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Regulation of Adaptive Immunity in Health and Disease by Cholesterol Metabolism

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Abstract

Four decades ago, it was observed that stimulation of T cells induces rapid changes in cellular cholesterol that are required before proliferation can commence. Investigators returning to this phenomenon have finally revealed its molecular underpinnings. Cholesterol trafficking and its dysregulation are now also recognized to strongly influence dendritic cell function, T cell polarization, and antibody responses. In this review, the state of the literature is reviewed on how cholesterol and its trafficking regulate the cells of the adaptive immune response and *in vivo* disease phenotypes of dysregulated adaptive immunity, including allergy, asthma, and autoimmune disease. Emerging evidence supporting a potential role for statins and other lipid-targeted therapies in the treatment of these diseases is presented. Just as vascular biologists have embraced immunity in the pathogenesis and treatment of atherosclerosis, so should basic and clinical immunologists in allergy, pulmonology, and other disciplines seek to encompass a basic understanding of lipid science.

Keywords

Cholesterol; Lipoprotein; T Cell; Dendritic Cell; Asthma; Statins

Introduction

Recent literature has begun to define the central importance of cholesterol homeostasis to the programming, initiation, and resolution of the adaptive immune response. Whereas lipid trafficking may have formerly been considered a topic reserved for vascular biologists and endocrinologists, the rising tide of dyslipidemia and increased use of cholesterol-targeted therapeutics mandate an improved understanding of cholesterol in immunity. In the present review, after opening with a brief overview of cholesterol homeostasis and lipid raft microdomains, recent literature is discussed that has identified roles for cholesterol and the proteins that regulate its intra- and extracellular trafficking, in the biology of the major cells that interact in the adaptive immune response – T cells, B cells, and dendritic cells (DCs). Next, the impact of sterols on allergic sensitization and on diseases of adaptive immunity,

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including atopic asthma and autoimmune disease, is discussed. Last, potential therapeutic implications are addressed, in particular, emerging roles for 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitors (statins) in the treatment of diseases of the adaptive immune response.

A Brief Overview of Cholesterol Trafficking and Lipid Rafts

As a central determinant of membrane fluidity and development and a precursor to steroid hormones, cholesterol is vital to health. Dysregulation of cholesterol levels has been associated with disease in virtually every organ system. Here, key points on cellular cholesterol and its regulation are discussed. For a comprehensive overview of the biochemistry and intra- and extracellular trafficking of cholesterol, the reader is referred to recent scholarly reviews [1, 2].

Nucleated cells accumulate cholesterol via *de novo* synthesis from acetyl CoA (the mevalonate pathway) and internalization of lipoprotein-associated cholesterol via either the low density lipoprotein receptor (LDLR) or scavenger receptors (SRs). Cellular cholesterol is regulated via the antagonistic actions of two families of transcription factors: i) the Liver \times Receptors (LXR α and - β), which induce expression of genes that promote cellular cholesterol efflux (e.g., ATP Binding Cassette [ABC] transporters A1 and G1) and degrade LDLR; and ii) the Sterol Response Element Binding Proteins (SREBPs), which induce genes that promote cholesterol accumulation (e.g., LDLR, and enzymes of the mevalonate pathway such as HMGCR). LXRs and SREBPs are coordinately controlled via cholesterol and oxysterols (enzymatically oxidized cholesterol, e.g., 25-OH-cholesterol [25HC]). Oxysterols activate LXRs and (along with cholesterol) reciprocally suppress SREBPs. Conversely, during cellular sterol deficit, LXRs are inactive, whereas SREBPs become activated.

Extracellularly, cholesterol is carried through the organism on lipoprotein particles, the cellular docking of which is determined by apolipoproteins (apo). The liver, in response to dietary cholesterol and other inputs, synthesizes triglyceride-rich very low density lipoprotein (VLDL) and exports it into the plasma. VLDL is either internalized by cells via interactions of apoE with VLDLR, or processed by lipases ultimately into LDL, which serves as the major vehicle for cholesterol delivery to peripheral cells via interactions of its apoB component with LDLR. In turn, the liver and intestines also produce and release HDL, which, in large part due to its component apoA-I, serves as the major plasma acceptor and return vehicle for ABCA1/ABCG1-effluxed cellular cholesterol. Plasma HDL cholesterol is cleared by the liver via hepatic SR-BI, and then processed into bile acids for receptor-dependent export into the biliary tract, and thereby, into the feces. This completes the disposal pathway of 'reverse cholesterol transport'. Increased peripheral cholesterol delivery (LDL excess) and defective reverse cholesterol transport (deficits of HDL, apoA-I, LXR, ABCA1, or ABCG1) both lead to peripheral cell cholesterol overload, the classical example of which is the macrophage 'foam cell' observed in atherosclerotic lesions. During dyslipidemia, bioactive oxysterols are also increased both in circulating LDL (i.e., oxidized LDL [oxLDL]) and in vascular lesions.

In normal cells, the majority of cholesterol resides in the plasma membrane, much of it within cholesterol-enriched membrane microdomains called lipid rafts. Rafts are thought to serve as platforms that organize signaling by many receptors and accessory proteins, including the B cell receptor (BCR), T cell receptor (TCR), major histocompatibility class (MHC) II, high-affinity IgE receptor (FcεRI), and Toll like Receptors (TLRs)[3]. The localization of proteins to rafts and their signaling interactions are critically sensitive to raft cholesterol content. Raft cholesterol, in turn, is regulated by intracellular cholesterol trafficking. Extracellular cholesterol acceptors such as apoA-I, HDL, and β-cyclodextrins reduce raft cholesterol and attenuate raft-dependent signaling, whereas raft cholesterol overload due to deficient efflux (e.g., ABCG1 deletion) or enhanced loading (e.g., diet-induced hypercholesterolemia) enhances raft-dependent signaling [3]. In this manner, as discussed below, cholesterol trafficking in health and disease ‘tunes’ the immune response by regulating signaling by immune cells.

