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Pathogenic immunity in SLE and atherosclerosis: common mechanisms and target possibilities for intervention

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune syndrome primarily affecting young women characterized by inflammation in several organs including kidneys, skin, joints, blood and the nervous system. Abnormal immune cellular and humoral responses play key roles in the development of the disease process. *Impaired clearance of apoptotic material is a key factor contributing to activation of self-reactive immune cells.* The incidence of atherosclerotic cardiovascular disease (CVD) is *increased with up to 50 times* in SLE patients compared to age and gender-matched controls and this can only partly be explained by traditional risk factors for CVD. Currently, there is no effective treatment to prevent CVD complications in SLE. Traditional preventive CVD therapies have not proven to significantly lower the incidence of CVD in SLE; therefore, there is a need for novel treatment strategies and increased understanding of the mechanisms involved in CVD complications in SLE. The pathogenic immune responses in SLE and development of atherosclerotic plaques share some similar characteristics, *such as impaired efferocytosis and skewed T cell activation*, suggesting the possibility to identify novel targets for intervention. As novel immune-based therapies for CVD are being developed and brought into clinical testing, it is possible that some of these may also show efficacy in CVD prevention and immunomodulation in SLE. *However, further understanding of the mechanisms leading to increased CVD in SLE is critical for development of such therapies.*

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune syndrome of unclear etiology that affects primarily women of child-bearing age. Patients affected by this condition can present with clinical damage to many organs including kidneys, skin, joints, blood and the nervous system. While the pathogenesis of SLE is not well understood, several predisposing factors are likely involved and play crucial roles in the initiation and maintenance of aberrant immune responses. These factors include genetic predisposition, gender, and environmental factors.

Both innate and adaptive immune responses appear to be involved in the development and perpetuation of SLE. Enhanced cell death and decreased clearance of dead cells have been detected in this disease. This phenomenon is considered key in promoting prolonged exposure of modified autoantigens and in triggering abnormal immune responses such as enhanced type I Interferon (IFN) synthesis. Many immunologic perturbations have been described in murine and human lupus, including B cell and T cell abnormalities, autoantibody and immune complex production, complement activation and dysregulation of synthesis of many cytokines and chemokines [1] [2]. This activation of self-reactive immune cells results in chronic sterile inflammation and tissue damage. SLE disease mechanisms are summarized in Figure 1.

While the diagnosis and treatment of SLE have significantly improved, the 5- and 10-year survival rates are significantly reduced in this disease when compared to the general population [3]. Importantly, while death due to lupus manifestations has decreased, deaths due to cardiovascular disease (CVD) in SLE have not diminished and in some studies represent more than one-third of all lupus deaths [4] and a leading cause of mortality [5]. Indeed, patients with SLE have a 5-10 fold increased risk of myocardial infarction, as compared with age- and sex-matched controls, even after adjusting for traditional Framingham CV risk factors [6, 7]. In the Framingham Offspring Study 35-44 years-old SLE women were found to have a 50-fold increased risk for myocardial infarction [8]. The increased CVD risk in SLE has also been associated with a more aggressive development of atherosclerosis, as assessed by carotid ultrasound [9], coronary calcium scoring by computerized tomography [10], positron emission tomography analysis of coronary flow reserve [11] and myocardial perfusion imaging [12].

Given that the Framingham risk equation cannot account for the enhanced CVD risk in SLE, it has been proposed that immune dysregulation characteristic of this disease plays fundamental roles in vascular damage and accelerated development of plaque [13]. Nevertheless, it should be emphasized that identification and treatment of traditional risk factors for CVD, such as dyslipidemia, smoking hypertension and diabetes is imperative in this patient population, in order to decrease additional burden on the vasculature. There are several features that make CVD in SLE atypical: the presentation in young women, the lack of clear protective effect by statins and the lack of a “classical” inflammatory burden typically associated with atherosclerosis in the general population [14] [15]. Therefore, there is a need to clearly understand the mechanisms leading to premature vascular damage in SLE in order to better identify and treat this potentially devastating complication. In this review, we will

focus on potential therapeutic strategies in SLE that target the immune system and their impact on atherosclerosis and CVD.

