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Review article

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Autoimmune diseases and atherosclerotic cardiovascular disease

Florentina Porsch & Christoph J. Binder

Abstract

Autoimmune diseases are associated with a dramatically increased risk of atherosclerotic cardiovascular disease and its clinical manifestations. The increased risk is consistent with the notion that atherogenesis is modulated by both protective and disease-promoting immune mechanisms. Notably, traditional cardiovascular risk factors such as dyslipidaemia and hypertension alone do not explain the increased risk of cardiovascular disease associated with autoimmune diseases. Several mechanisms have been implicated in mediating the autoimmunity-associated cardiovascular risk, either directly or by modulating the effect of other risk factors in a complex interplay. Aberrant leukocyte function and pro-inflammatory cytokines are central to both disease entities, resulting in vascular dysfunction, impaired resolution of inflammation and promotion of chronic inflammation. Similarly, loss of tolerance to self-antigens and the generation of autoantibodies are key features of autoimmunity but are also implicated in the maladaptive inflammatory response during atherosclerotic cardiovascular disease. Therefore, immunomodulatory therapies are potential efficacious interventions to directly reduce the risk of cardiovascular disease, and biomarkers of autoimmune disease activity could be relevant tools to stratify patients with autoimmunity according to their cardiovascular risk. In this Review, we discuss the pathophysiological aspects of the increased cardiovascular risk associated with autoimmunity and highlight the many open questions that need to be answered to develop novel therapies that specifically address this unmet clinical need.

Sections

Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria. e-mail: christoph.binder@meduniwien.ac.at

Key points

- Autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis, are associated with an increased risk of atherosclerotic cardiovascular disease and cardiovascular death.
- Epidemiological data in large cohorts of patients and experimental evidence in preclinical models have clearly established the link between autoimmunity and atherosclerosis.
- Both shared and distinct mechanisms increase the risk of atherosclerosis in patients with systemic lupus erythematosus, rheumatoid arthritis or other connective-tissue autoimmune diseases.
- Endothelial dysfunction, increased cytokine signalling (IL-1β, IL-6 and tumour necrosis factor) and leukocyte activation (monocytes, macrophages and neutrophils), and aberrant T cell and B cell functions are key mechanisms for accelerated atherosclerosis in patients with autoimmune diseases.
- Knowledge about the functional role of classic autoimmune disease-associated autoantibodies in promoting atherosclerosis is limited.
- Anti-inflammatory therapies that are being evaluated for atherosclerotic cardiovascular disease might represent important opportunities for reducing the risk of atherosclerosis particularly in patients with autoimmunity.

Introduction

In the past decade, the approaches to the treatment and prevention of atherosclerotic cardiovascular disease (ASCVD) by targeting modifiable risk factors, such as hypercholesterolaemia, hypertension and diabetes mellitus, have improved dramatically. However, a substantial residual cardiovascular risk persists even after optimal management of traditional risk factors. One major contributor to this residual risk is inflammation, which is primarily assessed in the clinic by measuring the circulating levels of C-reactive protein (CRP). Analyses of large clinical trials on lipid-lowering therapies have revealed that assessment of CRP levels is superior to LDL cholesterol measurements for the prediction of cardiovascular events and mortality in patients receiving optimal therapy[1]. This finding suggests the need for the addition of anti-inflammatory therapies to the management of these patients. Indeed, clinical trials on anti-inflammatory drugs, such as the IL-1β-neutralizing antibody canakinumab[2] and the broad anti-inflammatory agent colchicine[3], in patients with acute coronary syndrome or stable coronary artery disease have demonstrated the potential to reduce the inflammation-associated cardiovascular risk in these patients[4]. Notably, low-dose colchicine was approved by the US Food and Drug Administration for patients with established ASCVD, and the European Society of Cardiology guidelines include the option of adding colchicine to the standard-of-care for the prevention of recurrent cardiovascular events in patients with acute coronary syndrome[5]. In addition to abundant epidemiological data demonstrating an independent association between CRP and IL-6 levels in the plasma[6], several studies have shown clear associations between other markers of innate and adaptive immunity and cardiovascular events, independent of traditional cardiovascular risk factors[7–9]. Furthermore, experimental data have demonstrated the contribution of the immune system to different stages of atherosclerosis, from disease initiation to mechanisms that trigger clinical events[4,10] (Fig. 1). Therefore, it is not surprising that patients with autoimmune diseases have a substantially increased risk of developing ASCVD[11].

Autoimmune diseases are a highly heterogeneous group of pathologies with distinct clinical presentations, even within the same disease entities[12,13]. However, some pathophysiological features that are shared across different autoimmune diseases might also contribute to the exacerbated risk of cardiovascular disease (CVD) in these patients[14–16]. Generally, autoimmune diseases can arise in genetically susceptible individuals, and are influenced by environmental factors, resulting in loss of tolerance to self-molecules and dysregulation of adaptive and innate immune mechanisms, which can precede tissue damage and clinical disease onset by decades. Given the delayed onset of the clinical manifestations of the disease, the early identification of patients with autoimmune disease remains challenging. Therefore, assessing the effect of preclinical autoimmune disease on ASCVD is difficult. Whereas inflammation is a component of residual cardiovascular risk in patients with ASCVD, it is a more dominant contributor to cardiovascular risk in patients with autoimmune conditions. In this Review, we discuss the available evidence and the mechanisms of the increased and premature risk of ASCVD in patients with autoimmunity, with particular focus on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Discussion of other autoimmune manifestations and organ-specific autoimmune diseases is beyond the scope of this Review.

Link between autoimmune diseases and ASCVD

Epidemiological evidence

In an analysis of 446,449 individuals with any of 19 autoimmune diseases and without CVD at baseline, 15.3% of patients developed incident CVD within a period of 6.2 years compared with 11% of 2,102,830 matched controls without autoimmune diseases or CVD at baseline[11]. Moreover, the hazard ratio for CVD increased from 1.41 for individuals with one autoimmune disease to 3.79 for individuals with three or more autoimmune diseases. All connective tissue diseases were associated with an increased risk of CVD, with particularly strong effects for systemic sclerosis, SLE, Sjögren syndrome, RA and vasculitis[11]. Notably, an increased risk of CVD was particularly strong in young individuals. Among the different ASCVDs, the hazard ratio was highest for peripheral artery disease (PAD) (HR 2.09), followed by ischaemic heart disease (HR 1.6) and stroke (HR 1.39)[11]. A meta-analysis including 263,258 patients with SLE and 768,487 control individuals without SLE found an increased prevalence of PAD in patients with SLE (15.8% versus 3.9%)[17]. These findings are consistent with a meta-analysis of 12 studies on the risk of symptomatic CVD, which showed an increased relative risk of 1.98 in patients with SLE and a relative risk of 1.55 in patients with RA compared with individuals without autoimmune disease[18]. A Danish study of 3,411 patients with SLE and 13,644 controls found a 50–100% increased 10-year risk of myocardial infarction (MI) and stroke in patients with SLE[19]. Another study found that women with SLE aged 35–44 years have a 50-fold higher risk of MI than age-matched women without SLE[20]. Data from the Nurses' Health Study showed that women with incident RA have a higher risk of cardiovascular death (HR 1.45) than women without RA[21]. This increased risk of ASCVD and associated mortality has also been observed for other autoimmune diseases, such as Sjögren syndrome and systemic sclerosis[22,23] (Fig. 2).

Despite the increased prevalence of traditional cardiovascular risk factors, such as hyperlipidaemia and hypertension, in patients

with autoimmunity, additional markers to predict the cardiovascular risk in these patients are needed. For example, in the MESA study[14,24], women with SLE had higher coronary calcium scores after adjusting for conventional risk factors than those without SLE. Similarly, patients with mild-to-moderate SLE have increased aortic wall inflammation as assessed by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET–CT[25]. Smaller ^{18}F-FDG PET imaging studies have also found increased ^{18}F-FDG uptake in the aorta, and carotid and femoral arteries in patients with RA compared with patients with osteoarthritis[26], as well as an association between increased aortic inflammation and RA disease markers[27] independent of traditional risk factors. A meta-analysis of coronary CT studies in patients with RA found higher coronary calcium scores and a higher prevalence of high-risk plaques in patients with RA than in individuals without RA[28]. Likewise, a number of studies have found higher carotid intima–media thickness (IMT) in patients with autoimmunity than in healthy individuals[29]. Although these latter findings need to be carefully interpreted given that the usefulness of carotid IMT quantification to assess future cardiovascular risk is debatable, these measurements might have some value in the context of clinical studies[30]. These findings also emphasize the need to start monitoring patients with autoimmune diseases early on and to identify better markers of cardiovascular risk. In addition to imaging biomarkers, specific circulating biomarkers are needed because general markers of inflammation, such as CRP, have even more limitations than imaging biomarkers for reflecting the pathophysiology of atherosclerosis in these patients.

Preclinical evidence

Innate and adaptive immunity contribute to early and late stages of atherogenesis as well as to thrombotic events that lead to clinical manifestations (Box 1; Fig. 1). Thus, it is conceivable that the systemic immune dysregulation observed in patients with autoimmune diseases affects the development of atherosclerosis. In addition to robust epidemiological evidence, experimental evidence from different mouse models also supports the presence of an increased risk of atherogenesis in autoimmunity. Several studies have evaluated this link with the use of genetic and inducible models of autoimmunity. These models show various immunological aberrations, including dysregulation of adaptive immunity with hyperactive T cells and autoantibody generation, disrupted apoptosis pathways, and antigen-specific autoimmunity. Table 1 summarizes the studies that investigated the effects of these immunological aberrations in atherosclerosis-prone mice.

In models of SLE, most studies found increased atherosclerosis compared with non-autoimmunity controls, without differences in serum cholesterol levels[31–38]. However, hypercholesterolaemia itself also increased the autoimmune phenotype in some models[32,33,35,39,40]. Notably, in atherosclerotic mouse models, FAS ligand (FASL) or FAS deficiency was associated with increased numbers of apoptotic cells in the atherosclerotic lesions, consistent with a contribution of impaired efferocytosis to heightened plaque formation[31,32,34]. Other SLE-prone models, such as *Sle16* or *Sle1.2.3* mice (which carry SLE-susceptibility loci), also had increased atherosclerotic lesion formation compared with control mice, often in the presence of glomerulopathy (proteinuria)[35–37]. Interestingly, transfer of CD4$^+$ T cells from *Sle1.2.3.* mice into *Ldlr*$^{-/-}$*Rag*$^{-/-}$ mice was sufficient to increase atherogenesis[38]. In another genetic model of SLE (Nba2.Yaa), atherosclerotic lesion complexity was increased, which demonstrates the capacity of autoimmune-mediated responses to promote unstable plaque features[41].

Despite the documented increase in the plasma levels of various autoantibodies (Box 2) in atherosclerosis-prone mice with autoimmune conditions (Table 1) as well as in *Apoe*$^{-/-}$ mice[42–44], the contribution of specific autoantibodies, such as anti-phospholipid antibodies, to atherosclerotic lesion formation is not clear[45–47]. The effect of RA on atherosclerosis has been tested primarily with the use of the T cell receptor transgenic K/BxN mouse model, which develops autoantibodies against glucose-6-phosphoisomerase. Transfer of serum from these mice into hypercholesterolaemic mice was generally associated with increased arthropathy and inflammation as well as increased atherosclerosis[40,48,49] or reduced diet-induced plaque regression[50]. Although these studies give limited mechanistic insights, they provide evidence that, in general, mouse models of autoimmune disorders develop more atherosclerosis when the model is generated on an atherosclerosis-prone background. Of note, the renal impairment seen in some of these models might be a contributing factor for the increased atherogenesis, and the effect seems to be independent of alterations in serum cholesterol levels (Table 1), which points to a prominent effect of immune-mediated mechanisms.

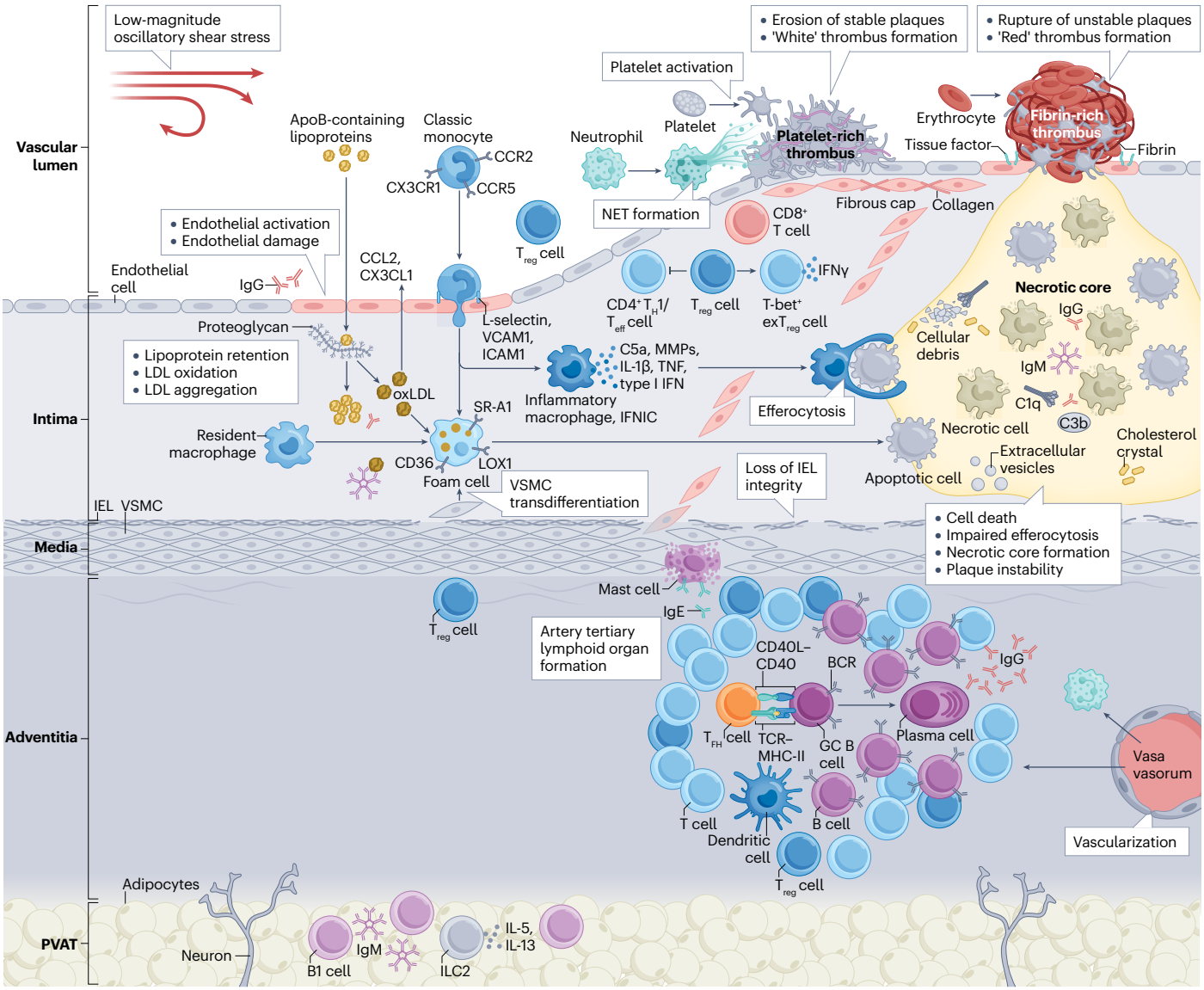
Interplay with traditional cardiovascular risk factors

The autoimmunity-mediated risk of ASCVD is independent of, but can be accentuated by, traditional cardiovascular risk factors[11]. However, the relative contribution of these factors might be different in patients with autoimmune disorders compared with the general population. For example, autoimmunity is more prevalent in young female individuals, who usually have a lower risk of ASCVD[51], but the autoimmunity-associated risk of ASCVD was found to be the same in men and women[11]. Certain ASCVD risk factors also result from organ manifestations of autoimmune diseases, such as impaired renal function and hypertension[52]. In addition, the different therapies for autoimmune diseases can alter the profile of ASCVD risk factors such as dyslipidaemia[53]. Finally, certain environmental risk factors, most prominently cigarette smoking, are common to ASCVD and SLE[54] and RA[55]. This interplay between genetic and environmental risk factors, autoimmunity and atherosclerosis adds to the complexity of the increased risk of ASCVD in patients with autoimmunity.

