Review

The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus

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Abstract

The increased burden of cardiovascular disease in patients with rheumatoid arthritis and systemic lupus erythematosus has recently become the focus of intense investigation. Pro-atherogenic risk factors and dysregulated inflammation are the main culprits, leading to enhanced atherosclerosis in subgroups of patients with inflammatory diseases. Common molecular pathways shared by atherosclerosis and inflammatory disease may be involved. In this review we map the key determinants of the increased incidence of cardiovascular disease in patients with inflammatory diseases at each step of the atherogenesis.

Introduction

Research during the past 20 years has driven a major shift in how atherosclerosis is conceptualized. Initially branded as a passive accumulation of lipids in the vessel wall, atherosclerosis is now recognised as an 'inflammatory disease' [1]. Striking similarities can be identified between atherosclerosis and prototypical inflammatory diseases (Figure 1). In parallel, there is growing evidence that cardiovascular disease (CVD) is the leading cause of mortality in patients with chronic inflammatory diseases [2], including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's disease and systemic sclerosis.

This review first summarizes the impact of CVD on the lives of patients with inflammatory diseases. Second, we map the key molecular determinants of the increased prevalence of CVD in patients with inflammatory diseases at each step of the progression of atherosclerosis (initiation, progression and thrombotic complications). We focus on RA and SLE, for which more evidence is currently available.

The clinical impact of atherosclerosis in inflammatory diseases

Atherosclerosis and rheumatoid arthritis

Cardiovascular manifestations such as pericarditis, myocarditis and atrioventricular block are classic complications of RA and SLE. However, most of the cardiovascular mortality in RA patients is not due to these manifestations but rather to ischaemic heart disease secondary to coronary atherosclerosis [3]. In the Nurses' Health Study [4], patients with RA had more than twofold greater risk for myocardial infarction (MI) compared with patients without RA. Worryingly, RA patients are almost six times more likely to have had an undiagnosed MI and twice as likely to experience sudden death [5]. RA patients are also far less likely to report forewarning symptoms, such as angina [5,6], potentially hampering early detection of atherosclerotic disease.

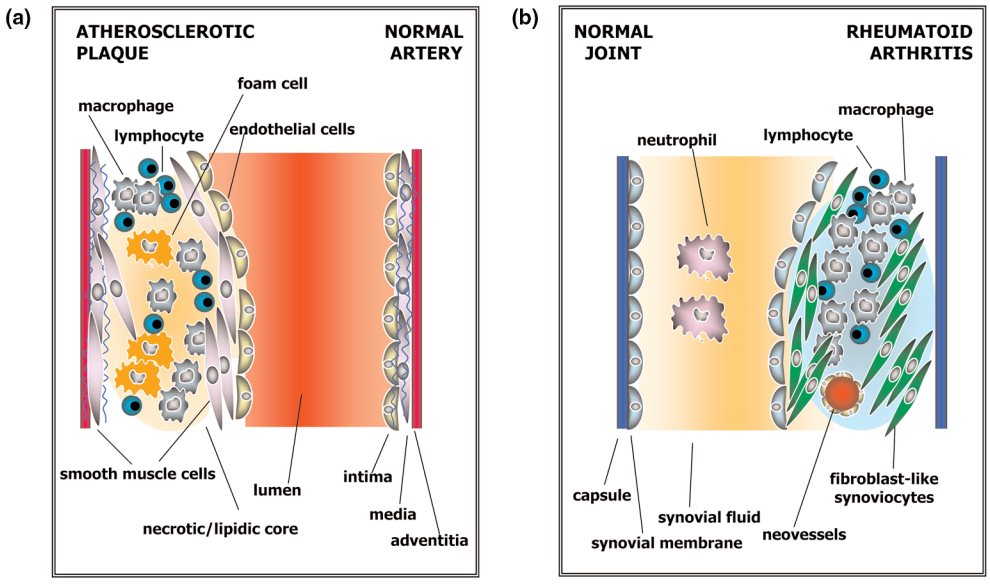
In support of these observations, RA patients have an increased prevalence of subclinical atherosclerosis, with a greater incidence of carotid artery plaque and increased carotid intima/media thickness (IMT) [7,8] as well as multivessel coronary artery disease compared with control individuals [9].

