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REVIEW

The interplay of inflammation and cardiovascular disease in systemic lupus erythematosus

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Abstract

Patients with systemic lupus erythematosus have up to a 50-fold increased risk of developing atherosclerotic cardiovascular disease. Recent advances in the etiology of vascular damage in this disease stress the interplay of lupus-specific inflammatory factors with traditional cardiac risk factors, leading to increased endothelial damage. This review analyzes the putative role that immune dysregulation and lupus-specific factors may play in the pathogenesis of premature vascular damage in this disease. The potential role of various cytokines, in particular type I interferons, in the development of accelerated atherosclerosis is examined. Potential therapeutic targets are discussed.

Epidemiology of premature vascular damage in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations, including internal organ damage, which can result in severe morbidity and even death and often requires aggressive immunosuppressive treatment. More than 30 years ago, a bimodal peak in mortality was described in lupus patients, with late increases in death commonly seen as secondary to premature cardiovascular disease (CVD) [1]. Indeed, this enhanced atherosclerotic risk increases with each year of disease duration. This is especially the case in young females with SLE, where the CVD risk can be up to 50-fold higher than in age-matched controls [2,3]. While traditional Framingham risk factors likely contribute to CVD in SLE, they cannot fully account for the increased risk. Instead, the pathogenesis of premature CVD in SLE may rely on factors unique to the disease itself [4].

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While systemic inflammation has been linked to atherosclerosis development in the general population and in specific conditions, SLE typically has a lower 'classical inflammatory burden' compared to what would be seen in rheumatoid arthritis or spondyloarthropathies; yet, lupus is associated with a higher CVD risk than these other diseases. This observation suggests that factors that trigger accelerated atherosclerosis in lupus differ from the typical proinflammatory factors (that is, high C-reactive protein (CRP)) linked to 'idiopathic' atherosclerosis. Atherosclerosis progression in lupus patients develops or progresses in 10% of SLE patients per year. Among other factors, this progression is associated with older age at diagnosis and with longer disease duration, supporting the hypothesis that chronic exposure to lupus immune dysregulation promotes CVD [5].

Subclinical and clinical vascular damage in SLE

Premature damage in SLE occurs in both the macro- and microvasculature. Vascular functional abnormalities in lupus are present even shortly after disease diagnosis [6]. SLE patients have significantly decreased flow-mediated dilation of the brachial artery and this correlates with increased carotid intima media thickness (IMT) [7]. Additionally, carotid plaque can be detected in 21% of SLE patients under the age of 35 years and in up to 100% of those over the age of 65 years [8]. Aortic atherosclerosis is also increased in SLE [9]. These macrovascular findings correlate with disease activity and disease duration [7-9]. Damage to the coronary circulation is also common in SLE patients, with 54% displaying non-calcified coronary plaque [10]. There is also impairment of coronary microvasculature flow reserve, even in patients with grossly normal coronary arteries. This dysfunction correlates with disease duration and severity, suggesting that microvascular damage and dysfunction are also part of SLE-related CV pathology [11]. Additionally, SLE patients have a higher probability of developing left ventricular hypertrophy, independent of baseline hypertension, again emphasizing the role of lupus-related factors in CVD damage [12].

Mechanisms of atherosclerosis development in the general population

Various groups have proposed that CVD, endothelial dysfunction and atherosclerosis arise from chronic injury to the endothelium, which allows for invasion of inflammatory cells and lipid deposition. Current dogma upholds that chronic inflammation instigates and perpetuates the atherogenic cycle. Factors such as oxidized low density lipoprotein (LDL) activate the endothelium to secrete chemokines, which recruit inflammatory cells, including T lymphocytes, dendritic cells (DCs) and monocytes. These monocytes differentiate into macrophages and foam cells under the influence of locally secreted factors [13]. Various stimuli, including cholesterol crystals, then activate macrophages and foam cells to secrete inflammatory cytokines, reactive oxygen and nitrogen species and proteases, all of which contribute to the atherogenic phenotype in the blood vessel [14]. Invasion of the atherosclerotic plaque by CD4+ T cells also contributes to vascular pathology by recognizing epitopes of various molecules, including oxidized LDL, and by secreting IFN-γ, which then leads to increased inflammatory cytokine production. This chronic production of inflammatory cytokines and proteases may lead to thinning of the plaque wall and eventual rupture, which results in exposure of the blood to phospholipids, tissue factor and platelet-adhesive matrix molecules, eventually promoting thrombosis and acute CVD events [13].

