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The problem of accelerated atherosclerosis in systemic lupus erythematosus: Insights into a complex co-morbidity

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Abstract

Rheumatic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), are associated with antibodies to “self” antigens. Persons with autoimmune diseases, most notably SLE, are at increased risk for developing accelerated cardiovascular disease. The link between immune and inflammatory responses in the pathogenesis of cardiovascular disease has been firmly established yet, despite our increasing knowledge, accelerated atherosclerosis continues to be a significant co-morbidity and cause of mortality in SLE. Recent animal models have been generated in order to identify mechanism(s) behind SLE-accelerated atherosclerosis. In addition, clinical studies have been designed to examine potential treatments options. This review will highlight data from recent studies of immunity in SLE and atherosclerosis and discuss the potential implications of these investigations.

Keywords

systemic lupus erythematosus; atherosclerosis; autoimmunity; cardiovascular disease

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disorder characterized by the production of autoantibodies to a variety of self-antigens, most notably double stranded DNA (dsDNA). The chronic inflammatory nature of SLE is hypothesized to lead to many co-morbidities including, but not limited to, renal disease, vasculitis, anemia, neuropathies and premature accelerated atherosclerosis. While the exact cause of SLE remains a mystery, there are a number of factors that are thought to contribute to disease pathogenesis including gender, race, environmental factors and genetics.

SLE disproportionately affects women, especially women of child bearing age. Although the exact etiology is unknown, it is thought that high estrogen levels, which are at their peak in this age range, contribute to the gender bias [1]. Additionally, race is thought to be a major factor in SLE onset as African-American and Hispanic women are more likely to develop SLE compared to their Caucasian counterparts. With regard to the environment, studies have linked exposure to certain toxins, such as heavy metals and silica as well as exposure to ultraviolet light, to SLE disease. Genetic predisposition is also associated with SLE pathogenesis as polymorphisms and mutations in a number of genes including the Fcγ

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receptor, the complement receptor C1q, and tumor necrosis factor α (TNF α) have all been associated with SLE [1, 2].

In addition to the lack of understanding regarding the predisposing risk factors for SLE, the trigger for SLE onset is likewise unknown, and most likely multifactorial. According to recent studies, ineffective clearance of apoptotic cells maybe a main culprit behind SLE. Under normal circumstances, apoptotic cells and debris are cleared through a phagocytic process termed efferocytosis. However, in SLE, this apoptotic debris accumulates in tissues, allowing the immune cells to be exposed to self-antigens to which they otherwise would not be exposed. These defects in apoptosis trigger a chronic sterile inflammatory situation that is thought to lead to the loss of B cell tolerance. This in turn mediates the production of anti-nuclear antibodies, which can then form immune complexes. Immune complex deposition in tissues and organs exacerbates inflammation and leads to tissue damage typically seen in lupus patients. [3] Furthermore, these events result in the over-expression of pro-inflammatory cytokines, most notably type I interferons, which have been shown to mediate disease activity in both humans and mouse models [4-7]. These events and others are thought to initiate and sustain SLE pathogenesis.

SLE and Cardiovascular Disease

Atherosclerosis, one of the most common cardiovascular diseases (CVD), continues to be a significant cause of morbidity and mortality despite recent advances in diagnosis and therapies. While it is widely recognized that hypertension, dyslipidemia and hypercholesterolemia predispose to atherosclerosis, studies in the past decades have revealed that the etiology of this disease is more complex than originally thought. Recent evidence suggests that the immune system is important in atherosclerosis pathogenesis and that these interactions occur early in the disease process.

Nearly thirty-five years ago, Urowitz *et al.* [8] first documented what was referred to as a bi-modal pattern of mortality in lupus, where early deaths in SLE were attributed to active SLE end organ disease, such as renal failure, while later deaths were mostly cardiovascular related. Since this pioneering discovery, many follow-up studies have demonstrated that, with all other risk factors being equal, the incidence of coronary artery disease in women with SLE is five to nine times higher compared to women without SLE. [9-11] Even more striking is the finding by Manzi *et al.* [12] that in premenopausal women—an age group normally protected against CVD—having SLE increases the likelihood of suffering from myocardial infarction by 50 times compared to their non-SLE premenopausal counterparts. All of these studies indicate that both classical and non-classical risk factors play a pivotal role in SLE-accelerated atherosclerosis. However, the mechanisms of accelerated CVD in lupus remain to be elucidated.

