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REVIEW

Inflammation in atherosclerosis: Drivers, mechanisms and therapies

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Abstract Atherosclerosis has traditionally been considered a lipid-driven disease. However, emerging evidence highlights the central role of inflammation in the development of atherosclerosis. Multiple cell types, including endothelial cells, macrophages, and other immune cells, interact within lesions to form a chronic inflammatory microenvironment. Unhealthy lifestyle, smoking and metabolic disorders like hyperlipidemia, hyperglycemia, and their derived pro-atherogenic products drive vascular inflammation. Recent evidence reveals that high-sensitivity C-reactive protein surpasses LDL-cholesterol in predicting future cardiovascular risk. Combining lipid-lowering with anti-inflammatory therapies significantly reduces event recurrence, underscoring the need for targeted drugs. Promising results have emerged from trials of anti-inflammatory agents. Statins and other lipid-lowering drugs also exhibit anti-inflammatory properties. However, cholesterol-independent strategies face challenges like infection risk from immunosuppression, requiring extensive safety evaluation. Enhancing intrinsic resilience mechanisms is a promising alternative in combating vascular inflammation and atherosclerosis. High-throughput screening accelerates drug development, while induced pluripotent stem cell-derived vascular organoids better simulate human atherosclerosis pathobiology, improving preclinical predictions. Research on organ interaction networks and trained immunity offers novel therapeutic targets. In this comprehensive review, we provide a state-of-the-art synthesis of the drivers, mechanisms, and potential therapies of atherosclerosis by targeting inflammation, with an aim to reducing residual cardiovascular risk in the post-statin era.

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1. Inflammation and atherosclerosis: Key milestones

Atherosclerosis is now recognized as a chronic inflammatory disease, a concept with roots extending back to 1858 when Dr. Rudolf Virchow[1] first described inflammatory cell infiltration in the arterial wall. This initial observation was later systematized by Dr. Russell Ross[2] in 1976 through the "response-to-injury" hypothesis, which was subsequently refined in the 1990s to establish the modern "inflammatory hypothesis"[3]. Building upon this foundation, the paradigm was firmly established through accumulating clinical evidence that positioned anti-inflammatory therapy as a new therapeutic avenue[4,5]. Clinical validation emerged with the CANTOS trial, where canakinumab (150 mg quarterly) targeting IL-1β significantly reduced cardiovascular events independent of lipid-lowering[6]. This breakthrough was followed by evidence confirming colchicine (0.5 mg/day) markedly lowers ischemic cardiovascular risk[7,8], leading to its landmark U.S. Food and Drug Administration approval in 2023, while ziltivekimab further demonstrated the promise of IL-6 pathway inhibition[9]. Parallel research identified age-related clonal hematopoiesis of indeterminate potential (CHIP) as a key genetic driver[10], with mutations (*e.g.*, *Dnmt3a*, *Tet2*, and *Jak2*) shown to exacerbate atherosclerosis through enhanced pro-inflammatory responses[11-14]. This cardiovascular risk is quantitatively governed by the hematopoietic stem cell proliferation rate in a unidirectional relationship[15]. The expansion of the mutant hematopoietic clone is unaffected by subclinical atherosclerosis[16]. More recently, dietary studies revealed that an alternating high-fat diet (HFD) exacerbates plaques *via* IL-1β-dependent neutrophilia and neutrophil extracellular traps (NETs)[17], while an early intermittent high-cholesterol diet exacerbates atherosclerosis by altering the quantity and phenotype of artery-resident macrophages and disrupting key pathways such as actin filament organization[18]. Another recent line of evidence demonstrates that cyclic long-chain ceramides exacerbate atherosclerosis by binding to G protein-coupled receptors (GPCRs), activating the G_q signaling pathway and NLRP3 inflammasome, and promoting IL-1β release[19] (Fig. 1).

2. Key cell types in vascular inflammation and molecular mechanisms involved

Atherosclerosis initiates with the accumulation of lipids in the vessel wall, where retained lipoproteins such as LDL become modified (*via* oxidation and glycation, etc.) and trigger the release of chemokines from endothelial cells and vascular smooth muscle cells (VSMCs)[20]. This promotes the recruitment of monocytes and neutrophils. Monocytes differentiate into macrophages that engulf lipids to form foam cells. Intracellular cholesterol crystals or oxidized LDL can activate the NLRP3 inflammasome, amplifying pro-inflammatory signaling. NETs further enhance monocyte recruitment, macrophage activation, and VSMC injury. Sustained inflammation drives plaque progression. VSMCs migrate into the intima and produce matrix to form a stabilizing fibrous cap[20]. However, under lipid and inflammatory stimulation, VSMCs undergo phenotypic switching, reducing matrix synthesis and increasing inflammation, which thins the fibrous cap[20]. Concurrently, foam cells, VSMCs, and other cells undergo apoptosis, necroptosis, and other types of cell death due to lipid toxicity and inflammatory damage, forming a lipid-rich necrotic core that exacerbates local inflammation (Fig. 2).

2.1. Endothelial cell inflammation

Atherosclerosis is initiated when vascular endothelial dysfunction, characterized by the upregulation of adhesion molecules and increased permeability, permits the infiltration and subsequent oxidation of LDL in the subendothelial space[20]. The expression of these adhesion molecules is dynamically regulated, being augmented by stimuli such as calcium *via* the calcium-sensing receptor (CaSR) and restrained by protective mechanisms including TIE2 kinase-mediated inhibition of forkhead box protein O1 (*FOXO1*) and the eNOS (endothelial nitric oxide synthase)−NO (nitric oxide) pathway activated by the adipokine 12,13-diHOME[21-23]. This activated endothelium produces chemokines that recruit circulating monocytes and neutrophils, amplifying the inflammation cascade. Central to this inflammatory cascade is the activation of the transcriptional regulator kappa-light-chain-enhancer of activated B cells (NF-κB), which drives expression of acute-phase response effectors, inflammatory cytokines, and adhesion molecules. The activity of NF-κB within endothelial cells is precisely modulated by a network of regulators.

Inhibitory control involves the orphan nuclear receptor Nur77, whose activity is inhibited by N-myc downstream-regulated gene 1 (*NDRG1*), upregulating IκBα expression[24-26]. Additionally, protein tyrosine phosphatase type IVA1 (PTP4A1) dephosphorylates upstream stimulatory factor 1 at S309 to enhance *A20* transcription and ultimately suppress NF-κB activity[27]. Endoplasmic reticulum stress also contributes by secreting 78-kDa glucose-regulated protein (GRP78), which exerts anti-inflammatory effects[28]. Conversely, multiple pathways promote NF-κB activation. Natriuretic peptide receptor C (NPRC) enhances IKK signaling by suppressing the cAMP/PKA−AKT1 axis[27]. *S*-Nitrosylated HSP90 facilitates CDC37 binding to activate NF-κB[29], while argonaute 1 (AGO1) serves as a nuclear coactivator for NF-κB p65 to drive pro-inflammatory gene transcription[30]. Parallel promotive mechanisms include ADAR2-dependent glycoprotein 130 (gp130) signaling and long non-coding RNA (lncRNA) PSMB8-AS1-mediated upregulation of proteasome 20S subunit beta 9 (PSMB9), recruiting NONO to enhance zinc finger E-box-binding (ZEB1) transcription factors to directly upregulate VCAM1/ICAM1[31,32].

Once activated, NF-κB accelerates atherosclerosis through multiple mechanisms. It upregulates adhesion molecules and inflammatory cytokines while promoting NLRP3 inflammasome assembly. This occurs *via* lncRNA MIR181A1HG-mediated FOXP1 occupation and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3)-driven CtBP1 oligomerization, which relieves FOXP1 repression[33,34]. In atherosclerotic patients, histone deacetylase 3 (HDAC3) is upregulated in inflamed endothelial cells, where it suppresses K703 acetylation of specificity protein 1 (SP1), thereby enhancing SP1 binding to the NLRP3 promoter and activating the NLRP3 inflammasome[35]. NF-κB also exacerbates oxidative stress by enhancing NADPH oxidase (NOX) activity, suppressing superoxide dismutase (SOD), and elevating malondialdehyde (MDA) and reactive oxygen species (ROS) levels. Sodium-glucose cotransporter 2 (SGLT2) overexpression under NF-κB activation further amplifies this oxidative stress while inhibiting NO production, creating a vicious cycle[36]. Counteracting these damaging processes, protective mechanisms help maintain cellular homeostasis. Mitochondrial calcium uptake protein mitochondrial calcium uptake 1 (MICU1) preserves mitochondrial calcium balance, sustaining mitochondrial sirtuin 3 (SIRT3) activity that

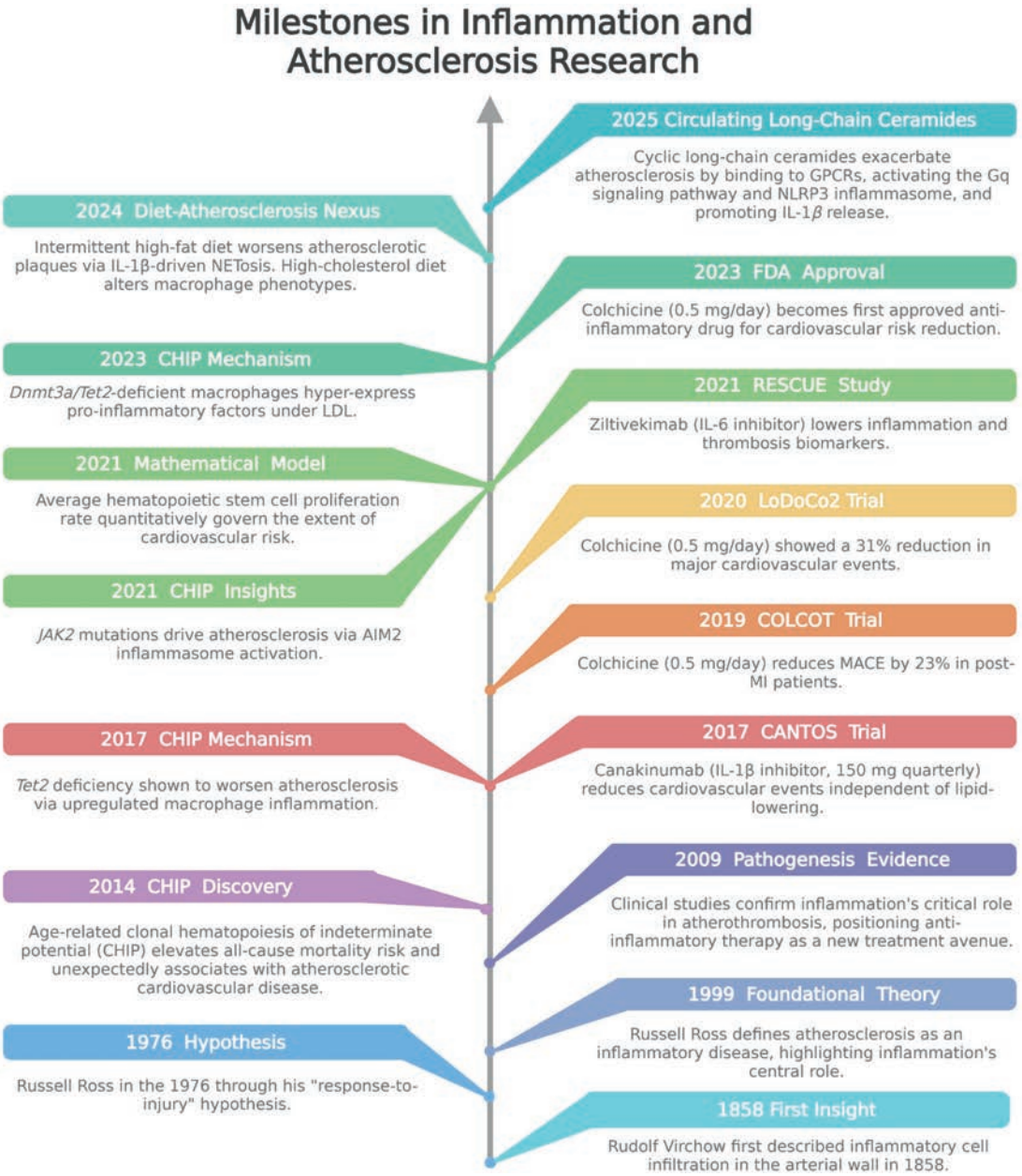

Figure 1 Timeline of key milestones in inflammation and atherosclerosis research (1858−2025). Abbreviations: AIM2, absent in melanoma 2; CHIP, age-related clonal hematopoiesis of indeterminate potential; Dmnt3a, DNA methyltransferase 3 alpha; FDA, Food and Drug Administration; Gq, Gq protein; GPCRs, G protein-coupled receptors; IL-1β, interleukin-1β; IL-6, interleukin-6; JAK2, Janus kinase 2; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; NETosis, neutrophil extracellular trap formation; NLRP3, NOD-like receptor thermal protein domain associated protein 3; Tet2, tet methylcytosine dioxygenase 2.

promotes SOD2 deacetylation and enhances antioxidant capacity[37]. Meanwhile, the pluripotency factor octamer-binding transcriptional factor 4 (OCT4) transcriptionally regulates ABCG2 to facilitate heme efflux, preventing mitochondrial ROS generation and protecting endothelial function[38] (Fig. 3).

2.2. *Inflammation in VSMCs*

VSMCs constitute the principal cellular component of the arterial medial layer, maintaining vascular tone through contractile functions[39]. Protein quality control systems critically regulate their homeostasis, where impaired chaperone-mediated autophagy promotes lipid accumulation and inflammasome activation[40], while ubiquitination-mediated sirtuin 6 (SIRT6) degradation induces cellular senescence[41]. Notably, a novel gene, *ITIH4,* has been found to be expressed in VSMCs of atherosclerotic plaques, and its co-expressed genes are believed to be enriched in cell adhesion and extracellular matrix organization.[42]. Alongside such structural regulation, dysregulated metabolic pathways also contribute to VSMC pathology. For instance, ADP-ribosylation factor 6 (ARF6) is a key regulator that promotes lipid uptake in VSMCs by specifically upregulating scavenger receptors LOX-1 and MSR1 (but not LDLR or CD36) and modulating the PI3K-dependent macropinocytosis pathway[43]. In atherosclerosis,

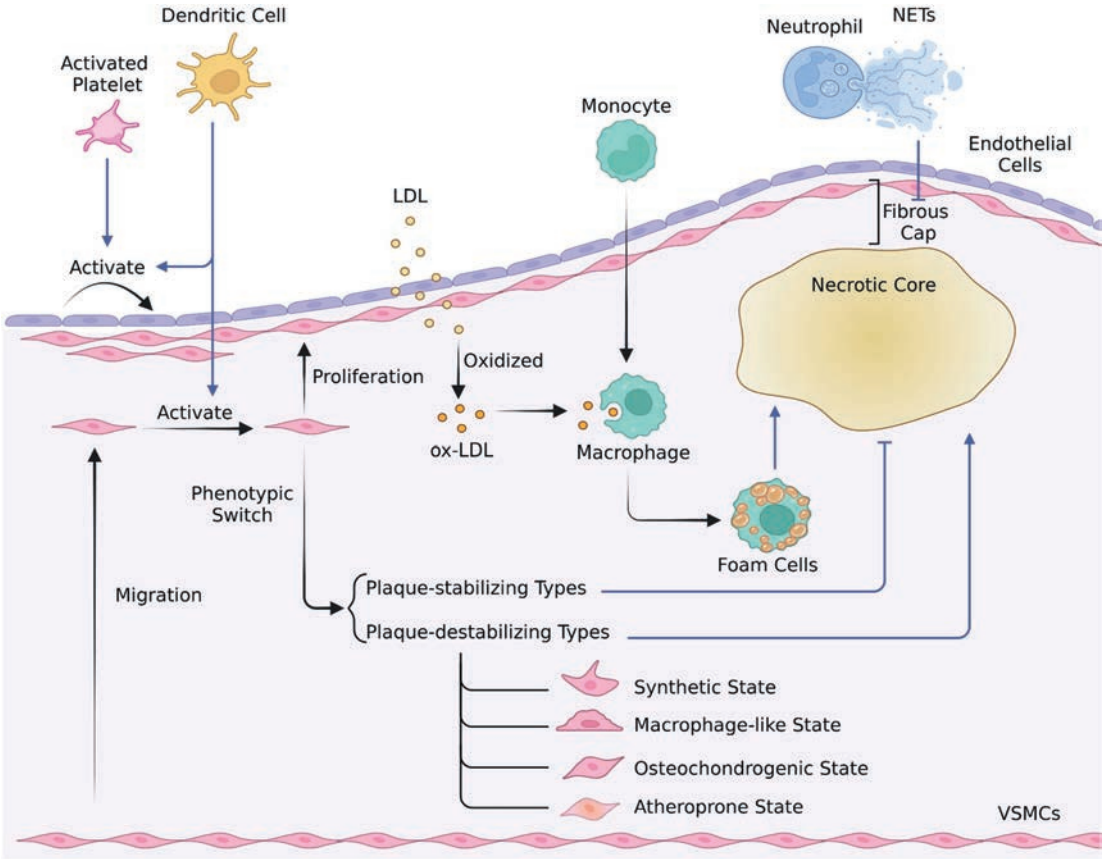

Figure 2 The pathogenesis of atherosclerosis. Dendritic cells, platelets and other pro-atherogenic factors induce endothelial dysfunction, allowing LDL infiltration and its subsequent oxidation to ox-LDL (and other forms of modified LDL). Macrophages engulf ox-LDL to form foam cells. Activated VSMCs proliferate, migrate, and undergo pro-atherogenic phenotypic switching. NETs degrade the extracellular matrix, thinning the fibrous cap. Plaque stability is determined by these cellular states. Abbreviations: LDL, low-density lipoprotein; ox-LDL, oxidized LDL; NETs, neutrophil extracellular traps; VSMCs, vascular smooth muscle cells. Figure was created using BioRender.