Reciprocal Effects Between Hypercholesterolemia and Adaptive Immune Cells

Arguing against cholesterol homeostasis and immunity being purely extrinsic and incidental bedfellows, recent literature has revealed bidirectional crosstalk between the two at the systems level. Deletion of either conventional DCs or T regulatory cells (Tregs) induces a significant increase in plasma cholesterol, and *in vivo* expansion of DCs reduces plasma cholesterol, in particular the pro-atherogenic VLDL- and LDL-cholesterol (LDL-C) fractions [4, 5]. Although the precise mechanism remains unclear, Tregs appear to play a role in promoting clearance of VLDL particles [5]. Further suggesting a fundamental role for T cells in cholesterol homeostasis, T cell-specific overexpression of the tumor necrosis factor superfamily member LIGHT induces hypercholesterolemia, likely through direct interactions with lymphotoxin β receptor on hepatocytes that downregulate the VLDL-metabolizing enzyme, hepatic lipase [6]. In addition, it has been shown that genetic deficiency of mast cells reduces serum cholesterol and triglyceride in mice [7].

Conversely, severe hypercholesterolemia has been shown to skew T cell programming, in particular promoting a T helper (Th)1-to-Th2 switch. Thus, hypercholesterolemic mice produce strong Th2-type antibody responses (increased IgG1 and IgE, decreased IgG2a) to both endogenous and exogenous antigens, in conjunction with increased IL-4 and reduced interferon (IFN)-γ in splenocytes [8, 9]. Th2 skewing during hypercholesterolemia may in part derive from oxLDL-induced attenuation of pro-inflammatory (Th1-promoting) cytokine production by CD8α- DCs [10]. Other reports have noted that hypercholesterolemia leads to sustained increases in Tregs in the spleen [11] and increased expression of IFN-γ in CD8⁺CD28⁺ T cells in lymph nodes draining the aortic root [12]. Taken together, these reports indicate reciprocal crosstalk between cholesterol and adaptive immune programming, suggesting that an improved understanding of the underlying cellular mechanisms may potentially reveal novel sites for therapeutic intervention.

Sterol Regulation of Cells of the Adaptive Immune Response

T cells

Decades ago, it was noted that mitogenesis of human T cells with either phytohemagglutinin or immobilized anti-CD3 antibody induces robust HMGCR-dependent cholesterol synthesis that precedes, and is required for, DNA synthesis and cell cycle progression [13, 14]. It was presumed that this requirement for cholesterol derives in large part from the need for rapid biogenesis of new cell membranes during cell division. Recently, investigators returning to this phenomenon of T cell cholesterol synthesis have shown that it arises from coordinated shifts in LXR and SREBP activity driven by changes in intracellular oxysterol availability that occur during T cell activation (Figure 1).

In a groundbreaking report, Bensinger and colleagues showed that T cell activation triggers simultaneous suppression of LXR β and de-repression of SREBPs (favoring net cholesterol accumulation) in part via induction of the oxysterol-metabolizing enzyme SULT2B1 [15]. Rapid SREBP activation is required for upregulation of enzymes of the cholesterol synthesis pathway and for cholesterol accumulation and endoplasmic reticulum membrane expansion; SREBP-deficient CD8⁺ T cells display defective proliferation and deficient clonal expansion during viral infection [16]. Upregulation of cholesterol synthesis in Tregs is also required for proliferation and suppressive function, and is itself dependent upon mechanistic target of rapamycin complex 1 (mTORC1)[17]. In resting T cells, LXR β activity suppresses proliferation in an ABCG1-dependent manner; thus, *Lxr β* ^{-/-} mice display increased steady state as well antigen-driven T cell expansion, whereas LXR agonists suppress cell cycle progression and proliferation in wild type but not *Abcg1*^{-/-} cells [15]. Suggesting that ABCG1 serves as a cell cycle checkpoint by limiting cellular cholesterol, *Abcg1*^{-/-} CD4⁺ T cells [18], T cells from *Apoai*^{-/-} mice with deficiency of HDL (the major inducer/acceptor of ABCG1-dependent cholesterol efflux)[19], and cholesterol-loaded wild type T cells [18] have all been shown to be hyperproliferative. Others have shown that LXR activation also interferes with IL-2-induced cell cycle progression of T cells due to inhibited phosphorylation of retinoblastoma protein and downregulation of cyclin B [20].

Recently, LXR has been shown to regulate not only proliferation but also polarization of T cells. LXR deficiency promotes, and LXR overexpression suppresses Th17 differentiation. This occurs through binding of Srebp-1 (an LXR target gene) to the E-box element on the *Il17* promoter, thereby inhibiting aryl hydrocarbon receptor-dependent *Il17* transcription [21]. Another group has recently shown that T0901317, a widely used synthetic LXR agonist, is also an inverse agonist for the master transcription factors of Th17 differentiation, RAR-related orphan receptor (ROR) γ t and α [22], and that this rather than LXR activation is the mechanism by which it suppresses Th17 differentiation and function [23]. Additional T cell-targeting actions recently attributed to T0901317 include inhibition of chemokine-induced migration [24] and attenuation of Th1 cytokine production [25].

It has recently also been shown that naturally occurring oxysterols impact Th17 polarization through LXR-independent mechanisms. For example, several non-LXR agonist oxysterols including 7 β ,27-dihydroxycholesterol were recently reported to be agonists for ROR γ t [26]. Exogenous treatment of murine and human CD4⁺ T cells with these oxysterols enhances

Th17 differentiation. Moreover, suggesting that endogenous sterol metabolism may program CD4⁺ T cells, ROR γ t-active oxysterols are preferentially produced in Th17 cells compared to Th1 cells, whereas mice deficient in CYP27A1, a key enzyme that oxidizes cholesterol into ROR γ t-active oxysterols, have Th17 cell deficiency comparable to that of ROR γ t knockout mice [26]. A recent report has also implicated mevalonate pathway intermediates that accumulate in activated T cells, desmosterol in particular, as endogenous ROR γ t agonists that are required for Th17 differentiation [27]. By contrast, it was recently reported that 25HC indirectly suppresses Th17 differentiation through inhibiting inflammasome-dependent IL-1 β production by macrophages through an LXR-independent mechanism; thus, mice deficient in Ch25h, the enzyme that synthesizes 25HC from cholesterol, have increased splenic Th17 cells [28].

