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Chapter

Lipid Metabolism and Associated Molecular Signaling Events in Autoimmune Disease

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Abstract

Lipid metabolism, when dysregulated paves the way to many autoimmune disease conditions. One such recently explored mechanism was that of Liver X receptor (LXR) signaling which acts as a molecular link between lipid metabolism and inflammation. LXR plays a critical role in coupling immune cell lipid homeostasis with systemic immune responses. In this chapter, we will discuss how an altered lipid metabolite environment causes inflammation signaling via LXR-mediated molecular events which could lead to autoimmune disease. In a hyperlipidemic environment, Interferon regulatory factor 3 (IRF3) mediated downregulation of LXR signaling in innate immune cells leading to an inflammatory auto-immune response. Meanwhile, dendritic cell-mediated cytokine generation amidst LXR downregulation leads to the differentiation of autoreactive T cells and B cells, conferring an autoimmune response. Recent advances in the therapeutic management of autoimmune diseases target specific metabolic events as a strategy to limit inflammation and the autoimmune outcome. Novel treatment regimes in autoimmune diseases featuring lipid metabolic pathways are also discussed.

Keywords: LXR, hyperlipidemia, cholesterol overload, macrophage differentiation, oxysterols

1. Introduction

Autoimmune diseases (AIDs) represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems and are chronic conditions instigated by the loss of immunological tolerance to self-antigens [1]. It has also been noted that the overactive immune system that drives autoimmune diseases, presents metabolic abnormalities that provide therapeutic opportunities. Dysregulated lipid metabolism impacts the pathogenesis of AIDs such as rheumatoid arthritis (RA), Multiple sclerosis, and Systemic lupus erythematosus (SLE). Immunometabolism—the new emerging field has unveiled how bioenergetic and biosynthetic needs of healthy immune cells achieve rapid growth and perform effector functions upon challenge with pathogens [2]. Studies have shown that lipid-lowering drugs improve SLE symptomatically. Therefore, it is essential to study the molecular inflammatory signaling events associated with lipid metabolism in the context of AIDs [3]. This
chapter comprehensively reviews Liver-X-Receptor (LXR) mediated regulation of inflammation and its downregulation in a hyperlipidemic environment, which is the highlight of this study.

Endogenous bioactive lipids play a decisive role in inflammatory processes and in triggering, coordinating, and confining immunity. In the case of excessive pro-inflammatory activity, these lipids contribute to the transition from acute to chronic inflammation. The major bioactive lipids involved in atherogenesis are eicosanoids, lysoglycerophospholipids, sphingolipids, and endocannabinoids. In-depth knowledge of the mechanism of action of these lipids in the pathogenesis of AIDs is required for the proper management of these diseases [4].

Atherogenic factors such as cholesterol oxidation products, malondialdehyde, and other aldehydes; trans-fatty acids; some saturated fatty acids (lauric, myristic, and possibly palmitic acids); and myristic acid plus cholesterol are involved in the regulation of innate and adaptive immune responses and lead to exacerbation of autoimmune diseases such as psoriasis, RA, and SLE. The phenotypes and functions of innate immune cells such as dendritic cells and macrophages are influenced by atherogenic risk factors, involved in lipid metabolism. Thus atherogenic risk factors have a major role in shaping the function of adaptive immune cells such as T and B cells. Microfluidics tools combined with biotechnological techniques and lipidomics have emphasized the role of different types of functional lipids and their derivatives in AIDs [5].

LXR signaling plays a critical role in coupling immune cell cholesterol homeostasis with systemic immune responses. This suggests that promoting reverse cholesterol transport via LXR signaling could have therapeutic utility in autoimmune diseases [6]. Cholesterol-lowering treatments such as a low-fat diet or statins were shown to be effective in ameliorating autoimmune symptoms [7].

