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Atherosclerosis and Systemic Lupus Erythematosus— Mechanistic Basis of the Association

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Premature atherosclerosis (ATH) has been recognized as a major co-morbid condition in systemic lupus erythematosus (SLE). Women with SLE in the 35-44 year old age group have an estimated 50-fold increased risk of myocardial infarction (MI) compared to age and sex matched controls [1]. Women with SLE also have an increased incidence of subclinical atherosclerosis; in a recent study using carotid ultrasounds, a 37.1 % prevalence of carotid atherosclerosis was found in lupus patients compared to 15.2% of controls [2]. Although traditional risk factors as defined by the Framingham studies (hypertension, hypercholesterolemia, diabetes mellitus, older age, post-menopausal status) are important in increasing risk for ATH in SLE, they do not adequately explain the increase in cardiovascular disease. In a Canadian cohort, after controlling for traditional risk factors, the relative risk attributed to SLE for myocardial infarction (MI) was 10.1 and for stroke 7.9 [3]. It has increasingly become evident that inflammation and immune mechanisms play an important role in the pathogenesis of atherosclerosis in SLE.

For many years, the development of atherosclerosis in the general population was regarded as a passive accumulation of lipids in the vessel wall. Recently, however, it has been realized that inflammation plays a role not only in the development of the atherosclerotic lesion, but also in the acute rupture of plaques that occurs during acute myocardial ischemic events [4,5]. As in the pathogenesis of SLE itself, the interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules, complement, as well as antibodies promotes damage of endothelium and formation of the plaques and vascular smooth muscle hypertrophy that narrow arteries in atherosclerosis [6].

The Role of Inflammation in the Pathogenesis of Atherosclerosis

The Recruitment of Inflammatory Cells to the Arterial Wall

Atherosclerotic lesions begin with the recruitment of inflammatory cells such as monocytes and T-cells to the endothelial wall. First, the vascular endothelial cells are stimulated to express leukocyte adhesion molecules, including E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) [6]. These cell-surface proteins are upregulated during periods of inflammation. For example, the expression of adhesion molecules can be induced by pro-inflammatory cytokines such as Tumor Necrosis Factor- α (TNF- α) and Interleukin-1 (IL-1), which upregulate leukocyte adhesion molecules in an NF-

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κB dependent process [6]. VCAM-1 is also induced when endothelial cells are exposed to other inflammatory signals, such as the lipopolysaccharides of Gram-negative bacteria, lysophosphatidylcholine (LPC), and oxidized phospholipids such as oxidized low density lipoprotein (OxLDL) [7,8]. High density lipoproteins (HDL) inhibit the expression of adhesion molecules [9,10].

The importance of these adhesion molecules in the development of atherosclerosis is highlighted by the fact that atherosclerosis-prone apoE deficient mice who are also deficient in E-selectin develop fewer plaque lesions [11]. Also, soluble levels of VCAM-1 can be detected in the systemic circulation, and elevated levels of this adhesion molecule have been found in humans with coronary artery disease [12,13]. In one cross sectional carotid ultrasound study of SLE patients, however, neither levels of soluble VCAM nor ICAM were significantly associated with carotid plaque [2]

After leukocytes adhere to the cell surface, they migrate through the endothelium and into the intima [6]. This transmigration is influenced by several factors; first, several chemotactic proteins such as monocyte chemoattractant protein-1 (MCP-1) are produced by the endothelial and smooth cell layers [14]. The expression of MCP-1 in smooth muscle cells and endothelial cells can be upregulated by cytokines such as TNF-α and IL-1 and by OxLDL [14,15]. Conversely, normal HDL inhibit the expression of MCP-1 [16]. The importance of MCP-1 in the development of the atherosclerotic plaque is emphasized by the fact that elevated circulating levels of MCP-1 are positively related to increased carotid artery IMT in humans [17]. Also, in LDLR^{-/-} mice, knockout of MCP-1 reduces the atherosclerosis induced by high fat diets [18].

Low Density Lipoproteins and the Development of Foam Cells

Next, low density lipoproteins (LDL) are transported into artery walls, where they become trapped and bound in the extracellular matrix of the subendothelial space [19]. These trapped LDL are then seeded with reactive oxygen species (ROS) produced by nearby artery wall cells, resulting in the formation of pro-inflammatory oxidized LDL [19]. When endothelial cells [20] are exposed to these pro-inflammatory OxLDL, they release cytokines such as MCP-1, M-CSF, and GRO, resulting in monocyte binding, chemotaxis, and differentiation into macrophages [20]. The OxLDL are phagocytized by infiltrating monocytes / macrophages, which then become the foam cells around which atherosclerotic lesions are built [21]. Elevated levels of circulating OxLDL are strongly associated with documented coronary artery disease in the general population [22]. Elevated levels of circulating OxLDL have also been described in SLE patients, especially in those with a history of cardiovascular disease [23,24].