Dyslipidaemia

The higher prevalence of dyslipidaemia in patients with autoimmune diseases compared with the general population[53,56] favours synergistic effects of lipid-driven and autoimmunity-mediated risk of ASCVD. Serum lipid profiles in patients with SLE are often characterized by increased triglyceride and VLDL levels and reduced HDL cholesterol levels compared with age-matched controls[57]. In addition, patients with primary Sjögren syndrome or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis have a higher prevalence of hypercholesterolaemia and metabolic alterations compared with the general population[22,58,59]. This dyslipidaemia can result from increased inflammation but also immunosuppressive therapies, such as steroids, which can confound the interpretation of clinical studies. Whether different lipoprotein particles (LDL versus HDL versus lipoprotein remnants) have a differential contribution in autoimmunity is unknown, but SLE and RA have been shown to be associated with altered HDL particles that lack anti-inflammatory potential and that can be pro-atherogenic[60–62], properties that can be modulated by anti-rheumatic therapy[63]. Interestingly, in some instances, lipid levels tend to decrease during the inflammatory phases of autoimmune disease, as has been described in patients with RA[64].

Hypercholesterolaemia can promote the production of autoantibodies in *Apoe*$^{-/-}$ mice and *Ldlr*$^{-/-}$ mice[42–44], and several studies in



mice have demonstrated exacerbated autoimmune manifestations (glomerulopathy and arthropathy) in the context of hypercholesterolaemia[32,33,35,39,40] (Table 1). However, in the case of apolipoprotein E (apoE) deficiency, this effect might be partly dependent on the immunoregulatory functions of apoE, given that acute loss of apoE in an inducible mouse model was found to be able to trigger cellular and humoral autoimmune responses[42]. Therefore, the effect of hypercholesterolaemia in mouse models of autoimmune conditions is inconclusive.

Hypercholesterolaemia could also precipitate certain autoimmune pathologies. Indeed, in women, high cholesterol levels are associated with an increased risk of developing RA[65]. However, a bidirectional Mendelian randomization study assessing the effect of genetically determined lipid traits on the risk of developing SLE found no causal relationship[66]. Also, a weighted genomic risk score for SLE was not associated with dyslipidaemia[67]. Nevertheless, one can speculate that hypercholesterolaemia contributes to autoimmune disease severity by modulating both innate and adaptive immunity. For example, monocytosis and neutrophilia are triggered by dyslipidaemia[68]. Additionally, cellular cholesterol metabolism modulates immune cell function, including lipid raft formation and associated T cell signalling, which can be disturbed in patients with SLE[69,70]. In experimental studies, dyslipidaemia has been shown to modulate the number and function of regulatory T (T_{reg}) cells[71–74]. This finding raises the possibility that dyslipidaemia favours a loss of tolerance that might facilitate the emergence of antibodies against atherosclerosis-associated antigens, resulting in the maladaptive immune response found in atherosclerosis that has been likened to an autoimmune response by some[75,76]. Moreover, cholesterol accumulation in dendritic cells heightens their activation status and promotes autoimmune manifestations[77,78].

Hypertension

Patients with autoimmune diseases frequently have hypertension[22,79]. The contribution of hypertension to the CVD risk in these patients has been extensively reviewed elsewhere[80]. Inflammatory stimuli

Fig. 1 | Pathogenesis of atherosclerosis. Disturbed, non-laminar flow conditions result in endothelial dysfunction and the retention of LDL and other apolipoprotein B (apoB)-carrying lipoproteins in the arterial intimal, where they subsequently become modified and trigger endothelial cell activation. Expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), and production of chemokines, such as CX3C-motif ligand 1 (CX3CL1; also known as fractalkine) and CC-motif chemokine 2 (CCL2), mediate the recruitment of pro-inflammatory monocytes to the vascular wall. Resident and monocyte-derived macrophages take up aggregated or oxidized LDL (oxLDL) via scavenger receptors, leading to the formation of foam cells. Subsequent intracellular accumulation of cholesterol crystals can trigger the activation of the NLRP3 inflammasome, leading to the production of IL-1β. Various types of macrophage, including pro-inflammatory macrophages termed interferon (IFN)-inducible cells (IFNIC), populate atherosclerotic plaques, where they secrete various cytokines, chemokines and complement factors that modulate multiple aspects of atherogenesis. IL-5-secreting and IL-13-secreting type 2 innate lymphoid cells (ILC2), IgM-secreting B1 cells in the perivascular adipose tissue (PVAT) and FOXP3$^+$ regulatory T (T_{reg}) cells are thought to mediate vascular homeostasis and atheroprotection. At later stages of atherosclerosis, CD4$^+$ effector T (T_{eff}) cells, including pro-atherogenic IFNγ-secreting T helper 1 (T_H1) cells, dominate the adaptive immune response in plaques. T_{reg} cells can also convert to pro-atherogenic T-bet$^+$ exT_{reg} cells. Cytotoxic CD8$^+$ T cells also promote atherogenesis. Disruption of the internal elastic lamina (IEL) coincides with the migration of vascular smooth muscle cells (VSMCs) to the intima, where they contribute to the formation of a collagen-rich fibrous cap that segregates the necrotic core from the vascular lumen. VSMCs can also transdifferentiate into macrophage-like cells and become foam cells. Advanced plaques are also surrounded by artery tertiary lymphoid organs (ATLOs) and can be vascularized (vasa vasorum) and innervated. ATLOs are sites for antigen presentation and germinal centre (GC) reactions involving T follicular helper (T_{FH}) cells and GC B cells, which promotes the generation of class-switched plasma cells that can secrete IgG or IgE. Immunoglobulins are present in atherosclerotic plaques, where they are complexed with antigens and can bind to different Fc receptors on macrophages and mast cells, which further modulates the inflammatory process. In addition, foam cells can undergo several forms of cell death, but the removal of dead cells (efferocytosis) aided by complement is impaired in atherosclerosis, resulting in the formation of cell-free necrotic areas that are hallmarks of unstable rupture-prone plaques. Atherothrombotic events are triggered by neutrophils and neutrophil extracellular traps (NETs) that promote plaque erosion as well as plaque rupture, which is a consequence of matrix metalloproteinase (MMP)-dependent degradation of the fibrous cap and the release of pro-coagulant tissue factor. BCR, B cell receptor; CCR, CC chemokine receptor; CD40L, CD40 ligand; CX3CR1, CX3C chemokine receptor 1; SR-A1, scavenger receptor type A1; TCR, T cell receptor; TNF, tumour necrosis factor.

associated with autoimmune disease can have direct effects on the cardiovascular system and on hypertension, including effects on endothelial cells and vascular reactivity. Additionally, renal pathologies resulting from autoimmune diseases can also contribute to hypertension. Moreover, some drugs, including long-term corticosteroids, can promote hypertension[81]. Notably, experimental data in mice suggest a pathophysiological link between hypertension and autoimmunity[37,82,83].

Diabetes mellitus

A Mendelian randomization study found a causal effect of RA-relevant single-nucleotide polymorphisms on the risk of developing type 2 diabetes and ASCVD, which supports the contribution of chronic inflammation to both diseases[84,85]. Dyslipidaemia is a major contributor to the development of type 2 diabetes[86–88]. Moreover, obesity predisposing to type 2 diabetes is highly prevalent in patients with RA[89], in part due to reduced physical activity.

Pathophysiological mechanisms

Endothelial dysfunction

Endothelial cell activation and dysfunction are the earliest steps in atherogenesis (Box 1; Fig. 1). Lesion formation typically arises in large-sized and medium-sized arteries where laminar flow is disturbed in arterial branching regions[90,91]. Interestingly, in the context of autoimmune diseases, vascular damage can occur at other locations, such as the microvasculature[92–94], suggesting that different pathophysiological mechanisms might be present. Autoimmune diseases are associated with increased endothelial dysfunction and activation, including the expression of vascular adhesion proteins such as vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1) and E-selectin[13,15] (Fig. 3). In some autoimmune diseases, such as systemic sclerosis, which can co-occur with SLE[95], intimal thickening and vascular stiffening are among the earliest events in disease pathogenesis[96].

Multiple mechanisms have been proposed for autoimmune-associated vascular dysfunction (Fig. 3). Circulating immune cells and pro-inflammatory cytokines, such as IL-1β, tumour necrosis factor (TNF) or type I IFN, can directly induce endothelial dysfunction[97–99]. Impaired vasodilatation occurs as a result of reduced nitric oxide bioavailability, which can be caused by decreased expression of endothelial nitric oxide synthase (eNOS) as a result of increased IFNα levels in SLE[100] or TNF levels in RA[101]. Patients with SLE have reduced endothelial-dependent flow-mediated vasodilatation (FMV) compared with healthy controls[102].

Circulating immune cells, including neutrophils that are enriched in SLE, can directly induce endothelial apoptosis, which is in part mediated by IFNα[103,104] or neutrophil extracellular traps (NETs) and their associated matrix metalloproteinases (MMPs)[105,106] (Fig. 3). Consistent with these findings, patients with SLE have higher numbers of circulating apoptotic endothelial cells than patients without SLE but with coronary artery disease, and higher numbers than healthy individuals[107]. Moreover, the number of circulating apoptotic endothelial cells correlates with vascular dysfunction as assessed by brachial artery FMV, a measure of early endothelial dysfunction[107]. Additionally, aberrant neutrophil activity and IFNα impair the regeneration of endothelial cells by endothelial progenitor cells and circulating angiogenic cells[103,104,108]. Moreover, NETs promote endothelial-to-mesenchymal transition, which contributes to atherosclerotic plaque growth[90,109]. NETs are also implicated in vascular damage in ANCA-associated vasculitis[110–112]. Circulating platelets in patients with SLE also induce endothelial dysfunction by secreting type I IFN[113] and IL-1β[114] or by shedding extracellular vesicles that can activate neutrophils[115]. Endothelial damage can further be triggered by anti-endothelial autoantibodies, which induce antibody-dependent cytotoxicity and immune cell infiltration[116,117]. Notably, antibodies against endothelial antigens promote atherosclerosis in experimental models[118,119].

Cytokines

Cytokines are key mediators of inflammatory responses in both ASCVD and autoimmunity. Elevated circulating levels of certain cytokines are associated with increased cardiovascular risk[120,121], and experimental data support a functional role for these cytokines in ASCVD[120,121] (Fig. 4). This knowledge is increasingly being translated into clinical trials aimed at interfering with the activity of these cytokines (Table 2).

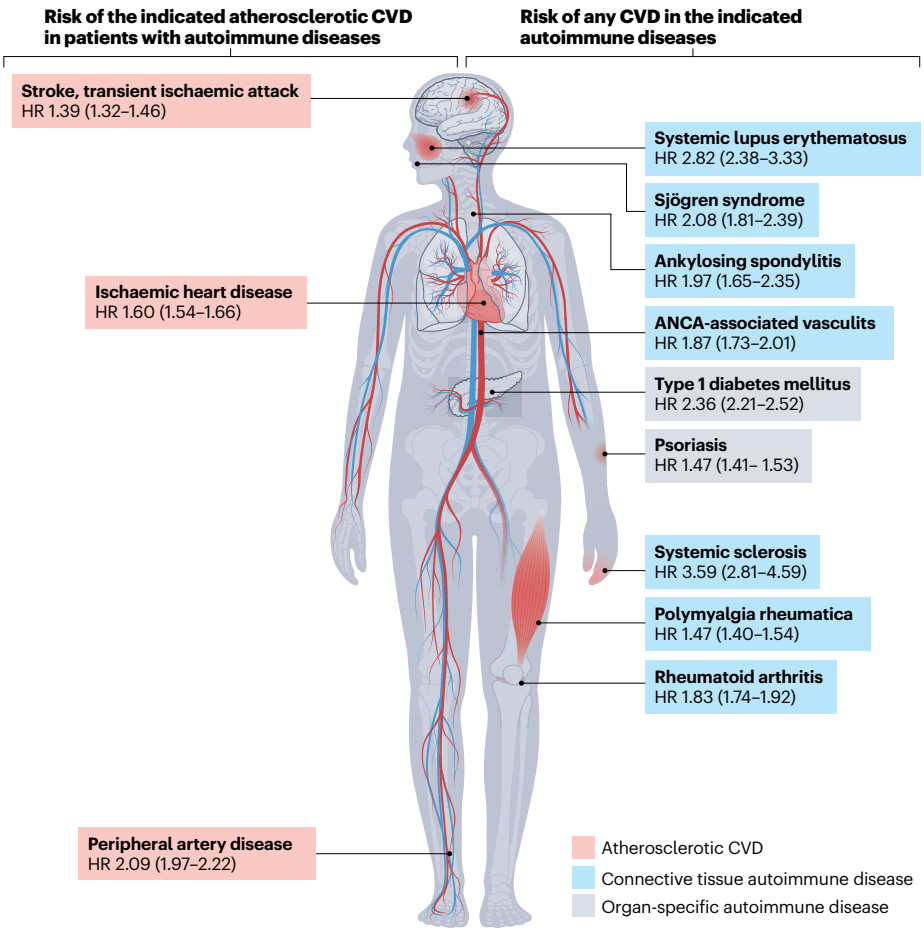


Fig. 2 | Autoimmune diseases are associated with an increased risk of atherosclerotic cardiovascular disease. Epidemiological data from a large, population-based study demonstrate that most autoimmune diseases are associated with a >50% increased risk of atherosclerotic cardiovascular disease (CVD), with many associated with a twofold increased risk[11]. Both connective tissue (shown in blue) and organ-specific (shown in grey) autoimmune diseases are associated with a high risk of atherosclerotic CVD (shown in red). The hazard ratios and 95% confidence intervals for incident ischaemic heart disease, ischaemic stroke or transient ischaemic attack and peripheral artery disease in patients with autoimmune diseases compared with matched controls are shown on the left. The hazard ratios (95% confidence intervals) for any CVD in patients with the indicated autoimmune diseases compared with matched controls are shown on the right. Data are from ref. 11. ANCA, anti-neutrophil cytoplasmic protein antibody.

