

Review



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Immunologic Aspects of Dyslipidemia: a Critical Regulator of Adaptive Immunity and Immune Disorders

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ABSTRACT

Dyslipidemia is a major cause of cardiovascular diseases which represent a leading cause of death in humans. Diverse immune cells are known to be involved in the pathogenesis of cardiovascular diseases such as atherosclerosis. Conversely, dyslipidemia is known to be tightly associated with immune disorders in humans, as evidenced by a higher incidence of atherosclerosis in patients with autoimmune diseases including psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. Given that the dyslipidemia-related autoimmune diseases are caused by autoreactive T cells and B cells, dyslipidemia seems to directly or indirectly regulate the adaptive immunity. Indeed, accumulating evidence has unveiled that proatherogenic factors can impact the differentiation and function of CD4⁺ T cells, CD8⁺ T cells, and B cells. This review discusses an updated overview on the regulation of adaptive immunity by dyslipidemia and proposes a potential therapeutic strategy for immune disorders by targeting lipid metabolism.

Keywords: Dyslipidemia; T cell; B cell Dendritic cell; Immune disorder

INTRODUCTION

Lipids such as cholesterols, fatty acids, and phospholipids are essential to higher organisms for energy storage, organ physiology, cellular proliferation and numerous aspects of cellular biology. In the cell, lipid serves as a critical energy source, and the main component of cellular membranes. Moreover, some lipids act as agonists or antagonists for transcription factors to meet diverse demands from various tissues and to maintain cellular homeostasis. On the other hand, chronic dyslipidemia triggers cardiovascular diseases including atherosclerosis-related coronary and cerebral artery diseases which represent the leading cause of death worldwide.^{1,2} The prevalence of dyslipidemia increases steadily in developed countries, likely due to westernized dietary patterns. In addition, it is evident that aberrant activation of innate and adaptive immune responses contributes to the pathogenesis of atherosclerosis.³⁻⁶ Proatherogenic factors have been shown to exhibit both pro- and anti-inflammatory effects on the innate immune system. For instance, several lipid species are known to stimulate macrophages to produce interleukin (IL)-1 β through MyD88 or the inflammasome.⁶⁻⁹ On the contrary, lipid species can activate the PPAR γ pathway and inhibit inflammatory responses in macrophages.^{10,12} Thus, lipid species can exert both pro-inflammatory and anti-inflammatory functions in a context-dependent manner.

Conflict of Interest

The authors declare no competing financial interest.

Author Contributions

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Of note, numerous epidemiologic studies indicate a strong incidental correlation between atherosclerosis and chronic autoimmune disorders, indicating a mutual regulation between immune and cardiovascular systems. For instance, a higher incidence of atherosclerosis is observed in patients with pre-existing autoimmune disorders such as rheumatoid arthritis,^{13,16} psoriasis^{17,20} systemic lupus erythematosus (SLE),^{21,23} and diabetes mellitus. In addition, dyslipidemia induced by a high-fat diet accelerates the progression of autoimmune lupus, arthritis and encephalomyelitis.²⁴⁻²⁷ More importantly, treatment of hyperlipidemia in patients with psoriasis leads to clinical improvement,²⁸⁻³¹ indicating a pathogenic role of dyslipidemia on the development and/or progression of autoimmune diseases in humans as well as in animal models. Given that the dyslipidemia-related immune disorders are mediated by aberrantly activated self-reactive T cells and/or self-reactive B cells, it is feasible to surmise that dyslipidemia directly or indirectly regulates the differentiation and function of adaptive immune cells *in vivo*.

In this review, we will provide an updated view on the role of dyslipidemia and lipid species in regulating T cells and B cells. In the first half, we discuss the association of dyslipidemia and immune disorders including autoimmune diseases, cancers, and infections. In particular, the suggested potential mechanisms by which lipid metabolism impacts such immune disorders will be discussed. In the second half, we discuss the role of cholesterol metabolism in the context of regulating the differentiation and functions of immune cells including dendritic cells, T cells, and B cells.

DYSLIPIDEMIA REGULATES IMMUNE-MEDIATED DISEASE BY SHAPING THE ADAPTIVE IMMUNE SYSTEM

Lipid homeostasis in adaptive immune cells is crucial, and any disruption to the balance may lead to an engenderment or exacerbation of immune-mediated diseases. This tipping may occur in antigen-presenting dendritic cells or effector cell population such as follicular helper T cells (Tfh) and B cells to mediate autoimmune diseases, tumor microenvironment, and infection.

Autoimmune disease

Autoimmune diseases including multiple sclerosis, SLE, and psoriasis are positively correlated with a risk of cardiovascular disease. Immune-mediated diseases including rheumatoid arthritis and lupus are known to be driven by pathogenic CD4⁺ T cells. Often, lipid-lowering treatments including low-fat diet and statins are utilized in the treatment of psoriasis and SLE.^{32,33} The link between autoimmunity and dyslipidemia is well corroborated in various reports.³⁴⁻³⁹

Hyperlipidemic condition promotes autoimmune phenotypes in dendritic cells which in turn, affect Tfh and B cells.^{34,36,37} For one, dendritic cells with augmented intracellular cholesterol drive lupus-like phenotypes such as glomerulonephritis and a surge in plasma anti-dsDNA antibodies. These splenic dendritic cells are mostly CD11b⁺ with enhanced ability to induce T-cell activation and disrupt immune tolerance, exacerbating the pathogenesis.³⁶ Cholesterol buildup in CD11c⁺MHCII⁺ cells impairs antigen presentation and activates toll-like receptor signaling, driving the production of Baff and April. Eventually, they facilitate the priming of autoreactive T cells, expansion of B cells, and production of autoantibodies.⁴⁰ Not only that, uptake of oxidized low-density lipoproteins (LDLs) and LDLs by dendritic cells significantly increases Th17 and Tfh differentiation via IL-6 and IL-1 β secretion. These pathogenic Tfh and Th17 cells in turn can

