Liver X Receptors: Regulators of Cholesterol Metabolism, Inflammation, Autoimmunity, and Cancer

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The interplay between cellular stress and immune response can be variable and sometimes contradictory. The mechanisms by which stress-activated pathways regulate the inflammatory response to a pathogen, in autoimmunity or during cancer progression remain unclear in many aspects, despite our recent knowledge of the signalling and transcriptional pathways involved in these diseases. In this context, over the last decade many studies demonstrated that cholesterol metabolism is an important checkpoint for immune homeostasis and cancer progression. Indeed, cholesterol is actively metabolized and can regulate, through its mobilization and/or production of active derivatives, many aspects of immunity and inflammation. Moreover, accumulation of cholesterol has been described in cancer cells, indicating metabolic addiction. The nuclear receptors liver-X-receptors (LXRs) are important regulators of intracellular cholesterol and lipids homeostasis. They have also key regulatory roles in immune response, as they can regulate inflammation, innate and adaptive immunity. Moreover, activation of LXRs has been reported to affect the proliferation and survival of different cancer cell types that show altered metabolic pathways and accumulation of cholesterol.

In this minireview we will give an overview of the recent understandings about the mechanisms through which LXRs regulate inflammation, autoimmunity, and cancer, and the therapeutic potential for future treatment of these diseases through modulation of cholesterol metabolism.

Keywords: liver-X-receptor, cholesterol, inflammation, autoimmunity, cancer metabolism, antitumor immune responses

INTRODUCTION

Cholesterol metabolism is deeply linked to different aspects of immunity and inflammation. It is generally thought as an exogenous player on immunity during disease, as in the case of pathologic cholesterol overloading of foam cells in atherosclerosis or more in general in hypercholesterolaemia. However, increasing evidences have recently changed this view by demonstrating that a number of
immune receptors and transcription factors such as Toll-like Receptors (TLRs), C-X-C motif chemokine receptor 2 (CXCR2), Stimulator of IFN genes (STING) and retinoic acid-related orphan receptor-γ (ROR-γ) are profoundly regulated by sterols (1–7). Moreover, regulation of intracellular cholesterol homeostasis controls lymphocyte proliferation and adaptive immune responses (8).

In this review we will discuss recent literature regarding aspects of lipid and cholesterol metabolism in tissues homeostasis, providing to the readers a synthetic overview of the main connections and regulatory interactions between cholesterol cellular metabolism and the activity of LXRs in the context of inflammation, autoimmunity and cancer. LXRs are transcription factors able to regulate specific gene networks implicated in cholesterol and lipid metabolism both in homeostatic and pathological conditions. Moreover, LXRs can mediate anti-inflammatory activities and modulate the immune response, promoting the expression of mediators which have a role in the control of inflammatory disorders and in the response to microbial infection. In a different scenario, accumulation of cholesterol has been also described in many types of cancer cells indicating metabolic addiction. This further expands the possible implications of its dysregulation in cancer progression (9, 10), configuring cholesterol as an important metabolic determinant. LXRs play relevant roles in cancer biology and in anti-tumor immune responses, opening new therapeutic possibilities (Figure 1) and (Table 1).

**LXRs: A LINK BETWEEN LIPID METABOLISM AND IMMUNE RESPONSE**

LXRs are transcription factors belonging to the nuclear receptors (NRs) superfamily. They are master regulators of cholesterol and lipid intracellular homeostasis (47). There are two isoforms of LXRs, LXRα (NR1H3), and LXRβ (NR1H2) (48, 49) that share extensive sequence homology ([77% identity in both the DNA binding domain (DBD) and ligand binding domain (LBD)]. Despite this similarity, they have rather different expression patterns (50); indeed, the expression of these NRs depends on the cell type and tissues analyzed, with LXRα more expressed in liver, intestine, adipose tissue and cells of the myelomonocytic lineage, while LXRβ is expressed more ubiquitously (51). Thus, their transcriptional role seems to be determined by their relative expression levels in specific tissues or cells, although important differences have also been identified in vivo between the two isoforms (52).

Different studies in vitro and in vivo have characterized a number of cholesterol derivatives including oxysterols, oxidized forms of cholesterol and cholesterol precursors (e.g., desmosterol) as LXR activators, able to bind with different affinities to the LXR LBD (47, 53, 54). When these endogenous ligands, or synthetic pharmacological agonists, trigger activation of LXRs, they heterodimerize with retinoid X receptors (RXR) and bind to target gene promoters on LXR-responsive-elements (LXREs), canonical binding sites composed of a repeated 6-mer sequence (5’-AGGTCA-3’) separated by four nucleotides (55).

**FIGURE 1** | Schematic representation of LXRs activators and the different effects on regulated genes and pathways involved in cholesterol and lipid homeostasis, regulation of immune system and cancer proliferation and progression. When these ligands trigger the activation of LXRs, they heterodimerize with RXR and bind to target gene promoters on LXR-responsive-elements, regulating the transcription and expression of specific target genes.
Activation of LXR leads SREBP-1 to act on IL-17 promoter (28).

LXR activation mediates anti-inflammatory effects in colon epithelial cells (36).

Lack of LXR induces colitis in DSS and TNBS murine models.

LXRs, Cholesterol, and Inflammation

The implications of direct LXR-mediated actions and regulation of cholesterol metabolism in the control of inflammatory diseases and cancer progression. This table summarizes the different experimental models and the roles of LXR in these pathologic conditions.