Many of these putative therapeutic approaches for ASCVD are already being used for autoimmune diseases.

IL-1β. IL-1, and particularly the secreted IL-1β isoform, is strongly implicated in atherosclerosis. IL-1β was the first pro-inflammatory cytokine to be targeted therapeutically in ASCVD, with the use of the anti-IL-1β monoclonal antibody canakinumab in the CANTOS trial[2] in patients with previous MI and elevated systemic inflammation (CRP >2 mg/l). This trial demonstrated for the first time the feasibility of therapeutically targeting inflammation in ASCVD (Table 2).

IL-1β is generated following activation of the NLRP3 inflammasome by various stimuli, including cholesterol crystals. Dying cells, hypoxia and mitochondrial or lysosomal damage all contribute to IL-1β production[97]. Interestingly, many of these features are not only hallmarks of atherosclerotic plaques but are also found in tissues affected by autoimmune diseases, such as the synovium in RA[122]. IL-1β can promote atherosclerosis via endothelial cell activation, vascular smooth muscle cell (VSMC) proliferation and MMP expression (Fig. 4). Interestingly, the increased cardiovascular risk observed in patients with clonal haematopoiesis of indeterminate potential (CHIP) might be mediated by IL-1β[123,124]. Consistent with this finding, a subgroup analysis of the CANTOS trial revealed higher treatment efficacy of canakinumab in patients with *TET2*-driven CHIP than in those without CHIP[125]. Notably, the occurrence of CHIP might be increased in patients with SLE[126]. Although this study did not find an increased risk of CVD in patients with SLE with CHIP compared with patients with SLE without CHIP, the low variant allele frequency, potentially due to the young age of the study participants (median age 38 years, interquartile range 29–47 years), might have been insufficient to substantially increase the risk of CVD[126].

Although IL-1 is a key mediator in many autoinflammatory conditions[127], this cytokine is probably not central to the pathogenesis of rheumatic autoimmune diseases, as suggested by the limited efficacy of IL-1-targeted therapies in these diseases[128]. Nonetheless, IL-1β is an important modulator of RA disease activity[129], and plasma IL-1β levels correlate with disease severity in patients with RA[130]. Therefore, although the contribution of IL-1 cytokines to autoimmune pathologies is limited, increased levels of IL-1 cytokines could contribute to the exacerbated risk of ASCVD in patients with autoimmune diseases. Therefore, these patients could potentially benefit from IL-1-targeted therapeutics for the prevention of ASCVD. Notably, the IL-1 receptor antagonist anakinra is approved for the treatment of RA.

IL-6. IL-6 is a central hub in several cytokine circuits and a key orchestrator of the acute phase reaction. As such, IL-6 drives the generation of many other important cytokines, such as IL-17, TNF and IL-1β, while IL-6 expression is promoted by IL-1β and TNF[131,132]. IL-6 is a potent pro-atherogenic driver and is a biomarker of vascular risk[133]. A role for IL-6 in ASCVD is supported by genetic evidence showing associations between

variants in *IL6* or *IL6R* and ASCVD in genome-wide association studies and Mendelian randomization studies[134–137]. Interestingly, a genetic variant in *IL6R* that reduces IL-6 signalling has been shown to mitigate the increased cardiovascular risk in patients with CHIP[138]. Importantly, a subgroup analysis of the CANTOS trial showed that only patients who achieved a reduction in plasma IL-6 to below median levels had profound reductions in cardiovascular mortality (−52%), whereas other patients did not show a clinical benefit compared with those who received placebo[139].

The majority of studies in mice support a pro-atherogenic role for IL-6, although some studies suggest that lifetime deficiency of IL-6 might be deleterious[133]. Functionally, IL-6 regulates endothelial-dependent relaxation, potentiates vascular permeability, promotes loss-of-barrier function and upregulates the expression of vascular adhesion proteins, thereby promoting inflammatory cell accumulation in the arterial wall[140,141]. Moreover, IL-6 can promote the occurrence of ASCVD complications such as arterial thrombosis by favouring a procoagulant environment by promoting tissue factor expression[142] (Fig. 4).

The plasma levels of IL-6 are also elevated in many patients with autoimmune diseases, including RA[143], and IL-6 is a therapeutic target in these patients. In a mouse model of MRL-*Fas*^{lpr}-driven SLE, IL-6 receptor blockade restored vascular function and reduced vascular inflammation and aortic IMT[144]. In patients with RA, plasma IL-6 levels are associated with increased coronary microvascular dysfunction, which is associated with an increased risk of cardiovascular death[145]. Studies in patients with RA have demonstrated potential benefits of IL-6 inhibition on CVD markers beyond reducing systemic inflammation. For example, patients with RA receiving the anti-IL-6 receptor antibody tocilizumab had improved FMV and aortic stiffness as assessed by pulse-wave velocity compared with baseline[146,147]. However, multiple studies have shown an increase in plasma lipid levels with IL-6 inhibitor therapies[146–150]. Despite this finding, a study in patients with RA demonstrated no increase in major adverse cardiovascular events (MACE) with tocilizumab compared with etanercept treatment[151] (Table 2). Interestingly, the plasma levels of lipoprotein(a), which is considered to be highly

Box 1 | Immunopathogenesis of atherosclerosis

Atherosclerosis is a chronic inflammatory disease of arterial blood vessels and the underlying cause of myocardial infarction, ischaemic stroke and peripheral artery disease[4]. Atherosclerosis is a lipid-driven disease that is strongly modulated by both innate and adaptive immune mechanisms. Traditional risk factors include high LDL cholesterol levels, hypertension, type 2 diabetes mellitus, male sex and smoking. High levels of LDL cholesterol, a major causal factor for disease initiation and progression, precede the development of atherosclerotic plaques. The accumulation and retention of LDL (and other apolipoprotein B-containing lipoproteins) in the subendothelial space trigger their aggregation and oxidation by enzymatic and non-enzymatic processes[379]. Oxidized LDL (oxLDL) contains several pro-inflammatory moieties that activate endothelial cells and induce the expression of adhesion molecules, which results in the recruitment of pro-inflammatory monocytes into the arterial intima. Oxidized phospholipids in oxLDL also trigger inflammatory responses in resident macrophages and newly recruited monocyte-derived macrophages, which take up oxLDL via scavenger receptors, resulting in the formation of foam cells[380]. Several innate immune pathways are implicated in the response to oxLDL, including signalling through Toll-like receptor 4 (TLR4), TLR6 and nuclear factor-κB (NF-κB), which induces the expression of chemokines and cytokines, and activation of the intracellular NLRP3 inflammasome by cholesterol crystals, which results in the secretion of IL-1β and IL-18.

Atherosclerosis also triggers maladaptive immune responses that involve T cells and B cells[7,8]. In the perivascular adipose tissue, resident B1-like cells secrete natural IgM antibodies that are likely to be involved in maintaining tissue homeostasis. The pro-inflammatory environment of developing plaques favours the activation of dendritic cells, which present plaque antigens and promote the generation of mature T cells, including effector T (T_{eff}) cells (such as interferon-γ (IFNγ)-producing T helper 1 (T_H1) cells), that are recruited to the lesions[7]. Regulatory T (T_{reg}) cells mediate atheroprotection by controlling the activity of these pro-atherogenic T cells, but with disease progression, T_{reg} cells can convert to exT_{reg} cells with a T_H1 phenotype, which dominate advanced atherosclerotic lesions[7]. Similarly, cytotoxic CD8$^+$ T cells are present in atherosclerotic plaques[7]. Whereas B cells are typically absent from the intimal lesions, they are found in artery tertiary lymphoid organs (ATLOs) that surround atherosclerotic plaques[290]. Germinal centre reactions in ATLOs and secondary lymphoid organs lead to the production of class-switched IgG (and IgE) antibodies, which are found in the intima of atherosclerotic plaques[8,290]. Depending on their subclass, IgG (and IgE) can modulate atherogenesis via local complement activation and ligation of different Fc receptors on macrophages and mast cells[8]. Several antigens have been implicated, including lipoprotein-derived oxLDL and apolipoprotein B peptides, vascular wall-derived modified matrix proteins and proteins expressed by stressed endothelial cells (HSP60 and GRP78), as well as mitochondrial antigens (ALDH4A1)[8].

Oxidation-specific epitopes (OSEs) are of particular interest, because they are found on oxLDL, dying cells and subsets of extracellular vesicles, which are all implicated in atherogenesis[381]. These epitopes are derived from lipid peroxidation products of polyunsaturated fatty acids of membrane phospholipids that have formed adducts with proteins or other phospholipids. The most prominent examples are phosphocholine-containing oxidized phospholipids, malondialdehyde and 4-hydroxynonenal adducts. OSEs are recognized as neoepitopes by both innate and adaptive immune receptors, most prominently antibodies.

At later stages of atherosclerosis, when the integrity of the internal elastic lamina is disrupted, medial vascular smooth muscle cells migrate to the intima of the plaques and form a protective collagen-rich cap that separates from the lumen the lipid core that is formed from dying foam cells that are not efficiently removed by other phagocytes. Impaired efferocytosis contributes to the progression and non-resolving inflammation of atherosclerotic lesions and the formation of a necrotic core. The fibrous cap can be degraded by matrix metalloproteinases secreted by macrophages and can ultimately rupture, thereby releasing lipids and tissue factor, which initiate thrombus formation and subsequent clinical events. In addition, thrombus formation can also be initiated by plaque erosion in the absence of plaque rupture, a process that is largely driven by the activation of neutrophils and the formation of neutrophil extracellular traps[223].

Table 1 | Studies on the effects of immunological aberrations in atherosclerosis-prone mice

Mouse model	Sex	Autoimmune model	Atherosclerosis model	Autoimmune manifestations	Effect on blood lipids	Effect on atherosclerosis	Ref.
Systemic lupus erythematosus							
gld-Apoe$^{-/-}$	NA	*gld* (FASL deficiency)	*Apoe*$^{-/-}$; regular chow diet	Versus *gld* only: ↑ Splenomegaly ↑ Lymphadenopathy ↑ ANA, aCL and total IgG levels	Versus *Apoe*$^{-/-}$ only: No change in TC levels	Versus *Apoe*$^{-/-}$ only: ↑ Aortic plaque size (en face)	32
			Apoe$^{-/-}$; Western diet (0.15% cholesterol, 21% fat)	Versus *gld* only: ↑ Splenomegaly ↑ Lymphadenopathy ↑ Glomerular tuft volume ↑ Proteinuria ↑ ANA, aCL and total IgG levels ↑ CD86^{+} B cell and CD69^{+}CD4^{+} T cell	Versus *Apoe*$^{-/-}$ only: ↓ TC (driven by VLDL)	Versus *Apoe*$^{-/-}$ only: ↑ Aortic plaque size (en face) ↑ Macrophage and T cell numbers ↑ TUNEL^{+} apoptotic cells	32
gld BMT in *Ldlr*$^{-/-}$ mice	Male	*gld* (FASL deficiency)	*Ldlr*$^{-/-}$; Western diet (0.15% cholesterol, 20% fat)	Versus wild-type donor: ↑ Splenomegaly ↑ ANA, anti-dsDNA antibody and total IgG levels ↑ Anti-MDA–LDL IgG and IgM levels No change in urinary protein content	Versus wild-type donor: No change in TC and TG levels	Versus wild-type donor: ↑ Aortic root plaque size (oil-red O) ↑ CD68^{+} macrophage numbers ↑ TUNEL^{+} apoptotic cells Expression of CCL2, ICAM1 and P-selectin	31
Fas$^{-/-}$*Apoe*$^{-/-}$	Male and female	*Fas*$^{-/-}$ (*lpr*/*lpr*)	*Apoe*$^{-/-}$; regular chow diet	Versus *Apoe*$^{-/-}$ only: ↑ IgG, anti-dsDNA IgG, aCL and anti-oxPL IgG levels ↑ Glomerular tuft area ↑ Proteinuria	Versus *Apoe*$^{-/-}$ only: ↓ TC levels No change in TG levels	Versus *Apoe*$^{-/-}$ only: ↑ Aortic root plaque size ↑ IgG deposition ↑ TUNEL^{+} apoptotic cells	34
			Apoe$^{-/-}$; regular chow diet	Versus *lpr* only: No change in IgG, anti-dsDNA IgG and anti-chromatin IgG levels ↑ Anti-oxLDL IgG and IgM levels ↑ aCL IgG and IgM levels	Versus *Apoe*$^{-/-}$ only: ↓ TC levels	Versus *Apoe*$^{-/-}$ only: ↑ Aortic plaque size (en face) ↑ Aortic root plaque size (oil-red O)	33
MRL/*lpr*-*Apoe*$^{-/-}$	Male and female	MRL/MpJ-*Fas*^{lpr}	*Apoe*$^{-/-}$; regular chow diet	Versus MRL/*lpr* only: No change in IgG, anti-dsDNA IgG and anti-chromatin IgG levels ↑ Anti-oxLDL IgG and IgM and aCL IgG and IgM levels	Versus *Apoe*$^{-/-}$ only: ↑ TC levels	Versus *Apoe*$^{-/-}$ only ↑ Aortic plaque size (en face) ↑ Aortic root plaque size (oil-red O)	33
Sle16-Ldlr$^{-/-}$	Female	*Sle16* (SLE susceptibility locus in Chr1 in B6 mice)	*Ldlr*$^{-/-}$; low-fat diet	Versus *Sle16* only No change in anti-MDA–LDL IgG levels ↑ Anti-MDA-LDL IgG2c and anti-chromatin IgG levels ↓ Serum C3 levels	Versus *Ldlr*$^{-/-}$ only: No change in TC and TG levels	Versus *Ldlr*$^{-/-}$ only: ↑ Aortic plaque size (en face) ↑ Aortic root plaque size (oil-red O) ↓ C3d deposition	35
			Ldlr$^{-/-}$; high-fat diet (0.25% cholesterol, 15% fat)	Versus Sle16 only: No change in anti-MDA–LDL IgG levels ↑ Anti-ssDNA IgG, anti-dsDNA IgG and anti-chromatin IgG ↓ Serum C3 levels ↑ Glomerulonephritis and C3 deposition in the kidney	Versus *Ldlr*$^{-/-}$ only: No change in TC and TG levels	Versus *Ldlr*$^{-/-}$ only: ↑ Aortic plaque size (en face) ↑ Aortic root plaque size ↑ VSMC numbers ↑ TUNEL^{+} apoptotic cells ↓ C3d deposition	35
Sle1.2.3 BMT in *Ldlr*$^{-/-}$ mice	NA	B6.*Sle1.Sle2.Sle3* (SLE susceptibility locus in Chr17 in B6 mice)	*Ldlr*$^{-/-}$; Western diet (0.15% cholesterol, 21% fat)	Versus wild-type donor: ↑ Splenomegaly ↑ CD4^{+} cells ↑ Proteinuria ↑ Serum urea and creatinine levels ↑ Anti-dsDNA IgG, anti-oxLDL IgG1 and IgG2a, and aCL IgM, IgG1, IgG2a levels	Versus wild-type donor: ↓ TC (VLDL and LDL) and TG levels	Versus wild-type donor: ↑ Aortic root plaque size ↑ CD3^{+} and CD4^{+} T cells ↑ Systolic blood pressure	36

