Atherosclerosis: Recent Advances, Emerging Insights, and Future Challenges

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Abstract

Atherosclerosis (AS) is recognized not only as a disorder of lipid accumulation but also as a chronic inflammatory disease. Its pathogenesis involves a complex interplay of multiple risk factors, including dyslipidemia, genetic predisposition, and diabetes. Hallmark pathological features of AS include fibrous tissue proliferation, lipid deposition, and localized calcification. Patients with AS frequently develop vulnerable or erosive plaques, which may precipitate severe cardiovascular events such as coronary artery disease, stroke, and myocardial infarction. This review systematically explores the pathological features of AS, disruptions in lipid metabolism, the role of inflammatory and immune responses, and advances in genetically engineered animal models. By elucidating the intricate relationship between lipid dysregulation and inflammation, and by highlighting emerging therapeutic strategies, we aim to provide a comprehensive understanding that may inform the refinement of animal models and the development of more effective anti-atherosclerotic therapies.

Keywords: Atherosclerosis; Lipid Metabolism Disorder; Inflammatory Immunity; Genetically Engineered Animal Models; Coronary Heart Disease

Atherosclerosis (AS) is a multifactorial chronic disease driven by progressive dyslipidemia and inflammation. It is not merely a lipid deposition disorder; rather, inflammation plays a pivotal role in linking abnormal lipid metabolism with other risk

factors in the development of AS. Pathologically, AS is characterized by fibrous tissue proliferation, lipid accumulation, and calcium deposition in affected vascular regions, often resulting in the formation of vulnerable and erosive plaques [1]. AS serves as the principal underlying cause of coronary heart disease (CHD) and contributes to the pathogenesis of other clinical conditions such as stroke and angina. It also affects various peripheral arteries, including the coronary, renal, cerebral, and thoracic aortic arteries [2]. Major risk factors for AS include dyslipidemia, diabetes, hypertension, obesity, and genetic predisposition. Low-density lipoprotein (LDL), a lipid particle enveloped by its signature apolipoprotein B (ApoB), has been shown to be a key driver in the initiation and progression of AS [3]. Classical epidemiological studies indicate that AS predominantly affects middle-aged men and populations in developed regions. Although AS-associated mortality has declined, its incidence continues to rise, with a higher prevalence observed in men compared to premenopausal women [4]. Mechanistic studies have revealed that this sex difference may be attributed to estrogen, which exerts a protective effect against AS by reducing endothelial cell apoptosis through activation of autophagy mediated by estrogen receptor α [5].

Recent epidemiological studies suggest that atherosclerosis (AS) is becoming increasingly prevalent among younger populations, with a growing disease burden observed in women and individuals in developing countries. While cardiovascular mortality has declined in developed regions, the overall global mortality from cardiovascular diseases has plateaued, with an annual change of less than 1%, indicating a state of stagnation [6]. Emerging research has expanded and challenged traditional views on AS risk factors and diagnostic markers. In contrast to the classical focus on low-density lipoprotein cholesterol (LDL-C), recent findings emphasize that elevated triglyceride-rich lipoproteins (TGRLs) and reduced high-density lipoprotein (HDL) levels represent the predominant dyslipidemic profile associated with AS [7–8]. Given the global trend of declining LDL levels, its relative contribution to long-term AS risk appears to be decreasing. Studies have increasingly highlighted inflammation as a central mechanism in AS pathogenesis, offering new therapeutic

perspectives beyond LDL-lowering strategies [9].

HDL, traditionally considered a protective factor against AS, exerts anti-atherosclerotic effects primarily through promoting cholesterol efflux and exerting anti-inflammatory actions. However, clinical interventions aimed at raising HDL levels pharmacologically have largely failed to reduce AS-related events, calling into question the causal role of HDL in disease prevention [8,11,12]. A similar controversy surrounds apolipoprotein CIII (ApoCIII). Epidemiological and genetic studies have demonstrated that loss-of-function mutations in the ApoCIII gene are associated with lower plasma triacylglycerol (TG) levels and a reduced risk of coronary heart disease (CHD) [13–15]. ApoCIII deficiency confers cardioprotective effects and its elevation is considered a high-risk factor for hypertriglyceridemia and ischemic heart disease. Clinically, the antisense oligonucleotide therapy Volanesorsen, which targets ApoCIII, has been approved by the European Medicines Agency. Additionally, next-generation therapeutics such as AKCEA-APOCIII-LRx and monoclonal antibodies targeting ApoCIII are currently under clinical investigation. ApoCIII plays a critical role as a regulator of triglyceride metabolism via lipoprotein lipase (LPL)-independent pathways [16–18].