Systemic lupus erythematosus and cardiovascular disease

Three decades ago, Urowitz and coworkers [10] recognized that CVD and MI were major causes of mortality in patients with SLE. In fact, patients with SLE are five or six times more likely to have a significant coronary event compared with the general population. Remarkably, women with SLE between the ages of 35 and 44 years have a 50-fold increased risk for

aCL = anticardiolipin; ACS = acute coronary syndrome; apo = apolipoprotein; CVD = cardiovascular disease; GPI = glycoprotein I; HDL = high-density lipoprotein; IFN = interferon; IL = interleukin; IMT = intima/media thickness; LDL = low-density lipoprotein; MHC = major histocompatibility complex; MI = myocardial infarction; MIF = macrophage migration inhibitory factor; MMP = matrix metalloproteinase; NF-κB = nuclear factor-κB; oxLDL = oxidized low-density lipoprotein; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SMC = smooth muscle cell; SNP = single nucleotide polymorphism; TGF = transforming growth factor; Th = T-helper; TLR = Toll-like receptor; TNF = tumour necrosis factor.

Figure 1



Similarities between the atherosclerotic plaque and rheumatoid arthritis joint. The **(a)** atherosclerotic plaque has many features in common with **(b)** rheumatoid arthritic synovium. First, in both diseases, blood-borne mononuclear cells are recruited to sites that are devoid of any significant inflammation in physiological conditions. Second, upregulation of cytokines and matrix-degrading enzymes is central to the pathogenesis of both diseases. Third, both in rheumatoid arthritis and atherosclerosis, immune cells do not target resident cells in the same way that diabetogenic T cells directly destroy pancreatic islets. Instead, immune cells begin complex interactions with the resident cell types, which proliferate, change their properties and phenotype, and contribute to the inflammatory process and tissue destruction.

MI compared with age-matched and sex-matched control individuals [11]. In a Canadian cohort of SLE patients, the relative risk for MI was 10.1, that for death due to CHD was 17, and that for stroke was 7.9 [12]. SLE patients have increased subclinical atherosclerosis compared with the general population, with a greater prevalence of carotid plaques and increased IMT [13,14]. Myocardial single photon emission computed tomography scanning has revealed coronary artery disease in 40% of patients with SLE [15,16], although coronary artery calcification is more prevalent in lupus without underlying CVD [17].

Risk factors for cardiovascular events in patients with rheumatoid arthritis and systemic lupus erythematosus

Clustering of traditional atherogenic risk factors

RA and SLE patients have an overall increased frequency of traditional cardiovascular risk factors [3,10,18,19]. Smoking is associated with subclinical atherosclerosis in patients with RA [20]. Hypertension is also an important risk factor for CVD in RA and SLE [21,22].

A particular type of dyslipidaemia is present in patients with RA. This is characterized by low high-density lipoprotein (HDL), raised triglycerides and low levels of low-density lipoprotein (LDL) [23]. Interestingly, such a lipid profile is detectable in those individuals who go on to develop RA at least 10 years before the onset of symptoms [24]. Dyslipoproteinaemia in SLE is slightly different from that in RA, characterized by elevated levels of very-low-density lipoprotein cholesterol and triglycerides, high or unchanged LDL, low levels of HDL and disturbance in chylomicron metabolism. Hence, low HDL levels are a common trait in RA and SLE. Low HDL in the general population exhibits a strong inverse correlation with CVD events, even in the presence of low LDL or statin therapy. Changes in lipoprotein functions have also been described. For instance, LDL from RA patients has an increased capacity to bind proteoglycans, which is considered an important early step in atherogenesis [25]. High levels of the pro-atherogenic lipid particle lipoprotein-a have been detected in both diseases, as well as elevated levels of circulating oxidized LDL (oxLDL) [26]. Paraoxonase, an enzyme that binds to HDL and prevents oxidation of LDL, was shown to have reduced activity in patients with SLE and primary antiphospholipid syndrome [27].

Patients with RA and SLE have a higher prevalence of metabolic syndrome [28], which includes obesity, dyslipidaemia, hypertension and insulin resistance. Additionally, patients with RA and SLE are less physically active than individuals without the disease, which may also contribute to accelerated atherosclerosis.

Traditional therapies and cardiovascular risk

The effect of chronic use of drugs commonly employed to treat RA and SLE in promoting or suppressing atherogenesis

is extensively reviewed elsewhere [23,29]. Such drugs can affect the progression of atherosclerosis either by acting on the inflammatory process or by altering cardiovascular risk factors. Corticosteroids, for instance, promote insulin resistance, weight gain, fluid retention and hypertension. Nonetheless, within the context of inflammatory diseases their net effect is likely to be complex because of their beneficial effects on the ongoing inflammation. In the COBRA (Combination Therapy in Early Rheumatoid Arthritis) study [30], high-dose steroids used in conjunction with other disease-modifying antirheumatic drugs improved the total cholesterol to HDL ratio, with a linear association with the Disease Activity Score. However, in a different study [31] glucocorticoid exposure was associated with carotid plaque and arterial incompressibility.