Table 1 (continued) | Studies on the effects of immunological aberrations in atherosclerosis-prone mice

Mouse model	Sex	Autoimmune model	Atherosclerosis model	Autoimmune manifestations	Effect on blood lipids	Effect on atherosclerosis	Ref.
Systemic lupus erythematosus (continued)							
			Ldlr$^{-/-}$; regular chow diet	Versus wild-type donor: ↑ Anti-dsDNA IgG, anti-oxLDL IgM, IgG1 and IgG2a, and anti-b2GP1 IgM, IgG1 and IgG2a	Versus wild-type donor: No change in TC and TG levels	Versus wild-type donor: ↑ Aortic root plaque size ↑ CD4$^+$ cells	37
			Ldlr$^{-/-}$; Western diet (0.15% cholesterol, 21% fat)	Versus wild type-donor: ↑ Anti-dsDNA IgG, anti-oxLDL IgM, IgG1 and IgG2a, and anti-b2GP1 IgG1 and IgG2a ↑ Glomerular immune complexes ↑ Proteinuria	Versus wild-type donor: ↓ TC and TG levels	Versus wild-type donor: ↑ Aortic root plaque size ↑ CD4$^+$ cells ↑ Systolic blood pressure	37
Sle1.2.3 CD4$^+$ T cell transfer to *Ldlr*$^{-/-}$*Rag1*$^{-/-}$ mice	Female	B6.*Sle1.Sle2.Sle3*	*Ldlr*$^{-/-}$*Rag1*$^{-/-}$; Western diet (0.15% cholesterol, 21% fat)	Versus wild-type CD4$^+$ T cell transfer: ↑ Proteinuria	Versus wild-type CD4$^+$ T cell transfer: No change in TC and TG levels	Versus wild-type CD4$^+$ T cell transfer: ↑ Aortic root plaque size	38
Sle1.2.3 T_{eff} cell and T_{reg} cell transfer to *Ldlr*$^{-/-}$*Rag1*$^{-/-}$ mice	Female	B6.*Sle1.Sle2.Sle3*	*Ldlr*$^{-/-}$*Rag1*$^{-/-}$; Western diet (0.15% cholesterol, 21% fat)	Versus wild-type T_{eff} cell transfer: ↑ Proteinuria	Versus wild-type T_{eff} cell transfer: NA	Versus wild-type T_{eff} cell transfer: ↑ Aortic root plaque size (oil-red O) ↑ CD4$^+$ T cells	38
Sle3 BMT in *Ldlr*$^{-/-}$ mice	Female	*Sle3* (SLE susceptibility locus in Chr17 in B6 mice)	*Ldlr*$^{-/-}$; Western diet (0.15% cholesterol and 21% fat)	Versus wild-type donor: ↑ Splenomegaly ↑ Anti-dsDNA IgG, aCL IgM and IgG1, anti-b2GP1 IgM and IgG1, and anti-oxLDL IgG levels	Versus wild-type donor: ↓ TC (VLDL, LDL) levels No change in TG levels	Versus wild-type donor: No change in aortic root plaque size (oil-red O)	355
Nba2. Yaa-*Apoe*$^{-/-}$	NA	New Zealand black autoimmunity 2 locus (Chr1) and Y-linked autoimmune acceleration (Yaa) locus (X-linked *Tlr7* duplication on ChrY)	*Apoe*$^{-/-}$; (1.25% cholesterol, 20% fat)	Versus *Apoe*$^{-/-}$ only: Splenomegaly ↓ Platelet numbers ↑ Anti-dsDNA IgG and anti-apoA-I IgG levels ↓ Blood urea nitrogen	Versus *Apoe*$^{-/-}$ only: No change in TC and TG levels	Versus *Apoe*$^{-/-}$ only: No change in aortic plaque size (en face) or aortic root plaque size (oil-red O) ↓ Neutrophils ↑ CD68$^+$ cells ↑ MMP9 content ↓ Collagen content ↓ Fibrous cap thickness ↑ Necrotic core area	41
Antiphospholipid syndrome							
β_2-GPI immunization	Female	β_2-GPI immunization (in CFA)	*Apoe*$^{-/-}$; high-fat diet (1.125% cholesterol, 0.5% cholate)	↑ Anti-β_2-GPI IgG levels	Versus ovalbumin-immunized control: No change in TC levels	Versus ovalbumin-immunized control: ↑ Aortic root plaque size (oil-red O)	45
	Male	Polyclonal rabbit β_2-GPI IgG injection	*Apoe*$^{-/-}$; high-fat diet (2% cholesterol. 10% lard, 0.5% cholate)	None	Versus control IgG: No change in TC and TG levels	Versus control IgG: ↑ Carotid artery and aortic arch plaque size ↑ CD68$^+$ macrophages ↑ MMP9 levels ↓ Collagen content	46
Anti-phospholipid antibody immunization	NA	Monoclonal anti-phospholipid antibody IgG2b (from NZW x BXSB)F1	*Ldlr*$^{-/-}$; high-fat diet (1.25%cholesterol, 20% fat, 0.5% cholate)	None	Versus control IgG2b: No change in TC levels	Versus control IgG2b: ↓ Aortic plaque (en face) and aortic root plaque size (oil-red O)	47

Table 1 (continued) | Studies on the effects of immunological aberrations in atherosclerosis-prone mice

Mouse model	Sex	Autoimmune model	Atherosclerosis model	Autoimmune manifestations	Effect on blood lipids	Effect on atherosclerosis	Ref.
Arthritis							
CIA	Male	CIA (type II chicken collagen in CFA ID and type II chicken collagen IP boost)	*Apoe*$^{-/-}$; Western diet (0.15%cholesterol, 21% fat)	Versus wild-type: ↓ Arthropathy ↓ Anti-collagen IgG levels ↓ Serum IL-17 levels	Versus no CIA: No change in TC and TG levels	Versus no CIA: No change in aortic root plaque size	356
	Male	B10.RIII (H-2^{r}) (type II bovine collagen in CFA ID)	*Apoe*$^{-/-}$; regular chow diet	Versus wild-type: ↑ Arthropathy ↓ Anti-CII IgG1 ↑ IL-1β, IL-6, IL-17, IL-21 and IFNγ levels in joints	Versus wild-type: ↑ TC and TG levels	Versus wild-type: No change in aortic root plaque size	39
K/BxN	Female	K/BxN (express the TCR transgene KRN and the MHC class II allele H-2k (Ag7))	Background not reported; high-fat diet	Versus chow diet: ↑ Arthropathy ↑ Anti-G6PI IgG	Versus chow diet: ↑ TC and TG levels	Versus chow diet: ↑ Aortic root plaque size (oil-red O)	40
	Male and female	K/BxN	C57BL/6 K/BxA^{g7}; Western diet (1.2% cholesterol, 15.8% fat)	Versus chow diet: No change in arthropathy ↑ Pro-inflammatory cytokines and chemokines in serum	Versus chow diet: No change in TC levels ↑ LDL/VLDL levels	Versus chow diet: ↑ Aortic plaque size (en face) ↑ Macrophage numbers in aortic root	48
K/BxN STIA	Male and female	Transfer of K/BxN serum (anti-G6PI antibodies)	C57BL/6; Western diet (1.2% cholesterol, 15.8% fat)	None	Versus no STIA: ↓ TC levels ↑ LDL/VLDL levels	Versus no STIA: ↑ Aortic plaque size (en face)	48
			Apoe$^{-/-}$; Western diet (1.25% cholesterol, 15.80% fat)	Versus wild-type: ↑ Arthropathy ↑ Articular and extra-articular inflammation ↑ Collagen content	Versus *Apoe*$^{-/-}$ without STIA: No change in TC (LDL/VLDL) levels	Versus *Apoe*$^{-/-}$ without STIA: Trend for ↑ aortic plaque size (en face) ↑ IL-6 levels in serum	49
	Male	Transfer of K/BxN serum (anti-G6PI antibodies)	*Ldlr*$^{-/-}$; atherosclerosis regression study; Western diet (0.15% cholesterol, 22% fat) followed by chow diet	Versus *Ldlr*$^{-/-}$: ↑ Monocytosis (Ly6C^{high}) ↑ Plasma IL-6 and TNF levels	Versus *Ldlr*$^{-/-}$: No change in TC levels	Versus *Ldlr*$^{-/-}$: ↑ Aortic root plaque size (H&E and oil-red O) ↑ CD68^{+} macrophages	50
DR4tg-*Ldlr*$^{-/-}$	Male and female	HLA-DRB1*04:01 (DR4tg)	*Ldlr*$^{-/-}$; Western diet (0.2% cholesterol, 21.2% fat)	None	Versus *Ldlr*$^{-/-}$: ↓ TC (driven by LDL) ↑ oxLDL levels	Versus *Ldlr*$^{-/-}$: No change in aortic plaque size (en face) No change in citrullinated protein levels and liver inflammation	357

β_2-GPI, β_2-glycoprotein 1; aCL, anti-cardiolipin antibodies; ANA, anti-nuclear antibodies; apoA-I, apolipoprotein A-I; BMT, bone marrow transplantation; CCL2, CC-motif chemokine 2; CFA, complete Freund's adjuvant; Chr, chromosome; CIA, collagen-induced arthritis; dsDNA, double-stranded DNA; FASL, FAS ligand; G6PI, glucose-6-phosphoisomerase; H&E, haematoxylin–eosin; ICAM1, intercellular adhesion molecule 1; ID, intradermal; IFNγ, interferon-γ; IP, intraperitoneal; MDA, malondialdehyde; MMP9, matrix metalloproteinase 9; NA, not available; oxLDL, oxidized LDL; oxPL, oxidized phospholipid; SLE, systematic lupus erythematosus; ssDNA, single-stranded DNA; STIA, serum transfer-induced arthritis; TC, total cholesterol; TCR, T cell receptor; T_{eff}, effector T; TG, triglycerides; TNF, tumour necrosis factor; T_{reg}, regulatory T; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling; VSMC, vascular smooth muscle cell.

pro-atherogenic, were decreased following tocilizumab treatment[149,151]. The novel anti-IL-6 antibody ziltivekimab does not elevate plasma lipid levels[152] and is being tested for the prevention of cardiovascular events in the large-scale ZEUS trial[153] in patients with chronic kidney disease and elevated plasma CRP levels. Given that IL-6-targeted therapies are approved for RA, they might become an option in the future to address the increased risk of ASCVD in patients with autoimmune diseases.

TNF. TNF is a key driver of autoimmunity, particularly RA, where it is also one of the most prominent therapeutic targets. TNF elicits largely pro-inflammatory responses, but can also have immunosuppressive functions[154,155]. TNF is generally considered to be pro-atherogenic through multiple mechanisms[99,121]. Most of the studies in mice support a pro-atherogenic role for TNF, but some studies suggest potentially atheroprotective functions of TNF or downstream signalling

receptors[121]. Generally, TNF can promote leukocyte recruitment to atherosclerotic lesions via activation of endothelial cells and their expression of adhesion molecules, chemokines and pro-inflammatory cytokines such as IL-1β and IL-6 (refs. 121,155). In addition, TNF can increase the subendothelial accumulation of oxidized LDL by upregulating the expression of the lectin-type oxidized LDL receptor 1 (LOX1) on endothelial cells[101].

TNF might be an important mediator of the increased risk of ASCVD in patients with autoimmune disease, given that systemic TNF levels are increased in these patients[156]. Consistent with this observation, elevated serum TNF and IL-6 levels are associated with increased coronary artery calcification in patients with RA independently of Framingham risk factors[157]. TNF inhibitor treatment was associated with significant reductions in carotid IMT in patients with RA within 6–12 months of treatment initiation[158,159]. One study demonstrated that patients with RA treated with TNF inhibitors have a reduced incidence of first MACE compared with patients with RA who are not taking TNF inhibitors[160]. Another study showed that patients with RA who respond to TNF inhibitor therapy have a reduced incidence of MI within 6 months of treatment initiation compared with patients receiving traditional disease-modifying antirheumatic drugs (DMARDs)[161]. Two meta-analyses demonstrated that patients with RA treated with a TNF inhibitor have a reduced risk of cardiovascular events (relative risk 0.46 compared with traditional DMARDs[162], and relative risk 0.7 compared with non-TNF inhibition standard-of-care or no treatment[163]). However, several studies have also found increased plasma cholesterol levels after TNF inhibitor therapy[164], which could have detrimental effects on the cardiovascular risk in these patients. In the acute setting after MI, elevated serum TNF levels are associated with an increased risk of recurrent MI[165]. However, TNF inhibitor therapy had no effect or even detrimental effects on disease outcomes in patients with heart failure[166,167]. Therefore, despite the potential beneficial effects of TNF inhibition on vascular inflammation in patients with RA in the TARGET trial[168] (Table 2), the feasibility of TNF inhibitor therapy in autoimmunity-accelerated ASCVD requires further investigation.

Box 2 | Autoantibodies

In autoimmunity, the development of autoantibodies is typically the result of aberrant B cell selection or increased plasma cell differentiation, which indicates a loss of tolerance to self-molecules. The presence of autoantibodies is a major criterion for the diagnosis of autoimmune diseases, although they are not always present in these diseases. Typically, the production of autoantibodies precedes the onset of autoimmune disease manifestations[382], such as synovitis in rheumatoid arthritis (RA) or flares in systemic lupus erythematosus (SLE), which are thought to require several steps of aberrant immune activation[12,13,272]. Each of these autoantibodies is associated with different functional effects and mediates tissue damage by promoting inflammation via different mechanisms, including complement activation, Fc receptor-mediated signalling, and Toll-like receptor activation by nucleic acid-containing immune complexes[383]. Depending on the antigens that the autoantibodies recognize, they can also trigger neutrophil extracellular trap formation or thrombosis[384,385].

In SLE, autoantibodies are typically directed against nuclear antigens, such as anti-nuclear antibodies (ANA), but also other self-antigens, including C1q, platelets and erythrocytes. ANAs include autoantibodies against nucleosome components, such as double-stranded DNA, histones and RNA-binding proteins (anti-Sjögren syndrome-related antigen A (anti-SSA; also known as anti-SSA/Ro), anti-SSB (also known as anti-SSB/La), anti-Smith (anti-Sm) and anti-ribonucleoproteins antibodies). Low titres of ANAs can also be found in the general population. Antiphospholipid autoantibodies, present in antiphospholipid syndrome and in some patients with SLE, are directed against lipid antigens, including cardiolipin and the associated protein β_2-glycoprotein 1, and are linked to venous and arterial thrombosis[386]. Autoantibodies against apolipoprotein A-I, the major protein in HDL, have also been described in the context of SLE and could modulate HDL functions and inflammation[14,387]. Anti-neutrophil cytoplasmic protein antibodies are prototypic for the vasculitis associated with SLE[388].

