Cellular and Molecular Links between Autoimmunity and Lipid Metabolism

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The incidence of atherosclerosis is higher among patients with several autoimmune diseases such as psoriasis, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is well documented that innate immune cells including macrophages and dendritic cells sense lipid species such as saturated fatty acids and oxidized low-density lipoprotein and produce pro-inflammatory cytokines and chemokines. However, whether a hyperlipidemic environment also impacts autoimmune T cell responses has been unclear. Among CD4^{+} T cells, Th17 and follicular helper T (Tfh) cells are known to play pathogenic roles in the development of hyperlipidemia-associated autoimmune diseases. This review gives an overview of the cellular and molecular mechanisms by which dysregulated lipid metabolism impacts the pathogenesis of autoimmune diseases, with specific emphasis on Th17 and Tfh cells.

Keywords: autoimmune diseases, hyperlipidemia, lipid metabolism, Tfh cell, Th17 cell

INTRODUCTION

Autoimmune diseases are caused by the loss of immune tolerance to self-antigens and the prevalence of the diseases is rising worldwide (Anaya, 2012; Bao et al., 2019; Lerner et al., 2015). Autoreactive T cells and autoantibodies are key attackers of self-antigens that induce tissue inflammation, although how the activation and differentiation of autoreactive T and B cells occur is not completely understood. For instance, multiple sclerosis is an autoimmune disease mediated by T cells specific for myelin and other autoantigens in the central nervous system. Recent advances suggest a pathogenic role for Th17 cells in the disease development in experimental models as well as in humans (Cua et al., 2003; Lee et al., 2018; Volpe et al., 2015). Similarly, autoreactive Th17 cell has been suggested as a key pathogenic immune cell in the animal models of rheumatoid arthritis (RA) and psoriasis (Fitch et al., 2007; Nistala et al., 2008). Of note, treatment with anti-interleukin (IL)-17 or anti-IL-17RA antibodies was found to significantly ameliorate clinical severity of skin inflammation in patients with psoriasis in multiple clinical trials, validating the pathogenic role of Th17 cells in the autoimmune skin disease (Papp et al., 2012; 2013). Successful clinical trials in psoriasis stimulated translational and clinical studies to investigate whether targeting IL-17/IL-17RA or RORγt, a master transcription factor for Th17 cells, would be beneficial for other autoimmune diseases. On the other hand, Tfh cells have been suggested to be pathogenic in the development of antibody-mediated autoimmune diseases including systemic lupus erythematosus (SLE), Sjögren's syndrome, and possibly RA because of their capacity to provide help for B cell responses (Tangye et al., 2013). In experimental animal models, targeting Tfh cells by anti-ICOS or anti-IL-21/21R has shown to reduce the severity of SLE (Choi et al., 2017; Zhang et al., 2015). Patients with antibody-mediated autoimmune diseases have increased fre-
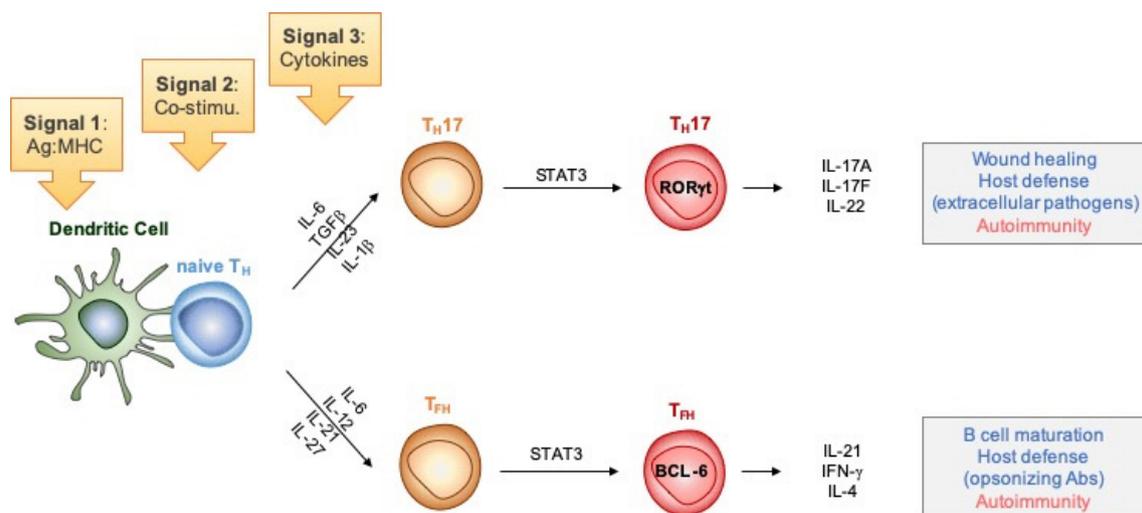
Fig. 1. Differentiation of Th17 and Tfh cells. Upon the stimulation by dendritic cells, naive CD4+ T cells can be activated and differentiated into Th17 and Tfh cells based on the cytokine environment they are exposed to. Aberrant activation of Th17 and Tfh cells can raise autoimmunity.

