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Accelerated Vascular Disease in Systemic Lupus Erythematosus: Role of Macrophage

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Abstract

Atherosclerosis is a chronic inflammatory condition that is considered a major cause of death worldwide. Striking phenomena of atherosclerosis associated with systemic lupus erythematosus (SLE) is its high incidence in young patients. Macrophages are heterogeneous cells that differentiate from hematopoietic progenitors and reside in different tissues to preserve tissue integrity. Macrophages scavenge modified lipids and play a major role in the development of atherosclerosis. When activated, macrophages secrete inflammatory cytokines. This activation triggers apoptosis of cells in the vicinity of macrophages. As such, macrophages play a significant role in tissue remodeling including atherosclerotic plaque formation and rupture. In spite of studies carried on identifying the role of macrophages in atherosclerosis, this role has not been studied thoroughly in SLE-associated atherosclerosis. In this review, we address factors released by macrophages as well as extrinsic factors that may control macrophage behavior and their effect on accelerated development of atherosclerosis in SLE.

Keywords

Macrophage; lupus; atherosclerosis; sphingolipids; lipoprotein immune complexes; autoantibodies

1. Introduction

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Atherosclerosis is a chronic inflammatory disease affecting the arterial intima (1), involving adaptive and innate immunological responses (2, 3). Noninvasive investigations have shown increases in intima-media thickness, carotid plaque build-up, and coronary artery

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calcifications in subjects with SLE (4). Atherosclerosis has been recognized as a major co-morbid condition in systemic lupus erythematosus (SLE) with a 5-10 fold increase in risk of developing cardiovascular disease (CVD) compared to age-matched controls (5). Women with SLE in the 35-44 year age group have an estimated 50-fold increased risk of myocardial infarction compared to age and sex-matched controls (6). Although patients with SLE are subject to the same traditional CVD risk factors (e.g., hypertension, dyslipidemia, diabetes, old age, tobacco use, and postmenopausal status) as the general population, several studies showed that these factors do not sufficiently account for the increased level of CVD in SLE patients (reviewed in 7-9). Controlling for traditional risk factors as defined by the Framingham studies, there is a substantial and statistically significant increase in CVD and stroke among SLE patients (10). It has been found, however, that 53% of patients with SLE had at least three traditional CVD risk factors (11). Some traditional risk factors may also interact with the management of SLE disease activity (e.g., smoking, diabetes and hyperlipidemia) (7). Systemic inflammation, anti-phospholipid antibodies, and low levels of the natural anti-phosphorylcholine antibodies are examples of non-traditional CVD risk factors in lupus (7-9). Anti-phospholipid antibodies (anticardiolipin antibody, anti- β 2-glycoprotein I, and lupus anticoagulant), which are usually generated against phospholipid binding proteins, have been associated with myocardial infarction in the general population (12). However, the association of anti-phospholipid antibodies with CVD in patients with SLE has been inconsistent (7). The underlying mechanisms responsible for the increase in morbidity and mortality due to SLE-related CVD remain unclear.

Atherosclerosis is identified by a passive accumulation of lipids in the vessel wall forming an atherosclerotic plaque. However, inflammation plays a role not only in the development of the atherosclerotic lesion but also in acute plaque ruptures resulting in acute myocardial ischemic events (13, 14). Lupus is an autoimmune disease in which the immune system attacks its own cells and tissues causing inflammation. A hallmark of both atherosclerosis and SLE-related inflammation is increased modification of lipoproteins and increased production of autoantibodies (15-18). In addition, SLE patients have a tendency to develop pro-atherogenic lipids (19, 20), and/or a defect in endothelial cell function (21). More specifically, SLE patients show decreased levels of high-density lipoproteins (HDL) with increased triglycerides and oxidized low-density lipoproteins (oxLDL) levels compared to healthy controls (22-24), thus predisposing them to coronary artery disease. Moreover, modified lipoproteins and circulating antibodies act in concert, accelerating chronic inflammation and the development of atherosclerosis largely by the transformation of monocytes into foam cells (25). While it is established that foam cell accumulation is a critical event in atherogenesis, the underlying mechanisms responsible for CVD intensification in SLE are not yet fully understood. Numerous studies have improved our understanding of the diverse components of immune dysregulation in SLE; however, the pathophysiologic role(s) of monocytes/macrophages remains unclear.