The effect of methotrexate is similarly complex. Methotrexate use causes elevation in serum homocysteine levels by folate depletion. This effect could promote atherogenesis as because hyperhomocysteinaemia is an independent risk factor associated with CVD in the general population as well as in patients with SLE [32]. However, in a prospective study involving 1,240 patients with RA [33], therapy with methotrexate was associated with improved survival by reducing CVD mortality by 70%. Folate supplementation is a plausible approach to counteract hyperhomocysteinaemia [34] and is currently a matter of debate. It is worth noting that in a trial of 5,442 women conducted over 7 years [35], daily supplementation with a combination of folate and vitamins B_6 and B_{12} was able to reduce hyperhomocysteinaemia, but it was unable to abolish CVD risk.

Nonsteroidal anti-inflammatory drugs are among the most commonly used anti-inflammatory interventions. This group of drugs has a much broader range of actions than simply inhibition of inflammation, including their effect on prostaglandin metabolism, in which atheroprotective mediators (for example, prostacyclin) are also inhibited. In a recent meta-analysis [36] selective cyclo-oxygenase-2 inhibitors and high-dose regimens of ibuprofen and diclofenac were found to be associated with a moderate increase in the risk for adverse cardiovascular events.

Inflammatory burden and atherosclerosis

Both SLE and RA patients exhibit an increased prevalence of pro-atherogenic risk factors, which may very well contribute to the burden of CVD events and atherosclerotic disease. However, there is growing evidence that this is only one side of the story.

In a number of studies, even after correction for classical risk factors for CVD, both RA and SLE remain independently associated with clinical and subclinical atherosclerosis [9,18] (Tables 1 and 2). In a cohort of 296 SLE patients followed for a mean of 8.6 years, CVD events were substantially higher than would be predicted on the basis of traditional factors alone, using the Framingham risk stratification method [12]. In a study conducted in the Pima Indian population, the number of swollen joints was predictive of death from CVD [37]. Similarly, the presence of severe extra-articular disease clearly increased the risk for cardiovascular events in patients with RA [2,38]. Duration of the disease has also been associated with the presence of carotid plaques [39]. A recent study conducted in 631 RA patients [40] showed that the rate at which IMT increased was proportional to the duration of disease. Another study [41], in 155 RA patients, also demonstrated that patients with longstanding disease have an increased Framingham risk score compared with patients with early disease. (The Framingham risk score is used to derive an estimated risk for developing coronary heart disease within 10 years and is based on age, sex, total and HDL cholesterol, blood pressure, diabetes and smoking.) High Framingham scores were associated with coronary artery calcification. The increased risk for CVD in RA patients was also shown to be present 2 years before the fulfilment of criteria for RA [7]. In addition, patients with very early inflammatory polyarthritis are at increased risk for premature death from CVD when their serum is positive for rheumatoid factor [42]. These findings suggest that even preclinical inflammation may contribute to increased risk for cardiovascular events.

Disease initiation and endothelial activation

In humans, atherosclerotic lesions occur in the large and medium sized arteries and are characterized by an asymmetrical focal thickening of the innermost layer of the arterial wall, the intima. Atherosclerosis is a multifactorial disease with strong epidemiological associations with a variety of lifestyle-related and genetics-related risk factors (for example, dyslipidaemia, smoking, diabetes mellitus and hypertension). The common pathway, through which all of these risk factors lead to atherosclerosis development, is endothelial activation and subsequent endothelial dysfunction. The sequence of events that leads to early stages of atherogenesis has been mostly characterized under conditions of hypercholesterolaemia. Excess LDLs enter the intima where they are retained by matrix proteoglycans. Here they are subject to oxidative and enzymatic modifications, leading to formation of pro-inflammatory phospholipids that may induce endothelial cell activation [43].

Pro-inflammatory mediators such as tumour necrosis factor (TNF)-α, are strongly linked to endothelial activation and dysfunction [44]. Persistent endothelial activation leads to endothelial dysfunction, characterized by reduced production of nitric oxide and increased expression of adhesion molecules and chemokines [1], resulting in impaired vasorelaxation and recruitment of blood-borne mononuclear cells such as monocytes and T lymphocytes. Endothelial dysfunction has been detected in RA and SLE patients by noninvasive tests such as the brachial flow-mediated dilatation, as extensively reviewed elsewhere [45,46]. Endothelial