quencies of CXCR5+PD1+ICOS+ Tfh cells in circulation (Gong et al., 2017). Whether targeting Tfh cells ameliorate SLE or other antibody-mediated autoimmune diseases remains to be tested in humans.

Upon the antigenic cytokine stimulation by antigen-presenting cells (APCs), naive CD4+ T cells are activated and differentiated into effector subsets; Th1, Th2, Th17, regulatory T cells (Treg) or Tfh cells. Th17 cells are differentiated by IL-6, transforming growth factor β (TGFβ), IL-23, and IL-1β stimulation, express RORγt and RORα, and secrete IL-17A, IL-17F, IL-22 (and IL-26 in humans) to promote wound healing and to eliminate extracellular pathogens via recruiting neutrophils (Fig. 1). Tfh cells are differentiated by IL-6, IL-12, IL-21, and IL-27 stimulation, express BCL6 and Ascl2, and secrete IL-21 (Batten et al., 2010; Liu et al., 2014; Nurieva et al., 2008). Tfh cells provide a crucial help for B cells to induce class-switching, affinity maturation, and differentiation into plasma cells and memory B cells through germinal center reactions (Fig. 1). Proper activation of Th17 and Tfh cells protect the body from infection, but an uncontrolled generation of the cells can also contribute to the pathogenesis of autoimmune diseases (DuPage and Bluestone, 2016).

MUTUAL RELATION BETWEEN AUTOIMMUNITY AND ATHEROSCLEROSIS

Numerous epidemiological studies have shown that autoimmune diseases and atherosclerosis have a tight association. Patients with autoimmune diseases such as psoriasis, RA and SLE exhibit an increased cardiovascular risk and an exacerbated outcome in the case of cardiovascular events (Durante and Bronzato, 2015). Moreover, cholesterol-lowering treatments such as low-fat diet or statins were shown to be effective in ameliorating autoimmune symptoms (Aktas et al., 2003; Youssef et al., 2002) (Fig. 2). Nonetheless, the cellular and molecular mechanisms by which atherogenic factors
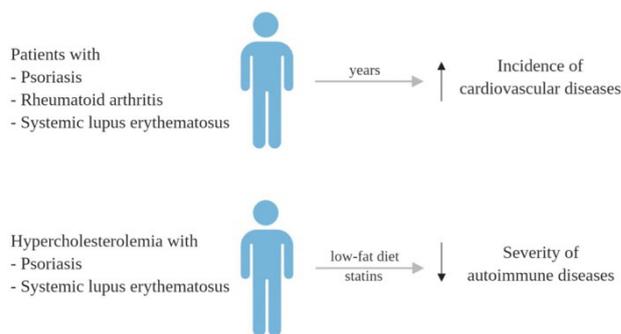

Fig. 2. Links between atherosclerosis and autoimmune diseases. Patients with systemic autoimmune disorders show an increased incidence of atherosclerosis; these hyperlipidemia-associated autoimmune diseases include psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. Cholesterol-lowering treatment has been shown to ameliorate psoriasis and systemic lupus erythematosus, suggesting a detrimental role of hyperlipidemia in the autoimmune disease.

contribute to the pathogenesis of autoimmune diseases are poorly understood. Since atherosclerosis is induced by the imbalance of lipid metabolism, it is possible to surmise that hyperlipidemic environment *in vivo* induced by dysregulated lipid metabolism is involved in the pathogenesis of the hyperlipidemia-associated autoimmune diseases.