LXR, Inflammation, and Autoimmunity

| LXR/cholesterol-mediated responses | Immune mechanisms | Experimental models |
|-----------------------------------|-------------------|---------------------|
| Cholesterol enrichment in macrophage plasma membrane promotes the activity of TLRs (11, 12). | Cholesterol crystals uptake in macrophages activate NF-κB/Parasitism, and the pro-inflammatory cytokines IL-1β and IL-18 (13). Prevention immune system anomalous activation (15, 16). | Atherosclerosis susceptibility (14). Atherosclerosis plaque (15). |
| Upregulation of ABCA1 and ABCG1 on engulfed apoptotic cells (15, 16). Differentiation of M2 macrophages (15, 16). | Transcriptional repression of NF-κB, AP-1, STAT1, Inhibition of primary cytokine production (17, 19, 20). Repression of pro-inflammatory cytokine maturation to their active form (e.g., IL-1β) (21). Decrease of transactivation mediated by NF-κB of inflammatory genes (24). Reduced production of the pro-inflammatory cytokines IL-17 and IFN-γ and reduced expression of IL-23R (28, 29). Decreased pro-inflammatory cytokines production in CIA models (23, 31–32). Enhanced TLR-driven cytokines and chemokines secretion in RA synovitis (33–34). LXR activation can suppress Th1 and Th17 polarization in vitro and promote the differentiation of gut associated Tregs (37). | Inflammation and autoimmune diseases (atherosclerosis, dermatitis, neuroinflammation, lupus and arthritis) (22–23). Inflammation control. |
| Transrepression: LXR binds to the NCoR-SMRT co-repressor preventing signal-dependent clearance from the promoter of pro-inflammatory genes (17, 18). | | Efferocytosis (15, 16). |
| Indirect activity on inflammation: induction of lcPUFAs (e.g., omega 3 fatty acid) (24). LXRα maintains BBB integrity and its activation modulates the pro-inflammatory response in astrocytes/microglia (25–27). Activation of LXR leads SREBP-1 to act on IL-17 promoter (28). Activation of LXR by pharmacologic agonists or ligands present in synovial fluid. LXR activation mediates anti-inflammatory effects in colon epithelial cells (36). Lack of LXR induces colitis in DSS and TNBS murine models. | | Rheumatoid Arthritis (35). CIA models (23, 31–32). |

| LXR activity | Immune mechanisms | Experimental models |
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To activate target gene transcription, unliganded LXRs and co-activators such as nuclear receptor corepressor 1 (NCoR1) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT), bound to LXRs, have to be displaced from chromatin to allow the binding of transcriptional co-activators [i.e., nuclear receptor co-activator 1 (NCOA1) and activating signal co-integrator 2 (ASC2)], leading to transcription (17).

Recent findings suggest that LXRs may be also recruited de novo to the promoter of target genes when triggered by ligands (18).

Once activated, they regulate the expression of genes involved in lipid and glucose metabolism (51, 56). In this context, LXRs are master regulators of cholesterol sensing; they counteract aberrant cellular cholesterol overload by upregulating the expression of sterol transporters such as the ATP binding cassette (ABC) family members ABCA1 and ABCG1, together with the transcription factors sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate-response element-binding protein (ChREBP) that regulate critical lipogenic pathways. Moreover, the activation of LXRs also induces the expression of inducible degrader of the LDL-receptor (IDOL), which is able to reduce the expression of low-density lipoprotein receptor (LDLR) on the cell surface and the uptake of LDL/cholesterol particles (57).

Besides the regulation of cholesterol homeostasis, genetic and pharmacological studies have pointed out the role of LXRs as an important link between lipid metabolism, regulation of immune cell function and inflammation (58). Indeed, these NRs can both promote and repress the expression of specific immune regulatory gene networks (59). As discussed below, LXRs can induce anti-inflammatory activities in macrophages and Dendritic Cells (DCs) and represent a critical link between cholesterol metabolism, proliferation and migration of activated T and B lymphocytes (8, 15, 21, 28, 60–65), thus playing an important role in the control of inflammatory, autoimmune and infectious diseases.

LXRs, Cholesterol, and Inflammation

Different pathways link inflammation to cholesterol metabolism and LXRs activity. Alteration of cellular cholesterol homeostasis
can both enhance or reduce innate receptor signalling and inflammasome activation. Cholesterol enrichment in macrophage plasma membrane promotes the activity of TLRs as in the case of the TLR4-MD2 and TLR4-CD14 complexes activated in response to lipopolysaccharide (LPS) (11, 12). On the other hand, the activation of the reverse cholesterol transport (RCT) mediated by ABCA1 and ABCG1 transporters limits the formation of cholesterol-enriched lipid rafts in the plasma membrane and/or in the endosomal system. This inhibits MyD88-dependent TLRs trafficking by selective reduction of free cholesterol content and suppresses macrophage inflammatory responses (66). This mechanism has been elegantly demonstrated in mouse models deficient for ABCA1 and ABCG1, shown to accumulate cholesterol in peritoneal macrophages and to exhibit enhanced inflammatory responses to TLR agonists (11). In line with these observations, in a model of atherosclerosis susceptibility, pathogens can interfere with macrophage cholesterol metabolism through inhibition of the LXRs. Here, the activation of TLR-3 and -4 by microbial ligands has been shown to repress the expression of selected target genes including ABCA1 in macrophages, as clearly shown in aortic tissue in vivo, with a mechanism connected to reduced cholesterol efflux from macrophages regulated by interferon regulatory factor-3 (IRF3)-mediated inhibition of LXRs on their target promoters (14). Activation of efferocytosis is also associated to the activity of LXRs, which results in the efflux of free cholesterol derived from engulfed apoptotic cells by upregulating ABCA1 and ABCG1 transporters. This mechanism, together with the LXR-mediated alternative (M2) macrophage differentiation, can prevent aberrant activation of the immune system (15, 16). Moreover, the removal of apoptotic cells helps avoiding autoimmunity, as shown in murine models of lupus-like autoimmunity where treatment with LXR agonists ameliorated disease progression (15, 67). In a different context, increased cellular content of cholesterol can trigger cholesterol crystal formation, as shown in atherosclerotic plaques. In this disease model, cholesterol crystals uptake or formation in macrophages has been shown to activate NLR family pyrin domain containing 3 (NLRP3)/inflammasome with the secretion of pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 and to promote the progression of atherosclerosis (13).