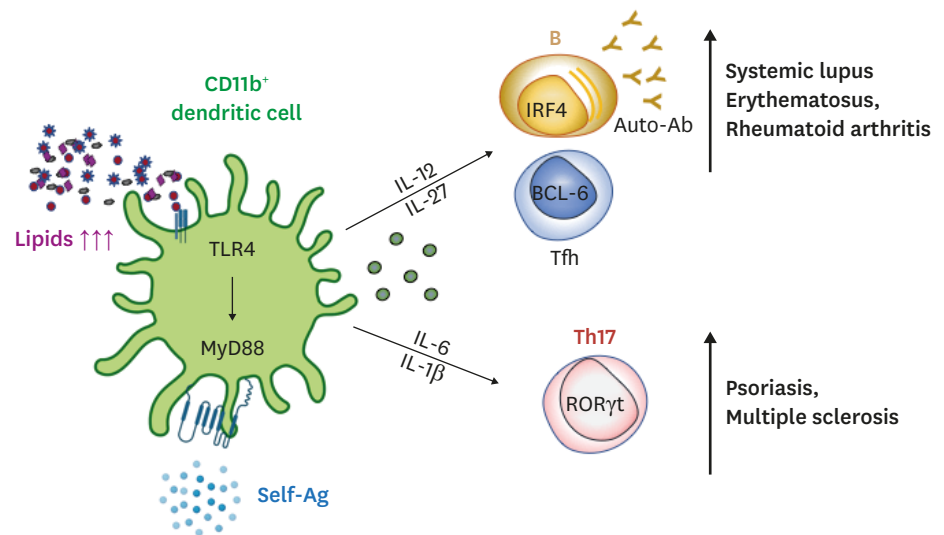


Fig. 1. Hyperlipidemia impacts autoimmune Tfh cells and Th17 cell responses. Atherogenic dyslipidemia can be recognized by CD11b⁺ dendritic cells through pattern recognition receptors, leading to the increased production of pro-inflammatory cytokines including IL-12, IL-27, IL-6, and IL-1. These cytokines in turn promote the differentiation of autoimmune Tfh and Th17 cells *in vivo*. Thus, dyslipidemia contributes to the onset or progression of Tfh- or Th17-mediated autoimmune diseases. Tfh, follicular helper T cell; IL, interleukin.

enhance the susceptibility to other autoimmune diseases such as psoriasis and rheumatoid arthritis (**Fig. 1**).^{36,39,41} Furthermore, a double-transgenic mouse expressing human CD1b, CD1c, and CD1b-autoreactive T cell receptor (TCR) in the Apolipoprotein E (ApoE)-deficient background spontaneously develops psoriasiform characterized by an upregulation of IL-6 and IL-17A secretion by CD1b⁺ dendritic cells and CD1b-autoreactive T cells.⁴¹

One of our recent studies provides a potential mechanism by which atherogenic conditions mediate Tfh cell differentiation and the following autoimmune response. Bone marrow cells from lupus-prone BXD2 mouse were transferred into bone marrow-ablated ApoE-deficient or wild-type mouse. Compared to the wild-type mouse, the ApoE-deficient mouse displayed a surge of autoreactive CXCR3⁺ Tfh cells and B cells that led to an escalation of total IgG and IgG2c autoantibodies to dsDNA and rheumatoid factors. Among the elevated cytokines in the sera of dyslipidemic mice, IL-27 produced by Toll-like receptor 4-dependent CD11b⁺ splenic dendritic cell alone was sufficient to generate germinal center reactions and Tfh cells in ApoE-deficient atherogenic mouse (**Fig. 1**). This inflation of IL-27 is not only observed in atherogenic mice but also in humans as patients with hypercholesterolemia display a correlation between increased IL-27 and circulating IgG.³⁷ Therefore, we postulate that hyperlipidemic condition facilitates the generation of autoimmune Tfh cell responses via IL-27 and that this proposed axis has relevance in both humans and mice (**Fig. 1**).

Cancer

Depending on a specific signal or a factor provided to the adaptive immune cells, they could either enhance or inhibit tumorigenesis. For instance, cytokines such as interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) enable cytotoxic CD8⁺ T cells to lyse tumor cells, but type 2 cytokines or IL-2 could induce pro-tumorigenic Th2 and regulatory T cells. Like the cytokine, cholesterol acts as a signal to the adaptive immune cells to mediate immune responses against the tumor cells.⁴²⁻⁴⁷

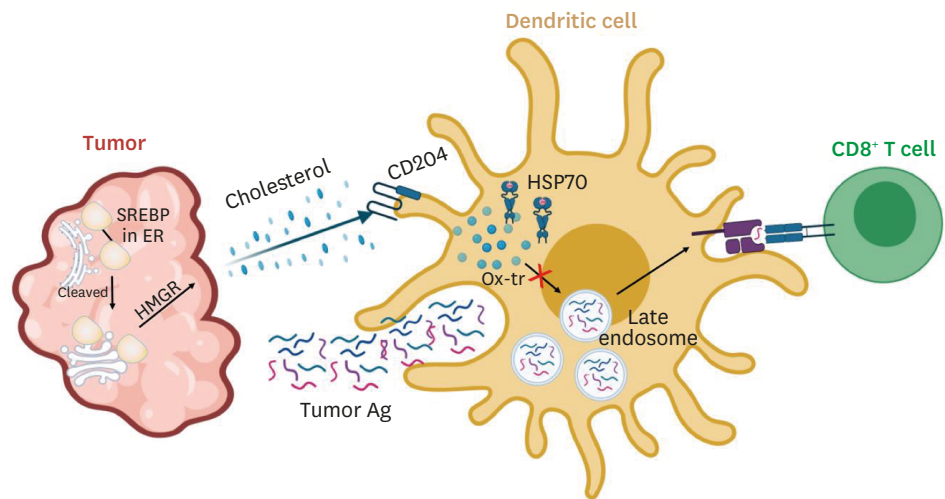


Fig. 2. Tumors incapacitate anti-tumor immunity by regulating lipid metabolism. The tumor itself creates a hyperlipidemic tumor microenvironment via cleavage of SREBP and the subsequent conversion of HMG-CoA into mevalonate. This tumor intrinsic-pathway elevates the uptake of oxidatively truncated lipids by overexpressing CD204 in dendritic cells and inhibits their cross-presentation by impeding the translocation of lysosomes with amasssed pMHC. Prevention of lipid buildup in the dendritic cells may play a crucial role in anti-tumor immunity. SREBP, sterol regulatory-element binding protein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; pMHC, peptide-MHC class I complexes.

