Accelerated atherosclerosis in SLE: mechanisms and prevention approaches

Ashley J. Wilhelm and **Amy S. Major**
Department of Medicine, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Summary

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterized by increased serum autoantibody levels and tissue damage. With improved diagnosis and more effective treatment of the resultant kidney disease, accelerated atherosclerosis has become a major cause of morbidity in patients suffering from SLE. Although the exact mechanisms for SLE-accelerated atherosclerosis are unknown, multiple factors have been established as potential players in this process. Among these potential players are dysregulation of T and B cell populations and increased circulating levels of inflammatory cytokines. In addition, SLE patients exhibit a proatherogenic lipid profile characterized by low HDL and high LDL and triglycerides. Recent therapeutic approaches have focused on targeting B cells, the producers of autoantibodies, but most studies do not consider the effects of these treatments on atherosclerosis. Evidence suggests that T cells play a major role in SLE-accelerated atherosclerosis. Therefore, therapies targeted at T cells may also prove invaluable in treating SLE and atherosclerosis.

Keywords

Systemic lupus erythematosus; atherosclerosis; T cells; B cells; HDL; Regulatory T cells; Regulatory B cells; belimumab; rituximab

Atherosclerosis and SLE

Atherosclerosis is a chronic inflammatory disorder that typically occurs when excess lipoproteins deposit in the intima and are oxidized [1], leading to recruitment of monocytes/macrophages and T cells to the artery wall [2]. These cells then produce inflammatory cytokines, increasing recruitment of T cells and macrophages to the lesion as part of an inflammatory cascade [3]. Dendritic cells (DC) and B cells are also present in the plaque and adventitia and play important roles in the disease process [4]. Given the strong involvement of the immune system and that recognition of oxLDL is involved in the initiation of atherosclerosis, the idea that atherosclerosis is an autoimmune disease has gained support [5,6]. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease involving multiple organs and is characterized by increased serum autoantibody levels and tissue damage [7]. T cells in SLE exhibit impaired function and increased apoptosis, while B cells are hyperactivated and immune cell production of proinflammatory cytokines is increased [8]. Both SLE and cardiovascular disease (CVD) pose threats to human health, with CVD being the leading cause of death in the US [9], and SLE currently affecting more than 1 million Americans [10]. Evidence suggests interplay between the two diseases as both

Correspondence to: Amy S. Major, PhD Vanderbilt University Medical Center 2220 Pierce Avenue, Room 352 PRB Nashville, TN 37232 Tel.: +1 615 936 1816 Fax: +1 615 936 1872 amy.major@vanderbilt.edu.

mouse and human studies have shown increased atherosclerosis in SLE [11–14]. With the increased life expectancy resulting from more effective treatments that address common complications such as nephritis, atherosclerosis now poses a significant health threat to SLE patients [14]. This review will summarize potential mechanisms for SLE-accelerated atherosclerosis and therapies aimed at targeting SLE and atherosclerosis.

Accelerated Atherosclerosis in SLE

In 1976, Urowitz *et al*. first reported increased risk of CVD in SLE patients [13]. This study outlined a bimodal curve of mortality for SLE, where early deaths (<1 year after diagnosis) were attributable to kidney disease and infection, while later deaths were associated with CVD. Since that time, reports have shown that, on average, the risk of CVD is 2-10-fold higher in SLE patients compared to healthy controls [15–18]. Due to their lower risk at baseline, the relative risk for CVD is highest in premenopausal women with SLE, as they have been shown to be 50 times more likely to experience myocardial infarction than their age matched counterparts [14]. With treatments for SLE disease activity becoming more effective, CVD is now a leading cause of death in SLE patients[19,20]. However, the mechanisms contributing to increased risk of CVD in SLE are not fully understood. We will begin this review by summarizing the contribution of immune cells to accelerated atherosclerosis in SLE.

Role of T cells in SLE and Atherosclerosis

T cells can be found in atherosclerotic plaques in both humans and mice [21–23], making up approximately 10% of the cells in the lesion [23]. Of the T cells present in atherosclerotic lesions, CD4+ T cells with a Th1 phenotype are the primary T cell subset [22,24]. These cells are thought to play a pathogenic role in atherosclerosis, demonstrated by the fact that in immune-deficient *scid/scid*, ApoE−/− mice, transfer of CD4+ T cells resulted in increased atherosclerosis [25]. Importantly, these T cells infiltrated the atherosclerotic plaques and T cell transfer was accompanied by an increase in circulating IFNγ [25], which has been established as an atherogenic cytokine [26]. Furthermore, in hypercholesterolemic mice lacking CD4+ T cells (CD4−/−, ApoE−/− mice), atherosclerosis was reduced [27]. These studies and others highlight a pathogenic role for CD4+ T cells in atherosclerosis. This pathogenesis is thought to occur through their production of inflammatory cytokines, such as IFNγ, which activate macrophages and other cell types in the atherosclerotic lesion [21]. These reports, however, did not take into account the potential divergent effects of various T cell subsets. For example, maintenance of the Th1/Th2 balance has been shown to be important in atherosclerosis. Schulte *et al*. demonstrated that mice skewed more towards a Th1 phenotype demonstrated increased atherosclerosis, while a bias towards a Th2 phenotype resulted in less atherosclerosis [28], indicating differential effects of each of these subsets on atherosclerosis. In addition, more recent atherosclerosis studies have focused on the role of regulatory T cells (T_{reg}) in this process, identifying these cells as having atheroprotective properties (discussed in more detail below). Thus, while the majority of T cells in atherosclerotic lesions are of the atherogenic Th1 phenotype, the presence of Th2 and T_{reg} can be important for controlling the atherosclerotic response.

Just as T cells play an important role in atherosclerosis, they also have a significant role in SLE pathogenesis. The idea that they contribute to disease pathogenesis is highlighted by mouse studies demonstrating that depletion of CD4+ cells through use of a monoclonal antibody was beneficial in the prevention and treatment of SLE [29]. Furthermore, T cells were shown to be required for development of SLE in NZB/W mice, as thymectomized mice failed to develop the disease [30]. Since that time, much focus has been placed on the pathogenic properties of T cells in SLE. Overall, SLE T cells have been shown to be hyperactive, with a reduced threshold of activation [31]. Upon activation, these cells secrete

inflammatory cytokines such as IFNγ and IL-17 [32]. In addition, SLE T cells exhibit increased survival and are resistant to apoptosis [33]. These properties of SLE T cells contribute to disease pathogenesis and result in activation of dendritic cells (DCs) and B cells [34].

Given that T cells play such important roles in both atherosclerosis and SLE, it is reasonable to think that dysregulated T cells might contribute to the increased risk of CVD observed in SLE patients. In fact, studies from our laboratory have demonstrated increased infiltration of $CD4^+$ T cells into the atherosclerotic lesions of $LDLr^{-/-}$ mice following transfer of bone marrow from lupus-susceptible mice [12]. This increase was independent of high-fat diet feeding [35], and unpublished data suggest that trafficking or accumulation of T cells in the lesions is required for the acceleration of atherosclerosis in this model.

In contrast to the pathogenic role of T cells, T_{reg} maintain self-tolerance through suppression of T cell activation or by preventing effector T cell (T_{eff}) responses and have important regulatory roles in both SLE and atherosclerosis. T_{reg} can also act to induce apoptosis or inhibit function of DCs, macrophages and B cells [36]. Suppression by T_{reg} occurs in a contact-dependent manner or through their secretion of the anti-inflammatory cytokines IL-10 and TGFβ [36,37]. Atherosclerosis studies have demonstrated a protective role for T_{reg}, as a reduction of T_{reg} in $LDLr^{-/-}$ mice and neutralization or deficiency of TGFβ in $ApoE^{-/-}$ mice led to increased atherosclerosis [38,39]. T_{reg} are equally important in preventing autoimmune disease, as experiments have shown that severe autoimmune disease is a consequence of T_{reg} deficiency [40,41]. Reports in SLE patients and mouse models have indicated a reduction in the number of $CD4^+CD25^+$ and $FoxP3^+$ T_{reg} [42,43]. However, in both mice and humans, reports as to their suppressive activity differ; with some experiments showing normal suppressive activity [42,44] and others demonstrating reduced suppressive capacity of SLE T_{reg} [43,45]. It has also been suggested that T_{eff} in SLE may be able to overcome suppression by T_{reg} [44,46,47]. The observation of the possible impaired suppression by T_{reg} and/or resistance of T_{eff} to suppression provides a potential explanation for the increased CVD in SLE.