As shown for other NRs, LXRs are anti-inflammatory; they can inhibit the transcriptional induction of pro-inflammatory genes mediated by critical transcription factors as NF-kB, AP-1 or STAT-1. In this regard, pharmacological activation of LXRs has been shown to ameliorate the severity of the inflammatory response in murine models of atherosclerosis (22), neuroinflammation (30, 68), dermatitis (22, 69), lupus (67) and arthritis (23), inhibiting primary cytokine production. Mechanistically, studies using LXR agonists in macrophages have shown that, depending on the LXR isoform, these NRs can repress the induction of pro-inflammatory genes through a molecular mechanism known as “transrepression”. Here, after histone deacetylase-4 (HDAC-4)-dependent conjugation of LXR with small ubiquitin-related modifier (SUMO)-2/3 at specific lysine residues in the LBD, LXR becomes able to bind to the NCoR-SMRT co-repressor, thus preventing signal-dependent clearance from the promoters of pro-inflammatory genes (17, 19). With a different mechanism, LXRs can inhibit Interferon-γ-induced genes in astrocytes, where LXRα and LXRβ are SUMO-conjugated by HDAC4 or by protein inhibitor of activated STAT1 (PIAS1), respectively, and interact with phosphorylated signal transducer and activator of transcription-1 (STAT-1) preventing its binding to gene promoters (20). Furthermore, LXRs activation can repress pro-inflammatory cytokine maturation to their active form as demonstrated for IL-18 and can induce specific endogenous inhibitors (i.e., IL-18BP) (21).

In addition to direct transrepression activity on pro-inflammatory genes, LXRs can mediate other important integrated mechanisms contributing to the control of inflammation. LXRs can induce the synthesis of long-chain polyunsaturated fatty acids (lcPUFAs) such as omega 3 fatty acids. The presence of lcPUFAs can decrease transactivation mediated by NF-kB of inflammatory genes, modifying histone acetylation in their regulatory regions (24). Moreover, lcPUFAs have been shown to increase the production of eicosanoids and selected pro-resolving lipid mediators (70, 71). Interestingly, increased LXRs activity can also induce macrophage polarization toward a more pro-resolving phenotype, directly upregulating the expression of MER proto-oncogene Tyrosine Kinase (MERTK), a receptor that promotes the synthesis of mediators implicated in inflammation resolution (15, 72). Furthermore, as demonstrated in hepatic inflammation models, induction of the polyunsaturated phospholipids (PLs) remodeling enzyme lysophosphatidylcholine acyltransferase 3 (Lpcat3) by LXRs increases the formation of PLs and decreases membrane saturation, counteracting endoplasmic reticulum stress induced by fatty acids in hepatocytes, improving hepatic metabolic stress and inflammation by modulating aberrant c-Src activation (73). An additional consideration that can add a layer of complexity is that LXRs are highly expressed by haematopoietic stem cells (HSCs) and myeloid progenitor cells. In these cells, activation of LXRs can increase the ABCA1/ABCG1/apolipoprotein E (APOE)-mediated cholesterol efflux, which is able to reduce their proliferative responses to IL-3 and GM-CSF, thus indirectly modulating the production of inflammatory cells (74).

**LXRS AND AUTOIMMUNITY**

The activity of LXRs and cholesterol metabolites is implicated in the control and progression of several autoimmune diseases.

Altered lipid profiles have been associated with poor outcome of multiple sclerosis (MS) (75–80), an autoimmune disease characterized by inflammatory cell infiltrates and demyelination (81, 82). In this regard, obesity, among other environmental factors, has been described as a risk factor for MS in several epidemiological studies (83–86). In animal models of experimental autoimmune encephalomyelitis (EAE), the most common experimental model for human inflammatory demyelinating disease, selected agonists of LXRs (e.g., T0901317) have been shown to improve the severity of central nervous system inflammation (30). In line with this
evidence, the activity of LXRα is indispensable for maintaining blood-brain barrier (BBB) integrity and its immune quiescence. Indeed, in a model of EAE, the specific knockout of LXRα in brain endothelial cells has been shown to increase BBB permeability and endothelial inflammation (25). Moreover, activation of LXRs using agonists in vivo has been shown to repress the production of the pro-inflammatory cytokine IL-17 (28), together with IFNγ and IL-23R expression (29). Noteworthy, Th17 cell differentiation is modulated by LXRs via induction of sterol regulatory element-binding protein 1c (SREBP-1c), which is able to bind to the E-box element on the IL-17 promoter and to physically interact with the aryl hydrocarbon receptor (AHR), inhibiting its transcriptional activity (28). Interestingly, the activity of LXRs mediated by oxysterols can also modulate pro-inflammatory responses in microglial and astrocytes (26, 27) possibly contributing to ameliorate inflammation.

LXRs have also been hypothesized as a possible therapeutic target for rheumatoid arthritis (RA), a chronic autoimmune disorder characterized by infiltration of inflammatory leukocytes in the synovial compartment, which causes cartilage and bone damage (87). Initial conflicting reports have described both protective and promoting actions of LXRs-mediated pathways in murine models of inflammatory arthritis. LXR agonists such as T0901317 or GW3965, attenuated the symptoms, decreasing the production of pro-inflammatory cytokines in different murine collagen-induced arthritis (CIA) models (23, 31, 32, 88) and suppressed inflammatory gene expressions in RA fibroblast-like synoviocytes (35). By contrast, other reports described increased inflammation and cartilage destruction mediated by ligand activated LXRs (T0901317 or GW3965) in CIA models and found that LXR pathways are significantly upregulated in RA synovial macrophages. Interestingly, in these models the activity of both LXR isoforms was required in control mice to induce the progression of inflammation, in respect to single LXRα−/− or LXRβ−/− mice (33), thus implying overlapping and exclusive effects in these models. Moreover, activation of LXRs by ligands present within synovial fluids enhanced TLR-driven cytokine and chemokine secretion, suggesting a novel mechanism that can promote RA synovitis (33, 34, 89).

