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The role of the immune system in atherosclerosis: molecules, mechanisms and implications for management of cardiovascular risk and disease in patients with rheumatic diseases

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Abstract

Rapid-onset cardiovascular disease is a major concern for many patients suffering from SLE. Cardiovascular events are more frequent and occur much earlier in SLE patients compared to healthy controls. Traditional risk factors such as altered lipid levels, older age and smoking do not fully explain the increased risk of cardiovascular disease, strongly suggesting that autoimmunity contributes to accelerated atherosclerosis. Altered immune system function is recognized as the primary contributor to both the initiation and progression of atherosclerosis. Multiple manifestations of autoimmunity, including autoantibodies, altered cytokine levels and innate immunity response, adipokines, dysfunctional lipids, and oxidative stress appear to contribute to atherosclerotic risk. In addition, multiple SLE therapeutics appear to affect the development and progression of atherosclerosis both positively and negatively. SLE-specific biomarkers for identifying patients at risk of developing accelerated atherosclerosis are starting to be identified by multiple groups, and a comprehensive, clinically testable biomarker panel could be invaluable for identifying and treating these patients.

Introduction

Atherosclerosis, once believed to be caused by passive lipid deposits into arterial walls subsequently covered by smooth muscle and endothelial cells, is now known to be a dynamic accumulation of oxidized cholesterol over time that is primarily driven by the immune system[1]. Not surprisingly, many diseases defined by autoimmunity and immune system dysfunction are associated with significantly increased morbidity and mortality due to cardiovascular disease (CVD), often defined by accelerated atherosclerosis. Researchers and physicians studying accelerated atherosclerosis in SLE have three major goals: understanding the biological differences in pathology that define autoimmune CVD versus non-autoimmune CVD, identifying at-risk patients before the onset of atherosclerosis, and developing therapeutic options for prevention of atherosclerosis progression. In this Review, we will discuss the epidemiology and pathogenesis of SLE-driven atherosclerosis, the essential role of a dysregulated immune system in the progression of CVD, and strategies for minimizing and treating atherosclerosis in SLE.

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Epidemiology : Increased risk of atherosclerosis in systemic lupus erythematosus (SLE) and subclinical measures

Increased risk of CVD in SLE was first described 35 years ago[2]. Early deaths (<1 year) were due to SLE disease activity, and later deaths were primarily due to CVD[2]. Subsequent analysis confirmed this bimodal pattern of SLE death, although more recent data suggest that due to improvements in SLE diagnosis and treatments, CVD and infection are the leading causes of SLE mortality, regardless of time following diagnosis[3].

The overall risk of myocardial infarction (MI) in SLE patients is 10-fold higher than in the general population, even after accounting for traditional Framingham risk factors[4]. This risk is even more pronounced in young SLE women aged 35-44-years old, who were over 50 times more likely to have a MI than age-matched women in the Framingham Offspring Study[5].

Despite the increased risk of cardiovascular events in the SLE population in general, the absolute number of events per year in any given cohort is relatively small; thus, recent research into biomarkers of atherosclerosis and treatment strategies in SLE has focused on measuring multiple surrogate (subclinical) measures of atherosclerosis. In a cross-sectional study By utilizing carotid ultrasound as a surrogate measure of atherosclerosis, multiple groups, both cross-sectionally and longitudinally, found that carotid plaque increased more that two-fold in SLE patients versus controls and progressed significantly faster in this SLE cohort[6–9]. More than four times as many SLE patients have coronary calcification versus healthy controls, as measured by electron beam computerized tomography (11). Using dual-isotope single photon emission computed tomographic (SPECT) myocardial perfusion imaging, 38% of SLE patients had perfusion defects indicating subclinical atherosclerosis. More than half of SLE subjects examined also have endothelial dysfunction, measured by flow-mediated dilation, versus 26% of controls[10]. There is also evidence that in addition to abnormalities of the macrovasculature in SLE, there is abnormal coronary microvascular function as well, as abnormal Coronary Flow Reserve (CFR) (measured using positron emission tomography scanning) was seen even in SLE patients with normal coronary arteries[11]. It should be noted, however, that although these measures of subclinical atherosclerosis are significantly linked to coronary events in the general population[12], only abnormal myocardial perfusion has been linked to cardiovascular events in SLE.