In the current review, we will: 1) briefly summarize the association between autoimmunity and atherosclerosis; 2) summarize recent data highlighting risk factors associated with atherosclerosis and SLE-accelerated atherosclerosis; 3) highlight current models used to study these phenomena and 4) offer our perspectives for future studies and therapeutics.

Autoimmunity and Atherosclerosis

While the role of the immune system in atherosclerosis is fairly well established, it is not completely understood. Over the past two decades, the literature describing the role of the immune system in atherosclerosis has continued to grow. In general, the body of work can be summarized by stating that the role of immunity in atherosclerosis is complex and, depending on the cell or immune axis of choice, can be either pro-atherogenic or anti-atherogenic. Therefore, it is probably not surprising that immune dysregulation would have

detrimental effects on cardiovascular health. There is a growing body of evidence supporting a causal link between chronic autoimmune inflammation and development of accelerated atherosclerosis. Although much is still not known regarding autoimmunity and atherosclerosis, many studies have illustrated a correlation between several autoimmune diseases and CVD [11, 13, 14]. To date, the best characterized autoimmune diseases associated with atherosclerosis include rheumatoid arthritis (RA), antiphospholipid syndrome and SLE.

RA and CVD

Rheumatoid arthritis is characterized by inflammation, mainly of the synovial joints. Increased expression of adhesion molecules, matrix metalloproteinases and pro-inflammatory cytokines all contribute to bone and joint erosion in RA. These processes are hypothesized to contribute to accelerated atherosclerosis in patients with RA [14, 15]. Furthermore, an accumulation of CD4⁺ T cells within both the synovial fluid and atherosclerotic plaques point to a role for lymphocytes in propagating the atherosclerotic process [16]. These T cells are unique in that they lack expression of the co-stimulatory molecule CD28. As a result, they do not depend on the B7/CD28 pathway for co-stimulation [14]. This expanded T cell population has been associated with clinical markers of atherosclerosis [14, 17] and a study by Gerli *et al.* [16] found that RA patients had increased CD4⁺CD28⁻ T cells compared to control patients. This was accompanied by increased intima-to-media thickness and arterial endothelial dysfunction. This study and others indicate that modulating T cell response would be an attractive therapeutic target in RA-associated CVD.

APS and CVD

Antiphospholipid (aPL) syndrome is an autoimmune disease characterized by excessive production of antibodies against phospholipids, mainly cardiolipin and β 2-glycoprotein1 (β 2GP1). This disease can cause dangerous blood clots due to increased formation of circulating immune complexes, and can lead to miscarriage and premature birth in pregnant women. Phospholipids play an integral role in cardiovascular disease and several studies have uncovered a link between aPL syndrome and cardiovascular disease. In human studies, β 2GP1 was found in the atherosclerotic plaque, mostly in association with CD4⁺ T cells [18]. Immune complexes composed of antibodies against oxLDL/ β 2GP1 are capable of being taken up via Fc γ receptors and facilitating the differentiation of macrophages into foam cells [19]. Moreover, studies have shown that anti-cardiolipin antibodies contribute to accelerated atherosclerosis by inducing endothelial activation and the adherence of monocytes to the endothelium [20]. In addition to occurring alone, aPL syndrome can also be presented in conjunction with SLE. The remainder of this review will highlight features relevant to SLE and SLE-accelerated cardiovascular disease (SACVD).

Risk factors for SACVD

Several clinical studies have suggested that while traditional risk factors for cardiovascular disease—such as hypertension, dyslipidemia, and diabetes mellitus—can be present in the SLE population, these risk factors do not fully explain the increased prevalence of cardiovascular disease [8, 10, 21]. Recent evidence suggests that a number of factors contribute to SACVD. Therefore, it is not surprising that since the association of premature cardiovascular disease with SLE was discovered, basic and pre-clinical studies have been focused on determining the mechanism(s) driving this very serious co-morbidity in SLE patients.

