Systemic lupus erythematosus and atherosclerosis: Review of the literature

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Abstract

The purpose of this manuscript is to extensively review the literature related to systemic lupus erythematosus and atherosclerosis. The conclusion of this review has covered accelerated atherosclerosis in systemic lupus erythematosus, the role of complement, interferon in premature atherosclerosis, in inflammatory mediators such as cytokines, leukocytes, innate and adaptive immunity, hydrolytic enzymes, reactive oxygen species, vascular endothelial growth factor, toll receptors in lupus nephritis, several specific anti-inflammatory pharmacological therapies, and potential prevention strategies for atherothrombotic events, interferons and the inflammasome.

It is important for allergist-immunologists, rheumatologists both in academic institutions and in practice to understand this important disorder.

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1. Introduction

1.1. Immunology and pathogenesis

Systemic lupus erythematosus (SLE) is an autoimmune disease with a wide spectrum of disease expression, with aberrant host innate and adaptive immune response, and chronic inflammation.

The pathogenesis of many autoimmune diseases is initially based on a redundant or prolonged activation of the innate immune system [1]. It was suggested that an excessive activation of innate immunity is often the result of a chronic inflammatory process in the organism and this inflammation can be induced by exogenous and endogenous alarm factors, or alarmins. The authors of this paper believe that the recently discovered neutrophil extracellular traps, or NETs, completely meet the criteria of alarmins [1]. This review summarized current knowledge concerning the general characteristics of NETs, their antimicrobial properties, and their role in the development of chronic inflammatory processes that underlie the pathogenesis of atherosclerosis. Studies on NET can provide the foundation for developing new diagnostic methods and effective treatment of chronic inflammatory and autoimmune diseases [1].

Recent discoveries implicate neutrophils as important regulators of both innate and adaptive immunity and in the development of organ damage in systemic autoimmune diseases, including SLE [2]. Various SLE biomarkers are neutrophil-related, including neutrophil granular proteins and histones undergoing post-translational modifications during neutrophil extracellular trap (NET) formation. Hampering NET formation through peptidylarginine deiminase inhibitors abrogates lupus phenotype and atherosclerosis in murine studies [2]. Thus, recent discoveries support the notion that neutrophils, low-density granulocytes and aberrant NET formation and clearance play important roles in lupus pathogenesis. Future studies should focus on how to selectively target these immunostimulatory pathways in this disease [2].

Abnormal immune cellular and humoral responses and complement factors play important roles in the development of SLE and impaired clearance of apoptotic material is a key factor contributing to activation of self-reactive immune cells [2]. The incidence of atherosclerotic cardiovascular disease (CVD) is increased up to 50-fold in SLE compared to age- and gender-matched control subjects, and can partly be explained by traditional risk factors [2].

There is a need for novel treatment strategies and increased understanding of the mechanisms involved in the pathogenesis of CVD. SLE complications and a larger scale investigation of varying composition of apolipoproteins related to atherogenic LDL are seen in CVD [2]. Pathogenic SLE immune responses and development of atherosclerotic plaques share some characteristics, due to skewed T cell activation, suggesting the possibility of identifying novel intervention targets. Novel immune-based therapies for CVD are being developed that some may be effective in the prevention of CVD and for immunomodulation [3]. Complement activation occurs in SLE and immunomodulation of autoimmune and inflammatory disorders related to complement components and deficiency of C1q, C1r, C1s, C4, C2 and failure to activate the classical pathway [4]. Several rheumatologic and autoimmune disorders can masquerade as allergic disease. Identification of these in an office setting can be a challenge for the practicing allergist-immunologist, rheumatologist and an earlier article addressed this topic and clinical uses of immunologic tests [5].

A recent article reviewed the complex interactions in SLE using data of the important literature in peer-reviewed journals [6]. The study evaluated clinical and immunologic features, pathogenesis, epidemiology, laboratory evaluation, and treatment. New immune cell targeted therapies are now available that are specifically designed to block cellular pathways and the practicing physician should understand diagnosis, immunology, pathogenesis, laboratory evaluation, and updated treatment options in their clinic or daily practice [6]. Signs and symptoms vary, may be intermittent, and can be mild, moderate, or severe. Diagnosis can be difficult because SLE mimics many other diseases and requires recognition of clinical and serologic criteria. Interaction and coordination with a rheumatologist are also helpful in the diagnosis and the treatments of SLE [6].