Pathogenesis of atherosclerosis in SLE

It is unclear why patients with SLE and other autoimmune diseases are at increased risk of atherosclerosis. Traditional (Framingham) cardiac risk factors[13] contribute to atherosclerosis but do not fully explain the increased CVD risk in SLE[4]. As atherosclerosis is currently appreciated as a process intimately intertwined with the immune system, multiple aspects of autoimmunity most likely contribute to accelerated CVD in concert with traditional cardiac risk factors.

Initiation and progression of atherosclerosis and the essential role of immune cells

Monocyte and T cell recruitment to the arterial wall—Accumulation of low density lipoproteins (LDL) in the subendothelial space, followed by the oxidation of LDL (oxLDL) by reactive oxygen species (ROS) and the activation of endothelial cells (EC) in the artery, are commonly regarded as initiating events in atherogenesis (Figure 1). Monocytes attach to EC via upregulated adhesion molecules on both cell types and upregulated cytokine release (MCP-1, IL-6, TNFα)[14].

After monocytes adhere to endothelial cells, they migrate to the intima and differentiate into macrophages. Monocyte activation is globally higher in SLE, but monocyte activation does not correlate with increased coronary atherosclerosis[15] (Figure 1).

T cells are also recruited to nascent plaques by similar mechanisms, although at lower numbers. These T cells are generally Th1 CD4+ cells that secrete pro-inflammatory and pro-atherogenic IFNγ.

Progression of the atherosclerotic plaque and prevention of CVD by HDL— Macrophages phagocytose abundant oxLDL and become foam cells, and form the basis of the plaque lesion. Smooth muscle cells (SMC) then grow around the expanding lesion and encroach on the vessel lumen, leading to fibrosis (Figure 1). MI can occur when a plaque ruptures or after platelet aggregation in an occluded artery[14].

HDL protect against atherosclerosis in two major ways. First, reverse cholesterol transport (RCT), where cholesterol and phospholipids shuttle out of foam cells, is mediated by the interactions of lipoproteins in HDL with lipid transporters on foam cells. The lipoprotein ApoA-I, the most abundant protein component in HDL, is necessary in promoting RCT[16].

The second major mechanism for the protective capacity of normal HDL is their antioxidative function. Both proteins and lipids in LDL are protected from accumulation of oxidation products by the presence of normal HDL (Figure 1).

Vascular damage and endothelial cell dysfunction in SLE—In addition to early-onset atherosclerosis, SLE patients are at risk of accelerated vascular damage versus healthy controls. Blood flow at the forearm, brachial artery, and heart is significantly impaired in SLE patients[17, 18]. Recent work suggests that, in SLE, vascular damage is accelerated and vascular repair mechanisms are ineffective. SLE patients have high levels of circulating apoptotic EC – indicating increased vascular damage - and lower levels of circulating endothelial progenitor cells (EPC) that repair damaged arterial tissues[19, 20]. Generation of reparative myelomonocytic circulating angiogenic cells (CAC) is also impaired. Secretion of IFNα, largely by plasmacytoid DC (stimulated in part by low density granulocytes undergoing NETosis, also increased in SLE patients)[21] induces EPC apoptosis[21] and converts CAC to dendritic cells, thus losing ability to repair vascular damage to EC[20].

Immune system molecules and particles involved in atherosclerosis

Autoantibodies

Antiphospholipid antibodies (aPL): Data on the role of aPL in promoting atherosclerosis in humans is mixed[22]. Patients with primary antiphospholipid syndrome have thicker carotid intima media thickening (CIMT) at multiple artery sites than controls, especially those > 40 years old[23]. Higher aPL levels correlate with increased MI risk in healthy men[24, 25]. However, even though about half of SLE patients have aPL[26], there is little agreement on whether the presence of aPL correlates with accelerated atherosclerosis[6, 8, 9, 27–29], Patients with aPL syndrome do not have significantly more EC dysfunction[30]. aPL, therefore, might contribute to a “2-hit hypothesis” where circulating aPL contribute to early EC dysfunction via interaction with beta2 glycoprotein 1 in vascular walls but other thrombotic events are probably necessary to trigger plaque and clot formation.