The macrophage is a heterogeneous cell that differentiates from hematopoietic progenitors which can generate dendritic cells, osteoclasts, and monocytes as well as macrophages (26). Monocytes circulate in the blood, but when activated reside in tissues as macrophages. Macrophages are active in both innate and adaptive immune responses, in addition to their known role in reverse cholesterol transport (27). They are also involved in normal tissue

homeostasis through the uptake and clearance of apoptotic cells, and in resorption of bone during normal bone remodeling (26). A classically activated macrophage requires both interferon gamma (IFN- γ) and either the induction of tumor necrosis factor alpha (TNF- α), or the engagement of toll-like receptors typically by a microbial product (28). In response, the macrophage secretes inflammatory cytokines such as interleukin-1 β (IL-1 β) and TNF- α , and chemokines that drive an immune reaction (29).

Theories formulated in the 1980s proposed that monocytes/macrophages in lupus display a defective phagocytic function, enabling the aberrant accumulation of apoptotic debris. This in turn can lead to a sequel of autoimmune events. However, studies exploring lupus nephritis suggested a more active role of monocytes/macrophages in mediating tissue inflammation and injury (30). The mechanisms by which SLE disease activity could be related to CVD have not been fully defined. The goal of this review is to focus on the role of monocytes/macrophages in developing accelerated vascular disease in SLE and describing the factors influencing the monocyte/macrophage function in this disease including inflammatory cytokines/chemokines, reactive oxygen and nitrogen intermediates, lipid profile changes, autoantibodies, and the potential role of bioactive sphingolipids in macrophage activation (**Figure 1**).

2. Macrophage phagocytosis, activation and proliferation

Defective clearance of apoptotic bodies by monocytes may present one model in which SLE patients may develop Atherosclerosis (31). The build-up of unphagocytosed apoptotic bodies can at once both present an important source of autoantigens and also, through natural degradation, release proteins and enzymes that exacerbate local inflammation. While defective phagocytosis has been proposed to contribute to the build-up of immune-complexes in lupus nephritis, studies using lineage-specific transgenic reconstitution of Fc- γ R in Fc- γ R knockout animals have suggested that the build-up of immune complexes in the kidney activate monocyte/macrophages (32). Additionally, it has been suggested that monocytes from SLE patients have impaired IL-12p70 secretion (T cell stimulating factor) leading to high levels of IL-10 release (33). Interestingly, while B cell-derived IL-10 is anti-inflammatory, monocyte-derived IL-10 leads to increased estradiol-2-mediated anti-dsDNA antibody release (34).

Monocytes/macrophages play a key role in the early pathogenesis of atherosclerosis by ingesting modified lipoproteins, transforming into lipid-laden foam cells, and recruiting additional monocytes and macrophages to the vessel wall. Many clinical observations also acknowledge the role for monocyte/macrophage activation in the pathogenesis of atherosclerosis and its complications (35), and were concordant with histological studies in which monocytes/macrophages were prominent in atherosclerotic lesions (36). These findings suggest that high levels of macrophage activation and inflammatory chemokines mediate atherosclerosis development in SLE patients. In fact, macrophage activation syndrome (MAS), a life-threatening inflammatory emergency of children with rheumatic diseases, is increasingly recognized in pediatric systemic lupus erythematosus (37). Recently, it has been shown that concentrations of neopterin, a marker of macrophage activation and IFN- γ activity, are increased in large cohorts of patients with SLE or

rheumatoid arthritis (RA), and have a more robust association with mediators of inflammation and homocysteine in SLE than in RA (38). More studies will be required to determine whether the increased concentrations of neopterin in patients with SLE could reflect a greater burden of unstable atheromatous plaque, or an increase in the processes by which stable plaque becomes unstable.

It has been recently suggested that expansion of macrophages necessary for pathogen control or wound repair can occur without recruitment of potentially tissue-destructive inflammatory cells. It has been found that proliferation of local macrophages (F4/80 negative) rather than recruitment from the blood (F4/80 positive) is fundamental in T helper-related inflammation (39). In aortas obtained from lupus mice lacking *NOS2* or *NOS3* genes encoding inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS), respectively, we have shown that F4/80-positive macrophages are mostly in the center of the nodule-like lesions found in the adventitia (40). Furthermore, sphingosine kinase (SK), the enzyme that generates sphingosine 1-phosphate (S1P), was found present in abundance around the F4/80-negative macrophages in the periphery of the lesion (40). It is now established that S1P promotes cell division and proliferation (41). It has been previously shown that the more advanced the atherosclerotic lesion, the greater the cell infiltration in the adventitia (42), predominantly the infiltration of B lymphocytes (42, 43). B-cells from RA patients are resistant to Fas-mediated apoptosis due in part to heightened SK activity and increased levels of S1P that can inhibit apoptosis and regulate lymphoid migration from the lymph node (44, 45). Hence, it is reasonable to suggest that increased SK levels in aortic lesions may be generating S1P, thus promoting B-cell infiltration and production of auto-antibodies that include anti-oxLDL IgG required to form oxLDL immune complexes (oxLDL-IC) (40). The oxLDL-IC-induced S1P generation that we have shown in human monocytic cells can lead to macrophage proliferation in the aorta and could expose more auto-antigens to be recognized by auto-antibodies generated locally (40). More studies to identify the exact role of macrophages in SLE are needed in order to mitigate the deleterious complications of this disease.