In a different scenario, both LXR subtypes are expressed in human and murine colon and were described to mediate anti-inflammatory effects in colon epithelial cells (36). Furthermore, in a murine experimental model of intestinal bowel disease (IBD), it was reported that LXR-deficient mice were more susceptible to dextran sodium sulphate (DSS) and 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis. In this regard, the activation of LXRs can suppress Th1 and Th17 polarization in vitro, lowering the expression of their secreted pro-inflammatory cytokines and promoting differentiation of protective gut-associated regulatory T cells in mice, where systemic LXR activation was obtained by oral treatment with the LXR agonist GW3965 (37). These data confirmed a dual role of LXR in the control of inflammation by the suppression of pro-inflammatory T cells and the parallel induction of regulatory T cells.

**LXRS AS REGULATORS OF LIPID METABOLISM, CANCER PROGRESSION, AND ANTITUMOR IMMUNITY**

Genes involved in cholesterol homeostasis are often mutated or dysregulated in cancer cells (10, 90). A higher intracellular cholesterol level due to an enhanced uptake by LDLRs, a decreased efflux by ABC transporters and the upregulation of de novo synthesis can sustain the metabolic need for cancer cell proliferation (90–93), and accumulation of cholesterol has been described in many types of tumors (9, 49, 91–93). Cells usually obtain cholesterol via different mechanisms including direct synthesis via the transcriptional activity of SREBPs, which promote the transcription of enzymes involved in cholesterol and fatty acid biosynthesis [i.e., 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) reductase] (94, 95). In this regard, the recent use of HMG-CoA inhibitors (Statins) to block the mevalonate pathway and cholesterol de novo biosynthesis showed promising results (96). However, cancer cells often gain selective proliferative advantage by enhancing LDLR-mediated uptake of exogenous cholesterol (38), rendering these therapies often unsuccessful. Perhaps, one of the best characterized examples of cancer cholesterol addiction is glioblastoma multiforme (GBM). The treatment of these cancer cells with LXR agonists induced degradation of LDLR and increased apoptosis in glioblastoma cells expressing mutant epidermal growth factor receptor (EGFR), where tumor growth and survival is strongly dependent on SREBP-1-mediated lipogenesis (38). Moreover, triggering of LXRs increases cellular cholesterol efflux by ABCA1, lowering its levels and inducing severe GBM cell death. Accordingly, LXR agonists (e.g., LXR-623) prolonged survival of mice models bearing GBM, indicating that targeting cholesterol metabolism may be a promising strategy in the treatment of this cancer (39, 97).

Pharmacological studies on various types of cancer models such as prostatic carcinoma, colon, mammary and skin cancer have shown that the activation of LXRs generates antiproliferative effects due to the destruction of growth signalling pathways and to the activation of pro-apoptotic signals (9). LXRs can reduce the expression/activity of cell-cycle regulators, as shown for S-phase Kinase associated protein (SPK2) in cancer cell lines (40) and, at the same time, are able to induce the expression of cell-cycle inhibitors as demonstrated for p21 and p27 (cyclin-dependent kinase inhibitors) in prostate and ovarian cancer cells, with a concomitant reduction in phospho-RB protein levels (41, 98). Moreover, in mouse models, activation of LXRs delayed the progression of androgen-dependent tumors towards androgen independence (41, 42).

In addition to these direct activities on cancer cell metabolism and survival, in the last few years experimental evidences have highlighted the importance of LXRs in anti-tumor immune responses. In this context, the role of LXR activation is still controversial. Several tumors can produce oxysterols that play an essential role in cholesterol homeostasis by activating LXRs (99, 100), and many of these metabolites can have antiproliferative activity in cancer cells (101). However, oxysterols can also inhibit...
the expression of CCR7 on DCs, a chemokine receptor critical for the migration of DCs to tumor-draining lymph nodes (44). Circulating and tumor-derived oxysterols have been also described to recruit pro-tumor neutrophils and to increase neo-angiogenesis and immunosuppression in a CXCR2-dependent and LXR-independent manner (6, 102). This highlights the capability of selected oxysterols to regulate a broad range of pro-tumor activities—depending on the LXR isoform expressed by the tissue from which tumor cells originate and on the surrounding microenvironment. Moreover, in breast cancer, 27-hydroxycholesterol has been shown to act as an estrogen receptor agonist inducing tumor growth and metastasis (103). On the other hand, LXRβ were reported to control cancer cell growth by inducing LXRβ-dependent pyroptosis of cancer cells and the activation of LXRβ in macrophages, promoted the phagocytosis of dying cancer cells (45). More recently, in different mouse cancer models treated with specific LXR agonists (i.e., RGX-104), has been observed a slower tumor growth which correlated with a decreased expansion of myeloid derived suppressor cells (MDSCs); these data were also validated in cancer patients, in a multicentre dose escalation phase 1 trial (43). Moreover, RGX-104 also partially abrogated the immunosuppressive effects of radiotherapy in a murine model of Non-Small-Cell Lung Carcinoma (NSCLC) (104). Mechanistically, the induction of ApoE, a transcriptional target of LXR, can induce MDSC depletion by triggering the low-density lipoprotein receptor-related 8 (LRP8) receptor on these cells, and potentiate activation of cytotoxic lymphocytes. In these settings, activation of LXRs together with PD-1 inhibition, improved the efficacy of cytotoxic T lymphocyte (CTL) and natural killer (NK) cells from cancer patients (43). In a different scenario, LXRs activation could upregulate MHC class I polypeptide-related sequence-A (MICA) and MICB expression in multiple myeloma cells, two ligands of the NK cell-activating receptor NK group 2 member D (NKG2D), by enhancing MICA promoter activity and inhibiting MICB degradation in lysosomes, thus improving NK cell-cytotoxicity (46).