In murine models, transgenic overexpression of ApoCIII promotes atherogenesis, whereas knockout models do not exhibit significant protective effects. ApoCIII does not appear to contribute to diet-induced non-alcoholic fatty liver disease in mice, yet overexpression results in severe hypertriglyceridemia, enhanced atherosclerotic lesion development, and increased neointimal formation following carotid endothelial denudation. However, ApoCIII knockout (ApoCIII–/–) mice do not show clear atheroprotection [19–22]. In contrast, studies in rabbits have demonstrated that ApoCIII deficiency attenuates atherosclerosis by reducing macrophage and foam cell accumulation, inhibiting smooth muscle cell proliferation, and significantly decreasing lesion size. These effects are accompanied by reduced deposition of oxidized LDL and C-reactive protein (CRP), a key inflammatory marker [23].

Similarly, in hamster models, ApoCIII knockout mitigates high-fat diet–induced lipid metabolic disturbances and AS progression. ApoCIII inactivation alters lipid distribution in an anti-atherogenic manner, supporting its potential as a therapeutic target for hypertriglyceridemia and AS-related cardiovascular diseases [24]. The underlying reasons for these species-specific differences remain unclear and may reflect interspecies variability in ApoCIII expression and function.

The success of the CANTOS trial marked a pivotal turning point in the treatment of atherosclerosis (AS), ushering in a new era of anti-inflammatory therapies. In this trial, Canakinumab— a fully human monoclonal antibody targeting interleukin-1β (IL-1β)— significantly reduced baseline levels of C-reactive protein (CRP) without affecting low-density lipoprotein cholesterol (LDL-C). Notably, the 150 mg dose of Canakinumab significantly lowered the incidence of recurrent cardiovascular events compared with placebo [25]. Further evidence has demonstrated that disruption of interleukin-10 (IL-10) signaling using CRISPR/Cas9 technology compromises lipid and tissue homeostasis, thereby accelerating AS progression. In hamster models, silencing of IL-10 signaling exacerbated AS via dysregulation of the gut microbiota–adipose tissue–liver axis, indicating a systemic network by which IL-10 modulates disease progression [26].

Research into classic acute-phase reactants, particularly the pentraxin family of CRP proteins, further reinforces the concept that AS is fundamentally an inflammatory disease. Clinical data have shown that patients with coronary heart disease (CHD) and myocardial infarction exhibit elevated plasma CRP levels, supporting its role as both a biomarker and a potential mediator of vascular inflammation [27–28].

Given the current advances in understanding endothelial injury, vascular inflammation, and lipid metabolic disorders, along with ongoing debates in the field, this review systematically explores the pathological characteristics of AS, lipid–inflammation interactions, and the utility of genetically engineered animal models. By summarizing these key areas, we aim to clarify the mechanistic links between dyslipidemia and inflammation in AS and propose novel therapeutic insights.

Moreover, this review contributes to the rational optimization of AS animal models. A schematic overview of AS-related risk factors and contributing elements is presented in **Figure 1.**