The immune system and atherosclerosis

Inflammation triggered by aggregation and oxidation of LDL in the arterial wall plays a key role in the development of atherosclerosis [16]. This inflammation drives a fibrotic remodeling of the arterial intima resulting in plaque development and, in more advanced stages of the disease, leading to plaque rupture. Danger signals generated by LDL oxidation and the tissue injury caused by oxidized LDL activate inflammation through interaction with Toll-like receptors (TLR) and other types of innate immunity receptors [17]. The level of inflammation in the plaque is also affected by a complex array of adaptive immune responses against oxidized LDL and other plaque antigens. These immune responses may dampen inflammation and promote vascular repair through the action of regulatory T (Treg) and B (Breg) cells as well as specific autoantibodies that facilitate the removal of oxidized LDL. In the absence of hypercholesterolemia and other CV risk factors, this regulatory immunity will normally protect the arterial wall from atherosclerosis. However, chronic exposure to high levels of LDL is associated with a risk for loss of tolerance against oxidatively-modified LDL antigens and activation of pro-inflammatory Th1 immune responses. Consequently, the balance between regulatory and pro-inflammatory immunity plaque antigens may determine if the atherosclerotic disease process will regress or progress [18]. The mechanisms responsible for failure of maintaining tolerance against plaque antigens in atherosclerosis remains to be fully understood. Presentation of LDL antigens in lymph nodes and the spleen is likely to primarily induce tolerogenic responses. However, when presentation of LDL antigens occurs in atherosclerotic lesions factors such as concomitant activation of TLRs, expression of cytokines favoring Th1 maturation, and/or inhibition of dendritic cell migration to draining lymph nodes are likely to shift local immune responses towards pro-inflammatory immunity and aggravate the disease process.

Impaired efferocytosis – a common link between SLE and atherosclerosis

The loss of tolerance against LDL and other plaque antigens in atherosclerosis shares many characteristics with the loss of tolerance against self-antigens associated with disease development and organ damage in SLE. In particular, an impaired capacity to clear apoptotic cells and necrotic debris has been implicated as an important factor in both diseases. In SLE patients, apoptotic cells accumulate in various tissues including germinal centers where they may trigger inflammatory responses and breakdown of B-cell tolerance [19]. Advanced atherosclerotic plaques not only contain significant accumulations of apoptotic cells but also elevated levels of cells undergoing secondary necrosis [20]. Atherosclerotic plaques also contain large amounts of oxidized LDL which competes with apoptotic cell ligands in the binding to phagocyte scavenger receptors, further reducing the local efferocytosis capacity. In addition to uptake by scavenger receptors, opsonins such as milk fat globule epidermal growth factor 8 (MFG-E8), Gas-6, Protein-S and complement factors such as C1q and C3b play important roles in mediating binding of apoptotic cells to various endocytic receptors on phagocytes. MerTK, a receptor for Gas-6 and Protein-S on M2 macrophages, appears to play

a particularly important role in the activation of anti-inflammatory responses by apoptotic cells. Experimental evidence indicates that some of these pathways may be impaired in SLE (reviewed in [21]). Recent studies have suggested that these pathways may also play an important role in atherosclerosis, as a shift towards a pro-inflammatory Th1 phenotype accompanied by increased plaque necrosis has been demonstrated in apo E^{-/-} mice deficient in MFG-E8, MerTK and C1q [22-24]. *Table 1 is summarizing common disease mechanisms in CVD and SLE.*

Autoantibodies and vascular dysfunction

Endothelial dysfunction is an early marker of atherogenesis and the result of damage to endothelial cells that no longer can maintain the normal balance between vasodilation and vasoconstriction, blood clot formation and fibrinolysis and control of smooth muscle cell proliferation and migration. Damaged endothelium promotes atherogenesis via increased endothelial permeability, leukocyte adhesion and transmigration, cytokine production and platelet aggregation. Endothelial dysfunction can be induced by several conditions, many of them risk factors for atherosclerosis, such as diabetes, hypertension and hypercholesterolemia [25]. Rajagopalan et al showed that patients with SLE have impaired endothelial function and that this is associated with an increased number of circulating apoptotic endothelial cells [26], suggesting presence of an autoimmune response against the endothelium in SLE. This notion is further supported by the finding of anti-endothelial cell antibodies in patients with SLE [27]. However, SLE is also characterized by generation of many other autoantibodies that can affect endothelial function [28]. Antiphospholipid (aPL) antibodies, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and beta 2-glycoprotein (b2-GPI) are present in 20-30% of all patients with SLE [29] and have been linked to an increased risk of venous and arterial thrombosis [30]. The pathophysiological role and mode of action of aPL antibodies remains to be fully elucidated but studies performed in cell cultures suggest that they enhance expression of adhesion molecules on endothelial cells and increase monocyte adhesion. Although some studies have demonstrated increased levels of aPL antibodies in SLE patients with prevalent CVD [31, 32] this association is still a matter of controversy.