In addition to supporting cell cycle/proliferation in T cells, cholesterol promotes TCR signaling through formation of lipid raft microdomains in the plasma membrane. Although controversy persists over the nature and size of raft microdomains, studies using a variety of techniques continue to support the existence of cholesterol-sensitive membrane microdomains [3]. Several reports have suggested that in resting T cells TCR and CD3 reside outside of rafts, but that they translocate to aggregated rafts upon ligation, where they encounter Lck and are phosphorylated [29]. The TCR β chain may itself bind to cholesterol in membranes, thereby causing TCR dimerization, nanoclustering, and increased antigen avidity [30]. An additional potential implication of raft-localization of the TCR is that raft clustering may regulate pathway activity. Interestingly, crosslinking of the raft-specific ganglioside GM1 using its ligand, cholera toxin B subunit, induces TCR-dependent signaling and provides efficient co-stimulation, suggesting that 'passive' raft aggregation in T cells may be sufficient to activate the TCR [31, 32]. In support of the possibility that native co-stimulatory proteins may also remodel rafts, CD28 engagement induces clustering of kinase-rich rafts at the site of TCR engagements, enhancing and sustaining tyrosine phosphorylation events [32].

A growing number of reports have confirmed that TCR signaling is sensitive to cholesterol. Cholesterol-loading and ABCG1 deletion in CD4⁺ T cells both increase lipid rafts and TCR-dependent signaling, including Zap70 and ERK phosphorylation [18, 33]. Administration of squalene, a precursor of cholesterol, to mice also increases membrane cholesterol and GM1 in CD4⁺ T cells, and promotes raft-localization of IL-2R α , IL-4R α , and IL-12 β R2, as well as Th1 skewing after TCR stimulation [34]. Interestingly, endogenous cell type-dependent differences in cholesterol handling may possibly underlie developmental differences in the T cell lineage. Thus, gammadelta T cells display higher cholesterol, lipid raft content, and TCR-dependent signaling than $\alpha\beta$ T cells, and all of this is reversible by cholesterol depletion [35]. The impact of cholesterol trafficking may vary by cell type as *Abcg1*^{-/-} invariant NKT cells display reduced membrane lipid raft content, impaired proliferation, and altered cytokine production in response to CD3/CD28 stimulation [36].

B cells

B cells carry out key roles as amplifiers and effectors of the adaptive immune response. Like DCs, they present antigen to T cells on MHC II molecules via an 'immunological synapse.'

B cells also produce and release antigen-specific immunoglobulin (Ig) that modifies the function of other immune cells through its Fc domain (e.g., activation of mast cells by IgE via FcεRI). Interestingly, analogous roles for cholesterol have recently been identified in B cells to those observed in T cells.

Human peripheral B cells express both LXRα and LXRβ [37]. Parallel to the case in T cells, LXR suppresses BCR-driven mitogenesis; this endogenous checkpoint is released by BCR stimulation, at which time reciprocal LXR suppression and SREBP activation occur [15]. LXR activation also reduces anti-CD40 and IL-4-mediated IgE secretion by B cells *in vitro* and reduces allergen-specific IgE in ovalbumin (OVA)-sensitized mice *in vivo* [37]. On the other hand, LXR agonists increase serum IgM in mice, and this may arise from their direct induction of macrophage IL-5 through binding to a LXR response element in the IL-5 promoter [38].

Important LXR-independent roles have also been identified for oxysterols in B cell biology. 25HC, an oxysterol secreted by macrophages and DCs in response to TLR activation [39], suppresses IgA class switching in B cells by reducing IL-2-mediated cell proliferation and repressing induction of activation-induced cytidine deaminase; thus, Ch25h-null mice have increased serum and airspace IgA [40]. Further processing of 25HC by Cyp7b1 produces 7α,25-dihydroxy-cholesterol (7α,25-OHC), an oxysterol recently shown to chemoattract several immune cell types, including B cells, via the G-protein coupled receptor Epstein-Barr virus-induced gene 2 (Ebi2). Interestingly, both Ebi2-null and Ch25h-null mice fail to position activated B cells within the spleen to the outer follicle and mount a reduced plasma cell response after immune challenge [41, 42].

Several reports have now shown that lipid rafts regulate signaling by the BCR and also play important roles in antigen trafficking in B cells [43, 44]. In resting mature B cells, the BCR appears to be excluded from rafts, whereas BCR crosslinking by antigen induces its recruitment to rafts in a cholesterol-dependent manner, where it interacts with Lyn and other signaling proteins [43]. Interestingly, the relationship of the BCR to rafts appears to be developmentally regulated. Thus, transitional immature B cells have significantly lower membrane cholesterol than mature B cells, impairing aggregation-induced translocation of their BCR into cholesterol-enriched membrane microdomains as well as downstream signaling; remarkably, cholesterol loading the cells corrects BCR translocation and signaling to the level seen in mature B cells [45]. This suggests that BCR biology may be developmentally modified by changes in cholesterol handling that occur during B cell maturation in the spleen.

Rafts regulate the full course of antigen trafficking through the B cell, ranging from initial BCR-mediated uptake, to intracellular trafficking through MHC II-loading compartments, to presentation to T cells at the immunological synapse [44]. MHC II molecules are constitutively present in B cell rafts, and raft disruption by cholesterol-targeting agents (nystatin, cyclodextrin) dramatically compromises antigen presentation at limiting concentrations of antigen [46]. B cell rafts also deliver specific MHC II-peptide complexes to the immunological synapse, and are required for T:B cell conjugate formation and for T cell activation at low densities of class II-peptide complexes [47].

Dendritic Cells

DCs bridge innate and adaptive immunity, in particular through internalizing and processing antigens and then migrating to lymph nodes, where they serve as antigen-presenting cells (APCs) that activate and program T cells. As with B and T cells, a growing array of roles for cholesterol trafficking continue to be identified in DC biology (Figure 1).

