frontiers | Frontiers in Lupus

TYPE Review
PUBLISHED 25 June 2025
DOI 10.3389/flupu.2025.1607792

OPEN ACCESS

EDITED BY
Mónica del Rosario Meza Meza,
University of Guadalajara, Mexico

REVIEWED BY
Emanuela Del Giudice,
Sapienza University of Rome, Italy
Rahul Kakalij,
University of Nebraska Medical Center,
United States

*CORRESPONDENCE
Konstantinos Tselios
✉ tseliosk@mcmaster.ca

RECEIVED 08 April 2025
ACCEPTED 16 June 2025
PUBLISHED 25 June 2025

CITATION
Bilodeau P and Tselios K (2025) Immune dysregulation and lipid interactions in systemic lupus erythematosus-associated atherosclerosis: mechanisms and pathogenesis.
Front. Lupus 3:1607792.
doi: 10.3389/flupu.2025.1607792

Immune dysregulation and lipid interactions in systemic lupus erythematosus-associated atherosclerosis: mechanisms and pathogenesis

Philippe Bilodeau and Konstantinos Tselios*

Department of Medicine, McMaster Lupus Clinic, Division of Rheumatology, McMaster University, Hamilton, Ontario, ON, Canada

Atherosclerosis is increasingly recognized as a chronic inflammatory process, involving intricate interactions among the endothelium, lipids, coagulation system, and components of both the innate and adaptive immune systems. In the context of systemic lupus erythematosus (SLE), these interactions are even further disrupted, contributing to accelerated atherosclerosis. This narrative review explores how immune system dysregulation plays a central role in the development of atherosclerosis in SLE patients, where cardiovascular disease remains the leading cause of mortality despite recent advancements. We aim to present a model based on current scientific evidence that compares the immune mechanisms driving atherosclerosis in the general population with the accelerated form observed in SLE patients, highlighting the key immunological distinctions that set SLE-associated atherosclerosis apart. Particular emphasis was given to the interactions between interferon, lipid alterations and adaptive immunity as mediators of atherogenesis. This model may help identify gaps in our understanding and generate new hypotheses for potential therapeutic targets to modulate immune responses within atherosclerotic plaques.

KEYWORDS

systemic lupus erythematosus (SLE), neutrophil extracellular trap (NET), dyslipidemia (DLP), type I interferon (IFN-I), b cell subset, mitochondrial dysfunction, immune dysregulation, atherosclerosis

Introduction

Since the description of the bimodal pattern of mortality in systemic lupus erythematosus (SLE) in 1976 (1), atherosclerosis remains a major focus of interest in systemic autoimmunity. Large epidemiological studies in the 1990s and 2000s demonstrated that SLE patients have a substantially increased risk for cardiovascular events (CVEs) compared to non-lupus individuals (2).

Indeed, SLE more than doubles the risk of myocardial infarction and ischemic stroke compared to controls, with the most dramatic increase in risk observed among adults younger than 50 years of age, reaching up to 52-fold and 22-fold, respectively (2). This heightened risk parallels ultrasound data showing that subclinical atherosclerosis in the femoral and carotid arteries is almost twice as prevalent in SLE as in healthy controls, and comparable to the burden observed in type 2 diabetes (3). Despite the major advances in disease management during the past two decades, atherosclerosis and its

sequelae remains the leading cause of death in SLE with a standardized mortality ratio that exceeds 3 in recent studies (4).

Although most of the traditional risk factors have been reported with increased prevalence in SLE patients, they do not fully account for the atherosclerotic burden. However, adequate control of the modifiable factors (i.e., arterial hypertension, dyslipidemia, diabetes and smoking) was shown to have a significant impact on the cardiovascular complications over time (5, 6). Most of these factors are intrinsically related to immune dysregulation and proinflammatory mediators. Consequently, this complex interplay between traditional and disease-related risk factors is believed to instigate and perpetuate accelerated atherosclerosis in SLE. Furthermore, certain medications that are commonly used in disease management have been shown to modify the immunometabolic profile and affect cardiovascular risk.

Herein, we review the pathophysiology of atherosclerosis in SLE with particular emphasis on the interactions between immune dysregulation and lipid metabolism as well as the central role of certain cytokines in the pathogenetic process.

Endothelial dysfunction as the initiator of atherosclerosis

Endothelial dysfunction (ED) is probably the earliest identifiable event triggering atherogenesis in SLE, as a result of endothelial cell (EC) injury and activation from both immune and non-immune mechanisms (7, 8) (Figure 1). Several observational studies have consistently shown that endothelial function is impaired in SLE, with a recent meta-analysis of 18 studies revealing a 4.3% reduction in mean flow-mediated dilation (FMD) of the brachial artery compared to healthy controls (9). This was demonstrated even in the absence of clinical cardiovascular disease (CVD), suggesting that subclinical dysfunction precedes CVEs (9–11). Brachial artery endothelial-dependent FMD is the most commonly used non-invasive method to assess ED and is strongly correlated with atherosclerosis as well as traditional and disease-related cardiovascular risk factors including hypertension, dyslipidemia, metabolic syndrome, glucocorticoid use and lupus nephritis (7, 12). Meta-analyses in non-SLE populations have shown that a 1% increase in FMD reduces the odds of CVE by 12%–13%,

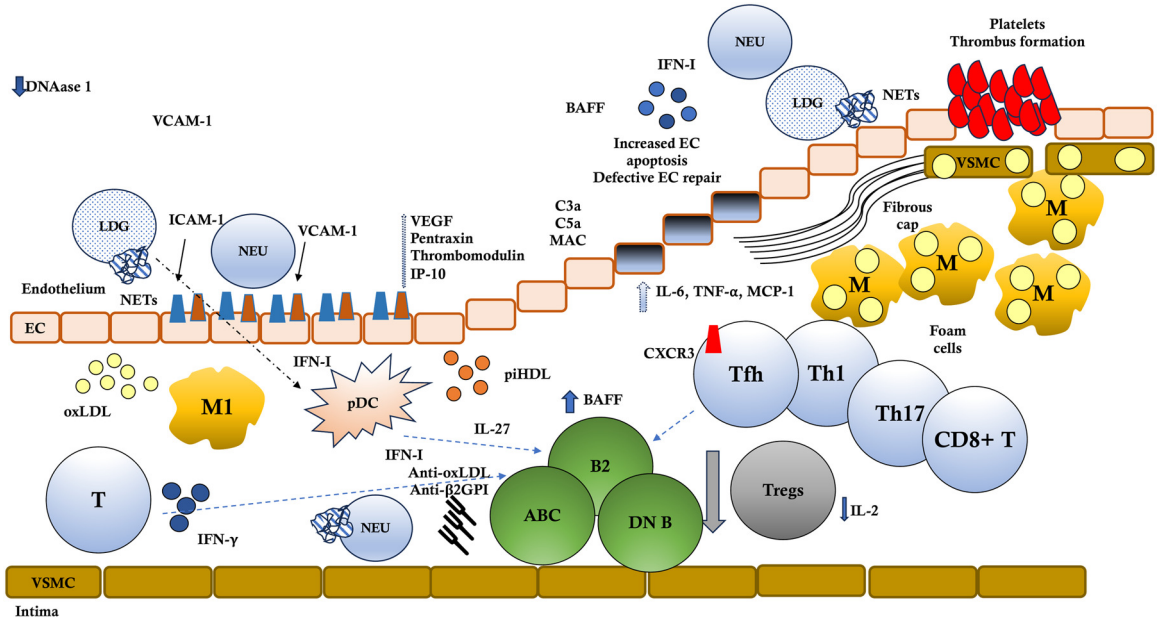

FIGURE 1
The pathophysiology of atherosclerosis in SLE. Endothelial dysfunction via upregulation of adhesion molecules is the earliest identifiable event of the pathogenetic cascade. This will facilitate the subintimal recruitment of LDG (with enhanced NETosis potential), macrophages and T cells. Macrophages are polarized towards the pro-inflammatory M1 phenotype, phagocytose oxLDL and transform to foam cells (along with VSMC). IFN-I, mainly produced by pDC further amplifies the autoimmune response. T cells are polarized towards the inflammatory Th1, Th17, Tfh and CD8+ T cells while Tregs fail to suppress local inflammation. B cells (mainly B2 and DN B) contribute mainly through autoantibody production and dendritic cell activation. Several inflammatory mediators (including IFN-I, BAFF, IL-6, TNF-α, MCP-1 etc.) participate in the process while tissue damage is mediated by MMPs, complement proteins and/or direct cytotoxicity. ABC, age-associated B cell; BAFF, B cell activating factor; $CD8^+$ T, CD8-positive T cell; CXCR3, C-X-C motif chemokine receptor 3; DN B, double-negative B cell; EC, endothelial cell; ICAM-1, intercellular adhesion molecule 1; IFN-I, type I interferon; IFN-γ, interferon gamma; IL, interleukin; IP-10, interferon gamma-induced protein 10; LDG, low-density granulocyte; MAC, membrane attack complex; MCP-1, monocyte chemoattractant protein-1; MMPs, matrix metalloproteinases; M, macrophage; NETosis, neutrophil extracellular trap formation; NETs, neutrophil extracellular traps; NEU, neutrophil; oxLDL, oxidized low-density lipoprotein; pDC, plasmacytoid dendritic cell; piHDL, pro-inflammatory high-density lipoprotein; SR-A, scavenger receptor class A; Th, T helper cell; Tfh, T follicular helper cell; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell.

while a 1 SD decrease doubles the risk, independently of other traditional risk factors (13).

The precise mechanisms leading to ED are only partially elucidated. Several studies have demonstrated increased expression of adhesion molecules (ICAM-1, VCAM-1), as well as other soluble mediators (VEGF, pentraxin-3, thrombomodulin and IP-10) in lupus patients, that are crucial in immune cell recruitment into the subintima and initiate atherogenesis (8). Activated EC also release proinflammatory cytokines and chemokines such as IL-6, TNF-α and MCP-1, particularly during active disease (8, 14).

There is increasing evidence that defective endothelial repair is another key factor in SLE, with augmented apoptosis and impaired capability of replacement by endothelial progenitors. In young women with SLE, circulating apoptotic EC are significantly elevated and correlate with abnormal vascular function as well as increased tissue factor (TF) levels, suggesting ongoing vascular injury (15, 16). Rafael-Vidal et al. identified endothelial progenitor cells (EPC)-like populations in SLE patients with defective angiogenic functions (17, 18). The functional impairment of these cells correlated with increased disease activity as well as the interferon (IFN) signature (18). EPC are a heterogeneous group of hematopoietic (Colony-forming Angiogenic Cells, CAC; Monocyte-derived Angiogenic Cells, MAC) and non-hematopoietic (Endothelial Colony-Forming Cells, ECFC) cells that contribute to vascular repair through distinct mechanisms such as re-endothelialization, paracrine support and angiogenesis regulation. Their characterization is technically challenging and studies in SLE have reported conflicting results; however, it seems that they are universally decreased (7, 18).

Several soluble mediators are implicated in ED in SLE. BAFF-induced EPC dysfunction and apoptosis were demonstrated using *ex vivo* and *in vitro* experiments on lupus patients and healthy donors, which were reversed after incubation with belimumab, a BAFF inhibitor that has been used successfully in SLE (19). Interferons type I (IFN-I) are also involved in ED in SLE (7), notably by inducing apoptosis of EC, EPC and CAC, which could be reversed by interferon blockade in experimental models (20–22). IFN-I has been shown to suppress IL-1β and VEGF-A proangiogenic signaling (23), while paradoxically potentiating IL-18 production in SLE patients (24). Both altered IL-1 pathway and increased IL-18 signaling have detrimental effects on the numbers and function of the EPC and CAC (25). Of note, IL-18 is also a driver of cardiovascular comorbidities in non-SLE populations (12). Furthermore, IFN-α leads to disruption of the nitric oxide (NO) signaling in EC (26). Other mechanisms of EC activation and apoptosis in SLE will be explored in more detail in the following sections.

The emerging role of neutrophils in atherosclerosis

SLE patients have a distinct subset of immature activated neutrophils, the low-density granulocytes (LDG) (27). LDGs are notably amongst the immune cells displaying the highest expression of IFN gene signature (28) and are implicated in disease pathogenesis as well as vascular inflammation and subclinical atherosclerosis (29–33). Kaplan and colleagues substantially contributed to characterize these cells from SLE patients' peripheral blood, highlighting their increased pathogenicity compared to other neutrophil subpopulations (34). LDG exhibit reduced phagocytosis, resistance to apoptosis and ability to activate macrophages and Th1 responses (32, 35, 36). Their propensity to spontaneously undergo NETosis is possibly one of the major elements linking them to atherosclerosis (33).

NETosis is a form of programmed cell death in which neutrophils release reticular chromatin structures composed of DNA, histones, reactive oxygen species (ROS) and antimicrobial enzymes, designed to capture and neutralize pathogens (32). Whether NETosis occurs in the context of SLE or not, it has been widely identified as a mediator of endothelial damage (37–39). Release of MMP-9 has been specifically implicated in ED (29), whereas histones (40, 41), MPO and neutrophil elastase are directly cytotoxic to endothelial and vascular smooth muscle cells (VSMC), leading to apoptosis, increased vascular permeability and overexpression of adhesion molecules (38, 42). In atherosclerosis, NETosis is triggered by oxidized low-density-lipoprotein (oxLDL), mitochondrial oxidative stress, and inflammatory cytokines like IL-1β and TNF-α. Cholesterol crystals are also capable of simultaneously inducing NETosis and fueling NLRP3 inflammasome activation (43). IFN-primed LDGs in SLE are further exposed and easily triggered by RNA immune complexes (IC), dsDNA and antiphospholipid antibodies (aPL), as well as IL-18 (25, 44, 45). This process is dependent on FcγRIIa and TLR7 engagement, and mitochondrial ROS release (46, 47).

LDGs themselves are a significant source of IFN-I when undergoing NETosis, driving a feedback loop that exacerbates inflammation (34, 46, 47). They activate plasmacytoid dendritic cells (pDCs) by releasing large amounts of self-DNA that interact with TLR9 along with immunostimulatory proteins like LL-37 and HMGB1, inducing robust IFN-α production (47). Additionally, oxidized mitochondrial DNA (mtDNA) in NETs is highly immunogenic and able to trigger the cGAS-STING pathway along with NLRP3 inflammasome activity (46, 48). NETs also participate in the production of proinflammatory HDL by oxidation via MPO, NOX and NOS enzymes (49).

In healthy individuals, DNase I efficiently degrades NETs, preventing prolonged exposure to nuclear autoantigens and neutrophil granule proteins (50). However, SLE patients exhibit defective NET clearance that potentiates their atherogenic impact (50, 51). DNase I dysfunction in SLE may result from DNase I loss-of-function mutations, DNase I inhibitors or anti-NET antibodies that shield NET structures from degradation. Indeed, DNase I-mediated NET degradation and PAD4 inhibitors have emerged in experimental models as promising strategies to mitigate NET-driven vascular damage and reduce cardiovascular risk (52).

Ferroptosis is an alternative neutrophil death pathway that is also increased in SLE through type I IFN-mediated suppression of glutathione peroxide-4 (GPX4), enhancing systemic

autoimmunity (53). Interestingly, GPX4 exerts an atheroprotective effect by limiting lipid peroxidation, a main driver of ferroptosis. In the early stages of atherosclerosis, ferroptotic cell death of vascular EC and VSMCs may occur as a result of altered redox capacity, contributing to ED and atherosclerosis progression. OxLDL contribute to this process by promoting iron accumulation, generating lipid ROS, and downregulating GPX4 expression (54).

T cells enabling atherosclerosis

Over the past two decades, intensive research was undertaken to characterize the immune cellular infiltrate within the human atherosclerotic plaques (55, 56). Recent studies have shown that T cells account for 25%–65% of leukocytes within the plaque (57–59). These plaque T cells are clonally expanded, likely reflecting reactivity to self-epitopes in the plaque microenvironment and are enriched in the fibrous cap and adventitia of advanced plaques (60, 61). Th1 cells are the dominant CD4+ T cell subset within the plaques and enriched compared to peripheral blood mononuclear cells (PBMC) (57, 62). Their role has consistently been described as atherogenic in experimental models and largely mediated by IFN-γ secretion (55). This is particularly apparent in murine lupus models where CXCR3 + CD4+ T cells accumulate in the arterial wall, driven by an IFN-α-mediated increase in CXCR3 ligand expression on EC, and drive plaque progression (63).

Th17 cells are considered predominantly atherogenic, although this appears context-dependent (55). IL-17 induces other proinflammatory cytokines such as IL-6, driving vascular inflammation and acting synergistically with Th1-derived IFN-γ (64). IL-17 levels and RORγt expression are elevated in the serum of SLE patients, illustrating a Th17/T regulatory cell (Treg) imbalance, which associates with atherosclerosis, tissue damage and disease activity (65–67). In a murine lupus model, the transfer of effector T (Teff) cells from a B6.SLE model significantly increased the number of IL-17 + cells and accelerated atherosclerosis (68). These Teff cells were less responsive to Treg-mediated suppression, reaffirming previous findings in SLE (69). Interestingly, most of the IL-17 + cells originated from Tregs transitioning to an IL-17 + phenotype, resembling the "exTreg" phenotypes observed in human atherosclerosis (70).

