

Update on vascular disease in systemic lupus erythematosus

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Purpose of review

Young women with systemic lupus erythematosus have strikingly high rates of coronary heart disease. Current knowledge indicates that atherosclerosis is an active inflammatory and immune-mediated process. Therefore, the chronic inflammation and immune dysregulation characteristic of systemic lupus erythematosus undoubtedly contribute to the accelerated vascular disease seen in these patients. Carefully considering what is known about atherogenesis in the general population will provide clues to unraveling the complexity of why systemic lupus erythematosus and atherosclerosis are linked so frequently.

Recent findings

Inflammation is involved in all aspects of atherogenesis from the initial endothelial "response to injury," to foam cell formation leading to the atherosclerotic lesion, to the rupture of the "vulnerable" fibrous cap, resulting in the acute coronary syndrome and potentially in death. The authors review how factors commonly seen in systemic lupus erythematosus or inherent to the underlying disease mechanism may contribute to each of the stages of atherogenesis.

Summary

Our focus on the causes of vascular disease in systemic lupus erythematosus must now include nontraditional risk factors such as immune and inflammatory mediators. With the advent of noninvasive screening tools for atherosclerosis, we are better equipped to measure subclinical vascular disease and associated risk factors, including immune and inflammatory mediators. When considering strategies for preventing premature cardiovascular disease in systemic lupus erythematosus, modifying immune and inflammatory risk factors will likely become a major component of the program in addition to modifying the current traditional risk factors.

Keywords

systemic lupus erythematosus, inflammation, vascular disease, atherosclerosis, cardiovascular disease

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Abbreviations

aPLs	antiphospholipid antibodies
CRP	C-reactive protein
LDL	low-density lipoprotein
ox-LDL	oxidized low-density lipoprotein
PON	paraonase
SLE	systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a prototypic inflammatory disease that targets the vascular system. Vascular manifestations typically associated with SLE span a broad range, including vasculitis, vasculopathy, vasospasm, and thromboembolism. However, since new and improved therapies have extended the lives of many lupus patients, another serious vascular complication has emerged: premature atherosclerotic vascular disease. This threat is particularly troublesome among young female patients with lupus who would otherwise be protected from such a problem. In fact, there is a 50-fold increased risk of myocardial infarction among women with lupus age 35 to 44 years [1].

Epidemiologic studies have evaluated risk factors associated with cardiovascular events in patients with lupus. Not surprisingly, traditional cardiovascular risk factors such as hypertension, smoking, diabetes, and dyslipidemia are important. However, the increased risk of coronary heart disease in lupus patients cannot be fully accounted for by these traditional factors: The underlying disease and/or its treatment also play a role [2].

The establishment of inflammation as a key factor in atherogenesis [3,4••] provides potential clues to the underlying mechanisms of atherosclerosis in a chronic inflammatory vascular disease such as SLE. In this review we explore the prevailing thoughts on how the immunologic and inflammatory processes inherent to the pathogenesis of SLE may also contribute to atherosclerotic vascular disease.

The vascular biology of atherogenesis

Historically, atherosclerosis has been viewed as the storage and accumulation of lipids in the arterial wall that eventually leads to stenosis of the vessel, culminating in an acute coronary event. However, we now understand that an acute coronary event is more often caused by rupture of a nonstenotic, vulnerable atherosclerotic