The role of autoantibodies in atherosclerosis remains to be fully elucidated. Most studies have focused on association between autoantibodies against oxidized LDL and CVD [33]. The results of these studies have been inconsistent, possibly due to difficulties in standardizing the antigen used in the antibody detection assay [34]. However, studies analyzing antibodies against specific antigens in oxidized LDL have been more consistent and are generally in line with a protective role of such antibodies. One of the most important antigens in oxidized LDL is a phospholipid, oxidized phosphatidylcholine, which is recognized by germline-encoded natural IgM released by B1 cells [35]. This class of IgM also recognizes phospholipid epitopes on the surface of apoptotic cells and several types of microorganisms. They are considered to play an important role in the first line defense against infections as well as in tissue homeostasis by facilitating removal of cellular debris. Increasing the level of circulating natural IgM by active or passive immunization has been shown to reduce the development of atherosclerosis in hypercholesterolemic mice [36, 37], while atherosclerosis is aggravated in mice lacking circulating IgM [38]. Similarly, lupus-prone MRL/lpr mice develop more severe

autoimmunity when deficient in circulating IgM [39]. *Furthermore, it has been shown that low levels of natural IgM against phosphorylcholine is associated with occurrence of plaques in the carotid arteries of SLE patients [40].* Taken together, these findings suggest that natural IgM could have an athero-protective role in SLE. Other LDL autoantibodies that have demonstrated an association with CVD are IgG and IgM against the apolipoprotein B-100 peptides p45 (amino acids 661-680) and p210 (amino acids 3136-3155). Low levels of these antibodies have been associated with more severe atherosclerosis and an increased risk for development of myocardial infarction [41-43]. Treatment of hypercholesterolemic mice with recombinant malondialdehyde-p45 IgG has been shown to inhibit development of atherosclerosis and to promote plaque regression when combined with lowering of plasma cholesterol levels [44, 45]. It remains to be determined if these antibodies can protect against atherosclerosis also in the setting of SLE. *Table 2 is summarizing the cardiovascular complications present in SLE patients.*

Immune cells in atherosclerosis and SLE

Neutrophils: Neutrophils are the most abundant immune cells in the circulation and they have the ability to release peptides and reactive oxygen species with bactericidal properties when activated. Recent advances have shown that neutrophils play a role in both atherogenesis and in plaque destabilization [46]. The alarmins S100 A8, A9 and A8/A9 are secreted by activated neutrophils and their presence in plasma has recently been shown to correlate with neutrophil count, CVD risk factors and CVD incidence in a prospective study [47]. Similar studies have been performed in SLE patients showing that plasma levels of S100A8/A9 and S100A12 are elevated in SLE patients compared to healthy controls. Furthermore, SLE patients with a history of CVD have increased levels of these proteins compared to SLE patients without CVD [48]. This suggests that detection of S100 proteins could be used as a tool to determine risk of CVD in persons with or without SLE.

Neutrophils also extrude extracellular traps (NETs), chromatin containing fibers with bactericidal function, into the extracellular space [49]. Furthermore, endothelial cytotoxicity induced by NETs is a cause of vascular damage [50] and these lattices are strong promoters of thrombosis. As NET formation is more common in SLE patients, this phenomenon may be central in the induction of vascular damage in this disease. A distinct, pro-inflammatory type of neutrophils, so called low density granulocytes (LDGs), was first described in SLE. LDGs are cells with increased capacity to release NETs leading to enhanced externalization of autoantigens and induction of type I IFN responses. NETs have been shown to be cytotoxic to endothelial cells through MMP-9 and histone-associated processes [51, 52] and to promote endothelial dysfunction, thrombosis and vascular damage [53, 54]. Furthermore NETs carry all the oxidative machinery to modify high-density lipoprotein (HDL) rendering it proatherogenic [55]. Recent evidence indicates that inhibition of NET formation *in vivo* in animal models of lupus and atherosclerosis can improve vascular function, decrease plaque formation and abrogate thrombosis [56]. Inhibition of NET formation might therefore be a

potential future therapy against CVD in SLE, however, no such treatment strategies are in clinical testing at the moment.

Monocytes and macrophages: Monocytes and macrophages in SLE are characterized by an enhanced activation status with increased expression of costimulatory molecules, an altered presence of Fc gamma receptors and overproduction of proinflammatory cytokines such as IL-6, TNF- α and type I IFNs [57]. SLE macrophages are reduced in number and show a reduced uptake of apoptotic cells leading to accumulation of apoptotic material. Apoptotic material does normally not induce inflammatory responses but when presented in an inflammatory context it can lead to activation of autoreactive T cells. The function of SLE monocytes and macrophages in atherosclerosis development are not fully understood but human monocytes and macrophages primed with type I IFNs are more prone to take up lipids which lead to increased foam cell formation [58]. Furthermore, *in vitro* experiments with human macrophages have shown that SLE plasma increases foam cell formation compared to plasma from healthy controls, which can be linked to an increased expression of the scavenger receptor CD36 [59, 60]. Fc gamma receptors are expressed on monocytes and their expression is dysregulated in SLE. Mouse models indicate that absence of the inhibitory Fc gamma receptor IIb promotes both SLE and atherosclerosis development; these observations suggest that dysregulation of Fc receptors may be an important factor contributing to the increased CVD in SLE [61, 62].