Next, monocytes and T cells infiltrate the margin of the plaque formed by foam cells [21], and muscle cells from the media of the artery are stimulated to grow [25]. These muscle cells encroach on the lumen of the vessel and ultimately lead to fibrosis, which renders the plaques brittle. The occlusion that results in MI can occur when one of these plaques ruptures, or when platelets aggregate in the narrowed area of the artery [25].

Normal HDL Clears OxLDL from the Endothelium: Abnormal pro-inflammatory HDL Associate with Accelerated Atherosclerosis

There are many mechanisms designed to clear OxLDL from the subendothelial space, including macrophage engulfment using scavenger receptors [26,27], and enhanced reverse cholesterol transport mediated by lipoprotein transporters in HDL [28-31]. In addition to reverse cholesterol transport, HDL removes reactive oxygen species from LDL (via anti-oxidant enzymes in the HDL, such as paraoxonase), thus preventing the formation of OxLDL and the subsequent recruitment of inflammatory mediators [20,32].

Thus, although quantities of HDL partially determine atherosclerotic risk (low levels are associated with increased risk), HDL function is equally significant [33]. For example, during the acute phase response HDL can be converted from their usual anti-inflammatory state to pro-inflammatory, and can actually cause increased oxidation of LDL [34]. This acute phase response can also become chronic [35], and may be a mechanism for HDL dysfunction in SLE. Indeed, our group has found that HDL function is abnormal in many women with SLE; 45% of women with SLE, compared to 20% of rheumatoid arthritis patients and 4% of controls, had pro-inflammatory HDL (piHDL) that was not only unable to prevent oxidation of LDL but caused increased levels of oxidation [36]. In this study, 4 of 4 SLE patients with a history of documented atherosclerosis had pro-inflammatory HDL, further suggesting that HDL play an important role in the pathogenesis of atherosclerosis. In preliminary data, published to date in abstract form, 86% of patients with SLE who had plaque on carotid ultrasound had piHDL, compared to 39% who do not have plaque ($p < 0.0001$) [37]. This suggests that detecting piHDL may identify SLE patients at high risk for clinical atherosclerosis. The interplay of LDL, HDL and OxLDL with endothelial activation, monocyte migration, foam cell formation, and reverse cholesterol transport is illustrated in Figure 1.

The Contribution of Adaptive Immunity to the Pathogenesis of Atherosclerosis

T-cells, primarily of the Th1 subtype, are abundant in atherosclerotic lesions, and may play a role in the formation of plaque through the cascade of cytokines that is initiated by their activation [38]. At least two stimuli for Th1 differentiation are present in the atherosclerotic plaque. IL-12 is expressed by macrophages, smooth muscle cells, and endothelial cells, and is an important stimulus for Th1 differentiation [39]. IL-12 production is upregulated in monocytes exposed to oxidized LDL [39]. Elevated levels of IL-12 have been found in atherosclerotic plaques [39], and the inhibition of IL-12 using a vaccination technique that fully blocks the action of IL-12 has been shown to decrease atherosclerosis in mice [40].

IFN- γ has also been detected in human plaques [6]. It is a powerful growth inhibitor for smooth muscle cells, endothelial cells, and collagen production, and thus promotes plaque instability [41]. IFN- γ also improves the efficiency of antigen presentation, and leads to increased synthesis of TNF- α and IL-1 [42]. All of these actions contribute to the formation of the atherosclerotic plaque, and indeed, in atherosclerosis-prone apoE $-/-$ mice who are also IFN- γ $-/-$, atherosclerosis is decreased by nearly 60% [43,44]. The administration of IFN- γ also accelerates atherosclerosis in apo-E knockout mice. Increased serum levels of both IFN- γ and IL-12 have been found in humans with unstable and stable angina compared with controls [45].

TNF- α and IL-1 are also present in human atherosclerotic lesions. Like IFN- γ , they also affect smooth muscle proliferation. TNF- α and IL-1 induce local inflammation in blood vessels by stimulating the activation of macrophages [33], inducing the secretion of matrix metalloproteinases [46], and promoting the expression of cell surface adhesion molecules [6]. Additionally, TNF- α and IL-1 enhance production of M-CSF, GM-CSF, and G-CSF by smooth muscle cells, endothelial cells, and monocytes. These mediators activate monocytes and stimulate their transformation into macrophages and foam cells [47]. Inhibition of TNF- α decreased the progression of atherosclerosis in apoE knockout mice [48]. Elevated levels of TNF- α may also play a role in the increased risk of atherosclerosis in the general population [49]. TNF- α has been linked to vascular injury in both acute and chronic inflammatory conditions. TNF- α has been identified in human endothelial and smooth muscle cells in all stages of atherosclerosis, from early intima thickening to established occlusive atherosclerosis [50,51]. The role of major cytokines and chemokines in atherosclerosis is summarized in Table 1.