Hyperlipidemia-associated autoimmune diseases include psoriasis, RA, and SLE, all of which are mediated by autoreactive CD4+ T cells (Diani et al., 2015; Goodson et al., 2005). For instance, SLE and RA are thought to be mediated by Tfh cells and consequent autoantibody production (Choi et al., 2015). The disease activity of SLE, including the SLE disease activity index (SLEDAI) and the levels of anti-double strand DNA (dsDNA), is positively associated with the level of circu-

lating triglycerides and cholesterols (Yuan et al., 2016). Inversely, lowering blood lipid levels by diet and drugs improves symptoms of autoimmune disease and T cell-mediated autoantibody responses (Ghazizadeh et al., 2011; Roman et al., 2003; Yu et al., 2015). Taken together, these clinical reports suggest that the autoimmune disease is promoted by the activation of pathogenic autoimmune T cell response by the hyperlipidemic environment.

A group of nuclear receptors are involved in the sensing, catabolism/anabolism balance and export of intracellular lipid species. Among them, liver X receptor (LXR) induces cholesterol transporters on cell surface that mediate the export of intracellular cholesterol (Kiss et al., 2013). Of interest, polymorphisms of LXR are found in patients with SLE, and LXR-deficiency in mice leads to lupus-like phenotypes (A-Gonzalez et al., 2009; Jeon et al., 2014). LXR promotes phagocytosis by upregulating MERTK expression, which controls self-tolerance and pathogenesis of lupus, and inhibits the induction of proinflammatory genes through repression of NF-κB–dependent inflammatory pathways (A-Gonzalez et al., 2009).

INNATE IMMUNITY PRELUDES ATHEROSCLEROSIS-RELATED AUTOIMMUNE RESPONSES

Innate immune cells such as macrophages and dendritic cells (DCs) regulate CD4+ T cell responses through antigen presentation and cytokine production. Dysfunction in lipid metabolism results in an abnormal increase of lipid species in plasma levels, which in turn stimulates innate immune cells through the recognition of the lipids via their receptors. LXRs are critical regulators of cholesterol and fatty acids. In atherogenic hyperlipidemia, LXR down-regulation leads to the activation of NF-κB signaling and induces the expression of pro-inflammatory cytokines from innate immune cells. Several molecular mechanisms have been suggested as to how the alteration in lipid metabolism affects the antigen presentation and cytokine production by innate immune cells.

Macrophages
Macrophages act as immune sentinels because they reside in almost all tissues of the body and sense the invasion of pathogens by pattern-recognition receptors. In addition to their critical contribution to sensing pathogens, macrophages also act as tissue sentinels by recognizing dead cells/debris and tissue injuries to maintain tissue integrity. In atherosclerosis, macrophages represent the majority of immune cells

atherosclerotic lesion, and their pathogenic roles in the development and progression of the cardiovascular disease are well-documented (Ait-Oufella et al., 2006; Dickhout et al., 2008).

Among atherogenic risk factors, several lipid species such as modified low-density lipoproteins (LDLs), fatty acids, and cholesterol crystals are suggested to modulate the activation and inflammatory function of macrophages. Accumulation of cholesterol crystals in the murine mouse model of atherosclerosis promotes the activation of caspase-1 via NLRP3 inflammasome. This process triggers the maturation of IL-1β, which in turn induces the differentiation of pathogenic Th17 differentiation (Duewell et al., 2010). TLR4 stimulation by palmitate induces reprogramming of the macrophage metabolism and inflammatory responses (Lancaster et al., 2018). Moreover, cholesterol extraction by miltefosin and high-density lipoprotein (HDL) treatment inhibits IL-1β and IL-6 release by human and murine macrophages (De Nardo et al., 2014; Iacano et al., 2019). Interestingly, miltefosin treatment decreases the lipid receptor TLR4 expression on the cell surface to reprogram the macrophages to become more sensitive to lipid species, which reduces *IL1B* mRNA levels upon lipid stimulation (Iacano et al., 2019).