Seropositive RA, which might be pathophysiologically different from seronegative RA, is typically characterized by the presence of rheumatoid factors, which are antibodies directed against the Fc portion of IgG. Post-translational modifications targeted by autoantibodies include citrullination (anti-citrullinated protein autoantibodies (ACPA)), carbamylation (anti-carbamylated protein antibodies) and acetylation[389]. Compared with rheumatoid factor, which is also found in a small percentage of healthy individuals, ACPAs are more specific for RA[390]. Rheumatoid factor appears much later than ACPAs (closer to disease onset) and seems to be more associated with disease activity[12]. Typically, both rheumatoid factor and ACPAs are present when RA is clinically manifest; however, the presence of ACPAs alone seems to be less robustly associated with overt disease. Functionally, rheumatoid factor–ACPA immune complexes trigger complement activation as well as monocyte and macrophage activation, leading to the production of pro-inflammatory cytokines, including tumour necrosis factor, IL-1β, IL-6 and IL-8 (ref. 391), which are all relevant to atherosclerotic cardiovascular disease. These immune complexes can also trigger the activation of neutrophils, which leads to the generation of reactive oxygen species and the formation of neutrophil extracellular traps[230,231], which contain citrullinated proteins that further fuel the inflammatory process. The majority of autoantibodies in autoimmune diseases are class-switched IgG antibodies that are generated over time from polyreactive IgM antibodies and are more pathogenic than the IgM antibodies[13,392]. Interestingly, autoreactive IgA and IgE antibodies have also been described in autoimmune diseases[392]. Rheumatoid factor is typically of the IgM isotype, but IgG and IgA rheumatoid factor antibodies have also been described. The potential functions of different IgG subtypes in autoimmunity are not well established, but different affinities for Fcγ receptors and different complement-activating capacity might influence their pathogenicity. For example, ACPA IgG1 might have higher pro-inflammatory potential than other ACPA subclasses, which might also activate inhibitory Fcγ receptors, such as FcγRIIB. However, the functional relevance of different autoantibody subclasses for autoimmunity or atherosclerotic cardiovascular disease is unknown.

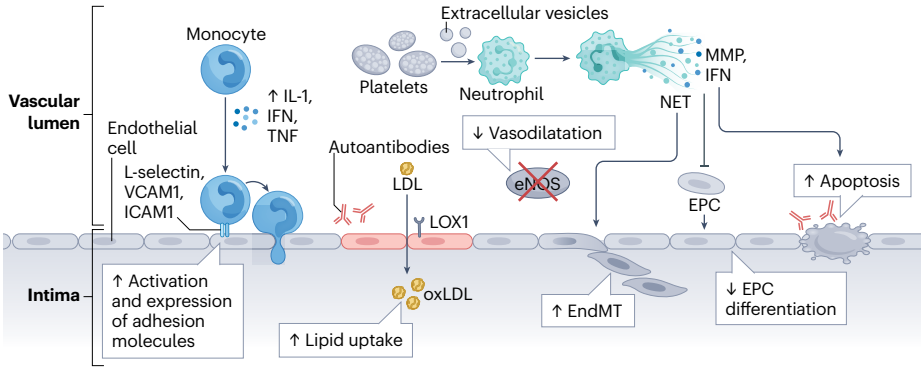


Fig. 3 | Shared immune pathways in ASCVD and autoimmunity and their potential effects on endothelial dysfunction. Endothelial dysfunction is a central feature of autoimmunity-mediated increased risk of atherosclerotic cardiovascular disease (ASCVD). After endothelial cell activation, increased endothelial expression of adhesion molecules, including L-selectin, vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1), promotes the recruitment of leukocytes, including monocytes, whereas increased expression of lectin-type oxidized LDL receptor 1 (LOX1) on endothelial cells promotes oxidized LDL (oxLDL) uptake into the vascular wall. Vasorelaxation is impaired due to reduced endothelial nitric oxide synthase (eNOS) activity. Endothelial-to-mesenchymal transition (EndMT) is promoted by pro-inflammatory, matrix metalloproteinase (MMP)-carrying neutrophil extracellular traps (NET) and contributes to atherosclerotic plaque growth. Endothelial damage is exacerbated by increased endothelial cell apoptosis that could be further promoted by endothelial cell-specific autoantibodies and impaired endothelial progenitor cell (EPC) differentiation. IFN, interferon; TNF, tumour necrosis factor.

Type I IFN. Type I IFN exacerbates multiple aspects of atherosclerosis in mice[98]. IFN-associated genes increase leukocyte recruitment to the atherosclerotic plaque in a chemokine-dependent manner, resulting in increased macrophage accumulation[169]. In mononuclear cells, type I IFN causes the upregulation of scavenger receptor A1 (SR-A1) expression and increased lipid uptake[170–172] (Fig. 4).

After lipid loading, foamy macrophages show reduced expression of inflammatory genes, including IFN-responsive genes[173,174]. However, single-cell RNA sequencing studies of atherosclerotic plaques have revealed a macrophage subtype termed type I IFN-inducible cells (IFNICs) that express high levels of IFN-inducible genes[175]. Although the function of IFNICs in atherosclerosis is unknown, they have been found to accumulate in the injured myocardium in mouse models of MI, where these cells promote inflammation and impair cardiac function[176]. Additionally, in mice, IFNIC numbers are increased in plaques during atherosclerosis progression versus regression[177], suggesting that these cells might have pro-atherogenic roles. However, type I IFN can have both pro-inflammatory effects, such as epigenetic reprogramming to render macrophages more sensitive to inflammatory stimuli[178], and anti-inflammatory effects, including the suppression of IL-1β production[179,180]. In light of the prominent presence of IFNICs in human and mouse atherosclerotic plaques, it will be interesting to evaluate whether these macrophages contribute to an increased risk of ASCVD in patients with autoimmune diseases.

An IFN signature characterized by heightened type I IFN (IFNα and IFNβ) expression as well as IFN-stimulated target genes in circulating cells and in affected tissues is a hallmark of many autoimmune diseases[181]. Type I IFN expression is driven by the activation of endosomal TLRs, such as TLR7 and TLR9, or cytosolic DNA sensors by nucleic acids, including oxidized mitochondrial DNA and RNA. These nucleic acids are present in immune complexes with anti-nuclear autoantibodies, in NETs or on circulating extracellular vesicles[182–187]. The main cellular source of type I IFN is likely to be plasmacytoid dendritic cells, which have also been shown to promote atherosclerosis in experimental models[188]. Notably, platelets, which have a more activated phenotype in patients with SLE than in individuals without SLE, also have a prominent IFN signature and can activate both plasmacytoid dendritic cells and endothelial cells[113,114,189,190]. These activated platelets could promote ASCVD progression in patients with autoimmune disease by modulating leukocyte recruitment and endothelial–leukocyte adhesion as well as activation of monocytes, consistent with the pro-atherogenic functions that have been proposed for platelets[191–193].

The IFN signature is the most prominently enriched pathway in the blood in patients with SLE[194,195], which strongly contributes to disease severity. Systemic sclerosis and Sjögren syndrome are also linked to type I IFN signatures[196–199], whereas this signature is less pronounced in RA[199]. In a study in patients with SLE, serum type I IFN activity was independently associated with reduced FMV and increased carotid IMT and coronary calcification independently of Framingham risk factors[200]. This finding further supports a key role for type I IFN in promoting endothelial dysfunction and CVD in patients with SLE.

Innate immunity

Monocytes. Monocytes and macrophages are crucially involved in chronic inflammatory conditions including atherosclerosis and autoimmunity-associated tissue damage. In humans, monocyte numbers, particularly $CD14^{++}CD16^{+}$ intermediate monocytes, are positively correlated with cardiovascular events[201]. Interestingly, this monocyte subtype is also increased in RA, in which they display increased adhesiveness, heightened expression of cytokines and chemokine receptors such as CCR5, and an increased capacity to activate T helper 17 (T_H17) cells[202,203]. Similarly, monocytes from patients with SLE display extensive epigenetic changes in IFN-related enhancer regions and heightened expression of the IFN signature and of pro-atherogenic cytokines including CCL2 (refs. 204–206). In patients with SLE, non-classic $CD16^{+}CD14^{dim}$ monocyte numbers correlated with carotid IMT in a small study[207], but this correlation was not observed in another study[208]. Given the central role of the CCL2–CCR2 and CX3CL1–CX3CR1 axes and CCR5 and its ligands in regulating leukocyte recruitment to the atherosclerotic plaque[209,210], the increased number of monocytes with high chemokine receptor expression in RA or with high

chemokine expression in SLE might contribute to increasing the risk of atherosclerosis (Fig. 5).

Neutrophils. Neutrophils are emerging players in ASCVD. Multiple studies have found that the neutrophil-to-lymphocyte ratio as well as a neutrophil-related plasma proteomic signature independently predict cardiovascular events[211,212]. Neutrophil numbers have been shown to be predictive of cardiovascular end points in observational and genetic analyses of the Copenhagen General Population study and in Mendelian randomization studies of the UK Biobank and Blood Cell Consortium, which suggests a causal role for neutrophils in ASCVD[213]. Interestingly, the latter analyses showed no significant associations between ASCVD and other leukocyte types[213].

Mechanistically, neutrophils can affect atherosclerosis and the associated complications by multiple mechanisms (Fig. 5), including NET formation and release of their granule contents and cytokines. Neutrophil depletion ameliorates atherosclerosis development in mice, particularly when depletion occurs during early disease stages[214,215]. Neutrophils promote endothelial activation and the oxidation of subendothelially retained lipoprotein particles via myeloperoxidase and the generation of reactive oxygen species[216]. Moreover, neutrophil granule contents, such as cathelicidins, have been implicated in promoting monocyte recruitment[217] and cellular LDL uptake[218]. NETs modulate multiple stages of atherosclerosis, including the early activation and damage of endothelial cells[105,106,219,220] and VSMCs[221] as well as microvascular obstruction during MI[222].

Importantly, neutrophils are implicated in superficial plaque erosion, which is becoming an increasingly important cause of thrombotic complications of atherosclerosis in the era of widely available, strong lipid-lowering therapies[223]. Neutrophils contribute to arterial intima injury through the release of their granule contents, reactive oxygen species and NET formation[224]. Indeed, granulocyte depletion or impairment of NET formation improved endothelial cell survival and integrity in mouse carotid cuff models, which generate intimal lesions that resemble human erosion-prone plaques[225,226]. Moreover, NETs contribute to the propagation of thrombosis via entrapment of tissue factor, fibrin and platelets[227,228]. Consistent with these findings, white thrombi overlying eroded plaques are rich in platelets and myeloperoxidase-positive inflammatory cells[229].

Neutrophils and NETs also have a key role in the perpetuation of autoimmune diseases[230,231], where they are functionally and phenotypically altered. In RA, neutrophils are essential mediators of

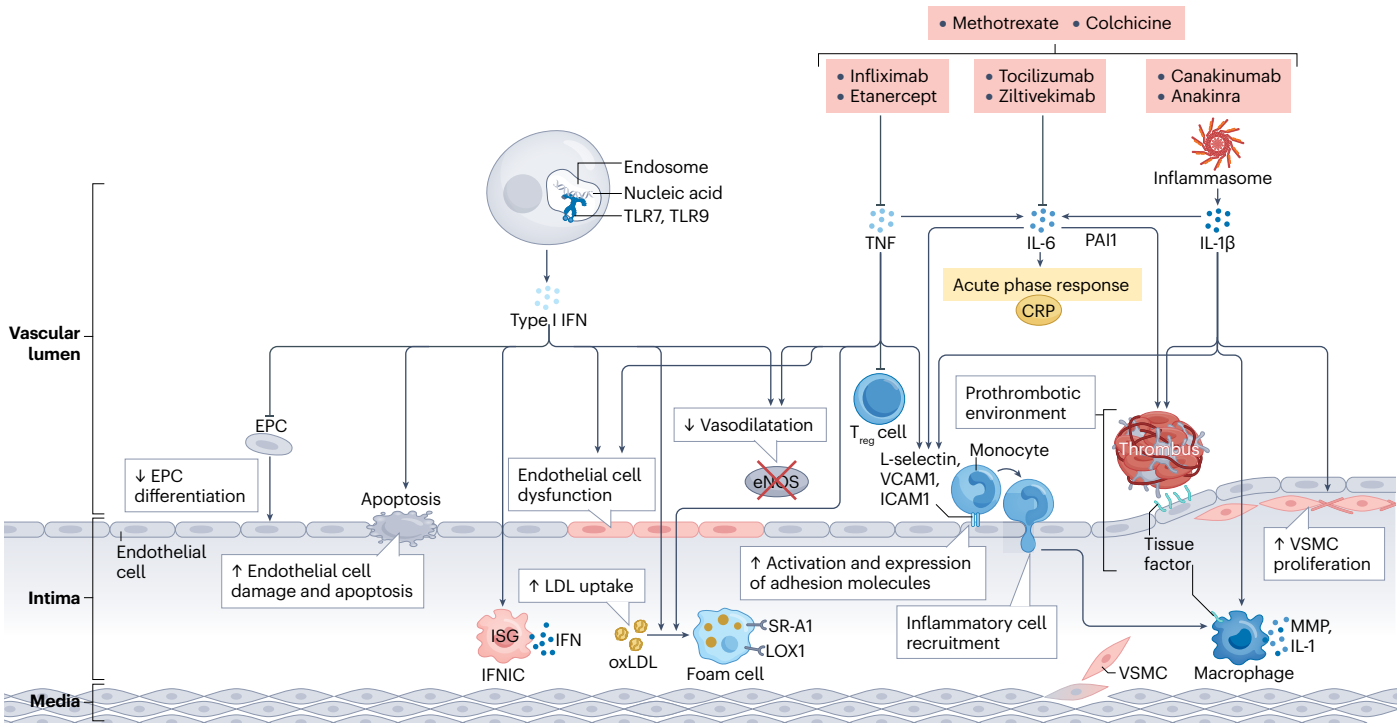


Fig. 4 | Shared cytokine pathways in autoimmunity and ASCVD and their potential effects on atherogenesis and its complications. Cytokines can promote atherosclerotic cardiovascular disease (ASCVD). Increased nucleic acid sensing via Toll-like receptors (TLR7 and TLR9) promotes type I interferon (IFN) production. Tumour necrosis factor (TNF), as well as IL-1β, which is generated following NLRP3 inflammasome activation, promote IL-6 production to trigger an acute phase response, including generation of C-reactive protein (CRP). Pro-atherogenic mechanisms of these cytokines include endothelial dysfunction and damage (TNF and type I IFN), leukocyte activation and recruitment (TNF, IL-1β and IL-6), impairment of vasorelaxation (TNF and type I IFN), promotion of modified LDL and oxidized LDL (oxLDL) uptake (TNF and type I IFN), promotion of vascular smooth muscle cell (VSMC) proliferation (IL-1β) and regulatory T cell (T_{reg}) dysfunction (TNF), and favouring of a prothrombotic environment by increasing the expression of tissue factor (IL-1β and IL-6) and plasminogen-activator inhibitor 1 (PAI1) (IL-6). Potential therapeutics (red boxes) and their targets include infliximab and etanercept (TNF), tocilizumab (IL-6 receptor), ziltivekimab (IL-6), canakinumab (IL-1β), anakinra (IL-1 receptor) and methotrexate and colchicine (broad anti-inflammatory drugs). eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; ICAM1, intercellular adhesion molecule 1; IFNIC, interferon-inducible cell; ISG, IFN-stimulated gene; LOX1, lectin-type oxidized LDL receptor 1; MMP, matrix metalloproteinase; SR-A1, scavenger receptor type A1; VCAM1, vascular cell adhesion molecule 1.