1.2. Risk of cardiovascular disease

Multiple studies suggest that these patients have between a 9-fold and 50-fold increase in risk of developing CVD compared with non-SLE patients. These increases result from a combination of traditional risk factors, and dysfunctional immune and inflammatory mechanisms [7]. The relative risk of myocardial infarction is five to eight times greater than that of the general population, and more than 1/3 of SLE patients exhibit evidence of carotid plaques of coronary artery calcifications.

Premature atherosclerosis has been recognized as a major comorbid condition in SLE. Women with SLE in the 35- to 44-year-old age group have an estimated 50-fold increased risk of myocardial infarction compared with age- and sex-matched controls, as well as an increased incidence of subclinical atherosclerosis [8]. Accelerated atherosclerosis is a major cause of morbidity and death in SLE. The purpose of this recent study was to determine whether the prevalence and extent of coronary artery calcium (CAC) is higher in female SLE patients compared with a non-SLE sample from the Multi-Ethnic Study of Atherosclerosis (MESA) [8]. CAC was measured in 80 female SLE patients and 24 female MESA controls from the Baltimore Field Centre, ages 45–64 years, without evidence of clinical cardiovascular disease. Binary regression was used to estimate the ratio of CAC prevalence in SLE vs. MESA controls, controlling for demographic and cardiovascular risk factors. To compare the groups with respect to the quantity of CAC among those with non-zero Agatston scores, linear models were used in which the outcome was a log-transformed Agatston score. The prevalence of CAC was substantially higher in SLE [8]. The differences were most pronounced and statistically significant in those aged 45–54 years but were still observed among those aged 55–65 years after controlling for age, ethnicity, education, income, diabetes mellitus, hypertension, hyperlipidemia, high-density lipoprotein levels, smoking, education and BMI, SLE patients still had a significantly higher prevalence of CAC than controls. Among those with CAC, the mean log Agatston score did not differ significantly between SLE and MESA participants. Women with SLE have a higher prevalence of CAC than comparable women without SLE, even after adjusting for traditional cardiovascular risk factors, especially among those aged 45–54 years [8].

Atherosclerosis is an inflammatory disease. Its lesions are filled with immune cells that can orchestrate and effect inflammatory responses. In fact, the first lesions of atherosclerosis consist of macrophages and T cells. Unstable plaques are particularly rich in activated immune cells, suggesting that they may initiate plaque activation [9].

Antiphospholipid syndrome is a rare autoimmune disease characterized by a high tendency of developing thrombotic events, diagnosed in the presence of specific laboratory criteria (positivity for lupus anticoagulant, and the presence of anticardiolipin and aβ2GPI antibodies) and clinical criteria such as thrombosis in any district (arterial or venous) and pregnancy morbidity [10].

The heart is commonly affected by direct (autoimmune mediated action) or indirect (thrombosis) pathological mechanisms. Heart valve lesions are the most frequent manifestations, however the hemodynamic significance is quite uncommon but when it occurs it may require surgery that further complicates the picture due to the high risk of thrombosis. Coronary arteries and myocardium are also affected leading to ischemic heart disease and left ventricular dysfunction. Other findings include chronic thromboembolic pulmonary hypertension and accelerated atherosclerosis. The consequences of heart involvement may be significant in overt disease. The treatment of cardiac complications is challenging and requires an in-depth knowledge of the disease [10].

Various autoimmune rheumatic diseases (ARDs), including SLE are associated with premature atherosclerosis and although experimental models of atherosclerosis support the role of antiphospholipid...
antibodies in atherosclerosis, there is no clear evidence of premature atherosclerosis in antiphospholipid syndrome (APA) [11].