plaque [5]. The formation, progression, and rupture of the plaque is now viewed as a process related directly to inflammation. Under normal circumstances, the vascular endothelium does not bind leukocytes well. However, injury to the endothelium causing inflammation results in expression of adhesion molecules that facilitate binding of monocytes and T cells to the arterial wall (Fig. 1A). Proinflammatory cytokines such as monocyte chemoattractant protein-1 and a family of T-cell chemoattractants then stimulate these cells to migrate into the intima where they cause local inflammation. Monocytes then differentiate into macrophages, and macrophage colony-stimulating factor induces them to express scavenger receptors. These scavenger receptors bind and facilitate the uptake of oxidized low-density lipoprotein (ox-LDL) or otherwise modified LDL by macrophages, resulting in the formation of lipid-laden foam cells, which form the basis of the fatty streak (Fig. 1B). T cells produce inflammatory mediators that stimulate macrophages, endothelial cells, and smooth muscle cells. These cells in turn produce fibrogenic mediators that eventually lead to the formation of an elaborate collagenous extracellular matrix, or fibrous cap, surrounding the advanced lesion. Inflammation also plays a role in rupture of the plaque and formation of the thrombus (Fig. 1C). Continued activation of macrophages in the lesion eventually results in production of collagenases that enhance breakdown of collagen in the extracellular matrix, making it vulnerable to rupture. In addition, collagen synthesis by smooth muscle cells is impaired by the release of interferon γ from activated T cells in the plaque, thus interfering with restructuring of the fibrous cap. Once the plaque ruptures, macrophages contribute to thrombus formation by producing the strongly procoagulant tissue factor in response to inflammatory mediators. Interaction of blood components with tissue factor promotes coagulation and recruitment of platelets, ultimately resulting in the formation of a thrombus. Thus, inflammatory mechanisms have been implicated in all stages of atherogenesis from initiation and promotion of lesion development to physical disruption of the plaque and thrombus formation.

Atherogenesis and systemic lupus erythematosus

In the following sections we consider how factors commonly seen in SLE or inherent to the underlying mechanism of disease may contribute to each of the stages of atherogenesis described earlier.

Endothelial injury and leukocyte recruitment

In the "response-to-injury" hypothesis of atherosclerosis [3], endothelial cell dysfunction can result from various sources of injury, including shear stress, immune complexes, and other toxins such as homocysteine, all of which are also relevant to SLE (Fig. 1A). Such injury results in the upregulation of adhesion molecules on the

endothelial surface, increased permeability, and subsequent trapping of inflammatory cells at the site of activation. Factors commonly seen in SLE may contribute to endothelial injury and recruitment of inflammatory cells.