Coupled to this inflammatory injury, a loss of endothelial cells can occur, which, if not repaired, leads to increased inflammatory cell invasion, vascular smooth muscle proliferation and neo-intima formation [15]. Endothelial cell apoptosis is a phenomenon with potentially significant deleterious effects on vascular health, including loss of nitric oxide, generation of phosphatidylserine-rich microparticles with significant tissue factor activity, and potential predisposition to acute coronary events [16,17].

Under normal conditions, vascular damage triggers a response leading to an attempt to repair the endothelium. Although our understanding of vascular repair is rapidly evolving, it is still unclear how it occurs. Several groups have proposed that repair of the vasculature occurs primarily by bone marrow-derived endothelial progenitor cells (EPCs) and myelomonocytic circulating angiogenic cells (CACs) [18]. Indeed, decreased numbers or dysfunction of these cell types may contribute to CVD as EPC numbers inversely correlate with CVD risk, time to first CVD event, and in-stent restenosis risk [19,20]. Additionally, functional impairment of EPCs correlates with coronary artery disease risk [21]. Various mechanisms have been implicated in EPC/CAC dysfunction in these conditions, including reactive oxygen species, telomere shortening/senescence and cytokines such as TNF [22-24].

Mechanisms of endothelial injury and atherosclerosis in SLE

Induction of an imbalance of vascular damage and repair by type I IFNs

Patients with SLE have increased numbers of circulating apoptotic endothelial cells, which correlates with endothelial dysfunction and generation of tissue factor [6]. Various soluble adhesion molecules, such as vascular cell adhesion molecule (VCAM), inter-cellular adhesion molecule and E-selectin, which are released after endothelial cell damage, are increased in SLE and correlate with increased coronary calcium scores. Additionally, soluble levels of the antithrombotic endothelial protein C receptor, which is released secondary to inflammatory activation of metalloproteinases, are increased in SLE and correlate with the presence of carotid plaque [25]. These findings suggest that chronic vascular insult and inflammation may be important for atherosclerotic pathology [26]. Despite evidence that accelerated endothelial cell death occurs in lupus, a phenomenon that should trigger enhanced vascular repair, the latter is significantly impaired in lupus patients. SLE patients have decreased circulating EPCs/CACs, and those that persist are characterized by increased apoptosis, even during quiescent disease, decreased proangiogenic molecule synthesis, and decreased capacity to incorporate into formed vascular structures and differentiate into mature endothelial cells [27,28] (Figure 1). Thus, patients with SLE have compromised repair of the damaged endothelium, likely leading to the establishment of a milieu that promotes the development of plaque.