VSMCs undergo phenotypic switching from a contractile state to diverse functional subtypes, including matrix-producing fibromuscular cells that stabilize plaques, as well as inflammatory, osteogenic, and macrophage-like cells that promote plaque destabilization[44,45].

This phenotypic transition is regulated by multiple pathways. The METTL3 (methyltransferase-like 3)−YTHDF3 (YTH N^6-methyladenosine RNA-binding protein F3) axis promotes inflammatory and macrophage-like transitions *via* m^6A-dependent translation[46,47], while *S100A4* deletion preserves contractile markers[48]. *FHL5* autoregulates through serum response factor (SRF)-myocardin enhancers to drive osteogenic differentiation[49], whereas thioredoxin-interacting protein (TXNIP) inhibits VSMC transition toward chondro-osteogenic phenotypes by blocking bone morphogenetic protein (BMP) signaling[50]. Extracellular vesicles from VSMCs carry pro-calcific miRNAs that enhance calcification through Notch and Wnt pathways. Multi-omics studies identified specific vesicular miRNAs (miR-199b-5p, miR-381-3p) as key promoters of VSMC apoptosis and calcification, which act by targeting oxidative stress and mitochondrial dynamics genes[51,52]. Circadian rhythm gene *ARNTL* downregulation reduces VSMC proliferation while increasing contractile marker expression to promote the contractile phenotype[53], and SMAD3 forms a complex with HOXB2/SOX9 to suppress transitions to synthetic and chondromyocyte-like states[54]. Additionally, cezanne activates Wnt/β-catenin signaling *via* β-catenin deubiquitination[55]. Concomitantly, glucagon-like peptide-1 receptor (GLP-1R) overexpression specifically in dedifferentiated VSMCs within human/murine atherosclerotic plaques positively correlates with Krüppel-like factor 4 (KLF4) level[56].

Plaque progression is driven by inflammatory activation and specific molecular pathways. VSMC-derived extracellular traps activate stimulator of interferon genes (STING)-SOCS1 (suppressor of cytokine signaling 1)/TLR4 (Toll-like receptor 4) signaling[57], while lncRNAs MIR181A1HG and INKILN promote inflammasome assembly and pro-inflammatory gene upregulation, respectively[58,59]. The methyltransferase disruptor of telomeric silencing 1-like (DOT1L) modulates NF-κB signaling and chemokine production[60,61]. Plaque destabilization involves dipeptidyl peptidase 4 (DPP4)-mediated VSMC senescence and immune recruitment *via* complement factors[62], while Von Willebrand factor (VWF) deposition promotes VSMC proliferation and neointimal hyperplasia through LDL Receptor-related Protein 4 (LRP4) binding and $\alpha v\beta 3$ integrin/Src/ERK1/2 pathway activation[63]. Integrin $\alpha_9\beta_1$-SVEP1 (Sushi, VWF type A, EGF, and Pentraxin domain-containing protein 1) interactions accelerate atherosclerosis *via* Notch and fibroblast growth factor receptor (FGFR) pathways[64,65]. Activating transcription factor 3 (ATF3) downregulation activates the complement cascade[66], and tumor necrosis factor receptor-associated protein 1 (TRAP1)-mediated histone lactylation switches promote

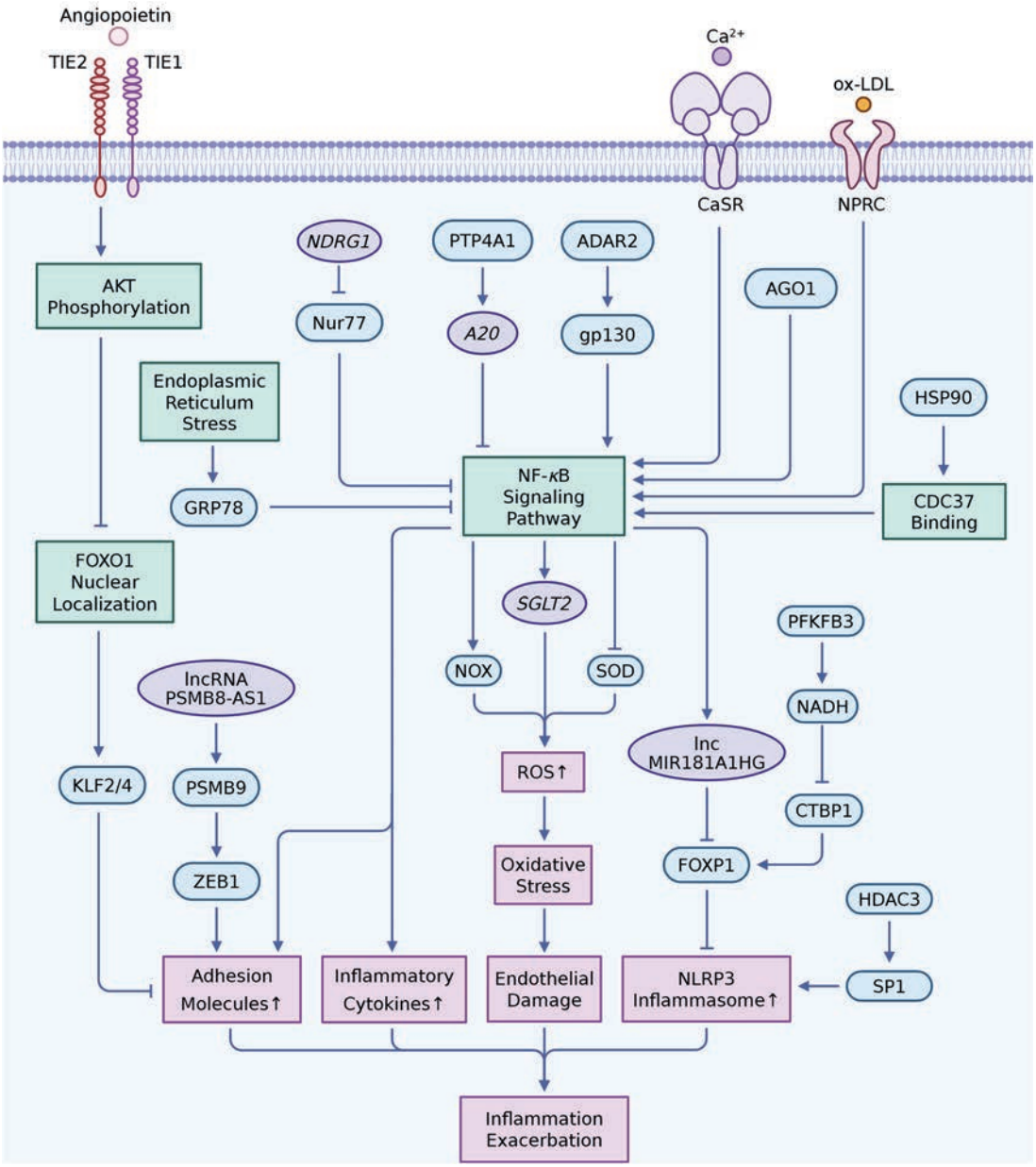

Figure 3 Inflammation-related pathway interactions in endothelial cells. Abbreviations: ADAR2, adenosine deaminase acting on RNA 2; AGO1, argonaute 1; AKT, protein kinase B; CaSR, calcium-sensing receptor; CtBP1, C-terminal binding protein 1; FOXO1/FOXP1, forkhead box O1/P1; GRP78, glucose-regulated protein 78; HDAC3, histone deacetylase 3; HSP90, shock protein 90; NADH, nicotinamide adenine dinucleotide; NDRG1, N-myc downstream-regulated gene 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated b cells; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NOX, NADPH oxidase; gp130, glycoprotein 130; NPRC, natriuretic peptide receptor C; Nur77, nuclear receptor subfamily 4 group A member 1; ox-LDL, oxidized LDL; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PSMB9, proteasome 20S subunit beta 9; PTP4A1, protein tyrosine phosphatase type IVA1; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; SOD, superoxide dismutase; SP1, specificity protein 1; TIE1/2, TEK receptor tyrosine kinase 1/2; ZEB1, zinc finger E-box binding homeobox 1. Figure was created using BioRender.

senescence-associated secretory phenotypes[67], collectively accelerating disease progression.

2.3. *Monocyte/macrophage inflammation*

In atherosclerosis, circulating monocytes are recruited to vascular lesions to differentiate into macrophages, a process governed by several molecular pathways. Key regulators include the polypeptide *N*-acetylgalactosamine transferase 4 (GalNAc-T4), which enhances monocyte adhesion and migration by modifying *O*-glycosylation of P-selectin glycoprotein ligand-1 (PSGL-1)[68], and the glycolytic enzyme PFKFB3, which provides essential energy for monocyte proliferation and infiltration[69]. The 15q26.1 risk variant reduces FES expression in monocytes, thereby promoting migration and proliferation while reducing apoptosis[70]. Furthermore, SVEP1 binding to integrins $\alpha_4\beta_1/\alpha_9\beta_1$ activates Rho

(at 24 h) and Rac1 (at 48 h)[71], while integrin $\alpha_D\beta_2$ levels determine macrophage migration *versus* retention at sites[72]. Furthermore, elevated circulating follicle-stimulating hormone (FSH) binds macrophage FSHR receptors, triggering IL-1β production. Secreted IL-1β activates NF-κB *via* autocrine signaling and amplifies plaque macrophage infiltration and inflammation[73].

Within plaques, macrophages differentiate into distinct subtypes, such as pro-inflammatory M1-type, anti-inflammatory M2-type, and specialized populations like colony-stimulating factor 1 (CSF1)-dependent resident macrophages and ox-LDL-derived MOX macrophages[74-76]. The local extracellular matrix actively regulates macrophage behavior, as evidenced by collagen VI antibodies decreasing pro-inflammatory Ly-6C^{high} monocytes[77]. Intracellularly, ox-LDL upregulates the E3 ligase TRIM64 to ubiquitinate IκBα, activating NF-κB and forming a feedforward loop with NLRP3 to amplify inflammasome activity and IL-1β release[78,79]. Olfactory receptor 2 (Olfr2) concurrently activates NLRP3 and drives foam cell formation[80,81]. Specifically, the lipid peroxidation product octanal binds to Olfr2/OR6A2 on macrophages, triggering ROS generation through the Gαolf−Adcy3−cAMP−Ca^{2+} pathway and thereby activating the NLRP3 inflammasome[82]. Additionally, IL-1/TLR signaling promotes sustained NLRP3 activation *via* a SENP1/βarr2-dependent pathway[83]. SENP1-mediated deSUMOylation of βarr2 at K295 enhances its binding to TRAF6-CCD, which blocks βarr2-mediated OR6A2 endocytosis, prolongs OR6A2 surface retention, and perpetuates NLRP3 inflammasome signaling[83]. The 21q22 enhancer activates *ETS2* transcription through an open chromatin conformation, thereby driving pro-inflammatory M1 polarization[84]. Regulatory non-coding RNA mechanisms further modulate macrophage polarization. The lncRNA Morrbid upregulates *S100A10* to promote M1 commitment[85,86], while miR-155 potentiates NLRP3 activation and M2 suppression, amplified by miR-342-5p-mediated AKT inhibition[87]. Conversely, miR-223 and miR-21 synergistically promote M2 polarization by inhibiting TLR4/NF-κB and inflammatory factors while enhancing IL-10, an effect augmented by miR-33 inhibition[87,88]. In humoral immunity, IgG (particularly IgG1) binds Fcγ receptors to activate downstream signaling and IL-10 release, driving monocyte differentiation into anti-inflammatory M2 macrophages while suppressing M1 activation[89]. Another key regulator in plaque macrophages is Dll1. Its upregulation promotes plaque progression by activating a non-canonical Notch−NF-κB pathway, which drives the expression of pro-inflammatory cytokines and MMP-9, thereby enhancing inflammation and collagen degradation[90].

Foam cell formation arises from a fundamental disruption in cholesterol homeostasis, characterized by both excessive lipid influx and defective efflux. On the influx side, scavenger receptors are dysregulated. *Trem2* modulates scavenger receptor CD36 activity[91-93]. Furthermore, purinergic receptor $P2Y_6$ receptor deletion suppresses lipid accumulation through the PLCβ/Ca^{2+}/calreticulin/SR-A axis[94], and antimicrobial peptide LL37 synergistically boosts LDL uptake efficiency by the class B scavenger receptor (SR-B), LDLR, and CD36 upon LDL binding[95]. Ubiquitin-specific peptidase 9 X-linked (USP9X) stabilizes SR-A1, and the E3 ubiquitin ligase RNF128 promotes SR-B1 membrane recycling, both enhancing lipid internalization[96,97]. Concurrently, cholesterol efflux is crippled by deficiencies in the transporters ABCA1 and ABCG1[98], or by *Dax1*-mediated suppression of their transcriptional regulator, liver X receptor (LXR)[99]. The resulting lipid overload not only fills the cell but also activates the NLRP3 inflammasome. This metabolic stress triggers distinct cell death pathways. Ox-LDL activates caspase-3 to cleave gasdermin E, inducing pyroptosis[100], while reduced methyltransferase-like protein 4 (METTL4) causes mitochondrial dysfunction and mtDNA release, further activating inflammasome[101]. The clearance of these dead cells is critically impaired by defective efferocytosis. CD147 impairs efferocytosis by suppressing growth arrest-specific 6 (GAS6) and skewing macrophages to M1 *via* TRAF6−IKK−IRF5[102], while IRF5 represses efferocytosis-related proteins (including MFGE8 and ITGB3)[103]. This failure to clear apoptotic debris directly fuels necrotic core expansion, culminating in increased plaque vulnerability. Conversely, resolvin T4 (RvT4) enhances cholesterol clearance *via* neutral cholesteryl ester hydrolase (nCEH) activation and SR-B1-mediated transport[104] (Fig. 4).

2.4. *Neutrophil inflammation*

Neutrophils, the most abundant peripheral blood leukocytes, contribute to atherosclerosis through NETosis, a process of releasing NETs *via* two distinct pathways. Vital NETosis generates mitochondrial DNA-based NETs *via* mitochondrial ROS without nuclear involvement, whereas lytic NETosis involves ROS-activated peptide arginine deiminase 4 (PAD4)-mediated histone citrullination leading to chromatin depolymerization. Then, myeloperoxidase (MPO) and neutrophil elastase (NE) disrupt the nuclear membrane, releasing NETs composed of nuclear DNA, histones, and granule proteins[105-107]. In plaques, chemokine-recruited neutrophils are regulated by IL1RAP, a co-receptor for IL-1, IL-33, and IL-36 signaling whose inhibition attenuates plaque size and inflammation[108]. IL-33, acting through IL1RAP, upregulates CD16 on neutrophils and promotes NETosis, thereby linking this axis to plaque destabilization[109]. NET components like histones and high mobility group box 1 (HMGB1) prime macrophages *via* TLRs, triggering NLRP3 inflammasome activation and caspase-1-dependent IL-1β maturation[110,111]. Secreted IL-1β further amplifies inflammation by inducing endothelial adhesion molecules and activating neutrophil NLRP3 to drive additional NETosis[98]. Neutrophil-derived S100A8/A9 proteins engage endothelial TLR4 and receptor for advanced glycation end-products (RAGE), activating NF-κB and pro-inflammatory cytokines[112], while bilirubin deficiency elevates MPO activity, leading to ROS-mediated collagen degradation and fibrous cap thinning[113].