Neopterin, a purine nucleotide produced by macrophages activated by IFN- γ , is a marker of macrophage activation. In atherosclerosis, high neopterin is associated with increased disease. Neopterin is also increased in SLE but there is no correlation with severity of coronary atherosclerosis [63]. The cytokine macrophage migration inhibitory factor (MIF) plays a role in activation of macrophages and lymphocytes and has been shown to be increased in SLE, both in patients and in mouse models of the disease [64]. Moreover, a single-nucleotide polymorphism (SNP) in the MIF gene has been shown to be associated with increased prevalence of SLE indicating that this cytokine might have an important role in the disease development [65]. Mouse models of atherosclerosis demonstrate that when MIF is absent, there is a reduction in plaque developments and monocyte recruitment [64]. As MIF seems to have a central role in disease development, blocking or inhibiting MIF function could be a potential novel therapeutic target in both SLE and atherosclerosis.

Lymphocytes: B cells are important and often discussed in the context of SLE. As the functions and activities of B cells often are controlled by T cells, this heterogeneous group of cells is also important in SLE pathogenesis. Also in atherosclerosis, B and T cells are central players and both protective and disease promoting functions have been described.

A key function of B cells and derived plasma cells in SLE is the production of auto-antibodies which is a central feature of the disease and also used as a diagnostic marker. B cells are also antigen presenting cells and can also secrete cytokines with immunomodulatory functions. Mouse studies on B cells in SLE have shown that B cell deficiency inhibits disease development whereas defect antibody secretion played a minor role in SLE progression showing that the antibody-producing role of the B cells may not be as important as first

assumed [66]. Recently, the knowledge of the role of B cells in atherosclerosis has expanded. Based on results from mouse studies it was previously believed that B cells are protective in atherosclerosis, mainly because of the protective auto-antibodies produced by them. However, more recent studies where mature B cells were depleted in atherosclerotic mice have shown that B cells also have pro-atherogenic functions [67]. These results emphasize the complexity of the functions of the B cells, as well as other immune cells, in both atherosclerosis and SLE. As cells with regulatory capacity exists among both B and T cells, therapies targeting these cells needs to be very specific for the disease-promoting cells while maintaining the pool of immunoregulatory/protective cells and their functions. In SLE, therapies targeting B cells include general B cell depletion via blockade of CD20 or CD22 with monoclonal antibodies (anti-CD20 is used in SLE although not an approved for that indication) and blocking of co-stimulatory pathways or neutralizing growth factors as B cell activation factor (BAFF) important in B cell activation [66]. The effect of these B cell targeting therapies on atherosclerosis is almost completely unknown. As described above, blocking B cells with antibodies against CD20 reduces atherosclerosis in mice but if this is true also in humans with SLE needs to be further elucidated.

SLE T cells display abnormal phenotypes, an altered activation threshold and triggering of signaling pathways that lead to increased activation and expression of co-stimulatory molecules such as CD40 ligand (CD40L) [68]. T cell expression of CD40L is important in B cell differentiation, proliferation, class switch and antibody production via CD40 interactions on the B cell. Increased CD40L-CD40 interactions lead to enhanced B cell activity and increased production of disease promoting auto-antibodies [69]. CD40L signaling is central also in atherosclerosis development, and inhibition of CD40L-CD40 interactions resulted in a more stable plaque phenotype [70]. Blockade of CD40L could therefore be a potential therapeutic target in both SLE and atherosclerosis; however, in SLE the role of this therapeutic modality remains unclear [68].

T cell activation is dependent on interactions between the T cell receptor and its associated molecules that are concentrated to lipid rafts. When T cells become activated, the lipid rafts are clustered to allow the signaling molecules to come in close contact [68]. However, in SLE T cells the lipid rafts appear to be already clustered in the inactivated state, resulting in a lower activation threshold of the cell [71]. Statins can disrupt lipid rafts and may promote abrogation of the T cell signaling abnormalities in SLE T cells [72]. Statins was therefore assigned as potentially beneficial in SLE, both as lipid lowering therapy and with regard to its action on T cells. However, the vasculoprotective role of statins in SLE remains to be determined and trials to this date have not shown a major beneficial role in CV risk and immune dysregulation in SLE [73, 74].