2. The mechanism of LXR mediated autoimmunity

LXRs belong to the subfamily 1 of the nuclear hormone receptors super family (thyroid hormone receptor-like) that regulates cholesterol and lipid metabolism as well as inflammatory gene expression including nuclear factor-κB (NF-κB) and activator protein-1 (AP1). LXR deficiency and hypercholesterolemia lead to the accumulation of cholesterol in antigen presenting cells (APCs) including macrophages. The accumulation improves antigen presentation as well as T cell priming and the production of B cell activation factor (BAFF) and A proliferation-inducing ligand (APRIL) by APCs, all of which increase B cell differentiation and thus autoantibody production [6]. Thus, an inflammatory autoimmune response is established and leads to autoimmune disease pathogenesis.

Atypical increase of lipid species in plasma levels due to alteration in lipid metabolism sequentially stimulates innate immune cells like macrophages and dendritic cells through the recognition of the lipids via their receptors. A group of nuclear receptors is involved in metabolic balance, the sensing, and the export of intracellular lipid species. Among them, LXR induces cholesterol transporters on the cell surface that mediate the export of intracellular cholesterol. LXRs are critical regulators of cholesterol and fatty acid metabolism along with the regulation of inflammatory gene expression [8].

Antigen-presenting cells such as macrophages function to scavenge pathogens and apoptotic cells as well as to coordinate the inflammatory response to such stimuli through the production of cytokines and other mediators. The activation
and inflammatory function of macrophages is modulated by several lipid species such as modified low-density lipoproteins (LDLs), fatty acids, and cholesterol crystals through LXR signaling. Gene expression studies in activated macrophages have revealed that LXR antagonizes inflammatory gene expression and reduces inflammation 

2.1 LXR inhibition leads to autoimmunity in a hyperlipidemic environment

In a hyperlipidemic environment, macrophages form foam cells. Foam cells are cytoplasmic lipid droplets formed as a result of the accumulation of cholesterol esters, by virtue of uncontrolled uptake of oxidized low-density lipoprotein (ox-LDL), excessive cholesterol esterification and impaired cholesterol release [10]. Foam cell formation in macrophages has been shown to activate the NLR (Nod Like Receptor) family pyrin domain containing 3 (NLRP3)/inflammasome with the secretion of the proinflammatory cytokines, interleukin-1β (IL-1β) and IL-18 and to promote the progression of atherogenesis [11]. Activation of foam cells can lead to the production of cytokines like IL-23, IL-6, and IL-27. IL 23 leads to tissue differentiation whereas IL-27 and IL-6 induce Tfh cell proliferation and differentiation. Tfh cells are newly identified CD4+ T helper subsets that mainly drive autoimmune germinal center reaction and autoantibody responses, which exacerbate autoimmune symptoms like an immune complex deposition. The hyperlipidemia-IL-27-Tfh cell axis is quintessential in the development of atherosclerosis-mediated SLE.

Dendritic cells, by virtue of the strength of antigen presentation and cytokine environment, govern CD4+ T cell activation and differentiation. It has been shown that hyperlipidemia and the nature of lipid species regulate antigen stimulating capacity and cytokine production of dendritic cells. Hyperlipidemic condition promotes the production of proinflammatory cytokines such as IL-1β, IL-6, and IL-27. When compared with control mice, mice subjected to a high-fat diet exhibited increased numbers of CD11b+ dendritic cells, which secrete more IL-1β. Cholesterol accumulation in dendritic cells leads to autoimmune phenotypes such as immune complex deposition in kidneys and increased plasma dsDNA antibodies in mice [11].