Notably, a new study presents an NE-activated ratiometric photoacoustic nanoprobe (SPNE) for non-invasive, real-time quantification of plaque NE activity. By employing a dual-signal design with responsive and reference modules, SPNE enables accurate *in vivo* imaging of NE, effectively correcting for probe concentration and tissue depth variations[114]. The photoacoustic signal ratio strongly correlates with a histologically validated plaque vulnerability index, demonstrating the probe's capacity to assess rupture risk and monitor therapeutic efficacy, thereby offering a powerful tool for cardiovascular research and potential clinical translation[114].

2.5. *Platelet inflammation*

In atherosclerosis, platelets mediate disease progression through multifaceted interactions with vascular and immune cells. Platelet-derived mediators critically influence plaque development, with platelet factor 4 (PF4) enhancing macrophage ox-LDL uptake and foam cell formation while inducing an inflammatory phenotype in VSMCs *via* KLF4 signaling[115-118]. Recent research reveals that soluble TREM-like transcript-1 (sTLT-1) forms immune

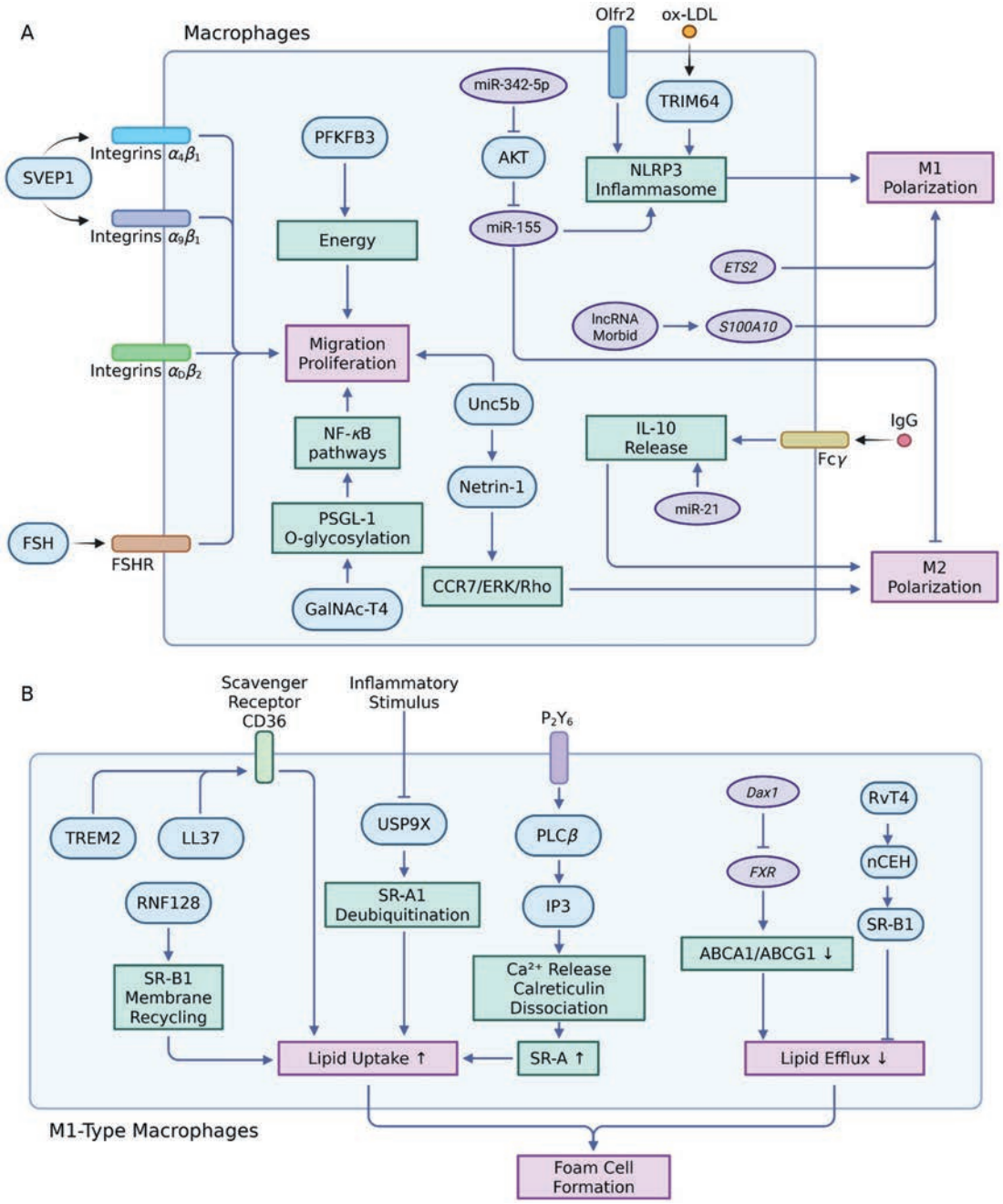

Figure 4 Molecular regulators of lipid metabolism, polarization, and inflammatory responses in macrophages. (A) Macrophages are recruited to inflammatory sites by diverse signals and undergo phenotypic polarization. (B) M1-type macrophages exhibit increased lipid uptake and impaired efflux, which exacerbates their progression into foam cells. Abbreviations: ABCA1/ABCG1, ATP-binding cassette transporter A1/G1; CCR7, C−C chemokine receptor 7; ERK, extracellular signal-regulated kinase; FSH, follicle-stimulating hormone; FXR, farnesoid X receptor; Fcγ, Fc fragment of IgG receptor; GalNAc-T4, *N*-acetylgalactosamine transferase 4; IgG, immunoglobulin G; IL-10, interleukin-10; IP3, inositol 1,4,5-trisphosphate; LL37, antimicrobial peptide LL37; nCEH, neutral cholesteryl ester hydrolase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated b cells; Olfr2, Olfactory receptor 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PLCβ, phospholipase C beta; PSGL-1, P-selectin glycoprotein ligand-1; P_2Y_6, purinergic receptor P_2Y_6; RNF128, ring finger protein 128; RvT4, resolvin T4; SR-A1/SR-B1, scavenger receptor class A/B type 1; SVEP1, sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1; TRIM64, tripartite motif-containing protein 64; TREM2, triggering receptor expressed on myeloid cells 2; UNC5B, uncoordinated-5 homolog B; USP9X, ubiquitin-specific peptidase 9 X-linked. Figure was created using BioRender.

complexes that sustain inflammatory responses[119]. Platelet-neutrophil interactions, regulated by IRGM/*Irgm1*, modulate NETosis, with IRGM/*Irgm1* deficiency alleviating atherosclerosis-associated thrombosis and suppressing NETosis[120]. Meanwhile, $P2Y_{12}$ receptor activation by ADP enhances platelet aggregation, granule release, platelet−leukocyte interactions, and secretion of pro-inflammatory and procoagulant mediators[121]. Platelet-derived microparticles deliver miRNAs such as miR-320b that suppress

ETFA in endothelial cells, reducing inflammation while increasing IL-10 secretion[122,123]. In advanced stages, CLEC-2 recognition of PDPN drives monocyte infiltration[124-127], while CD40L−CD40−TRAF6 signaling exacerbates plaque inflammation through TRAF6-mediated downstream signals[128]. Concurrently, the CXCL12−CXCR4 axis promotes thrombosis, with CCL5 serving as a competitive inhibitor to modulate this inflammatory cascade[128].

2.6. *Dendritic cell inflammation*

Dendritic cells (DCs) actively contribute to atherosclerosis progression through multiple inflammatory pathways. Beyond their classic antigen-presenting functions, DCs directly activate endothelial cells *via* exosomes[129]. In early plaque development, intimal DCs engulf ox-LDL to become foam cells while orchestrating T-cell responses and regulating lipid homeostasis, contributing to lipid core development[130-132]. Specifically, classical DC1 subsets (cDC1s) activate $CD8^+$ T cells to drive interferon-gamma (IFN-γ) secretion, while classical DC2 populations (cDC2s) promote Th2/Th17 polarization *via* MHC-II presentation[133]. Complementing these pathways, plasmacytoid DCs (pDCs) secrete high levels of interferon-alpha (IFN-α), which induce TRAIL-mediated VSMC apoptosis[133,134]. Counter-regulatory mechanisms help restrain excessive DC activation, where IL-27 suppresses DC maturation and promotes Treg generation while inhibiting Th1/Th17 differentiation[135]. Complementarily, research indicates that CCR4, highly expressed on $CD4^+$ $FOXP3^+$ Tregs, is essential for their suppressive function; its deficiency impairs Treg-mediated inhibition of CD80/CD86 on DCs, leading to increased Tconv production of IFN-γ, enhanced Th1 responses, and exacerbated inflammatory atherosclerosis[136] (Fig. 5).

3. Drivers of vascular inflammation

3.1. *Hyperlipidemia*

Hyperlipidemia establishes a pro-inflammatory state within the vascular wall through multiple lipid-derived mediators. Ox-LDL acts as a potent inflammatory trigger, promoting foam cell formation and cytokine secretion from macrophages[137-139]. Activated platelets further contribute by facilitating LDL oxidation, generating ROS, and releasing PCSK9 to degrade the LDL receptor, thereby reducing LDL clearance and exacerbating lipid accumulation[140]. Furthermore, lipid peroxidation induces ferroptosis, a form of cell death in endothelial cells and macrophages, leading to the release of damage-associated molecular patterns (DAMPs) like HMGB1 that perpetuate inflammation *via* TLR4 and RAGE signaling[141-144]. Concurrently, elevated triglyceride-rich lipoproteins (TRLs) and their remnants sustain inflammation. Defective clearance, driven by factors such as ANGPTL proteins, apolipoprotein C-III, and soluble LDL receptor-related protein 1 (LRP1), leads to remnant accumulation[145-148]. Notably, postprandial remnants induce endothelial dysfunction and vascular inflammation. Insulin resistance exacerbates this in metabolic syndromes, where non-fasting triglycerides $\geq$175 mg/dL or elevated apoB48 serve as diagnostic markers. Fibrates and GLP-1 analogs mitigate this by enhancing TRL clearance[149]. These remnants promote endothelial dysfunction by inducing adhesion molecules and generating ROS. They also trigger endothelial apoptosis through the secretion of pro-apoptotic factors such as TNF-α, collectively amplifying inflammatory cascades[147]. Further amplifying inflammation, soluble LRP1 binds macrophage receptors, stimulating TNF-α release and NF-κB activation, creating a pro-inflammatory feedback loop[148]. Apolipoprotein C-III itself directly stimulates monocyte activation and endothelial adhesion while counteracting the anti-inflammatory effects of HDL[147].

Cholesterol crystals (CCs) accumulate in macrophage lysosomes, disrupting lysosomal membrane integrity, which in turn triggers the assembly of the NLRP3 inflammasome. Cathepsin B has been proven to participate in the formation of the NLRP3 inflammasome[150,151]. Additionally, cholesterol transport to the endoplasmic reticulum *via* Aster-B activates CaMKII/JNK signaling and BRCC3-mediated NLRP3 deubiquitination, enhancing inflammasome formation[152]. CCs further activate the complement system through mitochondrial C5aR1, disrupting metabolism to increase ROS and glycolysis, thereby boosting IL-1β production[152,153]. This NLRP3-driven cascade amplifies pro-inflammatory cytokine release, exacerbating plaque inflammation and instability.

Hyperlipidemia also induces broader metabolic dysregulation that reprograms immune and vascular cells. It promotes a pro-inflammatory M1 macrophage shift, while suppressing anti-inflammatory M2 phenotypes. Macrophages metabolize cholesterol to 27-hydroxycholesterol (27HC) through CYP27A1, which subsequently activates LXRs in endothelial cells. This 27HC−LXR activation suppresses LRP1-mediated cholesterol efflux and upregulates adhesion molecules[154]. Furthermore, intermittent hyperlipidemia reduces protective arterial-resident

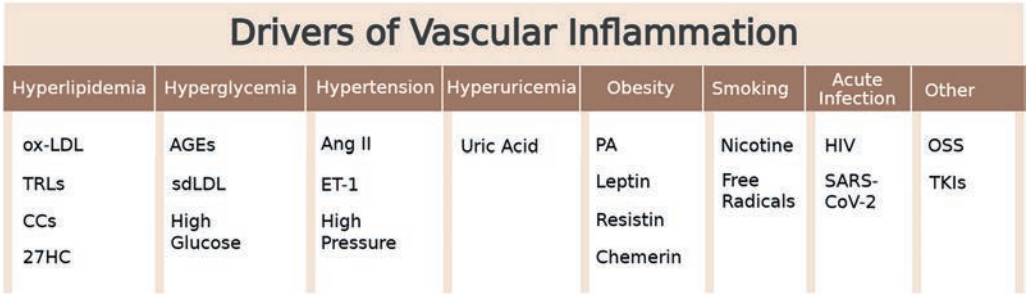

Figure 5 Key drivers of vascular inflammation. Abbreviation: ox-LDL, oxidized low-density lipoprotein; TRLs, triglyceride-rich lipoproteins; CCs, cholesterol crystals; 27HC, 27-hydroxycholesterol; AGEs, advanced glycation end products; sdLDL, small dense low-density lipoprotein; Ang II, angiotensin II; ET-1, endothelin-1; PA, palmitic acid; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OSS, oscillatory shear stress; TKIs, tyrosine kinase inhibitors.

macrophages marked by lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) and T cell immunoglobulin mucin domain 4 (TIMD4) and downregulates macroautophagy, thereby impairing efferocytosis or the clearance of dead cells[18]. This impairment leads to expanded necrotic cores and the accumulation of pro-inflammatory debris within plaques. Genetic metabolic defects such as *Agpat2* or *Trib1* deficiency worsen hepatic lipid metabolism dysfunction. *Agpat2* deficiency inhibits lipoprotein receptors and activates lipogenic genes, leading to severe hepatic steatosis and fibrosis. In *Agpat2*$^{-/-}$ *Ldlr*$^{-/-}$ mice, this dysmetabolism reduces plaque stability *via* decreased VSMCs and collagen[155]. *Trib1* deficiency in *Ldlr*$^{-/-}$ mice elevates very-low-density lipoprotein (VLDL) cholesterol and triglycerides, drives hepatic pro-inflammatory ceramide accumulation and JNK-mediated inflammation, resulting in larger aortic plaques with expanded necrotic cores[156]. In contrast, IL-38 modulates CD4$^+$ T cell differentiation by inhibiting Th17 cells while promoting Treg and Th2 development, and suppresses atherosclerosis by reducing apoptosis and lipid accumulation[157]. NgBR overexpression activates SR-BI to enhance reverse cholesterol transport and inhibit sterol regulatory element-binding protein 2 (SREBP2)-mediated synthesis, lowering LDL-C and hepatic lipids, attenuating TNF-α/IL-1β-driven inflammation, and improving plaque stability *via* thickened fibrous caps[158].

3.2. Hyperglycemia

Chronic hyperglycemia drives vascular inflammation in diabetes primarily through the formation of advanced glycation end products (AGEs), which act as pivotal molecular triggers. AGE−RAGE signaling pathway suppresses PI3K/AKT/mTOR-mediated autophagy and promotes the accumulation of damaged cellular components[159,160]. They also activate NOX while suppressing eNOS function, disrupting endothelial homeostasis and reducing NO bioavailability[161]. AGEs also directly promote ROS accumulation *via* binding to extracellular matrix receptors and amplify oxidative damage by activating pathways like protein kinase C (PKC) signaling[161]. Crucially, AGEs-induced ROS synergize with cytokines and the NLRP3 inflammasome to intensify vascular injury, accelerating the development of diabetic atherosclerosis.