Ischemic events in APA are more likely to be caused by prothrombotic state than by enhanced atherosclerosis. Cardiovascular disease (CVD) in ARDs is caused by traditional and non-traditional risk factors and besides other factors, inflammation and immunologic abnormalities, the quantity and quality of lipoproteins, hypertension, insulin resistance/hyperglycemia, obesity and underweight, presence of platelets bearing complement protein C4d, reduced number and function of endothelial progenitor cells, apoptosis of endothelial cells, epigenetic mechanisms, renal disease, hypothyroidism, sleep apnea and vitamin D deficiency may contribute to the premature CVD [11]. Although most research has focused on systemic inflammation, vascular inflammation may play a crucial role in the premature CVD in ARDs and it may be involved in the development and destabilization of both atherosclerotic lesions and of aortic aneurysms, a known complication of ARDs. Inflammation in subintimal vascular and perivascular layers appears to frequently occur in CVD, with a higher frequency in ARD than in non-ARD patients. It is possible that this inflammation is caused by infections and/or autoimmunity, which might have consequences for treatment. Drugs targeting immunologic factors participating in the subintimal inflammation (e.g., T- and B-cells) might have a protective effect on CVD and interestingly, vasa vasmorum and cardiovascular adipose tissue may play an important role in atherogenesis [11]. Inflammation and complement depositions in the vessel wall are likely to contribute to vascular stiffness. Based on biopsy findings, also inflammation in the myocardium and small vessels may contribute to premature CVD in ARDs such as cardiac ischemia and heart failure. There is an enormous need for an improved CVD prevention in ARDs. Studies examining the effect of DMARDs/biologics on vascular inflammation and CV risk are warranted [11].

1.3. Mechanisms

Atherosclerosis is a chronic disease of the arterial wall which innate and adaptive immunoinflammatory mechanisms are involved as reported in the formation of early fatty streaks when the endothelium is activated and expresses chemokines and adhesion molecules, leading to monocyte/lymphocyte recruitment and infiltration into the subendothelium [12]. It also acts at the onset of adverse clinical vascular events when activated cells within the plaque secrete matrix proteases degrading extracellular matrix proteins and weaken the fibrous cap, with rupture and thrombus formation [12].

1.4. Role of cytokines and TGFβ

Cells involved in the atherosclerotic process secrete and are activated by cytokines. Mechanisms of atherosclerosis provide evidence that the immunologic inflammatory response in atherosclerosis is modulated by regulatory pathways in which IL-10 and transforming growth factor (TGF)-β play a critical role [12]. The role of cytokines and novel strategies to combat this disease were discussed, addressing the potential of circulating cytokine levels as biomarkers of CAD [12]. Cytokines, master regulators of the innate and adaptive immune response are known to regulate and coordinate many stages of atherosclerosis IL-1, IL-6, IL-10, IFN-γ, and TNF-α, are highly expressed in atherosclerotic areas and exhibit pro- and antiatherogenic actions [12]. Understanding of the role played by inflammation in atherosclerosis has a significant implication for current and future therapeutic approaches to primary and secondary prevention of atherothrombotic events [12].

1.5. Vascular endothelial growth factor, toll receptors and lupus nephritis

The nuclear protein high mobility group box 1 (HMGB1) has been suggested to be involved in the pathogenesis of several vascular diseases such as systemic vasculitis and atherosclerosis [13]. In atherosclerotic disease, HMGB1 displays increased expression in nuclei and cytoplasm of macrophages and smooth muscle cells in the atherosclerotic lesions, and is implicated in the progression of the atherosclerotic plaque [13]. Experimental models of acute coronary syndromes and cerebrovascular accidents show that HMGB1 is not only involved in the amplification of the inflammatory response during acute ischemic injury, but also in the recovery and remodeling process after ischemia. Patients with acute coronary syndromes or stroke present significantly higher serum levels of HMGB1 than healthy controls and levels are associated with disease severity and mortality. This article reviewed clinical and experimental studies dealing with the role of HMGB1 in vascular diseases.

The role of TLRs and endogenous ligands in various renal diseases were reviewed and their activation in the inflammatory response of immune mediated glomerulonephritis [14]. VEGF is a tightly cytokine in the kidney. CVD is characterized by increased VEGF, alters vascular hemostasis and promotes neoangiogenesis. VEGF plasma levels have been associated with disease activity and correlated with lupus nephritis (LN), higher mean carotid intima media thickness, and can be a novel cardiovascular risk factor in premature coronary atherosclerosis [14]. This paper was a novel basic science study on the role of TLRs and VEGF in human kidneys from LN patients [14]. Toll receptors are important in SLE.