Our group has proposed that the mechanism by which vascular repair is impaired in SLE is through increased levels and enhanced effects of type I IFNs. Human and murine studies from various groups indicate that IFN-α may be crucial in the pathogenesis of SLE. SLE patients have an 'IFN signature' in peripheral blood mononuclear cells, kidneys and other tissues that correlates with disease activity [29], and type I IFN levels are increased in lupus serum [30]. Further, lupus cells appear to be more sensitive to the effects of type I IFN [31]. As part of this pathology, we and others have suggested that the development of lupus-related CVD is, at least partially, attributable to IFN-α and, potentially, to other type I IFNs. Our group has reported that dysfunction of EPC/CAC differentiation in SLE is mediated by IFN-α, as neutralization of this cytokine restores a normal EPC/CAC phenotype [28]. This is further reinforced by the observation of abrogated EPC/CAC numbers and function observed in lupus-prone New Zealand black/New Zealand white F_1 mice, a strain that depends on type I IFNs for disease development. Additionally, non-lupus-prone mice EPCs are unable to properly differentiate into mature endothelial cells in the presence of IFN-α [32,33].
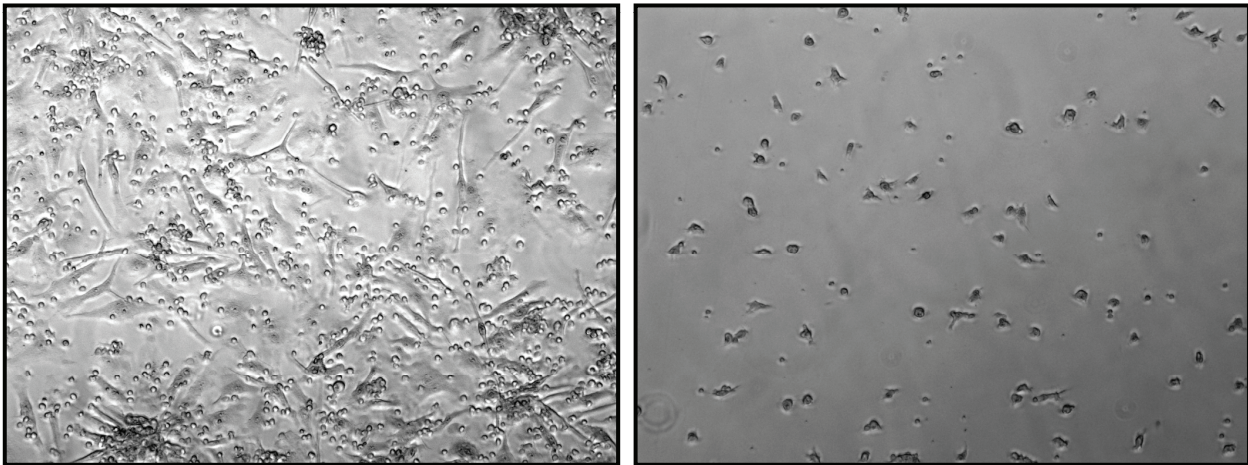
Figure 1. Endothelial progenitor cells/circulating angiogenic cells from patients with systemic lupus erythematosus are unable to differentiate into mature endothelial cells in culture. Photomicrographs of primary blood mononuclear cells from a healthy control (left) and a patient with systemic lupus erythematosus (right) after 2 weeks of culture in proangiogenic media on fibronectin-coated plates. Cells were imaged via inverted phase microscopy at a total magnification of 100×. Photomicrographs by Seth G Thacker.

The pathways by which IFN-α mediates aberrant vascular repair may depend on repression of the proangiogenic factors IL-1β and vascular endothelial growth factor and on upregulation of the antiangiogenic IL-1 receptor antagonist. Indeed, addition of recombinant human IL-β to SLE EPC/CAC cultures restores normal endothelial differentiation [32]. Further supporting a role for type I IFNs in premature vascular damage in SLE, patients with high type I IFN signatures have decreased endothelial function, as assessed by peripheral arterial tone measurements [34]. Preliminary evidence indicates that type I IFN signatures correlate with carotid IMT in a lupus cohort [35]. Furthermore, there is evidence that an antiangiogenic phenotype is present in patients with SLE, manifested by decreased vascular density and increased vascular rarefaction in renal blood vessels *in vivo*, associated with upregulation of the IL-1 receptor antagonist and decreased vascular endothelial growth factor in both the kidney and serum [28,36].

The cellular source of type I IFNs leading to abnormal vascular repair was recently examined. Depletion of plasmacytoid DCs (the major producers of IFN-α) does not lead to abrogation of abnormal lupus EPC/CAC differentiation in culture [37]; therefore, other cellular sources for this cytokine have been sought. Neutrophil-specific genes are abundant in peripheral blood mononuclear cell microarrays from lupus patients because of the presence of low-density granulocytes (LDGs) in mononuclear cell fractions [38,39]. The functionality and pathogenicity of these LDGs was recently investigated by our group. Among other findings, these cells are significantly cytotoxic to endothelial cells. In addition, LDGs have the capacity to secrete sufficient amounts of IFN-α to interfere with vascular repair. LDG depletion from lupus peripheral blood mononuclear cells restores the ability of EPC/CACs to differentiate *in vitro* into endothelial monolayers [37]. This suggests that the presence of these abnormal granulocytes contributes to endothelial dysfunction and vascular damage in SLE.

The above findings suggest that abrogation of the aberrant effects of type I IFNs in SLE may not only decrease disease activity but also lead to decreases in CVD risk. Future clinical trials should assess this possibility.