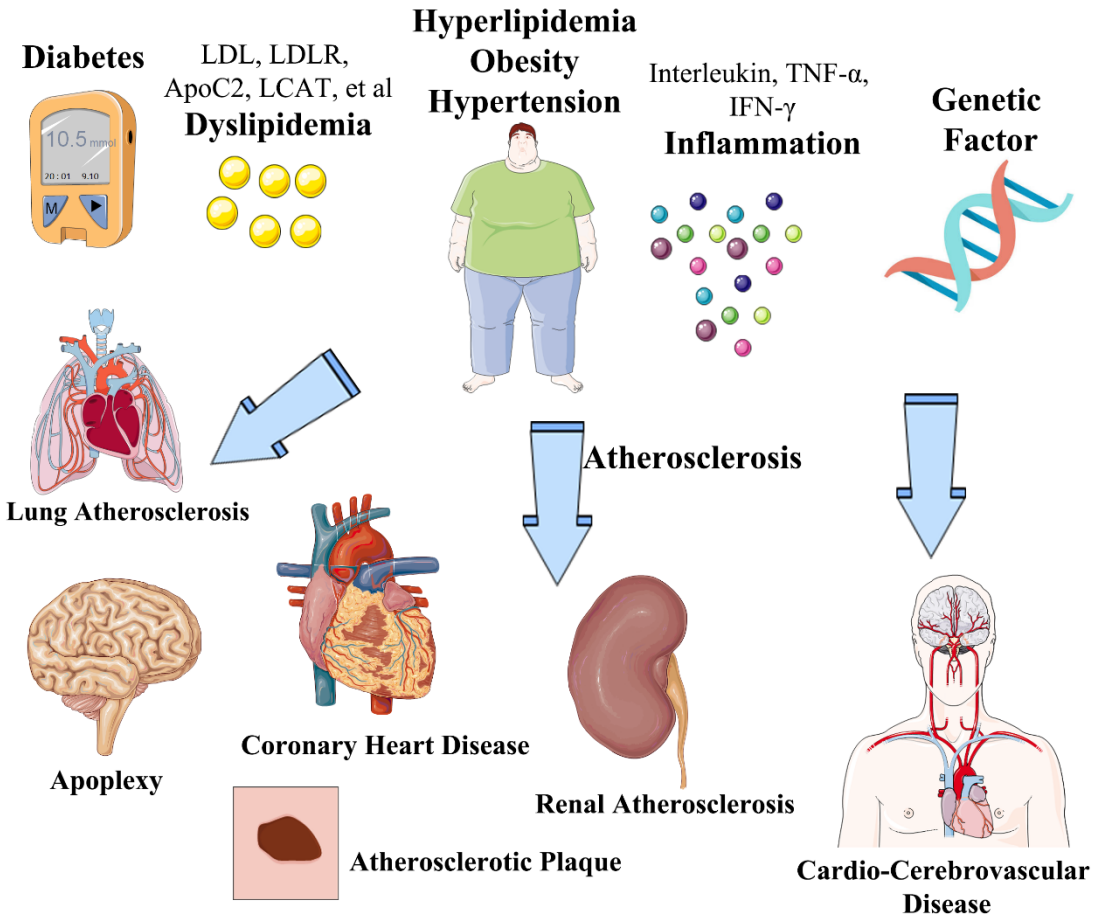

Figure 1 Risk factors and complications of AS

1. Dyslipidemia and Atherosclerosis (AS)

Lipoprotein metabolism plays a pivotal role in the initiation and progression of atherosclerosis (AS), involving the transport and turnover of lipids, particularly total cholesterol (TC) and triglycerides (TG). The lipid metabolic process is highly complex and regulated by multiple factors, including chylomicrons (CM), very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), as well as the interconversion between TC and cholesterol esters (CE) [29]. Dietary fats are absorbed by the intestine and assembled into CM, followed

by their transformation into nascent and mature HDL, VLDL, and LDL. These processes are mediated by apolipoproteins such as ApoA and ApoB, along with receptors including the low-density lipoprotein receptor (LDLR). Enzymes such as lecithin–cholesterol acyltransferase (LCAT) and phospholipid transfer protein (PLTP) are not only crucial in lipid metabolism but also influence AS progression and therapeutic responses [30]. A schematic of lipid metabolism is illustrated in **Figure 2**.

Metabolic disorders such as dyslipidemia, diabetes, and obesity synergistically contribute to AS development and are closely tied to plaque formation and lipid metabolism dysregulation, making them promising targets for anti-atherosclerotic therapy. Apolipoproteins (Apos) are protein components of CM, VLDL, LDL, and HDL that transport lipids across cells and tissues while participating in intracellular signaling pathways. Key members include ApoA, ApoB, ApoC, and ApoE, all of which are implicated in lipid homeostasis and AS pathogenesis [31].