LXRs are one of the nuclear hormone receptor superfamily that regulates cholesterol and lipid metabolism as well as inflammatory gene expression including NF-κB and AP1 (Thomas et al., 2018). LXR deficiency and hypercholesterolemia in mice promote the accumulation of cholesterol in APCs including macrophages. The accumulation enhances antigen presentation and T cell priming as well as the production of BAFF and April by APCs, all of which increases B cell differentiation and autoantibody production (Ito et al., 2016). In parallel, LXR agonist inhibits the expression of inflammatory responses including IL-6 and IL-1β (Joseph et al., 2003; Pourcet et al., 2016). Taken together, LXR expression in macrophages has a negative effect on inflammatory responses through the regulation of NF-κB signaling. Macrophages found in germinal centers are called tingible body macrophages, and they are known to impede germinal center responses (Smith et al., 1998). However, the contribution of these cells in autoimmunity and atherosclerosis needs to be clarified.

Dendritic cells
Dendritic cells are responsible for T cell activation and differentiation by regulating antigen presentation and cytokine stimulation (so-called 'signal 3'). The strength of antigen
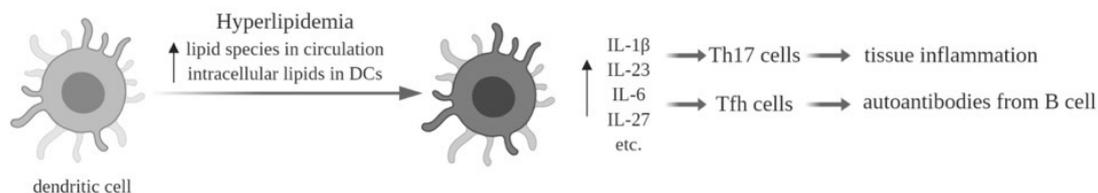

Fig. 3. Modulation of autoreactive Th17 and Tfh cells by hyperlipidemia. Hyperlipidemia induces accumulation of lipid species in DCs, which augments the production of proinflammatory cytokines. These cytokines enhance the differentiation of autoreactive Th17 and Tfh cells.

presentation and cytokine environment, which are mainly governed by dendritic cells, determines CD4^{+} T cell activation and differentiation. It has been shown that the stimulation by lipid species or increased lipid content regulates antigen stimulating capacity and cytokine production of dendritic cells.

Several studies show that hyperlipidemic condition promotes the production of proinflammatory cytokines such as IL-1β, IL-6, and IL-27. Mice subjected to a high-fat diet exhibited increased numbers of CD11b^{+} dendritic cells, which are more susceptible to secrete IL-1β secretion compared with control mice (Reynolds et al., 2012). Cholesterol accumulation in dendritic cells, not in macrophages or T cells, leads to autoimmune phenotypes such as immune complex deposition in kidney and increased plasma dsDNA antibodies in mice. These accumulated cholesterols enhance NLRP3 inflammasome activity to promote IL-1β and IL-18 secretion and GM-CSF receptor expression to elevate IL-12, IL-6, and IL-23 production by CD11b^{+} dendritic cells (Westerterp et al., 2017). Also, direct administration of LDLs and oxidized LDL (oxLDL) to dendritic cells promotes IL-6 and IL-1β production, which in turn enhances susceptibility to autoimmune diseases by regulating pathogenic autoimmune Th17 and Tfh cell differentiation (Lim et al., 2014; Ryu et al., 2018) (Fig. 3).

How does dyslipidemia lead to proinflammatory responses by dendritic cells? Firstly, lipid species including LDLs and fatty acids can stimulate immune responses via LOX1, CD36, TLR2, or TLR4 (Fig. 4). Uptake of free fatty acids including palmitic acid and oleic acid increases the production of IL-23 and IL-1β from bone-marrow-derived DCs (Stelzner et al., 2016). Our recent studies have demonstrated that LDLs and oxLDL stimulation of dendritic cells enhances IL-6 and IL-27 production in CD36 and TLR4 dependent manner (Lim et al., 2014; Ryu et al., 2018). Secondly, the upregulation of lipid receptors directs dendritic cells to become more sensitive to immunostimulatory lipid species (Fig. 4). Uptake of oxLDL by dendritic cells induces CD36 expression on their surface and promotes IL-6 release (Nickel et al., 2009). We have shown that dendritic cells in atherogenic condition exhibit higher expression of pattern-recognition receptors such as LOX-1, TLR2, and TLR4, all of which are known lipid receptors (Ryu