The potentially deleterious effects of type I IFNs in cardiovascular health are also being explored in non-SLE-related atherosclerosis. For example, IFN-α-producing plasmacytoid DCs have been identified in areas of atheromatous plaque. IFN-α then activates plaque-residing CD4+ T cells to increase TNF-related apoptosis-inducing ligand (TRAIL) expression, which results in killing of plaque stabilizing cells and a potential increase in the risk of plaque rupture. Additionally, IFN-α sensitizes plaque-residing myeloid DCs, which may result in further inflammation and plaque destabilization. This cytokine appears to synergize with bacterial products (such as lipopolysaccharide) to increase the synthesis of various proinflammatory cytokines and metalloproteinases [40,41]. These findings indicate that type I IFNs could potentially be involved in atherosclerosis development not only in autoimmune disorders but also in the general population in the context of microbial infections. This hypothesis merits further investigation. Additionally, type I IFNs inhibit CRP upregulation [42], which may explain why the CRP response is usually downregulated in SLE flares and why it does not appear to correlate well with atherosclerotic burden in this disease [43].

Other cytokines

The inflammatory cytokine TNF-α appears to play an important role in the initiation and perpetuation of atherosclerotic lesions in the general population. It increases the level of adhesion molecules on the surface of vascular endothelium and promotes enhanced levels of chemotactic proteins, which allows for recruitment of monocytes and T cells into the endothelial wall [44]. In SLE, serum TNF-α levels have been reported to be elevated and correlate with coronary calcium scores [26]. TNF-α levels are also increased in SLE patients with CVD compared to those without CVD, and this correlates with altered lipid profiles [45]. Additionally, it has been postulated that elevated levels of TNF-α may increase soluble VCAM-1 in SLE [46]. However, the exact role this cytokine plays in the development of vascular damage in SLE remains unclear.

IFN-γ, secreted by glycolipid-activated invariant natural killer T-cells, may also contribute to a pathogenic role in SLE-related atherosclerosis [47]. The antiatherogenic cytokine transforming growth factor-β is decreased in SLE and this decrease may potentially play a role in related CVD [48]. The cytokine IL-17, which stimulates production of other pro-inflammatory cytokines, as well as upregulation of chemokines and adhesion molecules, has been linked to atherosclerotic plaque development in non-lupus-prone models. Atherosclerotic-prone mice have reduced plaque burden when transplanted with bone marrow deficient in the IL-17 receptor [49]. SLE patients have elevated levels of IL-17 and Th17 cells are expanded in SLE and can induce endothelial adhesion molecule upregulation [50,51]. Thus, there is a theoretical role for Th17 T cells and IL-17 in the upregulation of inflammatory mediators and adhesion molecules that contribute to CVD in SLE. Future studies should address if, indeed, any of these cytokines play a prominent role in vascular damage and atherosclerosis progression in this disease.

Adiponectin is an adipocytokine with potential beneficial effects at sites of blood vessel injury through inhibition of monocyte adhesion to endothelial cells and of migration and proliferation of smooth muscle cells. However, this molecule is increased in lupus serum and independently correlates with augmented severity of carotid plaque, but not coronary calcification, in lupus patients [25,52]. One hypothesis to explain this discrepancy is that chronic vascular damage in SLE leads to positive feedback on adiponectin-secreting cells. While this may lead to increases in levels of this cytokine, its effects are blunted at the site of endothelial damage due to the unique inflammatory milieu in SLE [53]. Supporting a putative protective role for adiponectin in SLE-mediated CVD, this molecule is required for the beneficial effects of rosiglitazone on atherosclerosis development in a mouse model of SLE [54].

T cells

Th1 CD4+ T cells play a pathogenic role in CVD and their differentiation is promoted in atherosclerotic lesions by the increased expression of IFN-γ and IL-12 [44]. Recent evidence suggests that these cells may also play a role in SLE-related CVD, as atherosclerosis-prone LDL receptor-deficient mice have increased vascular inflammation and CD4+ T cell infiltration in their plaques after bone marrow transplant with lupus-susceptible cells [55]. As mentioned above, CD4+ T cells increase TRAIL expression when exposed to IFN-α, which can lead to plaque destabilization [41]. A hypothetical role for autoreactive CD4+ T cells in endothelial damage in SLE also exists. SLE autoreactive T cells can kill antigen presenting cells [56]. Endothelial cells have the ability to act as antigen presenting cells upon activation, and research on transplant rejection suggests that graft endothelial cells are activated to a pro-inflammatory phenotype and killed by host T cells during antigen presentation [57]. Further research into whether interactions between endothelial cells and SLE autoreactive T cells result in endothelial damage and an increased risk of atherosclerosis should be considered.

