Molecules and Cells

Minireview

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-

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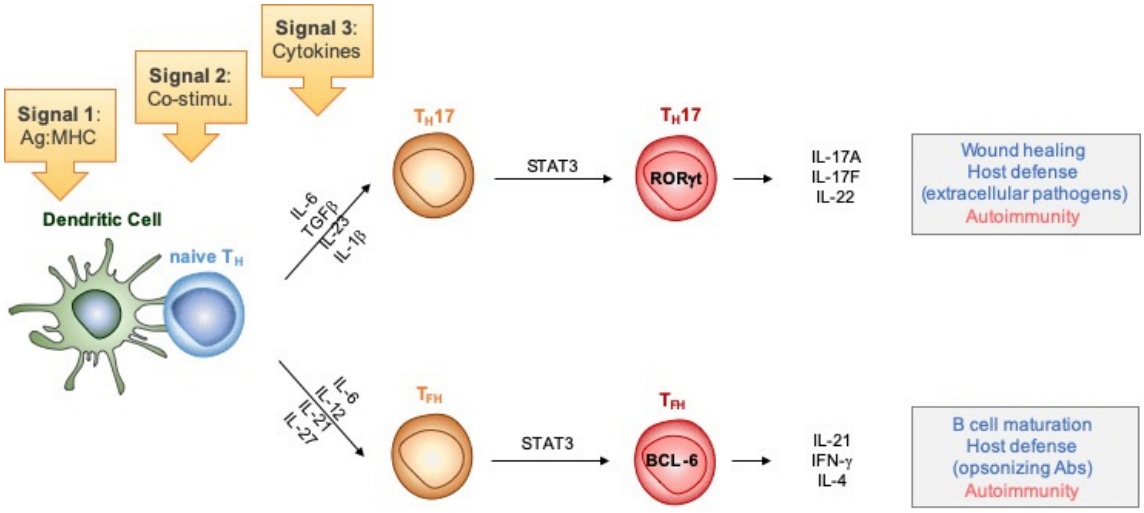

Fig. 1. Differentiation of Th17 and Tfh cells. Upon the stimulation by dendritic cells, naive $CD4^+$ T cells can be activated and differentiated into Th17 and Tfh cells based on the cytokine environment they are exposed to. Aberrant activation of Th17 and Tfh cells can raise autoimmunity.

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

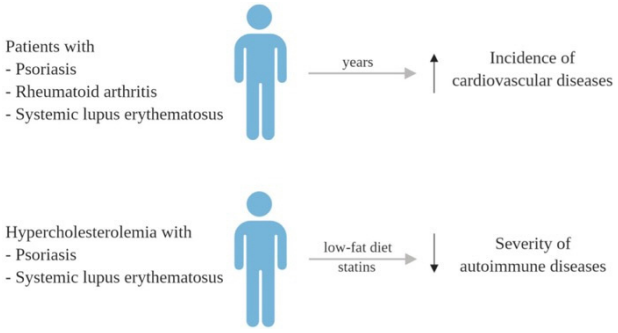

Fig. 2. Links between atherosclerosis and autoimmune diseases. Patients with systemic autoimmune disorders show an increased incidence of atherosclerosis; these hyperlipidemia-associated autoimmune diseases include psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. Cholesterol-lowering 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

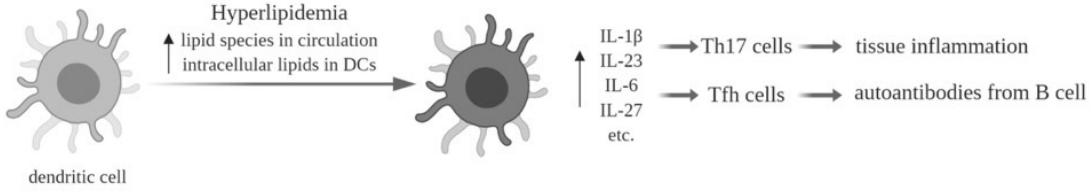

Fig. 3. Modulation of autoreactive Th17 and Tfh cells by hyperlipidemia. Hyperlipidemia induces accumulation of lipid species in DCs, which augments the production of proinflammatory cytokines. These cytokines enhance the differentiation of autoreactive Th17 and Tfh cells.