It is still uncertain which type of T helper (Th) cell that plays a dominant role in SLE development. The pro-inflammatory cytokine IL-17 and Th17 cells are increased in SLE patients and have in some studies been shown to correlate with disease activity [75, 76]. IL-17 in SLE can also be secreted from double negative (CD4-CD8-) T cells, a population of T cells that are normally rarely occurring but have an increased in frequency in SLE [76]. Furthermore, SLE patients have been shown to have higher Th17/Th1 ratio compared to

healthy controls but a predominance of Th1 cells when the Th1/Th2 balance was determined [77, 78]. In atherosclerosis, Th1 cells are described as proatherogenic whereas the role of Th2 and Th17 cells is not completely understood yet. Some studies have reported increased circulating IL-17 and Th17 cells in CVD patients but, moreover, several groups have reported that there are no differences [79]. Furthermore, it has recently been described that low circulating IL-17 in myocardial infarction patients was associated with an increased risk of a new cardiovascular event. These results suggest a protective role of IL-17 in vascular inflammation [80]. Blocking IL-17 and/or Th17 cells might be beneficial in SLE but the effect in atherosclerosis and CVD is more uncertain and needs to be carefully investigated.

Tregs have the ability to dampen immune responses and are thereby believed to be protective in autoimmune diseases. It has been described that Tregs are reduced in number and have reduced functional capacity in SLE patients [81]. However, it has also been reported that the percentage of Tregs correlates positively with disease activity in SLE and this discrepancy seems to depend on how the Tregs are defined [82]. Tregs have been associated with a protective role in atherosclerosis based on both human studies and mouse models [83-85]. Increased activity and/or increased frequency of Tregs might be a potential way to target both SLE and CVD in SLE.

Cytokines in SLE and atherosclerosis: Several cytokines play important roles both in atherosclerosis and SLE. When studying the actions of the most important cytokines it seems that some cytokines are protective in CVD and disease promoting in SLE or the contrary. The role of these cytokines in SLE accelerated atherosclerosis need to be fully elucidated [86].

Type I IFN: An overexpression of type I IFN-regulated genes, termed IFN signature, has been found in leukocytes and tissues from SLE patients and the level of expression of these genes correlates with disease activity [87]. Type I IFNs is a family of cytokines that are represented primarily by IFN- α and IFN- β , the former being primarily produced by plasmacytoid dendritic cells and the latter by many cell subsets, in response to viral infections leading to activation of a wide range of both innate and adaptive immune cell functions [88]. Several studies on type I IFNs show that they can be involved in the accelerated CVD in SLE as type I IFNs enhances macrophages migration into the vessel wall leading to increased foam cell formation [20]. Type I IFNs also activates platelets and changes their transcriptional profile resulting in increased thrombus formation [89, 90]. Endothelial progenitor cells (EPCs) are crucial in vascular repair as they can replace damaged endothelial cells. It has been shown that the reparative capacity of EPCs in SLE patients is disturbed, presumably because of the chronic inflammatory processes [15]. Type I IFNs influence the vascular repair processes by impairing the function of EPCs as well as decreasing the frequency of these cells leading to endothelial dysfunction and reduced angiogenesis [91]. The possibility of using type I IFNs as a target for future therapies for treatment of SLE is currently under investigation. An anti-IFN- α monoclonal antibody proved to be safe, well tolerated and effective and will be further investigated in clinical trials. Vaccinations strategies leading to induction of anti-IFN- α antibodies are also under further development [88]. As type I IFNs also have a disease promoting role in atherosclerosis, blocking of these cytokines may also be beneficial in regard to CVD, both in SLE patients and

non-SLE subjects. Additionally, type I IFNs may also promote atherosclerosis development via their actions on lipoprotein function. High density lipoproteins (HDL) normally protects against atherosclerosis development because of its ability to take up and clear lipids from the plaque. HDL also has anti-oxidative functions but under chronic inflammatory conditions, such as persistent exposure to type I IFNs, the anti-oxidative capacity can be lost and it is said that the HDL becomes pro-inflammatory. This can, at least partly, be a result of decreased amounts of Apo A-1 in HDL caused by the ongoing inflammation [92]. Antimalarials, particularly hydroxychloroquine and chloroquine, are widely used as treatments of mild-moderate SLE. Previous observations indicate that antimalarials may have a vasculoprotective role [93]. Part of the mechanism of action of antimalarials in SLE is related to their ability to block TLR-induced synthesis of type I IFNs and also NET formation. As such, it is possible that the vasculoprotective effect of antimalarials is mediated in part by their role in blocking type-I IFN pathways in SLE [55, 94].