3. Inflammatory chemokines and cytokines in the pathogenesis of atherosclerosis in SLE

Atherosclerotic lesions begin with the recruitment of inflammatory cells such as monocytes and T cells to the endothelial wall. In response to this recruitment, the endothelial cells release leukocyte adhesion molecules like E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) (46). The expression of adhesion molecules can be induced by pro-inflammatory cytokines such as TNF- α and IL-1, both of which up-regulate leukocyte adhesion molecules in an NF- κ B-dependent process (46). A recent study by Gerry et al showed that a modest decrease in extracellular pH (pH of 7.0) can have marked effects on NF- κ B activation and cytokine secretion in macrophages (47). Atherosclerotic lesions, as well as other sites of chronic inflammation, such as rheumatoid joints and tumors, have areas of low extracellular pH. It remains to be investigated whether this mechanism occurs in SLE patients.

VCAM-1 is induced when endothelial cells are exposed to lipopolysaccharides of gram negative bacteria, and oxidized phospholipids such as oxLDL (48, 49). Conversely, HDL inhibits the expression of adhesion molecules (50, 51). The soluble levels of VCAM-1 have been found elevated in humans with coronary artery disease (52, 53). However, in one cross sectional carotid ultrasound study of SLE patients neither levels of soluble VCAM nor ICAM were significantly associated with carotid plaque (54).

After the adherence of the leukocytes to the cell surface, they migrate through the endothelium into the intima (46). This transmigration occurs due to several chemotactic proteins including monocyte chemotactic protein-1 (MCP-1) produced by the smooth muscle layer and endothelial cells (55). MCP-1 expression in endothelial cells and smooth muscle cells can be up-regulated by cytokines such as TNF- α , and IL-1, as well as by oxLDL (55, 56). The elevated levels of MCP-1 in the circulation are positively correlated to increased carotid artery intima media thickness in humans (57). In addition, in LDLR^{-/-} mice (a model for atherosclerosis), knockout of MCP-1 reduces the atherosclerosis induced by a high-fat diet (58). It has been shown that patients with SLE have increased concentrations of pro-inflammatory IL-6 and MCP-1 and that these cytokines correlate with some traditional coronary risk factors (59).

Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine with roles in several inflammatory diseases. MIF has emerged as a potential link between SLE and atherosclerosis development (60, 61). Elevated levels of serum MIF have been detected in SLE patients compared with healthy control individuals. MIF also induces the pro-inflammatory mediators TNF- α , IL-1, IL-6 and matrix metalloproteinases. It can activate T cells, promote angiogenesis and induce proliferation of cells, while inhibiting p53 expression and apoptosis of the same cells (61, 62). MIF can be induced by oxLDL, which is an initiating factor in atherogenesis, and so expression of MIF early on may enhance pro-inflammatory responses and lesion progression (62). The role of MCP-1 and MIF in atherosclerosis and SLE suggest that both are likely promising targets to treat the accelerated vascular disease in lupus.

In atherosclerosis, macrophages also play an important role in remodeling the plaque morphology. Macrophage activation leads to the secretion of pro-inflammatory cytokines and cytotoxic substances. The following cytokines secreted by activated macrophages are thought to play a role in the development of the atherosclerotic plaque

3.1. TNF- α

TNF- α constitutes an activating cytokine and a maturation factor of dendritic cells, which are essential in immune regulation and have also been implicated in autoimmunity in general, and in SLE in particular (63). In addition, the elevated circulating levels of TNF- α in SLE patient have been found to be associated with high triglyceride and low HDL levels (64). TNF- α and IL-1 enhance production of macrophage colony stimulating factor (M-CSF), granulocyte-monocyte colony stimulating factor, and granulocyte colony stimulating factor by smooth muscle cells, endothelial cells, and monocytes (65). These mediators activate monocytes and stimulate their transformation into macrophages and foam cells (66). It has been shown for example that inhibition of TNF- α decreased the progression of

atherosclerosis in apolipoprotein E knockout mice (67). Whereas the association of TNF- α with human coronary atherosclerosis has been documented; its role in SLE-related atherosclerosis remains to be evaluated.