VEGF regulates angiogenesis through endothelial cell proliferation related to capillary repair in damaged glomeruli. Toll-like receptor (TLR) 9 and VEGF were investigated in glomerular and tubule interstitial expression in biopsies from humans with LN and healthy controls. Immunohistochemistry was performed, slides were incubated with anti-VEGF and TLR9, stained with hematoxylin and eosin, and scored [15]. Kidney biopsies in LN (n = 10) and healthy controls (n = 10) were evaluated for the expression of TLR9 and VEGF and the degree of kidney damage was analyzed according to the International SNR pathology classification. Intense staining was noted of glomeruli and tubules for TLR9 up to 3+ from patients with LN and samples showed 3+ staining of glomeruli, but only up to 2+ in tubules for VEGF. There was no significant staining for TLR9 and none for VEGF in control slides. No correlation was observed between LN, class severity and intensity of staining for VEGF or TLR9. This was the first study to investigate expression of TLR9 in human samples as well as combined expression of TLR9 and VEGF in this basic science study on the role of TLRs and VEGF in human kidneys from LN patients. This could be an important tool for understanding the role of TLR9 and VEGF in renal disease, and offer insight into the early detection and targeted treatment of LN [15]. The patients have diverse symptoms and may present in different specialty clinics of the hospital. This review discussed various aspects of SLE, its pathogenesis, role of accelerated atherosclerosis, proinflammatory cytokines and therapeutic approaches. The role of VEGF was also discussed. VEGF plasma levels have been associated with disease activity, classification of severity, side-effect profiling, diagnostics, current treatment options and prognosis as well as future therapeutic approaches [15].

Physicians in practice should be knowledgeable regarding several aspects of SLE and LN. These disorders can present to the clinician’s clinic and private office regardless of their specialty. This review discussed various aspects of SLE, mechanisms of disease, role of accelerated atherosclerosis, proinflammatory cytokines, and therapeutic approaches [16].

1.6. Innate cytokines and endothelial cell activation

Innate cytokines such as IL-1 or TNF may activate endothelial cells, vascular smooth muscle cells, monocytes/macrophages, lymphocytes (T, B, and natural killer cells), dendritic cells, and mast cells. Vascular cells can actively contribute to the inflammatory cytokine-dependent response in the vessel wall via cytokines production or cytokine elicitation or can be involved in cytokine-mediated interaction with invading cells. Pathways activation results in cell accumulation, increased low-
density lipoprotein (LDL) and extracellular matrix deposition, which may facilitate subsequent invasions [17].

Inflammatory expression profiles in monocyte-to-macrophage differentiation in patients with SLE and relationship with atherosclerosis was reviewed [18]. Monocytes were obtained from 20 patients with SLE and 16 healthy controls and were in vitro differentiated into macrophages.

1.7. Monocyte subsets and genetics in SLE

The emerging role of monocytes in atherosclerosis has been defined. A recent review investigated the relationship between subclinical atherosclerosis, endothelial dysfunction and the phenotype of peripheral blood monocytes in SLE patients. The phenotype of monocyte subsets was defined by the expression of CD14 and CD16 in 42 patients with SLE and 42 non-SLE controls using ultrasonography, intima-media thickness (IMT) of carotid arteries and brachial artery flow-mediated dilation (FMD) as well as nitroglycerin-induced dilation (NMD) [18]. Patients with SLE had significantly, but only modestly, increased IMT when compared with non-SLE controls. In spite of early atherosclerotic complications in the studied SLE group, marked endothelial dysfunction was observed. CD14dimCD16+ proinflammatory cell subpopulation was positively correlated with IMT in SLE patients. This phenomenon was not observed in control individuals. Interestingly, endothelial dysfunction assessed by FMD was not correlated with any of the studied monocyte subsets and CD14dimCD16+ monocytes were associated with subclinical atherosclerosis in SLE, although the mechanism appeared to be independent of endothelial dysfunction [19].

Whole-genome RNA expression microarray was performed, and gene expression was examined. Many genes were differentially regulated during monocyte-to-macrophage differentiation in SLE patients compared with controls. The expression of these genes in mononuclear cells is important in the pathogenesis of SLE, and molecular profiling using gene expression can help stratify SLE patients who may be at risk for development of atherosclerosis [20].