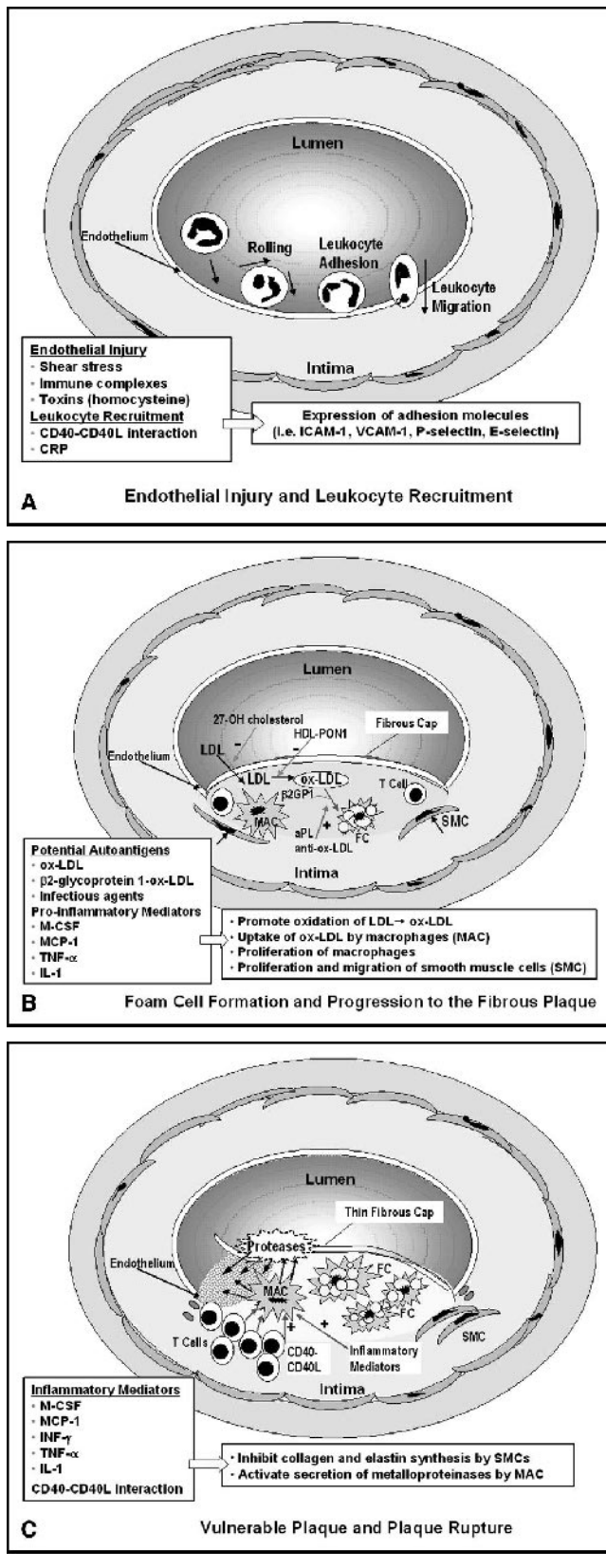
Immune complexes

In a recent population-based, prospective study of 257 healthy Swedish men, the level of circulating immune complexes at age 50 years predicted incident myocardial infarction over a 20-year follow-up, independent of conventional risk factors or the presence of antibodies to cardiolipin [6]. The composition of the circulating immune complexes was not determined. There is some evidence to suggest that the circulating immune complexes seen in myocardial infarction may contain antibodies to ox-LDL, β 2-glycoprotein 1, phospholipids, or viral particles. Immune complexes that fix C1q may also contribute to the formation of atherosclerotic lesions [7]. When these complexes bind to C1q receptors on endothelial cells, they trigger the expression of vascular cell adhesion molecule-1, which participates in the recruitment of monocytes/macrophages and T cells to the endothelial surface, one of the earliest events in lesion formation. C1q-fixing immune complexes may also contribute to atherosclerosis by interfering with cholesterol homeostasis in the arterial wall. Cholesterol is metabolized to 27-hydroxycholesterol by the P450 enzyme, cholesterol 27-hydroxylase, present in arterial endothelial cells and macrophages. The more soluble cholesterol metabolite (27-hydroxycholesterol) facilitates transport out of the arterial wall and into the liver. There are other potential beneficial effects of 27-hydroxycholesterol, including downregulation of cell surface LDL receptors resulting in diminished receptor-mediated uptake of LDL [8], and suppression of smooth muscle cell proliferation [9], key steps in the formation of the atherosclerotic plaque. Immune complexes can have an inhibitory effect on cholesterol 27-hydroxylase, thus diminishing the levels of the antiatherogenic 27-hydroxycholesterol. One might speculate that the chronic immune complex formation characteristic of lupus might contribute to the atherogenic potential of these patients, although this possibility has not been studied specifically in this population.

Complement activation

Complement activation, a process common to nearly all physiologic and pathophysiologic inflammatory processes, has surprisingly not been studied extensively in atherogenesis. However, there are some data to suggest that complement plays several roles in the development of vascular disease. Complement activation products have been shown to contribute to the progression of vascular lesions in atherosclerosis, vasoconstriction of coronary arteries, and ischemia/reperfusion injury after myocardial infarction [10]. In addition, immunohistochemical studies of human atherosclerotic lesions have revealed

Figure 1. Inflammation in atherosclerosis and formation of vulnerable plaque



deposits of both early and late complement components within the vessel wall. Furthermore, RNA analysis indicates that complement genes are expressed locally in plaques [11]. C5b-9 complex has been identified in fibrous plaques and in the deeper part of the intima, where it appears to colocalize with modified LDL, a reportedly potent activator of complement [12–14]. In a recent study by Buono *et al.* [15•] comparing C3-deficient mice and control mice, maturation of atherosclerotic lesions beyond the foam cell was strongly dependent on an intact complement system. In a study of 220 women with lupus followed at the University of Pittsburgh, a strongly independent and linear association was noted between serum C3 levels and aortic vascular stiffness measured by pulse wave velocity [16]. Loss of arterial compliance and thus stiffer vessels is a functional change in the arterial wall that can occur early in the development of vascular disease. It is interesting to speculate that early in the atherogenic process, mechanisms of SLE related to immune dysregulation and complement metabolism may reduce arterial elasticity, creating an atherogenic milieu. Further studies investigating how complement functions in vascular disease in lupus are needed. Novel therapies now being developed aimed at inhibiting complement activation may benefit both treatment of SLE and atherosclerotic vascular disease.