Immunostimulatory lipid species like LDLs and saturated fatty acids can stimulate immune responses via lectin-like oxidized low-density lipoprotein receptor-1 (LOX1), cluster of differentiation 36 (CD36), toll-like receptors 2 and 4 (TLR2 and TLR4) downstream signaling. The uptake of free fatty acids including palmitic acid and oleic acid increases the production of IL-23 and IL-1β from bone-marrow-derived dendritic cells (DCs) [12]. Recent studies have demonstrated that LDLs and oxLDL stimulation of dendritic cells enhances IL-6 and IL-27 production in CD36 and TLR4/Myeloid differentiation primary response 88 (MyD88) dependent manner [13]. Dendritic cells become more sensitive to immunostimulatory lipid species via the upregulation of lipid receptors. Dendritic cells induce CD36 expression on their surface and promote IL-6 release by uptake of oxLDL. Increased expression of lipid receptor CD36 due to upregulated transcriptional activity of LXR is positively correlated with autoimmune phenotypes suggesting the mutual relation between a lipid receptor and autoimmunity [14]. Dendritic cells in atherogenic conditions exhibit higher expression of pattern-recognition receptors such as LOX-1, TLR2, and TLR4, all of which are known lipid receptors. Down-regulated LXR expression in hyperlipidemic conditions enhances NF-κB signaling and the consequent production
of proinflammatory cytokines. Activation of LXR signaling by administrating LXR agonist to dendritic cells, reduced IL-27 production as well as the production of IL-23 and IL-12, all of which contribute to the differentiation of autoimmune Tfh and Th17 cells.

Phagocytosis of pathogens, such as Gram-negative bacteria by antigen processing cells, elicits a marked immune response. Pathogens contain molecules such as lipopolysaccharide (LPS) that are recognized by the Toll family of receptors (TLR) such as TLR-3 and 4. These in turn activate interferon regulatory factor-3 (IRF3)-mediated inhibition of LXR on their target promoters [15]. This could be a possible mechanism by which LXR downregulation leads to an inflammatory autoimmune response.

The successful clearance of invading pathogens depends on the neutrophil’s efficient migration into the infected tissues. LXR activation impaired the neutrophil chemotactic response toward chemokines like C-X-C motif chemokine ligand 2 (CXCL2) in a concentration-dependent manner. LXR activation in neutrophils represses neutrophil migration genes [16]. LXR downregulation leads to neutrophil chemotaxis and over recruitment of neutrophils to the infected site. This leads to marked inflammation at the site.

The cholesterol sensing function of LXR in macrophages is likely to be important for the scavenger function of these cells. Large amounts of fatty acids and cholesterol will be accumulated in cells by the internalization of apoptotic cells and cellular debris. In this context, the role of LXR is to activate the cholesterol efflux pathway to protect the cell from lipid overload. LXR activation in cholesterol-loaded cells limits the production of inflammatory mediators. An inflammatory response is not apt when apoptotic cells are being scavenged. The absence of inflammation is a hallmark of apoptotic body clearance [17]. Decreased apoptotic clearance could promote an inflammatory autoimmune response. LXR agonist inhibits the expression of inflammatory responses including IL-6 and IL-1β [18, 19]. LXR expression in macrophages has a negative effect on inflammatory responses through the regulation of NF-κB signaling.

Accumulated cholesterol in innate immune cells enhances NLRP3 inflammasome activity. It promotes IL-1β and IL-18 secretion and GM-CSF receptor expression in an LXR-independent manner to elevate IL-12, IL-6, and IL-23 production by CD11b+ dendritic cells. OxLDL plays a vital role in the activation of dendritic cells to promote IL-6 and IL-1β production, which enhances susceptibility to autoimmune diseases by regulating pathogenic autoimmune Tfh cell differentiation [20, 21]. Th17 cells are one of the key players in the pathogenesis of autoimmunity [22].

2.2 LXR activation by oxysterols

LXRs are activated by the oxysterols- 24(S),25-epoxycholesterol, and 24(S)-hydroxycholesterol. It is well known that oxysterols suppress de novo cholesterol biosynthesis as well as cellular uptake of cholesterol [23]. LXR and RXR (retinoid X receptor), have an amino-terminal transcriptional activation domain (AF-1), a ligand-binding domain (LBD), a DNA binding domain (DBD), domains responsible for nuclear translocation and dimerization, and a transcriptional activation domain (AF-2) at the extreme carboxyl terminus [24]. When oxysterols, or synthetic pharmacological agonists, trigger activation of LXRs, they heterodimerize with RXR and bind to target gene promoters on LXR-responsive-elements (LXREs) [25, 26].
2.3 Effects of LXR activation

2.3.1 LXR activation

**MODE OF ACTION 1**: LXR activates an ‘inducible degrader of the low-density lipoprotein’ (IDOL) receptor. IDOL in turn reduces the expression of low-density lipoprotein receptor (LDLRs) on the cell surface, reducing cholesterol intake into the cells [27, 28].