The atheroprotective role of HDL is largely attributed to ApoA-I, the main structural and functional component of HDL, which facilitates HDL biogenesis, lipid efflux, and cellular signaling [32]. Based on the "HDL hypothesis," increasing HDL levels was once believed to offer vascular protection and reduce AS risk. Pharmacological inhibitors of cholesterol ester transfer protein (CETP) were developed to increase HDL-C levels and reduce non-HDL cholesterol, particularly LDL-C. However, large-scale clinical trials with CETP inhibitors such as Torcetrapib (Pfizer), Dalcetrapib (Roche), and Evacetrapib (Eli Lilly) failed to show significant cardiovascular benefits [33–36]. In contrast, Anacetrapib (Merck) significantly reduced the composite endpoint of cardiovascular death and myocardial infarction, with HDL levels increasing by 104% and LDL levels decreasing by 18%. Despite strong epidemiological and preclinical evidence linking HDL and HDL-C to AS risk, the clinical failures of HDL-C-targeted interventions suggest that the protective effects may depend more on HDL particle quality and function—including Apo composition, cholesterol efflux capacity, and anti-inflammatory properties—rather than HDL-C levels alone [37–38].

Studies have further revealed the critical involvement of apolipoproteins in AS

pathophysiology. For instance, in hamster models, ApoC-III knockout ameliorated dyslipidemia and atherosclerosis induced by high-fat diets, suggesting that ApoC-III may serve as a therapeutic target for hypertriglyceridemia and AS-associated cardiovascular diseases [24]. ApoC-II is an essential activator of lipoprotein lipase (LPL)-mediated hydrolysis of TG-rich lipoproteins and is a component of CM, VLDL, and HDL. ApoC-II deficiency results in severe hypertriglyceridemia and spontaneous AS development [39].

Mouse models lacking ApoE or LDLR exhibit elevated plasma LDL levels and prominent AS phenotypes, underscoring their essential roles in lipid metabolism and atherogenesis. ApoE is particularly valuable in developing AS animal models in mice, hamsters, and dogs for mechanistic and pharmacological studies [40–41]. ApoB, which exists in two forms—ApoB-100 and ApoB-48—is a major structural component of CM, VLDL, and LDL, and serves as an early biomarker and risk factor for AS development [42].

Metabolic enzymes involved in lipid regulation are also key players in AS. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes LDL-C elevation by degrading LDL receptors, and PCSK9 inhibitors have been shown to significantly lower circulating LDL-C levels [43]. LCAT, synthesized in the liver and secreted into the bloodstream, is a critical enzyme in HDL homeostasis, function, and reverse cholesterol transport. It facilitates the esterification of free cholesterol by transferring unsaturated fatty acids from the C2 position of phosphatidylcholine in HDL to cholesterol, producing cholesteryl esters and lysophosphatidylcholine [44].

In conclusion, dyslipidemia represents a fundamental pathological mechanism of AS, driven by complex interactions among various lipids, proteins, and metabolic enzymes. Understanding the intricate roles of apolipoproteins and their regulatory pathways not only enhances our comprehension of AS pathogenesis but also facilitates the development of novel animal models and targeted therapeutic strategies for AS.