While dyslipidemia is a well-known risk factor for atherosclerosis, clinical studies have demonstrated that abnormal lipoprotein functions may contribute to SACVD. HDL is known for its participation in cholesterol efflux. In addition to efflux, HDL can also regulate oxidation of LDL and inhibit adhesion molecule expression adding to its anti-atherogenic functions. However, under chronic inflammatory conditions such as lupus, normal HDL can lose its anti-oxidant capacity. This HDL is said to be more pro-inflammatory and therefore thought to have deleterious effects in both traditional CVD and SACVD [22]. A study using autoimmune *gld* mice detected a significant reduction in HDL cholesterol and paraoxonase-1 activity, independent of HDL biogenesis. This phenotype was attributable to increased autoantibodies against apo-AI [23]. Moreover, a clinical study observed that women with SLE have increased pro-inflammatory HDL, which was strongly associated with a 17-fold increased risk for CVD [24]. Although not seen in this study, studies using other cohorts have found that SLE is also associated with an overall decrease in HDL and apoA-I levels and this decrease correlates with increased SACVD risk. [25, 26] The similar phenotypes seen in mice and human SLE studies could perhaps hint at HDL dysregulation as a culprit in SACVD.

Mouse models of SLE and SACVD

Clinical studies have been extremely useful in determining predictors for SACVD risk. However, because lupus and atherosclerosis are complex diseases, human studies to elucidate causal mechanisms for autoimmune-accelerated CVD could prove difficult. As with many animal models for human disease, the availability of mouse models for SLE can be staggering. These models include mice that develop lupus spontaneously, drug induced models of SLE and gene-knockout animals, such as the Fc γ RIIB-deficient mouse, which develops lupus, but only on a C57Bl/6 background [27]. To complicate the issue, many of the lupus mouse models only develop certain features of the human disease. For example, the MRL-*Fas*^{lpr} mouse is a good model for the cutaneous skin lesions often seen in human SLE patients [28]. However, except for the fluorouracil-induced model, skin lesions are not common in the other lupus animals [29]. In addition, few of the animal models develop the lupus-associated arthritis seen in human SLE. All of the animal models develop the characteristic anti-dsDNA antibodies and glomerulonephritis, although to varying degrees. [29, 30]

To date, there are relatively few mouse models specifically used to study the mechanism of SACVD (see Table 1). Published in 2004, the *gld.apoE*^{-/-} mouse model, which contains an inactivating FasL mutation, was found to be more susceptible to atherosclerosis. Arahamian *et al* [31] proposed that impaired macrophage function and inadequate clearance of apoptotic bodies were responsible for the observed accelerated atherosclerosis in their model. An alternative mouse model of SACVD was generated by Feng and colleagues using apoE^{-/-} Fas^{-/-} mice [32]. The authors of this study observed that in addition to the presence of lupus-like disease and increased antibodies to oxidized phospholipids, apoE^{-/-} Fas^{-/-} mice also uniquely develop osteopenia while exhibiting increased apoptosis similar to *gld.apoE*^{-/-} mice. Correspondingly, Ma *et al.* [33] combined apoE^{-/-} mice with three separate models of lupus and reported similar results.

While the abovementioned studies have significantly advanced our understanding of SACVD, one can argue that because SLE is likely a polygenic complex disease, it may be difficult to make human correlates from studies conducted in single-gene knockout animals. The development of the NZM2410-derived congenic B6.*Sle* mouse strains has made it feasible to examine lupus and atherosclerosis together on the susceptible C57Bl/6 background. Through linkage analyses, Morel *et al.* [34] identified three major genomic intervals linked to lupus susceptibility in the NZM2410 mouse strain. Using these three

chromosomal intervals, termed *Sle1*, *Sle2* and *Sle3*, the investigators made a series of single, bi-, and triple congenic mice on the atherosclerosis susceptible C57Bl/6 background [35, 36]. While having one or two intervals can lead to varying symptoms associated with lupus, all three intervals are necessary to display a fully penetrant lupus phenotype similar to the disease in humans.