Tumor cells are known to upregulate cholesterol synthesis through sterol regulatory-element binding protein (SREBP) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), inducing tumor-infiltrating CD8⁺ T cell exhaustion (**Fig. 2**).⁴³⁻⁴⁷ In order to reverse this pro-tumorigenic process, statins are used to inhibit HMGR, which is a rate-limiting enzyme in converting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) into mevalonate. As a result, the use of statins is negatively correlated with cancer grade, cancer risk, and cancer-specific mortality.⁴⁸⁻⁵⁰ One prime study utilizes an adoptive T-cell transfer model in which hgp100₂₅₋₃₃ pulsed splenocytes from Pmel-1 mice are injected intravenously into melanoma infected C57BL/6 mice. Intracellular cholesterol levels and exhaustion phenotypes of tumor-infiltrating CD8⁺ T cells are significantly higher than those of CD8⁺ T cells in the spleen or draining lymph node, suggesting that the immune checkpoint expression elevation and intracellular cholesterol buildup occur after they enter the tumor bed.⁴⁷ Also, treatment of avasimibe enhances cytotoxicity of CD8⁺ T cells in melanoma-bearing mouse. Avasimibe is a pharmacological drug to treat atherosclerosis by inhibiting acetyl-CoA acetyltransferase 1 (ACAT1), a key cholesterol esterification enzyme. Thus, avasimibe administration decreases plasma membrane cholesterol level in CD8⁺ T cell alone, which causes enhanced T-cell receptor clustering and signaling as well as more efficient formation of the immunological synapse to effectively kill melanoma.⁴³

Dendritic cells act as immune surveillance owing to their ability to detect and present tumor-associated antigens to enable various antitumor effector cells. However, tumor-associated dendritic cells in both humans and mice are known to be defective in their capacity to present antigens.⁵¹⁻⁵⁵ Emerging evidence show that intracellular lipid accumulation is the primary cause for this dysfunctionality.⁵⁶⁻⁵⁸ Dendritic cells from tumor-bearing mice and patients with non-small-cell lung carcinoma and head and neck cancer all upregulate their expression of scavenger receptor A, rapidly taking in extracellular triglycerides. And inhibition of acetyl-CoA carboxylase, a critical element in the fatty acid synthesis, revives the anti-tumor activity

of the dendritic cells.⁵⁶ Cross-presentation, crucial for its activation of cytotoxic CD8⁺ T cells, is also compromised in various tumors. This defect is due to the deposition of lipid bodies containing electrophilic oxidatively truncated (ox-tr) lipids inside the dendritic cells by overexpressing CD204. Ox-tr covalently attaches to chaperone heat shock protein 70, which stabilizes lysosomes trafficking peptide-MHC class I complexes (pMHC). The interaction causes the accumulation of pMHC inside the lysosome and prevents its translocation to the cell surface (**Fig. 2**).⁵⁸ Not only that, dendritic cells cultured in the presence of adipocyte-conditioned media from obese subjects or colorectal patients enhance their expression of PD-L1 and PD-L2 and reduce their secretion of IL-12 and IL-10 ratio.⁵⁷

Infection

Epidemiological studies demonstrate that cholesterol, LDL, and high-density lipoprotein (HDL) levels all increase the likelihood of developing an infection. Also, mortality among patients with sepsis, one of the direst symptoms of an infection, is foreseen by the degree of reduction in the HDL and the total cholesterol levels.⁵⁹⁻⁶² Cholesterol-reducing drugs such as statins, ezetimibe, and zetia are all implicated in the amelioration of various infections such as typhoid fever and murine cytomegalovirus.^{63,64} This link between dyslipidemia and infection susceptibility is well-documented in numerous studies. For instance, ApoE- and LDL receptor-deficient mice are susceptible to *L. monocytogenes*, *K. pneumoniae*, *C. albicans*, and lymphocytic choriomeningitis mammarenavirus (LCMV), and those with impaired immunity such as SCID mice, IFN- γ -deficient, and OVA-specific TCR transgenic mice are heavily affected by tuberculosis.^{65,70}

T cells play a central role in our fight against infections by killing infected cells using granzyme B and perforin or by releasing pro-inflammatory mediators that recruit other effector cells to the infected site.^{68,69,71} Hypercholesterolemic ApoE- and LDL receptor-deficient mice do not exhibit any change during the initial spread of LCMV, but the clearance of the virus is significantly delayed in the spleen and nonlymphoid organs including the liver. Activation and recruitment of LCMV-specific CD8⁺ T cells are suppressed in hypercholesterolemic mice with impaired IFN- γ production and cytotoxicity.⁶⁶ Not only that, ApoE knockout mouse fed with high cholesterol diet displays the direst symptoms associated with tuberculosis (TB) including heavy bacterial burden, severe lung inflammation, and early mortality. Surprisingly, the mortality rate of the hypercholesterolemic mouse matches that of the IFN- γ deficient mouse, the most TB-susceptible strain. Impaired priming of the adaptive immune system is the cause of the susceptibility since, despite an effective Th1 response, ApoE-deficient mouse fed with high cholesterol diet (HC) has a much-delayed immune response. Also, OT-II cells, which are introduced to ApoE-deficient HC mice via intravenous injection and stimulated by OVA-coated iron beads via subcutaneous injection, do not proliferate contrary to those in WT HC mice.⁷² CD4⁺ T cells with increased cholesterol efflux via ATP-binding cassette transporter 1 (ABCA1) reduce the susceptibility to HIV-1 infection. The effect was reversible with cholesterol replenishment.⁷³