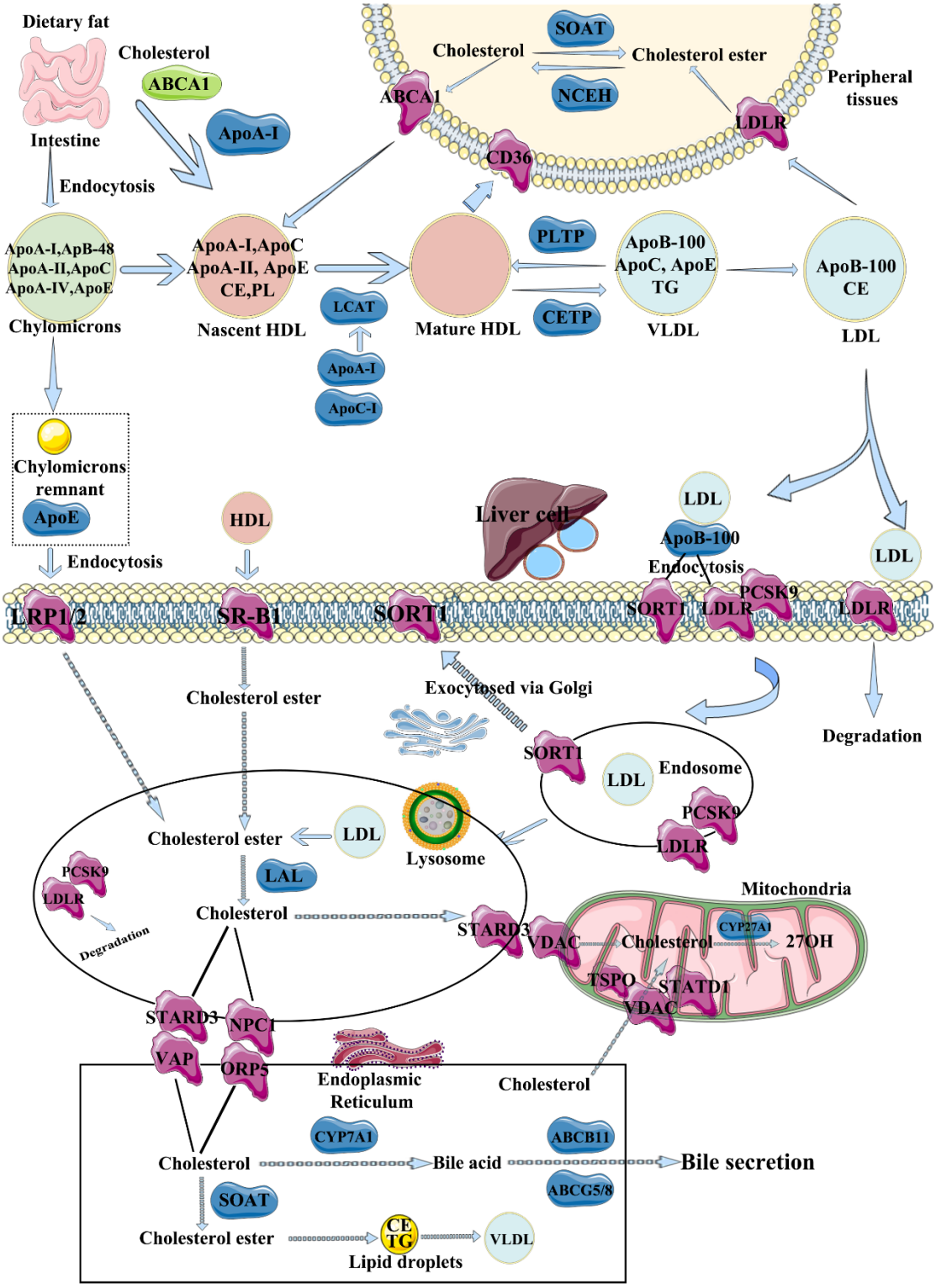

Figure 2 Diagram of lipid metabolism mechanism

2. Atherosclerosis and Inflammatory Immunity

Atherosclerosis (AS) is not only a metabolic disorder driven by dysregulated lipid metabolism, but also a chronic inflammatory disease. Inflammatory immune responses play a critical role throughout the pathogenesis of AS. During disease progression, chronic inflammation contributes to plaque rupture, platelet aggregation, and thrombus formation, ultimately resulting in vascular stenosis or occlusion. These events alter the behavior of vascular endothelial and smooth muscle cells, further recruiting inflammatory cells and exacerbating lesion development and related complications. Inflammation also serves as a key pathological link between AS and other cardiovascular diseases such as hypertension [45].

The inflammatory hypothesis of AS has gained increasing attention, especially following the success of inflammation-targeted clinical trials such as the CANTOS study. This study demonstrated that anti-inflammatory therapy can reduce cardiovascular risk without affecting lipid levels [25]. In both clinical and experimental contexts, inflammatory mediators such as C-reactive protein (CRP), interleukin-1β (IL-1β), IL-6, and IL-10 have been identified as biomarkers that influence the onset and progression of AS and other cardiovascular diseases [46].