Anti-oxLDL antibodies: IgM antibodies that recognize oxLDL are generally considered to be protective against atherosclerosis in murine models[31], although, paradoxically, the presence of anti-oxLDL antibodies increases risk for atherosclerosis in humans with SLE. A recent study suggests that anti-oxLDL antibodies develop after of anti-lipoprotein lipase

autoantibodies are detected and are responsible for increased atherosclerotic risk in an SLE cohort with high disease activity[32]. The underlying mechanism behind why IgG anti-oxLDL antibodies are atherogenic is unclear, but decreased immune complex clearing (e.g., SLE nephritis) or the presence of aggregated oxLDL in the subendothelial space could explain the increased atherosclerotic risk.

Anti-apoA-I antibodies: Approximately 20% of non-autoimmune patients with acute coronary syndromes have circulating anti-apoA-I antibodies[33], suggesting these autoantibodies might play a role in atherosclerosis development. Anti-apoA-I antibodies were noted in 32.5% of SLE patients and 22.9% of patients with primary antiphospholipid syndrome (APS)[34] and presence of these antibodies correlate with increased disease activity[35]. As apoA-I is a major anti-inflammatory component of HDL, it is presumed (but not known) that anti-apoA-I autoantibodies render the atheroprotective capabilities of apoA-I and HDL ineffective. Future work in the general population and SLE should address this and whether the presence of anti-apoA-I antibodies correlate with atherosclerosis initiation and progression.

Cytokines: Immune cells communicate with each other and other tissues in the body by secreting small proteins called cytokines. Many cytokines are found in atherosclerotic plaques and are known to contribute, both positively and negatively, to plaque development and progression, in nonautoimmune subjects (reviewed recently in[36]). Much less is currently known about the role many of these cytokines play in SLE accelerated atherosclerosis – somewhat surprising, given that dysregulated immunity defines SLE - although this area of research is the focus of many groups and will certainly be better understood in the future. Th1 T cells are abundant in atherosclerotic lesions. *IFNγ* is the prototypical Th1 cytokine and promotes plaque instability by inhibiting growth of SMC, EC and collagen production[37]. IFNγ promotes foam cell formation as well as plaque rupture[38], although no studies have directly examined the role of IFNγ in SLE-driven accelerated atherosclerosis.

IL-12 is expressed by macrophages, SMCs, and ECs, and is a major cytokine involved in Th1 differentiation. High levels of IL-12 have been found in atherosclerotic plaques in non-autoimmune subjects[39].

TNFα and *IL-1* are potent macrophage activators and can lead to arterial inflammation and EC dysfunction.[40]. Additionally, TNFα and IL-1 stimulate monocyte differentiation into macrophages/foam cells. High plasma TNFα levels[41, 42], along with high TNF receptor levels[41], have been observed in SLE patients with CVD. Conversely, lower IL-1 levels promote IFNα-driven vascular damage in SLE[43], suggesting the pro-angiogenic effects of IL-1 are both beneficial (in promoting vascular repair) and deleterious.

IL-6 is an independent marker of increased mortality in CVD through C-reactive protein (CRP) production. Its role in atherosclerosis progression in SLE is unclear; high levels of IL-6 are linked to atherosclerotic risk in certain cohorts[44, 45], but not in other cross-sectional[6] and longitudinal[46] studies.

IL-17 is secreted from a novel T cell phenotype (Th17 cells) and is believed to promote SLE disease activity[47]. Contradictory data exist in regard to the role of IL-17 in non-autoimmune CVD[36], although two recent papers suggest that IL-17 promotes atherosclerosis in autoimmune diseases. An atherosclerosis-prone mouse model treated with the common SLE therapeutic mycophenolate mofetil (MMF) decreased IL-17 levels along with size of aortic plaques and T cell infiltrates[48]. In addition, impaired endothelial function correlates with high IL-17 levels in RA patients (SLE data is not currently known)[49].

Although data is currently scarce, regulatory T cells are believed to play a protective role in atherosclerosis initiation[50]. The Treg cytokine *TGF*β, in contrast to the cytokines above, is probably protective against plaque formation in the general population[51]. Low serum TGFβ levels have been linked to increased CIMT and LDL in SLE[52]. *IL-10* also appears to prevent atherosclerosis in a mouse model of atherosclerosis[36]. However, in a study using the same mouse model transplanted with murine SLE bone marrow, reduction in plaque size by MMF treatment associated with lower IL-10 levels[53]. These data suggest IL-10 might have different atherogenic properties in SLE, or that MMF non-specifically targets IL-10-producing Tregs.