Table 1

Studies evaluating the risk of coronary heart disease in rheumatoid arthritis

[Reference] (year)	Study design	RA definition	*n*	Estimated risk
[18] (2001)	Prospective cohort	ACR 1987 criteria	236	3.86-fold of combined CV events (MI + revascularization + stroke)
[4] (2003)	Prospective cohort	ACR 1987 criteria	525	2-fold risk for MI 1.48-fold risk for stroke RA >10 years: 3-fold risk for MI
[84] (2003)	Cross-sectional survey	Rheumatologist diagnosis	9,093	2.15-fold risk for MI
[19] (2003)	Prospective cohort	Physician diagnosis	11,633	1.6-fold risk for MI
[5] (2005)	Retrospective cohort	ACR 1987 criteria	603	2-fold risk for MI 6-fold risk for unrecognized MI 2-fold risk sudden death
[85] (2007)	Retrospective cohort	ACR 1987 criteria	239	0.1% to 0.3%/year MI 0.07%/year stroke
[2] (2008)	Retrospective cohort	Rheumatologist diagnosis	4,363	3.2% prevalence MI 1.9% prevalence stroke

ACR, American College of Rheumatology; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; RA, rheumatoid arrthritis.

Table 2

Studies evaluating the risk of coronary heart disease in systemic lupus erythematosus

[Reference] (year)	Study design	SLE definition	*n*	Estimated risk
[11] (1997)	Prospective cohort	ACR criteria for SLE	498	5-fold risk for MI 50-fold risk in ages 35 to 44 years
[86] (1999)	Retrospective cohort	Rheumatologist diagnosis	8,742	2.27-fold risk for MI 3.8-fold risk for chronic heart failure
[12] (2001)	Retrospective cohort	Rheumatologist diagnosis	296	17.0-fold risk for CVD 10.1-fold risk for MI 7.9-fold risk for stroke
[87] (2004)	Cross-sectional, prospective	ACR criteria for SLE	202 (cross-sectional), 47 (prospective)	1.4-fold risk for CHD 0.6-fold risk for stroke 8.5% CHD events 10% stroke follow up
[88] (2004)	Case control	Physician diagnosis	770	1.46 risk for MI

ACR, American College of Rheumatology; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; SLE, systemic lupus erythematosus.

dysfunction might reflect CVD risk factor burden in these individuals, but it could also indicate systemic inflammation and prolonged exposure of endothelial cells to pro-inflammatory cytokines such as TNF-α (*vide infra*). Interestingly, in animal models as well as in human clinical trials in RA and SLE patients, high doses of statins can reduce inflammation and improve endothelial function [47]. Statins are effective in lowering LDL-cholesterol, but they also have immunomodulatory properties [48]. Both mechanisms of action might be at play in reducing endothelial dysfunction.