Another T cell subset with a potential role in SLE-accelerated atherosclerosis is the Th17 subset. Th17 cells produce IL-17, a cytokine known to play a role in both lupus and atherosclerosis. Th17 cells are present in atherosclerotic plaques of both mice and humans [48,49]. However, due to conflicting results, their role in atherosclerosis is unclear. It appears that IL-17 contributes to vascular inflammation. However, its effect on plaque size is less defined. Studies involving deficiency or neutralization of IL-17A have shown beneficial effects on atherosclerosis, with lesion size reduced by as much as 50% [50,51]. However, a recent report by Taleb *et al.* indicated a protective effect of IL-17 on atherosclerosis [48]. In this study, mice treated with anti-IL-17A had increased atherosclerotic lesions and treatment with rIL-17A reduced lesion size. The reason for these divergent findings on the role of IL-17 in atherosclerosis is not yet clear. In SLE, Th17 cells are thought to contribute to disease pathogenesis. Th17 cells and IL-17 are increased in SLE patients and mouse models [52,53]. In SLE patients, levels of circulating IL-17 correlate with disease activity [54] and tend to be higher in individuals with active nephritis [52]. The ratio of Th17/Th1 appears to be dysregulated in SLE patients, with an increase in Th17 in SLE [55]. In addition, the ratio of T_{reg}/Th17 is reduced in SLE patients [56]. Given their potentially pathogenic role in atherosclerosis, the fact that Th17 cells are increased in SLE and that T_{reg} are reduced suggests that the dysregulation of these cell types may be a factor contributing to accelerated atherosclerosis in SLE.

Role of B cells in SLE and Atherosclerosis

Another major immune cell playing a role in both SLE and atherosclerosis is the B cell. Previous data have assigned an atheroprotective role to B cells [57,58]. Studies showing increased atherosclerosis as a result of B cell deficiency support the idea that B cells are protective in atherosclerosis [57,58]. However, recent reports have shown that depletion of mature B cells results in reduced atherosclerosis [59,60], suggesting that the role of B cells in atherosclerosis is more complex. In a normal immune response, B cells have multiple functions, including antigen presentation [61], antibody production [62] and regulation of $CD4^+$ T cell responses to antigens [63]. In autoimmunity, B cells are hyperactivated [8] and can produce antibodies to self, termed autoantibodies. In addition to autoantibody production, SLE B cell dysregulation can lead to T cell activation, DC recruitment, induction of Th1 and Th17 cells and inhibition of T_{reg}, solidifying B cells as a major player in SLE pathogenesis [64].

In contrast to the potentially pathogenic nature of B cells, regulatory B cell (B_{reg}) populations are present and can act to suppress T cell-mediated inflammation through mechanisms that are either dependent on or independent of IL-10 [65–68] . B_{reg} subsets have been shown to suppress autoimmune diseases including experimental autoimmune encephalomyelitis (EAE) [69], SLE [65,70] and collagen-induced arthritis (CIA) [71]. However, recent studies have shown that B_{reg} from SLE patients have reduced regulatory capacity [70], warranting further examination of the function of B_{reg} in a lupus model. Given their production of IL-10, a cytokine with atheroprotective effects, these cells may also play a role in atherosclerosis. With current SLE therapies focused on B cells, the potential effects of these therapies on the B_{reg} population are important to consider. Moreover, given the controversial role of B cells in atherosclerosis, the effects of these therapies on atherosclerosis are important to consider given that CVD is a leading cause of mortality in SLE. This point will be discussed in more detail in a later section of this review.

The Contribution of Cytokines to SLE Pathogenesis

A number of cytokines are involved in the pathogenesis of SLE, with serum levels of many pro-inflammatory cytokines increased in SLE patients. Potential roles for IL-17, TGFβ and IL-10 in SLE-accelerated atherosclerosis were discussed earlier in this review as related to Th17 cells, T_{reg} and B_{reg}. Thus, they will not be discussed here. Instead, we will focus on interferon γ (IFNγ) and IFNα, two inflammatory cytokines that likely contribute to SLE-accelerated atherosclerosis.

IFNγ has been shown to be pro-atherogenic, with mice lacking IFNγ exhibiting reduced atherosclerosis [26]. Produced by activated T cells in atherosclerosis, IFNγ contributes to plaque instability [72]. In SLE, IFNγ levels are increased [73], potentially contributing to the accelerated atherosclerosis. Studies have shown a role for type I IFN, particularly IFNα, in this process. IFNα levels are increased in both adult and pediatric SLE patients, and are associated with SLE disease activity [74,75]. This cytokine contributes to endothelial cell damage and depletion of endothelial progenitor cells [76]. Because of these actions, vascular repair is reduced. In endothelial progenitor cells from SLE patients, neutralization of type I IFN led to these cells expressing a phenotype similar to that observed in healthy cells. Conversely, when healthy cells were treated with IFNα, they exhibited a phenotype characteristic of cells from SLE patients [77]. Furthermore, a recent study by Li *et al*. demonstrated that, through upregulation of SR-A, IFNα enhances the formation of foam cells [78]. Importantly, SR-A mRNA was increased in cells from SLE patients, indicating that this process is likely occurring *in vivo*. Thus, these reports establish IFNα as an important player in SLE-accelerated atherosclerosis.

SLE-associated Risk Factors for Atherosclerosis

Risk factors associated with atherosclerosis have been extensively studied. Traditional Framingham risk factors for atherosclerosis include hyperlipidemia, hypertension, age, hyperglycemia, smoking and genetic factors. The increased risk of CVD observed in SLE cannot be completely explained by these traditional risk factors. Instead, SLE-related risk factors for accelerated atherosclerosis include dyslipidemia, disease activity and duration, autoantibodies, nephritis and circulating immune complexes.

SLE patients also exhibit signs of traditional dyslipidemia observed in CVD, with a pro-atherogenic lipid profile consisting of low levels of high density lipoproteins (HDL) and increased levels of low density lipoproteins (LDL) and triglycerides [79]. HDL protects against atherosclerosis by facilitating reverse cholesterol transport and exerting anti-oxidant effects. Levels of HDL are inversely correlated to risk of developing chronic inflammatory disorders such as CVD. In fact, in terms of traditional CVD, HDL is the strongest lipid risk factor, independent of low density lipoprotein (LDL) levels [80]. HDL can inhibit the production of inflammatory cytokines such as IL-1β and TNF-α by binding to activated T cells and preventing them from contacting monocytes in the circulation [81]. Therefore, through this inhibition of contact under normal conditions, HDL may be preventing the occurrence of inflammatory disorders. Apolipoprotein A-I is the main protein component of HDL and is required for the formation of HDL particles. In a study of hyperlipidemic mice lacking apolipoprotein A-I and, consequently, HDL, an autoimmune-like phenotype was observed [82]. These mice exhibited increased atherosclerosis, enlarged spleen and lymph nodes, skin lesions and autoantibody production. Results from this study support the idea that HDL is important in maintaining immune homeostasis. As mentioned previously, however, HDL levels are significantly decreased in SLE patients compared to healthy controls. Studies have demonstrated that HDL function is just as important as the amount of HDL present. Under conditions of chronic inflammation, HDL can lose its anti-inflammatory properties and instead become pro-inflammatory (piHDL) [83]. Reports have indicated the presence of piHDL in 45% of women affected with SLE [83]. Rather than acting to prevent oxidation of LDL as normal HDL particles do, piHDL can instead lead to oxidation of LDL and impairment of reverse cholesterol transport. McMahon et al. demonstrated that the presence of piHDL in SLE patients can increase the likelihood of developing CVD by up to 17-fold [83], establishing HDL function as an important factor to consider when discussing atherosclerosis risk in SLE.