IL-6 is an inflammatory cytokine and both murine and human studies have shown that IL-6 has an important role in SLE pathogenesis. IL-6 deficient MRL/lpr mice have reduced renal damage. This finding has been supported by studies where mice have been treated with recombinant IL-6 or blocking IL-6 antibodies resulting in increased and decreased lupus nephritis, respectively. IL-6 has an important role in B cell maturation into plasma cells and it has been shown that blockade of IL-6 reduces the production in autoantibodies. Furthermore, increased levels of IL-6 in sera and IL-6 mRNA in freshly isolated PBMCs have been reported in SLE patients compared to healthy controls [95]. Mouse studies on atherosclerosis and IL-6 have shown both protective and disease promoting functions as administration of IL-6 exacerbates atherosclerosis but hypercholesterolemic mice lacking IL-6 had increased plaque area. As the role of IL-6 in atherosclerosis is not completely understood, the impact of the increased IL-6 in SLE on atherosclerosis development is unclear. Blockade of the IL-6 receptor (Tocilizumab) is currently investigated as a potential SLE therapy. It has shown good tolerability in phase I trials and it restores B and T cell homeostasis [96]. As the role of IL-6 in atherosclerosis and CVD is unclear, the impact on these conditions by blocking IL-6 signaling needs to be thoroughly monitored during clinical testing.

IL-10 seems to have dual roles in SLE. It is a cytokine with anti-inflammatory properties by inhibiting production of pro-inflammatory cytokines such as IFN- γ . Moreover, IL-10 is also important in B cell activity leading to proliferation and differentiation of B cells, antibody class switch and decreased apoptosis of B cells in germinal centers supporting autoantibody production. Experimental studies on mice with SLE-like disease have shown that anti-IL-10 antibodies can have a protective role but it has also been presented that MRL/lpr mice deficient in IL-10 have aggravated disease [97]. It has been shown in several studies that IL-10 is increased in SLE patients and also correlates with disease activity [98]. Blocking IL-10 might then be a potential therapy in SLE and preliminary data from clinical trials on monoclonal anti-IL-10 antibodies have shown protective effects in SLE indicating that the disease-promoting functions of IL-10 dominate over the protective properties. In atherosclerosis, IL-10 has been shown to have a protective role likely via its ability to down-regulate both innate and adaptive immune responses. Macrophages are the main cytokine

producing cell type in atherosclerotic plaques and the key source of IL-10 [99]. Opposed to in SLE, increased serum levels of IL-10 seems to be protective in CVD as IL-10 is an important prognostic determinant in patients with acute coronary syndromes [100]. Furthermore, increased expression of IL-10 on macrophages in the plaques leads to reduced inflammation and stimulates plaque healing [101]. The effect of anti-IL-10 antibodies as SLE treatment on atherosclerosis is unknown and needs to be thoroughly investigated as it can have potentially undesirable effects on atherosclerosis and CVD. Figure 2 summarizes the potential therapeutic strategies in SLE that target the immune system and their impact on atherosclerosis and CVD.

Perspectives

Cardiovascular disease is an important complication in SLE and effective preventive measures remain to be identified. The pathogenic immune responses in SLE and development of atherosclerotic plaques share some similar characteristics, suggesting novel targets for intervention. From a cardiovascular perspective SLE poses many challenges since it is a very heterogenous and relatively rare disease and demonstrating significant effects of intervention on clinical endpoints such as myocardial infarction and stroke usually requires study cohorts of many thousands of study subjects. Therefore, even if the relative increase in cardiovascular risk in SLE is high the absolute number of events is still low. Accordingly, it is likely that clinical testing of novel therapies for prevention of CVD in SLE will have to rely on surrogate markers for CVD risk such as vascular imaging and function. As novel immune-based therapies for CVD are being developed and brought into clinical testing (see Nilsson et al, this issue) it is likely that some of these may also show efficacy in SLE. Cardiovascular research may also benefit from studies of pathogenic immunity in SLE to reach a better understanding of how local tolerance in atherosclerotic plaques is lost and how this is associated with increased plaque inflammation and risk for clinical events.

***Visions for the future:** The fact that SLE is both a rare and complex disease has seriously hampered the development of novel therapies targeting key disease mechanisms. It has also been difficult to elucidate if different organ complications in SLE involve separate pathogenic processes. However, with the rapid advances in DNA, proteomic and immune-based multiplex technologies new opportunities are now becoming available that will change this situation dramatically. These technologies are also likely to provide a more personalized diagnosis of the disease with new opportunities of individualized treatment. Taken together with the increasing availability of a wide variety of biological pharmaceuticals we believe that there is good hope that suffering from the clinical consequences of SLE will be significantly reduced within the coming decades.*

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Figure legends

Figure 1

SLE disease mechanisms.