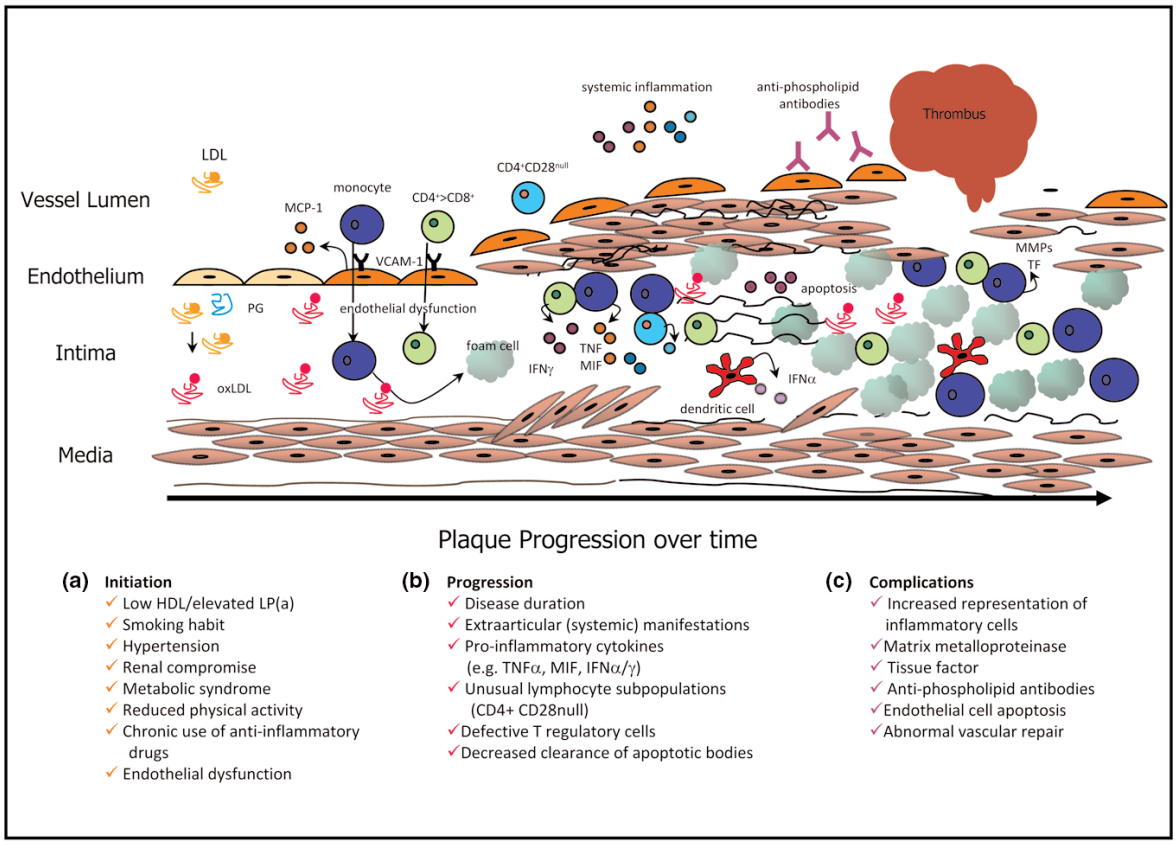
Progression of atherosclerotic disease

Although atherosclerosis is initiated by the exposure to traditional lifestyle risk factors, inflammation is a key driving force at each stage of atherosclerosis development [43], with both innate and adaptive cellular components of inflammation involved in disease progression (Figure 2).

Myeloid cells, cytokines and atherosclerosis progression

Recruitment of blood-borne mononuclear cells is a key step in atherogenesis. Even in hypercholesterolaemic murine models

Figure 2



Formation and progression of atherosclerotic lesions. **(a)** Atherosclerosis disease initiation. Patients with rheumatoid arthritis and systemic lupus erythematosus present with clustering of traditional risk factors, notably low high-density lipoprotein (HDL) levels and pro-atherogenic lipid particles, leading to premature establishment of atherosclerotic lesions compared with age-matched and sex-matched control individuals. **(b)** Progression. Inflammatory disease activity and duration is emerging as a key determinant of the clinical association between cardiovascular disease (CVD) and inflammatory disease. Pro-inflammatory mediators and immune dysregulation features may enhance susceptibility to risk factors and establish chronic inflammation in vascular lesions. **(c)** Complications. Both inflammatory features and prothrombotic pathways may enhance the likelihood of acute events, increasing mortality. IFN, interferon; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; oxLDL, oxidized low-density lipoprotein; PG, prostaglandin; VCAM, vascular cell adhesion molecule; TF, tissue factor; TNF, tumour necrosis factor.

of atherosclerosis, genetic deletion or blockade of chemokines (such as C-C chemokine ligands 2 and 5, and fractalkine and its cognate receptors) and adhesion molecules (such as vascular cell adhesion molecule-1) abrogates monocyte recruitment and atherosclerosis in mice [43]. Blood-borne monocytes recruited through the endothelium undergo differentiation into macrophages induced by macrophage colony-stimulating factor. During this process scavenger receptors are upregulated, mediating the uptake of oxLDL, causing the formation of foam cells, which are the hallmark of atherosclerotic lesions. Macrophages in atherosclerotic plaques exhibit features of activation and release a host of pro-inflammatory mediators including TNF-α, which leads to the engagement of the pro-inflammatory cytokine cascade, resulting in IL-1 and IL-6 production. IL-6 in turn stimulates production of large amounts of acute-phase reactants, including C-reactive protein, serum amyloid A and fibrinogen in the liver.

Cytokine upregulation is a general feature of inflammatory diseases and could be a mechanism that links increased atheroma formation in patients with RA and SLE. Several cytokines with relevance to CVD could contribute to the pathogenesis of atherosclerosis in RA and SLE.