et al., 2018). Lastly, diminished LXR expression in hyperlipidemic condition enhances NF-κB signaling and the consequent production of proinflammatory cytokines (Fig. 4). Rescuing the diminished expression of LXRβ by administrating LXR agonist to dendritic cells from atherogenic mice reduced IL-27 production as well as IL-12 and IL-23, all of which contributes to the differentiation of autoimmune Th17 and Tfh cells (Batten et al., 2010; Canavan et al., 2013; Ryu et al., 2018).

ADAPTIVE IMMUNITY LINKS HYPERLIPIDEMIC ENVIRONMENT AND AUTOIMMUNITY

Cellular lipid or cholesterol homeostasis plays an important role in adaptive immune cells by direct action on the cells as well as by indirect regulation of antigen presentation and cytokine production by innate immune cells. After antigen presentation ('signal 1'), co-stimulation ('signal 2') and cytokine stimulation ('signal 3') by dendritic cells, T cells are activated and further differentiated into specialized effector cell population. These cells can directly mediate tissue inflammation (as in Th17 cells) or help B cells (as in Tfh cells) to produce autoantibodies (as in B cells), which can bind to self-proteins.

Th17 cells

Th17 cells are differentiated by IL-1β and IL-6 stimulation and secrete IL-17A, IL-17F, and IL-21. These cells have been shown to regulate autoimmune responses by modulating tissue inflammation (Carr et al., 2017; Pesce et al., 2013). Some groups have shown that IL-17 secreted by Th17 cells can also promote autoantibody responses (Hsu et al., 2008). Of this notion, Th17 cells are one of the key players in the pathogenesis of autoimmunity.

Emerging evidence show that lipid species, though still controversial, positively regulate Th17 cell differentiation. Cholesterol and fatty acid biosynthesis programs are upregulated during Th17 differentiation (Berod et al., 2014; Hu et al., 2015). Also, oxysterol, 7b, 27-dihydroxy-cholesterol, directly acts as RORγt agonist to promote Th17 cell differentiation (Santori et al., 2015; Soroosh et al., 2014). Moreover, cholesterol accumulation is essential for IL-17A secretion in
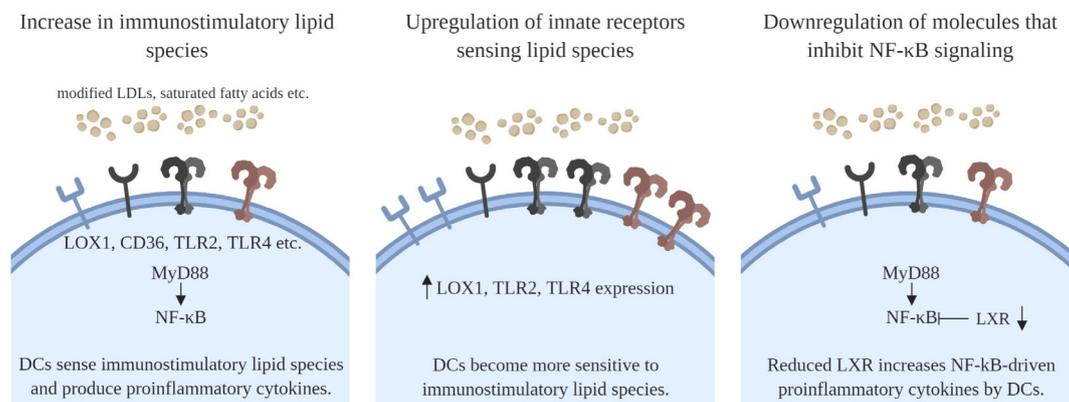

Increase in immunostimulatory lipid species

modified LDLs, saturated fatty acids etc.

LOX1, CD36, TLR2, TLR4 etc.
MyD88
↓
NF-κB

DCs sense immunostimulatory lipid species and produce proinflammatory cytokines.

Upregulation of innate receptors sensing lipid species

↑LOX1, TLR2, TLR4 expression

DCs become more sensitive to immunostimulatory lipid species.