Autoantibodies, Immune Complexes and Atherosclerosis

Antibodies may also play a role in the pathogenesis of atherosclerosis. Circulating antibodies to OxLDL (anti-OxLDL) have been described, although their relationship to the development and progression of atherosclerosis is unclear. Elevated levels of antibodies against OxLDL have been described in the general population, and in some studies are predictive of MI and the progression of atherosclerosis [52,53]. Other studies, however, have not found any such correlations [6,54]. Similarly, the presence of antibodies to OxLDL has uncertain significance in subjects with SLE. Anti-OxLDL have been described in up to 80% of patients with SLE and antiphospholipid antibody syndrome [22,55-57]. Titers of antibodies to OxLDL have also been associated with disease activity in SLE [58]. At least one study has demonstrated that autoantibodies to OxLDL are more common in SLE patients who have a history of cardiovascular disease than in SLE controls or normal subjects [23], although in two other studies, anti-OxLDL and arterial disease were not associated [59,60].

There is some speculation that the increased risk of thrombotic and atherosclerotic events seen in patients with SLE and antiphospholipid antibodies may be due in part to a cross-reactivity between anticardiolipin and OxLDL [55]. Cardiolipin is a component of LDL, [61] and indeed, a cross-reactivity between anti-cardiolipin and anti-OxLDL antibodies has been demonstrated [55]. Additionally, β_2 -glycoprotein I (β_2 -GPI), the protein recognized by most antibodies to cardiolipin, has been shown to bind directly and stably to oxidized LDL [62]. These OxLDL - β_2 -GPI complexes have been found in patients with SLE and antiphospholipid antibody syndrome (APS), and are associated with a risk of arterial thrombosis [63]. Interestingly, there is enhanced uptake of OxLDL/ β_2 -GPI complexes by macrophages, likely mediated by macrophage FC γ receptors [64]. Thus, OxLDL - β_2 -GPI complexes may contribute to atherosclerosis by increasing formation of foam cells.

Immune complexes (IC) have also been described as a risk factor for atherosclerosis in the general population. In one prospective study of 257 healthy men, the levels of circulating immune complexes at age 50 correlated with the future development of MI [65]. In vitro studies have also suggested that LDL containing immune complexes may play a role in atherogenesis. Macrophages that ingest LDL-IC become activated, and release TNF- α , IL-1, oxygen-activated radicals, and matrix metalloproteinase-1 [66]. LDL-containing immune complexes have been examined in several studies of SLE subjects, with varying results. In one study of a pediatric SLE population, there was an increase in levels of IgG LDL-immune complexes in SLE subjects compared to healthy controls, although there was no association with endothelial dysfunction [57]. Another study of an adult SLE population, however, demonstrated no difference from controls in levels of IgG or IgM LDL-containing immune complexes [24].

Innate Immunity in Atherosclerosis

In addition to the role the adaptive immune response plays in the pathogenesis of atherosclerosis, there is accumulating evidence that innate immunity also plays a role in the formation of plaques. In contrast to adaptive immunity, the components of innate immunity are essentially present at birth, and allow for immediate host defenses until adaptive responses mature. The receptors of innate immunity are known as "pattern recognition receptors" (PRRs); these receptors bind to preserved motifs on various pathogens which are termed "pathogen-associated molecular patterns" (PAMPs). Toll-like receptors (TLRs) are one type of PRR that respond to various PAMPs by activating their intracellular signaling pathway, leading to the activation of NF- κ B, and the upregulation of immune responsive genes. The ligands for Toll-like receptors can include either microbial ligands or endogenous ligands, which may explain some of the connections that have been postulated to exist between infectious organisms such as *Chlamydia pneumoniae* and the development of atherosclerosis. Examples of microbial ligands include Heat shock protein 60 (Hsp60) from *C. pneumoniae*, which has been shown

to trigger inflammatory responses via interactions with TLR4 [67], and bacterial lipopolysaccharide (LPS), which binds to both TLR2 and TLR4 [68,69]. LPS binds to the receptor CD14, which is anchored to the cell membrane via glycosyl-phosphatidylinositol (GPI). The CD14/LPS complex associates with TLR4 and its adaptor protein MD-2. The signaling domain of TLR4 then transduces the signal and triggers pro-inflammatory gene expression [70].