SLE patients have increased concentrations of circulating autoantibodies which may contribute to atherosclerosis. Antiphospholipid syndrome (APS), characterized by increased circulating levels of antiphospholipid antibodies (aPL), has been associated with increased risk of both CVD and stroke. For example, increased intima-media thickening (IMT) was observed in APS patients in both the internal carotid artery and carotid bifurcation [84]. In addition, increased levels of anticardiolipin antibodies in middle-aged men were predictive of myocardial infarction risk [85,86], suggesting a role for aPL in contributing to CVD. However, the role of aPL in SLE-accelerated atherosclerosis is unclear, as data are available supporting a positive correlation between aPL and atherosclerosis [87], while other studies indicate no correlation [17,83] or even that aPL levels, specifically anticardiolipin antibodies, are reduced in SLE patients with atherosclerosis compared to those with no plaque [88]. Although the role of aPL in contributing to SLE-accelerated atherosclerosis remains uncertain, more is known regarding the contributions of specific anti-oxLDL antibodies. SLE patients have increased levels of these antibodies as well. While IgM anti-oxLDL antibodies are generally thought to be atheroprotective, IgG anti-oxLDL antibodies have been shown to contribute to disease pathogenesis [89]. Thus, increased autoantibodies in SLE patients likely contribute to SLE-accelerated atherosclerosis.

Prevention approaches

Given that accelerated CVD is now a leading cause of death in SLE, it is only logical that future therapies would be targeted at this problem. Thus far, we have outlined the role of T cells, B cells and dyslipidemia in acceleration of atherosclerosis in SLE. Now, we focus on therapies and prevention approaches.

B cell-targeted Therapies and Implications in SLE

While therapies for SLE are limited, the majority of the effort towards development of therapeutics is focused on B cells. Initial therapies focused on complete depletion of B cells using an anti-CD20 antibody, Rituximab. However, this therapy failed to reach treatment goals in two recent clinical trials, the EXPLORER and LUNAR trials [90,91]. In some cases, depletion of B cells led to development of additional autoimmune diseases including colitis and psoriasis [92,93]. Therefore, the use of Rituximab is currently reserved for those SLE patients with advanced disease (life-threatening) who fail to respond to other treatments. The role of anti-CD20 antibodies in atherosclerosis have been examined, with administration of this antibody resulting in reduced atherosclerosis in apoE$^{-/-}$ and LDLr$^{-/-}$ mice [59,60]. To date, no studies have assessed the effects of anti-CD20 antibodies on SLE-accelerated atherosclerosis. Given that accelerated CVD is now the leading cause of death in SLE, this is an important point to consider, especially since the role of B cells in CVD is not clear but subsets of B cells have been shown to be atheroprotective.

In 2010, belimumab (Benlysta) became the first therapy for lupus to be approved by the FDA in 50 years. As opposed to complete B cell depletion, belimumab binds to BLyS/BAFF (B lymphocyte stimulator/B –cell-activating factor), preventing it from binding to its receptor, BAFF-R. In turn, this prevents B cell stimulation and differentiation. This therapy has been shown to be moderately effective in treating SLE disease activity [94]. Unfortunately, however, belimumab was not effective in treating African American women with SLE [95]. This is an important point, as African Americans make up a large proportion of the SLE patient demographic. To date, no studies have directly assessed the effects of belimumab on accelerated atherosclerosis in SLE. Experiments in apoE$^{-/-}$ mice have examined the effects of BAFF-R deficiency on atherosclerosis. BAFF-R$^{-/-}$ mice exhibit selective depletion of B2 B cells, accompanied by a reduction in atherosclerosis [96,97]. These results suggest that belimumab inhibition of BAFF might also prove to be beneficial for SLE-accelerated atherosclerosis. However, additional investigation is needed to confirm this hypothesis.

An additional SLE therapy to be considered is expansion of B$_{reg}$. As discussed previously, B$_{reg}$ exert anti-inflammatory effects through mechanisms that are IL-10-dependent and some that are IL-10–independent. IL-10 has been shown to have beneficial effects on atherosclerosis, with overexpression inhibiting both fatty streak formation [98] and advanced lesions [99]. Although increased IL-10 has been shown to correlate with disease activity in SLE, the role of this cytokine in SLE is not clear. Data have suggested that IL-10 has both immunosuppressive [100] and immunostimulatory [101] roles in the SLE disease process. The fact that IL-10 has opposing functions, including the ability to activate B cells for antibody production and to inhibit T cell-mediated inflammation, highlights the importance of this cytokine in autoimmunity. Mouse studies have demonstrated the beneficial effects of B$_{reg}$ on SLE disease activity. Interestingly, expansion of IL-10-producing B$_{reg}$ through CD40 was effective in reducing autoimmunity [65]. Though small in number, B$_{reg}$ are a potent regulatory population [68]. Thus, through their production of IL-10, B$_{reg}$ may have anti-atherogenic properties. Therefore, B$_{reg}$ expansion might prove to be an important treatment for both SLE and accelerated atherosclerosis in SLE. Also of potential benefit is the IL-10-independent modulation of autoimmunity by B$_{reg}$. In a mouse

model of EAE, Ray *et al*. demonstrated that B cells suppressed autoimmunity by maintaining T_{reg} populations through glucocorticoid-induced TNF (GITR) ligand [67]. The fact that T_{reg} were reduced in B cell-deficient mice provides one possible explanation as to why depletion of B cells with Rituximab resulted in additional autoimmune disease in some cases. The importance of T_{reg} in atherosclerosis and SLE, as discussed earlier, is well-documented. The idea that B cells can work to maintain T_{reg} populations adds importance to these cells as a potential therapeutic target in SLE-accelerated atherosclerosis and warrants further investigation. Likewise, GITR ligand may also be an attractive therapeutic target in SLE and atherosclerosis.

T cell-targeted Therapies for SLE

Given their importance in lupus and atherosclerosis, therapies targeting T cells might also be a viable option for treatment of these diseases. In particular, therapies aimed at targeting the T_{reg}/Th17 balance are attractive given the potential of both cell types to affect atherosclerosis and lupus. All-trans retinoic acid (atRA) induces T_{reg} and can act to maintain FoxP3 expression on T_{reg}. Lu *et al*. demonstrated that addition of atRA and TGFβ to cultures resulted in increased suppressive function of T_{reg} *in vitro* and *in vivo* [102]. atRA also inhibits Th17 cell development by inhibiting IRF-4, IL-6Rα and IL-23R [103]. Currently, there are no *in vivo* reports examining the effects of atRA on SLE. However, *in vitro* experiments have suggested that T cells from SLE patients have a defective response to atRA, with the induction of T_{reg} reduced compared to cells from healthy controls [104]. Therefore more investigation, including *in vivo* studies, is needed to determine if this might be an effective therapy for SLE and atherosclerosis. As the role of T cells in SLE and SLE-accelerated atherosclerosis becomes more apparent, it will be important to shift some effort into developing more T cell-targeted approaches.