Downregulation of molecules that inhibit NF-κB signaling

MyD88
↓
NF-κB⊣—— LXR ↓

Reduced LXR increases NF-kB-driven proinflammatory cytokines by DCs.

Fig. 4. Possible mechanisms underlying how hyperlipidemia modulates dendritic cell functions. Atherogenic dyslipidemia augments the production of pro-inflammatory cytokines through the increase of circulating lipid species, regulation of innate receptors, and inhibition of NF-κB signaling.

psoriasis patients (Varshney et al., 2016). On the other hand, oxLDL binds to CD69 on human T cells and inhibits the development of Th17 cells (Tsilingiri et al., 2019).

LXR seems to exert negative effects on Th17 cell differentiation. The inhibition of LXR with oxysterol derivatives promotes Th17 cell differentiation by enhancing RORγt activities (Soroosh et al., 2014). *In vitro* differentiation of Th17 cells were increased with LXR-deficient T cells. Meanwhile, treatment of LXR agonist T091317 inhibits differentiation of Th17 cells, while its antagonist GSK2033 accelerates the differentiation (Cui et al., 2011). Similarly, administration of LXR ligands in mice inhibits Th17 development *in vitro* and suppresses EAE *in vivo* (Cui et al., 2011; Xu et al., 2009).

We reported that autoreactive Th17 cell differentiation is augmented under pro-atherogenic condition using the mouse model of EAE. The serum levels of IL-17 and the frequencies of Th17 cells were increased in atherogenic LDb mice. *In vitro* differentiation of Th17 cells was enhanced by oxLDL treatment, and ex vivo expanded MOG-reactive T cell co-treated with oxLDL led to an exacerbated EAE phenotypes. Of note, neutralization of oxLDL diminished autoreactive Th17 cell responses, validating a pathogenic role of oxLDL in inducing autoreactive Th17 cell responses (Lim et al., 2014). Collectively, the role of lipid species on Th17 cells is still controversial, but it is believed that imbalanced lipid metabolism aggravates the pathogenesis of autoimmune diseases.

Tfh cells

A newly identified CD4^{+} T helper cell subset, Tfh cell, is differentiated by IL-21, IL-6, IL-12, and IL-27 cytokine stimulation, and secrete IL-21, IL-4 and/or interferon γ (IFNγ) cytokines to help B cells. These cells mainly drive autoimmune germinal center reaction and autoantibody responses, which exacerbate autoimmune symptoms such as immune complex deposition in kidney and autoantibody elevation. It has been suggested that Tfh cells play a role in the development of atherosclerosis as shown by the depletion of Tfh cells and blockade of STAT4 signaling in atherogenic mice (Gaddis et al., 2018; Taghavie-Moghadam et al., 2017). Also, CD4 specific deletion of Bcl6, a master transcription factor of Tfh cells, reduces plaque formation in atherogenic mice (Gaddis et al., 2018). Follicular regulatory T cells (Tfr cells) are the subset of Tfh cells that negatively regulate Tfh cell population (Chung et al., 2011). When Tfr cells were adoptively transferred into atherogenic mice, the size of the plaque as well as the number of macrophages present in those plaques diminished, indicative of the atheroprotective role of the cells (Baptista et al., 2018).

Several studies have investigated the role of lipid species on Tfh cells. During the pathogenesis of atherosclerosis, regulatory T cells are converted into Tfh cells, which are proatherogenic. Administration of one of the components of HDL (ApoAl) inhibits the conversion into Tfh cells and lowers intracellular cholesterol levels in Treg cells via the regulation of IL-2Ra, IL-6Ra, and pSTAT5 (Gaddis et al., 2018). An oxysterol, 7α, 24-hydroxy cholesterol (7α, 25-OHC) guides the correct migration of Tfh cells to the proximal B cell zone via the regulation of the receptor called Ebi2 (Li et al., 2016).