TNF-α plays a dominant role in RA. TNF-α induces a pro-inflammatory cascade, with upregulation of other mediators, namely IL-1, IL-6 and IL-8, prostaglandins and matrix metalloproteinases (MMPs). Upregulation of adhesion molecules by TNF-α on the vascular endothelium leads to cellular recruitment of neutrophils and monocytes. It also stimulates the proliferation of fibroblasts [49]. Introduction of the anti-TNF

treatments has dramatically improved the outcome of severe RA [50]. Blockade of TNF-α in RA reduces circulating cytokine levels, leucocyte trafficking and platelet levels, all factors that may promote thrombotic and atherosclerotic complications [50]. In studies of hypercholesterolaemic apolipoprotein (apo)$E^{-/-}$ mice, genetic deletion of TNF-α or treatment with recombinant soluble TNF receptor I led to a reduction in atherosclerotic lesions [51]. Experimental studies using $apoE^{-/-}$ $TNF^{-/-}$ mice also demonstrated a significantly smaller lesion size in the aortic sinus compared with that of $apoE^{-/-}$ mice [51]. Although the failure of TNF blockers in heart failure has thus far discouraged further trials in other CVD, evidence to support the hypothesis that TNF blockers are protective against CVD has started to accumulate in RA cohorts. In a Swedish registry cohort [52], treatment with TNF inhibitors was associated with a lower incidence of first MI in patients with RA. Anti-TNF treatment in RA patients increases HDL-cholesterol levels [53], insulin sensitivity [54] and reduces carotid IMT [55] and MI [56].

Recently, macrophage migration inhibitory factor (MIF) has emerged as a potential link between RA, SLE and atherosclerosis development (for review, see [57]). Originally, described as 'a soluble factor released from T cells in delayed hypersensitivity responses inhibiting migration of macrophages', MIF is considered a pleiotropic cytokine with roles in several inflammatory diseases. MIF induces the pro-inflammatory mediators TNF-α, IL-1, IL-6 and MMPs. It can activate T cells, promote angiogenesis and induce proliferation of cells, while inhibiting p53 expression and apoptosis of the same cells [57,58]. MIF can be induced by oxLDL, which is an initiating factor in atherogenesis, and so expression of MIF early on may enhance pro-inflammatory responses and lesion progression [58]. MIF immunoneutralization or genetic deletion reduces disease activity in animal models of arthritis and lupus. In mice with advanced atherosclerosis, MIF blockade led to plaque regression and reduced monocyte and T-cell content in the plaques. Interestingly, glucocorticoids can induce the expression of MIF in multiple cell types [57], which is a function of potential relevance to the development of CVD in those patients receiving chronic treatment. Increased serum levels of MIF have been detected in SLE patients compared with healthy control individuals [57], and correlations were reported between MIF serum levels and SLE-related damage scores and glucocorticoid exposure.

The type I interferon cytokines (interferon [IFN]-α and IFN-β) play a causative role in SLE. Type I IFN-α is produced by dendritic cells in response to viral or bacterial infections, sensed through Toll-like receptor (TLR)-9. Auto-antigens such as self-DNA, exposed by apoptotic cells, may also trigger TLR-9 signalling, resulting in IFN-α production [59]. IFNs play many roles including inhibition of cell proliferation, interfering with viral infections, proliferation of memory T cells and increased antigen presentation activity by dendritic cells [60]. Type I IFNs were recently linked to impairment of vascular repair by circulating endothelial progenitor cells. SLE patients have decreased numbers of endothelial progenitor cells, with increased endothelial cell apoptosis, and decreased pro-angiogenic and repair capacity [59]. IFN-α has anti-proliferative effects on endothelial progenitor cells *in vitro*. SLE patients have elevated levels of IFN-α, which correlates with disease severity [60] and impaired endothelial function [61]. Interestingly, IFN-α produced by plasmacytoid dendritic cells has been detected in human carotid plaques, where it could sensitize antigen-presenting cells to the TLR-4 ligand lipopolysaccharide, thereby promoting the production of pro-inflammatory molecules [62]. By contributing to endothelial dysfunction/damage and inducing pro-inflammatory responses within the atherosclerotic plaque, IFN-α could promote atherosclerosis in patients with inflammatory diseases.

Lymphocytes and immune dysregulation

T cells infiltrate atherosclerotic lesions, even in early stages of disease. Such infiltrates are predominantly CD45RO-expressing memory $CD4^+$ T cells, most of which bear the T-cell receptor αβ. They appear to be in close contact with major histocompatibility complex (MHC) class II expressing macrophages and dendritic cells. Both human and animal studies have thus far shown a predominantly T-helper (Th)1 pattern in atherosclerosis, with immunopositivity for the classic Th1 cytokine IFN-γ and Th1-stimulating cytokines IL-12 and IL-18. In $apoE^{-/-}$ mice lacking IFN-γ or its receptor, the development of atherosclerosis is inhibited [43].