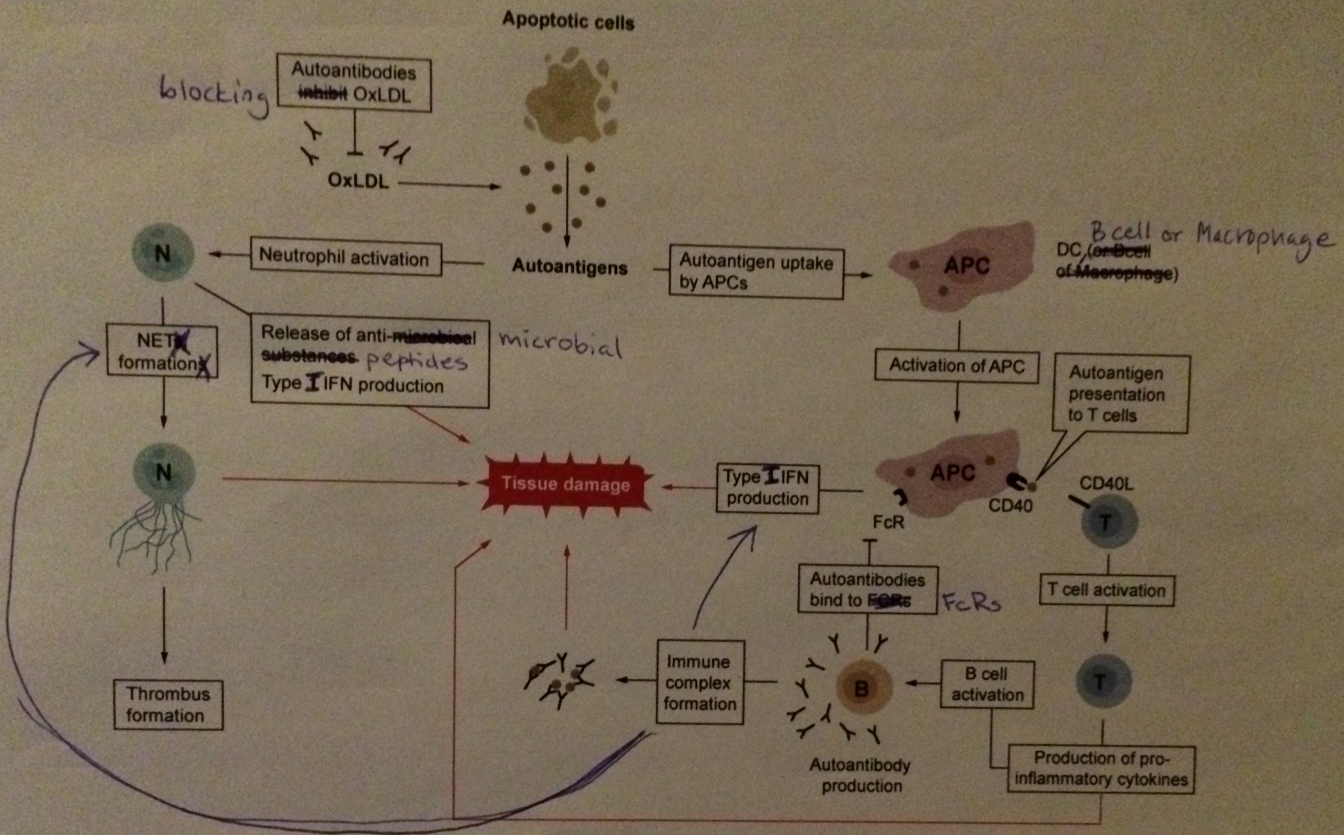
Autoantigens released by apoptotic cells, or other modified self-molecules, can be taken up by antigenpresenting cells (APCs) or activating neutrophils initiating different immune responses. Activated APCs will then activate T cells that start to produce cytokines, pro- or anti-inflammatory, and express co-stimulatory molecules to further activate other immune cells. Continued release of pro-inflammatory cytokines can induce damage of the surrounding tissue. T cells activated by auto-antigens can further activate B cells leading to autoantibody production. Autoantibodies then can form immune complexes (IC) with the respective auto-antigen and when IC is deposited in tissues inflammatory cells are recruited leading to tissue damage at the site of IC deposition. Activated neutrophils release proteins and reactive oxygen species with bactericidal properties. In addition to this, activated neutrophils extrude extracellular traps (NETs) that also have bactericidal functions and the actions of activated neutrophils will lead to tissue damage when there is a continued release of these substances. Furthermore, NETs promotes thrombosis leading to an increased risk of thrombus formation during inflammation.

Figure 2

Future therapies targeting the immune system in SLE and CVD.