**CONCLUSION**

The implication of cholesterol metabolism in the control of inflammatory diseases and cancer progression is the object of an interesting and controversial debate. Our increasing knowledge of the different roles mediated by LXRs in lipid homeostasis supports the idea that lipid metabolism and inflammation are closely connected and that their crosstalk is crucial for the evolution of different inflammatory diseases and, more in general, in the

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**FIGURE 2** | Summary of the most relevant pathways regulated by LXRs in the context of cholesterol homeostasis, inflammation, autoimmunity and tumor progression. These NRs act in a cell-, tissue- and context-dependent manner. In addition, many LXR-dependent and -independent pleiotropic effects mediated by oxysterols, produced in inflamed or tumoral microenvironments, add an additional level of complexity to these regulatory pathways. ABC, ATP binding cassette; AHR, aryl hydrocarbon receptor; APOE, apolipoprotein E; CTL, cytotoxic T lymphocyte; DC, dendritic Cell; DSS, IDOL, inducible degrader of the LDL-receptor; IRF3, interferon regulatory factor 3; LBD, ligand binding domain; PUFAs, long-chain polyunsaturated fatty acid; LDLR, low-density lipoprotein receptor; LRP8, low-density lipoprotein receptor-related 8; MDSC, myeloid derived suppressor cells; MERTK, MER proto-oncogene tyrosine kinase; NK, natural killer; SREBP-1, sterol regulatory element-binding protein 1; TLR, Toll-like receptor.
regulation of the immune response. The involvement of specific pathways regulated by LXRs during tumor progression and the possibility to pharmacologically modulate LXR activity, as an additional weapon for cancer therapy and for immunotherapy, have opened new therapeutic possibilities in this context. However, the activities of these NRs are often cell-, tissue-, and context-dependent, which makes it difficult to fully characterize their effects in disease conditions and to optimize specific therapeutic interventions in inflammatory disorders or in cancer therapy. In addition, many LXR-dependent and -independent pleiotropic effects of oxysterols produced in inflamed or tumoral microenvironments have been described in recent years, adding additional levels of complexity to these regulatory pathways (Figure 2). Another important issue is whether synthetic ligands that uncouple the anti-inflammatory and anti-cancer effects of LXRs from their role in cholesterol homeostasis can be developed. This is particularly important also in the context of different metabolic disorders with increased risk of developing diseases such as type 2 diabetes or cardiovascular disease, where beneficial effects of LXRs have been described (105). At the moment, different synthetic LXRs agonists have been optimized; however, their clinical application is limited by undesirable hyperlipidemic effects and other adverse side effects encountered in the central nervous system (106–111). The future development of isomorph- and/or tissue-specific LXR modulators and the possibility to target LXR-interacting co-factors involved in LXR transcriptional activation will open new therapeutic possibilities for treating these diseases.

**AUTHOR CONTRIBUTIONS**

MB and SP made substantial contributions to conception and design of the review. MC organized the study, together with AS, contributed to revision, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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**REFERENCES**

1. York AG, Williams KJ, Argus JP, Zhou QD, Brar G, Vergnes L, et al. Limiting Cholesterol Biosynthetic Flux Spontaneously Engages Type I IFN Signaling. Cell (2015) 163(7):1716–29. doi: 10.1016/j.cell.2015.11.045
2. Molnar E, Swamy M, Holzer M, Beck-Garcia K, Worch R, Thiele C, et al. Cholesterol and sphingomyelin drive ligand-independent T-cell antigen receptor nanoclustering. J Biol Chem (2012) 287(51):42664–74. doi: 10.1074/jbc.M112.386045
3. Reboldi A, Dang EV, McDonald JG, Liang G, Russell DW, Cyster JG. Inflammation. 25-Hydroxycholesterol suppresses interleukin-1-driven inflammation downstream of type I interferon. Science (2014) 345 (6197):679–84. doi: 10.1126/science.1254790
4. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol (2015) 15(2):104–16. doi: 10.1038/nri3793
5. Cyster JG, Dang EV, Reboldi A, Yi T. 25-Hydroxycholesterol in innate and adaptive immunity. Nat Rev Immunol (2014) 14(11):731–43. doi: 10.1038/ nri3755
6. Raccosta L, Fontana R, Maggioni D, Lanterna C, Villablanca EJ, Paniccia A, et al. The oxysterol-CXCR2 axis plays a key role in the recruitment of tumor-promoting neutrophils. J Exp Med (2013) 210(9):1711–28. doi: 10.1084/jem.20130440
7. Hu X, Wang Y, Hao LY, Liu X, Lesch CA, Sanchez BM, et al. Sterol metabolism controls T(H)17 differentiation by generating endogenous RORgamma agonists. Nat Chem Biol (2015) 11(2):141–7. doi: 10.1038/ nchembio.1714
8. Bensingir S, Bradley MN, Joseph SB, Zelker N, Janssen EM, Hausner MA, et al. LXR signaling couples sterol metabolism to proliferation in the acquired immune response. Cell (2008) 134(1):97–111. doi: 10.1016/ j.cell.2008.04.052
9. Lin CY, Gustafsson JA. Targeting liver X receptors in cancer therapeutics. Nat Rev Cancer (2015) 15(4):216–24. doi: 10.1038/nrc3912
10. Kuzu OF, Noory MA, Robertson GP. The Role of Cholesterol in Cancer. Cancer Res (2016) 76(8):2063–70. doi: 10.1158/0008-5472.CAN-15-2613
11. Yvan-Charvet L, Welch C, Pagler TA, Ranalletta M, Lamkanfi M, Han S, et al. Increased inflammatory gene expression in ABC transporter-deficient macrophages: free cholesterol accumulation, increased signaling via toll-like receptors, and neutrophil infiltration of atherosclerotic lesions. Circulation (2008) 118(18):1837–47. doi: 10.1161/CIRCULATIONAHA. 108.793869
12. Triantafillou M, Miyake K, Golenbock DT, Triantafillou K. Mediators of innate immune recognition of bacteria concentrate in lipid rafts and facilitate lipopolysaccharide-induced cell activation. J Cell Sci (2002) 115 (Pt 12):2603–11.
13. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimir G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature (2010) 464(7293):1357–61. doi: 10.1038/nature08938
14. Castrillo A, Joseph SB, Vaidya SA, Haberland AM, Fogelman AM, Cheng G, et al. and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism. Mol Cell (2003) 13(2):805–16. doi: 10.1016/ s1097-2765(03)00384-8
15. A-Gonzalez N, Bensingir S, Hong C, Beeceiro S, Bradley MN, Zelker N, et al. P. Tontonoz and A. Castrillo: Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. Immunity (2009) 31(2):245–58. doi: 10.1016/j.immuni.2009.06.018
16. Fond AM, Lee CS, Schulman IG, Kiss RS, Ravichandran KS. Apoptotic cells trigger a membrane-initiated pathway to increase ABCA1. J Clin Invest (2015) 125(7):2748–58. doi: 10.1172/JCI80300
17. Jakobsson T, Treuter E, Gustafsson JA, Steffensen KR. Liver X receptor biology and pharmacology: new pathways, challenges and opportunities. Trends Pharmacol Sci (2012) 33(7):394–404. doi: 10.1016/j.tips.2012.03.013
18. Boergesen M, Pedersen TA, Gross B, van Heeringen SJ, Hagenbeek D, Bindesboll G, et al. Genome-wide profiling of liver X receptor, retinoid X receptor, and peroxisome proliferator-activated receptor alpha in mouse liver reveals extensive sharing of binding sites. Mol Cell Biol (2012) 32(4):852–67. doi: 10.1128/MCB.06175-11
19. Ghisletti S, Huang W, Jepsen K, Benner C, Hardiman G, Rosenfeld MG, et al. Cooperative NCoR/SMRT interactions establish a corepressor-based strategy for integration of inflammatory and anti-inflammatory signaling pathways. Genes Dev (2009) 23(6):681–93. doi: 10.1101/gad.1773109
20. Lee JH, Park SM, Kim OS, Lee CS, Woo JH, Park SJ, et al. Differential SUMOylation of LXRxalpha and LXRbeta mediated transrepression of STAT1 inflammatory signaling in IFN-gamma-stimulated brain astrocytes. Mol Cell (2009) 35(6):806–17. doi: 10.1016/j.molcel.2009.07.021
21. Pourcet B, Gage MC, Leon TE, Waddington KE, Pello OM, Steffensen KR, et al. The nuclear receptor LXR modulates interleukin-18 levels in
macrophages through multiple mechanisms. *Sci Rep* (2016) 6:25481. doi: 10.1038/srep25481.