1.8. Plaque development

A recent study assessed the influence of different SLE characteristics and treatment regimens on increased carotid intima media thickness (IMT) and atherosclerotic plaques in 103 SLE patients and 95 age- and sex-matched control subjects. IMT was measured in the common carotid arteries bilaterally. Common carotid arteries, internal carotid arteries and superficial femoral arteries were also screened for the presence of plaques. The presence of plaques was correlated with age and male sex. Damage Index. IMT was associated with SLE duration and body mass index. Thus, a correlation was found between atherosclerosis and several classical cardiovascular risk factors and disease-related factors. A beneficial effect of continuous immunosuppressive treatment on IMT suggests that appropriate disease control with steroid-sparing agents may protect against atherosclerosis in SLE patients [20].

1.9. Plaque development and CD40 ligand

CD40/CD40L pathway actively participates in plaque development and progression and the important role for CD40/CD40L interactions in atherosclerosis was clearly established in apoE−/− and LDLr−/− mice. The important role of T-cell–TGF-β signaling in atherosclerosis suggests that regulatory pathways in adaptive immunity are essential in modulation of the development and SLE progression. Mimics or inducers of suppressor of cytokine signaling 1 might be useful to attenuate the effects of IFN-γ in the context of atherosclerosis [21]. Candidate antigens (oxidized lipoproteins, HSP, phosphoryl choline, apoptotic bodies) may induce T-helper type 1 (Th1), Th2, or both Th1 and Th2 pathogenic responses. Maturation of the antigen-presenting cell is necessary for T-cell priming. The CD40/CD40L pathway is critical for Th1 differentiation. IL-6 and IL-13 contributes to induction of Th2 cell type. IFN-γ (Th1) and IL-4 (Th2) promotes atherogenesis [21].

1.10. Role of Tim-1

SLE is a complex systemic autoimmune disease, characterized by tissue damage, with immune complexes in various organs, including the kidney. LN is a major contributor to the mortality of these patients and has been associated with dysregulation of either Th1 or Th2 responses. Based on its potential influence on Th1/Th2 regulation, Tim-1 and Tim-3 were investigated for their association with SLE. Expression of Tim-1 and Tim-3 in PBMCs from SLE patients was examined by RTPCR. Increased Tim-1 expression was observed in SLE patients when compared with sex matched healthy controls, which is positively correlated with IL-10 expression [2]. A significant increase of Tim-1 expression was observed in active SLE, indicating that Tim-1 expression might be related to active clinical phases. Increased Tim-1 expression has been shown in mononuclear cells from SLE patients and Tim-3 may also be involved in a protective role in rheumatoid arthritis [22]. The findings by several independent groups that two of the major counter regulatory cytokines in atherosclerosis, IL-10 and TGF-β, are those required for the immunoregulatory functions of natural or adaptive antigen-induced regulatory T cells leading to the hypothesis that adaptive or natural regulatory cells may play an important role in the control of the atherosclerotic process [22].

Chloroquine diphosphate alone or added to corticosteroids has a beneficial effect in SLE dyslipoproteinemia [23].

The risk of developing CVD is increased in SLE compared with the general population. A recent review summarized traditional and emerging risk factors of CVD in SLE and potential pathogenic mechanisms involved in CVD development [24]. The role of commonly used drugs and preventive strategies exploitable in everyday clinical practice were also discussed. Expert opinion: SLE-related risk factors involve both disease- and treatment-related features, including disease activity, disease phenotype, corticosteroid misuse and alterations of innate and adaptive immunity. Primary prevention is mandatory in management of lupus patients through appropriate disease control, corticosteroid tapering, use of antimalariais and eventually vitamin D supplementation [24]. Recent advances in our understanding of the genetic, molecular, and cellular bases of autoimmune diseases and especially SLE have led to the application of novel and targeted treatments. Although many treatment modalities are effective in lupus-prone mice, the situation is more complex in human subjects [25].

1.11. Role of antioxidants and quinones

Antioxidants could prove to be a positive adjunct to treatment manifested as reactive oxide intermediates (ROIs). Metabolites such as hydroxyl radicals and hydrogen peroxide are generated during the immune process as neutrophils and macrophages activate. ROIs directly damage the endothelium, creating wall holes, resulting in leaky membranes and interstitial edema. Apoptotic processes are also induced, along with deleterious effects on intracellular messaging [26].