Innate immunity

Toll-like receptors (TLRs) are a family of receptors on multiple immune cells that mediate innate immunity. There are multiple TLR ligands, including bacterial cell wall components that have been linked to atherosclerosis development[54].

Endogenous ligands, such as lipids and nucleic acids, can also trigger TLR signaling. When oxLDL binds TLR4 and CD14 on macrophages, apoptotic cell phagocytosis is inhibited, the scavenger receptor CD36 is upregulated, and oxLDL uptake is increased, leading to atherosclerosis initiation[55].

The roles of TLRs and innate immunity in atherosclerosis specific to rheumatic diseases are poorly understood. Aberrant activation of TLR7 and 9, resulting in IFNα upregulation, is linked to higher SLE disease activity[56].

Biomarkers: How traditional and autoimmune-specific risk factors play into risk for atherosclerosis in SLE

Framingham atherosclerosis risk factors

As defined by the Framingham heart studies, traditional risk factors for CVD are older age, male gender, smoking, high total cholesterol and LDL levels, high systolic blood pressure, diabetes, and left ventricular hypertrophy. A comprehensive review of the epidemiology of traditional cardiac risk factors to atherosclerosis in SLE was recently published in this journal[57]. The influence of traditional risk factors in CVD in SLE appears to be different than the nonautoimmune population, and the main focus of the clinician should be treating SLE while monitoring traditional CVD risk[57].

SLE-associated risk factors for atherosclerosis

Disease activity, duration, and damage—Associations between SLE disease manifestations and atherosclerosis are not clear. One cross-sectional study suggested that higher disease activity (measured by the SLAM index) was significantly associated with less plaque, but longer disease duration positively correlated with plaque[8]. In another cross-sectional cohort, longer disease duration was also significantly associated with higher coronary calcium[58]. Similarly, longer SLE duration and higher levels of damage from lupus indepentently predicted carotid plaque in a cross-sectional[6] and longitudinal study[7] from a different cohort.

Pro-inflammatory HDL (piHDL)—Although HDL quantities partially determine atherosclerotic risk, HDL function is equally significant. For example, during the acute phase response HDL can be converted from their usual anti-inflammatory state to pro-inflammatory, and cause increased LDL oxidation (Figure 1). This acute phase response can also become chronic, and may be a mechanism for HDL dysfunction in rheumatic diseases. Indeed, our group has found that HDL function is proinflammatory (piHDL) in many

women with SLE[59]. A follow-up study illustrated that 85% of SLE patients with carotid plaque have piHDL[28]. piHDL have also been identified as an independent risk factor in RA[59, 60] and aPL syndrome[61].

Oxidative stress—Oxidative stress - excess of ROS not counterbalanced by an adequate antioxidant defense system - associates with accelerated atherosclerosis in the general population. Increased oxidative stress has been identified in SLE patients, and is often elevated independent of disease activity. In one study, increased oxidative stress (F2 isoprostane excretion) was associated with patient-reported symptoms in SLE but not with inflammation or damage[62].

Homocysteine—High homocysteine levels have been linked to atherosclerosis in the general population[63]. Homocysteine is toxic to EC[64], is prothrombotic[65],[66], decreases nitric oxide availability[67], and stimulates foam cell formation[68]. High homocysteine levels result from both genetic background and diet. Some studies show that elevated homocysteine levels in SLE correlated with cross sectional[58, 69–72] and longitudinal progression[7, 46] of subclinical atherosclerosis, but other studies showed no correlation[6, 9, 73]. Renal insufficiency is a known cause of elevated homocysteine levels[74], but the relationship between renal function and hyperhomocysteinemia in SLE has not been fully established.

Adipokines/adipose-derived hormones—Adipokines, produced by white adipose tissue, regulate metabolism and energy homeostasis. The main function of *leptin* is to suppresses appetite in the hypothalamus, but leptin signaling also contributes to atherosclerosis progression[75]. Elevated leptin levels have been observed in adult[76] and pediatric[77] SLE. In addition, serum leptin levels are higher in SLE patients with carotid plaque versus patients without[78].