T follicular helper cells (Tfh), characterized by Bcl-6 expression, are mostly considered pro-atherogenic, notably by driving B cell class switching and producing pathogenic antibodies against plaque antigens (55). These cells are expanded in SLE patients when compared to healthy individuals and identify subsets of patients with more diverse and higher titers of autoantibodies as well as more severe end-organ damage (71). Regarding atherosclerosis, Morel and colleagues demonstrated that overexpression of the lupus-associated gene *Pbx1d* exacerbates plaque development by promoting Tfh expansion, impairing Treg homeostasis, and enhancing autoantibody production (72). Additionally, bone marrow transfer from lupus-prone mice into ApoE-/- or LDLr-/- mice led to the expansion of CXCR3+ Tfh cells, enhanced germinal center activity and pathogenic IgG2c production, accompanied by lupus-like manifestations (73). This process is driven by elevated IL-27 levels, primarily produced by CD11b + DC in response to oxLDL through TLR4 activation.

In SLE, a recently identified T cell subset, namely peripheral helper T cells (Tph), shares functional similarities with Tfh, but operates within the peripheral tissues rather than lymphoid organs (74). IFN-I has been identified as a key regulator promoting Tph polarization (75). Tph cells secrete CXCL13, a crucial chemokine that drives the recruitment of B and T cells and promotes the formation of tertiary lymphoid structures (TLS) around target tissues. In SLE, TLS support the persistence of autoreactive T and B cells, pathogenic B cell class-switching and sustained antigen-specific autoantibody production (76). Similarly, Sato et al. have described CD153 + PD-1 + CD4 + senescence-associated T (SAT) cells that are analogous to Tph cells (77). SAT interactions with age-associated B cells (ABC) are key drivers of age-dependent TLS formation and kidney injury via CD153/CD30 signaling, mirroring the Tph–DN2 (double negative B cells) axis in SLE. While direct evidence for Tph cells in atherosclerosis is lacking, their known role raises the possibility that they may similarly enhance local responses and tissue damage through TLS formation around atherosclerotic plaques in SLE patients, resembling the structure and function of well-described artery tertiary lymphoid organs (ATLOs) in atherosclerosis. ATLOs are located in the arterial adventitia near atherosclerotic plaques and facilitate local antigen presentation, clonal expansion of autoreactive T cells against plaque antigen (e.g., oxLDL, ApoB), and promote autoantibody production (78). However, under physiological conditions, it remains unclear whether ATLOs are atheroprotective or atherogenic, highlighting the need for further investigation.

In the general population, $CD8^+$ T cells are particularly abundant in advanced atherosclerotic plaques whereas their presence is minimal in early lesions, reflecting a potential role in plaque progression (55, 57, 79). CVD has been linked with age-associated accumulation of $CD8^+$ subsets displaying terminally differentiated and senescence markers, along with high IFN-γ secretion and cytotoxic phenotype (80, 81). Through mechanisms involving perforin, granzymes, and TNF-α, they can promote VSMC, macrophage, and EC apoptosis, thus destabilizing the plaque and contributing to necrotic core expansion (55). In juvenile-onset SLE, patients with high cardiometabolic risk show expanded $CD8^+$ T-cell populations that mirror those in atherosclerotic plaques (82).

Despite some parallels drawn between the roles of CD8+ T cells in SLE and atherosclerosis, the literature reveals several conflicting findings. Atheroprotective mechanisms involving CD8+ T cells have also been described, highlighting a context-dependent and potentially dualistic role (55, 79). Another consideration is that substantial heterogeneity exists in both the levels and functions of CD8+ T cells subsets reported in SLE (83, 84). Features such as exhaustion sometimes observed in circulating CD8+ T cells are not necessarily reflected in tissue-resident populations, as evidenced by the absence of exhaustion markers in kidney-infiltrating CD8+ T cells (85).

An imbalance between CD4 + CD25 + FoxP3+ Treg and Teff cells is a hallmark of SLE pathophysiology (86), where Treg numbers are reduced and their function is impaired (87, 88). Key molecular drivers include genetic factors, such as polymorphisms in the FoxP3 gene, and environmental influences, such as inflammatory cytokines, oxidative stress and epigenetic modifications, which destabilize Tregs by downregulating FoxP3 expression (86, 89). Physiologically, IL-2 signaling maintains a balance in Treg levels by inhibiting the expression of RORγT and inducing Blimp-1, thus limiting Th17 and Tfh differentiation, respectively. However, this mechanism is disrupted in SLE due to low IL-2 levels (90). Likewise, in atherosclerosis, Tregs often lose FOXP3 expression and convert into pro-inflammatory Th1-like or Th17-like "exTregs" that can secrete IFN-γ, TNF-α and IL-17 (70). This process may be driven by dysregulation of the FOXP3 locus, prolonged antigen exposure, chronic TLR and pro-inflammatory signaling, and metabolic reprogramming. Additionally, elevated intracellular cholesterol content in Treg impairs IL-2 signaling and favors pro-atherogenic Tfh polarization (91). It is hypothesized that apolipoprotein A-I (ApoAI) normally interferes with Treg-to-Tfh plasticity both directly, and indirectly by modulating DC function (91, 92).

Tregs generally exhibit a strong negative correlation with plaque instability in coronary artery disease (93). Local numbers of Tregs are significantly reduced in the human atherosclerotic plaque, irrespective of its developmental stage, and even more so in vulnerable coronary plaques (94). Moreover, Tregs secrete anti-inflammatory cytokines such as IL-10, TGF-β, and IL-35, supporting a relevant role in mitigating inflammation in both SLE and atherosclerosis (93). IL-10 suppresses pro-inflammatory M1 macrophages, while TGF-β promotes anti-inflammatory M2 polarization, thereby enhancing efferocytosis and reducing foam cell formation. Along with TGF-β-induced VSMC proliferation and collagen biosynthesis, these effects collectively contribute to plaque stabilization and inflammation resolution. Additionally, Tregs are essential in maintaining self-tolerance by modulating DC function through co-stimulatory molecule repression and impairing T cell activation through inhibitory cytokines and cell-contact mechanisms (93).

B cells as mediators of plaque progression

The involvement of B cells in atherogenesis was first suspected in the 1980s, supported by the detection of IgM and IgG immunoglobulins in human atherosclerotic plaques (95). Since then, the presence of B cells in the adventitia and ATLOs is widely accepted, while their presence in the intima is increasingly recognized (57, 96–98). B1 cells are considered innate-like B cells, originating in the fetal liver and residing in serosal cavities, mostly peritoneum. They self-renew, have strong antigen-presenting capability and produce IgM antibodies independently of T cells with a subset capable of providing long-term memory. In contrast, B2 cells are derived from bone marrow progenitors and mature into follicular and marginal zone B cells (MZB). Follicular B cells, the predominant subset, undergo germinal center activation to produce high-affinity IgG antibodies and differentiate into plasma cells or memory B cells (99).

B cells have shown opposing roles in murine atherosclerosis, driven by the distinct functions of B1 and B2 subsets (99). Indeed, in the early 2000s, Caligiuri et al. and Major et al. demonstrated an atheroprotective role for B cells in murine models using splenocyte transfer and B-cell deficiency, respectively (100, 101). Conversely, in the early 2010s, CD20 and BAFFR-mediated B cell depletion experiments both reduced plaques by selectively depleting B2 cells while sparing the atheroprotective B1a cells (102–105), while B2 cell transfer promoted atherosclerosis (102). B2 cells disruption led to marked reductions in plaque proinflammatory cytokines (IL-1β, TNF-α, IFN-γ), DC activation, T cell proliferation, macrophage infiltration and pathogenic IgG against oxLDL.

In human atherosclerosis, B cells infiltrates are clonally expanded and mostly composed of mature B2-like CD20- plasmablasts in the adventitia and B1-like IgM-secreting cells in ATLOs, suggesting their local regulation of atherogenesis (97). The alleged atheroprotective effect of B1 cells seems vastly attributable to their natural IgM secretion capability, as well as IL-10 and TGF-beta secretion (99, 106). Of note, the identification of human equivalents to murine B1 cells is challenging and still a matter of debate (107, 108). They produce a subset of IgM known as natural IgM, in contrast to immune IgM, which is a polyreactive and low-affinity antibody produced independently of external antigens (109). A significant amount of natural IgM is directed against oxidation specific epitopes (OSE) and facilitates the clearance of apoptotic cells, prevents autoimmunity, neutralizes pathogens, and promotes inflammation resolution through immunoregulatory effects. Innate-like B cells, comprised of B1 cells along with MZB, produce the vast majority of circulating natural IgM (107). Their exact role in SLE-accelerated atherosclerosis remains uncertain and poorly explored, but evidence of their dysfunction in SLE suggests both a loss of their atheroprotective properties and a role in amplifying autoimmunity. In SLE patients, natural IgM levels are consistently reduced (110), and confer strong associative risk with atherosclerosis. This is observed despite the frequent expansion of B1 subsets and sometimes MZB cells seen in SLE-prone mice (111), implying an altered immune function of these cells. Indeed, in mice models, B1 cells promote SLE disease activity and glomerulonephritis, while their depletion alleviates disease (112). Under certain conditions, B1 cells can undergo isotype switching to produce high-affinity anti-dsDNA IgG1 and IgG2b antibodies instead of protective IgM (112, 113), and MZB cells can become autoreactive and differentiate into IgG-secreting plasma-cells (107, 114, 115). Thus, they could participate in the production of pathogenic and atherogenic IgG antibodies and secrete less protective IgM in specific inflammatory conditions. Moreover, B1a cells in lupus mice models can aberrantly migrate in target organs, in part under CXCL13 influence, and interact locally with T cells (112). A CD11b + B1 cell population (B1b), qualified as "orchestrators" given their T cell regulation capacity and minimal IgM secretion, normally makes up less than 15% of the B1 cells

population but is expanded and dysfunctional in SLE, expressing high levels of co-stimulatory protein CD86 (116). B1b cells are normally present in high numbers in ATLOs (117).

MZB cells emerge as potentially major producers of the atheroprotective IgM against OSEs (118). Moreover, they engage in complex, bidirectional interactions with Tfh cells, which remain incompletely characterized but appear essential for the generation of IgM against OSEs (118, 119). MZB-deficient mice on high-cholesterol diet demonstrated markedly accelerated atherosclerosis progression due to unregulated proatherogenic Tfh response (119). In human studies, levels of IgM against OSEs correlate with MZB-like unswitched memory B cells (CD27 + IgD+) level, likely containing MZB cells (defined as CD27 + IgD + IgM+) (118, 120). Studies in SLE patients using the same innate-like CD27 + IgD + B cells subsets demonstrate impaired natural IgM and IL-10 production along with decreased numbers, correlating with disease activity, while their numbers and functions normalized with therapy (115, 121).

The functional equivalent of murine B2 cells in humans are the mainstream follicular naïve and memory B cells, comprising the vast majority of circulating B cells (99). They carry out classical T-dependent differentiation in secondary lymphoid organs, supported by Tfh cells, and lead to formation of memory B cells or antibody-secreting cells (ASC), including both plasmablasts and plasma cells. The origin of the proatherogenic IgG is hypothesized to be predominantly from germinal centers (GC), occurring in secondary lymphoid organs or ATLOs, and supported by mechanistic studies in murine models (98). ASCs during SLE flares demonstrate large polyclonal expansions dominated by highly autoreactive clones originating from activated naïve B cells that can bypass somatic hypermutation and generate pathogenic antibodies (122). Different CD11c + B cells sharing similar phenotypic and functional features, namely activated naïve B cells (aNAV; CD11c + CD27-IgD-) and double negative B cells (DN2; CD11c + CD27-IgD-CXCR5-), possibly form a developmental continuum in SLE with a propensity to escape B cell tolerance mechanisms and culminate in plasmablast differentiation (123).

DN2 cells are characterized by high expression of T-bet, Toll-like receptor 7 (TLR7) hyper-responsiveness and lack of typical germinal center markers. Both aNAV and DN2 B cells have been described with greater frequency in SLE patients compared to healthy controls, with DN2 subsets often becoming the predominant B cell population especially in highly active patients with elevated autoantibody burden (123). Both are also considered as a subset of ABC (ABC, $CD19^{+}CD21^{lo}CD11c^{+}T\text{-}bet^{+}$) (124), or ABC-like cells, which is a larger B cell subgroup widely described in autoimmune diseases, chronic infections, as well as healthy aging individuals (125). Interestingly, emerging research has revealed the presence of enriched ABCs in aortic plaques of aged Ldlr-/- mice as well as human carotid plaques, along with age-associated highly cytotoxic $Gmzk^{+}CD8^{+}$ T cells (126, 127). The ABCs were strongly enriched locally in the plaque compared to peripheral blood, aligning with their propensity to migrate at disease sites as displayed in autoimmune or infectious contexts (85, 125, 128), and exhibited strong antigen-presenting capacity as well as inflammatory cytokine secretion including TNF-α and IL-1β (126). Pattarabanjird et al. identified an increased frequency of ABC and DN2 cells in high CAD burden patients (127). DN2 were shown to infiltrate coronary atheroma and correlate with high levels of atherogenic MDA-LDL IgG, enrichment in autophagy, IFN-γ and TLR signaling pathways. Their implication in SLE-related accelerated atherosclerosis remains elusive.

The BAFF axis dysfunction is linked with SLE (129) and SLE-related accelerated atherosclerosis (130, 131). Elevated BAFF levels support antibody production and prolonged survival of pathologic B2 cells, notably aNAV and plasmablasts (129, 132, 133). Accordingly, in experimental studies, blocking BAFFR signaling protects against atherosclerosis by depleting B2 cells and sparing B1a subset as well as IgM levels (99). However, in a model using direct BAFF neutralization, the plaque burden was paradoxically increased despite B2 cell depletion (134), while a model overexpressing BAFF exhibited less atherosclerosis (135). More remarkably still, the impact of anti-BAFF mAb on plaque progression in ApoE-/- D227 K mice varied with plasma cholesterol levels, accelerating progression at low levels but reducing it at high levels (136). Indeed, Saidoune et al. demonstrated that TACI receptors are present on macrophages and, in context of high cholesterol levels in lupus-prone mice or high BMI in SLE patients, the lack of TACI signaling in macrophages via BAFF mAb therapy promoted foam cell formation and atherosclerosis progression (134). Similarly, in atherosclerosis-prone mice, protective IgM production and reduction in atherosclerosis was dependent on BAFF-TACI signaling in B cells (135), and BAFF-TACI signaling in macrophages inhibits IRF7-dependant TLR9 proatherogenic responses, such as CXCL10 production (134). These contrasting findings highlight a potential proatherogenic role of the BAFF-BAFFR signaling along with an atheroprotective role of BAFF-TACI signaling. However, in a pathological state such as SLE, multiple factors must be balanced, and the net effect of BAFF inhibition may therefore vary from one individual to another depending on disease activity, pathological state of B2 cells, metabolic status, pre-existing atherosclerosis, etc.

B regulatory cells (Bregs) primarily exert their effects through the secretion of IL-10, but also IL-35 and TGF-β. Two critical roles of Bregs are modulating T cell differentiation and inhibiting pro-inflammatory cytokine production. Unsurprisingly, their dysfunction has been implicated in a variety of autoimmune rheumatic diseases; their role in atherosclerosis remains uncertain (137). Bregs might reduce neointima formation and plaque inflammation through IL-10 secretion (138). Zhu et al. further demonstrated in an SLE-atherosclerosis model that $CD19^{+}CD5^{+}CD1d^{+}$ Bregs regulate the Th17/Treg balance through cytokine signaling, thus preventing a sustained inflammatory state that would otherwise drive atherogenesis (139). In SLE, the suppressive capacity of Bregs over T cells appears diminished, as increased BAFF levels and hyperactivated pDC might interfere with their activation and expansion (137). More recently, SLE patients with subclinical atherosclerosis and antiphospholipid syndrome (APS) exhibited lower Bregs frequencies, correlated with elevated carotid intima-media thickness and greater disease activity (138).

IFN type I as the orchestrator

IFN-I, predominantly IFN-α, exert widespread effects across immune, metabolic and vascular compartments. This results in the amplification of several well-characterized processes involved in atherogenesis that are observed in otherwise healthy individuals, thus positioning type I interferons as key orchestrators of the immunopathogenesis of CVD in SLE (Figure 2). Moreover, elevated IFN-I levels are linked to CVD in patients with various interferonopathies, in which vascular damage is a hallmark, as seen in conditions like STING-SAVI and Aicardi-Goutières syndrome (14, 140). The interferon signature detected in immune cells, tissues and peripheral blood of patients with SLE reflects heightened type I interferon activity, which has been shown to correlate with disease severity (51).

Along the same lines, it was proposed that IFN-α might act as a link between autoimmunity and metabolic syndrome (141). Both conditions share certain pathogenic mechanisms, replicating SLE-like immune activation, occurring within the borders of metabolically active tissues such as the adipose tissue, liver and atheroma. Central to this activation is the high burden of cell death in adipocytes, hepatocytes or vascular cells with subsequent recognition by plasmacytoid DCs and interferon type I release. Experimental and human models have shown that plasmacytoid DCs do localize in the human atherosclerotic plaque and secrete IFN-I upon TLR7/TLR9 stimulation, promoting plaque instability through various mechanisms (142). Other cells found in the plaque or neighboring arterial structures act as sources of IFN-I, including neutrophils and B cells (143).