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

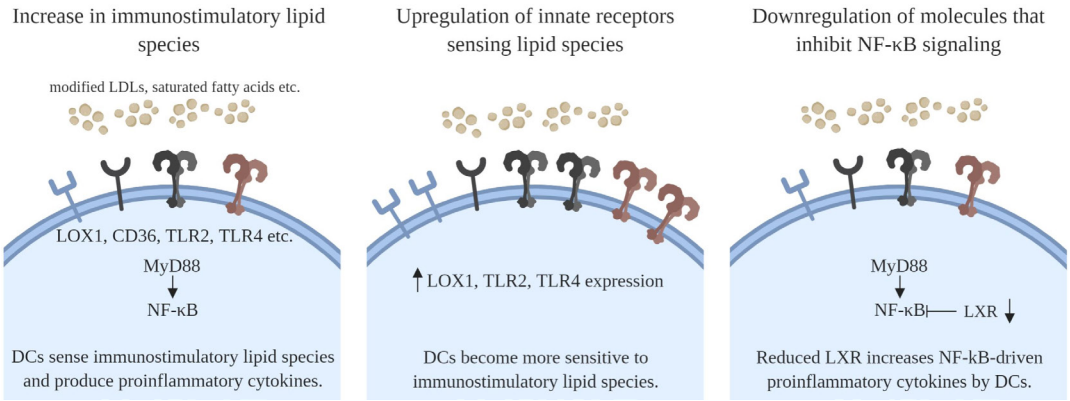

Fig. 4. Possible mechanisms underlying how hyperlipidemia modulates dendritic cell functions. Atherogenic dyslipidemia augments the production of pro-inflammatory cytokines through the increase of circulating lipid species, regulation of innate receptors, and inhibition of NF-κB signaling.

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 (ApoAI) 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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REFERENCES

A-Gonzalez, N., Bensinger, S.J., Hong, C., Beceiro, S., Bradley, M.N., Zelcer, N., Deniz, J., Ramirez, C., Díaz, M., Gallardo, G., et al. (2009). Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. Immunity *31*, 245-258.

Ait-Oufella, H., Salomon, B.L., Potteaux, S., Robertson, A.K.L., Gourdy, P., Zoll, J., Merval, R., Esposito, B., Cohen, J.L., Fisson, S., et al. (2006). Natural regulatory T cells control the development of atherosclerosis in mice. Nat. Med. *12*, 178-180.

Aktas, O., Waiczies, S., Smorodchenko, A., Dorr, J., Seeger, B., Prozorovski, T., Sallach, S., Endres, M., Brocke, S., Nitsch, R., et al. (2003). Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin. J. Exp. Med. *197*, 725-733.

Anaya, J.M. (2012). Common mechanisms of autoimmune diseases (the autoimmune tautology). Autoimmun. Rev. *11*, 781-784.

Bao, Y.K., Weide, L.G., Ganesan, V.C., Jakhar, I., McGill, J.B., Sahil, S., Cheng, A.L., Gaddis, M., and Drees, B.M. (2019). High prevalence of comorbid autoimmune diseases in adults with type 1 diabetes from the HealthFacts database. J. Diabetes *11*, 273-279.

Baptista, D., Mach, F., and Brandt, K.J. (2018). Follicular regulatory T cell in atherosclerosis. J. Leukoc. Biol. *104*, 925-930.

Batten, M., Ramamoorthi, N., Kljavin, N.M., Ma, C.S., Cox, J.H., Dengler, H.S., Danilenko, D.M., Caplazi, P., Wong, M., Fulcher, D.A., et al. (2010). IL-27 supports germinal center function by enhancing IL-21 production and the function of T follicular helper cells. J. Exp. Med. *207*, 2895.

Berod, L., Friedrich, C., Nandan, A., Freitag, J., Hagemann, S., Harmrolfs, K., Sandouk, A., Hesse, C., Castro, C.N., Bähre, H., et al. (2014). De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. Nat. Med. *20*, 1327.

Canavan, M., McCarthy, C., Larbi, N.B., Dowling, J.K., Collins, L., O'Sullivan, F., Hurley, G., Murphy, C., Quinlan, A., Moloney, G., et al. (2013). Activation of liver X receptor suppresses the production of the IL-12 family of cytokines by blocking nuclear translocation of NF-κBp50. Innate Immun. *20*, 675-687.

Carr, T.M., Wheaton, J.D., Houtz, G.M., and Ciofani, M. (2017). JunB promotes Th17 cell identity and restrains alternative CD4(+) T-cell programs during inflammation. Nat. Commun. *8*, 301.