Endogenous ligands can also trigger TLR signaling in a manner similar to microbial ligands. For example, minimally oxidized LDL also interacts with TLR4, with CD14, and with CD36 [70]. When oxidized LDL binds to the CD14 receptor on macrophages, there is a dramatic increase in the cellular content of polymerized actin, resulting in accelerated cell spreading. This oxLDL induced cell spreading leads to the inhibition of phagocytosis of apoptotic cells, and enhanced expression of the scavenger receptor CD36, which leads to increased uptake of OxLDL. Both of these effects are thought to be pro-inflammatory and pro-atherogenic [71].

Indeed, there is further evidence to support the hypothesis that TLR4 signaling is relevant to atherosclerosis. C3H/HeJ mice carry a mutation in the TLR4 gene, and appear to be resistant to atherosclerosis [72]. In addition, mice with this mutation lose the ability to respond to oxidized LDL with macrophage spreading [71]. Similarly, atherosclerosis-prone mice with a deficiency in MyD88, one of the TLR signaling molecules, had a reduction in plaque size, decreased macrophage recruitment to the artery cell wall, and decrease in pro-inflammatory cytokine and chemokine production [73]. Furthermore, humans with the D299G polymorphism have attenuated TLR4 receptor signaling, and have been shown to have a decreased risk of atherosclerosis [74].

Animal Models of Atherosclerosis and Lupus

There are animal models of atherosclerosis and systemic lupus-like disease. Among the more interesting are the apoE^{-/-} mouse with mutations in Fas or FasL (lpr for Fas; gld for FasL). All these animals are derived from C57Bl/J. In the gld.apoE^{-/-} mouse, atherosclerosis and autoimmunity are both increased compared to gld or apoE^{-/-} mice, and treatment with simvastatin decreases atherosclerotic lesion size in the aorta, autoantibody titers and nephritis [75]. In the apoE^{-/-}-Fas^{-/-} mouse, atherosclerosis is accelerated and there is significant increase in total IgG, IgG anti-dsDNA, IgG anti-cardiolipin and IgG anti-OxPL as well as dramatic acceleration of proliferative glomerulonephritis [76]. Osteoporosis was also present. IgG antibodies to OxPL correlated strongly with severity of glomerular lesions and bone loss. These animal models provide substantial opportunity to investigate connections between pro-inflammatory lipids, oxidized lipids, the immune responses to those molecules, and the tissue damage that can result. In addition, they provide excellent models for testing of novel therapeutic interventions.

Conclusions

In conclusion, atherosclerosis is a complicated inflammatory process characterized by the interactions of components of both adaptive and innate immunity. As in the pathogenesis of many lupus disease processes, the increased risk of atherosclerosis seen in SLE is likely due to the complex interplay of many of these inflammatory and immune mediators. Expanding our understanding of the pathogenesis of atherosclerosis in SLE is critical if we are to improve the quality of care and improve mortality in this vulnerable population.

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HDL Inhibit the Oxidative Modification of LDL

Adapted from Mackness MI et al. *Biochem J* 1993. Lipids Online 2004 (Baylor)

Figure 1.

Illustration of interaction of LDL, endothelial release of chemokines, entrance of monocytes into artery wall, formation of OxLDL, engulfment of OxLDL by macrophages to form foam cells. HDL interrupt this atherosclerotic process by reverse cholesterol transport by lipoprotein in the HDL and by prevention of oxidation of LDL by anti-oxidative enzymes such as paroxonase in the HDL.

Table 1

Some atherogenic cytokines and their mechanisms

Cytokine	Expressed By	Induced By	Biological Function	Evidence for role in ATH	References
MCP-1	Smooth muscle cells, foam cells	TNF- α IL-1 OxLDL Complement Elevated Homocysteine Inhibited by HDL	Chemotactic factor for Monocytes	Increased MCP-1 levels related to carotid artery IMT	[14,15] [77] [18,78] [17]
TNF- α IL-1	Endothelial Cells, Macs, T-cells, foam cells	IL-6 Inhibited by HDL	Activate Macs Increase adhesion molecules Increase SAA Increase MCP-1	Increased TNF- α levels increase ATH risk	[33] [46] [6] [79] [47] [48] [49] [50] [51]
IFN- γ	T-cells, foam cells		Inhibit SMCs, EC, collagen instability Increase TNF- α , IL-1 Inhibit LPL Prime Macs for activation Increase CD40L	Increased IFN- γ in unstable angina	[6] [6] [41] [80] [42] [43,44] [45]
IL-12	Macs, SMCs, ECs	OxLDL	Th1 differentiation	Increased levels seen in ATH plaques	[39] [40] [45]

ATH= atherosclerosis
CRP=C-reactive protein
EC= endothelial cell
LPL=lipoprotein lipase
Macs=macrophages
OxLDL= oxidized LDL
SAA= serum amyloid A
SMC= smooth muscle cells