Dendritic cells are responsible for activating T cells by presenting virus-specific antigens via MHC molecules and differentiating T cells by cytokine stimulation to effectively destroy infected cells.^{74,75} Once stimulated via toll-like receptors, dendritic cells from the obese individuals compared to the lean individuals', upregulate twofold more of IL-10, inducing a heightened level of IL-4 production from the T cells that dampens anti-viral Th1-type immunity.⁷⁶ Cholesterol accumulation in dendritic cells of ApoE-deficient mice reduces activation of CD8 α dendritic cells. This inactivation impairs Th1 cell responses while

enhancing Th2 cell response, consequently leading to an increased susceptibility to *L. major*. The dampened immune response is driven by oxidized low-density lipoprotein (oxLDL) via inhibition of nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) nuclear translocation and toll-like receptor (TLR)-mediated signaling in CD8 α dendritic cells.⁷⁷

CHOLESTEROL METABOLISM IN ADAPTIVE IMMUNITY

Cholesterol is one of the major components of the plasma membrane, particularly in lipid rafts, and a critical source of energy. It is well-known that dyslipidemia triggers pro- or anti-inflammatory responses from the innate and adaptive immune system. Particularly, TLR activation in macrophages leads to cholesterol accumulation via inhibition of cholesterol efflux, resulting in enhanced inflammasome activation and subsequent inflammatory responses.⁷⁸⁻⁸⁰ Cholesterol efflux (reverse cholesterol transport) in macrophages via ATP-binding cassette (ABC) transporters such as ABCA1 and ATP-binding cassette subfamily G member 1 (ABCG1) induces anti-inflammatory effects by suppressing TLR signaling.⁸¹ Genes encoding these transporters are known to be induced by a transcription factor called liver X receptor (LXR), which is activated by intermediates from the cholesterol biosynthetic pathway such as desmosterol and cholesterol-derived oxysterols. Although TLR activation decreases cholesterol efflux and enhances cholesterol accumulation, LXR is also activated by cholesterol accumulation and suppresses inflammatory responses. Desmosterol accumulation by inhibiting desmosterol reductase via cholesterol loading causes LXR activation and reduction in the expression of pro-inflammatory genes.⁸² Since cholesterol metabolism's impact on the innate immune system is well-established, we will direct our focus on defining the relationship between cholesterol metabolism and the adaptive immune system.

Dendritic cell (DC)

Dendritic cells are antigen-presenting cells that link the innate immune system to the adaptive immune system. One study proposed that the ability of antigen presentation to CD4⁺ T cells is comparable between DCs isolated from normal and hypercholesterolemic mice.⁸³ As in macrophages, cholesterol accumulation in DCs leads to inflammasome activation and enhanced secretion of IL-1 β and IL-18. The deficiency of cholesterol transporters, ABCA1 and ABCG1 that excrete cholesterol from the cells, causes cholesterol accumulation in dendritic cells and skews DCs to CD11b⁺ inflammatory DCs, resulting in the activation of NLRP3 inflammasome. Furthermore, the lack of cholesterol efflux promotes the secretion of cytokines such as IL-12, IL-8, and IL-23. These pro-inflammatory cytokines drive T cell differentiation towards Th1 and Th17 cells, which mediate autoimmune responses *in vivo*.³⁶

Cellular sterols are known to be sensed by lipid-activated transcription factor such as LXR, and several lines of evidence suggest that LXR regulates the function of DCs. In particular, LXR α is upregulated during the differentiation of human monocyte-derived DCs, while LXR β remains at a low level.⁸⁴ Although LXR activation inhibits LPS-dependent DC maturation and hinders its ability to stimulate T cells, it does not change the expression of antigen-presenting molecules including major histocompatibility complex class I and II. During the DC maturation via LPS, LXR inhibits the expression of actin-bundling protein fascin, an essential component in immune synapse formation, reducing its ability to activate T cells.⁸⁴ In addition, LXR is known to repress the production of pro-inflammatory cytokines such as TNF α and IL-6 in DCs and inhibit the TLR-induced expression of CCR7, undermining their migration to the chemokine CCL19/CCL21-expressing tissues.^{85,86} Also, prostaglandin

E2 (PGE₂), a crucial component in the chemokine induced-migration of DCs, has a role in inhibiting the expression of LXR α in human dendritic cells.^{86,87} Although these recent findings strongly propose a link between cholesterol metabolism and immune responses in DCs, further studies will be needed to uncover the underlying molecular mechanisms and define its role in the pathogenesis of dyslipidemia-related immune disorders in humans.

T cell

Since newly activated T cells require biosynthetic programs and energy for their clonal expansion, metabolism reprogramming is one of the prerequisites for T cell activation.^{88,89} Also, cholesterol forms lipid rafts in which TCR signaling complexes are clustered.^{90,91} Therefore, it is feasible to surmise that cholesterol metabolism is important for controlling T cell proliferation and functions. T cells enhance cholesterol biosynthesis upon activation for their growth and proliferation. For instance, α CD3-induced stimulation of T lymphocytes results in the induction of HMG-CoA reductase, an enzyme involved in the cholesterol biosynthesis required for cell cycle progression to the cell surface (**Fig. 3**). Inhibition of the mevalonate pathway via statin, an inhibitor of HMG-CoA reductase, or cholesterol derivatives suppresses α CD3-induced T cell mitogenesis.⁹² Here, we delve into the role of cholesterol metabolism in T cells in detail.