Choi, J.Y., Ho, J.H., Pasoto, S.G., Bunin, V., Kim, S.T., Carrasco, S., Borba, E.F., Gonçalves, C.R., Costa, P.R., Kallas, E.G., et al. (2015). Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity. Arthritis Rheumatol. *67*, 988-999.

Choi, J.Y., Seth, A., Kashgarian, M., Terrillon, S., Fung, E., Huang, L., Wang, L.C., and Craft, J. (2017). Disruption of pathogenic cellular networks by IL-21 blockade leads to disease amelioration in murine lupus. J. Immunol. *198*, 2578-2588.

Chung, Y., Tanaka, S., Chu, F., Nurieva, R., Martinez, G.J., Rawal, S., Wang, Y.H., Lim, H.Y., Reynolds, J.M., Zhou, X.H., et al. (2011). Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. Nat. Med. *17*, 983-988.

Cua, D.J., Sherlock, J., Chen, Y., Murphy, C.A., Joyce, B., Seymour, B., Lucian, L., To, W., Kwan, S., Churakova, T., et al. (2003). Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature *421*, 744-748.

Cui, G., Qin, X., Wu, L., Zhang, Y., Sheng, X., Yu, Q., Sheng, H., Xi, B., Zhang, J.Z., and Zang, Y.Q. (2011). Liver X receptor (LXR) mediates negative regulation of mouse and human Th17 differentiation. J. Clin. Invest. *121*, 658-670.

De Nardo, D., Labzin, L.I., Kono, H., Seki, R., Schmidt, S.V., Beyer, M., Xu, D., Zimmer, S., Lahrmann, C., Schildberg, F.A., et al. (2014). High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. Nat. Immunol. *15*, 152-160.

Diani, M., Altomare, G., and Reali, E. (2015). T cell responses in psoriasis and psoriatic arthritis. Autoimmun. Rev. *14*, 286-292.

Dickhout, J.G., Basseri, S., and Austin R.C. (2008). Macrophage function and its impact on atherosclerotic lesion composition, progression, and stability. Arterioscler. Thromb. Vasc. Biol. *28*, 1413-1415.

Duewell, P., Kono, H., Rayner, K.J., Sirois, C.M., Vladimer, G., Bauernfeind, F.G., Abela, G.S., Franchi, L., Nuñez, G., Schnurr, M., et al. (2010). NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature *464*, 1357-1361.

DuPage, M. and Bluestone, J.A. (2016). Harnessing the plasticity of CD4+ T cells to treat immune-mediated disease. Nat. Rev. Immunol. *16*, 149.

Durante, A. and Bronzato, S. (2015). The increased cardiovascular risk in patients affected by autoimmune diseases: review of the various manifestations. J. Clin. Med. Res. *7*, 379-384.

Finkelman, F.D., Holmes, J., Katona, I.M., Urban, J.F., Jr., Beckmann, M.P., Park, L.S., Schooley, K.A., Coffman, R.L., Mosmann, T.R., and Paul, W.E. (1990). Lymphokine control of in vivo immunoglobulin isotype selection. Annu. Rev. Immunol. *8*, 303-333.

Fitch, E., Harper, E., Skorcheva, I., Kurtz, S.E., and Blauvelt, A. (2007). Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. Curr. Rheumatol. Rep. *9*, 461-467.

Gaddis, D.E., Padgett, L.E., Wu, R., McSkimming, C., Romines, V., Taylor, A.M., McNamara, C.A., Kronenberg, M., Crotty, S., Thomas, M.J., et al. (2018). Apolipoprotein AI prevents regulatory to follicular helper T cell switching during atherosclerosis. Nat. Commun. *9*, 1095.

Ghazizadeh, R., Tosa, M., and Ghazizadeh, M. (2011). Clinical improvement in psoriasis with treatment of associated hyperlipidemia. Am. J. Med. Sci. *341*, 394-398.

Gong, Y., Tong, J., and Wang, S. (2017). Are follicular regulatory T cells involved in autoimmune diseases? Front. Immunol. *8*, 1790.

Goodson, N., Marks, J., Lunt, M., and Symmons, D. (2005). Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann. Rheum. Dis. *64*, 1595-1601.

Heine, G., Dahten, A., Hilt, K., Ernst, D., Milovanovic, M., Hartmann, B., and Worm, M. (2009). Liver X receptors control IgE expression in B cells. J. Immunol. *182*, 5276-5282.

Hsu, H.C., Yang, P., Wang, J., Wu, Q., Myers, R., Chen, J., Yi, J., Guentert, T., Tousson, A., Stanus, A.L., et al. (2008). Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat. Immunol. *9*, 166-175.