During the past decade, an unusual subpopulation of $CD4^+$ T cells lacking the co-stimulatory receptor CD28 have been suggested to link atherosclerotic syndromes with RA. Such $CD4^+$ T cells exhibit a spectrum of regulatory receptors that are usually only seen on natural killer cells. Such regulatory receptors include perforin, members of the killer immunoglobulin-like receptor family, and the receptor for the chemokine fractalkine. In RA, circulating $CD4^+CD28^{null}$ cells are increased and correlate with preclinical atherosclerotic disease and endothelial dysfunction. Such cells are also increased in the circulation and in plaques of patients with acute coronary syndrome (ACS) [63] and possess endothelial cell cytotoxic activity [64].

An additional mechanism that could also explain the increased incidence of CVD in patients with inflammatory diseases is the failure of regulatory feedback mechanisms, such as production of anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)-β by regulatory T cells. T-cell-specific genetic deficiency in the TGF-β receptor leads to plaque destabilization, whereas regulatory T cells have the ability to reduce atherosclerotic burden in hyperlipidaemic mice [43]. In RA $CD4^+CD25^+$ regulatory T cells have a defect in their suppressive functions, which was restored during treatment with TNF blockers [65].

The decreased clearance of apoptotic bodies has also been evoked to explain increased inflammation in lupus-like models of disease. The *gld* and *lpr* mouse strains have inactivating mutations in Fas ligand and Fas, respectively, and they suffer from lupus-like disease. (Fas ligand and Fas are transmembrane proteins on the cell surface; binding of Fas ligand to its receptor Fas induces apoptosis.) Although these mice typically do not exhibit signs of atherosclerosis, they are susceptible to atherosclerotic lesion formation when they are fed an atherogenic diet [66]. ApoE$^{-/-}$ mice crossed with *gld* mice developed lesions containing a twofold to threefold increase in macrophages and CD3^{+} lymphocytes as compared with apoE$^{-/-}$ mice [67]. A similar increase in lymphocytes and macrophage accumulation within the lesions were observed after bone marrow transfer from lupus-prone strains developed on a C57BL/6 background to LDL receptor-deficient mice [68,69], even in the presence of lower levels of cholesterol and triglycerides. Furthermore, an increase in the expression of the MHC class II molecule I-Ab in mice with lupus-like disease compared with control animals was observed, and there were significantly higher antibody titres to oxLDL and cardiolipin [67-69].

Thrombotic complications

ACS such as MI occur when thrombosis ensues on an atherosclerotic plaque, suddenly limiting blood flow through the coronary artery. Acute thrombosis is often triggered by sudden plaque rupture or erosion [43], but heterogeneity of pathological substrates for thrombosis has been documented [70]. MI is often caused by plaques that only moderately restrict the vessel lumen (by <50% of the lumen diameter) [71].

Plaque vulnerability

The chance of plaque rupture is determined by the strength and thickness of the fibrous cap, surrounding the inflammatory and necrotic 'core' of the plaque. The cap, made up of smooth muscle cells (SMCs) either recruited from the media or derived from progenitors, forms a protective barrier encasing the core, preventing the prothrombotic material - tissue factor and phospholipids - from contacting the arterial blood flow [43]. 'High-risk' atherosclerotic plaques are characterized by their composition rather than by their impact on the vessel lumen. A high-risk plaque is characterized by a large lipidic/necrotic core with increased number of activated monocytes and lymphocytes. The fibrous cap is also thinner due to SMC apoptosis and proteolytic degradation of the fibrous proteins. On the contrary, a 'stable' plaque is characterized by its thick fibrous cap, containing increased amounts of fibrous proteins and SMCs, and generally a smaller pro-inflammatory/prothrombotic core; such plaques are less prone to rupture.

There is evidence that plaques obtained from patients who have experienced an ACS have a higher content of macrophages and activated T lymphocytes at sites of coronary thrombosis [72]. Also, they are often found in clusters within the fibrous cap, in particular in the 'shoulder' area of the lesion, the border between normal vessel and atherosclerotic plaque, where plaque rupture is thought to occur most often. A retrospective autopsy study comparing 41 patients with RA with sex-, age- and autopsy date-matched control individuals did not identify significant differences between groups in severity of the coronary stenoses in cross-sectional area or the number of vessels affected. However, RA patients with clinical history of CVD were more likely to have coronary lesions with a 'high-risk' rather than a 'stable' plaque phenotype [73]. This finding is in agreement with a long 'silent' history of coronary artery disease, with increased incidence of MI and sudden death [5,6].