Several reports indicate that cholesterol, oxysterols, and proteins that regulate sterol traffic impact both the differentiation and maturation of DCs. Oxysterols, 27HC in particular, promotes the differentiation of monocytic cells into phenotypically mature DC-like cells, upregulating multiple signature cell-surface molecules (MHC II, CCR7, CD40, CD80) and inducing DC-like morphology [48]. Some of these effects are shared by oxLDL [49]. LXR may possibly mediate some of these changes as LXR activation enhances myeloid DC differentiation, perhaps through inhibition of STAT3 phosphorylation [50], and also upregulates CCR7 [51]. In human DCs, LXR activation also induces maturation markers (CD80, CD86) and augments pro-inflammatory cytokine production and capacity to promote T cell proliferation [52], although some reports suggest that LXR activation interferes with LPS-induced maturation of human DCs [53]. Conversely, apoA-I inhibits DC differentiation (surface marker upregulation, endocytic activity) and ability to activate T cells, possibly through induction of prostaglandin E2 and IL-10 [54]. HDL treatment also inhibits the ability of DCs to activate T cells after TLR stimulation; interestingly, this effect appears to derive at least in part from the phospholipid fraction of HDL [55].

Sterol homeostasis and its dysregulation also affect DC migration *in vivo*.

Hypercholesterolemic mice have impaired migration of DCs to lymph nodes associated with reduced contact hypersensitivity and delayed-type hypersensitivity responses; this appears to derive from an increase in platelet activating factor (PAF) or PAF-like activity in oxLDL, and is reversed by treatment with HDL [56]. LXR also plays a key role in CCR7-dependent egress of monocyte-derived cells from vascular lesions during atherosclerosis regression [51]. Finally, parallel to its chemotactic role in splenic B cell positioning mentioned above, $7\alpha,25$ -OHC plays a key role in EBI2-dependent maintenance and localization of CD4⁺ DCs in marginal zone bridging channels of the spleen [57].

Similar to the case in B cells, MHC II localization to lipid rafts in DCs has been shown to be functionally important. The majority of newly generated MHC II-peptide complexes in DCs cluster in cholesterol-dependent microdomains on the DC cell surface; cholesterol depletion disrupts these clusters as well as the APC function of DCs, especially in the setting of limiting concentrations of antigen [58]. Interestingly, structural studies indicate that cholesterol itself binds to the transmembrane domain of MHC II, altering its conformation in a manner that may allosterically modulate the MHC II peptide groove and promote T cell activation [59]. MHC II-peptide complex targeting to cholesterol-dependent microdomains in the DC appears to be required for Th1 programming [60], and raft clustering at the synaptic interface with T cells appears particularly important [61]. Of note, the cholesterol-dependence of MHC II clustering may have physiological and therapeutic implications. Cholesterol depletion of antigen-loaded DCs with HDL or apoA-I reduces their capacity to activate T cells in a manner that is reversed by cholesterol repletion [62]. Statins also reduce

MHC II display by DCs through disrupting cholesterol-dependent membrane microdomains [63].

Putting it All Together: Sterol Regulation of Adaptive Immunity in Disease

Allergic Sensitization

While several reports in rodent models have suggested that hypercholesterolemia promotes Th2 immunity [8, 9], the relationship of cholesterol to atopy in humans appears to be complex. Of interest, *ex vivo* treatment of mononuclear cells from latex-allergic atopic dermatitis patients with cholesterol enhances production of latex-specific IgE, IL-4, IL-10, and IL-13 in a dose-dependent fashion [64]. At a population level, however, varying relationships have been reported between serum cholesterol measures and allergic sensitization in cross-sectional studies. In a study of >1000 Chinese twins, low HDL-C and high LDL-C were associated with allergic sensitization as assessed by skin prick testing [65]. In a general population of 11 year old children, total cholesterol (TC) and LDL-C levels were also significantly positively associated with higher IgE and a higher rate of allergic sensitization [66]. On the other hand, in a longitudinal study that tracked 200 newborns prospectively up to age 20 years, those adolescents who developed allergic symptoms, skin test positivity, and elevated IgE had lower TC levels in infancy and childhood than non-atopic subjects [67]. Genetic background may be an important source of variation, as we have noted marked inter-racial differences between serum cholesterol and allergen-specific IgE in the U.S. population [68].

Atopic Asthma

Asthma imposes a tremendous public health burden. The majority of cases of asthma are associated with atopy, and it is thought that Th2 and Th17 immunity contribute to disease. Recent findings in human populations and animal models suggest an important role for cholesterol in asthma pathogenesis.

Reminiscent of past reports that diet-induced hypercholesterolemia increases airway eosinophils and Th2 cytokines in the murine OVA sensitization/challenge model of asthma [69], several investigators have recently found that high serum cholesterol is associated with asthma in humans. In a recent study of ~500 Taiwanese children, serum TC and LDL-C were significantly higher in asthmatic than non-asthmatic subjects [70]. Other investigators have found the relationship of serum cholesterol to asthma to vary by density subclass of LDL [71]. Conversely, some evidence suggests a potentially 'protective' role for serum HDL in asthma. Thus, low HDL-C was independently associated with wheezing in a study of >85,000 Spanish workers [72], and with reduced expiratory airflows in a study of >18,000 U.S. adults [73]. In adolescent subjects, asthma was also found to be associated with low HDL-C, particularly in those with a drop in HDL-C between childhood and adolescence [74]. That said, a wide and divergent range of relationships has been reported between different cholesterol measures and asthma [75, 76], suggesting that differences in study design and/or in unmeasured covariates may be responsible. Asthma may also conceivably impact lipoprotein metabolism. Indeed, asthma is associated with reduced airspace cholesterol [77] and apoA-I [78], increased plasma oxLDL [79] and lung levels of

oxidized lipids and anti-oxLDL antibodies [80], and impaired anti-inflammatory and anti-oxidant function of HDL [79, 80].

Mice targeted for cholesterol transport genes known to be expressed in the lung have recently provided new mechanistic insights into the connection between cholesterol and asthma. Mice deleted for ABCG1, the primary effector for HDL-induced cholesterol efflux, display augmented Th17-dependent airway neutrophilia in the OVA asthma model [81]. Consistent with this, mice deficient in HDL due to deletion of apoA-I have increased peripheral airway resistance, airway inflammation, and lung oxidative stress compared with wild type counterparts in the naïve state [82], and increased G-CSF-dependent airway neutrophilia after OVA sensitization and challenge [78]. On the other hand, mice engineered to have elevated HDL-C through inactivation of endothelial lipase have lower airway inflammation, Th2 cytokines, and airway hyperresponsiveness (AHR) than controls [83]. Suggesting a role for VLDL in asthma, VLDLR-null mice also display increased eosinophilia and Th2 cytokines in the house dust mite (HDM) asthma model, a finding that derives from cell-intrinsic alterations in DC function [84]. Finally, both LDLR-null and apoE-null mice have increased airway remodeling in the HDM model, suggesting a protective apoE-LDLR pathway in asthma [85]. Implying that variations in apoE function in humans may influence asthma, mice engineered to express the three major human *APOE* alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) display significant differences in HDM-induced airway disease [86].