CD4⁺ T cell

Although activated T cells induce cholesterol biosynthetic pathways for their growth, LXR inhibits T lymphocyte proliferation by promoting cholesterol efflux via cholesterol transporters such as ABCA1 and ABCG1. T cell activation promotes the induction of sulfotransferase family 2B member 1 (SULT2B1), which is an oxysterol-metabolizing enzyme, and thus suppresses the LXR pathway.⁹³ ABCG1, which is induced by LXR, is known as a negative regulator of CD4⁺ T cell proliferation. Cholesterol accumulation by the removal of *Abcg1* in CD4⁺ T cells enhances proliferation of the T cells (**Fig. 4**) via enhanced lipid raft formation and phosphorylation of TCR signaling molecules such as zeta-chain-associated protein kinase 70 (ZAP70) and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2).⁹⁴ By contrast, another study has shown that LXR β -deficient CD4⁺ T cells exhibit reduced proliferation compared to LXR β -sufficient ones.⁹⁵

In addition to the T cell activation and proliferation, cholesterol metabolism is also related to T cell differentiation and effector functions. It is reported that LXR suppresses Th17 cell polarization of naïve CD4⁺ T cells and thus mitigates the onset of experimental autoimmune encephalomyelitis in mice.⁹⁶ LXR negatively regulates Th17 cell differentiation in mice by reducing the expression of retinoic acid-related orphan receptor gamma t (ROR γ t) which is a crucial transcription factor for Th17 cell differentiation and Th17-related genes including *Il17*, *Il22*, *Il23r*, and *Ahr* in Th17 cells. LXR regulates the expression of SREBP-1 isoforms, SREBP-1a and SREBP-1c. SREBP-1 binds to *Il17* promoter and suppresses Th17 cell differentiation (**Fig. 4**), and it also inhibits AhR, a positive regulator of the Th17 differentiation. This effect of LXR is also shown in human Th17 cells.⁹⁶ These findings suggest the potential role of LXR in the mitigation of autoimmunity by suppressing Th17 cell differentiation via SREBP-1. On the one hand, a recent study reports that immune activation is exacerbated due to the dysfunctional regulatory T cells (Treg), while the number of CD4⁺ T cells is decreased in LXR β -deficient mice.⁹⁵ SREBPs also contribute to the regulation of Treg cell functions, specifically in the context of the tumor microenvironment.⁹⁷ In tumors, steroid receptor RNA activator protein/SREBP signaling is important in Treg cells to maintain their suppressive ability and programmed cell death protein 1 (PD-1) expression. By contrast, SCAP is not necessary for

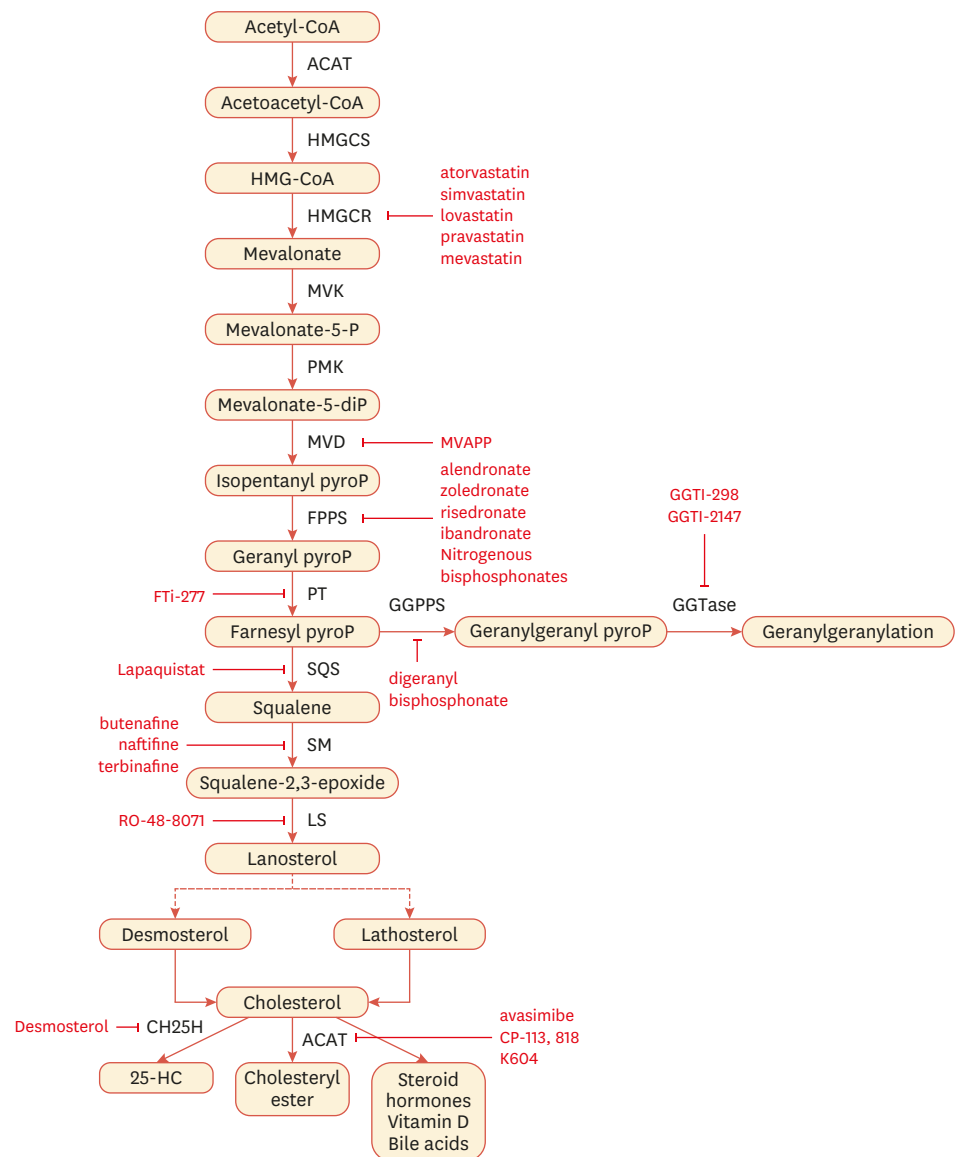


Fig. 3. Cholesterol synthesis pathways can be targeted by small molecules. Cholesterol biosynthesis takes place in all mammalian cells including immune cells. The enzymes that mediate the synthesis of indicated sterol intermediates and inhibitors of each enzyme are shown.