In contrast, high serum *adiponectin* levels are associated with low levels of adipose tissue and risk for atherosclerosis and metabolic syndrome, and adiponectin levels are lower in patients with CVD. Data on the link between adiponectin and atherosclerosis are limited and contradictory: in one study, adiponectin levels were associated with carotid plaque[79], but no correlation was found between adiponectin or leptin levels with coronary calcification in another SLE cohort[80].

Strategies for minimizing risk of accelerated atherosclerosis in SLE

Minimizing Framingham risk factors

It is likely that novel “SLE-specific” risk prediction panels will be developed and validated in the future for identification of high-risk patients who should be targeted for therapeutic interventions to prevent cardiovascular complications. Currently, however, our screening and treatment strategies are extrapolated from the best available evidence for the general population. Expert panels in the US and Europe recommend that SLE patients be annually screened for traditional modifiable risk factors for cardiovascular disease, including smoking status, blood pressure, BMI, diabetes, and serum lipids (including total cholesterol, HDL, LDL, and triglycerides)[81, 82]. There are no randomized clinical trials for atherosclerosis prevention specifically in SLE, however, so current guidelines for modifying cardiovascular risk factors in a SLE patient population are essentially strategies for treating CVD in the general population.

Smoking—Smoking has been identified as a modifiable atherosclerosis and CVD risk factor, and smoking cessation is recommended for SLE patients[82].

Diabetes Mellitus—Diabetes is considered to be a coronary artery disease equivalent by the National Cholesterol Education Panel (NCEP) guidelines[83], so treatment goals for diabetic lupus patients should aim to establish and maintain glycemic control, including minimization of glucocorticoid doses.

Hypertension—The ideal blood pressure for SLE patients is 130/80, as recommended by the Joint National Committee (JNC 7), and is the same as for patients with other high-risk co-morbid conditions[84, 85]. Difficulty in prevention trial recruitment has prevented the establishment of an optimum atheroprotective medication regimen in SLE[86]. ACE inhibitors, however, should be first-line therapy in SLE patients with renal involvement[87], and the EULAR guidelines also recommend them as first line therapy in hypertensive patients with inflammatory arthritis because of their potential favorable effects on inflammatory markers and EC function in RA[88]. Angiotensin receptor blockers (ARB) can also be considered in patients who cannot tolerate ACE inhibitor therapy. Thiazide diuretics are recommended by as first line therapy for hypertension in the general population by JNC 7, and would generally also be a safe choice in SLE subjects (although caution should be used, as thiazide diuretics also have dyslipidemic and diabetogenic effects)[85]. β–blockers have been shown to precipitate Raynaud's phenomenon[89], and thus should be used with caution in SLE subjects.

Treatment of Hypercholesterolemia: Statins—Statins are competitive inhibitors of HMG-CoA reductase and are widely used to reduce cardiovascular morbidity. In addition to their lipid lowering properties, statins also have a number of anti-inflammatory properties, including inhibition of inflammatory cytokines, ROS formation, T-cell activation, and upregulation of nitric oxide synthesis[90]. However, data for statin use in atherosclerosis prevention in SLE is inconsistent. For instance, in a short-term (8 week) trial, atorvastatin improved EC-dependent vasodilation, even after controlling for traditional cardiac risk factors[91]. In a longer (2 year) atorvastatin trial however, statins did not prevent progression of coronary calcium, IMT, or disease activity, and did not result in any significant improvements in measures of systemic inflammation or EC activation[92]. Preventive trials in the general population have utilized much larger sample sizes and longer study durations than the SLE studies, however[93]. Data from mouse models of atherosclerosis in lupus have also been inconsistent; although statins resulted in improvement in atherosclerosis in one SLE mouse model[94], in $LDLr^{-/-}$ mice reconstituted with bone marrow from SLE-prone mice, statins failed to attenuate atherogenesis despite reductions in cholesterol levels[53]. Therefore, the effectiveness of statin treatment to prevent atherosclerosis progression in SLE is unclear and physicians prescribing statins for SLE patients should adhere to guidelines from the National Cholesterol Education Panel[83].