Hu, X., Wang, Y., Hao, L.Y., Liu, X., Lesch, C.A., Sanchez, B.M., Wendling, J.M., Morgan, R.W., Aicher, T.D., Carter, L.L., et al. (2015). Sterol metabolism controls TH17 differentiation by generating endogenous RORγ agonists. Nat. Chem. Biol. *11*, 141-147.

Iacano, A.J., Lewis, H., Hazen, J.E., Andro, H., Smith, J.D., and Gulshan, K. (2019). Miltefosine increases macrophage cholesterol release and inhibits NLRP3-inflammasome assembly and IL-1β release. Sci. Rep. *9*, 11128.

Ito, A., Hong, C., Oka, K., Salazar, J.V., Diehl, C., Witztum, J.L., Diaz, M., Castrillo, A., Bensinger, S.J., Chan, L., et al. (2016). Cholesterol accumulation in CD11c+ immune cells is a causal and targetable factor in autoimmune disease. Immunity *45*, 1311-1326.

Jeon, J.Y., Nam, J.Y., Kim, H.A., Park, Y.B., Bae, S.C., and Suh, C.H. (2014). Liver X receptors alpha gene (NR1H3) promoter polymorphisms are associated with systemic lupus erythematosus in Koreans. Arthritis Res. Ther. *16*, R112.

Joseph, S.B., Castrillo, A., Laffitte, B.A., Mangelsdorf, D.J., and Tontonoz, P. (2003). Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. Nat. Med. *9*, 213.

Kiss, M., Czimmerer, Z., and Nagy, L. (2013). The role of lipid-activated nuclear receptors in shaping macrophage and dendritic cell function: from physiology to pathology. J. Allergy Clin. Immunol. *132*, 264-286.

Lancaster, G.I., Langley, K.G., Berglund, N.A., Kammoun, H.L., Reibe, S., Estevez, E., Weir, J., Mellett, N.A., Pernes, G., Conway, J.R.W., et al. (2018). Evidence that TLR4 is not a receptor for saturated fatty acids but mediates lipid-induced inflammation by reprogramming macrophage metabolism. Cell Metab. *27*, 1096-1110.e5.

Lee, K.H., Lee, C.H., Woo, J., Jeong, J., Jang, A.H., and Yoo, C.G. (2018). Cigarette smoke extract enhances IL-17A-induced IL-8 production via up-regulation of IL-17R in human bronchial epithelial cells. Mol. Cells *41*, 282-289.

Lerner, A., Jeremias, P., and Matthias, T. (2015). The world incidence and prevalence of autoimmune diseases is increasing. Int. J. Celiac Dis. *3*, 151-155.

Li, J., Lu, E., Yi, T., and Cyster, J.G. (2016). EBI2 augments Tfh cell fate by promoting interaction with IL-2-quenching dendritic cells. Nature *533*, 110-114.

Lim, H., Kim, Y.U., Sun, H., Lee, J.H., Reynolds, J.M., Hanabuchi, S., Wu, H., Teng, B.B., and Chung, Y. (2014). Proatherogenic conditions promote autoimmune T helper 17 cell responses in vivo. Immunity *40*, 153-165.

Liu, X., Chen, X., Zhong, B., Wang, A., Wang, X., Chu, F., Nurieva, R.I., Yan, X., Chen, P., van der Flier, L.G., et al. (2014). Transcription factor achaete-scute homologue 2 initiates follicular T-helper-cell development. Nature *507*, 513.

Mitsdoerffer, M., Lee, Y., Jäger, A., Kim, H.J., Korn, T., Kolls, J.K., Cantor, H., Bettelli, E., and Kuchroo, V.K. (2010). Proinflammatory T helper type 17 cells are effective B-cell helpers. Proc. Nat. Acad. Sci. U. S. A. *107*, 14292.

Mountz, J.D., Yang, P., Wu, Q., Zhou, J., Tousson, A., Fitzgerald, A., Allen, J., Wang, X., Cartner, S., Grizzle, W.E., et al. (2005). Genetic segregation of spontaneous erosive arthritis and generalized autoimmune disease in the BXD2 recombinant inbred strain of mice. Scand. J. Immunol. *61*, 128-138.

Nickel, T., Schmauss, D., Hanssen, H., Sicic, Z., Krebs, B., Jankl, S., Summo, C., Fraunberger, P., Walli, A.K., Pfeiler, S., et al. (2009). oxLDL uptake by dendritic cells induces upregulation of scavenger-receptors, maturation and differentiation. Atherosclerosis *205*, 442-450.