Our laboratory took advantage of this mouse strain and developed an animal model of SLE-accelerated atherosclerosis and demonstrated that transfer of lupus susceptibility by bone marrow transplantation increases atherosclerosis in LDLr^{-/-} mice [37]. The increase in atherosclerosis was later determined to be independent of diet and was accompanied by a three-fold increase in CD4⁺ T cell burden within the atherosclerotic lesion [38]. CD4⁺ T cells from the SLE-susceptible mice also displayed higher expression of activation markers such as CD69 [37] and CD40L [38]. Further studies from our laboratory revealed that transfer of *Sle3*-associated T cell dysregulation alone to LDLr^{-/-} mice was not sufficient to affect atherosclerotic lesion area but leads to exacerbated humoral immune responses that are frequently associated with atherosclerosis in LDLr^{-/-} mice [39]. This could mean that all three genetic loci are necessary to induce accelerated atherosclerosis in our model. Also, it could point to an essential role for B cell hyperactivity and dysregulation in this process. The latter would be an intriguing model as more data from recent literature show that certain B cell subsets may be pro-atherogenic in the absence of autoimmunity [40, 41]. Insights from these and other animal models will be extremely useful in delineating mechanisms of SLE and SACVD pathogenesis as well as targets for treatment of SACVD.

The Immune System in SACVD

Cytokines in SACVD

Traditional pro-inflammatory markers have been associated with SACVD risk; these include increased serum levels of pro-inflammatory cytokines such as IFN- γ , IL-6, TNF α , IL-10 and TGF- β [42-44]. While IFN- γ and TNF α are largely known as pro-atherogenic cytokines in both humans and mouse models it is still unclear whether IL-6 has strictly anti-atherogenic effects. One study showed that treatment of mice with IL-6 exacerbates atherosclerosis [45]. However, another study by Schieffer *et al.* [46] showed that 1 year old apoE^{-/-}IL-6^{-/-} mice had increased plaque area, although the plaques contained less inflammatory cell infiltration, indicating that IL-6 may have multiple roles in disease pathogenesis.

The traditional anti-inflammatory cytokines, IL-10 and TGF- β , have been shown to be protective in the more traditional mouse models of CVD: the apoE^{-/-} and LDLr^{-/-} mice [47-49]. However, both SLE patients and most animal models exhibit elevated serum levels of IL-10 and this cytokine is thought to mediate SLE pathogenesis [50, 51]. Therefore, it is not known whether responses to IL-10 in the context of SLE might exacerbate the atherogenic process in these patients. Interestingly, we have shown that treatment of SLE-susceptible LDLr^{-/-} mice with mycophenolate mofetil (MMF) (i.e. Cellcept[®]) leads to dramatic reductions in atherosclerotic plaque burden and significant decreases in circulating levels of IL-10 (van Leuven *et al.*; *in press*). Therefore, further investigations regarding the role of IL-10 in SLE-accelerated atherosclerosis are certainly warranted.

TGF- β , another largely anti-atherogenic cytokine, likewise remains a mystery in the context of SLE. While it has been found that TGF- β is protective against atherosclerosis [47] and that TGF- β deletion, specifically in T cells, accelerates atherosclerosis [52, 53], it is not known how TGF- β may function in SLE. Several studies have reported decreased TGF- β expression in lymphocytes of SLE patients, and one study found that peripheral blood mononuclear cells from SLE patients were resistant to exogenous TGF- β stimulation [54, 55]. A study by Jackson *et al.* [56] examined the efficiency of TGF- β activation in SLE

patients with early atherosclerosis. They found an inverse correlation between TGF- β activation and LDL levels along with IMT scores, where SLE patients with higher IMT and LDL levels had decreased TGF- β activation. These trends were not found in control patients, suggesting that this phenomenon was specific to SACVD. While many of the current studies show a favorable link between pro-inflammatory cytokines and SACVD, future studies are warranted in order to fully assess their role in the disease process.

The Role of T cells in SACVD

T cells have a major role in SLE initiation and development. Their importance is underscored in studies showing that T cell depletion ameliorates disease while lack of T cells inhibits lupus development [57-59]. Furthermore, the T cell phenotype in SLE patients and mouse models is characteristically different than normal T cells. These cells display a spontaneous hyperactive phenotype where there is a low threshold for activation, permitting increased T-B cell cooperation, increased antibody production by B cells and increased cytokine secretion. Additionally, these cells are resistant to antibody induced cell death and have altered signaling mechanisms. [60-62]