Extending upon the findings in apo-deficient mice and borrowing from the cardiovascular literature, investigators have recently tested the potential therapeutic efficacy of synthetic apolipoprotein mimetic peptides in asthma models. ApoA-I mimetic peptides decrease airway eosinophilia, lung oxidative stress, and IgE in the OVA model [80], and reduce airway inflammation, Th2 and Th17 cytokines, AHR, and airway remodeling in the HDM model [87]. An apoE mimetic peptide was also recently shown to suppress AHR/remodeling, Th2 and Th17 cytokines, and eosinophilia in the HDM model through an LDLR-dependent mechanism [85]. Also on the therapeutic frontier, studies suggest a potential therapeutic role for synthetic LXR agonists in asthma models [88], consistent with their reported anti-inflammatory efficacy in contact dermatitis models [89]. In the section on statins below, we discuss emerging roles for statins in asthma at further length.

Autoimmune Disease

Autoimmune diseases encompass a large number of discrete as well as overlapping syndromes in which dysregulated innate and adaptive immunity conspire to cause inappropriate host tissue damage. Recently, cholesterol regulatory pathways have been shown to intersect the pathogenesis of autoimmunity in the areas of apoptotic cell clearance and lipid raft composition, suggesting potential new strategies for therapeutic intervention.

Efferocytosis (phagocytic clearance of apoptotic cells) is executed by the TAM (Tyro3, Axl, Mer) receptor kinases and their ligands (Gas6, Protein S) as well as by additional phagocyte receptor-apoptotic cell ligand pairs. Defective efferocytosis is thought to play a central role in autoimmunity by delaying autoantigen clearance [90, 91]. Recently, a key role for LXR was identified in efferocytosis and prevention of autoimmunity. A-Gonzalez and colleagues demonstrated that the phagocyte receptor for apoptotic cells, Mer, is a direct LXR target

gene, and that apoptotic cell engulfment induces phagocyte expression of Mer via sterol-dependent activation of LXR [92]. Consequently, LXR-null macrophages display defective efferocytosis and LXR-null mice have increased apoptotic bodies in multiple tissues and develop autoantibodies and autoimmune glomerulonephritis [92]. Supporting a potential role for LXR in treatment of autoimmune disease, synthetic LXR agonists have now been shown to reduce lymphadenopathy and glomerular antibody deposition in B6^{lpr/lpr} mice [92], clinical scores in collagen-induced arthritis [93], clinical scores and Th17-associated inflammation in experimental autoimmune encephalomyelitis [94, 95], and Th1- and Th17-associated inflammation in experimental autoimmune uveitis [96].

Additional LXR targets and other genes involved in reverse cholesterol transport have been implicated in autoimmunity, potentially by acting as bridging ligands or receptors for efferocytosis. ApoE promotes efferocytosis, and apoE-null mice have increased apoptotic bodies in several tissues associated with low-level inflammation [97]. SR-BI has also been suggested to play a role in efferocytosis [98], and SR-BI-null mice spontaneously develop splenomegaly, increased autoantibodies, and autoimmune glomerulonephritis [99]. ABCA1 has been suggested to mediate efferocytosis [100], and recently mimetic peptides for its ligand apoA-I have been shown to reduce lymphadenopathy, autoantibody titers, glomerulonephritis, and proteinuria in a murine model of systemic lupus erythematosus (SLE)[101]. Consistent with a role for endogenous apoA-I in suppression of autoimmunity, apoA-I-deficient mice on an LDLR-null background display lymphadenopathy, splenomegaly, increased T cell activation, and autoantibodies [19].

Complex, reciprocal interactions have been identified between serum lipoproteins and autoimmunity. HDL, the major lipoprotein carrier for apoA-I, has been known for many years to suppress lymphocyte proliferation [102]; abnormal HDL from gene-targeted mice is deficient in this function [99]. Interestingly, several reports have documented reduced and/or dysfunctional HDL in patients with autoimmune disease [103, 104]. Defective HDL may arise as a consequence of systemic inflammation [105]; whether it reciprocally de-represses autoimmune inflammation is an interesting question worthy of study. An additional indirect feedback mechanism between serum lipoproteins and autoimmunity involves anti-oxLDL autoantibodies, which have been noted to increase in parallel with serum oxLDL during dyslipidemia and, interestingly, to cross-react with apoptotic cells [106]. Anti-oxLDL antibodies modulate efferocytosis by macrophages and dendritic cells, suppress inflammation, and inhibit collagen-induced arthritis [106, 107].

Several reports have recently shown that the hyperactivated B cells and T cells in SLE patients may arise from lipid raft abnormalities. B cells from SLE patients have reduced raft levels of lyn kinase, a negative regulator of BCR signaling, likely due to increased c-Cbl-dependent ubiquitination [108]. T cell rafts from SLE patients have multiple abnormalities, including elevations in cholesterol, gangliosides, activated Syk kinase, and CD45, and a reduction in Lck [109-111]. Moreover, SLE T cells display increased calcium signaling in response to raft cross-linking and relative resistance to cholesterol reduction with cyclodextrins, suggesting their hypersensitive phenotype stems from increased cholesterol-dependent rafts [110]. Supporting a potential role for statins in molecular therapy of SLE rafts, atorvastatin restores raft Lck and normalizes raft-associated TCR signaling in T cells

from SLE patients [111]. Statins may also theoretically indirectly rectify SLE rafts by normalizing dyslipidemia, given that the increased glycosphingolipid synthesis and trafficking to rafts in SLE T cells is reportedly driven by LXR activation in response to dyslipidemic serum [112]. Finally, suggesting an additional exciting frontier for raft therapy in SLE, NB-DNJ, a glycosphingolipid synthesis inhibitor approved for clinical use in Gaucher disease, partially normalizes rafts and TCR signaling in SLE T cells [112].