Mycophenolate Mofetil Therapy in SLE

Mycophenolate mofetil (MMF) is an immunosuppressant that inhibits development of T and B cells through inhibition of inosine monophosphate dehydrogenase (IMPDH) [105]. MMF has been shown to be effective in both SLE [106] and in atherosclerosis [107], but few studies have examined its effects on SLE-accelerated atherosclerosis. One study from our laboratory demonstrated effectiveness of MMF in reducing atherosclerotic lesion burden in LDLr$^{-/-}$ mice reconstituted with bone marrow from SLE-susceptible mice. The reduction of atherosclerotic lesion size in the aortic sinus was accompanied by reduced numbers of CD4$^+$ T cells in the atherosclerotic lesions and reduced CD4$^+$ T cell activation in the periphery [108]. A recent study in SLE patients reported no effects of MMF on carotid intima media thickness or coronary artery calcium, with measurements taken at baseline and after 2 years of treatment with MMF. However, given the small number of patients receiving MMF in this study (n=25), studies with larger cohorts are needed to more closely examine the effects of MMF on SLE-accelerated atherosclerosis [109].

Efficacy of Statins in SLE-Accelerated Atherosclerosis

Statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), are the most widely used lipid lowering agents, with well-established beneficial effects on atherosclerosis. Given the dyslipidemia observed in SLE patients, statins have been suggested as a potentially effective therapy for SLE. Studies in animal models have demonstrated conflicting results, with some indicating efficacy of statins in treating SLE-accelerated atherosclerosis [11] and others reporting no differences between study groups [110]. These divergent results are likely due to variability in study designs including differences in mouse models and statin dosages, among others. A more comprehensive review of statins in animal studies can be found in van Leuven *et al*. [111]

Thus far, few studies have evaluated the efficacy of statins on atherosclerosis in SLE patients. Ferreira *et al*. examined the effects of atorvastatin (20 mg/day) on endothelial function over an 8 week period, reporting improvement in endothelial-dependent vasodilation [112]. The Lupus Atherosclerosis Prevention Study (LAPS) followed patients receiving atorvastatin (40 mg/day) for 2 years. At the conclusion of the study, no effects of atorvastatin on coronary artery calcium, intima media thickness or endothelial activation were observed [113]. Another multicenter trial, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study, focused on the effects of atorvastatin in pediatric patients [114]. After 36 months of follow up, atorvastatin had no effects on carotid intima-media thickening. Thus, with conflicting results in both mouse and human studies, it is unclear what the effects of statins are on SLE-accelerated atherosclerosis.

The Role of Anti-malarial Agents in SLE-accelerated Atherosclerosis

Anti-malarial agents have been utilized to treat SLE and other rheumatic diseases for many years. Of these, the most commonly used is hydroxychloroquine. Hydroxychloroquine has both anti-inflammatory and immunomodulatory properties that make it an effective agent for the treatment of SLE. In addition to reducing the accumulation of damage in SLE [115], hydroxychloroquine has been shown to reduce levels of inflammatory cytokines, including IFNα [116], mentioned above as a potential contributor to SLE-accelerated atherosclerosis. Also important to its anti-atherosclerotic potential, hydroxychloroquine treatment has been shown to reduce total serum cholesterol [117–120]. Specifically, LDL cholesterol levels, which are positively correlated with CVD risk, were reduced in SLE patients after hydroxychloroquine treatment [120]. Along with its cholesterol lowering effects, a reduction in aortic stiffness has been associated with hydroxychloroquine treatment [121]. Importantly, a negative correlation between hydroxychloroquine treatment and atherosclerosis (as assessed by carotid ultrasound) was observed [88]. Collectively, these studies point towards hydroxychloroquine as potentially beneficial therapy for SLE-accelerated atherosclerosis.

ApoA-I mimetic Peptides as Treatment for SLE-accelerated Atherosclerosis

As discussed previously, the presence of piHDL in SLE patients confers increased CVD risk. Along with the presence of piHDL, SLE patients have reduced HDL levels. HDL is well-documented as having beneficial effects on atherosclerosis and may have beneficial effects on autoimmunity. In a study of hyperlipidemic mice lacking apoA-I, injection of apoA-I resulted in formation of HDL particles and, importantly, reduction of autoimmune-like symptoms and improved T_{reg} function [122]. Woo *et al*. evaluated the effects of an apoA-I mimetic peptide, L-4F, in an $apoE^{-/-}$, $Fas^{-/-}$ mouse model [110]. After 27 weeks of treatment, piHDL was reduced, along with a reduction in circulating autoantibodies to dsDNA and oxidized phospholipids. Interestingly, the study also included a group receiving both L-4F and pravastatin. Despite an increase in atherosclerotic lesion area, plaques in mice receiving combination therapy showed signs of increased stability, including an increase in smooth muscle cell content and a reduction in macrophages in the lesion. Thus, treatments focusing on HDL may prove to be beneficial in SLE and atherosclerosis and, perhaps, a combination of statins and HDL therapy should be considered.

Future perspective

Considerable advances have been made in the field of SLE research in the last 10 years. An important development came in 2010, when belimumab became the first therapy approved for SLE since the 1950s. However, the effects of B cell therapies on SLE-accelerated atherosclerosis have not been considered. Likewise, according to clinicaltrials.gov, there are currently several T cell-focused clinical trials underway, with none assessing CVD

outcomes. As evidence grows for the role of T cells in SLE-accelerated atherosclerosis, we might expect this to change. It is probable that, in the near future, T cell-focused therapies will be developed with the goal of treating both SLE and the resultant acceleration of atherosclerosis. Regulatory cell populations are emerging as important factors in the control of autoimmunity and atherosclerosis, also making them attractive therapeutic targets. This is an exciting time for SLE and atherosclerosis research, with important discoveries being made every day. As research continues, it is likely that the next 10 years will bring increased understanding of the mechanisms behind accelerated atherosclerosis in SLE and, along with that, new therapies that are able to address both SLE and SLE-accelerated atherosclerosis, improving the prognosis for these patients. With our understanding of these disease processes growing, it is evident that SLE patients will not be left waiting another 60 years before new therapies become available.

References

1. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nature Reviews. Immunology. 2006; 6(7):508–19.

2. Libby P, Ridker P, Maseri A. Inflammation and Atherosclerosis. Circulation. 2002; 105(9):1135–1143. [PubMed: 11877368]

3. Robertson A-KL, Hansson GK. T cells in atherogenesis: for better or for worse? Arteriosclerosis, Thrombosis, and Vascular Biology. 2006; 26(11):2421–32.

4. Weber C, Zernecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. Nature Reviews. Immunology. 2008; 8(10):802–15.

5. Blasi C. The autoimmune origin of atherosclerosis. Atherosclerosis. 2008; 201(1):17–32. [PubMed: 18585722]

6. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, Hansson GK. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proceedings of the National Academy of Sciences of the United States of America. 1995; 92(9):3893–7. [PubMed: 7732003]

7. Kotzin BL. Systemic Lupus Erythematosus. Cell. 1996; 85:303–306. [PubMed: 8616885]

8. Kyttaris VC, Juang Y-T, Tsokos GC. Immune cells and cytokines in systemic lupus erythematosus: an update. Current Opinion in Rheumatology. 2005; 17(5):518–22. [PubMed: 16093827]

9. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011; 123(8):933–44. [PubMed: 21262990]

10. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis and Rheumatism. 2008; 58(1):15–25. [PubMed: 18163481]

11. Aprahamian T, Bonegio R, Rizzo J, et al. Simvastatin treatment ameliorates autoimmune disease associated with accelerated atherosclerosis in a murine lupus model. The Journal of Immunology. 2006; 177(5):3028. [PubMed: 16920939]

12. Stanic AK, Stein CM, Morgan AC, et al. Immune dysregulation accelerates atherosclerosis and modulates plaque composition in systemic lupus erythematosus. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(18):7018–23. [PubMed: 16636270]

13. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. The American Journal of Medicine. 1976; 60(2):221–5. [PubMed: 1251849]

14. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. American Journal of Epidemiology. 1997; 145(5):408–15. [PubMed: 9048514]

15. Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. Current Opinion in Rheumatology. 2001; 13(5):345–51. [PubMed: 11604587]

16. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis and Rheumatism. 2001; 44(10):2331–7. [PubMed: 11665973]

17. Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. Arthritis and Rheumatism. 1999; 42(1):51–60. [PubMed: 9920014]

18. Hak AE, Karlson EW, Feskanich D, Stampfer MJ, Costenbader KH. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the nurses' health study. Arthritis and Rheumatism. 2009; 61(10):1396–402. [PubMed: 19790130]

19. Nossent J, Cikes N, Kiss E, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000--2004: relation to disease activity and damage accrual. Lupus. 2007; 16(5):309–17. [PubMed: 17576731]

20. Bernatsky S, Boivin J-F, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis and Rheumatism. 2006; 54(8):2550–7. [PubMed: 16868977]

21. Hansson GK, Holm J, Jonasson L. Detection of activated T lymphocytes in the human atherosclerotic plaque. The American Journal of Pathology. 1989; 135(1):169–75. [PubMed: 2505620]

22. Roselaar SE, Kakkanathu PX, Daugherty A. Lymphocyte Populations in Atherosclerotic Lesions of ApoE –/– and LDL Receptor –/– Mice: Decreasing Density with Disease Progression. Arteriosclerosis, Thrombosis, and Vascular Biology. 1996; 16(8):1013–1018.

23. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Arteriosclerosis, Thrombosis, and Vascular Biology. 1986; 6(2):131–138.

24. Frostegård J, Ulfgren AK, Nyberg P, et al. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. Atherosclerosis. 1999; 145(1):33–43. [PubMed: 10428293]

25. Zhou X, Nicoletti A, Elhage R, Hansson GK. Transfer of CD4+ T cells aggravates atherosclerosis in immunodeficient apolipoprotein E knockout mice. Circulation. 2000; 102(24):2919–22. [PubMed: 11113040]

26. Buono C, Come CE, Stavrakis G, Maguire GF, Connelly PW, Lichtman AH. Influence of interferon-gamma on the extent and phenotype of diet-induced atherosclerosis in the LDLR-deficient mouse. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003; 23(3):454–60.

27. Zhou X, Robertson A-KL, Rudling M, Parini P, Hansson GK. Lesion development and response to immunization reveal a complex role for CD4 in atherosclerosis. Circulation Research. 2005; 96(4): 427–34. [PubMed: 15662027]

28. Schulte S, Sukhova GK, Libby P. Genetically programmed biases in Th1 and Th2 immune responses modulate atherogenesis. The American Journal of Pathology. 2008; 172(6):1500–8. [PubMed: 18467709]

29. Wofsy D, Seaman WE. Reversal of Advanced Murine Lupus in NZB/NZW F1 Mice by Treatment with Monoclonal Antibody to L3T4. Journal of Immunology. 1987; 138(10):3247–3253.

30. Mihara M, Ohsugi Y, Saito K, et al. Thymus-Independent Occurrence of B Cell Abnormality and Requirement for T Cells in the Development of Autoimmune Disease, as Evidenced by an Analysis of the Athymic Nude Individuals. Journal of Immunology. 1988; 141(1):85–90.

31. Dawisha SM, Gmelig-Meyling F, Steinberg AD. Assessment of clinical parameters associated with increased frequency of mutant T cells in patients with systemic lupus erythematosus. Arthritis and Rheumatism. 1994; 37(2):270–7. [PubMed: 8129782]

32. Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. Journal of Immunology. 2009; 183(5):3160–9.

33. Budagyan VM, Bulanova EG, Sharova NI, Nikonova MF, Stanislav ML, Yarylin AA. The resistance of activated T-cells from SLE patients to apoptosis induced by human thymic stromal cells. Immunology Letters. 1998; 60(1):1–5. [PubMed: 9541455]

34. Zhou Y, Yuan J, Pan Y, et al. T cell CD40LG gene expression and the production of IgG by autologous B cells in systemic lupus erythematosus. Clinical immunology. 2009; 132(3):362–70. [PubMed: 19520616]

35. Braun NA, Wade NS, Wakeland EK, Major AS. Accelerated atherosclerosis is independent of feeding high fat diet in systemic lupus erythematosus-susceptible LDLr–/– mice. Lupus. 2008; 17(12):1070–8. [PubMed: 19029274]

36. André S, Tough DF, Lacroix-Desmazes S, Kaveri SV, Bayry J. Surveillance of antigen-presenting cells by CD4+ CD25+ regulatory T cells in autoimmunity: immunopathogenesis and therapeutic implications. The American Journal of Pathology. 2009; 174(5):1575–87. [PubMed: 19349365]

37. Mallat Z, Taleb S, Ait-Oufella H, Tedgui A. The role of adaptive T cell immunity in atherosclerosis. Journal of Lipid Research. 2009:S364–9. [PubMed: 19050311]

38. Grainger DJ, Mosedale DE, Metcalfe JC, Böttinger EP. Dietary fat and reduced levels of TGFbeta1 act synergistically to promote activation of the vascular endothelium and formation of lipid lesions. Journal of Cell Science. 2000; 113:2355–61. [PubMed: 10852815]

39. Mallat Z, Gojova A, Marchiol-Fournigault C, et al. Inhibition of transforming growth factor-beta signaling accelerates atherosclerosis and induces an unstable plaque phenotype in mice. Circulation Research. 2001; 89(10):930–4. [PubMed: 11701621]

40. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nature Genetics. 2001; 27(1):20–1. [PubMed: 11137993]

41. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *Journal of medical genetics* [Internet]. 2002; 39(8):537–45. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1735203&tool=pmcentrez&rendertype=abstract.

42. Scalapino KJ, Tang Q, Bluestone JA, Bonyhadi ML, Daikh DI. Suppression of disease in New Zealand Black/New Zealand White lupus-prone mice by adoptive transfer of ex vivo expanded regulatory T cells. Journal of Immunology. 2006; 177(3):1451–9.

43. Lee J-H, Wang L-C, Lin Y-T, Yang Y-H, Lin D-T, Chiang B-L. Inverse correlation between CD4+ regulatory T-cell population and autoantibody levels in paediatric patients with systemic lupus erythematosus. Immunology. 2006; 117(2):280–6. [PubMed: 16423064]

44. Venigalla RKC, Tretter T, Krienke S, et al. Reduced CD4+,CD25- T cell sensitivity to the suppressive function of CD4+,CD25high,CD127 -/low regulatory T cells in patients with active systemic lupus erythematosus. Arthritis and Rheumatism. 2008; 58(7):2120–30. [PubMed: 18576316]

45. Divekar AA, Dubey S, Gangalum PR, Singh RR. Dicer insufficiency and microRNA-155 overexpression in lupus regulatory T cells: an apparent paradox in the setting of an inflammatory milieu. Journal of Immunology. 2011; 186(2):924–30.

46. Monk CR, Spachidou M, Rovis F, et al. MRL/Mp CD4+,CD25- T cells show reduced sensitivity to suppression by CD4+,CD25+ regulatory T cells in vitro: a novel defect of T cell regulation in systemic lupus erythematosus. Arthritis and Rheumatism. 2005; 52(4):1180–4. [PubMed: 15818683]

47. Lee H-Y, Hong Y-K, Yun H-J, Kim Y-M, Kim J-R, Yoo W-H. Altered frequency and migration capacity of CD4+CD25+ regulatory T cells in systemic lupus erythematosus. Rheumatology (Oxford, England). 2008; 47(6):789–94.

48. Taleb S, Romain M, Ramkhelawon B, et al. Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis. The Journal of Experimental Medicine. 2009; 206(10):2067–77. [PubMed: 19737863]

49. Eid RE, Rao DA, Zhou J, et al. Interleukin-17 and interferon-gamma are produced concomitantly by human coronary artery-infiltrating T cells and act synergistically on vascular smooth muscle cells. Circulation. 2009; 119(10):1424–32. [PubMed: 19255340]

50. Smith E, Prasad K-MR, Butcher M, et al. Blockade of interleukin-17A results in reduced atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2010; 121(15):1746–55. [PubMed: 20368519]

51. Gao Q, Jiang Y, Ma T, et al. A Critical Function of Th17 Proinflammatory Cells in the Development of Atherosclerotic Plaque in Mice. Journal of Immunology. 2010; 185:5820–5827.