3.2. Interferon gamma (IFN γ)

IFN γ has also been detected in human plaques (46). IFN γ acts as a powerful growth inhibitor for smooth muscle cells, endothelial cells, and collagen production, thus promotes plaque instability (68). IFN γ has been shown to influence many features of atherosclerosis such as foam cell formation, the adaptive TH1-specific immune response and plaque development (69). IFNs, (IFN α , and IFN γ) are often profoundly dysregulated in SLE and induce B lymphocyte stimulator expression (70). IFN γ also improves the efficiency of antigen presentation, and leads to increased synthesis of TNF- α and IL-1 (71). Eid *et al.* reported a concomitant presence of IL-17 and IFN γ in patients and clinical specimens of coronary atherosclerosis (72). Both IL-17 and IFN γ increase T cells within coronary plaques, and a synergistic effect of IL-17 and IFN γ play an important role in the elicitation of pro-inflammatory cytokine and chemokine production by cultured human vascular smooth muscle cells (72). Significant evidence implicates IL-17 (produced by T cells) in the pathogenesis of SLE (73).

3.3. IL-1

The main role of IL-1 is to promote inflammation. In human atherosclerotic plaques, the expression of IL-1 α and IL-1 β seems to correlate with the progression of atherosclerotic plaques, with minimal expression in healthy coronary arteries, increased expression in simple atherosclerotic plaques, and high expression in complicated plaques (74). Experimental studies in atherosclerosis-prone animals have constantly revealed that genetic deletion or pharmacological inhibition of IL-1 signaling reduces the establishment and progression of atherosclerotic plaques, whereas increased IL-1 activity (by exogenous administration of IL-1 β or down regulation of the naturally occurring receptor antagonist IL-1Ra) favors its progression (75, 76). Bone marrow chimeric studies recognized IL-1 signaling in the vessel wall, rather than in leukocytes, as a major determinant of atheroma formation (77, 78). IL-1 has been associated with lupus through correlation between lupus activity and IL-1 and IL-1Ra levels, as well as IL-1 genetic polymorphism (79).

3.4. IL-6

IL-6 is another cytokine, whose level is elevated in patients with SLE. IL-6 is produced by a wide range of cells including macrophages, lymphocytes and others. It acts in a paracrine, autocrine and endocrine fashion on target cells (80). IL-6 shares similar biological effect with IL-1. Elevated IL-6 levels have been considered as markers for atherosclerosis and inflammation in patients with SLE as well as for disease activity (81).

3.5. IL-12

Monocytes exposed to oxLDL result in the production of IL-12 (82). Moreover, it has been found that IL-12 levels were elevated in atherosclerotic plaques (83). Inhibition of IL-12 using a vaccination technique that fully blocks the action of IL-12 led to decrease

atherosclerosis in mice (83). STAT4, which is a key transcription factor induced in response to IL-12 in macrophages, is implicated in the pathogenesis of autoimmune diseases, such as SLE, RA, Type 1 diabetes and systemic sclerosis (84).

3.6. IL-10

IL-10 is an anti-inflammatory, regulatory cytokine that inhibits Th1 cytokine production and proliferation of CD4⁺ T cells via its indirect effects on antigen presenting cell function or through direct effects on T cells (85). IL-10 secretion disturbs the initial segment of inflammation by impeding the attachment of circulating immune cells to the endothelial wall by down-regulating adhesion molecules such as CD18, CD60L, and ICAM-1 (86). Yin et al showed that knocking out IL-10 in a lupus mouse model leads to develop severe lupus in these mice, and they had higher mortality than their IL-10 intact littermate controls (87). However, enhanced IFN γ production by both CD4 and CD8 cells and increased serum concentration of IgG2a anti-dsDNA autoantibodies were associated with the severity of the lupus in this model (87). Our recent findings showed that plasma level of IL-10 in the NOS2 and NOS3 knockout MRL/lpr mice significantly decreased compared to controls (40). Modulation of the level of IL-10 and more complete understanding of the interplay between IL-10, immune-complexes, and IFN α may identify a target that can be of potential therapeutic benefit for human lupus.