Statins as Potential Therapeutics in Diseases of Adaptive Immunity

Effects of Statins on T Cell Activation and Polarization

Statins inhibit HMGCR, the rate-limiting enzyme of the mevalonate pathway, and are widely prescribed for hypercholesterolemia. In the last several years, studies have elucidated a wide range of immunomodulatory actions of statins on multiple cell types. In addition to reducing cellular/serum cholesterol, statins reduce the cellular pool of mevalonate-derived isoprenoids (geranylgeranyl [GG]-PP, farnesyl [F]-PP), lipids which, through protein post-translational modification ('prenylation'), serve important biologic roles in immune and other cells by promoting membrane-localization of key signaling proteins (e.g., Rho, Ras, Rab). Some statins also antagonize LFA-1-dependent cell adhesion of immune cells through mevalonate-independent mechanisms [113]. In most cases, it is difficult to know the physiological relevance of studies of statins, especially those conducted in rodents, wherein dosing on a body weight basis is generally far higher than that used in humans, and drug and lipid metabolism also differ. While a comprehensive review of the impact of statins on immunity is outside the scope of the present review, key findings relating to T cell activation/polarization are discussed below.

Statins attenuate T cell activation in part by impairing antigen presentation. In nonprofessional APCs including endothelial cells, monocytes, and microglia, statins reduce IFN γ -inducible upregulation of MHC II through inhibited transcription [114]. Additional actions on DCs and B cells include inhibition of co-stimulatory molecule (CD40, CD86) and chemokine receptor (CCR7) expression, antigen uptake, and cytokine expression [115]. Reduction of antigen uptake and processing by DCs arises from blocked prenylation of Rho and Rab GTPases [116]. *In vivo*, statins may also suppress T cell activation by reducing T cell numbers in the spleen and lymph nodes, an effect that has been ascribed to impaired homing [117].

Interestingly, several studies indicate that statins bias away from Th1 and Th17 and towards Th2 polarization. Statin-pretreated DCs promote Th2 polarization of CD4⁺ T cells by upregulation of the lectin Ym1 [118]. In addition, direct pro-Th2 effects of statins upon CD4⁺ T cells have been identified. Atorvastatin inhibits T cell proliferation and activation and favors Th2 differentiation by decreasing prenylation of RhoA and Ras in T cells, thereby compromising TCR activation of mitogen-activated protein kinases and the pro-Th1 transcription factor *c-fos* [119]. Consistent with isoprenoid depletion as the mechanism, Th2 skewing is observed *in vitro* and *in vivo* and occurs without a discernible change in serum or T cell raft cholesterol [114, 119, 120]. *In vivo* treatment of immunized mice with statins reduces Th1 responses upon antigen restimulation [121]. Reduced *ex vivo* proliferation of T cells from statin-treated patients has also been observed [122], although not all studies have

confirmed effects on Th1/Th2 balance in humans [123] and important differences among statin formulations have been noted [124]. Statins also inhibit Th17 polarization through effects on both APCs and T cells. Simvastatin inhibits expression of Th17-promoting cytokines (IL-1 β , IL-6, IL-23, IL-21) by APCs through induction of suppressor of cytokine secretion (SOCS)1, SOCS3, and SOCS7 [125, 126], and directly suppresses T cell IL-17 by inhibiting expression of ROR γ t [125]. Finally, statins also enhance induction of Tregs by blocking geranylgeranylation, potentially through a mechanism involving demethylation of the Foxp3 promoter [127], and augment the capacity of steroids to increase the Treg/Th17 ratio of CD4⁺ T cells [128], although another report indicates that statins reduce Treg proliferation and suppressive function [17].

Statins in Asthma

Their reported pro-Th2 effects notwithstanding, statins have many actions that might be predicted to ameliorate asthma pathogenesis, including inhibition of antigen presentation, and inhibition of proliferation, homing, and Th17 polarization of CD4⁺ T cells. In addition, statins inhibit eosinophil adhesion [129], IgE-dependent release of histamine by mast cells [130], matrix-remodeling responses of airway smooth muscle cells and fibroblasts to TGF β 1 [131, 132], and proliferation and antigen-induced hypercontractility of airway smooth muscle cells [133, 134]. Multiple reports have in fact now confirmed that several statins, delivered through a variety of routes, reduce disease measures in murine models of asthma. Pravastatin and simvastatin administered intraperitoneally reduce airway leukocytes, Th2 cytokines, and OVA-specific IgE in the OVA/alum model [69, 135, 136]. Interestingly, metabolic rescue of mice by *in vivo* co-treatment with mevalonic acid, the product of HMGCR, reverses the reduction in airway leukocytes but not Th2 cytokines by simvastatin [137]. Statins inhibit antigen presentation by CD11c⁺ lung cells and IL-17 production by thoracic lymph node cells [138]. Efficacy is also observed with intragastric delivery of statins, and in both C57BL/6 and Balb/C mice [69, 136]. Simvastatin, pravastatin, and atorvastatin also reduce AHR [137, 139], possibly by inhibiting RhoA-dependent signaling [140]. Reduction of AHR by simvastatin is not blocked by *in vivo* co-treatment of mice with mevalonic acid [137], whereas its inhibition of airway goblet cell hyperplasia is [141]. A recent report interestingly indicates that simvastatin delivered to mice by aerosol inhalation also potently reduces OVA/alum-induced airway cellular inflammation, Th2 cytokines, and AHR, and achieves much higher lung deposition and potency in the face of reduced serum concentrations compared with systemic administration [140].

Several reports of statins in human asthma have now appeared, including both observational studies (Table 1) and prospective, randomized treatment trials (Table 2). Although some minor improvements in intermediate endpoints have been noted in some trials, results have been mixed, and few trials have found meaningful effects on hard clinical outcomes. A recent systematic review of randomized controlled trials and observational studies of statins in asthma found no consistent statistically significant improvements in clinical or airway function outcomes [142], and a meta-analysis of randomized controlled trials found no significant improvement in spirometry [143]. That said, the trials to date have been relatively small and short-term, have not tested all statins on the market, and have been underpowered to properly test asthma subphenotypes (e.g., obese asthmatic, non-atopic

asthmatic). Inhaled statin formulations have not yet been developed for clinical use, and remain untested. Finally, a recent report has identified a polymorphism in HLA-G that modifies statin benefit in asthma [144]. Thus, several research gaps remain and further results are anticipated.