Homocysteine

Another source of potential vascular injury in lupus is elevated homocysteine levels. Homocysteine, a metabolite in methionine metabolism, may have both direct and indirect injurious effects on the endothelium [17,18]. It is prothrombotic, increases collagen production, and decreases the availability of nitric oxide [19–21]. In several epidemiologic studies, elevated levels of plasma homocysteine have been associated with increased risk for initial and recurrent myocardial infarction [22–24]. In the Air Force/Texas Coronary Atherosclerosis Prevention Study, a randomized trial of lovastatin in the primary prevention of myocardial infarction, a high-risk subgroup of 5569 participants with elevated LDL and homocysteine levels benefited from statin therapy (relative risk, 0.46; 95% confidence interval, 0.29 to 0.75). However,

(A) The three major steps to an acute coronary event include: endothelial injury and leukocyte recruitment, (B) Foam cell formation and progression to the fibrous plaque, and (C) Plaque rupture and thrombosis. These are factors common to systemic lupus erythematosus (SLE) that may enhance endothelial injury, leukocyte recruitment, and may act as autoantigens to promote local inflammation, foam cell and fibrous plaque formation. This unchecked inflammatory response can lead to increased vulnerability of the plaque to rupture and to form an acute occlusive thrombus. anti-ox-LDL, antioxidantized LDL antibodies; aPL, antiphospholipid antibodies; β 2GP1, β 2-glycoprotein-1; CRP, C-reactive protein; FC, foam cell; HDL-PON1, high-density lipoprotein-associated paraoxonase-1; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; MAC, macrophage; MCP, monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; SLE, systemic lupus erythematosus, SMC, smooth muscle cells, TNF, tumor necrosis factor, VCAM, vascular cell adhesion molecule.

homocysteine levels could not discriminate lovastatin efficacy among the participants with low to normal LDL cholesterol levels, the group currently outside treatment guidelines for statin therapy in primary prevention of cardiac events [25•]. In one group of SLE patients, homocysteine was found to be elevated and was associated with a 3.7-fold increased risk of arterial thrombosis [26]. Methotrexate, an antagonist of folate metabolism that can cause elevated plasma homocysteine levels [27], is used in SLE patients as a steroid-sparing agent for treatment of inflammatory arthritis or recurrent serositis. Other causes for hyperhomocystinemia in SLE may include the high prevalence of renal disease and dietary- and/or treatment-related factors. Although therapy to reduce homocysteine levels is relatively benign and includes folic acid and B vitamin supplementation, the value of this treatment in preventing cardiovascular disease is uncertain.

CD40–CD40 ligand interactions

In SLE, the interaction between CD40 ligand (CD40L) on T cells and CD40 on B cells is involved in the production of pathogenic autoantibodies [28,29]. Under normal circumstances the immune system allows only transient expression of CD40L. However, patients with SLE express abnormally high levels of CD40L, and the overall number of CD40L-positive cells is increased [28]. Furthermore, in patients with lupus nephritis, CD40 expression is upregulated on endothelial cells. CD40 ligation of endothelial cells can induce vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin [30], adhesion molecules important in facilitating vascular inflammation both in SLE and in atherosclerosis. Work during the past several years has revealed other roles for CD40L and CD40. Macrophages, smooth muscle cells, and activated platelets express CD40L, a molecule previously held to be limited to activated T cells [31,32,33•]. CD40 ligation can induce tissue factor in macrophages, which is crucial in rendering plaques thrombogenic [34], and can activate caspase-1, which is involved in maturing cytokines to their active form, and in inducing apoptosis [35]. Antibody neutralization of CD40 signaling in atherosclerosis-prone mice reduced arterial levels of vascular cell adhesion molecule-1 and the surface area and thickness of atheromas [36]. In studies extending to humans, healthy women with high levels of soluble CD40L had a higher incidence of cardiovascular events [37].