The inflammatory milieu is further amplified by endothelial-mesenchymal transition (EndMT) and diabetic dyslipidemia. Oscillatory low shear stress at susceptible vascular sites, combined with hyperglycemia, induces EndMT through TGF-β signaling activation[162-164]. This process results in loss of endothelial markers and acquisition of mesenchymal features, with cells upregulating pro-fibrotic factors and pro-inflammatory signals. The resulting fibroblast-like cells fuel inflammation and atherogenesis by secreting excessive matrix metalloproteinases (MMPs) that promote pathological extracellular matrix remodeling and recruiting monocytes[164]. Concurrently, diabetic dyslipidemia, characterized by elevated TRLs and small, dense LDL (sdLDL), markedly contributes to vascular inflammation[165]. Hyperglycemia drives increased hepatic VLDL synthesis and intestinal chylomicron production, leading to elevated remnant cholesterol. These remnant particles carry more cholesterol than LDL, are smaller and more oxidizable, and penetrate the endothelium more readily to deposit within the intima[166-170]. SdLDL is formed through triglyceride exchange between triglyceride-rich lipoprotein remnants and cholesteryl esters in HDL, a process enhanced by CETP activity[170]. It exhibits greater atherogenicity due to reduced LDL receptor affinity, increased oxidation susceptibility, and prolonged plasma half-life[171,172]. Their small size and low antioxidant capacity further facilitate endothelial penetration and accelerate conversion to highly pro-inflammatory ox-LDL, thereby promoting atherosclerosis[168].

Ultimately, chronic hyperglycemia establishes a vicious cycle of endothelial senescence and autophagy dysfunction that exacerbates diabetic vascular pathology. Hyperglycemia-induced inflammatory pathways, particularly persistent NF-κB activation, drive endothelial senescence through mechanisms including the upregulation of the AQR/PLAU signaling axis. This leads to G2/M cell cycle arrest and increased senescence markers[173], while senescent endothelial cells further upregulate NF-κB-dependent cytokines and adhesion molecules, enhancing monocyte adhesion[174]. Concurrently, hyperglycemia-induced mitochondrial ROS contribute to inflammatory activation and trigger cytochrome C release, activating the caspase cascade and inducing endothelial apoptosis[175-177]. While acute stress may induce protective autophagy, prolonged hyperglycemia and associated inflammation disrupt autophagy, leading to accumulation of damaged organelles and proteins, increasing oxidative stress, inflammatory signaling, and directly promoting cellular senescence and apoptosis[160,178,179]. Autophagy dysfunction also degrades endothelial junction proteins, compromising barrier integrity and facilitating inflammatory lipid and immune cell infiltration, thereby amplifying the pro-inflammatory vascular microenvironment. Converse factors like the mitochondrial deacetylase SIRT3 demonstrate protective counter-regulation, attenuating hyperglycemia-induced senescence and atherosclerosis by modulating senescence-associated proteins and likely counteracting inflammatory pathways[180].

3.3. Hypertension

According to the International Society of Hypertension, blood pressure is classified into four categories: normal (<130/85 mmHg), high-normal (130−139/85−89 mmHg), grade 1 hypertension (140−159/90−99 mmHg), and grade 2 hypertension ($\geq$160/100 mmHg)[181]. Mechanistically, elevated blood pressure directly damages endothelial barrier function, increasing permeability and promoting the infiltration of LDL and plasma components into the arterial wall[182]. These pro-inflammatory substances, together with hypertension-induced low wall shear stress from arterial dilation, initiate inflammation by predisposing the endothelium to dysfunction and pro-inflammatory activation[183]. Hypertension also causes structural alterations in the vascular wall, including compressive deformation, which significantly enhances LDL retention and accumulation within the vessel wall[183,184]. Retained LDL is oxidized into ox-LDL, prompting macrophage uptake and foam cell formation-the hallmark of atherosclerotic lesions. Hypertension amplifies this lipid-driven inflammation, which has minimal impact under normotension, leading to plaque thickening[183]. Furthermore, hypertension activates GSK3β, leading to mitochondrial dysfunction. GSK3β activation upregulates mitochondrial protease OMA1, cleaving OPA1 to induce mitochondrial fragmentation. Concurrent suppression of the mitochondrial biogenesis master regulator *PGC1*α amplifies ROS accumulation and oxidative stress[185]. The GSK3β−OMA1 axis drives vascular endothelial inflammation, apoptosis predisposition, and cholesterol dysregulation *via* PGC1α suppression. Erythrocyte-derived ATP potentially aggravates injury through DC-T cell-mediated inflammation. Together, these mechanisms form a self-perpetuating cycle of vascular inflammation and plaque instability, reversible *via* OMA1 knockdown or PGC1α overexpression[185].

Angiotensin II (Ang II) serves as a central regulator of pro-inflammatory and pro-atherosclerotic signaling, with its effects extending from the central nervous system to peripheral vasculature. In hypertension, Ang II crosses the compromised blood−brain barrier, activating central AT1a receptors in circumventricular organs and enhancing sympathetic output *via* the SFO−PVN pathway, which elevates corticosterone and promotes Th1/Th17 cell differentiation while suppressing Treg cells, establishing a systemic pro-inflammatory state that accelerates atherosclerosis[186-188]. Central to its pathogenicity is the activation of the AT1 receptor, which promotes oxidative stress, endothelial dysfunction, and vascular inflammation[189]. Notably, Ang II synergizes with oxLDL *via* the AT1−LOX-1 receptor complex, amplifying Gq-dependent signaling and aldosterone production in a blood pressure-independent manner[190]. Beyond its systemic effects, Ang II disrupts endothelial function by impairing the TRPV4/eNOS/NO vasoprotective axis, reducing TRPV4 membrane expression and eNOS phosphorylation[191]. It further induces VSMC phenotypic switching, proliferation, and MMP-mediated extracellular matrix degradation, promoting plaque instability[192,193]. In contrast to the pathogenic AT1R pathway, a counterregulatory renin−angiotensin−aldosterone system (RAAS) axis exists wherein ACE2 metabolizes Ang II to Ang(1−7), which subsequently activates the Mas receptor to promote vasodilation and confer anti-inflammatory and antioxidant effects[194]. The therapeutic importance of modulating this balance is strongly supported by clinical evidence demonstrating that RAAS inhibitors (ACEIs/ARBs) stabilize atherosclerotic plaques[194,195]. These pleiotropic benefits, which are partly independent of blood pressure reduction, are mediated through a direct reduction in inflammation and macrophage infiltration, suppression of MMP activity, and a concomitant increase in collagen content within the plaque[195].

Endothelin-1 (ET-1) synthesis begins with *Edn1* gene transcription/translation into preproET-1, cleaved by furin to big ET-1, then by endothelin-converting enzyme to mature peptide, with an alternative pathway involving chymase and neprilysin[196]. Endothelial ET-1 overexpression enriches exosomal miR-33, which suppresses macrophage nuclear receptor NR4A to promote pro-inflammatory M1 polarization, accelerating plaque growth[197]. In diabetic contexts, ET-1 activates perivascular NOX1, generating ROS that trigger significant monocyte/macrophage infiltration and plaque expansion while destabilizing lesions, effects reversed by *Nox1* knockout[198]. A clinical study in a south-eastern Iranian population revealed that genetic susceptibility links include the rs5370 T allele associating with coronary atherosclerosis risk and the rs10478694 3A allele correlating with hypertension susceptibility, with elevated plasma ET-1 observed in hypertensive coronary atherosclerosis patients[199].

3.4. Hyperuricemia

Hyperuricemia, defined as elevated serum uric acid levels, drives vascular inflammation through multiple interconnected pathways. Urate crystals act as DAMPs that activate the NLRP3 inflammasome, leading to the maturation of pro-inflammatory cytokines such as IL-1β and IL-18[200,201]. Even soluble urate functions as an inflammatory mediator, stimulating immune cells to release factors like TNF-α and IL-6, while simultaneously reflecting overactive purine metabolism that reduces anti-inflammatory adenosine effects[202-204].

Hyperuricemia critically induces NO/ROS disequilibrium by diminishing NO bioavailability and promoting ROS overproduction, which leads to leukocyte adhesion and exacerbated inflammation[205,206]. Hyperuricemia achieves this through the following mechanisms. Firstly, it activates NADPH oxidases to increase ROS production, promoting the reaction of superoxide anion with NO to form peroxynitrite ($ONOO^-$), which reduces NO bioavailability and impairs vasodilation[202,207]. Then, hyperuricemia inhibits dimethylarginine dimethylaminohydrolase-2 (DDAH-2), elevating asymmetric dimethylarginine (ADMA) levels and further suppressing eNOS activity[208,209].

Furthermore, hyperuricemia induces a pro-inflammatory shift in endothelial cells. It activates NF-κB *via* the HMGB1/RAGE signaling pathway, promoting adhesion molecule and chemokine expression for monocyte recruitment. Studies demonstrate that high uric acid levels (20 mg/dL) significantly upregulate intracellular HMGB1 expression and extracellular secretion in human umbilical vein endothelial cells, along with increased RAGE receptor expression[210]. The binding of HMGB1 activates NF-κB, elevating proinflammatory cytokines and impairing endothelial function[211]. Additionally, hyperuricemia activates YAP/TAZ through the Hippo pathway, upregulating SREBP2 to exacerbate inflammatory responses[212,213]. It also causes structural damage like glycocalyx shedding and endothelial-to-mesenchymal transition, disrupting barrier integrity[214]. Hyperuricemia additionally drives programmed cell death. Urate-induced ROS activates NLRP3, leading to pyroptosis *via* gasdermin D pore formation, releasing inflammatory mediators[213,215]. It also suppresses the nuclear factor erythroid 2-related factor 2 (NRF2)/SLC7A11/GPX4 axis, inducing ferroptosis characterized by glutathione depletion and iron/lipid peroxide accumulation in macrophages and endothelia, further fueling atherosclerosis[216]. In animal models, renal vascular endothelial tissues from hyperuricemic mice exhibit hallmark features of ferroptosis, including markedly increased iron deposition and downregulated GPX4 expression[217].

3.5. Obesity

Obesity elevates circulating free fatty acids such as palmitic acid (PA), which directly induces vascular inflammation through multiple signaling and epigenetic pathways. PA promotes NF-κB nuclear translocation and pro-inflammatory responses primarily through TLR4 signaling, utilizing both MyD88-dependent and independent pathways[218]. It further enhances NF-κB transcriptional activity by inducing nucleophosmin (NPM) expression, which binds to the p65 subunit[219]. This leads to upregulated adhesion molecules and cytokines, establishing a pro-inflammatory positive feedback loop that promotes monocyte−endothelial adhesion. Beyond direct signaling, PA induces extensive epigenetic reprogramming by remodeling super-enhancers (SEs), an effect reducible by bromodomain-containing protein 4 (BRD4) or NF-κB inhibition[220]. It also inhibits macrophage phagocytic and efferocytotic functions, preventing inflammation resolution[220]. Concurrently, PA disrupts metabolic homeostasis by inhibiting miR-133a-3p. This inhibition increases TRPM4 calcium channel expression, causing calcium overload, mitochondrial ROS accumulation, endothelial apoptosis, and amplified inflammation[221]. While PA-triggered inflammation normally upregulates the lncRNA PARAIL, which binds ELAVL1 to form an NF-κB-mediated feedback brake, the loss of PARAIL, which is common in cardiometabolic disease, removes this protection, permitting sustained inflammation[222]. Additionally, PA disrupts ciliary homeostasis. After sequestration into lipid droplets, PA's cytosolic availability decreases, reducing *S*-palmitoylation of the ciliary protein ARL13B. This leads to ARL13B degradation and

primary cilia loss, impairing endothelial sensing of protective shear stress and accelerating inflammation[223].

The overall lipid milieu in obesity critically regulates vascular inflammation, defined by a dysregulated balance between pro- and anti-inflammatory lipid species. Omega-6 polyunsaturated fatty acids (PUFAs) like linoleic acid (LA) exhibit context-dependent roles. Under high dietary omega-6 to omega-3 ratios, LA metabolizes into arachidonic acid, generating pro-inflammatory mediators, including leukotriene B_4 (LTB_4) that directly activate inflammation[224]. Yet when replacing saturated fatty acids, LA can lower plasma VLDL/LDL, ApoB, and CRP, attenuating atherosclerosis[225]. In contrast, omega-3 PUFAs, including EPA and DHA, exert anti-inflammatory effects by competitively inhibiting omega-6 metabolism, activating FFAR4 to suppress TLR4/NF-κB signaling, promoting M2 macrophage polarization, and producing specialized pro-resolving mediators[226,227]. Notably, high-dose pure EPA reduces cardiovascular events, whereas EPA/DHA combinations show no benefit, potentially due to DHA counteraction[226,228]. Beyond PUFAs, short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced through gut microbial fermentation of dietary fiber. These SCFAs activate FFAR2/3 receptors to inhibit the NF-κB pathway, reducing TNF-α and IL-6 secretion[229,230]. Furthermore, SCFAs suppress histone deacetylase (HDAC) activity, enhancing expression of the key transcription factor FOXP3 to promote anti-inflammatory Treg cell differentiation[229]. Additionally, SCFAs activate the NRF2 pathway, boosting antioxidant enzyme activity and protecting endothelial function[229,231]. However, succinate, an exception among microbial metabolites, accumulates during dysbiosis and exacerbates ischemia-reperfusion injury and plaque inflammation[232]. Other lipid mediators further contribute to this inflammatory milieu. Pinolenic acid (PNLA) suppresses the NF-κB/STATs pathway to reduce TNF-α, IL-6, and PGE_2 while activating PPARγ to improve insulin sensitivity[233]. Circulating fatty acid synthase (cFAS) binds to LDL, promoting macrophage foam cell formation and triggering inflammatory cytokine release[234]. In the inflammatory milieu of atherosclerosis, miR-127-3p-mediated inhibition of SCD1, which reduces the synthesis of unsaturated fatty acids like oleic acid, triggers acetyl-CoA accumulation, enhances oxidative phosphorylation, and promotes pro-inflammatory M1 macrophage proliferation[235].

Obesity further amplifies vascular inflammation through pathogenic adipokine shifts and adipose tissue hypoxia. Adipokine dysregulation involves both elevated pro-inflammatory factors and reduced protective ones[236]. Leptin activates endothelial NF-κB to upregulate VCAM-1/ICAM-1 and stimulates VSMC proliferation *via* platelet-derived growth factor (PDGF)[236,237]. Resistin enhances VSMC proliferation and macrophage lipid accumulation[238,239]. Chemerin upregulates CRP and cytokines, accelerating VSMC migration towards the intima[240]. Furthermore, in obesity, increased chemerin secretion from perivascular adipose tissue (PVAT) specifically impairs its normal vasoprotective functions[240,241]. Conversely, decreased levels of adiponectin impair cholesterol efflux *via* ABCA1/ABCG1 inhibition and reduce NO bioavailability, while reductions in fibroblast growth factor 21 (FGF-21) and CTRP9 exacerbate lipid dysregulation and endothelial oxidative stress[236]. This adipokine imbalance creates a self-perpetuating feedback loop that amplifies vascular damage. Simultaneously, adipose tissue expansion leads to adipocyte hypertrophy, insufficient angiogenesis, reduced capillary density, and hypoxia[242]. This hypoxic microenvironment activates hypoxia-inducible factor 1-α (HIF-1α) in adipocytes, triggering secretion of chemokines and cytokines that promote macrophage infiltration and establish a chronic low-grade inflammatory state, which systemically compromises endothelial function and drives metabolic dysregulation[243,244].

3.6. Smoking

Smoking and nicotine exposure drive atherosclerotic progression through interconnected inflammatory, oxidative, and metabolic pathways. Notably, nicotine itself exerts direct pro-inflammatory, pro-oxidative, and pro-thrombotic effects, which can be synergistically amplified by interactions with e-cigarette-specific components, independent of traditional smoke exposure[245,246]. At the cellular level, nicotine stimulates monocytes to release extracellular vesicles enriched with miR-155, which is epigenetically upregulated *via* HIF1α-dependent DNA methylation. These vesicles deliver miR-155 to endothelial cells, activating NF-κB signaling and promoting endothelial inflammation and apoptosis, a process attenuable by miR-155 inhibition[247]. These mechanisms contribute to impaired vascular repair, particularly after drug-eluting stent implantation, evidenced by elevated macrophage infiltration ($CD68^+$), reduced re-endothelialization (CD31), and VSMC proliferation (α-SMA), leading to increased neointimal area and stent stenosis[248]. Gender-specific responses reveal heightened vulnerability in the descending aorta region among females, manifested by elevated serum cotinine levels, more pronounced expression of inflammatory factors, greater nicotine-induced heart rate elevation, and significantly increased plaque burden in the descending aorta. In contrast, males primarily exhibit susceptibility in the aortic arch region[249].