Table 2 | Randomized clinical trials of anti-inflammatory therapies in CVD

Drug (target); approved use in autoimmune diseases	Trial name	Cohort	Intervention	End points	Follow-up	Outcomes	Notes
Methotrexate (broad anti-inflammatory); RA	CIRT[358]	4,789 patients with stable CAD (previous MI or multivessel CAD) and type 2 diabetes mellitus or metabolic syndrome	Low-dose methotrexate versus placebo	MACE (non-fatal MI, non-fatal stroke or cardiovascular death) and hospitalization for unstable angina leading to coronary revascularization	2.3 years	No significant difference in MACE (HR 0.96, 95% CI 0.79–1.16)	Prematurely stopped due to lack of benefit; no reduction in inflammatory parameters; small but significant increases in liver enzyme levels and incidence of non-basal skin cancer
Colchicine (broad anti-inflammatory); gout, Behçet syndrome (CVD prevention)	COLCOT[359]	4,745 patients with recent MI (<30 days)	Low-dose colchicine versus placebo	Composite of cardiovascular death, resuscitated cardiovascular arrest, MI, stroke, urgent hospitalization for angina leading to coronary revascularization	22.6 months	↓ Primary end point with colchicine (HR 0.77, 95% CI 0.61–0.96; P = 0.02)	Mild but significantly increased risk of pneumonia in the colchicine group
	LoDoCo[360]	532 patients with stable CAD (taking statins and aspirin or clopidogrel)	Low-dose colchicine versus placebo	Composite of ACS (AMI, unstable angina), out-of-hospital cardiac arrest, non-cardioembolic ischaemic stroke	36 months	↓ Primary end point with colchicine (HR 0.33, 95% CI 0.18–0.59; P < 0.001)	–
	LoDoCo2[361]	5,522 patients with stable, chronic CAD	Low-dose colchicine versus placebo	Composite of cardiovascular death, MI, ischaemic stroke, ischaemia-driven coronary revascularization	28.6 months	↓ Primary end point with colchicine (HR 0.69, 95% CI 0.57–0.83; P < 0.001)	Small, non-significant increase in the incidence of non-CVD-related death in the colchicine group (HR 1.51, 95% CI 0.99–2.31)
	CLEAR-Synergy (Oasis 9)[362]	7,063 patients with STEMI or NSTEMI undergoing primary PCI	Low-dose colchicine versus placebo, spironolactone versus placebo, or colchicine plus spironolactone versus placebo; administered via drug-eluting stent	MACE (death, recurrent target-vessel MI, stroke, ischaemia-driven target-vessel revascularization), and cardiovascular death or new-onset or worsening HF	1 year for MACE, estimated average of 3 years for cardiovascular death	Expected completion July 2024	–
	CONVINCE[363]	3,154 patients with ischaemic stroke or TIA (excluding cardioembolic stroke)	Low-dose colchicine plus standard care versus standard care alone	Recurrence of non-fatal ischaemic stroke, non-fatal cardiac event (MI, cardiac arrest, unstable angina), vascular death	Median follow-up 36 months	Non-significant reduction in primary end point (HR 0.84, 95% CI 0.68–1.05; *P* = 0.12)	–
Canakinumab (anti IL-1β antibody); gout flares	CANTOS[2,125,139]	10,061 patients with MI; hsCRP >2 mg/l	Canakinumab versus placebo	Composite of cardiovascular death, non-fatal MI, non-fatal stroke	3.7 years	For 150 mg canakinumab: 15% decrease in MACE (HR 0.85, 95% CI 0.74–0.98; P = 0.021) but no reduction in CVD death; no difference in all-cause death	↑ Incidence of non-fatal infection ↓ Cancer mortality (especially lung cancer) Subgroup analyses showed higher benefit in patients who had reduced hsCRP or IL-6 levels with canakinumab and in patients with TET2-driven CHIP

Table 2 (continued) | Randomized clinical trials of anti-inflammatory therapies in CVD

Drug (target); approved use in autoimmune diseases	Trial name	Cohort	Intervention	End points	Follow-up	Outcomes	Notes
Anakinra (IL-1 receptor antagonist); RA	MRC-ILA Heart[364]	182 patients with non-ST-segment elevation ACS, <48 h of symptom onset	Anakinra or placebo once daily for 14 days	AUC for hsCRP and other inflammatory and CVD markers; secondary end point: MACE (cardiovascular death, MI or stroke) and myocardial parameters	30 days for hsCRP, 1 year for MACE	↓ hsCRP and IL-6 AUC and absolute levels with anakinra after 14 days No difference in infarct size ↑ MACE with anakinra after 1 year (18.9% versus 5.4%; P=0.0233)	–
	VCU-ART[365]	10 patients with STEMI	Anakinra or placebo once daily for 14 days	Left ventricular remodelling: LVESVi, LVEDVi (assessed by CMR and echocardiography) hsCRP levels	10–14 weeks	Improved LVESVi and LVEDVi No difference in infarct size No difference in hsCRP, but CRP changes correlated with LVESVi	–
	VCU-ART2[366]	30 patients with clinically stable STEMI	Anakinra or placebo once daily for 14 days	LVESVi, LVEDVi, LVEF, hsCRP levels	10–14 weeks	No differences in LVESVi, LVEDVi or LVEF ↓ CRP increase with anakinra Trend for reduced new-onset HF	–
	VCU-ART3[367]	99 patients with STEMI	Anakinra or placebo once or twice daily for 14 days	hsCRP levels, preservation of left ventricular systolic function, HF incidence	14 days for hsCRP levels; 12 months for LVESVi, LVEF and HF	↓ hsCRP AUC (P<0.001) No difference in LVESVi or LVEF ↓ Incidence of new-onset HF or death	–
Tocilizumab (anti-IL-6R antibody); RA	MEASURE[149]	132 patients with moderate-to-severe RA and inadequate response to methotrexate	Methotrexate plus tocilizumab or placebo	Change in PWV and LDL particle number	24 weeks double-blind, 80 weeks open label	↑ LDL-C and ↓ SAA, PLA2 and Lp(a) levels in plasma with tocilizumab Greater reduction in PWV in placebo group at 12 weeks but not at 24 weeks	–
	Kleveland et al.[368,369]	117 patients with NSTEMI	Single-dose tocilizumab or placebo before coronary angiography	AUC for hsCRP and hsTnT during hospitalization	6 months	↓ Median hsCRP and hsTnT AUC with tocilizumab, primarily in patients treated within <2 days of symptom onset and who underwent PCI	Secondary analysis revealed increased plasma levels of some cytokines (CXCL10, CCL4) with tocilizumab
	STAT-MI[370]	27 patients with STEMI or NSTEMI	Tocilizumab or placebo within 24 h of hospital admission	MACE after 30 days; changes in CRP and QT/QTc	30 days	No difference in MACE, CRP or QT/QTc; potential trend for increases in tocilizumab group (low patient number)	Halted prematurely due to lack of benefit

Table 2 (continued) | Randomized clinical trials of anti-inflammatory therapies in CVD

Drug (target); approved use in autoimmune diseases	Trial name	Cohort	Intervention	End points	Follow-up	Outcomes	Notes
Tocilizumab (anti-IL-6R antibody); RA (continued)	ASSAIL-MI[371]	199 patients with STEMI undergoing PCI	Single-dose tocilizumab or placebo >6 h of symptom onset	Myocardial salvage index as assessed by MRI a median of 5 days after treatment; final infarct size 6 months after the intervention	Median 5 days for myocardial salvage index and 6 months for final cardiac MRI (final infarct size)	Improved myocardial salvage index (5.6%, 95% CI 0.2–11.3%; P=0.04), microvascular obstruction (P=0.03) and CRP AUC (P<0.001) with tocilizumab No difference in infarct size, hsTnT AUC or left ventricular volume	–
	DOBER-MANN[372,373]	100 patients with STEMI with high risk of cardiogenic shock undergoing PCI	Tocilizumab or dobutamine tocilizumab plus dobuta-mine versus placebo	NT-proBNP as a marker of cardiogenic shock and haemodynamic instability, post-MI salvaged myocardium and echocardiographic measurements of haemodynamics as secondary outcome	48 h for NT-proBNP, 3 months for imaging	Expected completion 2025	–
Tocilizumab and etanercept (TNF inhibitor); RA	ENTRACTE[151]	3,080 patients with RA with inadequate response to csDMARD, and CVD risk factors, including history of CVD event	Tocilizumab versus etanercept	Primary end point: time to occurrence of first MACE (cardiovascular death, non-fatal MI, non-fatal stroke)	Mean 3.2 years	↑ LDL-C, HDL-C and TG levels (all P<0.001) with tocilizumab No differences in MACE (HR 1.05, 95% CI 0.77–1.43)	↑ Risk of serious infections and gastrointestinal perforation with tocilizumab versus etanercept
Tocilizumab, adalimumab and etanercept (TNF inhibitors), and metho-trexate and leflunomide (csDMARD); RA	Bacchiega et al.[146]	40 patients with RA and no history of ACS or uncontrolled hypertension (<3 months)	Tocilizumab versus adalimumab or etanercept, versus methotrexate or leflunomide	Endothelial function as assessed by FMV after 16 weeks	16 weeks	↑ FMV with tocilizumab (P=0.03), non-significant trend for ↑ FMV with TNF inhibitors (P=0.09) and no difference with csDMARD ↑ Total cholesterol with tocilizumab (P=0.003) and csDMARD (P=0.04), no difference with TNF inhibitors	–
Adalimumab or etanercept; RA	TARGET[168]	115 patients with RA	Methotrexate plus adalimu-mab or etaner-cept versus methotrexate plus hydroxy-chloroquine plus sulfasalazine	Arterial inflammation as assessed 18F-FDG PET–CT	24 weeks	Reduction in arterial inflammation in both treatment groups	–
Ziltivekimab (anti-IL-6 antibody); no approval so far	RESCUE[152,211]	264 patients with CKD and hsCRP >2 mg/l	Different doses of ziltivekimab or placebo once per month for 24 weeks	Change in CRP and other CVD-associated markers	24 weeks; 12 weeks for primary end point	Dose-dependent reduction in CRP (77–92%) with ziltivekimab ↓ Fibrinogen, SAA, haptoglobin, secretory PLA2 and Lp(a) levels No effect on total cholesterol-to-HDL or apoB-to-apoA-I ratio	Secondary analysis suggests reductions in NLR (an independent predictor of CVD events) with ziltivekimab

Table 2 (continued) | Randomized clinical trials of anti-inflammatory therapies in CVD

Drug (target); approved use in autoimmune diseases	Trial name	Cohort	Intervention	End points	Follow-up	Outcomes	Notes
Ziltivekimab (anti-IL-6 antibody); no approval so far (continued)	ZEUS[153,374]	6,200 patients with stage 3–4 CKD, hsCRP >2 mg/l	Zilivekimab or placebo once per month for up to 4 years	MACE (cardiovascular death, non-fatal MI, non-fatal stroke); CKD parameters	48 months	Expected completion autumn 2025	–
	ARTEMIS[375]	10,000 patients with STEMI or NSTEMI and previous CVD, CKD or diabetes	Ziltivekimab or placebo once per month for up to 2 years	MACE (cardiovascular death, non-fatal MI, non-fatal stroke)	25 months	Expected completion autumn 2026	–
Rituximab (anti-CD20 antibody); RA	RITA-MI[376]	24 patients with STEMI	Single-dose rituximab	Safety and B cell and antibody changes in plasma	6 months	Treatment was well tolerated Efficient B cell depletion	–
	RITA-MI 2[311]	558 patients with acute anterior STEMI	Rituximab versus placebo	Cardiac remodelling as assessed by LVEF at 6 months	12 months	Expected completion 2027	–
Aldesleukin (recombinant IL-2); no approval for autoimmune disease so far	LILACS[377]	44 patients with stable ischaemic heart disease or patients with acute NSTEMI or unstable angina	Low-dose aldesleukin once daily for 5 days	Safety and immune cell changes	7 days and 7 days + median 7 days after final treatment	Dose-dependent increase in circulating regulatory T cell numbers	–
	IVORY[267,378]	60 patients with ACS (unstable angina, NSTEMI or STEMI) and hsCRP >2 mg/l	Low-dose aldesleukin versus placebo, once daily for 5 days followed by once weekly for 7 weeks	Vascular inflammation as assessed by 18F-FDG PET–CT, immune cell changes	61 days	Expected completion 2024	–

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under the curve; CAD, coronary artery disease; CCL4, CC-motif chemokine 4; CHIP, clonal haematopoiesis of indeterminate potential; CKD, chronic kidney disease; CMR, cardiac MRI; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CVD, cardiovascular disease; CXCL10, CXC-motif chemokine ligand 10; 18F-FDG, 18F-fluorodeoxyglucose; FMV, flow-mediated vasodilatation; HDL-C, HDL cholesterol; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; IL-6R, IL-6 receptor; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MACE, major adverse cardiovascular event; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; PLA2, phospholipase A2; PWV, pulse-wave velocity; RA, rheumatoid arthritis; SAA, serum amyloid A; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; TG, triglycerides; TNF, tumour necrosis factor.

disease progression[232] and particularly synovial neutrophils show a more pro-inflammatory gene expression profile (such as increased expression of *TNF*, *IL6* and *IFNG*) than circulating neutrophils from healthy individuals[233]. In SLE, neutrophils can be activated by circulating autoantibodies and readily undergo cell death, which causes the release of NETs that can potently activate plasmacytoid dendritic cells and thereby trigger IFNα release[105,234,235], a process that has also been observed in experimental models of atherosclerosis[236]. Moreover, SLE is associated with the presence of a subset of neutrophils named low-density granulocytes (LDGs)[103]. LDGs express IFN-stimulated target genes, produce high levels of cytokines (type I IFN, IFNγ and TNF), can activate T cells and have reduced phagocytic capacity and increased production of NETs[103,237], which are enriched in pro-inflammatory and oxidized mitochondrial DNA[182]. Importantly, LDGs promote endothelial cell death and impair endothelial progenitor cell differentiation in a type I IFN-dependent manner[103]. LDG numbers were associated with the presence of non-calcified plaques in patients with SLE, who had increased vascular inflammation and arterial stiffness compared with healthy controls[25]. However, the higher age and BMI of the patients with SLE might have contributed to this difference[25]. Another study demonstrated a positive correlation between LDG numbers and carotid IMT in patients with SLE[208].

It will be interesting to investigate whether pro-inflammatory subtypes of neutrophils, such as LDGs, or an increased propensity to form NETs in neutrophils in patients with autoimmune diseases contribute to accelerated atherosclerosis, or whether plaques are more likely to undergo erosion in these patients.