**MODE OF ACTION 2**: Liver-X-receptor-Nuclear receptor corepressor-Silencing mediator of retinoic acid and thyroid hormone receptor (LXR-NCoR-SMRT) complex prevents transcription of inflammatory genes leading to transrepression of NF-κB. NF-κB is the central transcriptional regulator of the innate immune response. Many of the genes inhibited by LXR are established targets of NF-κB signaling. NF-κB promotes autoimmunity as well as inflammation by mediating the activation and differentiation of autoimmune and inflammatory T cells, such as Th17 cells. Efficient and properly controlled NFκB signaling is important for mediating normal immune homeostasis and function and for preventing autoimmunity [29]. Analysis of the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) gene promoters indicates that inhibition of these genes by LXR is accomplished through antagonism of NF-κB [30, 31].

**MODE OF ACTION 3**: LXR activates efferocytosis receptor- Mer proto-oncogene Tyrosine Kinase (MERTK), which is linked to the resolution of inflammation [18]. It is also found that MERTK can reciprocally regulate LXR expression identifying a potential feedback loop that may function to tip the balance from inflammation to resolution and tissue repair [32]. When activation of LXRs is inhibited, MERTK is downregulated which leads to decreased apoptotic cell clearance and leads to autoimmunity.

**MODE OF ACTION 4**: LXRs can induce the synthesis of long-chain polyunsaturated fatty acids (lcPUFAs) such as omega 3 fatty acids and mono-unsaturated fatty acids (MUFA). LXR upregulates Stearoyl CoA desaturase (SCD) and Fatty Acid Synthase (FASN) in the fatty acid biosynthesis pathway [33, 34]. The presence of lcPUFAs can decrease transactivation mediated by NF-κB of inflammatory genes, modifying histone acetylation in their regulatory regions [35]. lcPUFAs have been shown to increase the production of eicosanoids and selected pro-resolving lipid mediators [36]. Pro-resolving lipid mediators include lipoxin, resolvin, protectin, and maresin families, collectively called specialized pro-resolving mediators (SPM) [37]. Increased LXRs activity can also induce macrophage polarization toward a more pro-resolving phenotype (M2), directly upregulating the expression of MERTK and inflammation resolution.

**MODE OF ACTION 5**: LXRs upregulate 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). These genes in turn regulate critical lipogenic pathways, counteracting aberrant cellular overload [38]. Induction of the sterol transporters Abca1 and Abcg1, in turn, promotes cholesterol efflux to lipid-poor apolipoprotein A-1 (ApoA-1) and high-density lipoprotein (HDL) acceptors. As a result, excess cholesterol from the periphery is shuttled by HDL to the liver for excretion through the reverse cholesterol transport pathway [39]. Thus, LXR activation counteracts sterol overload and resolves inflammation.

LXR deficiency or LXR inhibition leads to increased cholesterol in macrophages or dendritic cells. Cholesterol plays a key role in the regulation of immune responses through different mechanisms. Cholesterol is required for membrane synthesis during cell expansion and also it is a key constituent of lipid rafts. As a result, any changes in cholesterol content could regulate raft dependent signaling of
Hyperlipidemia can activate TLR-3 and TLR-4 mediated IRF3 activation, which in turn inhibits LXR, leading to an inflammatory autoimmune response. LXR activation and its effects are diagrammatically represented in Figure 1.