52. Xing Q, Wang B, Su H, Cui J, Li J. Elevated Th17 cells are accompanied by FoxP3+ Treg cells decrease in patients with lupus nephritis. Rheumatology International. 2012; 32(4):949–58. [PubMed: 21243492]

53. Hsu H-C, Yang P, Wang J, et al. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nature Immunology. 2008; 9(2):166–75. [PubMed: 18157131]

54. Chen XQ, Yu YC, Deng HH, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. Journal of Clinical Immunology. 2010; 30(2):221–5. [PubMed: 20107878]

55. Shah K, Lee W-W, Lee S-H, et al. Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. Arthritis Research & Therapy. 2010; 12(2):R53. [PubMed: 20334681]

56. Ma J, Yu J, Tao X, Cai L, Wang J, Zheng SG. The imbalance between regulatory and IL-17-secreting CD4+ T cells in lupus patients. Clinical Rheumatology. 2010; 29(11):1251–8. [PubMed: 20563617]

57. Caligiuri G, Nicoletti A, Poirier B, Hansson GK. Protective immunity against atherosclerosis carried by B cells of hypercholesterolemic mice. Journal of Clinical Investigation. 2002; 109(6): 721–724. [PubMed: 11901180]

58. Major AS, Fazio S, Linton MF. B-Lymphocyte Deficiency Increases Atherosclerosis in LDL Receptor-Null Mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002; 22(11):1892–1898.

59. Ait-Oufella H, Herbin O, Bouaziz J-D, et al. B cell depletion reduces the development of atherosclerosis in mice. The Journal of Experimental Medicine. 2010; 207(8):1579–87. [PubMed: 20603314]

60. Kyaw T, Tay C, Khan A, et al. Conventional B2 B Cell Depletion Ameliorates whereas Its Adoptive Transfer Aggravates Atherosclerosis. Journal of Immunology. 2010; 185:4410–4419.

61. Constant S, Schweitzer N, West J, Ranney P, Bottomly K. B Lymphocytes Can Be Competent Antigen-Presenting Cells for Priming CD4+ T cells to protein antigens in vivo. Journal of Immunology. 1995; 155:3734–3741.

62. Gray D, Gray M, Barr T. Innate responses of B cells. European Journal of Immunology. 2007; 37(12):3304–10. [PubMed: 18000957]

63. Lund FE, Randall TD. Effector and regulatory B cells: modulators of CD4(+) T cell immunity. Nature Reviews. Immunology. 2010; 10(4):236–47.

64. Sanz I, Lee FE-H. B cells as therapeutic targets in SLE. Nature Reviews. Rheumatology. 2010; 6(6):326–37.

65. Blair PA, Chavez-Rueda KA, Evans JG, et al. Selective Targeting of B cells with Agonistic Anti-CD40 is an Efficacious Strategy for the Generation of Induced Regulatory T2-Like B Cells and for the Suppression of Lupus in MRL/lpr Mice. The Journal of Immunology. 2009; 182:3493–3502.

66. Teichmann LL, Kashgarian M, Weaver CT, Roers A, Müller W, Shlomchik MJ. B Cell-Derived IL-10 Does Not Regulate Spontaneous Systemic Autoimmunity in MRL.Faslpr Mice. Journal of Immunology. 2011

67. Ray A, Basu S, Williams CB, Nita H, Dittel BN. A Novel IL-10 – Independent Regulatory Role for B Cells in Suppressing Autoimmunity by Maintenance of Regulatory T Cells via GITR Ligand. The Journal of Immunology. 2012

68. DiLillo DJ, Matsushita T, Tedder TF. B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer. Annals of the New York Academy of Sciences. 2010; 1183:38–57. [PubMed: 20146707]

69. Matsushita T, Yanaba K, Bouaziz J-david, Fujimoto M, Tedder TF. Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression. Journal of Clinical Investigation. 2008; 118(10):3420–3430. [PubMed: 18802481]

70. Blair PA, Noreña LY, Flores-Borja F, et al. CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic Lupus Erythematosus patients. Immunity. 2010; 32(1):129–40. [PubMed: 20079667]

71. Evans JG, Chavez-Rueda KA, Eddaoudi A, et al. Novel suppressive function of transitional 2 B cells in experimental arthritis. Journal of Immunology. 2007; 178(12):7868–78.

72. McLaren JE, Ramji DP. Interferon gamma: a master regulator of atherosclerosis. Cytokine & Growth Factor Reviews. 2009; 20(2):125–35. [PubMed: 19041276]

73. Theofilopoulos AN, Koundouris S, Kono DH, Lawson BR. The role of IFN-gamma in systemic lupus erythematosus: a challenge to the Th1/Th2 paradigm in autoimmunity. Arthritis Research. 2001; 3(3):136–41. [PubMed: 11299053]

74. Postal M, Sinicato NA, Peliçari KO, Marini R, Lavras Costallat LT, Appenzeller S. Clinical and serological manifestations associated with interferon-α levels in childhood-onset systemic lupus erythematosus. Clinics (São Paulo, Brazil). 2012; 67(2):157–62.

75. Ko K, Franek BS, Marion M, et al. Genetic Ancestry, Serum Interferon-α Activity, and Autoantibodies in Systemic Lupus Erythematosus. The Journal of Rheumatology. 2012

76. Kaplan MJ, Salmon JE. How does interferon-α insult the vasculature? Let me count the ways. Arthritis and Rheumatism. 2011; 63(2):334–6. [PubMed: 21279989]

77. Denny MF, Thacker S, Mehta H, et al. Interferon-alpha promotes abnormal vasculogenesis in lupus: a potential pathway for premature atherosclerosis. Blood. 2007; 110(8):2907–15. [PubMed: 17638846]

78. Li J, Fu Q, Cui H, et al. Interferon-α priming promotes lipid uptake and macrophage-derived foam cell formation: a novel link between interferon-α and atherosclerosis in lupus. Arthritis and Rheumatism. 2011; 63(2):492–502. [PubMed: 21280004]

79. Toms TE, Panoulas VF, Kitas GD. Dyslipidaemia in rheumatological autoimmune diseases. The Open Cardiovascular Medicine Journal. 2011; 5:64–75. [PubMed: 21660202]

80. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. The American Journal of Medicine. 1977; 62(5):707–14. [PubMed: 193398]

81. Hyka N. Apolipoprotein A-I inhibits the production of interleukin-1beta and tumor necrosis factor-alpha by blocking contact-mediated activation of monocytes by T lymphocytes. Blood. 2001; 97(8):2381–2389. [PubMed: 11290601]

82. Wilhelm AJ, Zabalawi M, Grayson JM, et al. Apolipoprotein A-I and its role in lymphocyte cholesterol homeostasis and autoimmunity. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009; 29(6):843–9.

83. McMahon M, Grossman J, Skaggs B, et al. Dysfunctional proinflammatory high-density lipoproteins confer increased risk of atherosclerosis in women with systemic lupus erythematosus. Arthritis and Rheumatism. 2009; 60(8):2428–37. [PubMed: 19644959]

84. Ames PRJ, Margarita A, Sokoll KB, Weston M, Brancaccio V. Premature atherosclerosis in primary antiphospholipid syndrome: preliminary data. Annals of the rheumatic diseases. 2005; 64(2):315–7. [PubMed: 15155372]

85. Wu R, Nityanand S, Berglund L, Lithell H, Holm G, Lefvert AK. Antibodies Against Cardiolipin and Oxidatively Modified LDL in 50-Year-Old Men Predict Myocardial Infarction. Arteriosclerosis, Thrombosis, and Vascular Biology. 1997; 17(11):3159–3163.