The roles of other T-cell subsets in atherosclerosis development are being investigated. Invariant natural killer T cells, which recognize glycolipids and increase with the duration of lupus, may be proatherogenic [47]. In addition, whether the abnormalities reported in T regulatory cells in SLE contribute to atherosclerosis development is unknown [58]. A putative role is suggested by the observation that if regulatory T cell function is compromised in mouse models of atherosclerosis, CVD development is significantly more pronounced [59].

Complement and immune complexes

Inhibition of complement regulatory proteins increases atherosclerosis in mice and decreases in the membrane-attack complex attenuate atherosclerotic plaque formation [60]. Complement activated by inflammatory stimuli can interact with immune complexes (ICs), such as seen in SLE, and result in upregulation of endothelial adhesion molecules, including E-selectin and VCAM-1. These molecules may enhance neutrophil recruitment and endothelial damage [61]. High levels of oxidized LDL/β2 glycoprotein 1 complexes and anti-complex IgG or IgM have been reported in SLE. As the titers of these complexes correlate with a number of CVD risk factors [62], it is possible that they could be proatherogenic. The complement component C1q has anti-atherosclerotic effects by facilitating macrophage clearance of oxidized and acetylated LDL. As C1q deficiency is linked to SLE predisposition, its absence may also have a potential role in SLE-mediated atherosclerosis [63]. A role for

complement activation in atherogenesis has been proposed [64], but the exact role this phenomenon plays in premature vascular damage in SLE remains unclear. ICs may also potentially play a role in atherosclerosis development. IC formation in rabbits accelerates diet-induced atherosclerosis, and mice deficient in IC receptors have limited atherosclerotic development [65].

Lupus-related dyslipidemias

SLE patients have disturbances in lipoprotein levels and their processing in the bloodstream. High density lipoprotein (HDL) is decreased, while LDL, very low density lipoprotein and triglyceride levels are increased. These alterations may be related to abnormal chylomicron processing secondary to low levels of lipoprotein lipase [66]. Additionally, SLE patients have higher levels of pro-inflammatory HDL, which is unable to protect LDL from oxidation and promotes endothelial injury. Increased pro-inflammatory HDL in SLE is associated with augmented atherosclerosis [67]. In addition, the lipid profile of SLE patients may be more susceptible to environmental effects. Lupus-prone mice exposed to high-fat chow showed increased pro-inflammatory HDL and lipid deposition in vessels when compared to non-lupus mice [68]. A high fat diet administered to LDL receptor-deficient mice, made susceptible to SLE via bone marrow transplantation, resulted in very elevated lipid levels and significant increases in mortality when compared to similar mice fed regular chow [55]. Thus, predisposition to SLE may increase sensitivity to lipid perturbations by diet and other exposures.

Oxidative stress

Endothelial damage and the initiation of the atherogenic cycle may be influenced by the redox environment. SLE patients have increased levels of reactive oxygen and nitrogen species and antibodies to resultant protein adducts, which correlate with disease activity and provide an environment for oxidation of lipoproteins and atherosclerosis development [69]. Homocysteine, a molecule with the capacity to increase reactive oxygen species in the bloodstream, is also increased in SLE patients and correlates with carotid IMT and with coronary calcification [5,70,71]. Further, defense mechanisms against an altered redox environment are decreased in SLE. For example, paraoxonase, an enzyme with antioxidant activity that circulates attached to HDL and prevents LDL oxidation, is decreased in this disease. This correlates with the presence of antibodies to HDL and β2-glycoprotein and with enhanced atherosclerosis risk [72].

Antiphospholipid antibodies

The role of antiphospholipid (APL) antibodies in premature CVD remains a matter of debate. β2-glycoprotein I, abundantly found in vascular plaques, has been hypothesized to be protective against atherosclerosis development. Antibodies against this molecule could, in theory, be detrimental to the vessel wall and promote activation of inflammatory cascades by IC formation [73]. APL antibodies may increase the likelihood of abnormal ankle brachial index and anti-cardiolipin antibody titers correlate with carotid IMT [70,74]. However, a recent study examining flow-mediated dilation and EPC numbers in primary APL syndrome (APS) did not detect any difference in these early markers of CVD risk compared with age and gender matched healthy controls [75]. This supports previous work in which the presence of APL antibodies did not correlate with endothelial dysfunction or carotid IMT in SLE [7,76]. Using cardiac MRI to find evidence of subclinical ischemic disease, 26% of patients with APS had occult myocardial scarring compared to 11% of controls. This study, however, enrolled patients with secondary APS from SLE (22% of their APS cohort) and it is unclear whether a significant number of the patients with myocardial damage also had lupus [77]. Thus, the role of APL antibodies in atherosclerosis development in SLE remains unclear. Nevertheless, because of the arterial thrombosis associated with APS itself, there remains a putative role for these antibodies in the triggering of unstable angina and acute coronary syndromes.