It is important therefore to find a link between chronic inflammation and the initiation and progression of vascular stiffening and atherosclerosis. Comprehensive characterization of the cytokines involved in the pathway of accelerated vascular complication in SLE is important to find the safest and most effective pharmacologic approaches to limit the flare up of this disease.

4. Reactive oxygen and nitrogen intermediates and accelerating vascular disease in SLE

There are two forms of nitric oxide synthase (NOS), inducible NOS (iNOS), and endothelial NOS (eNOS). SLE patients display a defect in eNOS functions that leads to reduced endothelium-dependent vasodilation (88). This results in increased vascular lesion formation, thus contributes to the severity of atherogenesis (89-91).

Nitric oxide (NO) has a dual effect on the cellular processes based on its concentration. NO can have a protective and proliferative effect at a concentration range 30-100nM (92). However, concentrations above 400nM can lead to cell cycle arrest and apoptosis, and more than 800nM of NO may cause nitrosative stress with the formation of N₂O₃ (93). Mitochondrial NO can combine with superoxide to form a peroxynitrate (ONOO⁻), which nitrates cytochrome c, leading to mitochondria-mediated apoptosis. On the other hand, NO in the cytoplasm has an anti-apoptotic effect (94). ONOO⁻ also can oxidize lipids such as those found in LDL or arachidonic acid (95). Antibodies to the oxidized LDL and β 2 glycoprotein I complexes were shown to be elevated in SLE. This antibody/antigen complex enhances oxLDL influx into foamy macrophages, providing a mechanism for accelerated atherosclerosis in SLE (96). In vascular tissue of murine models of lupus, prostacyclin

synthase (97) and eNOS (98) are inactivated by ONOO-, a by-product of iNOS activity, leading to vasoconstriction. This suggests that iNOS activity has a pathogenic effect via deactivation of tissue protective enzyme.

Based on experimental evidence and clinical studies, oxidative and nitrosative stresses have been shown to be induced by atherosclerosis risk factors and to contribute to the onset and development of atherosclerotic vascular damage (99). There are several independent studies which have demonstrated a significant correlation between markers of systemic NO production and global lupus disease activity (100). Oates *et al.* demonstrated more increase in markers of NO production among African-Americans with lupus disease activity (101). It has been shown that excess production of reactive oxygen species and reactive nitrogen species has been implicated with vascular lesion formation and functional defects (102, 103), and are currently being pursued as possible new biomarkers for lupus (100). Recently we showed that human monocytic cells treated with free oxLDL had decreased mitochondrial membrane potential and significantly increased intracellular H₂O₂ and NO compared to cells treated with the vehicle alone (104).

In an attempt to study the effect of the iNOS inhibitor drug SD-3651 on prevention of SLE glomerulonephritis, it was shown that the drug prevented endothelial cell and podocyte pathology in MRL/lpr lupus mouse model lacking iNOS gene (105). However, the drug might have also acted via a non iNOS-mediated mechanism, indicating that other mechanisms can be involved in SLE. Our previously published findings suggest that advanced vascular disease in *NOS2* and *NOS3* knockout MRL/lpr mice may be caused by increased plasma triglycerides, ceramide and S1P; decreased plasma IL-10; and accumulation of oxLDL-IC in the vessel wall (40). This information provides a rational to develop therapeutic interventions that may modify the harmful effects of iNOS. Also, restoration of eNOS function may be another approach that can be used to treat SLE and prevent the flare up of its complications

5. Modified lipoproteins in SLE-associated atherosclerosis

One of the known mechanisms of atherosclerosis is that LDL particles are transported into artery walls, where they are trapped and bound to the extracellular matrix of the sub-endothelial space. These trapped LDL particles are then modified by reactive oxygen species, resulting in the formation of pro-inflammatory oxLDL (106). Cytokines such as MCP-1 and M-CSF are released when the endothelial cells are exposed to oxLDL, resulting in monocyte binding, chemotaxis, and differentiation into macrophage (107). It has been shown that SLE patients have higher levels of circulating oxLDL, especially in those with a history of CVD (17, 108). The higher levels of circulating oxLDL are strongly associated with coronary artery disease in the general population (109).