steady-state Treg cells, indicating a context-specific requirement of this pathway in Treg cell homeostasis. SREBP cleavage-activating protein (SCAP)/SREBP signaling induces PD-1 expression in Treg cells in a TCR signaling-dependent manner. Furthermore, geranylgeranyl pyrophosphate-dependent geranylgeranylation induced by SCAP/SREBP promotes PD-1 expression in Treg cells. SREBP and PD-1 suppress IFN γ expression in Treg cells by controlling phosphatidylinositol-3-kinase (PI3K) signaling in the tumors. Targeting SCAP/SREBP signaling in Treg cells presents antitumor effects without unleashing any autoimmune responses *in vivo*,⁹⁷ suggesting that it can be a potent target for cancer immunotherapy. The mechanistic target of rapamycin (mTOR) also links cholesterol metabolism to Treg cell functions. Raptor/mTORC1 in Treg cells plays an important role in the proliferation of Treg cells and their suppressive activity by promoting cholesterol metabolism.⁹⁸ Moreover,

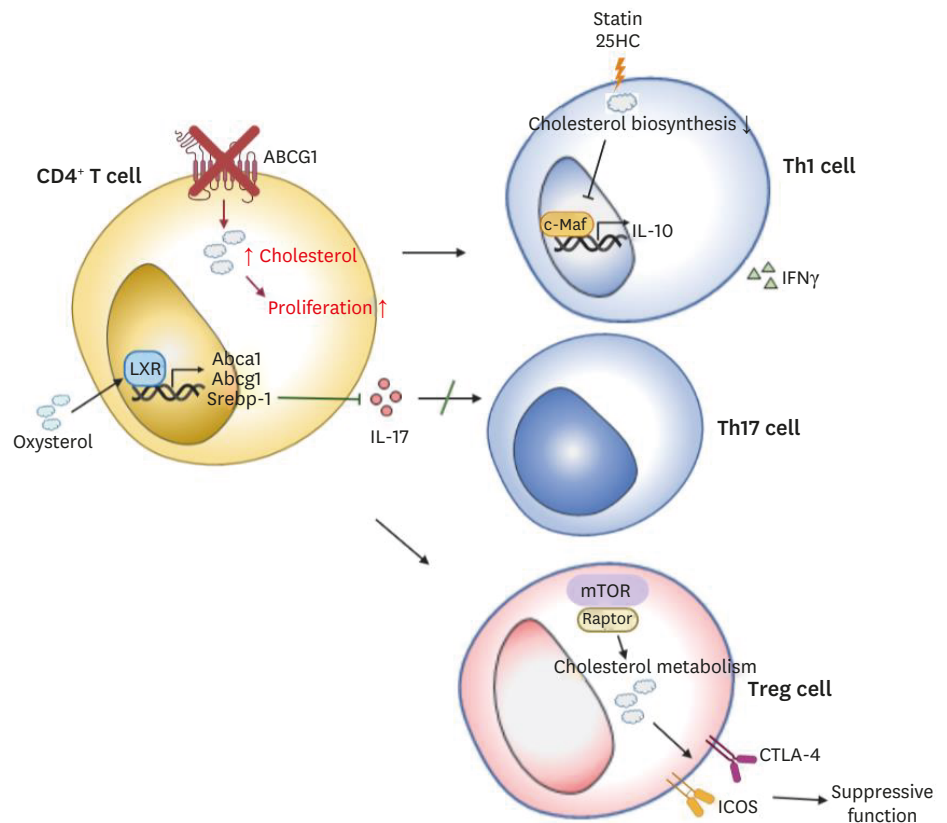


Fig. 4. Intracellular cholesterol metabolism controls the proliferation and the differentiation of helper or regulatory T cells. Cholesterol accumulation promotes proliferation in CD4⁺ T cells. LXR, an important transcription factor regulating cholesterol metabolism, inhibits Th17 differentiation. Moreover, cholesterol biosynthesis regulates the immune resolution by coordinating the switching of IFN γ into IL-10 in Th1 cells. mTORC1 also contributes to the immune resolution in Treg cells via regulation of cholesterol metabolism. LXR, liver X receptor; IFN, interferon; mTOR, mechanistic target of rapamycin; IL, interleukin.

treatment of atorvastatin of 25-hydroxycholesterol in human Th1 cells to inhibit cholesterol biosynthetic pathways impedes immune resolution by suppressing the switch from IFN γ ⁺ to IL-10⁺ phenotype in Th1 cells via decreased c-Maf, a master transcription regulator for IL-10 in CD4⁺ T cells (Fig. 4).⁹¹ Therefore, disruption in cholesterol metabolism may trigger inflammatory diseases such as rheumatoid arthritis (RA) in humans.⁹⁹

CD8⁺ T cell

SREBP can activate the expression of genes encoding cholesterol metabolism-related molecules. SREBP has an important role in CD8⁺ T cell activation by controlling the lipid biosynthesis program in a context-dependent manner as observed in Treg cells.⁹⁷ SREBP is not necessary for quiescent CD8⁺ T cells, but for activated CD8⁺ T cells. Therefore, SREBP contributes to the metabolic reprogramming of CD8⁺ T cells during activation.¹⁰⁰ In addition to the role of LXR in innate immune cells and CD4⁺ T cells, LXR also contributes to controlling the activation and functions of CD8⁺ T cells (Fig. 5). As described above, LXR and SREBP are regulated reciprocally during T cell activation, and LXR inhibits lymphocyte proliferation but not its activation (Fig. 4).⁹³ In particular, LXR regulates CD8⁺ T cell functions by promoting IL-9 secretion. Cholesterol or cholesterol-derived oxysterol inhibits the expression of IL-9 by reducing p65 binding to *Il9* promoter via LXR SUMOylation.⁴⁶