Other autoantibodies

Autoantibodies against regulatory proteins in the atherogenic cycle in SLE may potentially contribute to CVD. Antibodies to the anti-atherogenic HDL and one of its components, Apo A-1, are increased in SLE and rise with disease flares [78]. SLE patients have increased levels of anti-lipoprotein lipase antibodies. These also increase with disease activity and may contribute to increased levels of triglycerides [79]. Antibodies to endothelial cells are common in SLE and have been proposed to mediate endothelial injury [80]; however, various groups have shown that these antibodies may not correlate with other markers of endothelial dysfunction [81]. Additionally, antibodies to oxidized LDL, lipoprotein lipase, CRP and annexin V may have a putative role in CVD in SLE [82,83]. Antibodies to heat shock proteins enhance atherosclerotic development in various non-lupus models and are increased in SLE serum [84,85]. Whether this class of antibodies contributes specifically to SLE-related atherosclerosis is unknown.

Preventive measures for cardiovascular disease in SLE

Various studies indicate that early and appropriate treatment of immune dysregulation in SLE could be key to hampering CVD development and progression in SLE.

Patients treated with lower doses of cyclophosphamide, azathioprine or corticosteroids had greater progression of CVD than those treated with higher doses [5]. Further, aortic atherosclerosis risk is lower in SLE patients who have undergone treatment with cyclophosphamide when compared to SLE patients who have not received this medication [9]. The role of corticosteroid treatment is complex and poorly understood, with potentially dual effects on CVD risk that may depend on dose and time of exposure [8].