Although the immune landscape within the atherosclerotic plaques of SLE patients has not yet been characterized, IFN-I is pluripotent and regulates multiple subsets of immune and non-immune cells that are central to atherogenesis, including monocytes, neutrophils and EC (143, 144). Firstly, IFN-α drives monocyte/macrophage and neutrophil infiltration of the subendothelial space by inducing adhesion molecules (VCAM-1, ICAM-1) and chemokine (CCL5) expression by ECs (143, 145). Moreover, it promotes atherosclerosis by increasing scavenger receptor class A (SR-A) expression in monocytes and macrophages, thus enhancing oxLDL uptake and subendothelial foam cell formation, the major substrate for fatty streaks development. Mice models of atherosclerosis identified atherogenic macrophage subsets expressing type I IFN-related genes, and similar high IFN-signature monocytes are present in both the circulation and the affected tissues (e.g., kidney) of SLE patients (12, 143). Studies in human atherosclerotic plaques show that IFN-α can upregulate TLR4 expression in antigen-presenting cells, leading to enhanced secretion of TNF-α and MMP-9 (146). Moreover, IFN-I affects VSMC function directly by suppressing their proliferation and inducing apoptosis, and indirectly, by

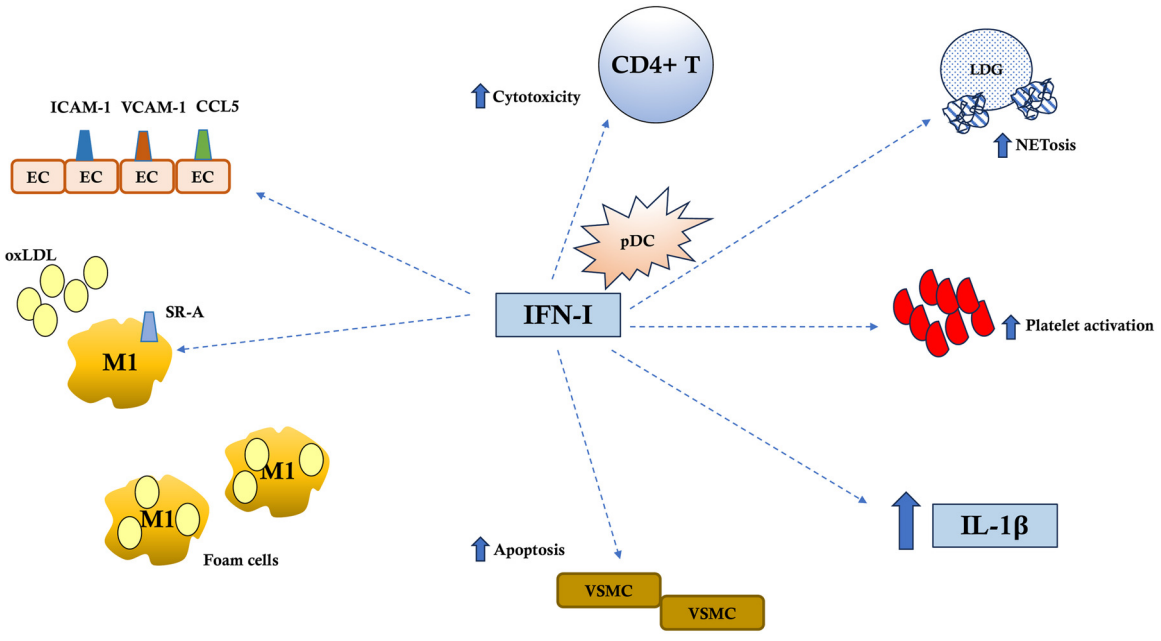

FIGURE 2
The central role of IFN-I in SLE-associated atherosclerosis. IFN-α is mainly produced by pDC and induces EC activation and upregulation of adhesion molecules, thus facilitating monocyte/macrophage and neutrophil infiltration of the subendothelial space. It promotes SR-A expression in monocytes/macrophages and enhances oxLDL uptake and foam cell formation. It promotes apoptosis of the VSMC as well as platelet activation. Moreover, it enhances CD4+ T cell cytotoxicity and promotes LDG-derived NETosis. Finally, it acts synergistically with IL-1β in promoting atherosclerosis. CCL5, C-C motif chemokine ligand 5; $CD4^+$ T, CD4-positive T cell; EC, endothelial cell; ICAM-1, intercellular adhesion molecule 1; IFN-α, interferon alpha; IFN-I, type I interferon; IL-1β, interleukin 1 beta; LDG, low-density granulocyte; M1, classically activated macrophage; NETosis, neutrophil extracellular trap formation; oxLDL, oxidized low-density lipoprotein; pDC, plasmacytoid dendritic cell; SR-A, scavenger receptor class A; VCAM-1, vascular cell adhesion molecule 1; VSMC, vascular smooth muscle cell.

enhancing CD4+ T cell cytotoxicity via TRAIL upregulation and promoting LDG-derived NETosis (12, 41, 144).

Even platelets in SLE display an IFN-dependent transcriptional signature that originates in megakaryocytes exposed to IFN-α, rendering them readily activated in the circulation (147). Once triggered, they can drive IL-1β–mediated EC activation, as shown *in vitro* for SLE patients (148). Several studies have established strong links between platelet activation and increased cardiovascular morbidity in SLE, particularly through thromboembolic events (147, 149, 150).

Type I IFNs and Il-1β: partners and opponents

IFN-I engages in a complex interplay with IL-1β, a pro-inflammatory cytokine that results from the assembly of the inflammasome complex, which has proven to be significantly involved in the progression of atherosclerotic plaque (151). Therapeutic targeting of IL-1γ in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) was the first large-scale, randomized controlled trial in over 10 000 atherosclerotic patients demonstrating protective cardiovascular and anti-inflammatory effects (152, 153). IL-1β accelerates atherosclerosis progression by promoting endothelial activation, leukocyte recruitment, and proinflammatory cytokine cascades (such as IL-6) that sustain chronic vascular inflammation and destabilize plaques (151).

Caielli et al. demonstrated that mitochondrial nucleic acids can sequentially activate innate sensors to sustain simultaneously IFN-I and NLRP3 signaling, while IFN-induced MxA enables unconventional, gasdermin- and pyroptosis-independent IL-1β secretion (154) (Figure 3). It has not been explored if this process contributes to atherosclerosis in SLE. Indeed, the atherosclerotic plaque provides a permissive microenvironment for chronic monocyte priming as they are rich in damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), oxLDL, and free fatty acids, which engage pattern recognition receptors, leading to sustained NF-κB priming. This is a well-established driver of atherogenesis in experimental and human studies, as genetic disruption of these pathways mitigates progression (151). Additionally, the plaque contains strong NLRP3

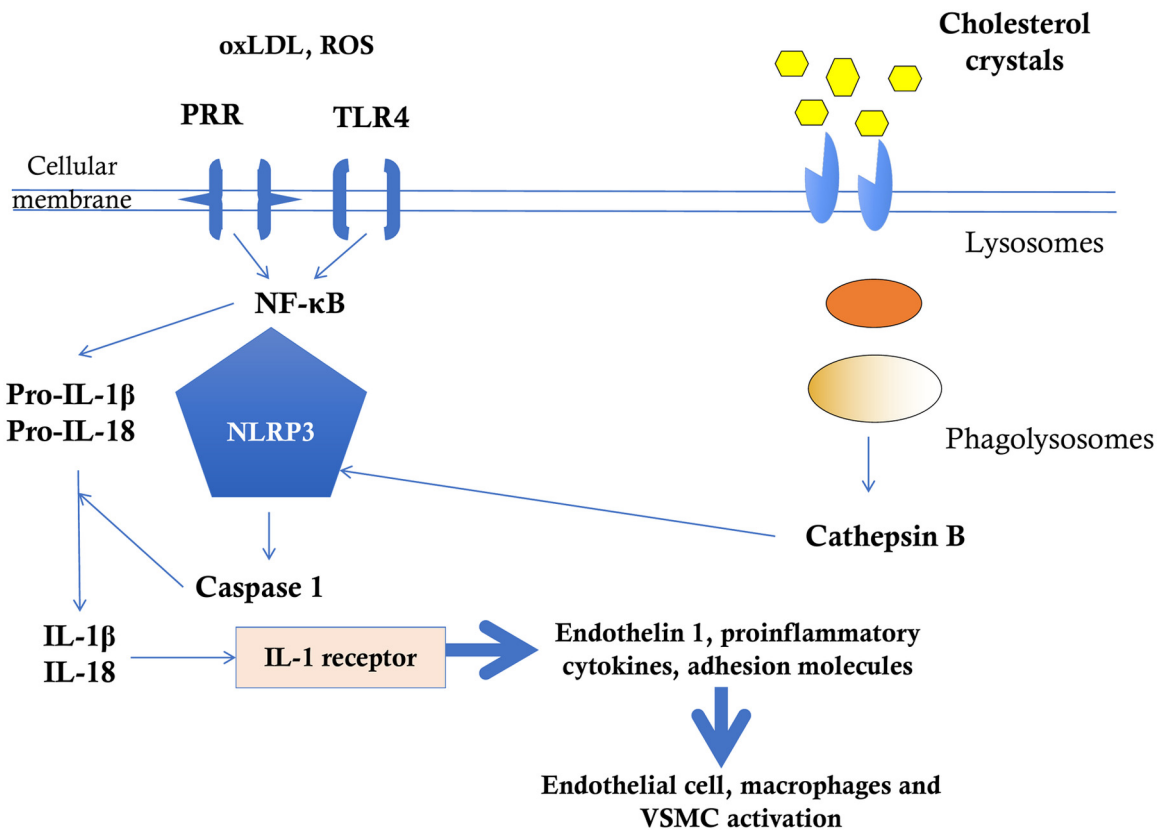

FIGURE 3
The role of IL-1β in atherosclerosis. Oxidized LDL and ROS activate NF-κB through interactions with TLR4 and other pattern recognition receptors. This activates the NLRP3 inflammasome and promotes the production of proforms of IL-1β and IL-18 (priming). Atherosclerotic plaques are rich in cholesterol crystals that enhance the production of caspase 1 that cleaves the inactive forms to active IL-1β and IL-18. The end result is increased endothelial, macrophage and smooth muscle cell activation, upregulation of adhesion molecules and proinflammatory cytokine secretion. IL-1β, interleukin 1 beta; IL-18, interleukin 18; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; oxLDL, oxidized low-density lipoprotein; PRR, pattern recognition receptor; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; VSMC, vascular smooth muscle cell.

inflammasome triggers, such as cholesterol crystals, which provide the second signal necessary for inflammasome activation.

Furthermore, monocytes in SLE are exposed to mitochondrial material and extracellular mitochondrial nucleic acids from various sources, including NETotic neutrophils, mitochondria-rich platelets, retained mitochondria in red blood cells, and microparticles (154, 155). These retained mitochondrial DAMPs strongly engage cGAS-STING and RIG-I-like receptors, leading to IFN-I production. Mitochondrial RNA sensing through MAVS triggers monocytes to release their own mtDNA into the cytosol, another potent inflammasome trigger, driving sustained IL-1β production. Chronic exposure to IFN-I induces MxA expression, which facilitates unconventional, gasdermin-independent IL-1β secretion, further propagating vascular inflammation (154). Overall, atherosclerotic plaques in SLE may function as an amplifying niche promoting IFN-driven IL-1β secretion, thus reinforcing atherosclerosis progression.

Conversely, IL-1β might also exert cardioprotective effects (23, 151), and studies have shown that IFN-I normally downregulates IL-1β pathways in SLE, with IL-1β levels being neither consistently elevated nor clearly linked to CVD risk. However, IL-1β-driven inflammation might be confined locally in the atherosclerotic milieu, similar to increased activity of the inflammasome found in other diseased tissues in SLE (e.g., kidney), possibly making serum levels an unreliable biomarker for this purpose (156, 157).

Antibodies and immunocomplexes

Immunocomplexes (IC) formed by pathogenic autoantibodies in SLE, a hallmark of the disease, can deposit in atherosclerotic lesions and generate further inflammation and vascular damage. Among the various responses elicited by IC in tissues, it is hypothesized that Fc receptor-mediated responses have proatherogenic capability (158). As an example, oxLDL and oxLDL/β2GPI complexes are found in SLE and recognized by anti-oxLDL and aβ2GPI IgG antibodies (159, 160). These large complexes are phagocytosed by macrophages through FcγR and TLR4, driving foam cell formation in the subintima and IL-1β secretion (161, 162). IC also stimulate pDC within plaques to locally secrete IFN-α (142). This response is further intensified by Fc-mediated platelet activation and NET release, which, among other effects, contribute further to vascular endothelium activation, damage (44, 149).

Anti-dsDNA antibodies are positively correlated to disease activity and major organ involvement (e.g., kidney, central nervous system), but also with CVE (HR 1.56), noncalcified coronary plaques, ED, oxidative stress markers, dyslipidemia and accelerated atherosclerosis, independently of traditional risk factors (163–166). Indeed, Patiño-Trives et al. demonstrated that, *in vitro*, IgG anti-dsDNA antibodies directly promote NETosis, monocyte apoptosis, and endothelial activation, again mediated through Fc receptor binding (166).

aPL are another group of autoantibodies found in up to 36% of SLE patients and directed against phospholipid-binding proteins such as cardiolipin and β2-glycoprotein 1 (167). The presence of anticardiolipin antibodies (aCL) was independent predictor of CVE (168), but also carotid plaques (HR 5.2) (169), and coronary calcifications (170). Similar findings regarding anti-β2 glycoprotein I (aβ2GPI) and lupus anticoagulant (LAC) have been described for CVE (168), coronary calcifications (HR 4.1 and 4.4, respectively) (170), and carotid plaque (LAC only, HR 5.2) (169). It is associated with higher subclinical atherosclerosis in primary APS and isolated positive aPL compared to healthy controls, and the risk of CVD is even higher in SLE patients with APS (171, 172). aPL contribute to atherosclerosis in SLE by triggering endothelial inflammation, activating EC through extracellular vesicles and TLR pathways and increasing tissue factor expression (163, 173). It was also shown to decrease NO bioavailability and increase endothelin-1 production and oxidative stress in various contexts including thrombosis, pregnancy morbidity, and vascular dysfunction (173).

A subset of SLE patients, ranging from 15%–88%, exhibit anti-endothelial cell antibodies (AECAs), which are also found in other autoimmune conditions associated with vascular impairment (174, 175). SLE patients with AECAs show increased endothelial activation and apoptosis through Fc receptor independent mechanism compared to AECA-negative SLE patients (175, 176). Their exact role in atherosclerosis remains unclear. Lastly, IC arising from IgG directed against plaque antigens can also participate in vascular damage through complement-mediated cellular cytotoxicity (CMCC) as well as antibody-mediated cellular cytotoxicity (AMCC) by interacting with FcγR on immune effector cells, such as Natural Killer cells (158). Antibodies against HSP60/65, a protein expressed on stressed EC, have been described as a mediator of vascular damage in atherosclerosis for over two decades ago, acting through CMCC and AMCC (158, 177).

The role of complement

Complement activation is a driver of tissue damage in SLE and reduced C3 and C4 serum levels serve as diagnostic markers, especially during disease flares (178, 179). While this pathway is well-recognized in SLE, its role in CVD is a growing area of research, although early evidence already suggests its involvement (95). In atherosclerosis, elements of the complement cascade, such as C1q, C3, C4, and the membrane attack complex (MAC, C5b-9), accumulate in the arterial plaques as early as the formation of fatty streaks, suggesting local complement activation (180).

MAC complex deposition can be found on infiltrating macrophages, apoptotic cells as well as EC. The complement system is directly involved in EC dysfunction and death (181). The membrane attack complex (MAC, C5b-9) and sublytic MAC formation on EC induce pro-inflammatory cell death and NLRP3-inflammasome mediated IL-1β secretion. Complement components C3a and C5a further drive ED by engaging their respective receptors (C3aR and C5aR1). Chronic complement activation leads to EC exhaustion, characterized by mitochondrial dysfunction, oxidative stress, and senescence-associated secretory

phenotype (SASP) expression, barrier dysfunction and decreased NO production (181, 182). Senescent EC can also be induced through multiple stimuli including mechanical and oxidative stress and emerge as significant players in atherogenesis (182).

Clinical findings support these mechanisms, as C5a and C5b-9 deposition correlate with plaque vulnerability and necrotic core expansion. All three complement pathways (classical, alternative, lectin) are activated in the atherosclerotic process, with cholesterol crystals serving as a common trigger (180). Additionally, the classical pathway is activated through interactions with local IC, while both the classical and lectin pathways are triggered by modified lipids, apoptotic cells, microparticles and oxLDL. Of interest, genetic mutations resulting in early classical complement pathway components deficiency or loss-of-function, such as C1q, C4A, C4B, or C2, have all been linked to monogenic SLE in humans, often with severe phenotype (183). Similarly, single nucleotide polymorphisms resulting in C2 and C4B deficiency were both associated with increased risk of myocardial infarction and death in human studies (181). The implication of both C2 and C4 in IC clearance mechanisms through C3b generation is possibly the connection between both observations. However, although C1q displays strong atheroprotective function in murine models (184), human genetic data are scarce, while clinical studies have yielded conflicting results (181).

A possible explanation is the complex and pleiotropic role of C1q in autoimmunity, distinct from other classical pathway components. Importantly, it facilitates the non-inflammatory clearance of apoptotic cells and IC via FcγR-mediated phagocytosis. C1q protects against autoimmunity by modulating monocytes/macrophages, regulating cytokine release and DC differentiation, and suppressing IFN-α production, thereby skewing adaptive immunity toward an anti-inflammatory response (185). However, the efferocytotic effect of C1q is possibly overwhelmed in advanced atherosclerotic lesions (186). Combined with a microenvironment rich in classical pathway inducers (e.g., CRP, oxLDL, cholesterol crystals), its balance may shift toward a more pro-atherogenic role. The higher prevalence of anti-C1q antibodies in SLE patients adds complexity to understanding C1q's role in atherosclerosis (187). Although these antibodies have clearly been linked to target organ damage, especially lupus nephritis, their impact on atherosclerosis remains unexplored (187, 188).