Statins in Autoimmune Disease

Several features of statins, most notably their suppression of Th1 and Th17 polarization and T cell proliferation, suggest that they may be efficacious in the therapy of autoimmune disease. Multiple reports have now in fact confirmed that statins improve clinical and inflammatory measures in experimental models of autoimmune disease, as comprehensively summarized by Greenwood and colleagues [145]. This includes rodent models of experimental autoimmune myocarditis, experimental autoimmune encephalomyelitis (the animal model for multiple sclerosis), experimental arthritis, experimental autoimmune uveoretinitis, and experimental SLE, although some studies have found no significant therapeutic effect in individual models [145].

Of interest, some early clinical studies have also suggested clinical efficacy of statins in human autoimmune disease. In a randomized, double-blind, placebo-controlled trial of 116 patients with rheumatoid arthritis with a 6-month followup, patients treated with 40 mg atorvastatin daily in conjunction with their existing regimen had a statistically significant albeit modest improvement in disease activity score [146]. Recently, a meta-analysis of 15 studies involving 992 patients of statins in rheumatoid arthritis confirmed consistent, significant improvements in clinical scores and inflammatory measures [147]. In addition, in a multicenter, open-label, single-arm study of 30 patients with relapsing-remitting multiple sclerosis, 80 mg simvastatin daily was associated with a 44% reduction in the number of gadolinium-enhancing lesions on brain MRI compared with pretreatment scans [148]. Similarly, an observational trial of 7 patients with relapsing-remitting multiple sclerosis reported that lovastatin was associated with a reduction in the number in enhancing brain lesions [149]. On the other hand, mixed results have been reported so far as to whether statins enhance the clinical efficacy of IFN β therapy in multiple sclerosis [115].

In sum, several studies have suggested promise for statins in autoimmune disease, even if only as adjunctive agents, but larger, prospective trials will be required to resolve the issue. Importantly, accelerated atherosclerosis is observed in autoimmune diseases, including rheumatoid arthritis and SLE [150, 151], suggesting that there may be a compelling cardiovascular indication for statins in autoimmune disease patients. Whether or not statins will impose unacceptable increases in risk for myositis and/or hepatic injury in autoimmune disease patients is an important question that will, however, require further clinical experience to answer.

Conclusions

A growing basic, translational, and now clinical literature is providing compelling evidence that cholesterol metabolism fundamentally impacts the adaptive immune system, and that there may be exciting opportunities for repurposing of lipid-targeted therapeutics to immunological disease. Just as the cardiovascular sciences have embraced molecular

immunology in the pathogenesis and treatment of atherosclerosis, allergists, pulmonologists, and rheumatologists among other clinicians must now consider the potential role of cholesterol and dyslipidemia in clinical immunology. It appears almost certain that in coming years some of the emerging insights, research tools, and/or therapeutics in lipid science and vascular biology will prove of real and perhaps transformative value to scientists and clinicians of the adaptive immune response.

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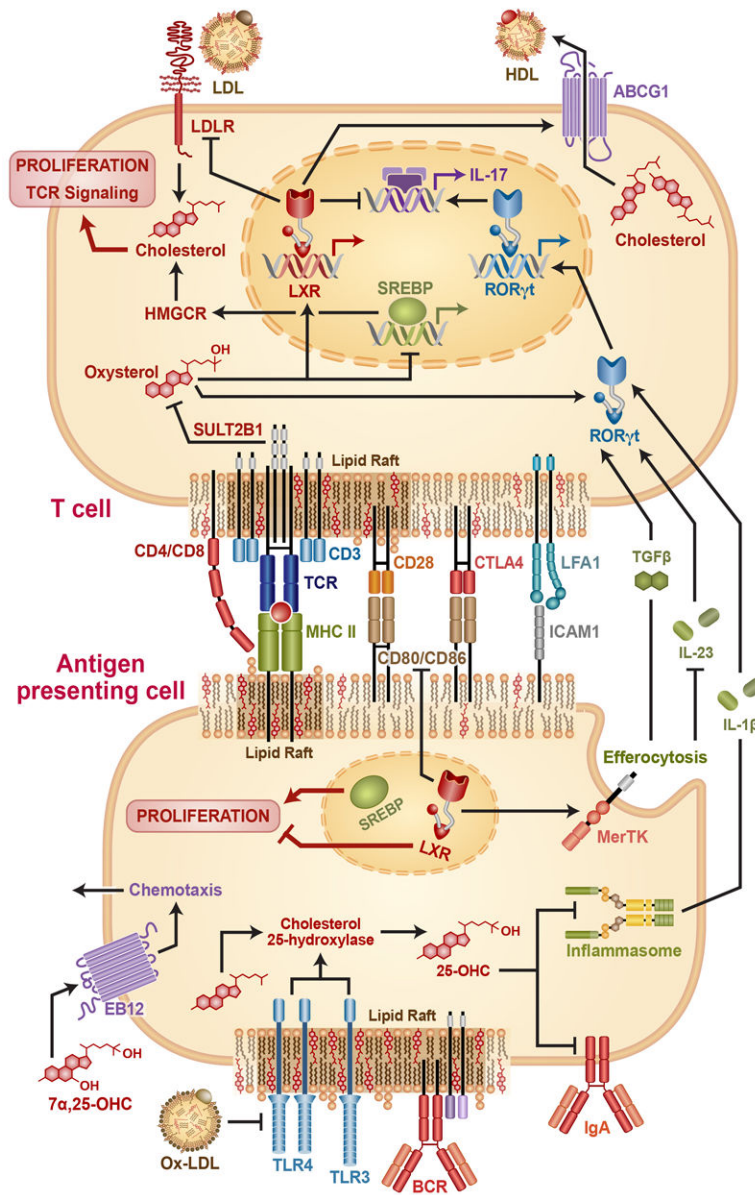