Complement. The role of complement in atherosclerosis is multifaceted and dependent on disease stage[238]. The involvement of complement ranges from complement-dependent mechanisms of endothelial cell activation to the modulation of atherothrombotic events through a complex crosstalk between complement, platelets and coagulation factors[239]. Many complement products and their activated forms are present in atherosclerotic lesions and seem to be enriched in the intima compared with the plasma[240,241]. All three complement pathways (classic, lectin and alternative) are active during atherogenesis, and several factors have been shown to trigger complement activation in this context, including immunoglobulins, CRP, modified lipoproteins and cholesterol crystals[238]. Several studies have documented

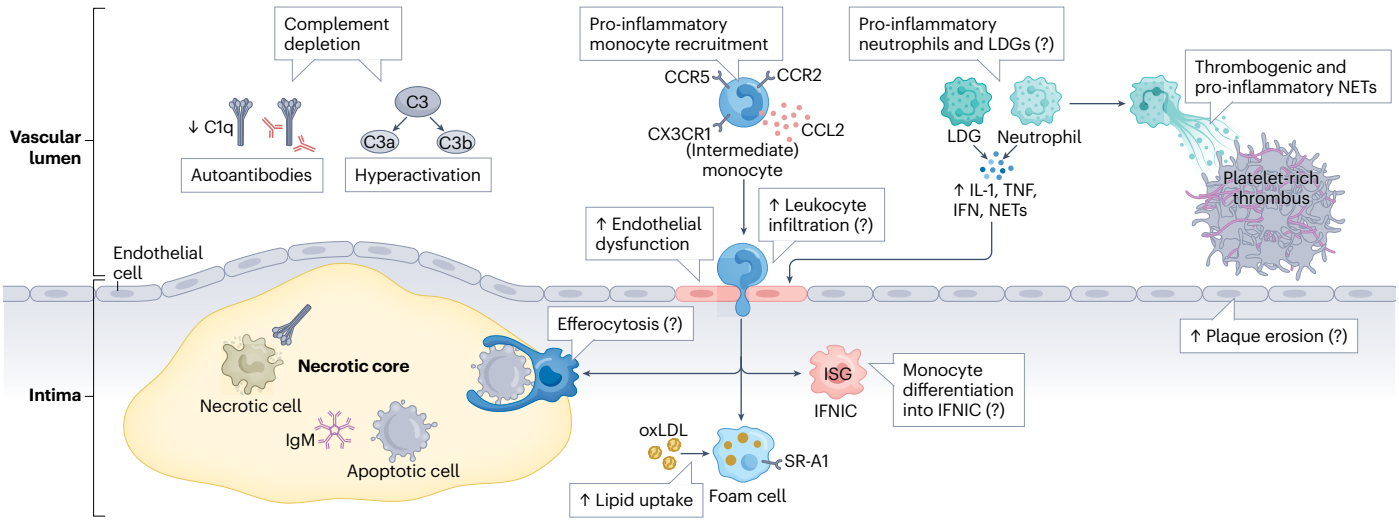


Fig. 5 | Shared innate immune pathways in autoimmunity and ASCVD and their potential effects on atherogenesis and its complications. Autoimmunity-associated monocytes express high levels of chemokines (such as CCL2) and chemokine receptors (such as CCR2, CCR5 and CX3CR1), which promotes their entry into the atherosclerotic plaque and the recruitment of more leukocytes. Monocytes can differentiate into macrophages with heightened lipid uptake capacity owing to the increased expression of scavenger receptor type A1 (SR-A1), or into interferon (IFN)-inducible cells (IFNIC) with a pro-inflammatory, IFN-stimulated gene (ISG) expression profile and potentially pro-atherogenic functions. Complement deficiency (owing to systemic lupus erythematosus-associated gene variants, anti-C1q autoantibodies or complement factor consumption) and hyperactivation might also affect atherosclerosis by impairing efferocytosis. Neutrophils and the autoimmune-associated low-density granulocytes (LDGs) are more pro-inflammatory than neutrophils from individuals without autoimmune disease, and readily undergo NETosis, which promotes endothelial dysfunction and possibly plaque erosion and the associated formation of platelet-rich 'white' thrombi. The question marks indicate mechanisms that so far have not been proven experimentally. ASCVD, atherosclerotic cardiovascular disease; NET, neutrophil extracellular trap; oxLDL, oxidized LDL; TNF, tumour necrosis factor.

an association between circulating levels of complement proteins and ASCVD, but the most compelling evidence for a causal role of complement in atherosclerosis comes from studies in mice. Certain factors, such as C1q and C3, have a protective role in experimental models of atherosclerosis (for example, by aiding in the clearance of apoptotic cells and cell debris[238]). By contrast, C5 activation and membrane attack complex formation can promote inflammation, plaque destabilization via complement-dependent cytotoxicity, and NETosis[238]. Moreover, emerging evidence demonstrates a role for intracellular complement factors and regulators in modulating atherogenesis[238,242].

Complement is a strong driver of some autoimmune diseases, as evidenced by the observation that monogenic loss-of-function variants in *C1Q*, *C4* and *C2*, although very rare, are sufficient to cause severe SLE[13,243]. Similarly, the presence of autoantibodies against C1q or C4 can result in SLE onset and flares[244,245]. The profound autoimmune manifestations associated with complement deficiencies might be due to impaired clearance of cellular debris and immune complexes in the absence of functional classic complement pathway activity, which results in increased self-antigen availability, loss of tolerance and heightened inflammation, including IFN responses[243,246,247]. Moreover, the abundance of inflammatory stimuli and autoantibody-containing immune complexes can trigger complement activation and its potential consumption and depletion in multiple autoimmune disorders, including SLE and RA, further exacerbating autoimmunity. Indeed, reduced levels of certain complement components (C3 and C4) are one of the diagnostic criteria for SLE, which can be particularly pronounced during disease flares[248]. Complement activation, particularly the activation-associated C5 cleavage product C5a, has also been implicated in the development of ANCA-associated vasculitis[249]. Alternative pathway activation promoted by scaffolding provided by NETs has been suggested to contribute to endothelial damage in ANCA-associated vasculitis[111].

Thus, complement represents a multilayered mechanistic interface for autoimmunity-mediated ASCVD. Nevertheless, given the heightened complement activation in the pro-inflammatory milieu in autoimmune conditions, as well as the hypocomplementaemia observed with genetic deficiency of complement components, immune complex formation with anti-complement autoantibodies, or complement consumption, it is difficult to predict the exact contribution of complement to the modulation of atherosclerosis in the context of autoimmunity (Fig. 5). Similarly, whether systemic complement changes mirror local complement activity in the context of the atherosclerotic plaques is unknown. In addition, the relative contribution of systemic versus local complement activity in the context of autoimmune disease remains to be addressed.

Adaptive immunity

T cells. T cells are crucial modulators of chronic inflammatory conditions, including autoimmune diseases and atherosclerosis (Fig. 6). Single-cell RNA sequencing data indicate that T cells are among the most abundant leukocyte populations in human atherosclerotic plaques, and increased T cell numbers in the plaque are associated with symptomatic ASCVD[250]. Experimental studies support pro-atherogenic functions for different T cell subtypes, particularly T_H1 cells, and protective functions for others, such as T_{reg} cells[7,74,251,252]. $CD8^+$ T cells can modulate

atherogenesis via cytotoxic and regulatory effects (as reviewed previously[7]). An imbalance of T cell effector and regulatory functions due to quantitative and qualitative differences in T cell subsets is found in both autoimmunity and atherosclerosis progression, during which T_{reg} cells decrease in number or function, whereas the largely pro-inflammatory T_{eff} cell functions are amplified[7,253,254].

Reduced numbers of, or functionally altered, T_{reg} cells are found in many patients with autoimmune diseases, including SLE, RA, Sjögren syndrome and systemic sclerosis[255]. IL-2, which is central to the survival of T_{reg} cells, is often dysfunctional in these patients[255], thus affecting T_{reg} cell fitness in these settings. Conversely, sustained T cell activation can promote T_{reg} cell instability via FOXP3 down-regulation[256]. Moreover, loss of T_{reg} cell function[257] or pathogenic conversion of FOXP3$^+$ T_{reg} cells into pro-inflammatory 'exT_{reg}' cells occurs during autoimmunity[258]. These exT_{reg} cells adopt a pathogenic RORγT$^+$$T_H$17-like state, which is partially driven by IL-6 (ref. 258). T_{reg} cell-derived T_H17 cells are more pathogenic than bona fide T_H17 cells owing to their T_{reg}-associated self-reactive nature[258]. TNF also has a role in RA-associated T_{reg} cell dysfunction, which can be reversed by TNF inhibitor therapy[257].

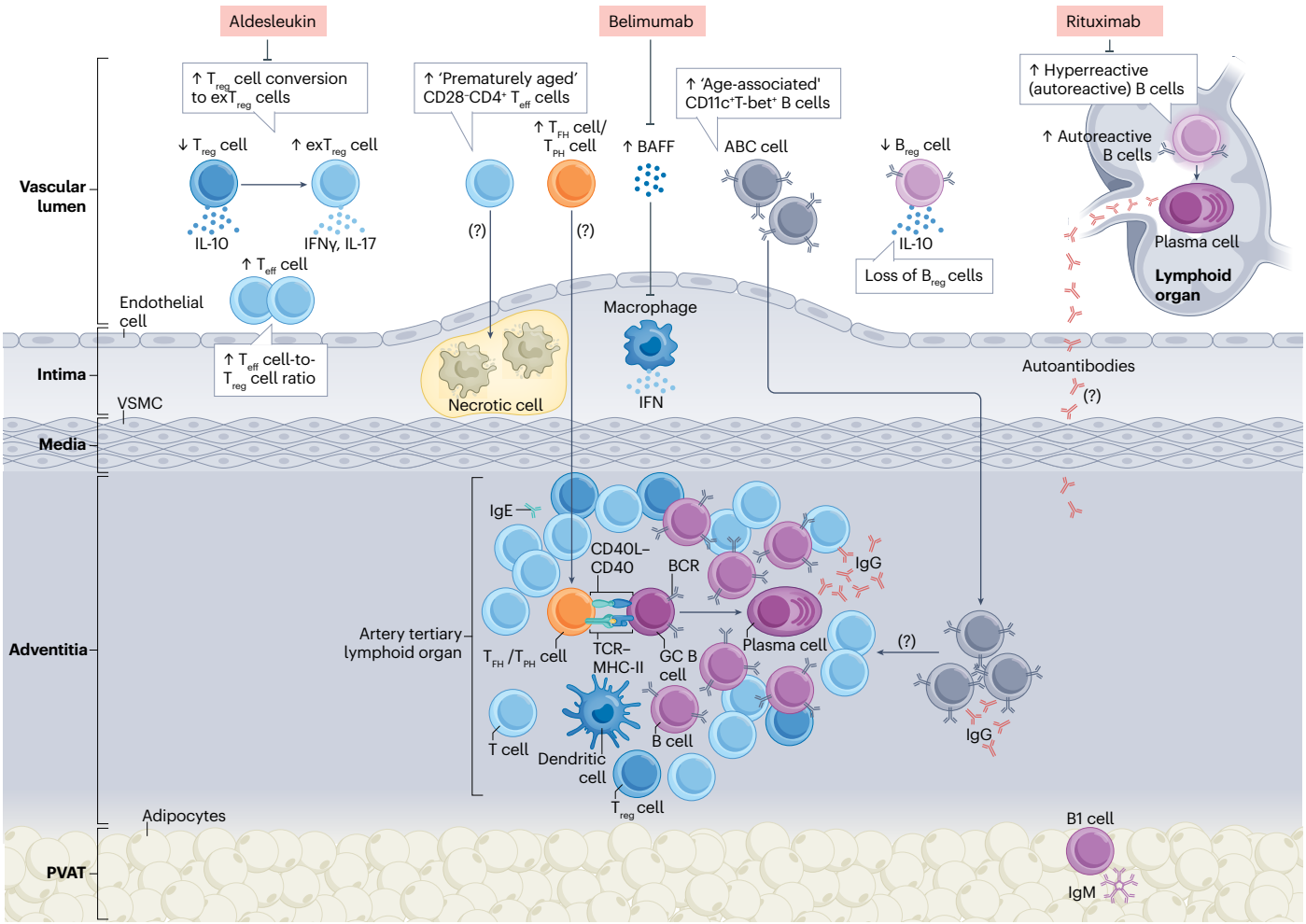


Fig. 6 | Shared adaptive immune pathways in autoimmunity and ASCVD and their potential effects on atherogenesis and its complications. Autoimmune-associated adaptive immune features with potential effects on atherosclerotic cardiovascular disease (ASCVD) include hyperactivation of (auto)reactive B cells and autoantibodies against various known, and potentially unknown, atherosclerosis-associated antigens. Reduced numbers of immunosuppressive cell types, including IL10$^+$ regulatory B (B_{reg}) cells and regulatory T (T_{reg}) cells, could lead to a reduced capacity to limit pathogenic T effector (T_{eff}) cell responses. Atheroprotective IgM-secreting B1 cells could be altered in autoimmunity (unknown). An increased T_{eff} cell to T_{reg} cell ratio, which is common in autoimmunity, could favour pro-atherogenic responses. T_{reg} cell conversion to pathogenic exT_{reg} cells that can secrete interferon-γ (IFNγ) or IL-17 could promote atherogenesis. Increased numbers of potentially pathogenic cell populations, such as CD11c$^+$T-bet$^+$ age-associated B cells (ABC) and rheumatoid arthritis-associated and age-associated CD28$^-$CD4$^+$ T cells, can accumulate in plaques. Follicular T helper (T_{FH}) cells or peripheral T_{FH} (T_{PH}) cells that are increased in autoimmunity could contribute to pathogenic B cell class switching, potentially in artery tertiary lymphoid organs. Increased levels of the cytokine B cell-activating factor (BAFF) could promote the expansion of pathogenic B cell subsets but could also repress pro-atherogenic IFN-associated macrophage responses. Therapeutic options include CD20-mediated B cell depletion (rituximab), BAFF depletion (belimumab) and promotion of T_{reg} cell subset expansion with the use of a low dose of the T cell survival factor IL-2 (aldesleukin). The question marks indicate mechanisms that so far have not been proven experimentally. BCR, B cell receptor; CD40L, CD40 ligand; GC, germinal centre; PVAT, perivascular adipose tissue; TCR, T cell receptor; VSMC, vascular smooth muscle cell.

During atherogenesis, circulating and lesional T_{reg} cell numbers initially increase, but eventually decline, which is likely to be a key step in atherosclerosis progression[72]. As the disease progresses, T_{reg} cells can acquire T-bet expression and adopt a pro-atherogenic T_H1-type phenotype[72,73,259,260]. Such T_{reg} cell conversion has been described for apoB-reactive T_{reg} cells, raising the possibility that these exT_{reg} cells could be particularly pro-atherogenic given their reactivity with atherosclerosis-associated antigens, analogous to exT_{reg} cells in experimentally induced arthritis[258]. Patients with subclinical atherosclerosis have decreased numbers of circulating FOXP3$^+$ T_{reg} cells and increased numbers of RORγT$^+$ or T-bet$^+$FOXP3$^+$T cells[261], which is consistent with the pro-atherogenic role of T_{reg} cell conversion.

T_{reg} cell impairment has been described in both autoimmunity and ASCVD and thus might be a key shared pathogenic mechanism. Therefore, it is not surprising that therapeutic approaches aimed at restoring the homeostatic balance between T_{reg} cells and T_{eff} cells are attractive strategies in both settings. Indeed, low-dose IL-2 treatment can correct T_{reg} cell defects in patients with SLE[262] and increase T_{reg} cell numbers in multiple autoimmune diseases[263–266]. Low-dose IL-2 is currently being evaluated in patients with acute coronary syndrome in the IVORY trial[267] (Table 2).