Nistala, K., Moncrieffe, H., Newton, K.R., Varsani, H., Hunter, P., and Wedderburn, L.R. (2008). Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers. Arthritis Rheum. *58*, 875-887.

Nurieva, R.I., Chung, Y., Hwang, D., Yang, X.O., Kang, H.S., Ma, L., Wang, Y.H., Watowich, S.S., Jetten, A.M., Tian, Q., et al. (2008). Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. Immunity *29*, 138-149.

Nus, M., Sage, A.P., Lu, Y., Masters, L., Lam, B.Y.H., Newland, S., Weller, S., Tsiantoulas, D., Raffort, J., Marcus, D., et al. (2017). Marginal zone B cells control the response of follicular helper T cells to a high-cholesterol diet. Nat. Med. *23*, 601.

Papp, K.A., Langley, R.G., Sigurgeirsson, B., Abe, M., Baker, D.R., Konno, P., Haemmerle, S., Thurston, H.J., Papavassilis, C., and Richards, H.B. (2013). Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. Br. J. Dermatol. *168*, 412-421.

Papp, K.A., Leonardi, C., Menter, A., Ortonne, J.P., Krueger, J.G., Kricorian, G., Aras, G., Li, J., Russell, C.B., Thompson, E.H.Z., et al. (2012). Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. N. Engl. J. Med. *366*, 1181-1189.

Pereira, J.P., Kelly, L.M., Xu, Y., and Cyster, J.G. (2009). EBI2 mediates B cell segregation between the outer and centre follicle. Nature *460*, 1122.

Pesce, B., Soto, L., Sabugo, F., Wurmann, P., Cuchacovich, M., Lopez, M.N., Sotelo, P.H., Molina, M.C., Aguillon, J.C., and Catalan, D. (2013). Effect of interleukin-6 receptor blockade on the balance between regulatory T cells and T helper type 17 cells in rheumatoid arthritis patients. Clin. Exp. Immunol. *171*, 237-242.

Pourcet, B., Gage, M.C., León, T.E., Waddington, K.E., Pello, O.M., Steffensen, K.R., Castrillo, A., Valledor, A.F., and Pineda-Torra, I. (2016). The nuclear receptor LXR modulates interleukin-18 levels in macrophages through multiple mechanisms. Sci. Rep. *6*, 25481.

Reinhardt, R.L., Liang, H.E., and Locksley, R.M. (2009). Cytokine-secreting follicular T cells shape the antibody repertoire. Nat. Immunol. *10*, 385-393.

Reynolds, C.M., McGillicuddy, F.C., Harford, K.A., Finucane, O.M., Mills, K.H.G., and Roche, H.M. (2012). Dietary saturated fatty acids prime the NLRP3 inflammasome via TLR4 in dendritic cells—implications for diet-induced insulin resistance. Mol. Nutr. Food Res. *56*, 1212-1222.

Roman, M.J., Shanker, B.A., Davis, A., Lockshin, M.D., Sammaritano, L., Simantov, R., Crow, M.K., Schwartz, J.E., Paget, S.A., Devereux, R.B., et al. (2003). Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N. Engl. J. Med. *349*, 2399-2406.

Ryu, H., Lim, H., Choi, G., Park, Y.J., Cho, M., Na, H., Ahn, C.W., Kim, Y.C., Kim, W.U., Lee, S.H., et al. (2018). Atherogenic dyslipidemia promotes autoimmune follicular helper T cell responses via IL-27. Nat. Immunol. *19*, 583-593.

Santori, F.R., Huang, P., van de Pavert, S.A., Douglass, E.F., Jr., Leaver, D.J., Haubrich, B.A., Keber, R., Lorbek, G., Konijn, T., Rosales, B.N., et al. (2015). Identification of natural RORγ ligands that regulate the development of lymphoid cells. Cell Metab. *21*, 286-298.

Smith, J.P., Burton, G.F., Tew, J.G., and Szakal, A.K. (1998). Tingible body macrophages in regulation of germinal center reactions. Dev. Immunol. *6*, 285-294.

Soroosh, P., Wu, J., Xue, X., Song, J., Sutton, S.W., Sablad, M., Yu, J., Nelen, M.I., Liu, X., Castro, G., et al. (2014). Oxysterols are agonist ligands of RORγt and drive Th17 cell differentiation. Proc. Nat. Acad. Sci. U. S. A. *111*, 12163.