Beyond nicotine, cigarette smoke delivers abundant free radicals that induce profound oxidative stress in vascular endothelium. These radicals react with NO to form peroxynitrite, severely reducing NO bioavailability and impairing endothelium-dependent vasodilation, a hallmark of endothelial dysfunction. Polycyclic aromatic hydrocarbons and aldehydes in smoke further amplify ROS production by activating NADPH oxidase and xanthine oxidase, while simultaneously suppressing antioxidant defenses[250-252]. Critically, smoking activates the RhoA/ROCK pathway, which destabilizes *eNOS* mRNA and inhibits Akt phosphorylation, further suppressing NO synthesis and exacerbating endothelial injury[252,253]. Beyond endothelial disruption, smoking increases circulating levels of neutrophils, monocytes, and $CD8^+$ T cells. These cells release inflammatory factors, promoting vascular wall inflammation[254,255]. Furthermore, recent evidence suggests partial reversibility of endothelial injury after cessation, with some trials reporting improved vascular function and reduced inflammatory biomarkers[252]. However, recovery potential depends on initial damage severity and smoking history, and advanced injury is often permanent, underscoring the urgency of early cessation[252].

3.7. Physical inactivity

Sedentary lifestyles characterized by minimal physical activity and prolonged screen time are associated with unhealthy cholesterol levels that contribute to atherosclerosis. Prolonged sitting directly impairs lower limb blood vessels through key hemodynamic alterations. It reduces anterograde shear rates in arteries like the superficial femoral artery, significantly increases blood viscosity specifically in the lower limbs without affecting the

upper limbs, and generates low, oscillatory disturbed flow patterns due to arterial bending in the seated posture[256]. These abnormal shear stresses collectively promote the initiation and progression of atherosclerosis in the affected region.

Atherosclerotic plaques predominantly form at arterial bifurcations, curvatures, and other disturbed flow regions characterized by low shear stress (LSS) or oscillatory shear stress (OSS), whereas laminar shear stress in straight segments exerts atheroprotection[257]. Disturbed flow activates mechanosensors, including integrin $\alpha_5\beta_1$ and the ion channel Piezo1. Piezo1 activation promotes atherosclerosis *via* G_q/G_{11} and NF-κB pathways, whereas TRPV4 agonism mimics atheroprotective flow to reduce plaque[258-260]. Downstream, activated integrin $\alpha_5\beta_1$ engages c-Abl kinase, which phosphorylates YAP at Y357, prompting nuclear translocation where phosphorylated YAP complexes with BACH1 to drive pro-inflammatory gene transcription[261-263]. Concurrently, disturbed flow or TNF-α stimulates BACH1 nuclear translocation, creating a positive feedback loop that amplifies YAP expression and inflammatory signaling by binding the YAP promoter[263]. The NF-κB subunit c-REL is enriched in susceptible areas, promoting inflammation *via* TXNIP−p38 MAPK and non-canonical NF-κB pathways[264]. Disturbed flow also critically disrupts endothelial barrier function. Disturbed flow impairs VE-cadherin junctions *via* GRK2-mediated vinculin (VCL) phosphorylation at Ser721, inactivating VCL and destabilizing VE-cadherin/catenin complexes to accelerate atherosclerosis[265]. Additionally, disturbed flow promotes atherosclerosis by inhibiting MST1 kinase, which decreases Connexin 43 (Cx43) phosphorylation and triggers pathological hemichannel opening facilitated by filamin B. This effect is blocked by *MST1* overexpression or the hemichannel inhibitor TAT-GAP19[266]. Beyond VCL and Cx43, cleavage of γ-protocadherin (γ-Pcdh) under disturbed flow releases its intracellular domain (ICD), which translocates to the nucleus, binds Notch ICD, disrupts the protective Notch−RBPJ complex, and consequently suppresses the transcription of atheroprotective factors KLF2 and KLF4[267]. Epigenetically, disturbed flow activates PKN1, which phosphorylates histone H3.3 at Ser31 to promote H3K27 acetylation at FOS/FOSB promoters and H3K36 trimethylation in gene bodies, driving inflammatory expression[268]. Additionally, OSS promotes endothelial inflammation through a YAP/TAZ−SWAP70 axis. OSS upregulates SWAP70 expression *via* YAP/TAZ[269]. SWAP70 then binds CAV1, facilitating its nuclear translocation. Within the nucleus, the SWAP70−CAV1 complex cooperates with IRF1 to enhance the transcription of pro-inflammatory genes[269].

In contrast, laminar shear stress activates transcription factors KLF2 and NRF2, suppressing inflammation and enhancing barrier function. Under laminar flow, PECAM-1 activation activates the PI3K/Akt pathway to stimulate eNOS, producing vasoprotective NO for vasodilation[270,271]. KLF2 upregulates IGFBP6, which binds major vault protein (MVP) to suppress JNK and NF-κB phosphorylation, inhibiting adhesion molecule expression[272]. Deficiency in IGFBP6 increases plaque susceptibility under disturbed flow conditions[272]. Simultaneously, KLF2 induces UCP2 expression, activating AMPK to inhibit FOXO1 and subsequently reduce pro-inflammatory genes. Loss of UCP2 elevates mitochondrial ROS production, promoting inflammation[273]. These protective mechanisms are significantly compromised in disturbed flow regions, where low shear stress alternatively induces endothelial apoptosis through FOXO1 signaling, collectively contributing to endothelial dysfunction and atherosclerotic progression.

3.8. Acute infection

SARS-CoV-2 induces atherosclerosis through multiple specific pathways. The virus directly infects vascular endothelial cells *via* the ACE2 receptor, triggering endothelial apoptosis, dysfunction, and Ang II accumulation, while activating the NF-κB pathway to upregulate adhesion molecules, mediating monocyte adhesion and migration[274,275]. The virus also triggers cytokine storms and NETs, exacerbating vascular inflammation and thrombosis. Additionally, SARS-CoV-2 infection triggers the complement cascade, producing anaphylatoxins C3a and C5a, which amplify inflammation and endothelial injury[276]. The terminal complement product C5b-9 disrupts endothelial membrane integrity, increasing vascular permeability and promoting lipid deposition and atherosclerotic plaque formation. Excessive complement activation and vascular injury are also observed in systemic lupus erythematosus (SLE), indicating that the complement system is a common pathway driving atherosclerosis in both infectious and autoimmune diseases[276,277]. Concurrently, SARS-CoV-2 directly binds to platelet surface receptors or indirectly activates platelets through endothelial injury, releasing procoagulants such as P-selectin and PF4[274,278]. Furthermore, viral infection disrupts circulating miRNAs, upregulating proinflammatory miR-155 and downregulating anti-inflammatory miR-146a/miR-27, further modulating inflammatory and fibrotic processes[279]. Even post-acute infection, persistent viral antigens, or autoimmune responses may lead to "long COVID", promoting plaque progression through sustained endothelial dysfunction and chronic inflammation. These diverse mechanisms collectively drive the initiation, progression, and acute complications of atherosclerosis in the context of COVID-19, significantly increasing cardiovascular risk, particularly in individuals with preexisting conditions.

HIV promotes atherosclerosis through interactions between viral-specific pathways and host inflammatory responses. Viral proteins (*e.g.*, Tat, Nef, Env) activate the NF-κB pathway to directly induce pro-inflammatory cytokines and adhesion molecules in monocytes and endothelial cells. Tat mimics chemokines to recruit monocytes and upregulate TF expression, while Nef damages endothelial cells *via* oxidative stress[280]. HIV selectively depletes gut $CD4^+$ T cells, disrupting the mucosal barrier and triggering microbial translocation, which activates monocytes through TLR4 to release sCD14 and amplify systemic inflammation[281]. HIV also activates the NLRP3 inflammasome, driving caspase-1-mediated IL-1β/IL-18 release and pyroptosis, while upregulating scavenger receptors (*e.g.*, CD36) in macrophages to enhance ox-LDL uptake[282]. Additionally, viral proteins induce endothelial apoptosis, platelet activation, and TF-positive extracellular vesicle release, synergistically promoting thrombosis[281]. Even after viral suppression by ART, chronic inflammation and immune dysregulation persist, driving atherosclerosis progression[281]. Moreover, ART itself can directly promote vascular lesions by downregulating eNOS, inducing mitochondrial dysfunction in endothelial cells. Indirectly, ART contributes to vascular pathology[283]. It causes dyslipidemia and insulin resistance, accelerating atherosclerosis[284].

3.9. Chemical inducers

Tyrosine kinase inhibitors (TKIs), including first-generation imatinib and newer agents like nilotinib, ponatinib, and dasatinib, have revolutionized chronic myeloid leukemia (CML) treatment but significantly induce vascular inflammation. Though designed to target BCR-ABL in leukemia cells, they non-specifically inhibit

endothelial molecules (VEGFR), disrupting vascular homeostasis[285]. Nilotinib/ponatinib causes endothelial apoptosis *via VEGFR* suppression (ponatinib additionally elevates VWF), while imatinib/dasatinib triggers oxidative stress[286,287]. Clinical cases reveal cumulative cerebrovascular damage after long-term use[286]. *In vitro*, dasatinib shows toxicity at clinical doses (0.1 μmol/L) and upregulates ICAM-1 more strongly than imatinib at 10−20 μmol/L[287]. TKIs promote atherosclerosis *via* elevated IL-6/IL-1β, altered adhesion molecule expression, and lipid metabolism disruption. Imatinib accumulates saturated lipids and cholesterol esters, while dasatinib disturbs membrane lipids, thereby sustaining a self-amplifying cycle involving oxidative stress, lipid dysregulation, and inflammation[287]. These effects fuel a self-amplifying "oxidative stress−lipid dysregulation-inflammation" cycle. Given differential risks (ponatinib > nilotinib for vascular occlusion, dasatinib > imatinib for inflammation), tailored vascular monitoring is essential during treatment[286,287].

4. Therapies targeting inflammation in atherosclerosis

A major clinical study (n = 15,494) in statin-treated percutaneous coronary intervention (PCI) patients demonstrated that residual inflammatory risk (hsCRP ≥2 mg/L) overwhelmingly surpasses residual cholesterol risk (LDL-C ≥ 70 mg/dL) in predicting MACE[288]. This finding underscores that hsCRP serves as a more potent predictor of future cardiovascular events than lipid measurements alone. Even with effective statin therapy, patients with elevated inflammation had a significantly higher one-year MACE risk (HR = 1.78) compared to those with only high cholesterol (HR = 1.01, non-significant), while those with both risks also faced increased risk (HR = 1.56)[288]. This shows hsCRP better reflects residual risk post-PCI than LDL-C. Thus, solely lowering LDL-C may be insufficient; actively targeting residual inflammation is now an equally crucial, and sometimes paramount, strategy alongside lipid-lowering to reduce ASCVD events.

4.1. Preclinical evidence

To address this need, drug discovery is now targeting specific inflammatory pathways. Recent preclinical advances have identified several promising strategies, detailed in Table 1[289-364]. These approaches aim for precision, avoiding broad immunosuppression. Key strategies include inhibiting IRAK1 and IRAK4, which mediate endothelial inflammation and VSMC phenotypic modulation[365-368]. Another strategy targets the JAK/STAT pathway. Comprising four JAK kinases and seven STAT transcription factors, this pathway is activated by various cytokines and growth factors and thus regulates fundamental processes like inflammation, cell proliferation, and apoptosis[369]. Beyond the JAK/STAT pathway, targeting NETosis *via* LTC4 inhibition shows therapeutic potential but faces challenges. While suppressing LTC4 ameliorates NET-driven endothelial damage, global NETosis impairment risks increased infection susceptibility[370,371]. Alternatively, targeting inflammation with endogenous specialized pro-resolving mediators (SPMs) provides a safe and effective strategy, as these mediators promote inflammation resolution without the immunosuppressive risks seen with broader pathway inhibition[372-374]. Concurrently, CRP promotes atherosclerosis under hyperlipidemia by upregulating hepatic Cidea, driving lipid droplet enlargement and systemic dyslipidemia *via* a hepato−vascular axis[375]. This pathway is essential for atorvastatin's efficacy,

Table 1 Emerging anti-atherosclerotic targets and drugs with preclinical efficacy.

Target	Drug	Mechanism	Research model	Experimental outcome
PCSK9 inhibition	SBC-115076[289]	Occupies the LDLR-binding site on PCSK9 to prevent PCSK9-LDLR interaction	High-methionine diet in *ApoE*$^{-/-}$ mice	Reduce Hcy and increase HDL-C Decrease lipid accumulation and stabilize plaques and suppress foam cell formation
	Alirocumab[290]	Neutralize free PCSK9	Lp(a)-stimulated human coronary artery endothelial cells	Reduce ICAM-1 at 1 and 10 μg/mL, but increase at 100 μg/mL Inhibit E-selectin by 18%−25% and monocyte adhesion by 14% at 1 and 10 μg/mL Increase IL-6 and NF-κB p65 Elevate eNOS at 100 μg/mL
	Evolocumab[290]			Dose-dependently reduce ICAM-1 Reduce E-selectin by 24%−29% Increase IL-6 by 310% at 1 μg/mL Significantly elevate eNOS at 100 μg/mL, better than Alirocumab
ACLY inhibitors	326E and 326E-CoA[291]	326E-CoA competitively binds to the CoA-binding site on ACLY	HFHC diet-induced golden hamster	Oral administration of 326E (30 mg/kg) for 2 weeks reduced TC by 57.8%, TG by 92.9% and LDL-C by 72.8%
			WD-induced *ApoE*$^{-/-}$ mice	Oral administration of 326E inhibited body weight gain, reduced aortic plaque area, and lowered hsCRP levels

			Rhesus monkeys with spontaneous hyperlipidemia	326E significantly reduced TC by 31.83%, TG by 20.94%, LDL-C by 20.11%, and ApoB100 by 20.88%
	Isoginkgetin[292]	Directly targets ACLY, inhibiting its enzyme activity	*ApoE*$^{-/-}$ mice	Significantly reduce TC, TG, and LDL-C in serum and liver Improve lipoprotein profile Decrease aortic plaque area and necrotic core size Show no significant changes in serum inflammatory factors (CRP, IL-1β, IL-6) or oxidative stress markers
			Ldlr$^{-/-}$ hamsters	Significantly reduce hepatic TC and serum TG levels Improve non-HDL-C Decrease aortic plaque area Alleviate hepatic lipid deposition.
	Bempedoic acid combined with Liraglutide[293]		NASH mouse model	Significantly reduce hepatic steatosis by 47%, hepatocyte ballooning by 94%, and liver fibrosis by 44%, with a 75% decrease in NAS and near-complete elimination of hepatocyte ballooning
IRAK1/4 inhibitors	HS-243[294]	Bind to ATP-binding pockets of IRAK/4	LPS-induced RA-FLS cells THP-1 human macrophages Challenged with LPS (100 ng/mL)	Significantly reduce the release of 15 pro-inflammatory factors
Inhibitors of NLRP3 inflammasome	MCC950[295,296]	Bind to Walker B motif within NLRP3	*ApoE*$^{-/-}$ mice with HFD	Reduce total aortic plaque area (4.84 *vs* 7.25 mm^2), aortic root plaque area by 17.53%, and lipid content by 23.55%
			Ox-LDL-induced THP-1 human macrophages	Reduce Caspase-1 vitality by 53.5%, ASC oligomerization and NLRP3 expression
	JT002[297]	Block NLRP3 inflammasome complex formation	The model of Muckle-Wells syndrome	Reduce systemic inflammation (prevents weight loss) and ameliorate liver pathology (liver/body weight ratio 9.4% to 5.7%) Downregulate fibrotic and inflammatory genes Reduce neutrophil infiltration
	Velutone F and compound 14c[298]		MSU-induced peritonitis in LPS-primed mice model	14c (6h) reduced splenic IL-1β levels (805 $\pm$ 141 pg/mL *vs* model 1519 $\pm$ 229 pg/mL)
JAK/STAT inhibitors	Ruxolitinib[299]	Inhibit JAK2/STAT3 phosphorylation and downregulate SOCS3 expression	New Zealand male rabbits	Reduce the formation of aortic atherosclerotic plaques Decrease the contents of plasma TG, TC, and LDL enhance HDL-C level Downregulate pro-inflammatory factors and upregulate anti-inflammatory factors
ASK1−JNK inhibitors	Neratinib[300]	Bind to and inhibit ASK1 (independent of its original HER2 target), thereby suppressing the downstream JNK/p38 and NF-κB	*Ldlr*$^{-/-}$ atherosclerotic mouse model (both sexes), alone or in combination with Rosuvastatin	Reduce atherosclerotic plaque area and necrotic core size Improve plaque stability (increase α-SMA$^+$

(*continued on next page*)

Table 1 (*continued*)