Lupus dyslipidemia fuels adaptive immunity towards plaque formation

Patients with SLE often present with characteristic alterations in their lipid profile, referred to as lupus dyslipidemia. Hyperlipidemia in SLE exhibits a high prevalence and progressive trend, with hypercholesterolemia affecting up to 60% of patients within three years of follow-up (189). More recent data found the condition in 20% of cases, with less lipid target attainment among APS-SLE patients and those from middle-income countries (190). The metabolic profile in lupus dyslipidemia typically includes elevated total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL), along with decreased high-density lipoproteins (HDL) (191). SLE patients also demonstrate higher serum malondialdehyde (MDA), apolipoprotein B (ApoB), and oxLDL than control groups, reflecting an increased state of oxidative stress and lipid peroxidation (192). These abnormalities are not restricted to adults, as 63% of pediatric SLE patients exhibit a similar dyslipidemia pattern at diagnosis (193).

Despite these metabolic alterations, there is no evidence of an intrinsic causal relationship between lipid traits and SLE in either direction. A 2022 Mendelian randomization study found no significant genetic causal link between SLE and major lipid traits (194), and conversely, a 2021 phenome-wide association study demonstrated that SLE genetic risk alleles are not significantly associated with dyslipidemia or other cardiometabolic disorders (195). These findings suggest that dyslipidemia in SLE is rather a result of inflammation-driven metabolic disruptions and comorbid factors. On a similar note, TNF-α, a key cytokine in SLE pathogenesis, has been shown to influence lipoprotein metabolism by raising triglyceride levels, potentially through enhanced hepatic very-low-density lipoprotein (VLDL) production and direct inhibition of lipoprotein lipase. Interestingly, ApoAI usually downregulates TNF-α and IL-1β, a mechanism likely defective in SLE given low HDL levels, which may indirectly increase inflammation. Elevated levels of MCP-1 and IL-6 have also been reported in patients with SLE, showing a correlation with higher triglyceride and lower HDL levels, respectively (191). Of note, non-immune mechanisms, including corticosteroid use, lupus nephritis, low vitamin D levels, and hypothyroidism, can significantly contribute to the exacerbation of dyslipidemia in lupus (191, 196, 197).

Several clinical studies have yielded mixed results regarding the use of statins for atherosclerosis progression in SLE (191, 198). In 86 SLE patients followed for 7 years, plaque progression risk was fourfold higher, but Tektonidou and colleagues found a 50% reduction for each modifiable cardiovascular risk factor that was optimally managed (6). In a recent study of 151 juvenile SLE patients stratified by a serum metabolic signature for CIMT progression and assigned to either statin therapy or placebo, 36% of treated patients experienced significant atherosclerosis progression despite improvements in lipid levels, which was not predicted by baseline metabolomic markers (198). This further supports the involvement of disease-specific mechanisms that are likely interconnected but not entirely dependent on lipids and traditional risk factors.

Autoantibodies involved in lupus dyslipidemia

Lipoprotein lipase (LPL), a crucial enzyme in lipid metabolism, has been implicated in lupus-associated dyslipidemia, though its precise role remains only partially understood. Autoantibodies against LPL, detected in nearly 50% of SLE patients, are believed to inhibit its enzymatic activity (199), with rare cases of severe hypertriglyceridemia linked to their presence (200). In SLE,

impaired LPL function delays the hepatic clearance of chylomicron remnants, leading to VLDL accumulation, elevated triglyceride levels, and reduced HDL concentrations (191). Additionally, anti-dsDNA antibodies have also been shown to interfere with LPL activity, reinforcing the connection between autoantibody-mediated immune dysregulation and lipid metabolism disturbances (201). Anti-LPL autoantibodies correlate with higher disease activity, lupus nephritis, anti-dsDNA antibodies, and elevated TG, ApoB, and ApoE levels, suggesting that chronic inflammation in SLE profoundly alters the balance between pro- and anti-atherogenic lipoproteins (199, 201).

In addition, IgG autoantibodies directed toward the anti-inflammatory lipoprotein HDL and ApoAI have been described recently in up to 43% of lupus patients (202, 203). Furthermore, these antibodies positively correlate with disease activity, inflammatory status and negatively correlate with PON1 activity (204). Their association with CVE has been shown in populations without coexisting autoimmune disease. It is hypothesized that an oxidative environment promotes ApoAI oxidation, misfolding, and dissociation from HDL, making it immunogenic and predisposing to antibody generation in SLE (203). Interestingly, a high degree of cross-reactivity among aCL antibodies, anti-HDL, and anti-ApoAI IgG has been reported in SLE patients (205).

Oxidized LDL—a link between atherosclerosis and SLE?

OxLDL has been recognized as a cornerstone of atherosclerosis, acting as a trigger and amplifier of plaque inflammation (79, 206). Its infiltration and retention in the arterial wall initiate the early plaque formation, inflammatory cascade, and immune cell recruitment. The oxidative modification of macromolecules on lipoproteins (e.g., LDL) or phospholipids (e.g., cardiolipin) generates OSEs, acting as neo-self-antigen (107, 172). OSEs are highly immunogenic and act as DAMP and PAMP in mice and humans. These epitopes trigger both innate and adaptive immune responses and lead to the production of autoantibodies (158). They interact with PRR, including scavenger receptors such as CD36, SR-A1, LOX-1, and stimulate phagocytosis, foam cell formation, IFN-γ production, cell death and necrotic core expansion. Their recognition by VSMC and EC drive ED and plaque instability (206).

OxLDL levels are not only elevated in SLE compared to controls, but they also exhibit more OSEs (160, 207, 208). Its presence is associated with active disease as well as overt and subclinical CVD (160, 207). Interestingly, these same epitopes also arise from apoptotic cell membranes and extracellular vesicles and are able to generate immunogenic responses (158). This overlap could be of particular relevance in SLE, since microparticles and cellular debris persistence is a hallmark of the disease. Additionally, aCL were demonstrated to cross-react with OSEs on oxLDL (209, 210). Given this shared immunological landscape, OSE might represent a common link between lupus-driven autoimmunity and the heightened cardiovascular risk observed in SLE patients.

These molecules are likely critical in modulating immune homeostasis, as OSEs are primary targets of natural IgM in both humans and mice, comprising over 30% of the natural IgM repertoire in mice (211). Phosphorylcholine (PC), among the most studied OSEs in both atherosclerosis and autoimmune disease, is derived from phosphatidylcholine, a major component of cellular membranes, organelles and lipoproteins, and is exposed following oxidation process (172). In SLE, natural IgM antibodies targeting PC and MDA enhance apoptotic cell clearance, reduce oxidative stress, neutralize inflammatory DAMPs, reduce foam cell formation and inhibit DC activation through p38-MAPK signaling, thus decreasing IL-6, TNF-α, CD86, and CD40 expression (212, 213). Furthermore, anti-PC IgM antibodies have been shown to enhance the proportion of Tregs in peripheral blood of patients with SLE, even restoring their Treg levels similar to those of healthy controls (214). SLE patients exhibit consistently reduced levels of anti-MDA and anti-PC IgM, which correlate negatively with disease activity (110, 212, 215–217); similarly, low levels of natural IgM against oxidized phospholipids were linked to plaque burden and vulnerability, independently of β2-glycoprotein I (218). In a cohort of 114 SLE patients, anti-PC and anti-MDA IgM levels above the 66th percentile strongly protected against plaque prevalence and vulnerability (OR 0.08 and 0.10), while levels below the 33rd percentile significantly increased risk (OR 3.79) (212). Anti-PC IgM was also independently inversely associated with plaque occurrence and cardiovascular risk scores across mixed systemic rheumatic diseases (110, 216). On a similar note, SLE patients exhibit significantly lower levels of autoantibodies against native and MDA-modified apolipoprotein B-100 peptides (both p45 IgM and p210 IgG), with more pronounced reductions in those with CVD or organ damage (219).

On the other hand, IgG against OSEs are mostly considered proatherogenic, although much variation exists in the relevant studies (98). Disparities might be the result of different IgG subclass (e.g., IgG1), antigen target (e.g., ALDH4A1), FcγR engagement (e.g., FcγRIIB) and post-translational alterations (e.g., glycosylation), among others, some being atheroprotective. However, in SLE, a wide array of IgG autoantibodies interacts with key components of atherogenesis (including lipids, EC, macrophages, and neutrophils) thereby potentiating the pathogenic role of IgG in promoting accelerated atherosclerosis.

Dysfunctional HDL

HDL is a structurally and functionally complex lipoprotein composed of various apolipoproteins, most notably ApoAI, alongside phospholipids, sphingolipids, free cholesterol, cholesteryl esters and triglycerides (220). HDL carries several enzymes, such as paraoxonase-1 (PON1), its most potent antioxidant, along with ApoAI, which constitutes 70% of HDL's protein fraction and supports PON1 stabilization, cholesterol homeostasis, and immunomodulation (174, 220). Beyond its role in protecting against oxidative stress, HDL exerts a strong cardioprotective effect, largely through reverse

cholesterol transport, a multi-step process in which cholesterol efflux capacity plays a critical role in macrophage cholesterol removal and preventing foam cell formation. HDL exerts significant protective and immunomodulatory functions in healthy state, through binding lipopolysaccharides, neutralizing bacterial toxins, regulating endothelial barrier integrity and immune cell trafficking, suppressing monocyte and macrophages activation, inhibiting DCs maturation and influencing T cell differentiation.

In SLE, a significant proportion of HDL loses its protective function, becoming dysfunctional with impaired ability to inhibit LDL oxidation (221). HDL molecules become pro-inflammatory as evidenced by findings from Smith et al. demonstrating increased macrophage inflammatory cytokines production through interaction with LOX-1 (222). This dysfunctional HDL molecule subset has been identified as an independent risk factor for subclinical atherosclerosis and carotid plaque in women with SLE. Moreover, its levels are significantly decreased as assessed in a recent meta-analysis, which is also among the most prevalent lipid abnormalities reported in SLE cohorts (191, 223). Disease activity is strongly linked to this finding, and various SLE-specific mechanisms might explain the altered HDL function and level (224, 225). In an inflammatory environment, HDL loses its anti-atherogenic properties through oxidative stress and interactions with acute phase reactants (226–228), translating in elevation of oxLDL levels in SLE and RA patients (228). In SLE, excessive NETosis releases oxidative enzymes like MPO and NADPH oxidase which directly contribute to HDL and LDL oxidation (49).

Mitochondrial dysfunction and oxidative stress as a bridge between interferons, lupus dyslipidemia and local inflammation

Mitochondrial dysfunction and mito-inflammation have emerged as crucial mediators of SLE, shedding light on the impact of disruptions in mitochondrial integrity on immune dysregulation and chronic inflammation (51, 155). This concept seems to be particularly relevant in the process of accelerated atherosclerosis that characterizes lupus. Indeed, patients with mtDNA mutations develop mitochondrial atherosclerosis even in the absence of traditional cardiovascular risk factors (229). Genetic mutations in mtDNA, including various SNPs and D-loop polymorphisms, also contribute to autoimmune diseases like SLE (155). Mitochondria are also the primary source of ROS overproduction and oxidative stress in SLE (230), and IFN-I emerges as a key driver in this process (51, 155). IFN-I enhance oxidative phosphorylation (OXPHOS) and fatty acid oxidation in immune cells, leading to mitochondrial mtROS accumulation. This phenomenon is strongly implicated in lipid peroxidation, forming 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA)-modified proteins among others. Such alterations are notably responsible for generating oxHDL, oxLDL, oxidized nuclear products and oxPL.

IFN-I also disrupt mitophagy mechanisms, leading to accumulation of dysfunctional mitochondria and cytoplasmic release of mtDNA and mitochondrial DAMPs, which amplifies inflammation, notably through cGAS-STING, TLR and NLRP3 inflammasome pathways (51). The NLRP3 inflammasome is the most extensively studied pathway linking mitochondria and inflammation, particularly in atherosclerosis (152).

In atherosclerosis, oxidative stress from excessive local mtROS, oxLDL, and aging leads to mitochondrial damage, triggering the release of mtROS, cardiolipin, and mtDNA. These components activate the NLRP3 inflammasome, fueling chronic inflammation and elevating IL-1β and IL-18 levels, which further impair mitochondrial function by promoting calcium influx (229). Mitochondria also play an important role in endothelial homeostasis, notably in NO production. The vicious cycle of mitochondrial dysfunction and ROS accumulation disrupts NO production and promotes ED and EC activation, ultimately accelerating atherosclerosis progression (229).

On another level, defective mitophagy has been observed in CD4+ and CD8+ T cells, monocytes, and DCs of SLE patients, further promoting atherogenic pathways (231). Indeed, as a result, excess mtROS and cytoplasmic mtDNA engage the MAVS pathway, which leads to even more IFN-I production (51). In monocytes, this IFN-α-induced mitochondrial dysfunction results in differentiation into pro-inflammatory DCs, which perpetuate the cycle of immune activation in SLE (232). In CD4+ T cells, mitochondrial dysfunction can activate the mammalian target of rapamycin (mTOR) pathway, which can skew their differentiation towards pro-inflammatory phenotypes (233). Restoring normal T cell metabolism has been suggested to potentially alter both SLE and atherosclerosis progression (231).

Finally, recent findings have suggested an intriguing role of intracellular complement (referred to as the complosome) in modulating metabolic processes including mitochondrial activity and autophagy in human immune cells (234). For instance, activation of intracellular C5aR1 on mitochondrial membranes in mouse models was shown to increase ROS production, glycolysis, and IL-1β secretion in macrophages (235). This process was promoted by cholesterol crystals and was shown to be a key player in atherosclerosis progression (235), alongside impaired intracellular C3-mediated efferocytosis (181). It is worth highlighting that various other pathological alterations of the complosome have been linked to autoimmunity and described in SLE, scleroderma as well as rheumatoid arthritis (185, 234). The complosome emerges as yet another potential bridge between autoimmunity, mitochondrial dysfunction and inflammation, although its specific contribution to accelerated atherosclerosis in SLE remains unexplored.

Immune senescence

Immunosenescence refers to the functional decline of the immune system with age, encompassing loss of self-tolerance, cell exhaustion, relative resistance to apoptosis, and chronic low-grade inflammation. This phenomenon is characteristic of aging individuals and is implicated in the emergence of various age-

related diseases, including cancer, increased infection susceptibility, autoimmune disorders, decreased vaccination response as well as promotion of atherosclerosis (236, 237). Cellular senescence refers to an irreversible cell cycle arrest and occurs as cells are exposed to non-fatal insults.

Both immune and non-immune senescent cells contribute to inflammaging, a chronic inflammatory state mediated by the senescence-associated secretory phenotype (SASP), characterized notably by secretion of IL-6, IL-1β, IL-8, TNF-α and metalloproteinases (238). Inflammaging is believed to play a significant role in atherosclerosis. Senescent cells are found in early atherosclerotic plaques and are likely strong contributors in initiating the disease and participating in plaque expansion and instability (238). Immunosenescence appears significantly accelerated in patients with SLE (236). Key mechanisms include mitochondrial dysfunction leading to oxidative stress, but also telomere shortening, DNA damage and genomic instability, epigenetic alterations, and chronic antigenic stimulation.

T cell senescence is notably associated with higher disease activity, kidney involvement, increased carotid intima-media thickness and decreased FMD (199–201). Senescent T cells are broadly identified by increased expression of CD57 and KLRG1, downregulation of CD27 and CD28, upregulation of p53, and the secretion SASP (237). They are terminally differentiated lymphocytes that can no longer proliferate but remain highly cytotoxic. Their identification in other autoimmune diseases such as rheumatoid arthritis, Grave's disease and ankylosing spondylitis reinforces their possible pathogenic role, all the more so given their association with severe clinical manifestations and poor treatment response (239). In relation to atherosclerosis, these T cells have been shown to secrete high levels of IFN-γ in addition to SASP, a major cytokine in driving macrophage M1 phenotype and promoting plaque instability (240).

As an example, angiogenic T cells (Tang, CD3 + CD31 + CXCR4+) are critical for endothelial repair and EPC levels, possibly through pro-angiogenic mediators such as IL-8 and MMP-9, although their activity is disrupted in SLE (241). Indeed, SLE patients exhibit an expanded senescent CD28null Tang phenotype. Unlike their CD28 + counterparts, CD28null Tang cells express cytotoxic markers (perforin, granzyme B) and pro-inflammatory cytokines (IFN-γ) impairing endothelial repair and contributing to vascular damage and atherosclerosis (242). These Tang cells correlate with reduced EPC activity, anti-dsDNA and anti-Ro antibody positivity, and LDL cholesterol levels (241, 242). In young SLE patients without prior CVE or significant conventional risk factors, dysfunction of Tang cells was shown to be an early, SLE-specific, event in the disease course toward CVD (241).