27. Joseph SB, Castrillo A, Laditka BA, Mangelsdorf DJ, Tontonoz P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat Med* (2003) 9(2):213–9. doi: 10.1038/nm820.

28. Park MC, Kwon YJ, Chung SJ, Park YB, Lee SK. Liver X receptor agonist prevents the evolution of collagen-induced arthritis in mice. *Rheumatol (Oxford)* (2010) 49(5):882–90. doi: 10.1093/rheumatology/keq007.

29. Li P, Spann NJ, Kaikkonen MU, Lu M, Oh DY, Fox JN, et al. NCoR repression of LXRα restricts macrophage biosynthesis of insulin-sensitizing omega 3 fatty acids. *Cell* (2013) 155(1):200–14. doi: 10.1016/j.cell.2013.08.054.

30. Wouters E, de Wit NM, Vannol J, van der Pol SMA, van Hét Hof R, Sommer D, et al. Liver X Receptor Alpha Is Important in Maintaining Blood-Brain Barrier Function. *Front Immunol* (2019) 10:1811. doi: 10.3389/fimmu.2019.01811.

31. Chintalacharuvu SR, Sandusky GE, Burris TP, Burmer GC, Nagpal S. Liver X receptor-dependent inhibition of inflammation and lipid metabolism by liver X receptor. *J Neuroimmunol* (2007) 183(1–2):50–9. doi: 10.1016/j.jneuroim.2006.11.007.

32. Secor McCoy JR, Oughli HA, Oh U. Liver X receptor-dependent inhibition of microglial nitric oxide synthase 2. *J Neuroinflammation* (2015) 12:27. doi: 10.1186/s12974-015-0247-2.

33. Cui G, Qin X, Wu L, Zhang Y, Sheng X, Yu Q, et al. Liver X receptor (LXR) mediates negative regulation of Th17 differentiation. *J Clin Invest* (2011) 121(2):658–70. doi: 10.1172/JCI42974.

34. Xu J, Wagoner G, Douglas IC, Drew PD. Liver X receptor agonist regulation of Th1 lymphocyte function in autoimmunity. *J Leukoc Biol* (2009) 86(2):401–9. doi: 10.1189/jl.2008.10600.

35. Hindinger C, Hinton DR, Kirwin JD, Atkinson RD, Burnett ME, Bergmann CC, et al. Liver X receptor activation decreases the severity of experimental autoimmune encephalomyelitis. *J Neurosci Res* (2006) 84(6):1225–34. doi: 10.1002/jnr.20130.

36. Chintalacharuvu SR, Sandusky GE, Burris TP, Burmer GC, Nagpal S. Liver X receptor agonist regulates inflammatory gene expressions and transcriptional network. *J Clin Immunol* (2013) 34(40):5128–8. doi: 10.1007/s10875-013-0152-6.

37. Herold M, Breuer J, Hucke S, Knolle P, Schwab N, Wiendl H, et al. Liver X receptors (LXRs) regulate inflammation and lipid metabolism by liver X receptor. *J Neuroimmunol* (2007) 183(1–2):50–9. doi: 10.1016/j.jneuroim.2006.11.007.

38. Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G, Pahl M. A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. *Mol Cell Biol* (1999) 14(10):7025–35. doi: 10.1128/mcb.14.10.7025.

39. Vedin LL, Gustafsson JA, Steffensen J. The oxysterol receptors LXRα and LXRβ enhance proliferation in the colon. *Mol Cancer* (2013) 5(11):835–44. doi: 10.1002/mc.21924.

40. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* (2006) 126(4):789–99. doi: 10.1016/j.cell.2006.06.049.

41. Wang B, Rong X, Palladino END, Wang J, Fogelman AM, Martin MG, et al. LXRα and LXRβ antagonists suppress innate immune responses of microglia and astrocytes. *J Neuroinflammation* (2007) 4(1):46. doi: 10.1186/1742-2094-4-46.