Humanized anti-CD40L antibody therapy has been tested for the treatment of lupus. Ironically, in one trial sponsored by Biogen, Inc (Cambridge, Massachusetts) [38], there appeared to be a potential enhancement of thromboembolic complications when applied to lupus; however, in another trial in lupus using a different humanized anti-CD40L antibody (IDEC Pharmaceuticals, San Diego, California), the agent was safe and well tol-

erated [39]. It is unclear how these initial studies will influence further trials examining the role of these monoclonal antibodies in primary and secondary cardiovascular disease prevention.

C-reactive protein

Inflammation at the site of endothelial injury is a necessary step in the formation of the foam cell and fibrous plaque. During the past decade, C-reactive protein (CRP), an acute-phase protein measured by high-sensitivity immunoassays, has been the most widely studied inflammatory marker in predicting cardiovascular risks. CRP is synthesized mainly in the liver in response to interleukin-6. There is sufficient evidence to suggest that CRP is more than just a reflection of an inflammatory response, but an active player in atherogenesis. Studies have shown that, *in vitro*, CRP activates the complement system [40]; induces endothelial production of monocyte chemoattractant protein-1; upregulates intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin [41,42]; mediates macrophage uptake of LDL [43]; and increases monocyte production of tissue factor [44].

Prospective epidemiologic studies have demonstrated that high levels of CRP predict coronary events in healthy individuals, patients with stable or unstable angina, or in those with prevalent coronary artery disease [45–49].

Prior studies have failed to establish an association between CRP and subclinical atherosclerosis, defined by carotid plaque and intima–media thickness (measured by B-mode ultrasound), and coronary and aortic calcification (measured by electron beam tomography), after adjusting for traditional cardiovascular risk factors and other markers of inflammation. These findings have led to the speculation that elevated CRP levels may reflect an increased tendency for plaque rupture rather than atherosclerotic burden [50–53]. However, a recent, large population-based study in the offspring cohort of the Framingham Heart Study described a strong association of elevated CRP levels with measures of carotid atherosclerosis in women but not in men after adjustment for traditional cardiovascular risk factors [54•]. Similarly, in the Rotterdam Study, investigators using noninvasive techniques found that CRP predicted progression of atherosclerosis at various sites in the arterial tree [55•]. Furthermore, both coronary calcification, a surrogate marker of coronary atherosclerosis, and CRP appear to be complementary in predicting cardiovascular risk and cardiac death [56•].

Many trials have demonstrated the clinical benefit of statin therapy in the primary and secondary prevention of coronary artery disease. Studies have documented that, in addition to lowering LDL cholesterol, statin

therapy has antiinflammatory effects. In patients with angiographically diagnosed coronary artery disease, those not on statin therapy and with elevated CRP (top quartile) had a 2.3-fold increase in cardiac death independent of LDL levels [57•].

How CRP and inflammation tie into the excessive coronary disease seen in SLE is uncertain. It is important to remember that in most previous studies, CRP levels considered in the “normal” range were associated with increased risk of cardiovascular disease. How this risk might change in individuals with significantly higher CRP levels, like those with rheumatoid arthritis and less frequently with SLE, is unknown. However, considering that CRP is thought to facilitate many of the inflammatory processes leading to plaque formation and rupture, it is reasonable to speculate that higher levels may lead to greater risk.

Foam cell formation and progression to the fibrous plaque

Low-density lipoprotein is taken up by endothelial cells via LDL receptors that recognize a domain of the apolipoprotein B component of the molecule (Fig. 1B). This process is influenced by the circulating levels of LDL and by the functional integrity of the receptors, which is in part influenced by feedback control via intracellular cholesterol levels, as well as genetic factors. LDL becomes susceptible to oxidation when it is trapped in the arterial wall, and this oxidative modification is believed to drive atherogenesis [58]. Significant modification of the LDL particle results in oxidative fragments that bind to scavenger receptors expressed on macrophages and smooth muscle cells. Although uptake of the proinflammatory ox-LDL particles by the macrophages may serve initially as a protective function, progressive accumulation ultimately leads to development of foam cells within the arterial wall. Several steps along this pathway may be influenced positively or negatively by immunologic factors related to lupus.