Disease Modifying Agents in SLE: Implications for Atherosclerosis Prevention

Anti-malarial therapeutics—Hydroxychloroquine (HCQ) is believed to be cardioprotective (although there are isolated reports of HCQ cardiotoxicity[95]), and HCQ use has been associated with less aortic stiffness[96] and less plaque on carotid ultrasound[6] in SLE. Additionally, anti-malarials minimize steroid-induced hypercholesterolemia[97]. In addition, HCQ may be associated with reduced thrombotic events and improved survival in SLE patients[98]. HCQ might be cardioprotective in part because it blocks TLR 7 and 9[99]. TLR 7 and 9 stimulation lead to increased IFNα, which, as discussed above, is implicated in EC dysfunction and abnormal vascular repair.

Glucocorticoids—Longer duration and high cumulative glucocorticoid treatment has been associated with atherosclerosis in SLE patients[8, 28, 69, 70, 100]. Additionally, prednisone doses >10mg/day have been shown to independently predict high cholesterol levels in

SLE[101]. Conversely, lower predisone use and dosage correlates with *more* plaque in a different cohort[6], suggesting that there might be an optimal window of glucocorticoid therapy where anti-inflammatory effects of steroids can be atheroprotective. Until such a threshold is determined, we recommend following the EULAR recommendations that the lowest possible dose of corticosteroids be used in individual patients[88].

Mycophenolate mofetil (MMF)—MMF, an immunosuppressive agent used frequently in SLE patients, has several potential anti-atherogenic effects. MMF has been shown in animal models to inhibit NADPH-oxidase, thereby inhibiting oxidative stress[102]. In patients with carotid artery stenosis, 2 weeks of MMF therapy resulted in decreased plaque expression of inflammatory genes and activated T cells with increased numbers of regulatory T cells[103]. In $LDLr^{-/-}$ mice reconstituted with SLE-prone bone marrow, MMF treatment significantly reduced atherosclerotic burden and recruitment of $CD4^+$ T cells to atherosclerotic plaques[53]. In addition, a retrospective study in diabetic renal transplant patients found that there was a 20% decrease in cardiovascular mortality among patients treated with MMF compared to those with immunosuppressive regimens without MMF[104]. A small prospective observational study from our own group suggests that treatment with MMF and hydroxychloroquine for 12 weeks, but not azathioprine, results in significant improvement of pro-inflammatory HDL function (McMahon, unpublished data). In a recently published longitudinal SLE cohort study, however, exposure of subjects to MMF was not associated with a reduction of IMT or coronary calcium progression[105]. Larger, prospective studies will need to be undertaken to clarify the potential role of MMF in prevention of progression of atherosclerosis in SLE.

Azathioprine—One retrospective case-control study of SLE patients with documented coronary artery disease found that patients with CAD were more likely to have been treated with azathioprine[106]. In multivariate analysis, azathioprine use was also associated with cardiac events in the multi-ethnic LUMINA cohort[27]. Azathioprine use was also associated with increased carotid IMT in the pediatric SLE APPLE cohort[107]. It is unclear if these associations are due to a direct effect of azathioprine, or the inability of azathioprine to overcome the inflammation that leads to atherosclerosis.

B cell directed therapies—Although not currently well understood, B cells might contribute to atherosclerosis progression. In contrast to monocytes and T cells, however, activated B cells appear to play a protective role, as the removal of B cells from atherosclerosis-prone mice lead to increased atherosclerosis[108, 109]. In addition, subsets of B cells produce atheroprotective molecules such as IL-10 and anti-oxLDL antibodies[110]. As anti-CD20 therapy depletes B cells, an unintended consequence of SLE therapy could be the risk of increasing CVD. Two studies, however, show that B cell depletion with anti-CD20 antibodies significantly reduced atherosclerosis in both the $ApoE^{-/-}$ and the $LDLr^{-/-}$ atherosclerosis-prone mouse models[111, 112]. Similar results have been observed in improvement of lipid profiles after anti-CD20 therapy in SLE patients[113], although, as observed with piHDL and statin therapy, improved lipid levels do not always predict less atherosclerosis. With the recent introduction of anti-CD20 and anti-BLyS therapies into clinical practice, it is unclear how B cell-directed therapy will impact atherosclerosis in SLE patients.