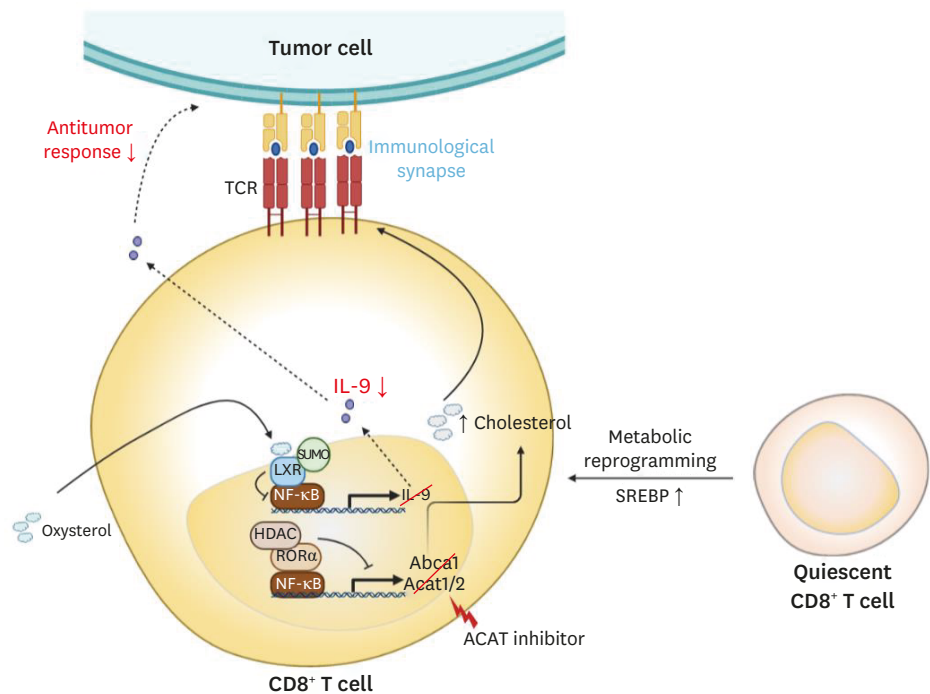


Fig. 5. Cholesterol metabolism regulates the activation of CD8⁺ T cells and the antitumor activity of Tc9 cells. Cholesterol biosynthetic pathways are required for CD8⁺ T cell in a context-dependent manner, and so they play a crucial part in its anti-tumor efficacy. Increased cholesterol levels promote strong TCR signaling and consequently result in enhanced effector functions of CD8⁺ T cells. On the other hand, LXR SUMOylation by cholesterol-induced oxysterol reduces the antitumor response in Tc9 cells. TCR, T cell receptor; LXR, liver X receptor; HDAC, histone deacetylase; ROR α , retinoic acid-related orphan receptor α ; SREBP, sterol regulatory-element binding protein; IL, interleukin.

Consistently, Tc9 cells, which exert stronger antitumor responses than Tc1 cells, have lower levels of cholesterol compared to Tc1 cells in mice (Fig. 5).⁴⁶

Although both cholesterol biosynthesis and efflux are crucial to the regulation of the adaptive immune responses, cholesterol esterification is equally paramount in immune cell activation and function. Cholesterol esterification converts cholesterol into cholesteryl ester, one of the constituents of lipoproteins. ACAT is an enzyme mediating cholesterol esterification, and its two isoforms are ACAT1 and ACAT2. Ablation of ACAT1 in T cells or inhibition of cholesterol esterification by ACAT inhibitors can enhance the proliferation of CD8⁺ T cells and CD8⁺ effector function, resulting in the suppression of tumor growth (Fig. 5).⁴³ As described above, cholesterol clusters TCR signaling complexes.^{90,91} Inhibition of cholesterol esterification in T cells also enhances TCR clustering and promotes efficient immunological synapse formation for CD8⁺ T cell proliferation and effector function.⁴³ Unlike CD8⁺ T cells, ACAT1-deficient CD4⁺ T cells do not display any differences in their function. It might be due to the compensation of ACAT2 for ACAT1 deficiency.⁴³ Lee et al.¹⁰¹ recently showed that retinoic acid-related orphan receptor α (ROR α) regulates cholesterol levels in CD8⁺ T cells by controlling the expression of NF- κ B target genes containing *Acat1* and *Abcg1*. They suggest that ROR α and histone deacetylase (HDAC) enhance cholesterol levels in CD8⁺ T cells, resulting in an enhanced TCR signaling, proliferation, and effector functions of CD8⁺ T cells (Fig. 5). Thus, cholesterol metabolism and sterol-sensing transcription factors have critical regulatory roles in the differentiation and function of T cells.

B cell

Cholesterol biosynthetic pathway is well-known to be involved in the formation of germinal center (GC) B cell. RHO-associated coiled-coil-containing protein kinase 2 (ROCK2) in GC B cells is known to promote GC formation and cholesterol biosynthesis by regulating transcriptional programs.¹⁰² ROCK2 phosphorylates IRF8 and supports its interaction with SREBP2, leading to the enhanced expression of cholesterol biosynthesis-related genes.¹⁰² Since it is known that IRF8 is linked to inflammation particularly in vascular cells,¹⁰³ it is possible that ROCK2 links cholesterol biosynthesis to inflammatory responses via IRF8 and SREBP.

As mentioned above, LXR activation also contributes to immune tolerance through its ability to promote apoptotic cell clearance via macrophages.¹⁰⁴ LXR α and LXR β double-deficient mice are shown to spontaneously develop autoantibodies and lupus-like autoimmune inflammation. Engulfment of apoptotic cells by macrophages leads to the accumulation of cellular components including cholesterol and consequently activates LXR signaling. LXR promotes the expression of Mer receptor tyrosine kinase (Mertk) in macrophages leading to the clearance of apoptotic cells, forming a positive feedback loop to further ingest apoptotic cells and suppress inflammatory responses. Accordingly, LXR activation can counteract the development of autoimmune disease by inhibiting autoantibody production by B cells and maintaining immune tolerance.¹⁰⁴

On the contrary, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is expressed on dendritic cells and promotes humoral responses, leading to B cell differentiation and secretion of immunoglobulin.¹⁰⁵ OxLDL, which acts as a ligand of LOX-1, is a well-established risk factor in the development of atherosclerosis. LOX-1 on DCs promotes B cell differentiation into plasmablasts by reducing paired box 5 (Pax5) and enhancing B lymphocyte-induced maturation protein 1 (Blimp-1) expression. In addition, LOX-1 on DCs induces cytokines, proliferation-inducing ligands (APRIL), and B cell-activating factors (BAFF) which all contribute to B cell proliferation, differentiation, class-switching, and plasma cell survival, promoting antibody production. Furthermore, LOX-1 on B cells plays an important part in humoral immune responses by guiding B cells into lymphoid tissues via lymphoid organ homing receptor CCR7.¹⁰⁵ Together, LOX-1 stimulated by oxLDL is expressed in both DCs and B cells and contributes to enhanced humoral immune responses *in vivo*.