Target	Drug	Mechanism	Research model	Experimental outcome
		signaling pathways to reduce vascular inflammation.		cells, decrease $CD68^+$ macrophages) Enhance efficacy when combined with statins and safe at the effective dose (20 mg/kg/day)
TLR4 inhibitors	Baicalein[301,302]	Upregulate miR-182 and suppress TLR4	SAP-ALI mouse model	Alleviate inflammatory cell infiltration and alveolar wall edema Reduce lung W/D ratio and TLR4/MyD88/TRIF levels Decrease inflammatory cytokines in pancreatic/lung tissues and BALF Lower ROS and elevate GSH.
	TAK-242[303]	Bind to the intracellular domain TIRAP of TLR4	Mouse allogeneic aortic transplantation model: BALB/c (H-2d) donors to C57BL/6 (H-2b) recipients	Ameliorate intimal hyperplasia and postpone neointimal formation Reduce levels of $Ly6C^{hi}$ cells in peripheral blood, bone marrow and spleen Downregulate pro-inflammatory cytokines and chemokines
cGAS−STING inhibitors[304,305]	RU.521[306,307]	Bind to the ATP/GTP-binding site of cGAS	T-cell kinase/macrophage co-culture system $ApoE^{-/-}$ mice	Impair the IL12p70 and IFNγ axis RU.521 (5 mg/kg/day, peritoneal injection) Reduced aortic plaque area, macrophage infiltration, and IL-6/MCP-1 levels, suppressed mtDNA-induced cGAS−STING activation in VSMCs and mitigated VSMC senescence and pro-inflammatory phenotypic switching
	PF-06928215[308]	Inhibit ATP/GTP binding by targeting cGAS (Lys362/350)	Diet-induced obese mice	Alleviate adipose tissue inflammation and insulin resistance
	C-176 and analogues C-178/H-151[304,309-312]	Modify the Cys91 residue of STING to inhibit palmitoylation and oligomerization	STING-activated macrophages	C176-significantly reduced IL-1β and TNF-α secretion.
			$ApoE^{-/-}$ mice	C-176 (1 μmol, 3 times weekly) decreased aortic root plaque area, suppressed foam cell formation, and inhibited NF-κB pathway activation. Analogues C-178 and H-151 exhibited similar anti-inflammatory effects, but H-151 showed higher selectivity for human STING
	Astin C[314]	Block the recruitment of IRF3 onto the STING signalosome	Wild-type C57BL/6 mouse model of HSV-1 infection	Increase viral susceptibility Reduce serum IFN-β Elevate tissue viral load Decrease survival rate
			$Trex1^{-/-}$ inflammatory model	Alleviate tissue inflammation Downregulate inflammatory genes Reduce autoantibody positivity and $CD8^+$ T-cell activation.
	Compound 18[313]	Bind to the inactive "open" conformation of STING	THP-1 cells	Inhibit cGAMP-induced IFNβ production (IC_{50} = 11,000 nmol/L)

YAP/TAZ inhibitors	CBL0137[315]	Suppress Src kinase activity, reducing phosphorylation at the YAP-Y357 site	*ApoE*$^{-/-}$ mouse	Attenuate plaque formation and macrophage infiltration without affecting lipid profiles
	Harmine[316]	Inhibit proteasomal degradation of PTPN14, inhibiting YAP activation	*ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ mouse	Dose-dependently reduce aortic root atherosclerotic plaque area Decrease plaque inflammatory cell infiltration Downregulate pro-inflammatory gene expression in aortic tissue.
AGO1 inhibitors	LNP-AGO1-ASO[30]	Reduce AGO1 in endothelium and liver through ASO-mediated RNA degradation.	WT mice with AAV9-PCSK9-induced hypercholesterolemia fed a high-fat/high-cholesterol diet	Reduce TC and LDL/VLDL levels while increasing HDL/TC ratio Decrease hepatic fibrosis and macrophage infiltration with normalized liver function Downregulate ICAM1 and CCL2 expression Reduce plaque area and calcification
Lysosomal zinc nanomodulation	CM@MS NPs[317]	Inhibit macrophage pyroptosis through MLs-mediated MCOLN1 activation and lysosomal zinc release.	Atherosclerotic *ApoE*$^{-/-}$ mice	Remodel the immune microenvironment Reduce ox-LDL and lipids Shrink necrotic cores *via* zinc release, ROS scavenging, and immune remodeling.
Inhibition of NETosis	GSK484[318]	Inhibit PAD4	*ApoE*$^{-/-}$ mice	GSK484 (10 mg/kg/day, 8 weeks) reduced serum MPO and the NETosis marker H3cit
	Yoda1[319]	Agonist of mechanosensitive ion channel Piezo1	Human umbilical vein endothelial cells	Reduce cell adhesion rate and apoptosis rate Inhibit NETosis, and decrease endothelial injury
	SCN^- and $SeCN^-$[320,321]	Inhibit MPO	PMA-stimulated neutrophils	Reduce NET release
	4-amino-TEMPO[320,321]	Target NADPH oxidase and MPO	Primary human neutrophils	100 μmol/L 4-amino-TEMPO significantly attenuated PMA and HOCl
Specialized pro-resolving mediators	Lipoxins[322,323]	Target ALX/FPR2 receptors		Inhibit endothelial expression of VCAM-1 and ICAM-1 to reduce monocyte adhesion Upregulate HO-1 and enhance macrophage efferocytosis of apoptotic neutrophils
	Resolvins[324-329]	RvD1 suppresses the NF-κB pathway RvE1 inhibits endothelial MCP-1 secretion *via* ChemR23		RvD1 downregulated pro-proliferative genes in VSMCs, and promoted M2 macrophage polarization by inhibiting microRNA RvE1 suppressed NOX activity in VSMCs to attenuate ROS production
	Maresins[322,330-332]	Target LGR6 membrane receptors and RORα nuclear receptors		Enhance macrophage efferocytosis by activating LGR6 Preserve vascular integrity by inhibiting VSMC phenotypic switching Rebalance inflammatory microenvironments through downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory
	Protectins[333-335]	Suppress neutrophil chemotaxis and oxidative burst		Enhance the survival of cardiomyocytes and endothelial cells by inhibiting apoptotic pathways

(*continued on next page*)

Table 1 (*continued*)

Target	Drug	Mechanism	Research model	Experimental outcome
Efferocytosis promotion	Disulfiram[336]	Upregulate MerTK and remodel macrophage membrane biophysics	Hyperlipidemic *ApoE*$^{-/-}$ mice	Reduce atherosclerotic lesions by 27%−29% and necrotic core areas by 16%−50% Enrich atheroprotective gut microbiota
	ZnDPA@siIRF5[337]	Target macrophages Release siRNA in a ROS-responsive manner to silence IRF5 to restore efferocytic function	*ApoE*$^{-/-}$ mice: high-fat diet model/AngII-accelerated inflammation model	Reduce necrotic core area Enhance plaque stability Demonstrate no significant adverse effects
Anti-inflammatory metabolites	Ginsenosides[338,339]	Target SIRT1−Beclin-1 autophagy axis	*ApoE*$^{-/-}$ mice	Promote M2 macrophage polarization Inhibit plaque inflammation
	Astragalosides[340,341]	Target circ-0000231/miR-135a-5p/CLIC4 axis	Human umbilical vein endothelial cells	Modulate apoptosis and migration Inhibit inflammatory response Alleviate oxidative stress Downregulate adhesion proteins
	SBAs[342-344]	Activate FXR to promote reverse cholesterol transport	Empagliflozin-treated *ApoE*$^{-/-}$ mice and FMT models	Reduce plaque area
	SCFAs[343,345]	Suppress NF-κB nuclear translocation	Inflammatory bowel disease (IBD) models	Lower pro-inflammatory cytokines Enhance intestinal barrier function to decrease plasma LPS levels
	Monoterpenoids[346] Meroterpenoids[347]			Reduce NO production Suppress pro-inflammatory mediator production and iNOS protein expression
	Aspulvinones U/V[348,349]			Inhibit NO production and MMP-9-mediated gelatin degradation
	Sclerketide D[348]			Inhibit NO production in macrophages
	Itaconate and its derivative 4-OI[350,351]	Activate the NRF2 pathway to suppress M1 polarization and ROS generation.		Attenuate advanced lesions Reduce necrotic cores Reprogram human immune cells toward an anti-inflammatory phenotype
NRF2 agonists	Rg1[352]	Activate NRF2	LPS-induced chronic inflammation models	Reduce IL-6 and IL-1β Inhibit ferroptosis by upregulating GPX4 and xCT
	Rg5[353]		HSV-1-infected neural cells	Reduce COX-2, IL-6, and TNF-α levels
	4F5C-QAME[354]	Inhibit TAK1 phosphorylation and TAK1−KEAP1 interaction		Clear ROS and reduce macrophage inflammation
	Puerarin[355]	Upregulate SIRT1 to promote NRF2 nuclear translocation	Dysfunction-associated fatty liver disease models	Suppress hepatic ferroptosis and inflammation
	Celastrol[356]	Induce autophagic degradation of Keap1 *via* the AMPK/p62 pathway	Diabetic vascular injury	Alleviate endothelial damage
	Paeonol[357]	Promote AMPK phosphorylation, NRF2 nuclear translocation, and Keap1 degradation	Inflamed chondrocytes	Inhibit both ferroptosis and inflammation
	Citraconate[358]	Competitively bind to the substrate- binding	IAV-infected dTHP1 cells	Reduce *CXCL10* and *IL-6* mRNA expression

		site of ACOD1, inhibiting its activity	Systemic inflammation model induced by intraperitoneal LPS injection	Reverse LPS-induced inflammatory metabolic dysregulation Modulate the accumulation and conversion of metabolites, including itaconate and mesaconate
	Liraglutide[359]	Promote NRF2 nuclear translocation	Chronic intermittent hypoxia-induced neuroinjury models	Alleviate oxidative stress through reduced ROS and MDA levels Suppress neuroinflammation
KLF2 agonists	Trichostatin D[360,361]	Enhance *KLF2* mRNA		Inhibit TNFα-induced monocyte-endothelial adhesion and VCAM-1/ICAM-1 expression
AMPK agonists	IMM-H007[362]	Activate hepatic AMPKα1/2 subunits	*ApoE*$^{-/-}$, *Ldlr*$^{-/-}$ and hepatocyte-specific *AMPK*α knockout mouse models under hyperlipidemic diets	Effectively lower serum TC, non-HDL-C, and TG levels Reduce aortic atherosclerotic plaque area and necrotic core size while increasing collagen content and plaque stability
Anti-inflammatory delivery system	2D03-IL-10 (Fab-IL-10 fusion protein)[363]	Utilize LDL to precisely deliver the anti-inflammatory cytokine IL-10 to plaques, suppressing local inflammation	*ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ atherosclerotic mouse models	Significantly prolong IL-10 half-life Specifically enriched in aortic plaques Effectively reduce plaque area, inflammatory cell infiltration, and pro-inflammatory macrophages Do not cause systemic immunosuppression or dyslipidemia.
Endothelial histone lactylation inhibition	Narciclasine[364]	Inhibits endothelial inflammation by suppressing glycolysis and the subsequent histone H3K18 lactylation, thereby downregulating the NF-κB pathway	*ApoE*$^{-/-}$ mice with partial carotid artery ligation fed a western diet	Significantly suppress endothelial adhesion molecule expression and monocyte adhesion Reduce carotid artery plaque formation and macrophage infiltration Independent of lipid-lowering.

Abbreviation: PCSK9, proprotein convertase subtilisin/kexin type 9; Hcy, homocysteine; ApoE, apolipoprotein E; Lp(a), lipoprotein(a); E-Selectin, endothelial-selectin; ACLY, ATP-citrate lyase; CoA, coenzyme A; HFHC, high-fat high-cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, LDL cholesterol; ApoB100, apolipoprotein B100; WD, western diet; NASH, non-alcoholic steatohepatitis; NAS, NAFLD activity score; IRAK1/4, interleukin-1 receptor-associated kinase 1/4; RA-FLS, rheumatoid arthritis fibroblast-like synoviocyte; LPS, lipopolysaccharide; THP-1, human acute monocytic leukemia cell line; ASC, apoptosis-associated speck-like protein containing a CARD; MSU, monosodium urate; JAK/STAT, janus kinase/signal transducer and activator of transcription; SOCS3, suppressor of cytokine signaling 3; SAP-ALI, severe acute pancreatitis-associated acute lung injury; W/D ratio, wet-to-dry weight ratio; TRIF, TIR-domain-containing adapter-inducing interferon-β; BALF, bronchoalveolar lavage fluid; ROS, reactive oxygen species; GSH, glutathione; TIRAP, TIR-domain containing adaptor protein; IL-12p70, interleukin-12p70; cGAS−STING, cyclic GMP−AMP synthase − stimulator of interferon genes; mtDNA, mitochondrial DNA; IRF3, interferon regulatory factor 3; HSV-1, herpes simplex virus type 1; Trex1, three-prime repair exonuclease 1; cGAMP, cyclic GMP−AMP; YAP/TAZ, yes-associated protein/transcriptional co-activator with PDZ-binding motif; PTPN14, protein tyrosine phosphatase non-receptor type 14; MLs, macropinocytosis-like structures; MCOLN1, mucolipin-1; H3cit, citrullinated histone H3; SCN-, thiocyanate; SeCN-, selenocyanate; HOCl, hypochlorous acid; ALX/FPR2, lipoxin A4 receptor/formyl peptide receptor 2; HO-1, Heme oxygenase-1; RvD1, resolvin D1; RvE1, resolvin E1; ChemR23, chemokine-like receptor 1; LGR6, leucine-rich repeat-containing G-protein coupled receptor 6; RORα, RAR-related orphan receptor alpha; GPX4, glutathione peroxidase 4; xCT, cystine/glutamate transporter; TAK1, TGF-β-activated kinase 1; KEAP1, kelch-like ech-associated protein 1; AMPK, 5′ AMP-activated protein kinase; ACOD1, aconitate decarboxylase 1; TSA, trichostatin A.

suggesting CRP's dual role as a therapeutic target and a predictive biomarker for statin response[375]. In parallel to direct anti-inflammatory strategies, restoring efferocytosis has emerged as a complementary approach to resolve plaque inflammation and reduce necrosis. Key mechanisms include inhibiting repressive signals like CD147 and CFH, activating "find-me" signals *via* pannexin channels, and blocking the "don't eat me" signal CD47 with miR-299-3p. Enhancing this process promotes the resolution of inflammation and improves plaque stability[102,376-382].

4.2. Clinical studies

The promising mechanistic insights from preclinical studies, as outlined above, have rapidly translated into clinical development programs aiming to validate the anti-atherosclerotic efficacy of inflammation targeting in humans. As summarized in Table 2[383-421], recent and ongoing clinical trials across diverse drug categories have begun to yield critical evidence, moving beyond lipid-lowering to directly address residual inflammatory risk.

The CANTOS trial provided seminal proof-of-concept that selectively targeting inflammation (*via* IL-1β inhibition with canakinumab) reduces cardiovascular events independent of lipid-lowering[6]. However, this benefit was counterbalanced by a significant increase in fatal infections, underscoring the inherent risk of systemic immunosuppression. Building on this, smaller studies with anakinra (MRC-ILA, VCUART3) confirmed potent anti-inflammatory effects but highlighted challenges such as inflammatory rebound upon withdrawal and uncertain long-term benefit[416]. Collectively, these trials demonstrate the efficacy of IL-1β blockade while delineating a narrow therapeutic window due to infection risk.

Additionally, the low-cost microtubule inhibitor colchicine has garnered significant attention. The LoDoCo2 trial demonstrated a clear reduction in cardiovascular events in chronic coronary disease, leading to its Class IIa recommendation in the 2024 ESC guidelines[419,422]. In contrast, the COLCOT trial in post-MI patients showed benefit for stroke and revascularization but not for the composite of CV death/MI[418,420]. This may suggest that the efficacy of colchicine may be context-dependent, influenced by patient population and timing of administration. The recent CLEAR trial further complicated the picture, showing no significant benefit, potentially due to dose modifications and COVID-19-related confounding[423]. These divergent results underscore the necessity for careful patient stratification and highlight that even repurposed drugs require thorough safety reassessment in the chronic atherosclerosis setting.