42. Apfel R, Benbrook D, Lernhardt E, Ortiz MA, Salbert G, Pahl M. A novel orphan receptor specific for a subset of thyroid hormone-responsive elements and its interaction with the retinoid/thyroid hormone receptor subfamily. *Mol Cell Biol* (1999) 14(10):7025–35. doi: 10.1128/mcb.14.10.7025.

43. Vedin LL, Gustafsson JA, Steffensen J. The oxysterol receptors LXRα and LXRβ enhance proliferation in the colon. *Mol Cancer* (2013) 5(11):835–44. doi: 10.1002/mc.21924.

44. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* (2006) 126(4):789–99. doi: 10.1016/j.cell.2006.06.049.

45. Wang B, Rong X, Palladino END, Wang J, Fogelman AM, Martin MG, et al. LXRα and LXRβ antagonists suppress innate immune responses of microglia and astrocytes. *J Neuroinflammation* (2007) 4(1):46. doi: 10.1186/1742-2094-4-46.
Bilotta et al. LXRs Regulate Inflammation, Autoimmunity and Cancer

59. Valledor AF. The innate immune response under the control of the LXR pathway. Immunology (2005) 102(4–5):127–32. doi: 10.1016/j.imunis.2005.05.007

60. Calkin AC, Tontonoz P. Liver X receptor signaling pathways and atherosclerosis. Arterioscler Thromb Vasc Biol (2010) 30(8):1513–8. doi: 10.1161/ATVBAHA.109.191197

61. Traversari C, Sozzani S, Steffensen KR, Russo V. LXR-dependent and -independent effects of oxysterols on immunity and tumor growth. Eur J Immunol (2014) 44(7):1896–903. doi: 10.1002/eji.201344292

62. Ceccio S, Pap A, Czirmerer Z, Sallam T, Guilen JA, Gallardo G, et al. LXR nuclear receptors are transcriptional regulators of dendritic cell chemotaxis. Mol Cell Biol (2018) 38(1):1–10. doi: 10.1128/MCB.00534-17

63. Geyeregger R, Shehata M, Zeyda M, Kiefer FW, Stuhlmeier KM, Porpaczy E, et al. Liver X receptors interfere with cytokine-induced proliferation and cell survival in normal and leukemic lymphocytes. J Leukoc Biol (2009) 86(5):1039–48. doi: 10.1189/jjlb.20088663

64. Solt LA, Kame neca TM, Burris TP. LXR-mediated inhibition of CD4+ T helper cells. PloS One (2012) 7(9):e46615. doi: 10.1371/journal.pone.0046615

65. Walcher D, Vasic D, Heinz P, Bach H, Durst R, Hau sser A, et al. LXR activation inhibits chemokine-induced CD4+ positive lymphocyte migration. Basic Res Cardiol (2010) 105(4):487–94. doi: 10.1007/s00395-010-0992-5

66. Zhu X, Owen JS, Wilson MI, Li H, Grimaldi RP, et al. Macrophage ABCA1 reduces MyD88-dependent Toll-like receptor trafficking to lipid rafts by reduction of lipid raft cholesterol. J Lipid Res (2010) 51(11):3196–206. doi: 10.1194/jlr.M006486

67. Han S, Zhuang H, Shumyak S, Wu J, Xie C, Li H, et al. Liver X Receptor Agonist Therapy Prevents Diffuse Alveolar Hemorrhage in Murine Lupus by Repolarizing Macrophages. Front Immunol (2018) 9:135–12. doi: 10.3389/fimmu.2018.00135

68. Pascual-Garcia M, Rue L, Leon T, Julve J, Carbo JM, Matalonga J, et al. Liver X receptors interfere with cytokine-induced proliferation and cell survival in normal and leukemic lymphocytes. J Leukoc Biol (2009) 86(5):1039–48. doi: 10.1189/jjlb.20088663

69. Fowler AJ, Sheu MY, Schmuth M, Kao J, Fluhr JW, Rhein L, et al. Adverse lipid profile is associated with relapse risk in MS: results from an observational cohort study. J Neurol Sci (2014) 340(1–2):230–2. doi: 10.1016/j.jns.2014.02.038

70. Steinman L. Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. Cell (1996) 85(3):299–302. doi: 10.1016/S0092-8674(00)81107-1

71. Bovenga F, Sabba C, Moschetta A. Uncoupling nuclear receptor LXR and atherogenesis differentially affects their capacity to handle lipids. Atherosclerosis (2020) 305:10–8. doi: 10.1016/j.atherosclerosis.2020.05.003

72. Bailly C, Vergoten G. Glycyrrhizin: An alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? Pharmacol Ther (2020) 214:1–16. doi: 10.1016/j.pharmthera.2020.071618

73. Thangadurai VR, Knittelfelder O, Brossch M, Patsenker E, Vvedenskaya O, Buch S, et al. Loss of hepatic Mboat7 leads to liver fibrosis. Gut (2020) 1:1–11. doi: 10.1136/gutjnl-2020-320853

74. Rondanelli M, Perna S, Alalwan TA, Cazzola R, Gasparri C, Infantino V, et al. A structural equation model to assess the pathways of body adiposity and inflammation status on dysmetabolic biomarkers via red cell distribution width and mean corpuscular volume: a cross-sectional study in overweight and obese subjects. Lipids Health Dis (2020) 19(1):154. doi: 10.1186/s12944-020-01308-5

75. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet (2016) 388(10055):2023–38. doi: 10.1016/S0140-6736(16)30173-8

76. Huang Y, Fu X, Lyu X, Xu Z, He Z, Zhang Y, et al. Activation of LXR attenuates collagen-induced arthritis via suppressing BLyS production. Clin Immunol (2015) 161(2):339–47. doi: 10.1016/j.clim.2015.09.015