Two subsets of T lymphocytes have recently garnered attention in both the lupus and atherosclerosis fields. The first type, termed regulatory T (Treg) cells, is a subset of suppressor T cells that control autoreactivity and maintain immunologic homeostasis. Tregs are characterized by the expression of CD25 and the transcription factor Foxp3. Impaired Treg function has long been associated with autoimmune disease development and progression. Their dysfunction and/or deficiency has been reported in human SLE and mouse models of SLE suggesting that Treg dysfunction may be one of the driving forces in SLE pathogenesis [63-66]. Along the same lines, Tregs have been associated with protection from atherosclerosis. Foxp3⁺ Tregs have been detected in the atherosclerotic lesions of both mice and humans [67]. Ait-Oufella *et al.* [68] first showed that Treg deficiency in LDLR^{-/-} mice leads to enhanced atherogenesis and that transfer of Tregs into Treg-poor apoE^{-/-} mice attenuated atherosclerosis and reduced T cell accumulation within the lesions of the mice. An additional study showed that transfer of Tregs to apoE^{-/-} hosts also led to decreased atherosclerotic plaque size [69].

Another T cell subset most recently implicated in the pathogenesis of lupus and atherosclerosis is the T helper 17 (Th17) cell. Th17 cells are regulatory CD4⁺ T helper cells characterized by their ability to secrete large amounts of the pro-inflammatory cytokine IL-17. Studies have found elevated levels of IL-17 in the sera of patients with SLE and an increased frequency of IL17⁺ cells in the peripheral blood of SLE patients [70, 71]. Changes in the IL-17 secreting cell population have been noted in other animal models of SLE such as the SNF₁ and BXD2, where it was shown that blockade of IL-17 signaling reduces germinal center formation and antibody production [72, 73]. These studies all indicate a potential role for Th17 cells in autoimmune disease progression.

The role of Th17 cells in the pathogenesis of atherosclerosis is not well defined. Increased circulating IL-17 was found in patients with coronary artery disease, and the authors from this study concluded that IL-17 and IFN- γ produced by T cells infiltrating the coronary artery induce pro-inflammatory responses in vascular smooth muscle cells [74]. Similar to this finding in patients, Pejnovic *et al.* [75] found that mice doubly deficient in both apoE and IL-18 have increased atherosclerosis and unstable plaques due to an increase in the Th17 cell population. Several studies have shown that blockade of IL-17A either through genetic deletion, retroviral inhibition or IL-17A neutralizing antibody, mediated a significant reduction in aortic lesion area and cellular infiltration [76, 77]. Transfer of IL-17 receptor deficient bone marrow into LDLR^{-/-} host caused a 46% decrease in lesion area along with a decrease in macrophage content in the lesion [78]. However, a divergent study by Taleb *et*

al. [79] found that loss of suppressor of cytokine signaling 3 (SOCS3) expression leads to an IL-17-dependent reduction in lesion size. Additionally, IL-17 administration in mice reduced vascular T cell infiltration and atherosclerosis development thus indicating an athero-protective role for Th17 cells and IL-17. To complicate the issue even more, a recent study by Cheng *et al.* [80] found that the host origin of the IL-17 neutralizing antibody used in mice can lead to differential effects on lesion area. Specifically, mice treated with an anti-IL-17 antibody derived from rat led to a decrease in lesion area, while neutralizing antibody generated in mouse had no significant effect on atherosclerosis despite reduced IL-17 serum levels. The role of IL-17 in atherosclerosis has been extensively reviewed by Taleb *et al.* [81]. Given the disparity in results from studies of this fascinating cytokine, it is obvious that additional studies are warranted to shed light on the role of IL-17 in the atherosclerotic process.