2.4 Adaptive immunity links autoimmunity with hyperlipidemia

Antigen presentation and cytokine production by innate immune cells are modulated by cellular lipid or cholesterol homeostasis and leads to direct activation of adaptive immune cells. Naïve T-cells are differentiated into Th 17 cells by IL-6, transforming growth factor β (TGF β), IL-23, and IL-1 β stimulation, express RXR-related Orphan nuclear receptors (RORγt) and (RORα) and secrete IL-17A, IL-17F and IL-22 to promote wound healing and eliminate extracellular pathogens via recruiting neutrophils. Th 17 cells lead to the autoimmune response either by modulating tissue inflammation or by IL-17 mediated autoantibody production. Tfh cells are differentiated by IL-6, IL-12,
IL-21, and IL-27 stimulation express B cell lymphoma 6 (Bcl6) and Achaete-scute complex homolog 2 (Ascl2), and secrete IL-21 [20, 41]. Proper activation of Th 17 and Tfh cells protect the body from infection but an uncontrolled generation of the cells can also contribute to the pathogenesis of autoimmune diseases.

B cells are responsible for the generation of pathogenic autoantibodies, thus intense research is carried out to study the function of autoreactive B cells and how they are triggered in autoimmune diseases. IL-17 produced by Th17 cells is required for autoreactive B cell production and germinal center reactions [42, 43]. Furthermore, IL-21, IFNγ, and IL-4 secreted by Tfh cells are required for class switching of IgG2a/c and IgG1, respectively, during Tcell- B cell interaction. IL-27 is sufficient to induce an increase in Tfh cells and germinal center reactions. Analysis of plasma from healthy controls and hypercholesterolemia patients showed that IL-27, but not IL-6, is increased in the patients with hypercholesterolemia and that IL-27 is associated with increased immunoglobulin G (IgG) in the circulation.

Tfh cells express Bcl 6 and secrete IL-21 which provides crucial help for B cells to induce class switching, affinity maturation, and differentiation into plasma cells through germinal center reactions [44].

A novel function of LXRs as modulators of lipid metabolism and associated molecular signaling events in autoimmune disease has been identified. LXR-mediated immune cell differentiation and cytokine expression is illustrated in Figure 2.

Figure 2. LXR mediated immune cell differentiation and cytokine expression. LXR-Liver X Receptor, RXR-Retinoid X Receptor, LXRE-LXR responsive elements, MERTK- Mer proto-oncogene tyrosine kinase, DC-dendritic cells, RXR related orphan nuclear receptor-gamma, STAT3-Signal transducer and activator of transcription 3, and BCL-B cell lymphoma.
B cell activation and in the control of Ig E synthesis suggests a beneficial function of LXRrs in allergic therapy [45]. LXR downregulation leads to activation of Tfh cell that promotes B cell activation which results in an overall surge of autoantibodies regardless of immunoglobulin subclass. The major roles of Bcl6 in the development and effector function of mature T cell subsets suggest that Bcl6, besides, being a regulator of germinal center reactions, is also an important regulator of T cell dependant inflammatory, autoimmune and memory response in the periphery [46]. Oxysterol directly acts as an RXR-related Orphan nuclear receptor γ (RORγt) agonist to promote Th17 cell differentiation [47, 48]. LXR-mediated immune cell differentiation and cytokine expression are represented as shown in Figure 2.

3. Mechanism of LXR down-regulation leading to SLE clinical manifestation

Upregulated atherosclerotic conditions can downregulate LXR signaling, thereby downregulating the expression of various genes involved in the resolution of inflammation and autoimmune response.

Figure 3. Downregulated LXR mediated clinical manifestations in systemic lupus erythematosus. LXR-Liver X Receptor; 1RF3-Interferon regulatory factor-3 MERTK- Mer proto-oncogene tyrosine kinase, ABCA1- ATP binding cassette, TNF-Tumor necrosis factor, IFN- interferons, HIF1A- Hypoxia-inducible factor-1-alpha, 6-phosphofructokinase, liver type.
Downregulation of LXR signaling leads to impaired ABCA1 at RNA and protein levels which causes cholesterol efflux from cell to periphery. This results in cholesterol overload. Upregulation of Hypoxia Inducible Factor 1A (HIF1A) and 6-phosphofructokinase, liver type (PFKL) genes leads to abnormal macrophage differentiation. Switching from M1 TO M2 phenotype is down-regulated which triggers diffuse alveolar hemorrhage or end-organ damage in the liver and other vital organs [49].