Conclusion

Endothelial dysfunction is the earliest identifiable event triggering atherogenesis in SLE, as a result of endothelial cell injury and activation as well as defective repair. This leads to immune cell recruitment into the subintima, mainly comprising of low-density granulocytes, macrophages, dendritic cells and T cells that promote inflammation and foam cell formation via the uptake of oxLDL. B cells contribute substantially to atherosclerosis via antibodies against various epitopes and immune complexes formation that further enhance the local inflammatory response. Several soluble mediators, mainly IFN type I and IL-1β, amplify this process via mechanisms involving complement and NLRP3 activation. The inflammatory microenvironment in SLE affects multiple lipoproteins that, in turn, induce the activation of the autoimmune response as well as autoinflammatory mechanisms. Mitochondrial dysfunction and oxidative stress are emerging factors further underlining the complexity of accelerated atherosclerosis in SLE and the need for deeper understanding and improved management of the CV risk in these patients.

Author contributions

PB: Writing – original draft, Writing – review & editing. KT: Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. The authors acknowledge the use of ChatGPT (OpenAI, GPT-4) in some drafting stages of the manuscript to assist with translation from French to English and to help refine English phrasing. No content generation or editing was performed by Generative AI.

Publisher's note

References

1. Urowitz MB. The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med*. (1976) 60(2):221–5. doi: 10.1016/0002-9343(76)90431-9

2. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. *Semin Arthritis Rheum*. (2013) 43(1):77–95. doi: 10.1016/j.semarthrit.2012.12.002

3. Tektonidou MG, Kravvariti E, Konstantonis G, Tentolouris N, Sfikakis PP, Protogerou A. Subclinical atherosclerosis in systemic lupus erythematosus: comparable risk with diabetes mellitus and rheumatoid arthritis. *Autoimmun Rev*. (2017) 16(3):308–12. doi: 10.1016/j.autrev.2017.01.009

4. Tselios K, Gladman DD, Sheane BJ, Su J, Urowitz M. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971–2013). *Ann Rheum Dis*. (2019) 78(6):802–6. doi: 10.1136/annrheumdis-2018-214802

5. Urowitz MB, Su J, Gladman DD. Atherosclerotic vascular events in systemic lupus erythematosus: an evolving story. *J Rheumatol*. (2020) 47(1):66–71. doi: 10.3899/jrheum.180986

6. Papazoglou N, Kravvariti E, Konstantonis G, Sfikakis PP, Tektonidou MG. The impact of traditional cardiovascular risk factor control on 7-year follow-up atherosclerosis progression in systemic lupus erythematosus. *Rheumatology*. (2024) 63(1):50–7. doi: 10.1093/rheumatology/kead184

7. Mak A, Chan JKY. Endothelial function and endothelial progenitor cells in systemic lupus erythematosus. *Nat Rev Rheumatol*. (2022) 18(5):286–300. doi: 10.1038/s41584-022-00770-y

8. Bergkamp SC, Wahadat MJ, Salah A, Kuijpers TW, Smith V, Tas SW, et al. Dysregulated endothelial cell markers in systemic lupus erythematosus: a systematic review and meta-analysis. *J Inflamm*. (2023) 20(1):18. doi: 10.1186/s12950-023-00342-1

9. Mendoza-Pinto C, Rojas-Villarraga A, Molano-González N, García-Carrasco M, Munguía-Realpozo P, Etchegaray-Morales I, et al. Endothelial dysfunction and arterial stiffness in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Atherosclerosis*. (2020) 297:55–63. doi: 10.1016/j.atherosclerosis.2020.01.028

10. Biswas T, Tarenia S, Bera S, Naiya S, Acharya S, Shukla S, et al. Subclinical atherosclerosis and endothelial dysfunction in cases of systemic lupus erythematosus: a hospital-based case-control study. *Cureus*. (2024) 16(8):e67473. doi: 10.7759/cureus.67473

11. El-Magadmi M, Bodill H, Ahmad Y, Durrington PN, Mackness M, Walker M, et al. Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. *Circulation*. (2004) 110(4):399–404. doi: 10.1161/01.CIR.0000136807.78534.50

12. Ambler WG, Kaplan MJ. Vascular damage in systemic lupus erythematosus. *Nat Rev Nephrol*. (2024) 20(4):251–65. doi: 10.1038/s41581-023-00797-8

13. Matsuzawa Y, Kwon T, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc*. (2015) 4(11):e002270. doi: 10.1161/JAHA.115.002270

14. Guzmán-Martínez G, Marañón C, CYTED RIBLES Network. Immune mechanisms associated with cardiovascular disease in systemic lupus erythematosus: a path to potential biomarkers. *Front Immunol*. (2022) 13:974826. doi: 10.3389/fimmu.2022.974826

15. Rajagopalan S, Somers EC, Brook RD, Kehrer C, Pfenninger D, Lewis E, et al. Endothelial cell apoptosis in systemic lupus erythematosus: a common pathway for abnormal vascular function and thrombosis propensity. *Blood*. (2004) 103(10):3677–83. doi: 10.1182/blood-2003-09-3198

16. Elshal M, Abdelaziz A, Abbas A, Mahmoud K, Fathy H, Mongy SE, et al. Quantification of circulating endothelial cells in peripheral blood of systemic lupus erythematosus patients: a simple and reproducible method of assessing endothelial injury and repair. *Nephrol Dial Transplant*. (2009) 24(5):1495–9. doi: 10.1093/ndt/gfn650

17. Rafael-Vidal C, Martínez-Ramos S, Malvar-Fernández B, Altabás-González I, Mouriño C, Pazos-López P, et al. Novel endothelial progenitor cells populations as biomarkers of damage and remission in systemic lupus erythematosus. *Arthritis Res Ther*. (2024) 26(1):170. doi: 10.1186/s13075-024-03397-4

18. Ding X, Xiang W, He X. IFN-I Mediates dysfunction of endothelial progenitor cells in atherosclerosis of systemic lupus erythematosus. *Front Immunol*. (2020) 11:581385. doi: 10.3389/fimmu.2020.581385

19. Spinelli FR, Barbati C, Cecarelli F, Morello F, Colasanti T, Vomero M, et al. B lymphocyte stimulator modulates number and function of endothelial progenitor cells in systemic lupus erythematosus. *Arthritis Res Ther*. (2019) 21(1):245. doi: 10.1186/s13075-019-2015-7

20. Tydén H, Lood C, Gullstrand B, Nielsen CT, Heegaard NHH, Kahn R, et al. Endothelial dysfunction is associated with activation of the type I interferon system and platelets in patients with systemic lupus erythematosus. *RMD Open*. (2017) 3(2):e000508. doi: 10.1136/rmdopen-2017-000508

21. Somers EC, Zhao W, Lewis EE, Wang L, Wing JJ, Sundaram B, et al. Type I interferons are associated with subclinical markers of cardiovascular disease in a cohort of systemic lupus erythematosus patients. *PLoS One*. (2012) 7(5):e37000. doi: 10.1371/journal.pone.0037000

22. Denny MF, Thacker S, Mehta H, Somers EC, Dodick T, Barrat FJ, et al. Interferon-α promotes abnormal vasculogenesis in lupus: a potential pathway for premature atherosclerosis. *Blood*. (2007) 110(8):2907–15. doi: 10.1182/blood-2007-05-089086

23. Thacker SG, Berthier CC, Mattinzoli D, Rastaldi MP, Kretzler M, Kaplan MJ. The detrimental effects of IFN-α on vasculogenesis in lupus are mediated by repression of IL-1 pathways: potential role in atherogenesis and renal vascular rarefaction. *J Immunol*. (2010) 185(7):4457–69. doi: 10.4049/jimmunol.1001782

24. Zhu Q, Kanneganti TD. Cutting edge: distinct regulatory mechanisms control proinflammatory cytokines IL-18 and IL-1β. *J Immunol*. (2017) 198(11):4210–5. doi: 10.4049/jimmunol.1700352

25. Kahlenberg JM, Thacker SG, Berthier CC, Cohen CD, Kretzler M, Kaplan MJ. Inflammasome activation of IL-18 results in endothelial progenitor cell dysfunction in systemic lupus erythematosus. *J Immunol*. (2011) 187(11):6143–56. doi: 10.4049/jimmunol.1101284

26. Buie JJ, Renaud LL, Muise-Helmericks R, Oates JC. IFN-α Negatively regulates the expression of endothelial nitric oxide synthase and nitric oxide production: implications for systemic lupus erythematosus. *J Immunol*. (2017) 199(6):1979–88. doi: 10.4049/jimmunol.1600108

27. Hacbarth E, Kajdacsy-Balla A. Low density neutrophils in patients with systemic lupus erythematosus, rheumatoid arthritis, and acute rheumatic fever. *Arthritis Rheum*. (1986) 29(11):1334–42. doi: 10.1002/art.1780291105

28. Mistry P, Nakabo S, O'Neil L, Goel RR, Jiang K, Carmona-Rivera C, et al. Transcriptomic, epigenetic, and functional analyses implicate neutrophil diversity in the pathogenesis of systemic lupus erythematosus. *Proc Natl Acad Sci*. (2019) 116(50):25222–8. doi: 10.1073/pnas.1908576116

29. Carmona-Rivera C, Zhao W, Yalavarthi S, Kaplan MJ. Neutrophil extracellular traps induce endothelial dysfunction in systemic lupus erythematosus through the activation of matrix metalloproteinase-2. *Ann Rheum Dis*. (2015) 74(7):1417–24. doi: 10.1136/annrheumdis-2013-204837

30. López P, Rodríguez-Carrio J, Martínez-Zapico A, Pérez-Álvarez ÁI, Suárez-Díaz S, Mozo L, et al. Low-density granulocytes and monocytes as biomarkers of cardiovascular risk in systemic lupus erythematosus. *Rheumatology*. (2020) 59(7):1752–64. doi: 10.1093/rheumatology/keaa016

31. Carlucci PM, Purmalek MM, Dey AK, Temesgen-Oyelakin Y, Sakhardande S, Joshi AA, et al. Neutrophil subsets and their gene signature associate with vascular inflammation and coronary atherosclerosis in lupus. *JCI Insight*. (2018) 3(8):e99276. doi: 10.1172/jci.insight.99276

32. Smith CK, Kaplan MJ. The role of neutrophils in the pathogenesis of systemic lupus erythematosus. *Curr Opin Rheumatol*. (2015) 27(5):448–53. doi: 10.1097/BOR.0000000000000197

33. Villanueva E, Yalavarthi S, Berthier CC, Hodgin JB, Khandpur R, Lin AM, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. *J Immunol*. (2011) 187(1):538–52. doi: 10.4049/jimmunol.1100450

34. Denny MF, Yalavarthi S, Zhao W, Thacker SG, Anderson M, Sandy AR, et al. A distinct subset of proinflammatory neutrophils isolated from patients with systemic lupus erythematosus induces vascular damage and synthesizes type I IFNs. *J Immunol*. (2010) 184(6):3284–97. doi: 10.4049/jimmunol.0902199

35. Martin KR, Day JA, Hansen JA, D'Silva DB, Wong HL, Garnham A, et al. CD98 Defines a metabolically flexible, proinflammatory subset of low-density neutrophils in systemic lupus erythematosus. *Clin Transl Med*. (2023) 13(1):e1150. doi: 10.1002/ctm2.1150

36. Rahman S, Sagar D, Hanna RN, Lightfoot YL, Mistry P, Smith CK, et al. Low-density granulocytes activate T cells and demonstrate a non-suppressive role in systemic lupus erythematosus. *Ann Rheum Dis*. (2019) 78(7):957–66. doi: 10.1136/annrheumdis-2018-214620

37. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. *Circ Res*. (2017) 120(4):736–43. doi: 10.1161/CIRCRESAHA.116.309692

38. Wang Y, Wang C, Li J. Neutrophil extracellular traps: a catalyst for atherosclerosis. *Mol Cell Biochem*. (2024) 479(12):3213–27. doi: 10.1007/s11010-024-04931-3

39. O'Neil LJ, Kaplan MJ, Carmona-Rivera C. The role of neutrophils and neutrophil extracellular traps in vascular damage in systemic lupus erythematosus. *J Clin Med*. (2019) 8(9):1325. doi: 10.3390/jcm8091325

40. Pérez-Cremades D, Bueno-Betí C, García-Giménez JL, Ibañez-Cabellos JS, Hermenegildo C, Pallardó FV, et al. Extracellular histones disarrange vasoactive

mediators release through a COX - NOS interaction in human endothelial cells. *J Cell Mol Med*. (2017) 21(8):1584–92. doi: 10.1111/jcmm.13088

41. Silvestre-Roig C, Braster Q, Wichapong K, Lee EY, Teulon JM, Berrebeh N, et al. Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death. *Nature*. (2019) 569(7755):236–40. doi: 10.1038/s41586-019-1167-6

42. Knight JS, Kanthi Y. Mechanisms of immunothrombosis and vasculopathy in antiphospholipid syndrome. *Semin Immunopathol*. (2022) 44(3):347–62. doi: 10.1007/s00281-022-00916-w

43. Karasawa T, Takahashi M. Inflammasome activation and neutrophil extracellular traps in atherosclerosis. *J Atheroscler Thromb*. (2025) 32(5):535–49. doi: 10.5551/jat.RV22033

44. Van Der Linden M, Van Den Hoogen LL, Westerlaken GHA, Fritsch-Stork RDE, Van Roon JAG, Radstake TRDJ, et al. Neutrophil extracellular trap release is associated with antinuclear antibodies in systemic lupus erythematosus and anti-phospholipid syndrome. *Rheumatology*. (2018) 57(7):1228–34. doi: 10.1093/rheumatology/key067

45. Van Den Hoogen LL, Fritsch-Stork RDE, Van Roon JAG, Radstake TRDJ. Low-density granulocytes are increased in antiphospholipid syndrome and are associated with anti-β_2 -glycoprotein I antibodies: comment on the article by yalavarthi et al. *Arthritis Rheumatol*. (2016) 68(5):1320–1. doi: 10.1002/art.39576

46. Lood C, Blanco LP, Purmalek MM, Carmona-Rivera C, De Ravin SS, Smith CK, et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat Med*. (2016) 22(2):146–53. doi: 10.1038/nm.4027

47. Garcia-Romo GS, Caielli S, Vega B, Connolly J, Allantaz F, Xu Z, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med*. (2011) 3(73):73ra20. doi: 10.1126/scitranslmed.3001201

48. Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap–associated protein activation of the NLRP3 inflammasome is enhanced in lupus macrophages. *J Immunol*. (2013) 190(3):1217–26. doi: 10.4049/jimmunol.1202388

49. Smith CK, Vivekanandan-Giri A, Tang C, Knight JS, Mathew A, Padilla RL, et al. Neutrophil extracellular trap–derived enzymes oxidize high-density lipoprotein: an additional proatherogenic mechanism in systemic lupus erythematosus. *Arthritis Rheumatol*. (2014) 66(9):2532–44. doi: 10.1002/art.38703

50. Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc Natl Acad Sci*. (2010) 107(21):9813–8. doi: 10.1073/pnas.0909927107

51. Caielli S, Wan Z, Pascual V. Systemic lupus erythematosus pathogenesis: interferon and beyond. *Annu Rev Immunol*. (2023) 41(1):533–60. doi: 10.1146/annurev-immunol-101921-042422

52. Van Avondt K, Maegdefessel L, Soehnlein O. Therapeutic targeting of neutrophil extracellular traps in atherogenic inflammation. *Thromb Haemost*. (2019) 119(04):542–52. doi: 10.1055/s-0039-1678664

53. Li P, Jiang M, Li K, Li H, Zhou Y, Xiao X, et al. Glutathione peroxidase 4–regulated neutrophil ferroptosis induces systemic autoimmunity. *Nat Immunol*. (2021) 22(9):1107–17. doi: 10.1038/s41590-021-00993-3

54. Xu X, Xu XD, Ma MQ, Liang Y, Cai YB, Zhu ZX, et al. The mechanisms of ferroptosis and its role in atherosclerosis. *Biomed Pharmacother*. (2024) 171:116112. doi: 10.1016/j.biopha.2023.116112

55. Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis. *Nat Rev Cardiol*. (2020) 17(7):387–401. doi: 10.1038/s41569-020-0352-5

56. Wu X, Zhang H. Omics approaches unveiling the biology of human atherosclerotic plaques. *Am J Pathol*. (2024) 194(4):482–98. doi: 10.1016/j.ajpath.2023.12.007

57. Fernandez DM, Rahman AH, Fernandez NF, Chudnovskiy A, Amir EaD, Amadori L, et al. Single-cell immune landscape of human atherosclerotic plaques. *Nat Med*. (2019) 25(10):1576–88. doi: 10.1038/s41591-019-0590-4

58. Depuydt MAC, Prange KHM, Slenders L, Örd T, Elbersen D, Boltjes A, et al. Microanatomy of the human atherosclerotic plaque by single-cell transcriptomics. *Circ Res*. (2020) 127(11):1437–55. doi: 10.1161/CIRCRESAHA.120.316770

59. Bashore AC, Yan H, Xue C, Zhu LY, Kim E, Mawson T, et al. High-Dimensional single-cell multimodal landscape of human carotid atherosclerosis. *Arterioscler Thromb Vasc Biol*. (2024) 44(4):930–45. doi: 10.1161/ATVBAHA.123.320524

60. Chowdhury RR, D'Addabbo J, Huang X, Veizades S, Sasagawa K, Louis DM, et al. Human coronary plaque T cells are clonal and cross-react to virus and self. *Circ Res*. (2022) 130(10):1510–30. doi: 10.1161/CIRCRESAHA.121.320090