Our recent study proposes a possible mechanism by which hyperlipidemic condition regulates Tfh cell differentiation and autoimmune responses *in vivo* (Ryu et al., 2018). Studies with lupus-prone mice with normolipidemia or hyperlipidemia generated by transferring bone marrow cells from lupus-prone BXD2 mice into bone marrow-ablated wild-type or ApoE-deficient showed that the elevation of autoantibodies against dsDNA in atherogenic mice was associated with an increase in Tfh cells, particularly in CXCR3^{+} subset, and germinal centers. BXD2 mice spontaneously develop autoimmune lupus-like symptoms including glomerulonephritis and erosive arthritis due to the excessive production of rheumatoid factor and autoantibodies (Mountz et al., 2005). Interestingly, we observed that the frequency of Tfr cells was diminished in ApoE-deficient recipients of BXD2 bone marrow. While levels of IL-6, IFNβ, and IL-27 were increased in the sera of atherogenic mice in comparison with wild-type mice, we found that IL-27 is sufficient to induce an increase in Tfh cells and germinal center reactions in the ApoE-deficient atherogenic mice *in vivo*. Furthermore, analysis of plasma from normocholesterolemia 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 (Ryu et al., 2018). Thus, we propose that the hyperlipidemia-IL-27-Tfh cell axis plays a role in atherosclerosis-associated SLE in both mice and humans. Additional studies will be needed to determine if atherogenic risk factors have a role in stimulating T cells in a T cell-intrinsic manner.

B cells

B cells are responsible for the generation of pathogenic autoantibodies, which explains why a number of studies have been conducted to analyze the function of autoreactive B cells in autoimmune diseases. It has been reported that IL-17 produced by Th17 cells is required for autoreactive B cell production from BXD2 mice and germinal center reactions (Hsu et al., 2008; Mitsdoerffer et al., 2010). Furthermore, IL-21, IFNγ and IL-4 secreted by Tfh cells are required for class switching of IgG2a/c and IgG1, respectively, during T- B interaction (Finkelman et al., 1990; Reinhardt et al., 2009).

A few studies have demonstrated the role of lipid metabolism in B cells and germinal center reactions. Lipid receptor CD36 is increased in B cells in a non-obese diabetic mouse model of Type 1 diabetes, and the level of CD36 expression is positively correlated with autoimmune phenotypes, suggesting the mutual relation between a lipid receptor and autoimmunity (Wilson et al., 2016). An oxysterol 7α, 25-OHC are required for B cell accumulation and plasma cell responses by regulating the positioning of activated B cells during humoral responses in Ebi2-dependent manner (Pereira et al., 2009). Bcl6 inhibitor leads to the accumulation of cholesterol of atherosclerotic lesions, which resulted in the decreased formation of germinal center B cells. It has been shown that LXR inhibits IgE expression in human B cells *in vitro*; however, further studies will be needed to address whether LXR directly affects germinal center responses *in vivo* (Heine et al., 2009). Aside from direct effects on germinal center reaction, high-cholesterol diets regulate marginal zone B cells to limit

the development of atherosclerosis through the inhibition of Tfh cells and germinal center responses (Nus et al., 2017).

CONCLUSION AND PERSPECTIVES

In this review, we discuss the pathogenic role of imbalanced lipid metabolism in autoimmune responses with particular interests in Th17 and Tfh cell responses. Regulation of innate and adaptive immune responses by atherogenic factors exacerbates the pathogenesis of autoimmune diseases such as psoriasis, RA, and SLE. It seems evident that atherogenic risk factors significantly impact the phenotypes and functions of innate immune cells such as dendritic cells and macrophages. Less is known if the same atherogenic risk factors, or factors involved in lipid metabolism, will have any role in shaping the function of adaptive immune cells including T and B cells. Moreover, explicit mechanisms of how these lipid species or imbalanced lipid metabolism lead to the preferential increase of inflammatory responses and immune cells are still poorly understood.

Based on current advances, it seems clear that atherogenic risk factors as well as factors involved in lipid metabolism would be a promising therapeutic target for T cell-mediated autoimmune diseases. A number of small molecules targeting lipid synthesis/metabolism have been developed for the prevention of cardiovascular diseases. The use of these small molecules will be useful in determining the immunomodulatory role of factors involved in lipid metabolism. Further studies are necessary to advance the interdisciplinary research between circulation systems and immune systems to develop novel therapeutic strategies targeting immune-lipid metabolism links.

Disclosure
The authors have no potential conflicts of interest to disclose.

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