Quinones are lipid soluble electron and proton carriers and undergo highly regulated redox reactions in the mitochondria. Important consequences of these electron transfer reactions are the production of and protection against ROS [26]. Quinones have been extensively studied for both their cytotoxic and cellular protective properties. In this literature review, the role of quinones was explored with a particular focus on renal diseases, due to their high basal metabolism and detoxification role, since kidneys are particularly sensitive to oxidative stress [26]. Regardless of the underlying etiology, ROS plays an important role in both acute kidney injury (AKI) and chronic kidney diseases (CKD). Depending on the oxidative state of the kidney, quinones can be nephrotoxic or nephro-protective. Many factors play a role in the interaction
between quinones and the kidney and the consequences of this are just beginning to be explored [27].

1.12. Immunosuppressive drugs

Immunosuppressive drugs may reduce the progression of atherosclerosis and cardiovascular events, yet their exact mechanisms require further elucidation. Belimumab is a fully human monoclonal antibody that has been recommended for approval by the US FDA for treatment of active autoantibody-positive SLE patients [28].

This article explained the precise mechanism of action of Belimumab on BlyS, its soluble protein that plays a major role in the pathogenesis of LN. In addition, the extensive pharmacokinetics and clinical implications are exemplified in this review with Belimumab's comparison with standard therapeutic guidelines for the treatment of LN. Healthcare practitioners should be knowledgeable regarding several aspects of autoimmune disorders, especially SLE and LN [28].

Recently introduced into the market, Belimumab is a monoclonal antibody that has potential clinically efficacious applications for the treatment of LN which is a major complication of SLE that can lead to significant illness or even death without proper intervention and treatment [28]. Belimumab may also produce an action in the spleen by blocking BlyS-mediated transition of immature B cells from the T1 to T2 stage, preventing the eventual generation of mature B cells. The T1 to T2 transition is a key checkpoint for negative selection of B cells; hence, explaining the novel logic of Belimumab's mechanism of action. Belimumab is very useful for the treatment of LN, as listed above [28].

There have been significant advances in the treatment of SLE, and experts see great promise in B cell-targeted therapy, especially Belimumab, in addition, anticytokine therapies against IL-6, INF-α, and INF-γ, and tyrosine kinase inhibitor have offered possibilities for the future using new pathways for the treatment of lupus [29].

1.13. Role of interferons

Anti-IFN-γ therapy IFN-γ classified as a type II IFN is mainly produced by Th1-type T cells and natural killer (NK) cells. Not only does the type I IFN signature contribute an important feature in human SLE, the expression of IFN-Anti-IFN-γ therapy the expression of IFN-γ has also been demonstrated as an association with the immunopathogenesis in human and murine SLE [30].

With improved management of the classical disease manifestations of SLE, CVD has emerged as one of the most important causes of morbidity and mortality. This review in particular focused on progress over the past year in clinical and basic aspects of SLE-driven accelerated atherosclerosis. CVD is a major complication of lupus and is now a leading cause of death with this disease. Additional studies are needed in order to identify the most effective preventive strategies and most predictive vascular risk biomarkers. Type I IFNs may play a critical role in lupus CVD pathogenesis, and it is recommended that vascular outcomes be included in ongoing trials testing the efficacy of anti-IFN biologics [30].

A recent paper by the first author of this paper with other authors on the role of interferon in premature atherosclerosis in SLE patients stated SLE is a chronic systemic autoimmune disease associated with significant cardiovascular morbidity and mortality. Studies have established that patients with SLE develop accelerated atherosclerosis related to endothelial cell dysfunction and acute vascular events not explained by Framingham risk score risk stratification [31]. In this article, we closely explored the role of interferons in endothelial cell apoptosis and vascular IFN plays an important role in the development of premature atherosclerosis of SLE patients. An imbalance between endothelial cell damage and repair develops as a result of alterations in EPCs and CACs which are mediated by IFN-α. IFN-1 promotes atherosclerosis by various mechanisms by affecting adhesion and migration of leucocytes to plaques and by promoting plaque rupture. Understanding the role of IFN in promoting premature atherosclerosis is critical to the development of appropriate target therapy [31].