Novel therapeutics to prevent atherosclerosis

Peptides mimicking HDL-related proteins such as *apoA-I* and *apoJ* in the prevention of atherosclerosis are currently under intense study. ApoA-I and apoJ peptides convert piHDL back to normal HDL by removing oxidation from oxLDL and HDL[114]. Thus, normal activity of anti-inflammatory HDL is restored and LDL are protected from oxidation. Both

the apoA-I peptide 4F and an apoJ peptide ([113–122]apoJ) improve vasodilation impairment and cause plaque regression in atherosclerosis animal models[114]. 4F treatment, alone or with pravastatin, significantly reduced SLE-like disease in a murine lupus/accelerated atherosclerosis model[115], and these therapeutics might be effective, non-toxic therapeutic options for SLE patients in the future.

Evidence for the role of *IFN*α at multiple points in the pathogenesis of atherosclerosis has recently emerged. Aberrant balance between apoptotic EC, lower numbers of EPC/CAC, and vasculogenesis as driven by IFNα was discussed above[20, 43, 116]. In addition, IFNα priming increases macrophage uptake of oxLDL[117]. Several IFNα inhibitors are currently in clinical trials for SLE, and future studies will be required to determine whether these medications are protective against atherosclerosis in SLE.

Should there be standardized guidelines for monitoring CVD risk in SLE patients?

EULAR has recently recommended that patients with SLE[118] and RA[88] be monitored for increased cardiac risk. The RA guidelines list ten unique parameters for evaluating CVD risk, including minimizing corticosteroid exposure, monitoring serum lipid levels, and traditional Framingham or Systematic Coronary Risk Evaluation (SCORE) risk. The SLE guidelines are not CVD-specific, and only one of the ten guidelines deals with CVD risk. Statin use is also recommended for RA patients, although, as discussed above, statin use might not be effective in slowing atherosclerosis in human and murine SLE. CVD-specific guidelines for SLE akin to the EULAR RA recommendations would be an effective tool for rheumatologists.

Conclusions

Atherosclerosis and CVD is a major cause of morbidity and mortality in multiple rheumatic diseases. We do not yet fully understand what causes accelerated autoimmune-specific atherosclerosis, but evidence strongly suggests that it relates to complex interplay between dysfunctional immune regulation, inflammation, traditional risk factors, aberrant endothelial cell function and repair, and therapeutics treating the underlying autoimmune disease. Recent data suggest that SLE-specific elements could contribute to increased atherosclerotic risk. A comprehensive biomarker panel incorporating these factors with more traditional CVD risk factors (homocysteine, lipid levels, etc.) could be an essential tool for identifying at-risk patients very early after rheumatic disease diagnosis. Clinical biomarker identification for some of these biomarkers remains in development (e.g., piHDL and EPC/CAC). The clinical complexity of accelerated atherosclerosis will most likely require an integrated approach for identification and treatment, and intensive study into this aspect of SLE will ultimately lead to improved cardiovascular outcomes for these patients.

Review Criteria

PubMed was searched in February, April, September and October 2011 for original and review articles in English using “lupus” along with the terms “atherosclerosis,” “vasculitis,” “cardiovascular,” “monocyte,” “therapy,” “review” and all titles of the subdivisions of this article (e.g., “antiphospholipid antibodies,” “IL-6,” etc.). Reference lists from relevant papers provided additional articles. No date restrictions were used in searches, but due to space restrictions more recent papers were sometimes cited when multiple papers had the same conclusions.

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Key Points

- Cardiovascular disease is a significant contributor to morbidity and mortality in SLE
- SLE-specific risk factors for accelerated atherosclerosis exist but are not well understood
- Endothelial cell dysfunction plays a major role in accelerated atherosclerosis in SLE
- Identification of SLE-specific mechanisms and biomarkers behind accelerated atherosclerosis should provide novel early detection screens and therapeutic targets