Several mechanisms by which oxLDL can be cleared from the sub-endothelial space have been previously described. One of these mechanisms is the macrophage engulfment of oxLDL by scavenger receptors (110, 111), then macrophages become foam cells around which atherosclerotic lesions are built (112). The other mechanism is enhanced reverse cholesterol transport mediated by lipoprotein transporters in HDL (113, 114). In addition,

HDL removes reactive oxygen species from LDL, thus preventing the formation of oxLDL and subsequent recruitment of inflammatory mediators (107). Moreover, it has been shown that normal HDL inhibits the expression of MCP-1 (115).

It is now established that oxLDL complexed to IgG (oxLDL-IC) can be internalized by macrophages and this process is mediated primarily through cross-linking of FC γ receptors on the cell surface and results in the release of pro-inflammatory cytokines (116, 117). We found that oxLDL-IC can induce an immediate translocation and release of SK1 into the medium (116), which indicate that S1P may be generated extracellularly in response to oxLDL-IC and may therefore promote cell survival and prolong cytokine release by activated macrophages. We have also found that oxLDL-IC can induce the synthesis and release of heat shock protein 70B' (HSP70B'), and once stimulated, HSP70B' binds to the cell-associated and internalized lipid moiety of oxLDL-IC (118). The data implicated HSP70B' in the regulation of SK1 activity and release of IL-10, which influence macrophage activation and survival (118). The cross-linking of the FC γ receptors can also induce the secretion of acid sphingomyelinase, which can bind to oxLDL-IC and allows for the uptake and trafficking of the complex (119). We also showed that treatment of U937 macrophage with exogenous sphingomyelinase increases the uptake of oxLDL-IC (119). Interestingly, activated acid sphingomyelinase induced by oxLDL-IC also stimulates the release of exosomes containing IL-1 β (119).

It has been shown that low levels of HDL are associated with increased risk of atherosclerosis (120). Also, during the acute phase response (occurring soon after the onset of infection, trauma, inflammatory processes, and some malignant conditions) HDL can be converted from anti-inflammatory state to pro-inflammatory and can usually cause increased oxidation of LDL (121). This acute phase response can become chronic, and may be a mechanism for HDL dysfunction in SLE (122). The pro-inflammatory HDL is significantly associated with carotid plaque and intima media thickness in patients with SLE (123). Moreover, in a study undertaken to determine the role of HDL in SLE, 45% of SLE patients were found to have abnormal HDL function, compared to 20% of RA patients and 4% of control patients, and had pro-inflammatory HDL that was not only unable to prevent oxidation of LDL but caused increased level of oxidation (24).

The interplay between HDL function, LDL oxidation, and macrophage activation might be a possible mechanism that can mediate vascular disease in SLE. Therefore, early detection of the levels of oxLDL and the pro-inflammatory HDL may identify the SLE patients at high risk of clinical atherosclerosis. Furthermore, HDL modification in SLE patients may protect from developing blood vessel complications.

6. Autoantibodies to modified lipoproteins in SLE

Elevated levels of antibodies against oxLDL in the general population and their role in the prediction of myocardial infarction and the progression of atherosclerosis have been previously described (124-126). Up to 80% of patient with SLE have elevated anti-oxLDL antibodies (16, 18, 109), and the titers of antibodies to oxLDL have also been associated with disease activity in SLE (15). Furthermore, SLE patients generate autoantibodies which

form complexes with the lipid metabolizing enzyme lipoprotein lipase with a consequent dyslipoproteinemia characterized by elevated levels of very low-density lipoproteins and triglycerides and lower HDL levels. This pattern favors an enhanced LDL oxidation with a subsequent detrimental foam cell formation (127). Serum IgG anti-apoA1, anti-HDL, and anti C-reactive protein (CRP) were higher in patients with SLE compared to controls. In addition, the persistence of disease activity is associated with significant increase in IgG anti-apoA1 and anti-HDL but not anti-CRP (128).

Immune complexes have also been described as a risk factor for atherosclerosis in the general population. In a study of 257 healthy men, the levels of circulating immune complexes at age 50 correlated with the development of myocardial infarction (126). Several *in vitro* studies showed that lipoprotein-containing immune complexes may play a role in atherogenesis. For instance, macrophages that ingest these complexes become activated, and release TNF- α , IL-1, oxygen activated radicals, and matrix metalloproteinase-1 (129). In several studies of SLE subjects, lipoprotein-containing immune complexes have been examined, with different results. In one study of a pediatric SLE population, there was an increase in the level of anti-oxLDL IgG and IgG immune complexes with LDL in SLE subjects compared to healthy controls; however, there was no association with endothelial dysfunction (16). Another study showed that the levels of autoantibodies to oxLDL are elevated in SLE patients with CVD compared to SLE control patients with no CVD (17). On the other hand, Romero et al showed that anti-oxLDL IgG was not associated with arterial disease in SLE patients (130). Recently, we showed that in a lupus mouse model, oxLDL-IC can accumulate in the blood vessel wall but mainly in the adventitia (40). This controversy on the role of immune complexes in the contest of accelerated vascular disease in lupus warrants further studies.