Type I interferons (IFNs) appear to play a prominent role in premature vascular damage in adult-onset SLE, by inducing impairments in the phenotype and function of endothelial progenitor cells (EPCs), hampering vascular repair. It is not clear whether EPC dysfunction is present in childhood-onset SLE in association with a type I IFN signature [28]. In a recent study the phenotype and numbers of EPCs were quantified in patients with childhood-onset SLE, patients with juvenile idiopathic arthritis (JIA), and matched healthy control subjects. In a separate cohort of patients with childhood-onset SLE, markers of subclinical atherosclerosis and endothelial dysfunction were quantified using standardized protocols and analyzed for associations with serum type I IFN activity [28]. EPC numbers and function were significantly decreased in patients with childhood-onset SLE compared with patients with JIA and healthy control subjects. Serum from patients with childhood-onset SLE impaired differentiation of EPCs into mature endothelial cells in healthy controls, and this effect was blocked by inhibition of the type I IFN pathway. Type I IFN activity in serum was not significantly associated with subclinical atherosclerosis and endothelial function in patients with childhood-onset SLE as in adult-onset SLE [32]. Childhood-onset SLE is characterized by phenotypic and functional EPC abnormalities, which are likely triggered by type I IFNs, although cross-sectional analysis revealed no global association between type I IFN signatures and vascular measures of subclinical atherosclerosis. Longitudinal assessments are needed to evaluate whether progression of vascular damage in patients with childhood-onset SLE is associated with type I IFNs, as observed in patients with adult-onset SLE [32].

CVD due to accelerated atherosclerosis is the leading cause of death in patients with SLE. The mechanisms that mediate the acceleration of atherosclerosis in SLE remain elusive. Based on experimental data which includes both humans (SLE patients and control subjects) and rodents (Apoe−/− mice), a recent paper proposed a multi-step model in which the immune dysfunction associated with SLE (i.e. high level of IFN-α production by TLR 9-stimulated pDCs) is associated with, an increased frequency of circulating pro-inflammatory CD4 + CXCR3 + T cells; an increased production of CXCR3 ligands by endothelial cells; an increased recruitment of pro-inflammatory CD4 + CXCR3 + T cells into the arterial wall, and the development of atherosclerosis [28]. The model also pointed to hypotheses for potential interventions, such as pDCs-targeted therapy, that might be studied in the future [33].

1.14. Role of the inflammasome

Kahnenberg and others showed that caspase-1 inhibition improves dysfunctional SLE EPC/CAC differentiation into mature endothelial cells and blocks IFN-α-mediated repression of this differentiation, implicating inflammasome activation as a crucial downstream pathway leading to aberrant vasculogenesis [34]. The effects of IFN-α are complex and contribute to an elevated risk of CVD by suppression of IL-1β pathways and by upregulation of the inflammasome machinery and potentiation of IL-18 activation [34].

2. Conclusion

This paper has reviewed the immunology of SLE, pathogenesis, role of complement, innate and adaptive immunity, cytokines and TGFβ, risk of CVD, VEGF in LN, genetics, plaque development and CD40 ligand, Tim 1, ROS and quinones, several immunosuppressive agents, role of interferons and the inflammasome. Combining immunosuppressant therapy with anti-inflammatory drugs will most likely provide for the best clinical outcomes for future SLE patients. There have been significant advances in the treatment of SLE, both T and B cell-targeted therapy, especially Belimumab, anticytokine therapies against IL-6, INF-α, and INF-γ,
and tyrosine kinase inhibitors for the future using new pathways for treatment. It is critical to understand the pathophysiology of this disease, mechanisms of action and proposed treatments. It is important for allergist-immunologists and rheumatologists both in academic institutions and in practice to understand this important disorder and the role of many immunologic factors.

**Take-home messages**

- This important paper has reviewed the immunology of SLE, pathogenesis, role of complement, innate and adaptive immunity, cytokines and TGFβ, risk of CVD, VEGF in LN, genetics, plaque development and CD40 ligand, Tim 1, ROS and quinones, several immunosuppressive agents, role of interferons and the inflamasome. It is important for allergist-immunologists and rheumatologists both in academic institutions and in practice to understand this important disorder and the role of many immunologic factors.

**References**


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