Autoimmunity is also associated with the presence of qualitatively altered T_{eff} cells. In SLE, T_{eff} cells can have a hyperactive phenotype[268–270], which can drive autoantibody production. Similarly, a central feature of progressive RA is an abnormal, RA-associated CD4$^+$ T cell repertoire that is considered to be 'prematurely aged', with a reduced naive T cell repertoire and selectively expanded, probably autoreactive T cell clones[271,272]. These RA-associated T cells are highly proliferative and pro-inflammatory, and readily undergo cell death and senescence[253,272]. Moreover, these cells readily develop into pro-inflammatory, short-lived T_{eff} cells that enter tissues such as the synovium[272] and thus possibly also atherosclerotic plaques. The RA-associated T cells are largely similar to the CD28$^-$CD4$^+$ T cells that are found in the context of ageing and declining immune function, as well as in CVD[7,273], where the number of these cells is generally increased[274–277]. A small study demonstrated that compared with age-matched individuals with osteoarthritis or fibromyalgia, patients with RA and elevated circulating levels of CD28$^-$CD4$^+$ T cells had even more increased carotid IMT and reduced brachial FMV than patients with RA without CD28$^-$CD4$^+$ T cell elevations[278]. Interestingly, human atherosclerotic plaques contain clonally expanded CD28$^-$ T cells[7,275], which indicates a potential response to atherosclerosis-associated antigens. These data suggest pro-atherogenic functions for CD28$^-$ T cells, but studying their functional role in vivo is challenging because these cells generally do not occur in mice[273].

Other T_{eff} cells, such as RORγT$^+$$T_H17$ cells or IL-22-producing T_H22 cells, have also been implicated in autoimmune disease and ASCVD[7,279,280]. However, experimental data on the functions of these cells and the cytokines that they produce in atherosclerosis are conflicting[7]. The numbers of T follicular helper (T_{FH}) cells, which promote the differentiation of B cells to class-switched plasma cells, are expanded in patients with SLE or RA compared with the numbers in healthy individuals[281,282]. In experimental models of atherosclerosis, T_{FH} cells have detrimental functions, probably by promoting B cell class switching and the production of pathogenic antibodies by plasma cells[73,283,284]. Interestingly, increased levels of a subset of circulating follicular T peripheral helper-like (T_{PH}) cells that readily infiltrate tissues are found in patients with autoimmune diseases[272,282,285]. T_{PH} cells could have a role in extrafollicular responses and in peripheral tissues, including artery tertiary lymphoid organs that develop in the vicinity of advanced atherosclerotic plaques[286,287]. However, whether quantitative and qualitative differences in T_{FH} cells are also a mechanism for autoimmunity-associated atherosclerosis is unknown.

Although clonal expansion of T cells has been described in both autoimmune diseases and atherosclerosis[75,288,289], the specific antigens that are recognized by the T cells are largely unknown. This knowledge gap is due to the technical difficulty of screening for antigens, which requires MHC tetramers customized to the individual and the use of antigenic peptides mixed with autologous antigen-presenting cells for restimulation assays. Novel high-throughput methods, such as single-cell T cell receptor sequencing, might help to establish whether similar T cell clones are expanded in both autoimmune diseases and ASCVD. This information would provide clues as to whether distinct antigen-specific T cell-mediated effects contribute to accelerated atherosclerosis in patients with autoimmune diseases.

B cells. Epidemiological and experimental data support key functions for B cells as modulators of ASCVD, as reviewed previously[8,290]. Various effects of B cells and antibodies have been described, with largely atheroprotective functions ascribed to B1 cells and marginal zone B cells, whereas follicular B cells are generally considered to be pro-atherogenic. Therefore, aberrant B cell responses in autoimmunity might contribute to the increased risk of atherosclerosis in patients with ASCVD.

Autoreactive B cells and abnormal B cell responses are a hallmark of several autoimmune diseases. B cells in SLE are typically hyperresponsive to antigenic stimulation due to factors that modulate B cell receptor signalling and activity[291,292] (such as TLR7 and TLR9 signalling[293–296]). Immature early B cells are particularly prone to displaying self-reactivity[297]. Moreover, SLE is associated with an expansion in the number of memory B cells and plasma cells, with a concomitant reduction in the number of naive B cells in peripheral blood[298]. Surprisingly, the expansion of unswitched memory B cell subsets has been linked to reduced cardiovascular risk in patients with advanced atherosclerosis[299]. However, this effect might be driven by B cells of the B1 subset, which have been proposed to resemble memory B cells, although the nature of human B1 cells remains controversial. Indeed, substantial data in mice show a protective role for B1 cells in atherosclerosis[290], but their role in SLE is less well established[300]. In RA, rheumatoid factor is thought to be derived from CD5$^+$ B1 cells[301], but whether these are the same cells that are responsible for the production of atheroprotective IgM is unclear.

Autoreactive CD11c$^+$T-bet$^+$ B cells are a hallmark of clinically manifest SLE, and the importance of T-bet in B cell-driven autoimmune pathologies has been established in several studies in mice[302,303]. T-bet deficiency protects mice from atherosclerosis[304], and although T-bet deficiency has been linked to reduced T_H1 immunity, a role for T-bet-expressing B cells cannot be excluded. Interestingly, CD11c$^+$T-bet$^+$ B cells have also been described as age-associated B cells (ABCs). Increased ABC numbers are linked to RA disease activity[305], and ABCs can activate synoviocytes[306,307]. ABCs have been found in the circulation and in carotid plaques from patients with ASCVD, where they contribute to 83% of B cells compared with 28% in the circulation[308]. This CD11b$^+$CD11c$^+$T-bet$^+$ ABC subset is expanded in the aorta of aged *Ldlr*$^{-/-}$ mice and is enriched in genes involved in plasma cell differentiation, co-stimulation, antigen presentation and inflammation, including those encoding TNF and IL-1β[308]. Although the functional role of ABCs in atherosclerosis is unknown,

these data suggest that with age, adaptive immune responses in ASCVD share features with autoimmunity.

B cells are important therapeutic targets in autoimmunity. For example, anti-CD20-mediated B cell depletion is effective for the treatment of patients with RA. Given that anti-CD20 antibodies have been shown to reduce lesion formation in atherosclerosis-prone mice[309,310], patients who receive the anti-CD20 antibody rituximab might also derive benefit from the reduction in cardiovascular risk. Indeed, rituximab is being investigated in an ongoing clinical trial examining myocardial remodelling after MI[311] (Table 2). Whether patients with autoimmune diseases receiving B cell-targeted therapies derive an additional cardiovascular benefit remains to be shown, given that CD20-targeted therapies might also deplete atheroprotective B cell subsets[312]. Notably, CD20-targeted therapy is effective in both seropositive and some seronegative patients with RA, which could be explained by indirect effects of B cell depletion.

Several cytokines contribute to autoreactive B cell expansion and autoantibody production, including B cell-activating factor (BAFF) (formerly known as BLyS, which promotes B cell survival and class switching), IL-21 (which induces plasma cell differentiation) and IFNs (which favour extrafollicular responses)[313,314]. The plasma levels of BAFF are increased in patients with SLE compared with the levels in healthy individuals[315–318]. These high levels of BAFF promote the maturation of transitional B cells and allow autoreactive B cells to mature to immunocompetence and thus correlate with increased plasma cell numbers and autoantibody levels. BAFF inhibition is the only approved B cell-targeting therapy for SLE. However, targeting BAFF–BAFF receptor (BAFFR) signalling in atherosclerosis is more complex. BAFFR targeting depletes B2 cells and limits atherogenesis in mice[319,320]. However, BAFF transgenic mice, which develop autoimmunity, have reduced atherosclerosis when crossed onto an *Apoe*$^{-/-}$ background, although this effect is likely to be due to reductions in serum cholesterol levels[321]. Notably, antibody-mediated depletion of BAFF aggravates atherosclerosis in mice, mediated by a BAFF-dependent reduction in TLR9–IFN regulatory factor 7 pro-inflammatory signalling in macrophages[322]. Whether this mechanism is operative in SLE is unknown, but blocking BAFF might unintentionally promote type I IFN production and ASCVD. Of note, in the presence of hypercholesterolaemia, anti-BAFF treatment promoted lesion formation in lupus-prone *Apoe*$^{-/-}$ D227K mice[323].

Protective B cell responses can also be altered in the context of autoimmunity. For example, CD1d^{high}CD5^{+} regulatory B (B_{reg}) cells are implicated in autoimmunity[324], and their frequencies are decreased in several rheumatoid diseases[325]. During hypoxia, IL-10-secreting B_{reg} cells exert important anti-inflammatory roles in RA lesions[326]. B_{reg} cell induction and the suppressive functions of B_{reg} cells are also altered in SLE[327]. Although the role of IL-10-secreting B_{reg} cells is less clear in atherosclerosis[8,290], impaired B_{reg} cell functions in autoimmune disease might be relevant for autoimmunity-induced atherosclerosis. A dysfunction of the anti-inflammatory Fcγ receptor IIB (FcγRIIB) on B cells can promote autoimmunity by controlling affinity maturation, memory B cell and plasma cell responses, and autoantibody production[328]. In experimental atherosclerosis, B cell-specific expression of FcγRIIB shows a robust sexual dimorphism, with protective effects in male but not female mice[329]. Given the strong sex-related bias of autoimmune conditions, which have a higher prevalence in female individuals[330], it will be interesting to understand the contribution of B cell-specific FcγRIIB signalling in autoimmunity-associated ASCVD.

Glossary

Clonal haematopoiesis of indeterminate potential
(CHIP). A common, age-related condition in which somatic mutations in some genes in haematopoietic progenitor cells result in the clonal expansion of leukocytes. The presence of CHIP is associated with a significantly increased risk of cardiovascular disease.

Endothelial-to-mesenchymal transition
A process in which endothelial cells change their molecular and cellular phenotype to that of mesenchymal cells (such as myofibroblasts and smooth muscle cells). Endothelial-to-mesenchymal transition has been implicated in the development of atherosclerosis.

Lipoprotein(a)
An LDL particle that contains apolipoprotein(a). Lipoprotein(a) is one of the strongest genetically determined risk factors for atherosclerotic cardiovascular disease.

Antibodies. Humoral immunity has been implicated in ASCVD for a long time, because immunoglobulins are deposited in atherosclerotic plaques and some of them form immune complexes with oxidized LDL[8]. In particular, data from atherosclerosis-prone mice indicate a protective role for IgM[331–333] and a pro-atherogenic role for germinal centre-derived IgG[334,335]. The exact function of IgG subtypes in atherosclerosis remains to be examined. Transfer of purified IgG from atherosclerotic *Apoe*$^{-/-}$ mice, but not from non-atherosclerotic wild-type mice, into *Ldlr*$^{-/-}$ mice led to vascular IgG accumulation and increased atherosclerosis[335]. Although these studies did not define the antigen specificities of the transferred IgG, they indicate the emergence of pathogenic IgG during atherogenesis. Whether these IgG include similar specificities as those in autoimmune diseases (Box 2) and whether classic autoimmune disease-associated autoantibodies affect atherogenesis is unknown. Experimental studies using antibodies of defined reactivities and subclasses will help to address these knowledge gaps. Similarly, more detailed studies on the association between autoantibodies and antibody-independent features of autoimmunity with ASCVD are needed.

Several studies in mice indicate potential pro-atherogenic functions for arthritis-promoting anti-glucose-6-phosphoisomerase (anti-GPI) IgG antibodies[40,48–50] (Table 1). RA-associated autoantibodies against post-translational modifications might also be important, given that structural components of the vasculature (such as proteoglycans and collagens) can become modified in atherosclerosis. However, in a large study, the increased cardiovascular risk in patients with RA was found not to be associated with levels of anti-citrullinated protein autoantibodies[336].

The role of anti-phospholipid antibodies in atherogenesis seems to be complex, given that studies in mice have conflicting findings (Table 1). The phospholipid cardiolipin is present in cell membranes and lipoproteins; therefore, anti-phospholipid antibodies could have a role in ASCVD by binding to these structures in atherosclerotic plaques. Notably, many anti-phospholipid antibodies bind to oxidized rather than native cardiolipin[337], in analogy to the antibodies against oxidation-specific epitopes (OSEs) that have been implicated in atherosclerosis[8] (Box 1). Although many studies have demonstrated an inverse association between plasma levels of OSE-specific IgM and ASCVD risk, the association with OSE-specific IgG is less clear[8]. Protective mechanisms of OSE-specific IgM include blocking foam cell formation, neutralizing

pro-inflammatory oxidized phospholipids and OSE-carrying extracellular vesicles, and promoting apoptotic cell clearance[338]. Therefore, OSE-specific IgM could also have beneficial effects in preventing autoimmune manifestations and reducing the cardiovascular risk associated with autoimmunity. Notably, high titres of phosphocholine-specific IgM are associated with reduced ASCVD in patients with SLE[339–341]. Low concentrations of OSE-specific IgM, such as anti-phosphocholine IgM, are also found in other autoimmune diseases and correlate with the potential to generate T_{reg} cells ex vivo[340]. Thus, anti-phosphocholine IgM might have additional immunoregulatory functions. Indeed, the prototypic atheroprotective IgM T15/E06, which binds to the phosphocholine of oxidized phospholipids[342,343], can suppress the activation of various TLRs in dendritic cells, thereby limiting the expression of pro-inflammatory cytokines[344]. Interestingly, T15/E06 infusion in mice has been shown to reduce vein graft atherosclerosis[345] and joint inflammation in collagen-induced and anti-collagen II antibody-mediated arthritis[344]. Therefore, anti-OSE IgMs have the potential capacity to limit autoimmunity as well as atherosclerosis.

Conclusions

Patients with autoimmune diseases, including SLE and RA, present with an increased and premature risk of ASCVD and cardiovascular death[11]. Immune mechanisms are responsible for a large part of this risk, and traditional risk factors are not sufficient for risk classification. Modified risk scores that include autoimmune-associated parameters such as autoimmune disease activity scores, or circulating inflammatory cytokines or autoantibodies, have been proposed, but are not widely adopted, and their effect on cardiovascular outcomes remains to be further investigated[346–351]. Thus, the presence of ASCVD in these patients needs to be assessed early on and monitored rigorously using suitable biomarkers, including imaging and laboratory parameters. Conventional biomarkers such as CRP and IL-6 might not be sufficient for this task, highlighting the need to identify novel, more specific markers. Patients with autoimmunity require earlier intervention and efficient control of traditional risk factors, including dyslipidaemia and hypertension, and need to pay particular attention to lifestyle-associated risk, which is recommended in current EULAR guidelines[352,353]. Considering the abundant evidence showing that inflammation and immune-mediated pathways contribute to an increased risk of ASCVD, patients with autoimmune diseases might benefit the most from our growing toolbox of anti-inflammatory therapies. Notably, the potential limitations of some drugs such as colchicine in patients with impaired kidney function, including lupus nephritis, need to be taken into consideration[354]. Overall, we still need to deepen our understanding of the precise pathophysiological mechanisms responsible for autoimmunity-mediated accelerated atherosclerosis and its clinical manifestations to enable a more personalized approach to treatment.

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