Furthermore, statins and PCSK9 inhibitors are well-established for their potent LDL-C-lowering effects, which indirectly attenuate vascular inflammation. Statins primarily inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, affecting the mevalonate pathway, while concurrently downregulating the expression of TLRs such as TLR2/4, blocking their downstream signaling, including NF-κB, to reduce the production of pro-inflammatory cytokines, thereby mitigating inflammatory responses[424]. Additionally, statins have been shown to upregulate KLF2, a key transcription factor with anti-inflammatory and atheroprotective properties, further contributing to their pleiotropic benefits[306]. However, emerging evidence suggests that PCSK9 may also exert direct pro-inflammatory effects independent of lipid modulation. Specifically, PCSK9 activates the TLR4/MyD88/NF-κB signaling pathway and upregulates NLRP3 inflammasome activity[425]. A recent study demonstrated that genetic disruption or pharmacological inhibition of PCSK9 suppressed abdominal aortic aneurysm (AAA) formation in mice, without altering plasma cholesterol levels[426]. Without altering cholesterol levels, PCSK9 knockdown attenuated macrophage infiltration, NF-κB activation, and MMP9 expression by upregulating SIRT1, thereby defining a cholesterol-independent pathway for PCSK9-driven vascular inflammation and remodeling[426]. These findings suggest that PCSK9 inhibitors may confer anti-inflammatory benefits beyond their lipid-lowering effects, extending their potential utility to non-atherosclerotic inflammatory vascular diseases such as AAA.

The clinical translation of anti-inflammatory therapies necessitates a rigorous evaluation of the risk-benefit balance. The JAK/STAT inhibitor ruxolitinib carries a black box warning for serious infections, among other risks[427]. Similarly, as evidenced by CANTOS, the primary concern is a dose-dependent increase in the risk of serious and sometimes fatal infections[6,421]. This risk appears to vary with the specificity and intensity of immunosuppression. While colchicine is not a classic immunosuppressant, its safety profile in the chronic setting requires ongoing vigilance, as signaled by non-cardiovascular safety signals in some trials. Future strategies to mitigate these risks may include targeting more specific inflammatory pathways, developing localized delivery systems, and implementing biomarker-driven patient selection. Biomarker screening and patient stratification strategies are critical to optimize the risk-benefit profile, enhancing personalized medicine. Beyond these targeted agents, a distinct challenge arises from therapy-induced immune activation in oncology. Immune checkpoint inhibitors (ICIs) may induce cardiovascular events such as ACS by activating plaque T cells, increasing inflammation, and plaque instability[428]. Clinical data show an elevated MI risk with an often atypical presentation[428]. Management requires immediate ICI discontinuation, careful ACS treatment balancing bleeding risks, and a multidisciplinary decision on resuming therapy. For prevention, lipid-lowering agents like statins and PCSK9 inhibitors show dual potential by slowing plaque progression and possibly enhancing antitumor efficacy. This emerging syndrome underscores the necessity of multidisciplinary collaboration to balance cardiovascular risk control with ongoing cancer treatment, further illustrating the complex landscape of managing inflammation across medical specialties.

4.3. Comparative analysis and translational potential

Building upon the preceding preclinical and clinical evidence, Table 3[429-435] systematically evaluates the translational landscape of anti-inflammatory therapies. This analysis categorizes targets based on their current validation status and risk-benefit profiles, outlining a clear direction for future development. PCSK9 and SGLT2i/GLP-1RA pathways are promising near-term targets, with dual lipid/metabolic and anti-inflammatory benefits yielding strong outcomes and safety. Looking ahead, highly specific targets such as the NLRP3 inflammasome and novel paradigms like SPMs hold considerable promise for overcoming current limitations but still await solid clinical validation. Furthermore, the feasibility of combination therapies represents a key area for exploration. Combining anti-inflammatory agents with established lipid-lowering drugs or metabolic modulators could synergistically address multiple pathways, potentially enhancing efficacy while allowing for dose reduction of individual components to mitigate side effects. However, this requires careful

Table 2 Key clinical trials of anti-inflammatory and investigational therapies in atherosclerosis.

Drug category	Trial	Study population	Study design	Outcome
Statins	RACING[383,384]	3780 ASCVD patients, 574 aged 75 years or older	Rosuvastatin (10 mg) + ezetimibe (10 mg) *vs* Rosuvastatin (20 mg)	No significant difference in 3-year cardiovascular events, but combination therapy showed better tolerability, greater LDL-C reduction, and lower long-term non-HDL-C and ApoB levels
PCSK9 inhibitors	ORION-11[385]	203 patients with persistent LDL-C $\geq$2.6 mmol/L on maximal lipid-lowering therapy	Inclisiran (284 mg on days 1 and 90, and every 6 months thereafter) *vs* placebo	Significantly higher rates of lipid target (LDL-C and non-HDL-C) attainment in the inclisiran group *vs* placebo
	PACMAN-AMI[386]	300 patients with acute myocardial infarction	Alirocumab (150 mg every 2 weeks) + rosuvastatin 20 mg/day *vs* placebo	Reduce plaque volume Lower lipid core Increase fibrous cap Achieve LDL-C reduction: 75% (placebo: 40%)
ACLY inhibitors	CLEAR Serenity[387,388]	345 statin-intolerant ($\geq$2 statins) hypercholesterolemia patients	Bempedoic acid *vs* placebo	Significantly reduce key atherogenic lipids and inflammation markers (non-HDL-C, TC, ApoB, hs-CRP) with fewer side effects (*e.g.*, myalgia)
	CLEAR harmony[391]	2230 patients, of whom 98% ASCVD, 4% HeFH		Reduce LDL-C by 16.5% and hsCRP by 22.4%
	CLEAR wisdom[391]	779 patients, of whom 94% ASCVD, 5% HeFH		Reduce LDL-C by 15.1% and hsCRP by 18.7%
	CLEAR outcomes[389,390]	13,970 patients		Achieve sustained LDL-C reduction Significantly lower MACE risk by 13%
Antiplatelet and anticoagulant drugs[416]		100 patients with high-risk branch atheromatous disease	Argatroban + DAPT *vs* DAPT	Combination therapy significantly reduced early neurological deterioration within 7 days and demonstrated superior 90-day functional outcomes
IL-1β targeting therapies	MRC-ILA heart Study[392]	182 patients with non-ST-segment elevation acute coronary syndrome	Anakinra *vs* placebo	Effective anti-inflammatory action Limited by rebound after withdrawal and increased long-term MACE
	VCUART3[393]	99 patients with ST-segment-elevation myocardial infarction	Anakinra once daily or twice daily *vs* placebo	Reduce hsCRP and decrease death or new heart failure No significant differences between anakinra dosing regimens
	CANTOS[6,421]	10,061 patients with stable post-myocardial infarction and hsCRP $\geq$2 mg/L	Canakinumab (50, 150, or 300 mg) *vs* placebo	150 mg every 3 months lowered cardiovascular events independent of lipid-lowering, but carried an elevated fatal infection risk
	LoDoCo2[7,419]	5522 patients with chronic coronary disease	Colchicine *vs* placebo	0.5 mg daily colchicine lowered CV events in chronic CAD patients, but may be associated with higher non-CV mortality
	COLCOT[8,418,420]	4745 patients with recent myocardial infarction		Significant reductions in stroke and urgent revascularization, with no CV death/MI difference

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Table 2 (*continued*)

Drug category	Trial	Study population	Study design	Outcome
				Similar diarrhea rates but increased serious pneumonia
	COPS[394,417]	795 patients with acute coronary syndrome for 2 years		Significantly reduced cardiovascular events and urgent revascularization risk Non-cardiovascular deaths trended higher Efficacy diminished after discontinuation
IL-6 targeting therapies	RESCUE[9,395]	264 patients with chronic kidney disease (CKD) and hsCRP ≥2 mg/L	Ziltivekimab (7.5/15/30 mg every 4 weeks) *vs* placebo	All dose groups dose-dependently reduced hsCRP and multiple atherosclerosis-related biomarkers, with stable anti-inflammatory effects, favorable tolerability No impact on relevant lipid ratios.
	Systematic review and meta-analysis[396]	14 studies	Non-TNFi Biologics *vs* TNFi csDMARDs *vs* TNFi	Compared to TNFi, tocilizumab may be associated with reduced risk of MACE, whereas csDMARDs may be associated with increased risk of MACE and stroke
Anti-diabetic drugs	LEADER[397]	9340 patients	Liraglutide *vs* placebo	Reduce the incidence of both cardiovascular mortality and all-cause mortality
	SUSTAIN-6[398]	3297 patients with 41.5% having a history of MI or stroke, and 76.8% diagnosed with CVD	Semaglutide *vs* placebo	Lower MACE risk and non-fatal stroke
	SELECT[400]	17,604 patients aged ≥45 years with BMI ≥27, established cardiovascular disease and no history of diabetes		Reduce MACE (6.5% *vs* 8.0%)
	SOUL[399]	9650 patients		Reduce MACE (12% *vs* 13.8%)
	HARMONY OUTCOMES[401]	9463 patients aged 40 years and older with type 2 diabetes and cardiovascular disease	Albiglutide (30−50 mg weekly) *vs* placebo	Reduce MACE (7% *vs* 9%)
	AMPLITUDE-O[402]	4076 patients	Efpeglenatide *vs* placebo, randomized with stratification by baseline SGLT2i use	Efpeglenatide's cardiovascular and renal benefits and safety are independent of SGLT2i use, with greater HbA1c reduction observed in SGLT2i-naive patients
	UK CPRD-based cohort study[403]	Two matched cohorts of adults with T2D: 6696 adding SGLT-2i to GLP-1 RA *vs* GLP-1 RA continuers, 8942 adding GLP-1 RA to SGLT-2i *vs* SGLT-2i continuers.		Compared to GLP-1 RA monotherapy, combination therapy reduced the risk of MACE by 30% and serious kidney events by 57% Compared to SGLT-2i monotherapy, combination therapy lowered MACE risk by 29%
	[404]	443 patients with T2DM	SGLT-2i *vs* GLP-1RA *vs* GLP-1RA+SGLT-2i	Combination therapy reduced MACE and improved myocardial salvage (higher MSI, more patients with MSI >50%) *vs* monotherapy

	CREDENCE[405]	4401 patients with T2DM	Canagliflozin *vs* placebo	Reduce the risk of MACE Demonstrate a consistent reduction in risk.
	EMPEROR-Reduced[406,407]	3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less	Empagliflozin (10 mg once daily) *vs* placebo	Reduce the incidence of the primary composite outcome (cardiovascular death or hospitalization for heart failure), with consistent effects observed regardless of diabetes status
	DAPA-HF[406]	4744 patients with LVEF ≤40%	Dapagliflozin *vs* placebo	Reduce the relative risk of heart failure hospitalization or emergency visits and cardiovascular mortality
	Systematic review and meta-analysis[408]	18 studies involving 5311 participants	Dapagliflozin *vs* empagliflozin *vs* canagliflozin	SGLT2i significantly reduced IL-6 levels, with HbA_{1c} being influencing factor Dapagliflozin showed the highest efficacy
	Retrospective cohort study[409]	9186 patients with T2DM	With *vs* without metformin	Metformin treatment reduced AMI risk in T2DM patients
	FIDELIO-DKD[413]	5734 patients with CKD and T2DM	Finerenone *vs* placebo	Reduce risks of CKD progression and cardiovascular events than placebo
	FIGARO-DKD[411]	7437 patients with CKD and T2DM		Reduce the incidence of the composite endpoint of CV, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (12.4% *vs* 14.2%)
	FIDELITY[410,412]	13,026 patients with CKD and T2DM		Reduce the incidence of CV death, nonfatal MI, nonfatal stroke, or HF hospitalization (12.7% *vs* 14.4%)
LOX-1 inhibition	GOLDILOX-TIMI 69[414,415]	423 patients with residual inflammation (hs-CRP ≥1 mg/L) 30−365 days after MI	MEDI6570 (50/150/400 mg) *vs* placebo	Dose-dependently reduce sLOX-1 Lower IL-6 at high doses with good tolerability Not significantly reduce the non-calcified plaque volume in the most diseased coronary segment

Abbreviation: non-HDL-C, non-high-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; ACS, acute coronary syndrome; CKD, chronic kidney disease; TNFi, tumor necrosis factor inhibitors; BMI, body mass index; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; sLOX-1, soluble LOX-1.

Table 3 Comparative analysis of key anti-inflammatory targets in atherosclerosis.

Target/pathway	Key strategic advantage	Major challenge	Translational potential
IL-1β signaling	Inhibit IL-1β-driven inflammation and modulate fibroblast-like cells to stabilize atherosclerotic plaques[429]	Increased infection risk Long-term safety in diverse populations	Ongoing trials exploring IL-1β inhibitors in broader cardiovascular cohorts
NLRP3 inflammasome	Phytochemicals and novel agents (*e.g.*, JAML) inhibit NLRP3 activation, reducing IL-1β secretion and plaque progression[430]	Selectivity of inhibitors Oral bioavailability	Phase I/II trials of natural product-derived NLRP3 inhibitors ongoing
PCSK9 inhibitors	Novel formulations reduce LDL-C and inflammation	High cost Long-term safety of new formulations	FDA review of Lerodalcibep (2025) and oral PCSK9 inhibitors in late-stage trials
SGLT2 inhibitors	Reduce non-calcified plaque volume and inflammation independently of glucose control, reversing atherosclerosis[431]	Efficacy variability in non-diabetic populations Genitourinary side effects.	Approved for CVD risk reduction
ACLY inhibitors	Natural small molecules (*e.g.*, isoginkgetin) target ACLY, reducing hypercholesterolemia and atherosclerosis[292]	Mild elevations in serum creatinine, liver enzymes, and uric acid[432] Higher incidence of gout	Preclinical success Potential for combination therapy with statins
TLR4 signaling	Inhibit M1 macrophage polarization and VSMC phenotypic switching[433]	Do not suppress neutrophil infiltration, potentially compromising the anti-inflammatory response[434]	Preclinical development of selective TLR4 inhibitors
YAP/TAZ signaling	Inhibit endothelial YAP/TAZ activation to reduce leukocyte accumulation and atherosclerosis in progeria models	Complex physiological role	Preclinical validation of YAP/TAZ inhibitors
IRAK1/4	Inhibit IRAK4 to modulate VSMC phenotypic conversion and inflammation in diabetic atherosclerosis	Early-stage development Immune homeostasis impact	Preclinical studies support efficacy Phase I trials of IRAK1/4 inhibitors ongoing
SPMs	Restore inflammatory homeostasis and plaque stability	High cost Short half-life *in vivo*[435]	Preclinical and early clinical trials of SPM analogs

Abbreviation: IL-1β, interleukin-1β; NLRP3, NOD-like receptor family, pyrin domain-containing 3; JAML, junctional adhesion molecule-like; PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low-density lipoprotein cholesterol; FDA, U.S. Food and Drug Administration; SGLT2, sodium-glucose cotransporter 2; CVD, cardiovascular disease; ACLY, ATP-citrate lyase; TLR4, toll-like receptor 4; VSMC, vascular smooth muscle cell; YAP/TAZ, yes-associated protein/transcriptional co-activator with PDZ-binding motif; IRAK1/4, interleukin-1 receptor-associated kinase 1/4; SPMs, specialized pro-resolving mediators.

evaluation in clinical trials to assess interactions, long-term safety, and additive benefits, particularly in high-risk populations.

5. Conclusions and outlook

5.1. scRNA-seq in dissecting the holistic landscape of inflammatory cell communication

Single-cell RNA sequencing (scRNA-seq) has revolutionized the dissection of inflammatory cell communication in atherosclerosis by resolving cellular heterogeneity at unprecedented resolution. For example, scRNA-seq has successfully resolved bidirectional neuro-immune regulatory circuits (*e.g.*, TRPA1/CALCA pathways) and plaque macrophage subpopulation heterogeneity, challenging the traditional "single-cell-type dominance" view[436-439]. It has also revealed the activation of immunogenic cell death pathways within atherosclerotic plaques[440]. Furthermore, scRNA-seq has identified key metabolic reprogramming nodes in $CD8^+$ T cells, such as asparagine synthetase (ASNS)-mediated fate regulation[441]. However, technical limitations persist. scRNA-seq has low efficiency in capturing rare cells, and discrepancies between *in vitro* and *in vivo* conditions may compromise physiological relevance. Future research urgently requires integrating spatial transcriptomics to resolve the spatiotemporal dynamics of cellular crosstalk in microenvironments, coupling with proteomics to validate RNA−protein functional correlations, and developing *in vivo* lineage tracing technologies to decode cellular dynamics. Additionally, innovating cross-scale data integration algorithms (single-cell/spatial/proteomic/metabolic) and conducting large-scale cohort studies to validate the clinical translational potential of single-cell discoveries (*e.g.*, biomarkers and therapeutic targets) will be critical for overcoming current limitations.