While no studies have shown a reduced incidence of CVD in patients taking antimalarials, these drugs have positive effects on glucose tolerance, lipid profiles, and thrombosis potential [86]. Studies using surrogate markers for CVD have provided mixed results. Antimalarials were significantly associated with decreased presence of carotid plaque in patients with SLE [87]. A correlation between lack of antimalarial use and increased vascular stiffness in SLE patients has been demonstrated, but no association between their use and coronary calcification was found [88,89]. A cohort study suggested a clear survival benefit in SLE patients taking antimalarials, but the mechanisms for this effect remain to be determined [90]. Because antimalarials can weakly inhibit IFN-α production through inhibition of IC formation and toll-like receptor-7 and -9 signaling [91], modulation of IFN-α levels with a potential improvement in endothelial function and vascular repair may contribute to the survival benefit. More research into the vascular effects of antimalarials is needed to understand their benefits and whether they have an impact on atherosclerotic development.
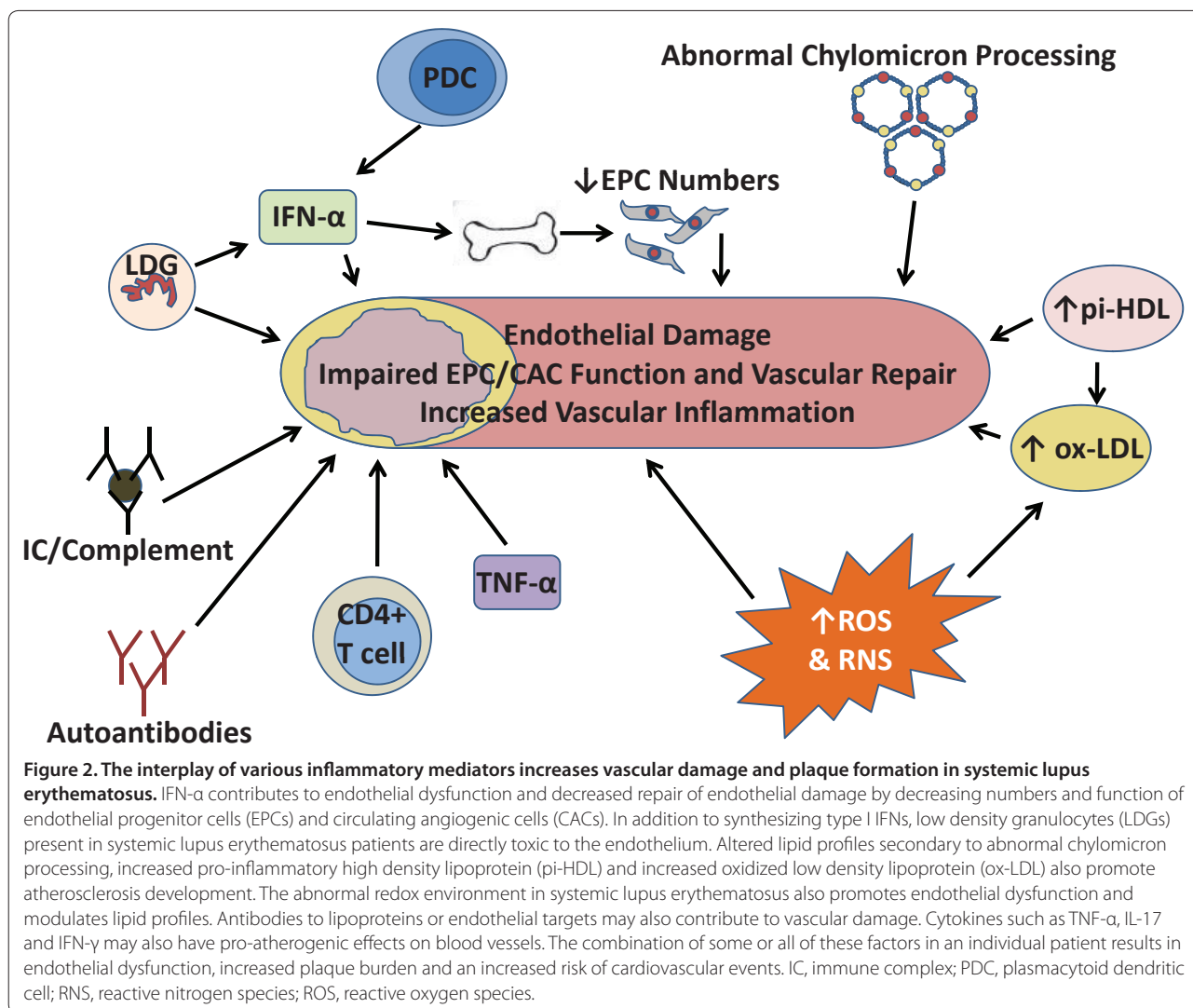
Mycophenolate mofetil (MMF), an immunosuppressive medication commonly used in SLE, may be potentially beneficial in atherosclerosis. MMF has a protective effect on the development of both transplant and diet-mediated atherosclerosis in animals and is also beneficial in preventing coronary pathology in cardiac transplant patients [92]. MMF decreases atherosclerotic plaque inflammation in patients treated for 2 weeks prior to carotid endarterectomy [93]. Whether this drug has a CVD benefit in SLE patients remains to be determined, and future studies will hopefully address this question.

The role of novel biologics in CVD prevention in SLE remains unknown. Currently, studies targeting type I IFNs, IL-17 and the various anti-B cell therapies are underway in SLE and other diseases. Long-term follow-up to assess atherosclerosis progression in these groups would be important to identify if favorable effects are identified. Given the recent observation that impairment in IL-1 pathways in SLE may mediate abnormal vascular repair in this disease [32], a note of caution is added with regards to the use of anakinra and other anti-IL-1 therapies, particularly in SLE, but also in other diseases where aberrant vasculogenesis is observed.

Other non-disease modifying medications may also have a benefit in SLE-related CVD. SLE patients have a higher incidence of metabolic syndrome and insulin resistance, and this correlates with increases in homocysteine and high sensitivity CRP [94]. Treatment of insulin-resistant states may improve CVD profiles in SLE. Our group reported that treatment of SLE-prone mice with the peroxisome proliferator-activated receptor γ (PPAR-γ) agonist pioglitazone, which is used to treat type II diabetes in humans, resulted in improved insulin sensitivity, improved endothelial function and restored EPC differentiation [94]. Additionally, rosiglitazone, another PPAR-γ agonist, decreased aortic atherosclerosis in lupus- and atherosclerosis-prone Gld.apoeE-/- mice [54]. How this class of medications would benefit CVD in SLE patients warrants additional studies.