The Role of B cells in SACVD

B cells, like T cells, are central to both lupus and atherosclerosis pathogenesis. The production of auto-antibodies is a hallmark feature of lupus and one of the main markers used to diagnose the disease. B cells can serve as antigen presenting cells, secrete cytokines which skew T helper cell responses, and modulate immune responses. While primarily known for their function in antibody production, B cells have been shown to have both antibody-dependent and independent functions in lupus. B cell deficiency or depletion in lupus-prone MRL/lpr mice was shown to inhibit disease progression while there was little change in lupus nephritis progression in mice with B cells that were unable to secrete antibodies [82]. Additionally, when B cell deficient mice were infused with serum from mice with autoantibodies, little to no nephritis was observed thus, supporting the varied functions of B cells in lupus [83]. In humans, B cells have been a long standing target in the race for therapeutic interventions. There have been several studies using antibodies toward B cells and B cell signaling mechanisms, most notable are the LUNAR and EXPLOROR trials which looked at the efficacy of rituximab, an antibody directed against CD20, in SLE patients with (LUNAR) or without (EXPLOROR) lupus nephritis [84]. Despite favorable preliminary data, both trials failed to meet their target expectations. However, there are several ongoing trials targeting B cells, which may prove to be promising in the treatment of lupus. An exciting development occurred earlier this year when the Federal Drug Administration approved the first drug specifically for the treatment of lupus since 1955. Benlysta® (Belimumab) is a human neutralizing antibody targeted against B Lymphocyte Stimulator (BLyS). BLyS, also known as BAFF (B-cell activating factor), is important for B cell selection, survival and activation [85, 86]. Clinical trials have reported an effective, albeit modest, reduction in disease activity compared to patients given placebo. It will be interesting to see how this drug and other BLyS inhibitors that are currently being investigated stand up against SLE.

The story of B cells in atherosclerosis has recently taking a sharp turn. While originally thought to be anti-atherogenic, recent data suggest that the effects of B cells on atherosclerosis may depend on their subtype and the antibody subclass they produce. An early study by Major *et al.* revealed that transfer of B cell deficient μ MT hematopoietic cells into LDLr^{-/-} mice led to aggravated atherosclerosis [87]. Moreover, transfer of splenic B cells from apoE^{-/-} mice to splenectomized mice resulted in protection from atherosclerosis [88]. Studies from the laboratory of Joe Witztum have indicated that while titers of antibodies against oxidized LDL (oxLDL) correlate with cardiovascular disease risk, immunization of atherosclerosis-susceptible mice with oxLDL and malondialdehyde (MDA)-LDL resulted in protection against atherosclerosis through an anti-inflammatory Th2 mechanism. Additionally, the authors showed that the atheroprotective effects of oxLDL and MDA-LDL are due to IL-5 mediated stimulation of B-1 B cells [89]. It was also

demonstrated that these B-1 B cells secreted natural IgM antibodies, including the T15/E06 idiotype, showing athero-protective effects by blocking oxLDL uptake through scavenger receptors [90] and controlling the immune response against apoptotic bodies containing oxidized phospholipids. Unfortunately, like many aspects of the immune system in atherosclerosis, things are not always how they first appear and the role of B cells in this disease is no different. In fact, the most recent data seem to point to a pro-atherogenic role for B cells. Specifically, depletion of mature B cells using an anti-CD20 antibody resulted in reduced atherosclerosis, while transfer of B-2 but not B-1 cells resulted in aggravated atherosclerosis [40, 41]. Taken together, these studies indicate that B cell subsets may have divergent effects on atherosclerosis pathogenesis.

Immunomodulators in SACVD

There have been very few published clinical trials that have examined the effect of immunomodulatory agents on SACVD. Statins, while widely known for their cholesterol lowering capabilities, can also control inflammatory responses making it an attractive therapy for SACVD. There have been a number of trials attesting to the lipid lowering abilities of statins in patients with high risk of CVD. Furthermore, recent studies suggest that high dose statin therapy may halt or even reverse the atherosclerotic process in non-SLE patients [91]. A review from our laboratory highlights clinical trials that have tested the potential benefits of these drugs in treating SACVD [92]. Interestingly, although perhaps disappointingly, a complete analysis of data from the Lupus Atherosclerosis Prevention Study (LAPS) recently revealed that while atorvastatin lowers cholesterol in SLE patients, it does not protect them from CVD [93].

Investigations in our laboratory and others have also been undertaken to assess the usefulness of currently marketed immuno-modulatory agents in treating SACVD in mouse models. Treatment of *gld.apoE^{-/-}* mice with simvastatin led to a significant reduction in autoantibody production, lymphoproliferation, lupus nephritis and atherosclerotic lesion area, compared to *gld* and *apoE^{-/-}* control mice [94]. Despite the fact that this study suggests that immuno-modulatory statins could prove beneficial in treating both SLE and SACVD in mice, the same results have unfortunately not been found in other models [93, 95] (van Leuven *et al.*, in press).