Figure 1. Cholesterol and its metabolism program T cell-APC interactions

The figure shows a T cell and a representative antigen presenting cell (APC) in contact at an immunological synapse (IS). Some synaptic proteins, as well as Toll like Receptors (TLRs) and the B Cell Receptor (BCR) either reside in or are recruited to cholesterol-enriched lipid rafts upon activation. Their signaling is thereby regulated by raft cholesterol levels. TCR activation leads to inhibitory sulfation of oxysterols via SULT2B1, repressing Liver × Receptor (LXR) and de-repressing sterol response element binding proteins (SREBPs), with consequent effects on expression of ATP Binding Cassette G1 (ABCG1) – a transporter that effluxes cholesterol to high density lipoprotein (HDL); HMGCR – the rate-limiting enzyme in cholesterol synthesis; and low density lipoprotein receptor (LDLR). Cellular cholesterol promotes TCR-induced signaling and cell proliferation. Some oxysterols also directly activate ROR γ t, the master regulator of T helper 17 differentiation, or induce chemotaxis of

APCs via the G-protein coupled receptor Ebi2. In APCs, TLR activation induces synthesis of the oxysterol 25-OH-cholesterol (25HC) via upregulating the enzyme Ch25h. In turn, 25HC represses IgA class switching and inflammasome-dependent generation of IL-1 β . LXR-dependent upregulation of Mertk in APCs also promotes efferocytosis (phagocytic clearance of apoptotic cells), which promotes release of TGF β and suppresses release of IL-23, two cytokines which, along with IL-1 β , impact T cell differentiation. Oxidized LDL (oxLDL) also suppresses activation of TLR4, with indirect cytokine-mediated effects upon T cell differentiation.

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Table 1

Observational studies of statins in clinical asthma.

	Design	N	Patients	Duration	Effect of statin therapy
Lokhandwala et al. [152]	Propensity-matched retrospective cohort analysis of Medicaid data	1437	Asthma	1 year	OR 0.55 (95% CI, 0.37-0.84) for asthma-related hospitalizations and/or ER visits; OR 0.48 (95% CI, 0.28-0.82) for asthma-related ER visits
Zeki et al. [153]	Retrospective cross-sectional study	165	Severe asthma	1 year (statin use, median)	Better asthma symptom control (increase in mean ACT symptom score by 2.2 ± 0.94 points; $p=0.02$). No differences in lung function, corticosteroid or rescue BD use, or eosinophilia
Huang et al. [154]	Population-based analysis of Taiwan National Health Insurance Database	11808	Asthma	4.66 ± 2.32 years	HR, 0.82 (95% CI, 0.71-.095; $p=0.006$) for asthma hospitalization
Ostroukhova et al. [155]	Retrospective cohort study	50	Atopic Asthma	2 years (3, 6, 12, and 24 month followup)	3-5% median worsening of FEV1; at 6 months, more patients needed increased maintenance medication ($p=0.005$), used albuterol more often ($p<.001$); had more nocturnal awakening ($p<.001$), and were seen more frequently in office for acute asthma ($p=0.003$).
Tse et al. [156]	Propensity score-matched cohort study	16696	Asthma	36 months	OR 0.64 (95% CI, 0.53-77; $p<0.0001$) for asthma-related ER visits; OR 0.90 (95% CI, 0.81-0.99; $p=0.04$) for 2 oral corticosteroid dispensings. No significant difference in asthma-related hospitalizations
Tse et al. [157]	Observational study using Medco Health Solutions admin. database	6652	Asthmatics with recent exacerbation	1 year followup	Among ICS users, statins had OR 0.77 (95% CI 0.64-0.94; $p=0.008$) for asthma-related ER visits, but no odds reduction for asthma-related hospitalizations. No significant associations among non-ICS users.

Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; AHR, airway hyperresponsiveness; AQLQ, asthma quality of life questionnaire; BD, bronchodilator; CI, confidence interval; d/c, discontinuation; ER, emergency room; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NO, nitric oxide; OR, odds ratio; PEF, peak expiratory flow.

Table 2

Prospective, randomized, placebo-controlled trials of statins in asthma.

	Design	N	Patients	Duration	Effect of statin therapy
Braganza et al. [158]	Double-blind: Atorvastatin 40mg/d vs. placebo (4 wks); then ICS added to both groups (4 wks)	71	Smokers with mild-to-moderate asthma	8 weeks	No improvement in morning PEF. Improvement in asthma AQLQ score (0.52, 95% CI, 0.17-0.87; p=0.005). No change in induced sputum cells
Maneechotesuwan et al. [159]	Double-blind: Simvastatin 10mg/d	50	Mild asthmatics on low-dose ICS	10 weeks (8 wk treatment)	Significant reduction in sputum eosinophil percentage
Menzies et al. [160]	Cross-over trial: Simvastatin vs. placebo after d/c of anti-inflammatory medications	16	Mild-to-moderate asthma on ICS	1 month	No significant change in exhaled NO, AHR, or eosinophilia
Moini et al. [161]	Atorvastatin 80 mg/d	62	Mild-to-moderate asthma	8 weeks	No significant difference in ACT score, spirometry, or blood eosinophil count
Hothersall et al. [162]	Double-blind crossover trial: Atorvastatin 80 mg/d	54	Atopic asthmatics on ICS	24 weeks (2 × 8 wk treatments)	No significant difference in mean morning PEF, spirometry, or AQLQ score. Significant reduction in sputum macrophages and leukotriene B ₄ .
Cowan et al. [163]	Crossover trial: Simvastatin 40 mg/d, simultaneous ICS reduction until loss of control, then ICS increase until control	43	Asthmatics on ICS	3 months treatment	No significant difference in minimal ICS dose required for control. In patients who stopped ICS, ACQ was lower (p=0.037), FEV1 higher (p<0.01), and sputum eosinophils lower (p=0.033) on simvastatin.

Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; AHR, airway hyperresponsiveness; AQLQ, asthma quality of life questionnaire; BD, bronchodilator; CI, confidence interval; d/c, discontinuation; ER, emergency room; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NO, nitric oxide; OR, odds ratio; PEF, peak expiratory flow.