Guidelines for CVD prevention in SLE remain nebulous. The latest European League Against Rheumatism (EULAR) recommendations suggest yearly monitoring of traditional and/or non-lupus-specific CVD risk factors, including smoking, activity level, oral contraceptive use, hormonal therapies and family history of CVD. Monitoring of blood pressure, lipids and glucose is also recommended [95]. One group has proposed treating SLE as a coronary heart disease equivalent, targeting recommendations as suggested by the Adult Treatment Panel guidelines (ATPIII) [96]. However, whether these guidelines will be sufficient to abrogate CVD risk in SLE remains to be determined. The use of statins in SLE has not been systematically or extensively studied, but they have been shown to improve endothelium-dependent flow-mediated dilation and possibly slow progression of carotid IMT in adult lupus as well as increase EPC numbers in other conditions, including diabetes mellitus [97-99]. While trending toward a protective effect for carotid IMT thickness in pediatric SLE, prophylactic statin use in children did not show a statistically significant difference compared to placebo [100]. A murine lupus/atherosclerosis model displayed decreased atherosclerosis and amelioration of renal disease when treated with simvastatin [101]. Statins can also block IFN-α production in peripheral blood from healthy controls in response to exposure to SLE patients' serum. This blockade occurs through inhibition of the Rho kinase, likely in plasmacytoid DCs [102]. Future research will hopefully clarify the role of statin use in SLE patients.

Finally, diet may be an important modifiable risk factor that can alter predisposition to atherosclerotic lesions. LDL receptor-deficient mice that underwent bone marrow transplant with SLE-prone cells had increased sensitivity to dietary fat. A Western-style diet containing 21% fat increased atherosclerotic lesions, pathogenic antibody formation and severity of renal disease when compared to mice fed a regular diet [55]. A different

Figure 2. The interplay of various inflammatory mediators increases vascular damage and plaque formation in systemic lupus erythematosus. IFN-α contributes to endothelial dysfunction and decreased repair of endothelial damage by decreasing numbers and function of endothelial progenitor cells (EPCs) and circulating angiogenic cells (CACs). In addition to synthesizing type I IFNs, low density granulocytes (LDGs) present in systemic lupus erythematosus patients are directly toxic to the endothelium. Altered lipid profiles secondary to abnormal chylomicron processing, increased pro-inflammatory high density lipoprotein (pi-HDL) and increased oxidized low density lipoprotein (ox-LDL) also promote atherosclerosis development. The abnormal redox environment in systemic lupus erythematosus also promotes endothelial dysfunction and modulates lipid profiles. Antibodies to lipoproteins or endothelial targets may also contribute to vascular damage. Cytokines such as TNF-α, IL-17 and IFN-γ may also have pro-atherogenic effects on blood vessels. The combination of some or all of these factors in an individual patient results in endothelial dysfunction, increased plaque burden and an increased risk of cardiovascular events. IC, immune complex; PDC, plasmacytoid dendritic cell; RNS, reactive nitrogen species; ROS, reactive oxygen species.

model of lupus-prone mice fed high-fat chow or administered leptin had accelerated and increased proteinuria, suggesting an interplay between diet and lupus [68]. Certainly, some murine lupus models have decreased life spans when fed a high-fat diet [103]. Thus, further understanding of the role of diet on immune modulation and CVD risk in SLE may be key in vascular damage prevention.

Conclusion

The CVD risk in SLE patients stems from a combination of traditional risk factors and SLE-specific mechanisms that incorporate chronic inflammation, endothelial dysfunction, decreased vascular repair through a type I IFN effect, antibody formation and perturbed lipid homeostasis and redox environment (Figure 2). Continued research into the mechanisms of lupus-related CVD will hopefully provide effective tools and targets to improve their survival and overall quality of life.

Additionally, it is crucial that future clinical trials in SLE include biomarkers of vascular damage, functional studies of vascular health and assessment of subclinical and clinical CVD as endpoints in their efficacy analysis.

Abbreviations

APL, antiphospholipid; APS, APL syndrome; CAC, circulating angiogenic cell; CRP, C-reactive protein; CVD, cardiovascular disease; DC, dendritic cell; EPC, endothelial progenitor cell; HDL, high density lipoprotein; IC, immune complex; IFN, interferon; IL, interleukin; IMT, intima media thickness; LDG,

low-density granulocyte; LDL, low density lipoprotein; MMF, mycophenolate mofetil; PPAR-γ, peroxisome proliferator-activated receptor γ; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; VCAM, vascular cell adhesion molecule.

Competing interests

The authors declare that they have no competing interests.

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