Plaque stability can be influenced by cytokines via a variety of mechanisms. First, cytokines can affect the amount of fibrous proteins produced by SMCs. IFN-γ inhibits collagen production, whereas TGF-β has the opposite effect. Second, cytokines such as TNF-α and IL-1 can induce expression of MMPs in SMCs and macrophages, which degrade the fibrous cap. MIF can induce MMP expression and may also contribute to plaque instability by increasing monocyte recruitment and retention in the plaque. Third, apoptosis of SMCs can be induced by IFN-γ and TNF-α. Finally, cytokines, in particular TNF-α, can induce expression of tissue factor, which is the major initiator of the thrombotic cascade and whose increased expression is a feature of plaques in patients with ACS. Therefore, pro-inflammatory cytokines can have both a localized effect on the plaque architecture and determine occurrence of thrombotic events, and a more systemic effect, in which they affect cholesterol levels, insulin resistance and endothelial function.

Genetic associations

Recently, single nucleotide polymorphisms (SNPs) with an impact on immune responses have emerged as shared genetic risk factors in RA and MI. The expression of MHC class II is regulated by the transactivator *MHC2TA*. A SNP, namely the A168G polymorphism in the type III promoter of MHC2TA, was recently associated with RA, multiple sclerosis and MI. This polymorphism was associated with lower expression of MHC2TA after stimulation of peripheral blood cells with IFN-γ, leading the authors to speculate that less efficient antigen presentation in response to inflammatory stimuli to regulatory T cells may promote disease [74]. Interestingly, statins have been shown to downregulate MHC2TA expression by inhibition of the inducible IV promoter of *MHC2TA* [48]. However, no evidence of association of this *MHC2TA* variant with RA could subsequently be detected in independent cohorts [75,76], and studies in larger sample sizes are awaited to clarify the role of this SNP in the aetiology of RA [75].

Interestingly, polymorphisms in the region of the *TNFAIP3* gene were recently linked to RA and SLE [77,78]. *TNFAIP3* encodes the de-ubiquitinating enzyme A20, an endogenous

inhibitor of the nuclear factor-κB (NF-κB) pathway. NF-κB is a transcription factor that is activated by TNF or IL-1/TLR signalling pathways, which induces transcription of pro-inflammatory genes. In atherosclerosis, NF-κB is activated at sites of the arterial wall that are prone to lesion development. In animal studies, $ApoE^{-/-}A20^{-/-}$ mice had increased atherosclerosis, whereas mice with A20 over-expression had decreased atherosclerosis [79]. SNPs in the *TNFAIP3* gene region may cause reduced expression or reduced activity of A20 [77], therefore contributing to an uncontrolled inflammatory response and autoimmunity and potentially accelerated atherosclerosis in these patients.

Antiphospholipid antibodies

Antiphospholipid antibodies are the hallmark of the antiphospholipid syndrome, which is characterized by recurrent thrombosis and is associated with SLE. Between 30% and 50% of patients with SLE have antiphospholipid antibodies, and approximately one-third develop antiphospholipid syndrome [23]. Many of these antibodies, such as anticardiolipin (aCL), recognize phospholipid-binding plasma proteins such as β_2-glycoprotein I (GPI), which is anticoagulant. Nevertheless, there is some new evidence to suggest that they may also play a role in the development of atherosclerotic disease. Antibodies to β_2-GPI may lead to endothelial activation and/or damage, as well as enhance oxLDL uptake by macrophages, contributing to recruitment of immune cells to the vascular wall. Furthermore, immunization with β_2-GPI leads to vascular lesions in LDL $receptor^{-/-}$ mice, suggesting that immune recognition might also play a role [80].

However, in SLE cohorts no correlation was found between aCL antibodies and indices of atherosclerosis extent and severity such as carotid IMT [81,82]. However, association was found with thrombotic complications such as MI. This paradox can potentially be explained by the ability of aCL to cause thrombosis even in the absence of underlying advanced atherosclerotic plaque [81]. Some patients with RA may have elevated levels of aCL [83]. In contrast with SLE patients, however, RA patients exhibited an increased carotid IMT compared with RA patients without elevated auto-antibodies [13]. However, in one study, only 17 out of 83 patients were found to have increased antibodies to aCL, and larger cohorts are needed to address this observation.

Conclusions

An increased prevalence of pro-atherogenic risk factors in patients with RA and SLE compared with age-matched control individuals may very well contribute to the initiating stages of disease. However, the dysregulated inflammation that characterizes inflammatory diseases may increase susceptibility to traditional risk factors and the likelihood that a chronic inflammatory response will ensue at the arterial sites. Potentially, shared pathogenic pathways are also at play. The dissection of the molecular mechanisms underlying atherosclerosis and classic inflammatory diseases will no doubt help us to understand how inflammation causes CVD in both the general population and in the subgroups of patients with inflammatory diseases.

Competing interests

The authors declare that they have no competing interests.

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