7. Sphingolipids and vascular complications in SLE

Sphingolipids are ubiquitous constituents of bio-membranes and their metabolic products sphingomyelin, ceramide, sphingosine, and S1P are involved in the regulation of cell growth, differentiation, and apoptosis by acting as messengers in specific signal transduction pathways (131, 132). There is strong evidence that NO-activated pathways regulate many of the biological processes in which sphingolipids are involved (133, 134). Ceramides are one of the lipid components that make up sphingomyelin, which is one of the major lipids in the cell membrane lipid bilayer. Ceramide generation can also occur through breakdown of complex sphingolipids that are ultimately broken down into sphingosine. Sphingosine is a carbon amino alcohol with an unsaturated hydrocarbon chain, which forms primary structures of sphingolipids. Sphingosine can be phosphorylated *in vivo* via two kinases, SK1 and SK2 leading to the formation of the bioactive molecule S1P (135, 136).

S1P is a blood borne lipid mediator, in particular in association with lipoproteins such as HDL (137-139). High concentrations of S1P are present in body fluids and at lower levels in tissues (135). In a study designed to test the ability of serum sphingolipids to predict obstructive coronary artery disease, serum S1P was found to be a remarkably strong and robust predictor of both the occurrence and severity of coronary stenosis (140). We have previously reported that S1P is able to induce increases in released TNF- α , cyclooxygenase,

and prostaglandin E2 in macrophages *in vitro* (141). Recently, we showed that levels of S1P in MRL/lpr mice lacking the eNOS and iNOS genes were significantly higher compared to their counterpart controls (40). Increased production of S1P has been linked to various pathological conditions suggesting that it may be a target for therapy for disorders such as cancer (142), atherosclerosis, and autoimmune diseases such as SLE and multiple sclerosis (143). A study by Snider *et al.* showed that inhibition of SK2 activity in MRL/lpr mice using the specific SK2 inhibitor ABC294640 can improve the glomerular pathology (144). Both S1P and dihydrosphingosine 1- phosphate (dh-S1P) levels in the circulation were significantly reduced with the SK2 inhibitor; however, kidney levels of dh-S1P were elevated. The authors suggested that inhibition of SK1 or perhaps both SK isoforms would better prevent elevations in circulating S1P and dh-S1P and potentially better protect against lupus nephritis (144).

It has been suggested that the sphingomyelin content of lipoprotein particles may influence lipid metabolism by affecting binding or activity of lecithin-cholesterol acyltransferase and lipoprotein lipase (145). However, sphingomyelin-rich lipoproteins can be converted to foam cell substrates by sphingomyelinase in the artery wall thereby promoting foam cell formation (146). Moreover, ceramide and related products of sphingomyelin synthesis and breakdown are potent regulators of cell proliferation, activation, and apoptosis and hence may affect plaque growth and stability (146).

Sphingomyelin in cellular membranes has a high affinity for cholesterol with which it associates in lipid rafts (147). T cells from SLE patients have been reported to contain larger lipid rafts compartments and that the lipid rafts formed are more robust when compared to T cells derived from normal individuals (148). The generation of these rafts was correlated with an increased response to CD3 cross-linking. Moreover, treatment of MRL/lpr mice with the immunosuppressor FTY720, an S1P receptor antagonist, induced apoptosis in double-negative splenic T cells and suppressed the development of SLE in these mice (149). It has been shown that natural killer (NK) T cell ablation decreases the total infiltration of macrophages in intra-abdominal adipose tissue (150). It has also been shown that in lupus patients NK cells up-regulates the secretion of anti-DNA antibodies(151). Morshed *et al.* showed that treatment with β -galactosylceramide, a glycolipid that reduces the cytokine secretion, down-regulated NK cell activity in NZB/W mice and ameliorated the symptoms of SLE (152). In contrast, repeated administration of α -galactosylceramide, a marine sponge-derived glycolipid that potently activates both mouse and human NK cells, led to the expansion of NK cells that could inhibit the development of inflammatory dermatitis in MRL/lpr mice (153) and pristane (hydrocarbon oils)-induced SLE in BALB/c mice. However, pristane could exacerbate SLE symptoms in SJL mice, known mouse model for immunological defects (154).