Elevated circulating lipid levels, specifically LDL, may promote endothelial cell uptake. Abnormal lipid profiles, commonly seen in patients with SLE, may arise via several mechanisms. For example, long-term corticosteroid therapy for active SLE is known to increase total cholesterol, triglycerides, and apolipoprotein B, and to promote an abnormal distribution of high-density lipoprotein subclasses (increase in high-density lipoprotein-3 and decrease in high-density lipoprotein-2) [59,60]. Nephrotic syndrome, commonly associated with lupus nephritis, can cause increased serum lipoprotein (a) and cholesterol [61,62]. In addition, several studies have reported higher serum lipoprotein (a) levels in patients with SLE [63–65]. Serum lipoprotein (a) is a cholesterol-rich lipoprotein accepted as an independent risk factor for cardiovascular disease.

Impaired lipoprotein lipase activity, an enzyme responsible for the catabolism of chylomicrons, may be responsible for elevated triglyceride levels in patients with SLE [66]. Autoantibodies to lipoprotein lipase that inhibit its enzymatic activity were found in 47% of 105 SLE patients [67•], a finding that may in part explain the dyslipidemia commonly seen in SLE.

Feedback control of LDL receptors may also be influenced by SLE-related mechanisms. As we discussed previously, complement-fixing immune complexes inhibit the enzyme responsible for formation of 27-hydroxycholesterol in the arterial wall. This inhibition results in a loss of the 27-hydroxycholesterol downregulatory effects on surface LDL receptors, leading to increased receptor-mediated uptake of LDL.

Low-density lipoprotein uptake into macrophages is dependent on the modification of LDL to ox-LDL, which may be influenced by genetic factors. Paraoxonase (PON) is a serum esterase synthesized by the liver that provides a relatively protective role in the risk of atherosclerosis. *In vitro* studies indicate that high-density lipoprotein-associated PON1 inhibits LDL oxidation and can destroy biologically active lipids in ox-LDL [68–70]. Low PON activity is associated with coronary heart disease risk [71]. Three PON genes, PON1, PON2, and PON3, are linked on chromosome 7. Common genetic variation in the PON1 gene has been associated with the ability to oxidize LDL as well as coronary heart disease risk [71].

Interestingly, in a preliminary study of 217 lupus patients followed at the University of Pittsburgh Medical Center, a higher frequency of aPLs was associated with PON1 polymorphism (PON1/codon 192 R allele; Kamboh, Personal communication, 2003). Current studies are underway to examine further the relation between PON1 genetic variation, PON activity, the oxidative potential of LDL, and the presence of aPLs in lupus patients.

The autoantigenic nature of ox-LDL may also contribute to its enhanced uptake by macrophages and to the local inflammatory response. A number of investigators have demonstrated a high frequency of antibodies to ox-LDL in patients with lupus and a strong correlation between antibodies to ox-LDL and antiphospholipid antibodies (aPLs), common in SLE [72–75]. This may in part be explained by observations that aPLs recognize ox-LDL in complex with β 2-glycoprotein-1 [76,77] and that binding of antibodies to ox-LDL- β 2-glycoprotein complexes increases LDL uptake into macrophages, facilitating formation of the foam cell and fatty streak [78].