Downregulation of LXR leads to increased generation of pro-inflammatory cytokines like Tumor necrosis factor (TNF) α and Interferon γ which causes an increased inflammatory response. Downregulation of MERTK genes leads to decreased efferocytosis, ie decreased clearance of apoptotic cells that result in autoimmune reactions via nucleosome presentation [50].

Therapeutic management of SLE involving LXR agonists can improve many of these SLE manifestations. A diagram outlining the mechanism of hyperlipidemia-mediated LXR downregulation in SLE is shown in Figure 3.

4. Mechanism of LXR down-regulation leading to RA clinical manifestations

Hyperlipidemia-mediated downregulation of LXR signaling can lead to many of the pathophysiological symptoms observed in rheumatoid arthritis. This LXR inhibition in turn could activate the production of pro-inflammatory cytokines such as C-X-C motif chemokine ligand 10 (CXCL10). Fibroblast-like synoviocyte (FLS) invasion, one of the major symptoms of RA, leading to joint damage could be due to an increased expression of CXCL10 [51]. Likewise, FLS invasion could also be brought about by the expression of another set of pro-inflammatory cytokines like IL-1 and IL-6, leading to matrix metalloprotease 2 (MMP-2) expression. Cartilage destruction and joint damage, another debilitating manifestation of RA is also brought about by MMP-3 expression. Moreover, LXR-mediated differentiation of Th cells could also lead to Synovial tissue hyperplasia causing tissue invasion and cartilage destruction [52].

LXR agonists as a therapeutic option for rheumatoid arthritis can suppress pro-inflammatory cytokines such as IL-1 and ILN-6 as well as modulate Th17 differentiation, thereby alleviating symptoms in rheumatoid arthritis.

5. Treatment

Therapeutic target 1: It is well known that ω-3 PUFAs have anti-inflammatory properties and their presence in nutrition contributes to the prevention of many inflammatory diseases, independently of the mechanism of action [53]. The administration or inclusion of ω-3 PUFAs in the human diet appears as the most natural way to reduce AIDs symptoms. In particular, the availability of ω-3 PUFAs in the human diet could dramatically change their benefits (Figure 4) [54].

Therapeutic target 2: Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have emerged as the leading therapeutic regimen for treating hypercholesterolemia. Statins can accomplish partial inhibition of an upstream common denominator of multiple regulatory signaling networks that control the immune system. Thus, statins may be a good choice for ameliorating AID symptoms.
Figure 4.
Downregulated LXR mediated clinical manifestations in rheumatoid arthritis. LXR-Liver X Receptor, 1RF3-Interferon regulatory factor-3, CXCL10 - C-X-C motif chemokine ligand 10, Matrix metalloproteinases, and FLS-Fibroblast like synoviocytes.

Figure 5.
Therapeutic management of auto-immune diseases. FASN-Fatty acid synthase, LXR-Liver X Receptor, PUFA-Poly Unsaturated fatty acids, MUFA-mono Unsaturated fatty acids, SCD-Stearoyl-CoA Desaturase, 1RF3-Interferon regulatory factor-3, HMG-CoA- 3-Hydroxy-3-methylglutaryl-coenzyme a reductase.
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Therapeutic target 3: LXR agonists activate the LXR pathway inhibiting the expression of pro-inflammatory genes. They also increase the flux of cholesterol into the liver, where it is metabolized.

The therapeutic management of Auto-immune diseases is summarized as shown in Figure 5.

All the illustrations are original and created by the authors using BioRender, an online web application used to create scientific figures and diagrams.

6. Conclusion

In the present review, the authors analyzed the different aspects of lipid metabolism which contribute to autoimmune disease via inflammatory signaling pathways. Reducing the hyperlipidemic environment could alleviate the pathophysiological complications of auto-immune diseases, by modulating the Liver-X-Receptor (LXR) signaling. LXR agonists along with fatty acid supplementation and statins are promising therapeutic targets for efficient clinical management of auto-immune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

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Conflict of interest

The authors declare no conflict of interest.

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