Stelzner, K., Herbert, D., Popkova, Y., Lorz, A., Schiller, J., Gericke, M., Klöting, N., Blüher, M., Franz, S., Simon, J.C., et al. (2016). Free fatty acids sensitize dendritic cells to amplify TH1/TH17-immune responses. Eur. J. Immunol. *46*, 2043-2053.

Taghavie-Moghadam, P.L., Waseem, T.C., Hattler, J., Glenn, L.M., Dobrian, A.D., Kaplan, M.H., Yang, Y., Nurieva, R., Nadler, J.L., and Galkina, E.V. (2017). STAT4 regulates the $CD8^+$ regulatory T cell/T follicular helper cell axis and promotes atherogenesis in insulin-resistant $Ldlr^{-/-}$ Mice. J. Immunol. *199*, 3453-3465.

Tangye, S.G., Ma, C.S., Brink, R., and Deenick, E.K. (2013). The good, the bad and the ugly — TFH cells in human health and disease. Nat. Rev. Immunol. *13*, 412.

Thomas, D.G., Doran, A.C., Fotakis, P., Westerterp, M., Antonson, P., Jiang, H., Jiang, X.C., Gustafsson, J.Å., Tabas, I., and Tall, A.R. (2018). LXR suppresses inflammatory gene expression and neutrophil migration through cis-repression and cholesterol efflux. Cell Rep. *25*, 3774-3785.e4.

Tsilingiri, K., de la Fuente, H., Relaño, M., Sánchez-Díaz, R., Rodríguez, C., Crespo, J., Sánchez-Cabo, F., Dopazo, A., Alonso-Lebrero José, L., Vara, A., et al. (2019). Oxidized low-density lipoprotein receptor in lymphocytes prevents atherosclerosis and predicts subclinical disease. Circulation *139*, 243-255.

Varshney, P., Narasimhan, A., Mittal, S., Malik, G., Sardana, K., and Saini, N. (2016). Transcriptome profiling unveils the role of cholesterol in IL-17A signaling in psoriasis. Sci. Rep. *6*, 19295.

Volpe, E., Battistini, L., and Borsellino, G. (2015). Advances in T helper 17 cell biology: pathogenic role and potential therapy in multiple sclerosis. Mediators Inflamm. *2015*, 475158.

Westerterp, M., Gautier, E.L., Ganda, A., Molusky, M.M., Wang, W., Fotakis, P., Wang, N., Randolph, G.J., D'Agati, V.D., Yvan-Charvet, L., et al. (2017). Cholesterol accumulation in dendritic cells links the inflammasome to acquired immunity. Cell Metab. *25*, 1294-1304.e6.

Wilson, C.S., Elizer, S.K., Marshall, A.F., Stocks, B.T., and Moore, D.J. (2016). Regulation of B lymphocyte responses to Toll-like receptor ligand binding during diabetes prevention in non-obese diabetic (NOD) mice. J. Diabetes *8*, 120-131.

Xu, J., Wagoner, G., Douglas, J.C., and Drew, P.D. (2009). Liver X receptor agonist regulation of Th17 lymphocyte function in autoimmunity. J. Leukoc. Biol. *86*, 401-409.

Youssef, S., Stuve, O., Patarroyo, J.C., Ruiz, P.J., Radosevich, J.L., Hur, E.M., Bravo, M., Mitchell, D.J., Sobel, R.A., Steinman, L., et al. (2002). The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature *420*, 78-84.

Yu, H.H., Chen, P.C., Yang, Y.H., Wang, L.C., Lee, J.H., Lin, Y.T., and Chiang, B.L. (2015). Statin reduces mortality and morbidity in systemic lupus erythematosus patients with hyperlipidemia: A nationwide population-based cohort study. Atherosclerosis *243*, 11-18.

Yuan, J., Li, L.I., Wang, Z., Song, W., and Zhang, Z. (2016). Dyslipidemia in patients with systemic lupus erythematosus: Association with disease activity and B-type natriuretic peptide levels. Biomed. Rep. *4*, 68-72.

Zhang, M., Yu, G., Chan, B., Pearson, J.T., Rathanaswami, P., Delaney, J., Ching Lim, A., Babcook, J., Hsu, H., and Gavin, M.A. (2015). Interleukin-21 receptor blockade inhibits secondary humoral responses and halts the progression of preestablished disease in the (NZB × NZW)F1 systemic lupus erythematosus model. Arthritis Rheumatol. *67*, 2723-2731.