61. Depuydt MAC, Schaftenaar FH, Prange KHM, Boltjes A, Hemme E, Delfos L, et al. Single-cell T cell receptor sequencing of paired human atherosclerotic plaques and blood reveals autoimmune-like features of expanded effector T cells. *Nat Cardiovasc Res*. (2023) 2(2):112–25. doi: 10.1038/s44161-022-00208-4

62. Frostegård J, Ulfgren AK, Nyberg P, Hedin U, Swedenborg J, Andersson U, et al. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. *Atherosclerosis*. (1999) 145(1):33–43. doi: 10.1016/S0021-9150(99)00011-8

63. Clement M, Charles N, Escoubet B, Guedj K, Chauveheid MP, Caligiuri G, et al. CD4 + CXCR3+ T cells and plasmacytoid dendritic cells drive accelerated atherosclerosis associated with systemic lupus erythematosus. *J Autoimmun*. (2015) 63:59–67. doi: 10.1016/j.jaut.2015.07.001

64. Eid RE, Rao DA, Zhou J, Lo SfL, Ranjbaran H, Gallo A, et al. Interleukin-17 and interferon-γ are produced concomitantly by human coronary artery–infiltrating T cells and act synergistically on vascular smooth muscle cells. *Circulation*. (2009) 119(10):1424–32. doi: 10.1161/CIRCULATIONAHA.108.827618

65. Chen XQ, Yu YC, Deng HH, Sun JZ, Dai Z, Wu YW, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. *J Clin Immunol*. (2010) 30(2):221–5. doi: 10.1007/s10875-009-9365-x

66. Xing Q, Wang B, Su H, Cui J, Li J. Elevated Th17 cells are accompanied by FoxP3+ Treg cells decrease in patients with lupus nephritis. *Rheumatol Int*. (2012) 32(4):949–58. doi: 10.1007/s00296-010-1771-0

67. Mengya Z, Hanyou M, Dong L, Xiaohong L, Lihua Z. Th17/Treg imbalance induced by increased incidence of atherosclerosis in patients with systemic lupus erythematosus (SLE). *Clin Rheumatol*. (2013) 32(7):1045–52. doi: 10.1007/s10067-013-2237-z

68. Wilhelm AJ, Rhoads JP, Wade NS, Major AS. Dysregulated CD4+ T cells from SLE-susceptible mice are sufficient to accelerate atherosclerosis in LDLr−/− mice. *Ann Rheum Dis*. (2015) 74(4):778–85. doi: 10.1136/annrheumdis-2013-203759

69. Chowdary Venigalla RK, Tretter T, Krienke S, Max R, Eckstein V, Blank N, et al. Reduced CD4+,CD25− T cell sensitivity to the suppressive function of CD4+, $CD25^{high}$, $CD127^{-/low}$ regulatory T cells in patients with active systemic lupus erythematosus. *Arthritis Rheum*. (2008) 58(7):2120–30. doi: 10.1002/art.23556

70. Khan A, Roy P, Ley K. Breaking tolerance: the autoimmune aspect of atherosclerosis. *Nat Rev Immunol*. (2024) 24(9):670–9. doi: 10.1038/s41577-024-01010-y

71. Simpson N, Gatenby PA, Wilson A, Malik S, Fulcher DA, Tangye SG, et al. Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum*. (2010) 62(1):234–44. doi: 10.1002/art.25032

72. Li W, Elshikha AS, Cornaby C, Teng X, Abboud G, Brown J, et al. T cells expressing the lupus susceptibility allele Pbx1d enhance autoimmunity and atherosclerosis in dyslipidemic mice. *JCI Insight*. (2020) 5(11):e138274. doi: 10.1172/jci.insight.138274

73. Ryu H, Lim H, Choi G, Park YJ, Cho M, Na H, et al. Atherogenic dyslipidemia promotes autoimmune follicular helper T cell responses via IL-27. *Nat Immunol*. (2018) 19(6):583–93. doi: 10.1038/s41590-018-0102-6

74. Del Carmen Crespo Oliva C, Labrie M, Allard-Chamard H. T peripheral helper (Tph) cells, a marker of immune activation in cancer and autoimmune disorders. *Clin Immunol*. (2024) 266:110325. doi: 10.1016/j.clim.2024.110325

75. Law C, Wacleche VS, Cao Y, Pillai A, Sowerby J, Hancock B, et al. Interferon subverts an AHR–JUN axis to promote CXCL13+ T cells in lupus. *Nature*. (2024) 631(8022):857–66. doi: 10.1038/s41586-024-07627-2

76. Wang M, Rajkumar S, Lai Y, Liu X, He J, Ishikawa T, et al. Tertiary lymphoid structures as local perpetuators of organ-specific immune injury: implication for lupus nephritis. *Front Immunol*. (2023) 14:1204777. doi: 10.3389/fimmu.2023.1204777

77. Sato Y, Oguchi A, Fukushima Y, Masuda K, Toriu N, Taniguchi K, et al. CD153/CD30 Signaling promotes age-dependent tertiary lymphoid tissue expansion and kidney injury. *J Clin Invest*. (2022) 132(2):e146071. doi: 10.1172/JCI146071

78. Yin C, Mohanta SK, Srikakulapu P, Weber C, Habenicht AJR. Artery tertiary lymphoid organs: powerhouses of atherosclerosis immunity. *Front Immunol*. (2016) 7:387. doi: 10.3389/fimmu.2016.00387

79. Pi H, Wang G, Wang Y, Zhang M, He Q, Zheng X, et al. Immunological perspectives on atherosclerotic plaque formation and progression. *Front Immunol*. (2024) 15:1437821. doi: 10.3389/fimmu.2024.1437821

80. Bergström I, Backteman K, Lundberg A, Ernerudh J, Jonasson L. Persistent accumulation of interferon-γ-producing CD8+ CD56+ T cells in blood from patients with coronary artery disease. *Atherosclerosis*. (2012) 224(2):515–20. doi: 10.1016/j.atherosclerosis.2012.07.033

81. Snijckers RPM, Foks AC. Adaptive immunity and atherosclerosis: aging at its crossroads. *Front Immunol*. (2024) 15:1350471. doi: 10.3389/fimmu.2024.1350471

82. Ciurtin C, Pineda-Torra I, Jury EC, Robinson GA. CD8+ T-Cells in juvenile-onset SLE: from pathogenesis to comorbidities. *Front Med*. (2022) 9:904435. doi: 10.3389/fmed.2022.904435

83. Radziszewska A, Moulder Z, Jury EC, Ciurtin C. CD8+ T cell phenotype and function in childhood and adult-onset connective tissue disease. *Int J Mol Sci*. (2022) 23(19):11431. doi: 10.3390/ijms231911431

84. Radziszewska A, Peckham H, Restuadi R, Kartawinata M, Moulding D, De Gruijter NM, et al. Type I interferon and mitochondrial dysfunction are associated with dysregulated cytotoxic CD8+ T cell responses in juvenile systemic lupus erythematosus. *Clin Exp Immunol*. (2025) 219(1):uxae127. doi: 10.1093/cei/uxae127

85. Arazi A, Rao DA, Berthier CC, Davidson A, Liu Y, Hoover PJ, et al. The immune cell landscape in kidneys of patients with lupus nephritis. *Nat Immunol*. (2019) 20(7):902–14. doi: 10.1038/s41590-019-0398-x

86. Tsai YG, Liao PF, Hsiao KH, Wu HM, Lin CY, Yang KD. Pathogenesis and novel therapeutics of regulatory T cell subsets and interleukin-2 therapy in systemic lupus erythematosus. *Front Immunol*. (2023) 14:1230264. doi: 10.3389/fimmu.2023.1230264

87. Zhu Y, Huang Y, Ming B, Wu X, Chen Y, Dong L. Regulatory T-cell levels in systemic lupus erythematosus patients: a meta-analysis. *Lupus*. (2019) 28(4):445–54. doi: 10.1177/0961203319828530

88. Li W, Deng C, Yang H, Wang G. The regulatory T cell in active systemic lupus erythematosus patients: a systemic review and meta-analysis. *Front Immunol*. (2019) 10:159. doi: 10.3389/fimmu.2019.00159

89. Yang J, Yang X, Zou H, Li M. Oxidative stress and Treg and Th17 dysfunction in systemic lupus erythematosus. *Oxid Med Cell Longev*. (2016) 2016(1):2526174. doi: 10.1155/2016/2526174

90. Ballesteros-Tato A, Papillion A. Mechanisms of action of low-dose IL-2 restoration therapies in SLE. *Curr Opin Immunol*. (2019) 61:39–45. doi: 10.1016/j.coi.2019.07.003

91. Gaddis DE, Padgett LE, Wu R, McSkimming C, Romines V, Taylor AM, et al. Apolipoprotein AI prevents regulatory to follicular helper T cell switching during atherosclerosis. *Nat Commun*. (2018) 9(1):1095. doi: 10.1038/s41467-018-03493-5

92. Black LL, Srivastava R, Schoeb TR, Moore RD, Barnes S, Kabarowski JH. Cholesterol-Independent suppression of lymphocyte activation, autoimmunity, and glomerulonephritis by apolipoprotein A-I in normocholesterolemic lupus-prone mice. *J Immunol*. (2015) 195(10):4685–98. doi: 10.4049/jimmunol.1500806

93. Gkougkourelas L, Boura P, Sarantopoulos A, Tselios K. T regulatory cells: a promising new target in atherosclerosis. *Crit Rev Immunol*. (2014) 34(5):389–97. doi: 10.1615/CritRevImmunol.2014010802

94. Ouyang X, Liu Z. Regulatory T cells and macrophages in atherosclerosis: from mechanisms to clinical significance. *Front Immunol*. (2024) 15:1435021. doi: 10.3389/fimmu.2024.1435021

95. Vlaicu R, Rus HG, Niculescu F, Cristea A. Immunoglobulins and complement components in human aortic atherosclerotic intima. *Atherosclerosis*. (1985) 55(1):35–50. doi: 10.1016/0021-9150(85)90164-9

96. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arterioscler Off J Am Heart Assoc Inc*. (1986) 6(2):131–8. doi: 10.1161/01.atv.6.2.131

97. Hamze M, Desmetz C, Berthe ML, Roger P, Boulle N, Brancherau P, et al. Characterization of resident B cells of vascular walls in human atherosclerotic patients. *J Immunol*. (2013) 191(6):3006–16. doi: 10.4049/jimmunol.1202870

98. Porsch F, Mallat Z, Binder CJ. Humoral immunity in atherosclerosis and myocardial infarction: from B cells to antibodies. *Cardiovasc Res*. (2021) 117(13):2544–62. doi: 10.1093/cvr/cvab285

99. Pattarabanjird T, Li C, McNamara C. B cells in atherosclerosis: mechanisms and potential clinical applications. *JACC Basic Transl Sci*. (2021) 6(6):546–63. doi: 10.1016/j.jacbts.2021.01.006

100. Caligiuri G, Nicoletti A, Poirier B, Hansson GK. Protective immunity against atherosclerosis carried by B cells of hypercholesterolemic mice. *J Clin Invest*. (2002) 109(6):745–53. doi: 10.1172/JCI7272

101. Major AS, Fazio S, Linton MF. B-Lymphocyte deficiency increases atherosclerosis in LDL receptor–null mice. *Arterioscler Thromb Vasc Biol*. (2002) 22(11):1892–8. doi: 10.1161/01.ATV.0000039169.47943.EE

102. Kyaw T, Tay C, Khan A, Dumouchel V, Cao A, To K, et al. Conventional B2 B cell depletion ameliorates whereas its adoptive transfer aggravates atherosclerosis. *J Immunol*. (2010) 185(7):4410–9. doi: 10.4049/jimmunol.1000033

103. Kyaw T, Tay C, Hosseini H, Kanellakis P, Gadowski T, MacKay F, et al. Depletion of B2 but not B1a B cells in BAFF receptor-deficient ApoE−/− mice attenuates atherosclerosis by potently ameliorating arterial inflammation. Schmidt HHHW, editor. *PLoS One*. (2012) 7(1):e29371. doi: 10.1371/journal.pone.0029371

104. Kyaw T, Cui P, Tay C, Kanellakis P, Hosseini H, Liu E, et al. BAFF Receptor mAb treatment ameliorates development and progression of atherosclerosis in hyperlipidemic ApoE−/− mice. *PLoS One*. (2013) 8(4):e60430. doi: 10.1371/journal.pone.0060430

105. Ait-Oufella H, Herbin O, Bouaziz JD, Binder CJ, Uyttenhove C, Laurans L, et al. B cell depletion reduces the development of atherosclerosis in mice. *J Exp Med*. (2010) 207(8):1579–87. doi: 10.1084/jem.20100155

106. Kyaw T, Tay C, Krishnamurthi S, Kanellakis P, Agrotis A, Tipping P, et al. B1a B lymphocytes are atheroprotective by secreting natural IgM that increases IgM deposits and reduces necrotic cores in atherosclerotic lesions. *Circ Res*. (2011) 109(8):830–40. doi: 10.1161/CIRCRESAHA.111.248542

107. Ransegnola BP, Pattarabanjird T, McNamara CA. Tipping the scale: atheroprotective IgM-producing B cells in atherosclerosis. *Arterioscler Thromb Vasc Biol*. (2024) 44(9):1906–15. doi: 10.1161/ATVBAHA.124.319847

108. Griffin DO, Holodick NE, Rothstein TL. Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20 + CD27 + CD43 + CD70−. *J Exp Med*. (2011) 208(1):67–80. doi: 10.1084/jem.20101499

109. Ehrenstein MR, Notley CA. The importance of natural IgM: scavenger, protector and regulator. *Nat Rev Immunol*. (2010) 10(11):778–86. doi: 10.1038/nri2849

110. Anania C, Gustafsson T, Hua X, Su J, Vikström M, De Faire U, et al. Increased prevalence of vulnerable atherosclerotic plaques and low levels of natural IgM antibodies against phosphorylcholine in patients with systemic lupus erythematosus. *Arthritis Res Ther*. (2010) 12(6):R214. doi: 10.1186/ar3193

111. Ma K, Du W, Wang X, Yuan S, Cai X, Liu D, et al. Multiple functions of B cells in the pathogenesis of systemic lupus erythematosus. *Int J Mol Sci*. (2019) 20(23):6021. doi: 10.3390/ijms20236021

112. She Z, Li C, Wu F, Mao J, Xie M, Hun M, et al. The role of B1 cells in systemic lupus erythematosus. *Front Immunol*. (2022) 13:814857. doi: 10.3389/fimmu.2022.814857

113. Enghard P, Humrich JY, Chu VT, Grussie E, Hiepe F, Burmester G, et al. Class switching and consecutive loss of dsDNA-reactive B1a B cells from the peritoneal cavity during murine lupus development. *Eur J Immunol*. (2010) 40(6):1809–18. doi: 10.1002/eji.200940050

114. Zhou Z, Niu H, Zheng YY, Morel L. Autoreactive marginal zone B cells enter the follicles and interact with CD4+ T cells in lupus-prone mice. *BMC Immunol*. (2011) 12(1):7. doi: 10.1186/1471-2172-12-7

115. Rodríguez-Bayona B, Ramos-Amaya A, Pérez-Venegas JJ, Rodríguez C, Brieva JA. Decreased frequency and activated phenotype of blood CD27 IgD IgM B lymphocytes is a permanent abnormality in systemic lupus erythematosus patients. *Arthritis Res Ther*. (2010) 12(3):R108. doi: 10.1186/ar3042

116. Griffin DO, Rothstein TL. A small CD11b+ human B1 cell subpopulation stimulates T cells and is expanded in lupus. *J Exp Med*. (2011) 208(13):2591–8. doi: 10.1084/jem.20110978

117. Srikakulapu P, Hu D, Yin C, Mohanta SK, Bontha SV, Peng L, et al. Artery tertiary lymphoid organs control multilayered territorialized atherosclerosis B-cell responses in aged *ApoE* $^{-/-}$ mice. *Arterioscler Thromb Vasc Biol*. (2016) 36(6):1174–85. doi: 10.1161/ATVBAHA.115.306983

118. Harrison J. Marginal zone B cells produce 'natural' atheroprotective IgM antibodies in a T cell–dependent manner. *Cardiovasc Res*. (2024) 120:318–28. doi: 10.1093/cvr/cvae027

119. Nus M, Sage AP, Lu Y, Masters L, Lam BYH, Newland S, et al. Marginal zone B cells control the response of follicular helper T cells to a high-cholesterol diet. *Nat Med*. (2017) 23(5):601–10. doi: 10.1038/nm.4315

120. Sanz I, Wei C, Jenks SA, Cashman KS, Tipton C, Woodruff MC, et al. Challenges and opportunities for consistent classification of human B cell and plasma cell populations. *Front Immunol*. (2019) 10:2458. doi: 10.3389/fimmu.2019.02458

121. Zhang W, Wang YF, Hu FL, Lu FA, Wu T, Feng YL, et al. Dysfunction of CD27 + IgD+ B cells correlates with aggravated systemic lupus erythematosus. *Clin Rheumatol*. (2022) 41(5):1551–9. doi: 10.1007/s10067-022-06051-z

122. Tipton CM, Fucile CF, Darce J, Chida A, Ichikawa T, Gregoretti I, et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus. *Nat Immunol*. (2015) 16(7):755–65. doi: 10.1038/ni.3175

123. Jenks SA, Cashman KS, Zumaquero E, Marigorta UM, Patel AV, Wang X, et al. Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. *Immunity*. (2018) 49(4):725–739.e6. doi: 10.1016/j.immuni.2018.08.015