To test the hypothesis that therapies targeted toward CVD and SLE could ameliorate atherosclerotic disease progress and osteopenia in their model, Woo and colleagues treated *apoE^{-/-} Fas^{-/-}* mice with a statin and/or apo-AI mimetic [95]. Perhaps counter-intuitively, combination therapy led to an increase in plaque size. However, this was associated with a beneficial remodeling of the plaque with decreased macrophage infiltration and increased smooth muscle content. This is a pivotal study as it suggests that while inhibition of atherosclerosis progression may be the current readout of success in our human studies of SACVD, the role of therapeutics on modifying plaque stability may be of equal or greater importance.

Our laboratory recently evaluated the effectiveness of atorvastatin and MMF treatment in ameliorating SACVD progression. We found that similar to human SLE trials, treatment of *LDLr.Sle1.2.3* mice with atorvastatin reduced cholesterol levels with no effect on atherosclerosis. However, MMF treatment had an athero-protective effect with decreased CD4⁺ T cell migration into the lesion. (van Leuven *et al.*; in press) While this is expounded upon in the manuscript, the results from this study and other human studies assessing the benefit of statin therapy in SLE imply that dysregulated lymphocytic activity could be the predominant driver in SACVD and that lipid-lowering by itself cannot resolve these perturbations. These studies and others, again, emphasize the complexities associated with SACVD.

Conclusions

While the link between autoimmunity and cardiovascular disease has been firmly established, more work needs to be done in order to fully understand the mechanisms of these co-morbidities. Commonalities between the two diseases are undeniable. As outlined in Figure 1, both processes deal with dysregulation, inflammation and ultimately lead to end organ disease. However, the complex nature of both of these diseases makes it hard to study them together. For instance, atherosclerosis is thought to be a Th1 mediated disease process; however studies show that under hypercholesterolemic conditions, and as atherosclerosis progresses, a Th2 dominant environment is observed [96, 97]. Additionally, several trials have been launched in order to understand how regulating B cell function affects human SLE. Unfortunately, as of late, none of these studies assess the role of B cells in SACVD. Given data that suggest depletion of certain B cell subsets can reduce atherosclerosis in mice, it would be interesting to see if B cell/antibody depletion could alter cardiovascular disease in SLE. Finally, there are currently understudied immune cell populations in SACVD such as neutrophils, $\gamma\delta$ T cells and regulatory B cells. Valuable information could possibly be extracted from investigation of the function of these cell types in SACVD.

Combined use of clinical trials and animal models should yield significant advances in our understanding of SACVD pathogenesis. As with all research, it is our hope that these studies will ultimately lead to the creation of therapies to treat both SLE and atherosclerosis.

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Figure 1. Immune mechanisms in common between lupus (left side of triangle) and atherosclerosis (right side of triangle). Both diseases involve immune dysregulation and increased inflammation leading ultimately to end organ disease.

Table 1

Mouse Models of SLE-Accelerated Atherosclerosis

Animal Model	Diet	Increased Atherosclerosis	Renal disease	Cholesterol	Splenomegaly	Antibody Production	Other Findings
<i>gld</i> . apoE ^{-/-} [31]	Western Diet (12 wks)	Yes	Yes	↓	Yes	Yes	• ↑ apoptosis • Impaired clearance of apoptotic debris
	Chow diet (12 wks)	Yes	Yes	↑	Yes	Yes	
LDLr.Sle1.2.3 [37, 38]	Western diet (8 wks) [37]	Yes	Yes	↑	Yes	Yes	• ↑ T cell activation • ↑ T cell accumulation in plaque
	Chow diet (8 wks) [38]	Yes	Yes	↑	Yes	Yes	
apoE ^{-/-} .Fas ^{-/-} [32]	Chow diet (5 mos.)	Yes	Yes	↓	Yes	Yes	• Osteopenia • Accumulation of apoptotic debris
MRL ^{lpr} . apoE ^{-/-} [33]	Chow diet (24 wks)	Yes	n/a	↑	n/a	Yes	-
cGVHD induced lupus in apoE ^{-/-} mice [33]	Chow diet (24 wks)	Yes	n/a	↔	n/a	Yes	• ↓ marginal zone B cells