86. Vaarala O, Manttari M, Manninen V, et al. Anti-Cardiolipin Antibodies and Risk of Myocardial Infarction in a Prospective Cohort of Middle-Aged Men. Circulation. 1995; 91(1):23–27. [PubMed: 7805207]

87. Toloza SMA, Uribe AG, McGwin G, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis and rheumatism. 2004; 50(12):3947–57. [PubMed: 15593203]

88. Roman MJ, Shanker B-A, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. The New England journal of medicine. 2003; 349(25):2399–406. [PubMed: 14681505]

89. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nature immunology. 2011; 12(3):204–12. [PubMed: 21321594]

90. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis and Rheumatism. 2010; 62(1):222–33. [PubMed: 20039413]

91. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The Lupus Nephritis Assessment with Rituximab study. Arthritis and Rheumatism. 2012; 64(4):1215–26. [PubMed: 22231479]

92. El Fassi D, Nielsen CH, Kjeldsen J, Clemmensen O, Hegedüs L. Ulcerative colitis following B lymphocyte depletion with rituximab in a patient with Graves' disease. Gut. 2008; 57(5):714–5. [PubMed: 18408106]

93. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. Arthritis and Rheumatism. 2007; 56(8):2715–8. [PubMed: 17665440]

94. Stohl W, Hiepe F, Latinis KM, et al. Belimumab reduces autoantibodies, normalizes low complement, and reduces select B-cell populations in patients with systemic lupus erythematosus. Arthritis and Rheumatism. 2012

95. Stohl W, Hilbert DM. The discovery and development of belimumab: the anti-BLyS-lupus connection. Nature Biotechnology. 2012; 30(1):69–77.

96. Kyaw T, Tay C, Hosseini H, et al. Depletion of B2 but Not B1a B Cells in BAFF Receptor-Deficient ApoE –/– Mice Attenuates Atherosclerosis by Potently Ameliorating Arterial Inflammation. Atherosclerosis. 2012; 7(1):1–10.

97. Sage AP, Tsiantoulas D, Baker L, et al. BAFF Receptor Deficiency Reduces the Development of Atherosclerosis in Mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012

98. Mallat Z, Besnard S, Duriez M, et al. Protective Role of Interleukin-10 in Atherosclerosis. Circulation Research. 1999; 85:e17–e24. [PubMed: 10521249]

99. Han X, Kitamoto S, Wang H, Boisvert W a. Interleukin-10 overexpression in macrophages suppresses atherosclerosis in hyperlipidemic mice. The FASEB Journal. 2010; 24(8):2869–80.

100. Yin Z, Bahtiyar G, Zhang N, et al. IL-10 regulates murine lupus. Journal of Immunology. 2002; 169(4):2148–55.

101. Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M. Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice. The Journal of Experimental Medicine. 1994; 179(1):305–10. [PubMed: 8270873]

102. Lu L, Ma J, Li Z, et al. All-trans retinoic acid promotes TGF-β-induced Tregs via histone modification but not DNA demethylation on Foxp3 gene locus. PloS One. 2011; 6(9):e24590. [PubMed: 21931768]

103. Xiao S, Jin H, Korn T, et al. Retinoic Acid Increases Foxp3 Regulatory T Cells and Inhibits Development of Th17 Cells by Enhancing TGF-b-Driven Smad3 Signaling and Inhibiting IL-6 and IL-23 Receptor Expression. Journal of Immunology. 2008; 181:2277–2284.

104. Sobel ES, Brusko TM, Butfiloski EJ, et al. Defective response of CD4+ T cells to retinoic acid and TGFβ in systemic lupus erythematosus. Arthritis Research & Therapy. 2011; 13(3):R106. [PubMed: 21708033]

105. Allison AC. Mechanisms of action of mycophenolate mofetil. Lupus. 2005; 14(3):s2–8. [PubMed: 15803924]

106. Zhao L, Jiang Z, Jiang Y, Ma N, Wang K, Zhang Y. Changes in immune cell frequencies after cyclophosphamide or mycophenolate mofetil treatments in patients with systemic lupus erythematosus. Clinical Rheumatology. 2012

107. van Leuven SI, van Wijk DF, Volger OL, et al. Mycophenolate mofetil attenuates plaque inflammation in patients with symptomatic carotid artery stenosis. Atherosclerosis. 2010; 211(1): 231–6. [PubMed: 20202636]

108. van Leuven SI, Mendez-Fernandez YV, Wilhelm AJ, et al. Mycophenolate mofetil but not atorvastatin attenuates atherosclerosis in lupus-prone LDLr–/– mice. Annals of the Rheumatic Diseases. 2011

109. Kiani AN, Magder LS, Petri M. Mycophenolate mofetil (MMF) does not slow the progression of subclinical atherosclerosis in SLE over 2 years. Rheumatology International. 2011

110. Woo JMP, Lin Z, Navab M, et al. Treatment with apolipoprotein A-1 mimetic peptide reduces lupus-like manifestations in a murine lupus model of accelerated atherosclerosis. Arthritis Research & Therapy. 2010; 12(3):R93. [PubMed: 20482780]

111. Van Leuven SI, Mendez-Fernandez YV, Stroes ES, Tak PP, Major AS. Statin therapy in lupus-mediated atherogenesis: two birds with one stone? Annals of the Rheumatic Diseases. 2011; 70(2):245–248. [PubMed: 21068103]

112. Ferreira GA, Navarro TP, Telles RW, Andrade LEC, Sato EI. Atorvastatin therapy improves endothelial-dependent vasodilation in patients with systemic lupus erythematosus: an 8 weeks controlled trial. Rheumatology. 2007; 46(10):1560–5. [PubMed: 17693444]

113. Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS. Lupus Atherosclerosis Prevention Study (LAPS). Annals of the Rheumatic Diseases. 2011; 70(5):760–5. [PubMed: 21177297]

114. Schanberg LE, Sandborg C, Barnhart HX, et al. Use of atorvastatin in systemic lupus erythematosus in children and adolescents. Arthritis and Rheumatism. 2012; 64(1):285–96. [PubMed: 22031171]

115. Fessler BJ, Alarcón GS, McGwin G, et al. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. Arthritis and rheumatism. 2005; 52(5):1473–80. [PubMed: 15880829]

116. Willis R, Seif A, McGwin G, et al. Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: data from LUMINA (LXXV), a multiethnic US cohort. Lupus. 2012; 21(8):830–835. [PubMed: 22343096]

117. Petri M. Hydroxychloroquine use in the Baltimore Lupus Cohort: effects of lipids, glucose and thrombosis. Lupus. 1996; 1(Suppl):S16–22. [PubMed: 8803905]

118. Wallace D, Metzger A, Stecher V, Turnbull B, Kern P. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. American Journal of Medicine. 1990; 89:322–26. [PubMed: 2393036]

119. Rahman P, Gladman D, Urowitz MB, Yuen K, Hallett D, Bruce I. The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. Journal of Rheumatology. 1999; 26:325–30. [PubMed: 9972966]

120. Cairoli E, Rebella M, Danese N, Garra V, Borba E. Hydroxychloroquine reduces low-density lipoprotein cholesterol levels in systemic lupus erythematosus: a longitudinal evaluation of the lipid-lowering effect. Lupus. 2012

121. Selzer F, Sutton-Tyrrell K, Fitzgerald S, Tracy R, Kuller L, Manzi S. Vascular Stiffness in Women With Systemic Lupus Erythematosus. Hypertension. 2001; 37(4):1075–1082. [PubMed: 11304506]

122. Wilhelm AJ, Zabalawi M, Owen JS, et al. Apolipoprotein A-I modulates regulatory T cells in autoimmune LDLr−/−, ApoA-I−/− mice. The Journal of Biological Chemistry. 2010; 285(46): 36158–69. [PubMed: 20833724]

Executive Summary

Accelerated Atherosclerosis and SLE

- The risk of atherosclerosis is increased, on average, 2-10-fold in SLE patients.