124. Sachinidis A, Xanthopoulos K, Garyfallos A. Age-Associated B cells (ABCs) in the prognosis, diagnosis and therapy of systemic lupus erythematosus (SLE). *Mediterr J Rheumatol*. (2020) 31(3):311. doi: 10.31138/mjr.31.3.311

125. Mouat IC, Goldberg E, Horwitz MS. Age-associated B cells in autoimmune diseases. *Cell Mol Life Sci*. (2022) 79(8):402. doi: 10.1007/s00018-022-04433-9

126. Smit V, De Mol J, Schaftenaar FH, Depuydt MAC, Postel RJ, Smeets D, et al. Single-cell profiling reveals age-associated immunity in atherosclerosis. *Cardiovasc Res*. (2023) 119(15):2508–21. doi: 10.1093/cvr/cvad099

127. Pattarabanjird T, Srikakulapu P, Ransegnola B, Marshall MA, Ghosheh Y, Gulati R, et al. Single-cell profiling of CD11c+ B cells in atherosclerosis. *Front Immunol*. (2024) 14:1296668. doi: 10.3389/fimmu.2023.1296668

128. Song W, Sanchez GM, Mayer DP, Blackburn HN, Chernova I, Flavell RA, et al. Cutting edge: iL-21 and tissue-specific signals instruct tbet + CD11c+ B cell development following viral infection. *J Immunol*. (2023) 210(12):1861–5. doi: 10.4049/jimmunol.2300027

129. Möckel T, Basta F, Weinmann-Menke J, Schwarting A. B cell activating factor (BAFF): structure, functions, autoimmunity and clinical implications in systemic lupus erythematosus (SLE). *Autoimmun Rev*. (2021) 20(2):102736. doi: 10.1016/j.autrev.2020.102736

130. Theodorou E, Nezos A, Antypa E, Ioakeimidis D, Koutsilieris M, Tektonidou M, et al. B-cell activating factor and related genetic variants in lupus related atherosclerosis. *J Autoimmun*. (2018) 92:87–92. doi: 10.1016/j.jaut.2018.05.002

131. Shater H, Fawzy M, Farid A, El-Amir A, Fouad S, Madbouly N. B-cell activating factor and A proliferation-inducing ligand in relation to intima-media thickness as biomarkers of premature atherosclerosis in systemic lupus erythematosus patients. *Am J Med Sci*. (2022) 364(5):646–54. doi: 10.1016/j.amjms.2022.05.008

132. Landolt-Marticorena C, Wither R, Reich H, Herzenberg A, Scholey J, Gladman DD, et al. Increased expression of B cell activation factor supports the abnormal expansion of transitional B cells in systemic lupus erythematosus. *J Rheumatol*. (2011) 38(4):642–51. doi: 10.3899/jrheum.100214

133. Álvarez Gómez JA, Salazar-Camarena DC, Román-Fernández IV, Ortiz-Lazareno PC, Cruz A, Muñoz-Valle JF, et al. BAFF dystem expression in double negative 2, activated naïve and activated memory B cells in systemic lupus erythematosus. *Front Immunol*. (2023) 14:1235937. doi: 10.3389/fimmu.2023.1235937

134. Tsiantoulas D, Sage AP, Göderle L, Ozsvar-Kozma M, Murphy D, Porsch F, et al. B cell–activating factor neutralization aggravates atherosclerosis. *Circulation*. (2018) 138(20):2263–73. doi: 10.1161/CIRCULATIONAHA.117.032790

135. Jackson SW, Scharping NE, Jacobs HM, Wang S, Chait A, Rawlings DJ. Cutting edge: BAFF overexpression reduces atherosclerosis via TACI-dependent B cell activation. *J Immunol*. (2016) 197(12):4529–34. doi: 10.4049/jimmunol.1601198

136. Saidoune F, Even G, Lamri Y, Chezel J, Gaston A, Escoubet B, et al. Effects of BAFF neutralization on atherosclerosis associated with systemic lupus erythematosus. *Arthritis Rheumatol*. (2021) 73(2):255–64. doi: 10.1002/art.41485

137. Sakkas LI, Daoussis D, Mavropoulos A, Liossis SN, Bogdanos DP. Regulatory B cells: new players in inflammatory and autoimmune rheumatic diseases. *Semin Arthritis Rheum*. (2019) 48(6):1133–41. doi: 10.1016/j.semarthrit.2018.10.007

138. Abdelaziz MM, Fathi N, Hetta HF, Abdel-Galeel A, Zidan M, Shawky EM, et al. Regulatory B cells evaluation in systemic lupus erythematosus patients with subclinical atherosclerosis and secondary antiphospholipid syndrome. *Mediterr J Rheumatol*. (2023) 34(4):486. doi: 10.31138/mjr.03823.rbc

139. Zhu Z, Chen X, Wei S, Xu J, Wang Y, Wu W, et al. Role of $CD19^+$ $CD5^+$ $CD1d^+$ Bregs in maintaining the Th17/Treg balance in mice with systemic lupus erythematosus complicated with atherosclerosis. *Int J Rheum Dis*. (2023) 26(6):1048–57. doi: 10.1111/1756-185X.14691

140. Federici S, Cinicola BL, La Torre F, Castagnoli R, Lougaris V, Giardino G, et al. Vasculitis and vasculopathy associated with inborn errors of immunity: an overview. *Front Pediatr*. (2024) 11:1258301. doi: 10.3389/fped.2023.1258301

141. Ganguly D. Do type I interferons link systemic autoimmunities and metabolic syndrome in a pathogenetic continuum? *Trends Immunol*. (2018) 39(1):28–43. doi: 10.1016/j.it.2017.07.001

142. Döring Y, Manthey HD, Drechsler M, Lievens D, Megens RTA, Soehnlein O, et al. Auto-Antigenic protein-DNA complexes stimulate plasmacytoid dendritic cells to promote atherosclerosis. *Circulation*. (2012) 125(13):1673–83. doi: 10.1161/CIRCULATIONAHA.111.046755

143. Chen HJ, Tas SW, De Winther MPJ. Type-I interferons in atherosclerosis. *J Exp Med*. (2020) 217(1):e20190459. doi: 10.1084/jem.20190459

144. Niessner A, Sato K, Chaikof EL, Colmegna I, Goronzy JJ, Weyand CM. Pathogen-Sensing plasmacytoid dendritic cells stimulate cytotoxic T-cell function in the atherosclerotic plaque through interferon-α. *Circulation*. (2006) 114(23):2482–9. doi: 10.1161/CIRCULATIONAHA.106.642801

145. Li J, Fu Q, Cui H, Qu B, Pan W, Shen N, et al. Interferon-α priming promotes lipid uptake and macrophage-derived foam cell formation: a novel link between interferon-α and atherosclerosis in lupus. *Arthritis Rheum*. (2011) 63(2):492–502. doi: 10.1002/art.30165

146. Niessner A, Shin MS, Pryshchep O, Goronzy JJ, Chaikof EL, Weyand CM. Synergistic proinflammatory effects of the antiviral cytokine interferon-α and toll-like receptor 4 ligands in the atherosclerotic plaque. *Circulation*. (2007) 116(18):2043–52. doi: 10.1161/CIRCULATIONAHA.107.697789

147. Lood C, Amisten S, Gullstrand B, Jönsen A, Allhorn M, Truedsson L, et al. Platelet transcriptional profile and protein expression in patients with systemic lupus erythematosus: up-regulation of the type I interferon system is strongly associated with vascular disease. *Blood*. (2010) 116(11):1951–7. doi: 10.1182/blood-2010-03-274605

148. Nhek S, Clancy R, Lee KA, Allen NM, Barrett TJ, Marcantoni E, et al. Activated platelets induce endothelial cell activation via an interleukin-1β pathway in systemic lupus erythematosus. *Arterioscler Thromb Vasc Biol*. (2017) 37(4):707–16. doi: 10.1161/ATVBAHA.116.308126

149. Linge P, Fortin PR, Lood C, Bengtsson AA, Boilard E. The non-haemostatic role of platelets in systemic lupus erythematosus. *Nat Rev Rheumatol*. (2018) 14(4):195–213. doi: 10.1038/nrrheum.2018.38

150. Svenungsson E, Gustafsson JT, Grosso G, Rossides M, Gunnarsson I, Jensen-Urstad K, et al. Complement deposition, C4d, on platelets is associated with vascular events in systemic lupus erythematosus. *Rheumatology*. (2020 Nov 1) 59(11):3264–74. doi: 10.1093/rheumatology/keaa092

151. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 pathway in atherosclerosis. *Circ Res*. (2018) 122(12):1722–40. doi: 10.1161/CIRCRESAHA.118.311362

152. Libby P. Interleukin-1 Beta as a target for atherosclerosis therapy. *J Am Coll Cardiol*. (2017 Oct) 70(18):2278–89. doi: 10.1016/j.jacc.2017.09.028

153. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. (2017) 377(12):1119–31. doi: 10.1056/NEJMoa1707914

154. Caielli S, Balasubramanian P, Rodriguez-Alcazar J, Balaji U, Robinson L, Wan Z, et al. Type I IFN drives unconventional IL-1β secretion in lupus monocytes. *Immunity*. (2024) 57(11):2497–2513.e12. doi: 10.1016/j.immuni.2024.09.004

155. Becker YLC, Duvvuri B, Fortin PR, Lood C, Boilard E. The role of mitochondria in rheumatic diseases. *Nat Rev Rheumatol*. (2022) 18(11):621–40. doi: 10.1038/s41584-022-00834-z

156. Mende R, Vincent FB, Kandane-Rathnayake R, Koelmeyer R, Lin E, Chang J, et al. Analysis of Serum interleukin (IL)-1β and IL-18 in systemic lupus erythematosus. *Front Immunol*. (2018) 9:1250. doi: 10.3389/fimmu.2018.01250

157. Kahlenberg JM, Kaplan MJ. The inflammasome and lupus: another innate immune mechanism contributing to disease pathogenesis? *Curr Opin Rheumatol*. (2014) 26(5):475–81. doi: 10.1097/BOR.0000000000000088

158. Deroissart J, Binder CJ, Porsch F. Role of antibodies and their specificities in atherosclerotic cardiovascular disease. *Arterioscler Thromb Vasc Biol*. (2024) 44(10):2154–68. doi: 10.1161/ATVBAHA.124.319843

159. Bassi N, Zampieri S, Ghirardello A, Tonon M, Zen M, Beggio S, et al. Oxldl/β2gpi Complex and anti-oxldl/β2gpi in sle: prevalence and correlates: brief research report. *Autoimmunity*. (2009) 42(4):289–91. doi: 10.1080/08916930902828247

160. Ye Y, Wu T, Zhang T, Han J, Habazi D, Saxena R, et al. Elevated oxidized lipids, anti-lipid autoantibodies and oxidized lipid immune complexes in active SLE. *Clin Immunol*. (2019) 205:43–8. doi: 10.1016/j.clim.2019.05.004

161. Rhoads JP, Lukens JR, Wilhelm AJ, Moore JL, Mendez-Fernandez Y, Kanneganti TD, et al. Oxidized low-density lipoprotein immune Complex priming of the Nlrp3 inflammasome involves TLR and FcγR cooperation and is dependent on CARD9. *J Immunol*. (2017) 198(5):2105–14. doi: 10.4049/jimmunol.1601563

162. Zhang X, Xie Y, Zhou H, Xu Y, Liu J, Xie H, et al. Involvement of TLR4 in oxidized LDL/β2GPI/anti-β2GPI-induced transformation of macrophages to foam cells. *J Atheroscler Thromb*. (2014) 21(11):1140–51. doi: 10.5551/jat.24372

163. Moschetti L, Piantoni S, Vizzardi E, Sciatti E, Riccardi M, Franceschini F, et al. Endothelial dysfunction in systemic lupus erythematosus and systemic sclerosis: a common trigger for different microvascular diseases. *Front Med*. (2022) 9:849086. doi: 10.3389/fmed.2022.849086

164. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol*. (2012) 176(8):708–19. doi: 10.1093/aje/kws130

165. Kiani AN, Vogel-Claussen J, Arbab-Zadeh A, Magder LS, Lima J, Petri M. Semiquantified noncalcified coronary plaque in systemic lupus erythematosus. *J Rheumatol*. (2012) 39(12):2286–93. doi: 10.3899/jrheum.120197

166. Patiño-Trives AM, Pérez-Sánchez C, Pérez-Sánchez L, Luque-Tévar M, Ábalos-Aguilera MC, Alcaide-Ruggiero L, et al. Anti-dsDNA antibodies increase the cardiovascular risk in systemic lupus erythematosus promoting a distinctive immune and vascular activation. *Arterioscler Thromb Vasc Biol*. (2021) 41(9):2417–30. doi: 10.1161/ATVBAHA.121.315928

167. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, De Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis*. (2015) 74(6):1011–8. doi: 10.1136/annrheumdis-2013-204838

168. Tselios K, Sheane BJ, Gladman DD, Urowitz MB. Optimal monitoring for coronary heart disease risk in patients with systemic lupus erythematosus: a systematic review. *J Rheumatol*. (2016) 43(1):54–65. doi: 10.3899/jrheum.150460

169. Ahmad Y, Shelmerdine J, Bodill H, Lunt M, Pattrick MG, Teh LS, et al. Subclinical atherosclerosis in systemic lupus erythematosus (SLE): the relative contribution of classic risk factors and the lupus phenotype. *Rheumatology*. (2007 Mar 27) 46(6):983–8. doi: 10.1093/rheumatology/kem002

170. Plazak W, Pasowicz M, Kostkiewicz M, Podolec J, Tomkiewicz-Pajak L, Musial J, et al. Influence of chronic inflammation and autoimmunity on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients. *Inflamm Res*. (2011) 60(10):973–80. doi: 10.1007/s00011-011-0358-x

171. Di Minno MND, Emmi G, Ambrosino P, Scalera A, Tufano A, Cafaro G, et al. Subclinical atherosclerosis in asymptomatic carriers of persistent antiphospholipid antibodies positivity: a cross-sectional study. *Int J Cardiol*. (2019) 274:1–6. doi: 10.1016/j.ijcard.2018.06.010

172. Frostegård J. Systemic lupus erythematosus and cardiovascular disease. *J Intern Med*. (2023) 293(1):48–62. doi: 10.1111/joim.13557

173. Velásquez M, Peláez LF, Rojas M, Narváez-Sánchez R, Velásquez JA, Escudero C, et al. Differences in endothelial activation and dysfunction induced by antiphospholipid antibodies among groups of patients with thrombotic, refractory, and non-refractory antiphospholipid syndrome. *Front Physiol*. (2021) 12:764702. doi: 10.3389/fphys.2021.764702

174. Narshi C, Giles I, Rahman A. The endothelium: an interface between autoimmunity and atherosclerosis in systemic lupus erythematosus? *Lupus*. (2011) 20(1):5–13. doi: 10.1177/0961203310382429

175. Cieślik P, Semik-Grabarczyk E, Hrycek A, Holecki M. The impact of anti-endothelial cell antibodies (AECAs) on the development of blood vessel damage in patients with systemic lupus erythematosus: the preliminary study. *Rheumatol Int*. (2022) 42(5):791–801. doi: 10.1007/s00296-022-05104-5

176. Dieudé M, Senécal J, Raymond Y. Induction of endothelial cell apoptosis by heat-shock protein 60–reactive antibodies from anti–endothelial cell autoantibody–positive systemic lupus erythematosus patients. *Arthritis Rheum*. (2004) 50(10):3221–31. doi: 10.1002/art.20564

177. Xu Q, Kiechl S, Mayr M, Metzler B, Egger G, Oberhollenzer F, et al. Association of serum antibodies to heat-shock protein 65 with carotid atherosclerosis. *Lancet*. (1993) 341(8840):255–9. doi: 10.1016/0140-6736(93)92613-X

178. Li NL, Birmingham DJ, Rovin BH. Expanding the role of complement therapies: the case for lupus nephritis. *J Clin Med*. (2021) 10(4):626. doi: 10.3390/jcm10040626

179. Sharma M, Vignesh P, Tiewsoh K, Rawat A. Revisiting the complement system in systemic lupus erythematosus. *Expert Rev Clin Immunol*. (2020) 16(4):397–408. doi: 10.1080/1744666X.2020.1745063

180. Kiss MG, Binder CJ. The multifaceted impact of complement on atherosclerosis. *Atherosclerosis*. (2022) 351:29–40. doi: 10.1016/j.atherosclerosis.2022.03.014

181. Maffia P, Mauro C, Case A, Kemper C. Canonical and non-canonical roles of complement in atherosclerosis. *Nat Rev Cardiol*. (2024) 21(11):743–61. doi: 10.1038/s41569-024-01016-y

182. Suda M, Paul KH, Minamino T, Miller JD, Lerman A, Ellison-Hughes GM, et al. Senescent cells: a therapeutic target in cardiovascular diseases. *Cells*. (2023) 12(9):1296. doi: 10.3390/cells12091296

183. Macedo ACL, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. *Front Immunol*. (2016) 7:55. doi: 10.3389/fimmu.2016.00055

184. Bhatia VK, Yun S, Leung V, Grimsditch DC, Benson GM, Botto MB, et al. Complement C1q reduces early atherosclerosis in low-density lipoprotein receptor-deficient mice. *Am J Pathol*. (2007) 170(1):416–26. doi: 10.2353/ajpath.2007.060406

185. Pickering MC, Botto M. Canonical and noncanonical functions of complement in systemic lupus erythematosus. *Eur J Immunol*. (2024 Jul) 54(7):2350918. doi: 10.1002/eji.202350918

186. Schrijvers DM, De Meyer GRY, Kockx MM, Herman AG, Martinet W. Phagocytosis of apoptotic cells by macrophages is impaired in atherosclerosis. *Arterioscler Thromb Vasc Biol*. (2005 Jun) 25(6):1256–61. doi: 10.1161/01.ATV.0000166517.18801.a7

187. Stojan G, Petri M. Anti-C1q in systemic lupus erythematosus. *Lupus*. (2016) 25(8):873–7. doi: 10.1177/0961203316645205

188. Trouw LA, Groeneveld TWL, Seelen MA, Duijs JMGJ, Bajema IM, Prins FA, et al. Anti-C1q autoantibodies deposit in glomeruli but are only pathogenic in combination with glomerular C1q-containing immune complexes. *J Clin Invest*. (2004) 114(5):679–88. doi: 10.1172/JCI200421075

189. Urowitz MB, Gladman D, Ibañez D, Fortin P, Sanchez-Guerrero J, Bae S, et al. Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. *Arthritis Care Res*. (2008) 59(2):176–80. doi: 10.1002/art.23353

190. Bolla E, Semb AG, Kerola AM, Ikdahl E, Petri M, Pons-Estel GJ, et al. Prevalence and target attainment of traditional cardiovascular risk factors in patients with systemic lupus erythematosus: a cross-sectional study including 3401 individuals from 24 countries. *Lancet Rheumatol*. (2024) 6(7):e447–59. doi: 10.1016/S2665-9913(24)00090-0

191. Tselios K, Koumaras C, Gladman DD, Urowitz MB. Dyslipidemia in systemic lupus erythematosus: just another comorbidity? *Semin Arthritis Rheum*. (2016) 45(5):604–10. doi: 10.1016/j.semarthrit.2015.10.010

192. Sam NB, Tabiri S, Amofa E. Plasma/Serum oxidant parameters in systemic lupus erythematosus patients: a systematic review and meta-analysis. *Autoimmune Dis*. (2024) 2024(1):9948612. doi: 10.1155/2024/9948612

193. Tyrrell PN, Beyene J, Benseler SM, Sarkissian T, Silverman ED. Predictors of Lipid Abnormalities in Children with New-Onset Systemic Lupus Erythematosus.