77. Asquith DL, Ballantine LE, Nijjar JS, Madkasy MK, Patel S, Wright PB, et al. The liver X receptor pathway is highly upregulated in rheumatoid arthritis synovial macrophages and potentials TLR-driven cytokine release. Ann Rheum Dis (2015) 74(12):2024–31. doi: 10.1136/annrheumdis-2012-202872

78. Murali T. Cholesterol lowering: role in cancer prevention and treatment. Mol Cell Biol (2015) 35(11):2831–5. doi: 10.1128/MCB.00311-15

79. Ferguson V, Sabba C, Moschetta A. Uncoupling nuclear receptor LXR and cholesterol metabolism in cancer. Cell Metab (2015) 21(4):517–26. doi: 10.1016/j.cmet.2015.03.002

80. Vedin LL, Lewandowski SA, Parini P, Gustafsson JA, Steffensen KR. The oxysterol receptor LXR inhibits proliferation of human breast cancer cells. Carcinogenesis (2009) 30(4):575–9. doi: 10.1093/carcin/bgp029

81. Lo Sasso G, Bovenga F, Murzilli S, Salvatore I, Di Tullio G, Martelli N, et al. Liver X receptors inhibit proliferation of human colorectal cancer cells and growth of intestinal tumors in mice. Gastroenterology (2013) 144(7):1497–507, 1507 e1–3. doi: 10.1053/j.gastro.2013.02.005

82. Horton JD, Goldstein JL, Brown MS. SREBP-activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest (2002) 109(9):1255–31. doi: 10.1172/JCI15593

83. Yang J, Wang L, Jia R. Role of de novo cholesterol synthesis enzymes in cancer. J Cancer (2020) 11(7):1761–7. doi: 10.7150/jca.38598

84. Iannelli F, Lombardi R, Milone MR, Pucci B, De Rienzo S, Budillon A, et al. Targeting Mevalonate Pathway in Cancer Treatment: Repurposing of Statins. Targeting Mevalonate Pathway in Cancer Treatment: Repurposing of Statins. Recent Pat Anticancer Drug Discov (2018) 13(2):184–200. doi: 10.2174/157589821866617129141211

85. Villa GR, Halic Z, Zanca C, Bi J, Igegami S, Cahill GL, et al. An LXR-Cholesterol Axia Creates a Metabolic Co-Dependency for Brain Cancers. Cancer Cell (2016) 30(5):583–93. doi: 10.1016/j.cccel.2016.09.008

86. Fukuchi J, Kokontis JM, Hiipakka RA, Chuu CP, Liao S. Antiproliferative effect of liver X receptor agonists on LNCaP human prostate cancer cells. Cancer Res (2004) 64(21):7686–9. doi: 10.1158/0008-5472.CAN-04-2332
99. York AG, Bensinger SJ. Subverting sterols: rerouting an oxysterol-signaling pathway to promote tumor growth. *J Exp Med* (2013) 210(9):1653–6. doi: 10.1084/jem.20131335

100. Dufour J, Viennois E, De Boussac H, Baron S, Lobaccaro JM. Oxysterol receptors, AKT and prostate cancer. *Curr Opin Pharmacol* (2012) 12(6):724–8. doi: 10.1016/j.coph.2012.06.012

101. Lin CY, Huo C, Kuo IK, Hiipakka RA, Jones RB, Lin HP, et al. Cholestane-3beta, 6beta-triol suppresses proliferation, migration, and invasion of human prostate cancer cells. *PloS One* (2013) 8(6):e65734. doi: 10.1371/journal.pone.0065734

102. Baek AE, Yu YA, He S, Wardell SE, Chang CY, Kwon S, et al. The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. *Nat Commun* (2017) 8(1):864. doi: 10.1038/s41467-017-00910-z

103. McDonnell DP, Park S, Goulet MT, Jasper J, Wardell SE, Chang CY, et al. Obesity, cholesterol metabolism, and breast cancer pathogenesis. *Cancer Res* (2014) 74(18):4976–82. doi: 10.1158/0008-5472.CAN-14-1756

104. Liang H, Shen X. LXR activation radiosensitizes non-small cell lung cancer by restricting myeloid-derived suppressor cells. *Biochem Biophys Res Commun* (2020) 528(2):330–5. doi: 10.1016/j.bbrc.2020.04.137

105. Faulds MH, Zhao C, Dahlman-Wright K. Molecular biology and functional genomics of liver X receptors (LXR) in relationship to metabolic diseases. *Curr Opin Pharmacol* (2010) 10(6):692–7. doi: 10.1016/j.coph.2010.07.003

106. Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, et al. Role of LXRs in control of lipogenesis. *Genes Dev* (2000) 14(22):2831–8. doi: 10.1101/gad.850400

107. Bradley MN, Hong C, Chen M, Joseph SB, Wilpitz DC, Wang X, et al. Ligand activation of LXR beta reverses atherosclerosis and cellular cholesterol overload in mice lacking LXR alpha and apoE. *J Clin Invest* (2007) 117(8):2337–46. doi: 10.1172/JCI31909

108. Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsuzuma KE, Walczak R, et al. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem* (2002) 277(13):11019–25. doi: 10.1074/jbc.M111041200

109. Joseph SB, McKilligin E, Pei L, Watson MA, Collins AR, Laffitte BA, et al. Synthetic LXR ligand inhibits the development of atherosclerosis in mice. *Proc Natl Acad Sci U S A* (2002) 99(11):7604–9. doi: 10.1073/pnas.112059299

110. Katz A, Udata C, Ott E, Hickey L, Burczynski ME, Burghart P, et al. Safety, pharmacokinetics, and pharmacodynamics of single doses of LXR-623, a novel liver X-receptor agonist, in healthy participants. *J Clin Pharmacol* (2009) 49(6):643–9. doi: 10.1177/0091270009335768

111. Kirchgessner TG, Sleph P, Ostrowski J, Lupisella J, Ryan CS, Liu X, et al. Beneficial and Adverse Effects of an LXR Agonist on Human Lipid and Lipoprotein Metabolism and Circulating Neutrophils. *Cell Metab* (2016) 24(2):223–33. doi: 10.1016/j.cmet.2016.07.016

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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