Like ox-LDL and β 2-glycoprotein-1, infectious agents may act as potential autoantigens at the site of plaque

formation, facilitating the local inflammatory and immune response [79,80]. The potential mechanisms of infection-induced atherosclerosis remain speculative. Although there is no convincing evidence that infectious agents cause atherosclerosis, they may aggravate preexisting lesions by several mechanisms. Host defense, the innate immune response, to extravascular infection can be initiated when lipopolysaccharides on pathogens or endotoxins bind to toll-like receptors, key components of pathogen-associated molecular pattern recognition machinery, on endothelial cells [81]. Ligation of these receptors induces the expression of inflammatory mediators such as leukocyte adhesion molecules, inducible nitric oxide synthase-2, endothelin, and interleukin-1 [82,83]. Observational evidence to support the role of remote infections in coronary heart disease is the emergence of chronic oral infections such as periodontitis as an independent risk factor for atherosclerotic events [84]. However, conflicting data from other observational and prospective studies appear to weaken the seroepidemiologic link between infection and atherosclerosis [85–87]. Although direct infection of vascular endothelial cells by *Chlamydia pneumoniae* and cytomegalovirus has been confirmed by the presence of these pathogens in atherosclerotic plaques, this observation alone does not determine causation [88].

Although the evidence is circumstantial, infectious agents have gained increasing attention as potential contributors to the development of SLE. They may initiate or flare SLE by disturbing immunoregulation, causing tissue damage and leading to the release of autoantigens, or by eliciting a specific immune response by molecular mimicry. Of particular interest is Epstein–Barr virus [89,90]. Although infection has not been examined in association with atherosclerosis in lupus, it is interesting to speculate that viral factors may play a role in the premature atherosclerosis seen in this population.

Vulnerable plaque and plaque rupture

The vulnerability of an atherosclerotic plaque to become unstable or rupture is largely determined by three major factors (Fig. 1C): a large central core of extracellular lipids, a thin overlying fibrous cap, and a pronounced infiltrate of inflammatory cells [91,92]. Macrophages and T cells are the dominant cells at the immediate site of rupture or erosion. There is a thinning of the smooth muscle cell layer, likely the result of the release of digestive enzymes (metalloproteinases) by tissue-invading macrophages [93].

Lupus is a disease characterized by the presence of many proinflammatory cytokines that likely facilitate the inflammatory process and increase plaque instability. CD40–CD40L interaction, which is upregulated in SLE, induces macrophages to synthesize and secrete matrix

metalloproteinases, which weaken the fibrous cap and facilitate plaque rupture [34]. In addition, CD40–CD40L interaction can promote thrombosis by inducing macrophages to secrete procoagulatory tissue factor [34]. Particularly relevant to SLE, aPLs provide an additional clotting risk.

Conclusion

Parallels between the inflammatory and immune-mediated mechanisms of both atherogenesis and SLE may provide clues to understanding premature vascular disease in these patients. SLE-related factors are likely involved in all stages of atherogenesis from formation of the atherosclerotic lesion to its rupture, as well as in the thrombotic event itself. Processes critical to the pathogenesis of SLE, such as immune complex formation and complement activation, are involved in endothelial injury and local inflammation, influence LDL uptake by regulating cholesterol metabolism, and affect the functional integrity (compliance) of the vessel, thereby promoting an atherogenic milieu. The upregulated CD40–CD40L interactions in SLE potentially influence many processes, ranging from promoting inflammatory processes to contributing to thrombus formation. Other links between SLE and atherosclerosis involve sources of injury to the endothelium, such as homocysteine, and contributions to local inflammation and plaque vulnerability by the effects of chronic viral infections. CRP, an acute-phase reactant commonly measured in inflammatory autoimmune diseases such as rheumatoid arthritis and SLE, is now known not to be an innocent bystander but an active participant. CRP activates complement, increases the inflammatory response, enhances uptake of LDL into macrophages, and induces monocyte production of tissue factor, leading to plaque formation and thrombosis. The enhancement of macrophage uptake of ox-LDL by antiphospholipid antibodies recognizing ox-LDL– β 2-glycoprotein-1 complexes illustrates how the propensity of autoantibodies in SLE may influence various atherogenic processes. Furthermore, macrophage uptake of LDL may be modulated by hyperlipidemia as well as genetic factors related to SLE. Given the striking similarities between processes inherent to SLE and atherogenesis, it is interesting to speculate that treatment strategies directed toward specific immune dysregulation in SLE will be beneficial in preventing premature vascular disease in this population.

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