Geranylgeranyl pyrophosphate (GGPP) is one of the derivatives of mevalonate. It is required for protein isoprenylation and links cholesterol metabolism and B cell immunity. Geranylgeranylation of proteins such as small GTPase, Ras, and Rho, regulates its functions. In B cells, geranylgeranylation controls CD40-dependent B cell activation. Blocking geranylgeranylation via geranylgeranyl transferase inhibitor (GGTI) suppresses CD40-dependent B cell activation while exerting minute effects on the production of cytokines and chemokines by activated B cells.¹⁰⁶ Moreover, GGPP regulates the function of regulatory B cells. The metabolic intermediate of mevalonate, GGPP, enhances IL-10 production in regulatory B cells and promotes their ability to suppress Th1 responses.¹⁰⁷ IL-10 is controlled via the RAS-PI3K δ -protein kinase B-glycogen synthase kinase 3 (RAS-PI3K δ -AKT-GSK3) pathway by GGPP and in a BLIMP-dependent manner.¹⁰⁷ Although not common, Epstein-Barr virus (EBV) leads to the expression of the mevalonate biosynthetic pathway-related genes by targeting transcription factors such as MYC and SREBP by EBV-encoded EBV nuclear antigen 2 (EBNA2) and subsequently promotes B cell proliferation and survival.¹⁰⁸ Mevalonate-derived GGPP contributes to the geranylgeranylation of Ras-associated binding (Rab) protein. EBV nuclear antigen 3C (EBNA3C) from EBV enhances the expression of Rab13. Together, EBV

leads to the proliferation and survival of the infected B cells by promoting the expression of cholesterol biosynthetic pathway, synthesizing GGPP, and activating Rab.¹⁰⁸ Thus, lipid metabolism critically regulates the differentiation of and antibody production from B cells. Additional studies will be needed to address whether targeting lipid metabolism can improve the antibody production from B cells in vaccination settings and ameliorate the pathogenesis of antibody-mediated immune disorders in humans.

CONCLUSION AND PERSPECTIVES

Dyslipidemia is a well-established risk factor of cardiovascular diseases in humans; however, it is becoming clearer that it also significantly impacts the pathogenesis of immune disorders, as discussed above (Fig. 6). In particular, accumulating evidences have demonstrated that a number of lipid species can be sensed by innate immune cells including macrophages and dendritic cells, which in turn can regulate adaptive immune cells. In addition, lipid species within immune cells also play a critical role, not only in the proliferation and signal transduction as shown in other cell types but also in the functions of innate and adaptive immune cells.

As a consequence, levels of extracellular, as well as intracellular lipid species, are critical determinants of the outcome of adaptive immune responses. Moreover, drugs targeting lipid metabolism also critically impact our immune system and defensive mechanisms. As discussed above, several FDA-approved drugs demonstrate the potentials to be used as immunological modulators that can improve antitumor immunity, vaccine efficacy, or ameliorate autoimmunity in animal models. Such immunological aspects of lipid metabolism are of great interest since they will uncover a novel immunopathogenesis regulated by lipid metabolism, and will also pave the development of new therapeutic approaches for immune disorders in humans by targeting lipid metabolism. Given that a number of enzymes and transcription factors in lipid metabolism are proven to be effective and safe targets in humans, further interdisciplinary researches involving immunology and lipid metabolism would be an important field of translational and clinical researches.

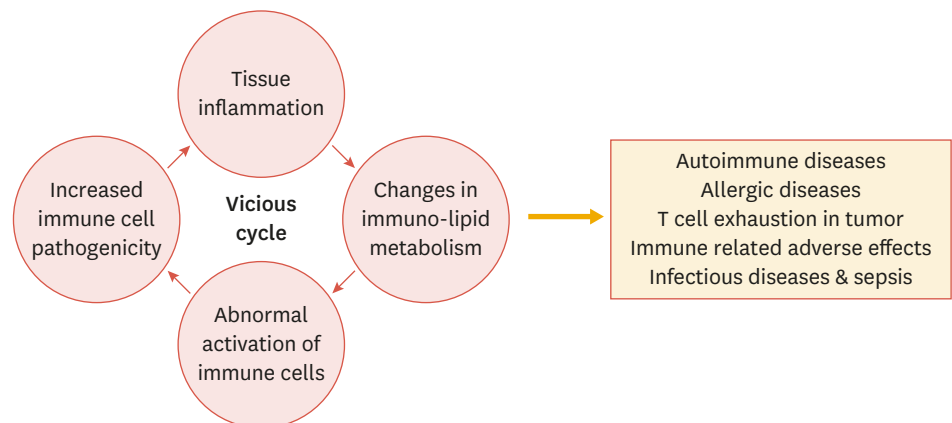


Fig. 6. Lipid metabolism is involved in the pathogenesis of immune disorders. Environmental dyslipidemia as well as disturbed cellular lipid metabolism critically impacts the aberrant activation and differentiation of immune cells, leading to enhanced pathogenicity of immune cells that triggers tissue inflammation. As a result, unbalanced lipid metabolism contributes to the development of a wide range of immune disorders including autoimmune diseases, allergies, cancers, and infectious diseases. Targeting lipid metabolic pathways may be effective in ameliorating immune disorders in humans.

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