194. Wang M, Huang S, Lin X, Wen C, He Z, Huang L. The causal relationship between blood lipids and systemic lupus erythematosus risk: a bidirectional two-sample Mendelian randomization study. *Front Genet*. (2022) 13:858653. doi: 10.3389/fgene.2022.858653

195. Kawai VK, Shi M, Liu G, Feng Q, Wei W, Chung CP, et al. Pleiotropy of systemic lupus erythematosus risk alleles and cardiometabolic disorders: a phenome-wide association study and inverse-variance weighted meta-analysis. *Lupus*. (2021) 30(8):1264–72. doi: 10.1177/09612033211014952

196. Wilkinson MJ, Shapiro MD. Immune-Mediated inflammatory diseases, dyslipidemia, and cardiovascular risk: a Complex interplay. *Arterioscler Thromb Vasc Biol*. (2024) 44(12):2396–406. doi: 10.1161/ATVBAHA.124.319983

197. Chew C, Reynolds JA, Lertratanakul A, Wu P, Urowitz M, Gladman DD, et al. Lower vitamin D is associated with metabolic syndrome and insulin resistance in systemic lupus: data from an international inception cohort. *Rheumatology*. (2021) 60(10):4737–47. doi: 10.1093/rheumatology/keab090

198. Peng J, Dönnes P, Ardoin SP, Schanberg LE, Lewandowski L, APPLE trial investigators and Childhood Rheumatology Research Alliance (CARRA), et al. Atherosclerosis progression in the APPLE trial can be predicted in young people with juvenile-onset systemic lupus erythematosus using a novel lipid metabolomic signature. *Arthritis Rheumatol*. (2024) 76(3):455–68. doi: 10.1002/art.42722

199. De Carvalho JF, Skare TL. Anti-lipoprotein lipase antibodies: a review. *Autoimmun Rev*. (2025) 24(1):103695. doi: 10.1016/j.autrev.2024.103695

200. Huang CS, Wu WF. Systemic lupus erythematosus associated with extreme hypertriglyceridemia. *Pediatr Neonatol*. (2008) 49(2):35–8. doi: 10.1016/S1875-9572(08)60009-1

201. Reichlin M, Fesmire J, Quintero-Del-Rio AI, Wolfson-Reichlin M. Autoantibodies to lipoprotein lipase and dyslipidemia in systemic lupus erythematosus. *Arthritis Rheum*. (2002) 46(11):2957–63. doi: 10.1002/art.10624

202. Nigolian H, Ribi C, Courvoisier DS, Pagano S, Alvarez M, Trendelenburg M, et al. Anti-apolipoprotein A-1 autoantibodies correlate with disease activity in systemic lupus erythematosus. *Rheumatology (Oxford)*. (2019) 59(3):534–44. doi: 10.1093/rheumatology/kez306

203. Kim SY, Yu M, Morin EE, Kang J, Kaplan MJ, Schwendeman A. High-density lipoprotein in lupus: disease biomarkers and potential therapeutic strategy. *Arthritis Rheumatol*. (2020) 72(1):20–30. doi: 10.1002/art.41059

204. Batuca JR, Ames PRJ, Amaral M, Favas C, Isenberg DA, Delgado Alves J. Anti-atherogenic and anti-inflammatory properties of high-density lipoprotein are affected by specific antibodies in systemic lupus erythematosus. *Rheumatology*. (2008) 48(1):26–31. doi: 10.1093/rheumatology/ken397

205. Delgado Alves J. Cross-reactivity between anti-cardiolipin, anti-high-density lipoprotein and anti-apolipoprotein A-I IgG antibodies in patients with systemic lupus erythematosus and primary antiphospholipid syndrome. *Rheumatology*. (2003) 42(7):893–9. doi: 10.1093/rheumatology/keg248

206. Thangasparan S, Kamisah Y, Ugusman A, Mohamad Anuar NN, Izzah IN. Unravelling the mechanisms of oxidised low-density lipoprotein in cardiovascular health: current evidence from *in vitro* and *in vivo* studies. *Int J Mol Sci*. (2024) 25(24):13292. doi: 10.3390/ijms252413292

207. Ahmad HM, Sarhan EM, Komber U. Higher circulating levels of OxLDL % of LDL are associated with subclinical atherosclerosis in female patients with systemic lupus erythematosus. *Rheumatol Int*. (2014) 34(5):617–23. doi: 10.1007/s00296-013-2875-0

208. Frostegård J, Svenungsson E, Wu R, Gunnarsson I, Lundberg IE, Klareskog L, et al. Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. *Arthritis Rheum*. (2005) 52(1):192–200. doi: 10.1002/art.20780

209. Vaarala O, Aho K, Palosuo T, Alfthan G, Jauhiainen M, Leirisalo-Repo M. Crossreaction between antibodies to oxidised low-density lipoprotein and to cardiolipin in systemic lupus erythematosus. *Lancet*. (1993) 341(8850):923–5. doi: 10.1016/0140-6736(93)91213-6

210. Hörkkö S, Olee T, Mo L, Branch DW, Woods VL, Palinski W, et al. Anticardiolipin antibodies from patients with the antiphospholipid antibody syndrome recognize epitopes in both β_2 -glycoprotein 1 and oxidized low-density lipoprotein. *Circulation*. (2001) 103(7):941–6. doi: 10.1161/01.CIR.103.7.941

211. Chou MY, Fogelstrand L, Hartvigsen K, Hansen LF, Woelkers D, Shaw PX, et al. Oxidation-specific epitopes are dominant targets of innate natural antibodies in mice and humans. *J Clin Invest*. (2009) 119(5):1335–49. doi: 10.1172/JCI36800

212. Rahman M, Sing S, Golabkesh Z, Fiskesund R, Gustafsson T, Jogestrand T, et al. Igm antibodies against malondialdehyde and phosphorylcholine are together strong protection markers for atherosclerosis in systemic lupus erythematosus: regulation and underlying mechanisms. *Clin Immunol*. (2016) 166–167:27–37. doi: 10.1016/j.clim.2016.04.007

213. Vas J, Grönwall C, Marshak-Rothstein A, Silverman GJ. Natural antibody to apoptotic cell membranes inhibits the proinflammatory properties of lupus autoantibody immune complexes. *Arthritis Rheum*. (2012) 64(10):3388–98. doi: 10.1002/art.34537

214. Sun J, Lundström SL, Zhang B, Zubarev RA, Steuer J, Gillgren P, et al. Igm antibodies against phosphorylcholine promote polarization of T regulatory cells from patients with atherosclerotic plaques, systemic lupus erythematosus and healthy donors. *Atherosclerosis*. (2018) 268:36–48. doi: 10.1016/j.atherosclerosis.2017.11.010

215. Su J, Hua X, Concha H, Svenungsson E, Cederholm A, Frostegard J. Natural antibodies against phosphorylcholine as potential protective factors in SLE. *Rheumatology*. (2008) 47(8):1144–50. doi: 10.1093/rheumatology/ken120

216. Thiagarajan D, Oparina N, Lundström S, Zubarev R, Sun J, The PRECISESADS Clinical Consortium, et al. Igm antibodies against malondialdehyde and phosphorylcholine in different systemic rheumatic diseases. *Sci Rep*. (2020) 10(1):11010. doi: 10.1038/s41598-020-66981-z

217. Grönwall C, Akhter E, Oh C, Burlingame RW, Petri M, Silverman GJ. Igm autoantibodies to distinct apoptosis-associated antigens correlate with protection from cardiovascular events and renal disease in patients with SLE. *Clin Immunol*. (2012) 142(3):390–8. doi: 10.1016/j.clim.2012.01.002

218. Su J, Frostegård AG, Hua X, Gustafsson T, Jogestrand T, Hafström I, et al. Low levels of antibodies against oxidized but not nonoxidized cardiolipin and phosphatidylserine are associated with atherosclerotic plaques in systemic lupus erythematosus. *J Rheumatol*. (2013) 40(11):1856–64. doi: 10.3899/jrheum.121173

219. Svenungsson E, Engelbertsen D, Wigren M, Gustafsson JT, Gunnarsson I, Elvin K, et al. Decreased levels of autoantibodies against apolipoprotein B-100 antigens are associated with cardiovascular disease in systemic lupus erythematosus. *Clin Exp Immunol*. (2015) 181(3):417–26. doi: 10.1111/cei.12651

220. Trakaki A, Marsche G. Current understanding of the immunomodulatory activities of high-density lipoproteins. *Biomedicines*. (2021) 9(6):587. doi: 10.3390/biomedicines9060587

221. McMahon M, Grossman J, Skaggs B, FitzGerald J, Sahakian L, Ragavendra N, et al. Dysfunctional proinflammatory high-density lipoproteins confer increased risk of atherosclerosis in women with systemic lupus erythematosus. *Arthritis Rheum*. (2009) 60(8):2428–37. doi: 10.1002/art.24677

222. Smith CK, Seto NL, Vivekanandan-Giri A, Yuan W, Playford MP, Manna Z, et al. Lupus high-density lipoprotein induces proinflammatory responses in macrophages by binding lectin-like oxidised low-density lipoprotein receptor 1 and failing to promote activating transcription factor 3 activity. *Ann Rheum Dis*. (2017) 76(3):602–11. doi: 10.1136/annrheumdis-2016-209683

223. Pérez-Ocampo J, Taborda NA, Yassin LM, Higuita-Gutiérrez LF, Hernandez JC. Exploring the association between systemic lupus erythematosus and high-density lipoproteins: a systematic review and meta-analysis. *ACR Open Rheumatol*. (2024 Oct) 6(10):648–61. doi: 10.1002/acr2.11700

224. Cardoso CRL, Signorelli FV, Papi JA, Salles GF. Prevalence and factors associated with dyslipoproteinemias in Brazilian systemic lupus erythematosus patients. *Rheumatol Int*. (2008) 28(4):323–7. doi: 10.1007/s00296-007-0447-x

225. Svenungsson E, Gunnarsson I, Fei G, Lundberg IE, Klareskog L, Frostegård J. Elevated triglycerides and low levels of high-density lipoprotein as markers of disease activity in association with up-regulation of the tumor necrosis factor α/tumor necrosis factor receptor system in systemic lupus erythematosus. *Arthritis Rheum*. (2003) 48(9):2533–40. doi: 10.1002/art.11264

226. Navab M, Ananthramaiah GM, Reddy ST, Van Lenten BJ, Ansell BJ, Fonarow GC, et al. Thematic review series: the pathogenesis of atherosclerosis the oxidation hypothesis of atherogenesis: the role of oxidized phospholipids and HDL. *J Lipid Res*. (2004) 45(6):993–1007. doi: 10.1194/jlr.R400001-JLR200

227. Van Lenten BJ, Hama SY, De Beer FC, Stafforini DM, McIntyre TM, Prescott SM, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *J Clin Invest*. (1995) 96(6):2758–67. doi: 10.1172/JCI118345

228. McMahon M, Grossman J, FitzGerald J, Dahlin-Lee E, Wallace DJ, Thong BY, et al. Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum*. (2006) 54(8):2541–9. doi: 10.1002/art.21976

229. Suárez-Rivero JM, Pastor-Maldonado CJ, Povea-Cabello S, Álvarez-Córdoba M, Villalón-García I, Talaverón-Rey M, et al. From mitochondria to atherosclerosis: the inflammation path. *Biomedicines*. (2021) 9(3):258. doi: 10.3390/biomedicines9030258

230. Perl A. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. *Nat Rev Rheumatol*. (2013) 9(11):674–86. doi: 10.1038/nrrheum.2013.147

231. Yennemadi AS, Jordan N, Diong S, Keane J, Leisching G. The link between dysregulated immunometabolism and vascular damage: implications for the development of atherosclerosis in systemic lupus erythematosus and other rheumatic diseases. *J Rheumatol*. (2024) 51(3):234–41. doi: 10.3899/jrheum.2023-0833

232. Gkirtzimanaki K, Kabrani E, Nikoleri D, Polyzos A, Blanas A, Sidiropoulos P, et al. IFNα impairs autophagic degradation of mtDNA promoting autoreactivity of SLE monocytes in a STING-dependent fashion. *Cell Rep*. (2018) 25(4):921–933.e5. doi: 10.1016/j.celrep.2018.09.001

233. Wang H, Tang R, Pan Q, Yin Q, Feng J, Deng L. Mitochondria dysfunction: a trigger for cardiovascular diseases in systemic lupus erythematosus. *Int Immunopharmacol*. (2025) 144:113722. doi: 10.1016/j.intimp.2024.113722

234. West EE, Kemper C. Complosome — the intracellular complement system. *Nat Rev Nephrol*. (2023) 19(7):426–39. doi: 10.1038/s41581-023-00704-1

235. Niyonzima N, Rahman J, Kunz N, West EE, Freiwald T, Desai JV, et al. Mitochondrial C5aR1 activity in macrophages controls IL-1β production underlying sterile inflammation. *Sci Immunol*. (2021) 6(66):eabf2489. doi: 10.1126/sciimmunol.abf2489

236. Tsai CY, Shen CY, Liao HT, Li KJ, Lee HT, Lu CS, et al. Molecular and cellular bases of immunosenescence, inflammation, and cardiovascular complications mimicking "inflammaging" in patients with systemic lupus erythematosus. *Int J Mol Sci*. (2019) 20(16):3878. doi: 10.3390/ijms20163878

237. Jiang J, Yang M, Zhu H, Long D, He Z, Liu J, et al. $CD4^+$ $CD57^+$ senescent T cells as promoters of systemic lupus erythematosus pathogenesis and the therapeutic potential of senolytic BCL-2 inhibitor. *Eur J Immunol*. (2024) 54(7):2350603. doi: 10.1002/eji.202350603

238. Stojanović SD, Fiedler J, Bauersachs J, Thum T, Sedding DG. Senescence-induced inflammation: an important player and key therapeutic target in atherosclerosis. *Eur Heart J*. (2020) 41(31):2983–96. doi: 10.1093/eurheartj/ehz919

239. Kalim H, Wahono CS, Permana BPO, Pratama MZ, Handono K. Association between senescence of T cells and disease activity in patients with systemic lupus erythematosus. *Reumatologia*. (2021) 59(5):292–301. doi: 10.5114/reum.2021.110318

240. Téo FH, De Oliveira RTD, Mamoni RL, Ferreira MCS, Nadruz W, Coelho OR, et al. Characterization of CD4 + CD28null T cells in patients with coronary artery disease and individuals with risk factors for atherosclerosis. *Cell Immunol*. (2013) 281(1):11–9. doi: 10.1016/j.cellimm.2013.01.007

241. Bortoluzzi A, Chighizola CB, Fredi M, Raschi E, Bodio C, Privitera D, et al. The IMMENSE study: the interplay between iMMune and ENdothelial cells in mediating cardiovascular risk in systemic lupus erythematosus. *Front Immunol*. (2020) 11:572876. doi: 10.3389/fimmu.2020.572876

242. López P, Rodríguez-Carrio J, Martínez-Zapico A, Caminal-Montero L, Suarez A. Senescent profile of angiogenic T cells from systemic lupus erythematosus patients. *J Leukoc Biol*. (2016) 99(3):405–12. doi: 10.1189/jlb.5HI0215-042R