Recently Nowling *et al.* found early and significant dysfunction of the glycosphingolipid metabolic pathway in the kidneys of lupus mice and patients with lupus nephritis and suggested that molecules in this pathway may serve as early markers in lupus nephritis (155). Future studies can be directed towards finding therapeutic targets to modulate sphingolipid metabolic pathway which may have anti-atherogenic effects with eventual protection from accelerated vascular disease in the SLE patients. Furthermore, the

development of methods to determine levels of circulating bioactive sphingolipids (156) in SLE patients and validation of these methods to be a routine clinical laboratory test could be a pioneering diagnostic and prognostic approach to SLE therapy.

8. Conclusions

In conclusion, SLE-associated atherosclerosis is a serious health problem for patients with SLE. More factors are involved in the development of this condition with SLE than with non-immune associated atherosclerosis. Many of these factors are cytokines and chemokines released by inflammatory cells, most significantly activated macrophages. Given the pivotal role of macrophages in the development, remodeling and thus stability of plaque in SLE, it is suggestive that macrophages play a similar role in the acceleration of development of atherosclerosis in SLE taking into consideration the amount of immune dysregulation associated with SLE. Future studies should be directed towards regulatory mechanisms of macrophage functions that can be targeted therapeutically to improve the outcome of SLE-associated atherosclerosis.

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Abbreviations

SLE	systemic lupus erythematosus
CVD	cardiovascular disease
oxLDL	oxidized low-density lipoprotein
oxLDL-IC	oxidized low-density lipoprotein immune complex
HDL	high-density lipoprotein
dsDNA	double stranded DNA
IFNγ	interferon gamma
TNFα	tumor necrosis factor alpha
IL-1α	interleukin 1 alpha
IL-1β	interleukin 1 beta
VCAM-1	vascular cell adhesion molecule-1
ICAM-1	intercellular adhesion molecule-1
MCP-1	monocyte chemotactic protein-1
MIF	macrophage migration inhibitory factor
CRP	C-reactive protein
SK	sphingosine kinase

S1P	sphingosine 1- phosphate
dh-S1P	dihydrosphingosine 1- phosphate
RA	rheumatoid arthritis
NO	nitric oxide
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
M-CSF	macrophage colony stimulating factor
ONOO-	peroxynitrate
HSP70B'	heat shock protein 70B'
NK cells	natural killer cells

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Highlights

- Accelerated atherosclerosis is a serious health problem for patients with SLE
- Macrophages play a role in tissue remodeling including plaque formation and rupture
- Macrophages release factors that accelerate development of atherosclerosis in SLE
- Extrinsic factors can control macrophage behavior in SLE
- Measuring and targeting sphingolipids in SLE can be a novel approach to therapy

Figure 1. Schematic representation of putative macrophage-related mechanisms contributing to accelerated atherosclerosis in SLE

Atherosclerotic plaques begin with the recruitment of inflammatory cells such as monocytes and T cells to the endothelial lining of the blood vessel. The endothelial cells release leukocyte adhesion molecules (e.g., VCAM-1, ICAM-1 and E-selectin) to facilitate sub-endothelial cell migration. MIF and MCP-1 levels are elevated in SLE patients and lead to increased pro-inflammatory cytokines. Increase in the production of reactive oxygen and nitrogen species (ROS and RNS) has been implicated in vascular lesion formation. LDL modified by the effect of ROS results in the formation of oxidized LDL (oxLDL). SLE and other autoimmune diseases produce autoantibodies which form complexes with either lipid metabolizing enzymes like lipoprotein lipase or with apolipoproteins and slow down lipoprotein catabolism, which may produce varieties of dyslipidemia. oxLDL complexed to IgG (oxLDL-IC) can be internalized by macrophages and results in the release of pro-inflammatory cytokines and promotes plaque formation. Pro-inflammatory HDL has been strongly associated with the development of carotid plaques and with intima media thickness in SLE patients. Targeting key metabolizing enzymes in the sphingolipid pathway (e.g., sphingomyelinases, ceramidases, and sphingosine kinases) that regulate the generation of the bioactive lipids sphingomyelin (SM), ceramide (Cer), sphingosine (Sph), and sphingosine 1- phosphate (S1P) in activated macrophages and foam cells might avert accelerated vascular disease in SLE.