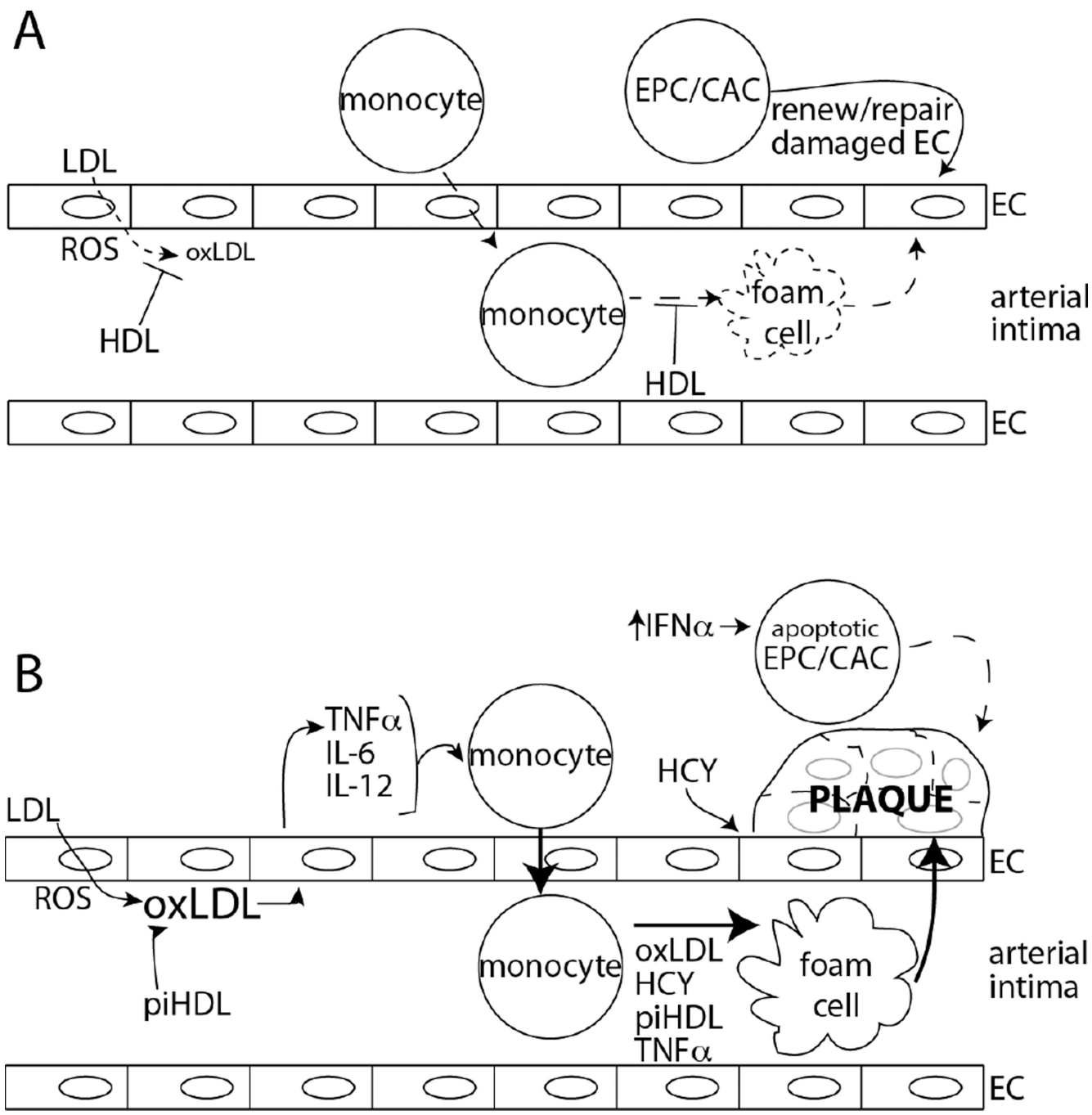

Figure 1.

Protection from and pathogenesis of atherosclerosis in SLE. A) Protective mechanisms from atherosclerosis: HDL protects LDL from oxidation by reactive oxygen species (ROS) in the arterial intima. In addition, HDL assists with reverse cholesterol transport and prevents the formation of lipid-rich foam cells, the precursor to plaque. Endothelial progenitor cells (EPC) and circulating angiogenic cells (CAC) are able to reseed and repair damaged pockets of arterial endothelial cells to minimize arterial damage. Dashed lines indicate minimized effect and influence of the cells or processes indicated. B) Initiation and progression of atherosclerosis in SLE: Pro-inflammatory HDL (piHDL), present in almost half of SLE patients, augments oxLDL production. EC release inflammatory cytokines after oxLDL

stimulation, stimulating monocytes to bind the EC layer and transmigrate into the intima. Monocytes then differentiate into foam cells, assisted by increased piHDL, oxLDL, TNFα, and homocysteine (HCY) found in SLE patients. Elevated HCY also leads to increase ROS and EC damage. Defective, apoptotic and lower overall numbers of EPC/CAC diminish the EC repair system, and all of these processes lead to increased arterial plaque.