseases.

Disease	LXR ligands
Allergic dermatitis	T0901317 (37), GW3965 (37, 38) 22R-hydroxycholesterol (38), 25-hydroxycholesterol (38)
Glomerulonephritis	GW3965 (12)
Experimental autoimmune encephalomyelitis	T0901317 (32, 39)
Arthritis	GW3965 (40)

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