Blocking monocyte inhibitory factor (MIF) has been shown to reduce plaque development in animal models of CVD. Moreover, MIF is increased in SLE, both in humans and in mouse models of the disease, and might therefore be a potential therapeutic target also in SLE. Activated neutrophils release inflammatory proteins, as the cytokines IFN- α and IFN- β , and NETs with bactericidal properties. In SLE, preliminary results on blocking IFN- α with an antibody show good tolerability and promising results. Blocking IFN- α in CVD might also be protective as the cytokine has been shown to have a disease promoting role and future studies are required to rule out the effect in CVD. Inhibition or blocking of NETs has shown a protective role in animal models of both SLE and CVD but no studies on humans are ongoing at the moment. T cells is a heterogeneous group of cells and the different T cell subtypes have specific, and sometimes unknown, functions in SLE and CVD. Th17 cells are increased in SLE and blocking Th17 cells or IL-17 can possibly reduce disease. In CVD, the role of Th17 cells and IL-17 is not fully understood and more studies are required to evaluate the effect of Th17 and IL-17 in CVD. Another type of T cells, Tregs, seems to be protective in both SLE and CVD and increased activity and/or number of these cells is a potential new therapeutic target in both diseases. CD40L is expressed on activated T cells and it has an important role in activation of other immune cells such as B cells. Blocking CD40L-CD40 interaction reduced plaque development in mouse models of CVD and it might also be a potential therapeutic target in SLE. However, further studies on CD40L-CD40 inhibition in both CVD and SLE are

required. Blocking the anti-inflammatory cytokine IL-10 in clinical trials has shown to be protective effects in SLE. As IL-10 seems to have a protective role in CVD, the effect of blocking IL-10 as SLE treatment need to be thoroughly investigated as it can have potentially undesirable effects on atherosclerosis and CVD. The cytokine IL-6 is produced by T cells and macrophages and IL-6 has an important role in SLE pathogenesis. Blockade of the IL-6 receptor is currently investigated as a potential SLE therapy. The role of IL-6 in CVD is, however, not fully understood and the impact of IL-6 signaling blockade on CVD needs to be thoroughly studied. Modulation of B cell activity is already used as SLE treatment and several new compounds targeting the B cell molecules CD20, CD22 or BAFF are in clinical trials at the moment. How B cell modulation will affect atherosclerosis and CVD is unclear as the role of B cells in CVD is unclear.



APC = antigen presenting cell

N = neutrophil

B = B cell

T = T cell

MIF

CVD
Blocking of MIF leads to reduced plaque formation in animal models

SLE
Unknown effect

Type I IFN

CVD
IFN- α have a disease promoting role and blocking may be beneficial

SLE
Preliminary results show protection

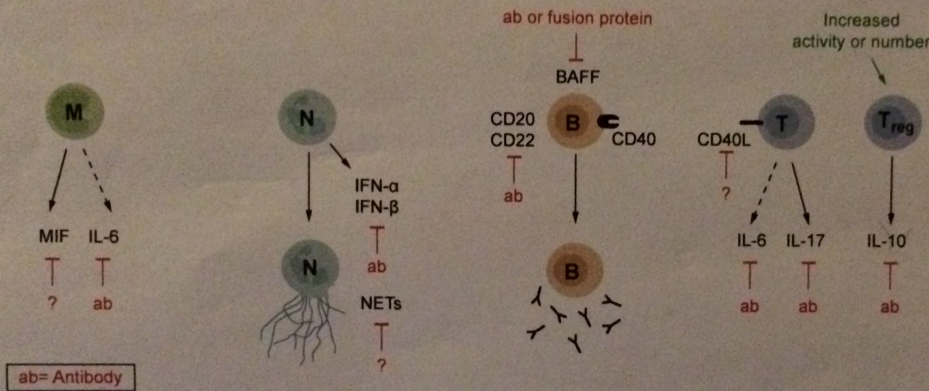
CD20/CD22

CVD
~~unknown effect~~
Unknown effect

SLE
Blocking CD20 or CD22 can be protective

Tregs

CVD/SLE
Increased Tregs can possibly have a protective role



IL-10

SLE
Blockade of IL-10 show protection in clinical trials

CVD
Unknown effect

IL-6

CVD
Unclear role of IL-6, both disease promoting and protective protection

SLE
Preliminary results on IL-6 receptor blockade show protection

NETs

SLE/CVD
Animal models show protection when NETs are inhibited

BAFF

CVD
unknown effect

SLE
protective role when blocked

IL-6

CVD
Unclear role of IL-6, both disease promoting and protective protection

SLE
Preliminary results on IL-6 receptor blockade show protection

IL-17

CVD
Unknown outcome by blocking IL-17

SLE
Possibly reduced disease by blocking IL-17

M = monocyte or macrophage

N = neutrophil

B = B cell

T = T cell

Treg = regulatory T cell

Table 1 Common disease mechanisms in CVD and SLE

• Impaired clearance of apoptotic cells
• Skewed Th1 activation
• Increased/changed activation of T cells
• B cell activation
• LDL oxidation

Table 2 Cardiovascular complications in SLE

• Endothelial dysfunction
• Increased thrombosis
• Myocarditis, pericarditis and endocarditis
• Increased cholesterol levels