5.2. *Trained immunity*

Trained immunity, a form of innate immune memory, accelerates atherosclerosis by driving metabolic reprogramming and epigenetic remodeling in monocytes and macrophages[442]. Recent studies identify glutaminolysis as a key metabolic driver in this process, mediating ox-LDL-induced rewiring (*e.g.*, enhanced TCA cycle flux and fumarate accumulation)[443]. Significant challenges remain, including the unclear roles of specific monocyte subsets, the persistent nature of the trained phenotype even after removal of the risk factor, and unconfirmed transgenerational effects[444-446]. Maladaptive trained immunity is now recognized as a key mechanism underlying residual inflammatory risk in CAD, presenting novel therapeutic targets. These include disrupting the hyperglycolytic state, modulating epigenetic regulators at pro-inflammatory loci, and inhibiting enhanced chemokine receptor signaling[447]. Future research should leverage single-cell technologies to decipher subset-specific mechanisms, validate the transgenerational inheritance of immune memory, and explore the potential of natural compounds like curcumin to reverse this reprogramming[448]. Ultimately, developing biomarker-based predictive models will be crucial for translating these insights into precise, targeted interventions for high-risk patients.

5.3. *Environmental risk factors*

Environmental factors synergistically drive atherosclerosis through shared pathways, including oxidative stress, inflammasome activation, immune dysregulation, and neuroendocrine activation. For instance, nanoplastics trigger the release of NETs[449], and PM2.5 induces oxidative stress[450,451]. Noise activates the hypothalamic−pituitary−adrenal (HPA) axis and autonomic nervous system, triggering chronic stress responses and elevating inflammatory cytokines[452,453], while SiO_2 activates T cells and macrophages, inducing pro-inflammatory cytokines and promoting neutrophil apoptosis to release autoantigens such as MPO, thereby triggering autoimmune responses[454,455]. Key challenges include environmental exposure complexity from multiple coexisting factors, nonlinear dose-response relationships, and complex causal inference and risk assessment. Additionally, interactions between environmental triggers and individual genetic backgrounds or traditional risk factors remain unclear. A deeper mechanistic understanding of specific pollutants like nanoplastics and silica is needed, while targeted interventions blocking environmental pathogenic pathways are currently lacking. Future research should focus on developing AI-powered multi-omic integration platforms by utilizing graph neural networks to decipher dynamic interactions between environmental stressors, synergies with epigenetic modifications, metabolic disruptions, and proteomic alterations in inflammatory mediators, alongside creating causal inference models to quantify multifactorial contributions. Besides, advancing spatial multi-omics and organoid technologies involves combining spatial transcriptomics with mass spectrometry imaging while establishing environmental exposure-simulating organoids to dynamically trace multi-organ crosstalk responses.

5.4. *Lesional inflammation-targeted nanotherapies*

Various nanotechnology platforms, including polymeric nanocarriers, lipid-based systems, carbon nanotubes, and bioinspired nanoparticles, have shown considerable potential for targeted atherosclerosis therapy by enabling site-specific drug delivery. Single-walled carbon nanotubes (SWNTs), for instance, can deliver the SHP1 inhibitor to inflammatory macrophages, enhancing efferocytosis to reduce plaque inflammation and necrotic core expansion *via* pH-responsive release and demonstrating a favorable safety profile with cross-species anti-inflammatory gene upregulation[456]. Bioinspired nanoparticles, leveraging membrane coatings from platelets or macrophages, achieve natural homing mechanisms. Platelet-coated versions bind exposed collagen to deliver anti-CD47 antibodies, enhancing efferocytosis and plaque stabilization[457]. Macrophage-coated nanoparticles achieve homologous targeting, reducing plaque area by 39% in $ApoE^{-/-}$ mice without systemic immune activation[458,459]. Despite these advances, critical challenges persist. Technical hurdles include long-term biocompatibility, insufficient targeting accuracy in complex vascular microenvironments, and difficulties in scalable manufacturing with batch uniformity[460,461]. Moreover, efficacy validation remains limited. SWNTs, for example, require late-stage plaque assessment as current data derive mainly from early disease models, and plaque structural repair often remains unaddressed. Moving forward, efforts must prioritize developing integrated multifunctional systems with targeting, therapeutic, and diagnostic capabilities, alongside stimuli-responsive mechanisms. Additionally, establishing standardized production under good manufacturing practice, improving pharmacokinetic/pharmacodynamic profiling, and advancing combinatorial strategies through rigorous preclinical and clinical studies will be essential to bridge the gap between laboratory innovation and viable atherosclerosis therapeutics.

5.5. *Inflammation-targeted high throughput drug screening*

High-throughput screening (HTS), rapidly assessing large compound libraries' biological activity, is a key drug development strategy for inflammation and atherosclerosis. Integrated with multi-omics, structural biology, computational models, etc., HTS advances innovation from target identification to lead optimization. Notable applications include using gene expression profile reverse matching to screen natural compounds and traditional Chinese medicine formulations that block the NF-κB pathway[462] and employing PPI target structure-guided screening to develop a FRET platform and discover novel NLRP3 inhibitors[463,464]. Additionally, engineered cellular models and zebrafish inflammation assays validate inhibitor efficacy in reducing atherosclerotic plaques and suppressing IKKβ activity[462,465], while molecular docking and dynamics simulations are being integrated with HTS to accelerate virtual screening[462]. Despite progress in HTS for inflammation and atherosclerosis research, significant challenges persist. Complex inflammatory crosstalk limits the efficacy of single-target approaches, demanding multi-target cooperative screening models. Discrepancies between *in vitro* and *in vivo* results necessitate optimized validation systems such as organoids, genetically engineered models, and integrated preclinical efficacy−toxicity evaluations. Additionally, the inherent complexity of traditional Chinese medicine requires combining HTS with systems pharmacology to decode multi-component, multi-target mechanisms. Critically, the potential impact of anti-inflammatory interventions on broader immune system function warrants careful consideration. Long-term suppression of specific inflammatory pathways may inadvertently compromise host defense or immune homeostasis, necessitating dedicated follow-up studies to evaluate these systemic immunological consequences.

Looking ahead, AI−HTS integration will accelerate target discovery, while spatial omics and single-cell technologies enable cell-specific screening. Precision medicine-driven stratified screening will further advance personalized anti-inflammatory therapies.

5.6. *Potential side effects of anti-inflammatory therapies*

Anti-inflammatory therapies hold significant promise in atherosclerosis and related cardiovascular diseases, but their potential side effects require careful attention. Traditional NSAIDs (*e.g.*, ibuprofen) inhibit COX-1, causing gastroduodenal ulcers in 15%−30% of chronic users[466,467]. COX-2 inhibitors (*e.g.*, celecoxib) reduce gastric injury but risk small intestinal damage and cardiovascular toxicity, exemplified by rofecoxib's market withdrawal due to myocardial infarction risk from prostaglandin imbalance[467,468]. Colchicine targets NLRP3 inflammasome inhibition but commonly causes gastrointestinal disturbances, requires renal dose adjustment and drug interaction vigilance, and may impair wound healing perioperatively[469]. In addition, IL-1β inhibition with canakinumab significantly increased fatal infections and sepsis (0.31 *vs.* 0.18 events/100 person-years) in the CANTOS trial[6]. Given that targeted anti-inflammatory therapy often entails immune suppression-related risks such as infections and malignancy, it is essential to specifically evaluate its safety profile and carefully weigh the risk-benefit balance in clinical practice. The core strategies encompass the following approaches to address these concerns. First, precise stratification leverages biomarkers such as hs-CRP and multi-omics technologies to identify individuals at genuine high inflammatory risk, thereby avoiding unnecessary treatment for those unlikely to benefit[470]. Second, targeted delivery employs novel drug delivery systems like nanocarriers to enhance drug accumulation at lesion sites and reduce systemic exposure, along with associated infection risks. Third, mechanism innovation focuses on exploring drugs targeting novel pathways or developing dual-effect therapies that combine

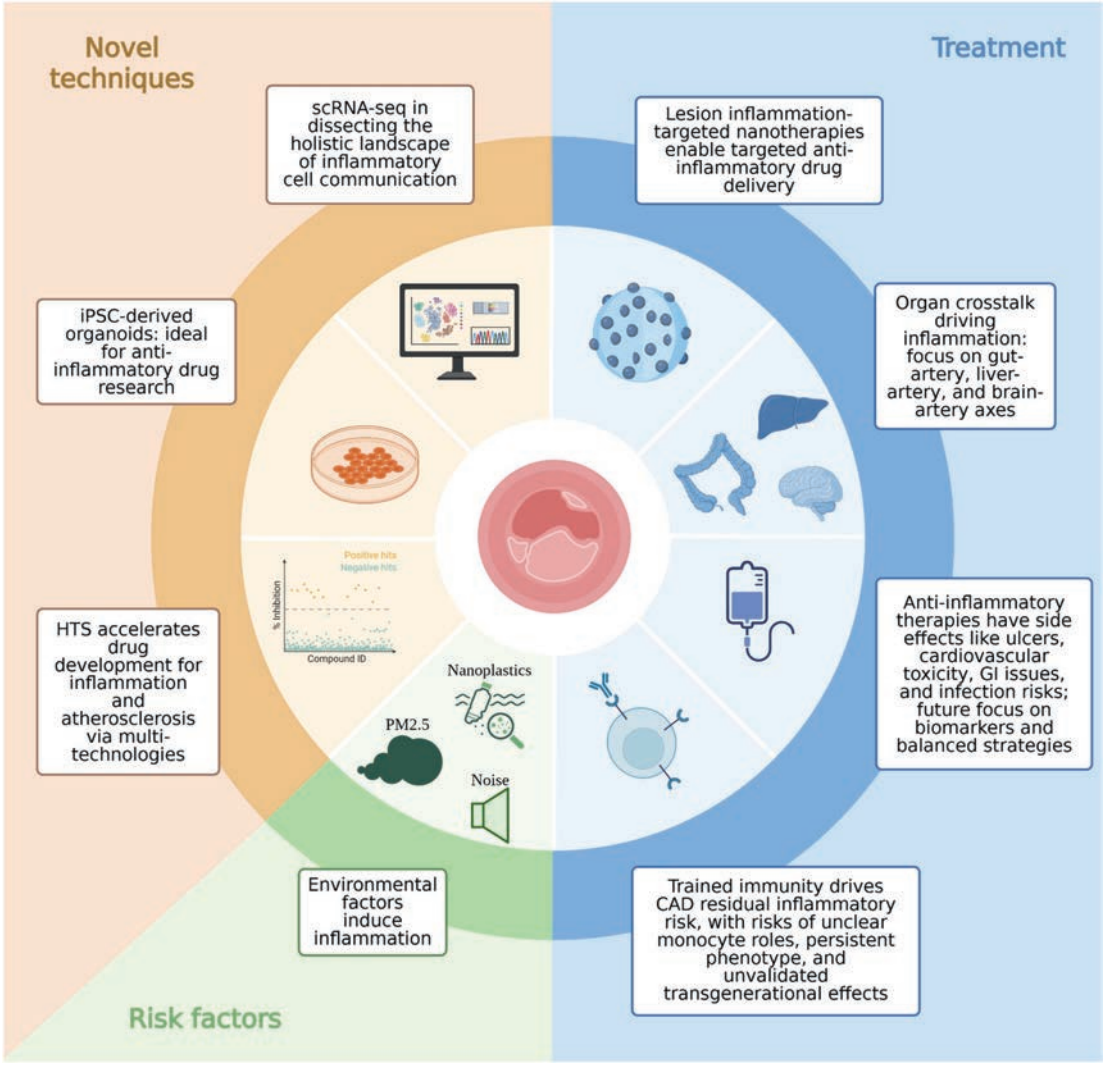

Figure 6 Integrated framework of inflammation mechanisms, interventions, and challenges. An integrated perspective on inflammation in atherosclerosis spans mechanistic drivers to clinical translation, with a focus on lesion-targeted nanotherapies and inter-organ crosstalk. Abbreviations: HTS, high-throughput screening; iPSC, induced pluripotent stem cell; $PM_{2.5}$, particulate matter $\leq$2.5 μm; scRNA-seq, single-cell RNA sequencing. Figure was created using BioRender.

anti-inflammatory and pro-repair functions. This approach fundamentally moves beyond traditional immunosuppression models and systematically optimizes the risk-benefit balance.

5.7. *Organ crosstalk in driving inflammation in atherosclerosis*

Atherosclerosis is a systemic disease orchestrated by complex, multi-organ signaling networks, primarily involving the gut−artery, liver−artery, and brain−artery axis. In the gut−artery axis, dietary choline is metabolized by gut microbes into trimethylamine (TMA), which is subsequently oxidized by hepatic FMO3 to the pro-atherogenic metabolite TMAO. TMAO promotes inflammation by activating NF-κB/NLRP3 inflammasomes, driving monocyte adhesion, macrophage foam cell formation, and impairing cholesterol transport, while also compromising gut barrier integrity[471-474]. Conversely, gut-derived SCFAs like butyrate exert protective effects by inhibiting NF-κB, activating receptors GPR41/43, promoting anti-inflammatory M2 macrophages, and enhancing the gut barrier[475-477]. Additionally, secondary bile acids such as deoxycholic acid and lithocholic acid modulate metabolism by activating receptors FXR/TGR5 to suppress hepatic cholesterol synthesis and inflammation, with lithocholic acid specifically inhibiting platelet activation by blocking the GPVI-dependent Syk/Akt/ERK pathway[478]. The liver−artery axis bidirectionally regulates disease progression through factors like FGF21, which suppresses arterial inflammation *via* central nervous system-activated thermogenesis, and ANGPTL4, which promotes triglyceride accumulation and monocyte adhesion[479]. Hepatocyte-derived extracellular vesicles can further stabilize or destabilize plaques by carrying molecules like miR-122 or pro-inflammatory cytokines[480]. Meanwhile, the brain−artery axis mediates bidirectional crosstalk where the central nervous system can suppress arterial inflammation *via* sympathetic activation of brown adipose tissue and norepinephrine-mediated inhibition of macrophage inflammasomes, but can also exacerbate it[481]. For instance, thyroid-stimulating hormone (TSH) promotes macrophage release of cytokines such as IL-1β *via* the MAPK−NF-κB pathway[482]. Peripheral inflammatory factors like IL-6 can cross the blood−brain barrier to trigger neuroinflammation[483], which in turn can feed back and aggravate peripheral vascular pathology, though the heterogeneity of the blood−brain barrier complicates the study of this selective signal exchange. Future research must integrate metagenomics and metabolomics to model these dynamic inter-organ interactions, validate the efficacy of natural compounds, develop organ-specific drug delivery systems to minimize systemic effects, and decode the selective permeability of the blood−brain barrier to clarify its role in modulating vascular inflammation.

5.8. *iPSC-derived vascular organoids*

The development of induced pluripotent stem cell (iPSC) technology has yielded revolutionary breakthroughs in the study of inflammation and atherosclerosis. The 2023 FDA Modernization Act 2.0 removed the mandatory animal-testing hurdle, explicitly endorsing human-specific platforms such as iPSC-derived organoids for regulatory-grade safety and efficacy data. Capitalizing on this policy shift, 2023−2024 studies generated 3D blood-vessel organoids from patient iPSCs that, under shear stress, modified LDL, TNF-α/IL-6 and monocyte co-culture, sequentially develop endothelial dysfunction, foam-cell cores, fibrous caps, and calcification, faithfully mirroring human plaque progression without species-extrapolation bias[484]. These vascular-plaque organoids have already validated lovastatin's anti-inflammatory efficacy[484]. Coupled to high-throughput 384-well plates and AI-assisted imaging, the platform accelerates compound triage while meeting GLP standards, positioning large-scale patient-derived organoid biobanks as the cornerstone for precision drug approval and personalized anti-atherosclerotic therapy in the post-animal era. Current challenges include the uniformity of large-scale production (such as batch-to-batch variability), the phenotypic stability of long-term cultures, and the immunogenicity of *in vivo* transplantation. Standardizing perfusable vascularization protocols, integrating immune-competent lineages, and establishing quality metrics will be essential to transform these patient-derived vascular-plaque organoids into robust, regulatory-ready platforms for large-scale clinical translation (Fig. 6).

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Author contributions

Zihan Su: Writing − original draft. Suowen Xu: Conceptualization.

Conflicts of interest

The authors declare no conflicts of interest.

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