- T cells are an important player in atherosclerosis and have been shown to accumulate in atherosclerotic lesions of lupus-susceptible mice

- T_{reg} play an important role in inhibiting atherosclerosis, but these cells may be dysfunctional in SLE.

- Increased numbers of Th17 cells and increased circulating levels of IL-17 may contribute to SLE-accelerated atherosclerosis.

- Dysregulation of B cells contributes to SLE and may be important in SLE-accelerated atherosclerosis. B_{reg} may be an important population to consider when examining SLE-accelerated atherosclerosis.

- IFNα levels are increased in SLE, and activity of this cytokine contributes to accelerated atherosclerosis in SLE.

Risk Factors

- SLE patients have a proatherogenic lipid profile, with reduced HDL and increased LDL and triglycerides. A dysfunctional form of HDL, piHDL, is found in SLE patients, contributing to LDL oxidation.

Prevention Approaches

- In 2010, Belimumab became the first therapy approved for SLE since the 1950s.

- Given their role in atherosclerosis and SLE, T cells might also be an attractive therapeutic target. Particularly, strategies to alter the T_{reg}/Th17 balance may prove effective.

- Other potential therapies for SLE-accelerated atherosclerosis include statins and apoA-I mimetics. Although the effects of statins on SLE-accelerated atherosclerosis have yielded conflicting results thus far, apoA-I mimetic peptides have not been studied in humans.

Table 1

The Role of T cells in SLE and Atherosclerosis

Statement	Experimental evidence	Clinical evidence
T cells contribute to atherosclerosis	**EVIDENCE SUPPORTING:**	
	T cells are present in atherosclerotic plaques of LDLr$^{-/-}$ and ApoE$^{-/-}$ mice (22)	T cells are present in human atherosclerotic plaques (21,23)
	CD4$^+$ T cells transferred into *scid/scid*, ApoE$^{-/-}$ mice increased atherosclerosis (25)	Th17 cells are present in human atherosclerotic plaques (49)
	Atherosclerosis is reduced in CD4$^{-/-}$, ApoE$^{-/-}$ mice (27)	
	Th1 bias results in increased atherosclerosis (28)	
	Th17 cells are present in atherosclerotic plaques (48)	
	Deficiency or neutralization of IL-17 results in up to 50% reduction in atherosclerosis (50,51)	
	EVIDENCE OPPOSING:	
	Bias towards Th2 reduces atherosclerosis (28)	
	Anti-IL17A treatment increased atherosclerosis, rIL-17A treatment decreased atherosclerosis (48)	
	Reduced T_{reg} or neutralization of TGFβ increased atherosclerosis (38, 39)	
T cells play a role in SLE pathogenesis	**EVIDENCE SUPPORTING:**	
	Depletion of CD4$^+$ T cells beneficial to SLE (29)	SLE T cells are hyperactive and have reduced threshold of activation (31)
	Thymectomized NZB/W mice did not develop SLE (30)	Increased survival, resistance to apoptosis by SLE T cells (33)
	Activated SLE T cells secrete inflammatory cytokines (32)	Th17 cells and IL-17 are increased in SLE (52)
	Th17 cells and IL-17 are increased in SLE (53)	Levels of circulating IL-17 correlate with disease activity (54)
	T_{eff} in SLE may become resistant to T_{reg} suppression (46)	IL-17 is increased during active nephritis (52)
		Th17/Th1 ratio is dysregulated, with increased Th17 (55)
		T_{eff} in SLE may become resistant to T_{reg} suppression (44,47)
	EVIDENCE OPPOSING:	
	T_{reg} deficiency results in severe autoimmune disease (40,41)	T_{reg} deficiency results in severe autoimmune disease (40,41)
	T_{reg} are reduced in SLE (42)	T_{reg} are reduced in SLE (43)
T cells contribute to increased CVD risk in SLE	In LDLr.S/e mice, atherosclerosis was increased, accompanied by infiltration of CD4$^+$ T cells into atherosclerotic lesions (12,35)	

T cell subsets can have divergent effects on both atherosclerosis and SLE, with Th1 and Th17 contributing to disease pathogenesis and T_{reg} protecting against disease.

Table 2

The Role of B cells in SLE and Atherosclerosis

Statement	Experimental evidence	Clinical evidence
B cells are atheroprotective	**EVIDENCE SUPPORTING:**	
	Increased atherosclerosis in B cell-deficient mice (57,58)	
	B_{reg} make IL-10, an atheroprotective cytokine (98,99)	
	T_{reg} are reduced in B cell-deficient mice (67)	
	EVIDENCE OPPOSING:	
	Depletion of mature B cells decreased atherosclerosis (59,60)	
	BAFF-R$_{-/-}$, ApoE$_{-/-}$ mice have reduced atherosclerosis (96,97)	
B cells contribute to SLE pathogenesis	**EVIDENCE SUPPORTING:**	
	B cells in SLE are hyperactivated and produce autoantibodies (8)	B cells in SLE are hyperactivated and produce autoantibodies (8)
	B cell dysregulation in SLE leads to T cell activation, DC recruitment, induction of Th1 and Th17 cells and inhibition of T_{reg} (64)	B_{reg} have reduced regulatory capacity (70)
	EVIDENCE OPPOSING:	
	B_{reg} suppress T cell-mediated inflammation (65–68)	
	B_{reg} reduce EAE (69), SLE (65,70), CIA (71)	

B cells are a major player in SLE pathogenesis, but the B_{reg} subset can be important for suppression of autoimmunity and may explain differing results concerning the role of B cells in atherosclerosis.

Table 3

Preventative Approaches for SLE-accelerated Atherosclerosis

Preventive approach	Experimental data	Clinical data
Rituximab	Reduced atherosclerosis in ApoE$^{-/-}$ and LDLr$^{-/-}$ mice (59,60)	EXPLORER and LUNAR trials did not reach treatment goals (90,91) Development of ulcerative colitis (92) or psoriasis (93) following treatment
Belimumab	BAFF-R$^{-/-}$, ApoE$^{-/-}$ mice have reduced atherosclerosis (96,97)	Moderately effective for SLE (94) Not effective in African American women (95)
CD40	Expansion of Breg through CD40 reduces autoimmunity (65)	
All-trans retinoic acid **(atRA)**	atRA and TGFβ increase T_{reg} suppressive function (102) atRA inhibits Th17 development (103)	Reduced induction of T_{reg} in SLE T cells by atRA (104)
Mycophenolate mofetil **(MMF)**	Reduced atherosclerosis (107) Atherosclerosis, CD4$^+$ T cells in atherosclerotic lesions and peripheral CD4$^+$ T cell activation reduced in LDLr.S/e mice (107)	Effective in treating SLE (106) No effects on CIMT or CAC (109)
Statins	Reduced atherosclerosis in gld.apoE$^{-/-}$ mice (11) No effects on atherosclerosis in apoE$^{-/-}$, Fas$^{-/-}$ mice (110)	Improved endothelial-dependent vasodilation in SLE (112) LAPS – no effects on CAC, IMT or endothelial activation in SLE (113) APPLE – no effect on CIMT in SLE
Hydroxychloroquine		Reduced accumulation of damage in SLE (115) Reduced inflammatory cytokines, including IFNα (116) Reduced serum cholesterol, reduced LDL cholesterol (117–120) Reduced aortic stiffness (121) Negative correlation between hydroxychloroquine treatment and atherosclerosis in SLE (88)
ApoA-l and mimetic peptides	Injection of ApoA-l led to decrease in autoimmune-like symptoms and improved Treg function in LDLr$^{-/-}$, ApoA-l$^{-/-}$ mice (122) L-4F reduced piHDL and circulating autoantibodies in apoE$^{-/-}$, Fas$^{-/-}$ mice (110) L-4F and pravastatin increased atherosclerosis but also increased lesion smooth muscle cell content and reduced macrophages in atherosclerotic lesions (110)	