Emerging evidence indicates that inflammatory immunity bridges lipid metabolic disorders with other risk factors. Suzanne E. Engelen provided a comprehensive overview of the inflammatory timeline in AS development [10]. As outlined in Table 1, early clinical studies identified HLA-DR expression and mononuclear cell infiltration in atherosclerotic plaques, along with T lymphocytes present in human AS lesions [47–49]. Elevated CRP levels have also been detected in patients with cardiovascular disease, supporting the role of inflammation in AS pathology. Furthermore, various growth factors and cytokines are expressed within atherosclerotic plaques [50–51]. Autoantibodies against oxidized LDL have been proposed as independent predictors of AS progression, establishing inflammation and immunity as not only mechanistic drivers but also potential prognostic tools for disease prevention and therapeutic intervention [52].

Animal models have further supported this association. For instance, mice deficient in macrophage colony-stimulating factor (M-CSF) exhibit reduced AS

incidence and progression, highlighting the essential role of M-CSF and its downstream effects on macrophage development and function in atherogenesis [53].

Inflammatory immune responses are central to several key processes in AS, including endothelial cell injury, lesion progression, and the development of plaque-related complications [45]. Certain inflammatory factors may exert protective effects in AS. For example, IL-10 has deactivating properties in macrophages and T cells, potentially stabilizing atherosclerotic plaques and limiting lesion expansion [54]. AS is also commonly associated with autoimmune disorders; patients with systemic lupus erythematosus frequently exhibit coexisting AS and cardiovascular diseases, suggesting that anti-inflammatory interventions may have therapeutic potential in these contexts [55].

A genome-wide association study involving over 14,000 individuals identified links between inflammatory genes and cardiovascular disease. Several genetic variants influencing lipid metabolism, thrombosis, inflammation, and vascular biology were discovered, although most findings require further validation [56]. Mechanistic studies have shown that blocking T cell receptor–dependent antigen recognition can prevent AS, with T cells responding to specific epitopes of the ApoB100 protein via restricted TCR clonotypes [57].

The anti-IL-1β monoclonal antibody canakinumab, evaluated in a trial with 10,061 participants, effectively reduced CRP levels and lowered the incidence of cardiovascular events without altering LDL levels [25]. In contrast, low-dose methotrexate did not significantly reduce IL-1β, IL-6, or CRP levels, nor did it improve cardiovascular outcomes in AS patients [58]. Another study involving 5,522 patients with chronic cardiovascular disease demonstrated that colchicine significantly reduced cardiovascular risk compared to placebo, providing further evidence for the clinical benefits of anti-inflammatory therapy in AS [59].

Single-cell transcriptomic analyses of AS plaques have identified at least 14 distinct cell populations. Notably, endothelial cells exhibited activated and potentially transdifferentiated phenotypes, T cells were predominantly in an activated state, and pro-inflammatory macrophages were abundantly present within plaques [60].

Overall, inflammatory immunity is a pivotal component of AS pathogenesis. It contributes to pro-coagulant activity, promotes leukocyte adhesion and migration, and stimulates vascular smooth muscle cell proliferation, all of which are essential for plaque formation and stability. While several experimental and clinical studies have confirmed the effectiveness of anti-inflammatory approaches in treating AS, some clinical trials have failed, highlighting both the challenges and opportunities in this field. Future research should aim to identify more effective inflammatory biomarkers and therapeutic targets for cardiovascular diseases. A historical overview of inflammatory immunity in AS is summarized in **Table 1**.。

Table 1 A brief history of research on the role of inflammatory immunity in AS

Year	Type	Description	Reference
1985	Clinical research	Expression of HLA-DR on vascular smooth muscle cells in atherosclerotic plaques	[48]
1988	Clinical research	A potential role for mononuclear cells in human atherosclerotic plaques	[49]
1989	Clinical research	Detection of activated T lymphocytes in the human atherosclerotic plaque	[50]
1990	Clinical research	High level of CRP in coronary artery disease	[51]
1991	Fundamental research	Expression of Cytokines and Growth Factors in AS plaques	[52]
1992	Clinical research	The autoantibodies to Oxidised-LDL is an independent predictor of the progression of AS	[53]
1995	Fundamental research	Deficient in macrophage colony-stimulating factor in mouse models reduces the development and function of AS	[54]
1999	Review	AS is an inflammatory disease	[45]
1999	Fundamental research	Inflammatory factors are therapeutic targets of AS	[55]
2003	Clinical research	The increased prevalence of AS in Systemic lupus erythematosus	[56]
2007	Clinical research	Genetic association between inflammatory genes and Cardiovascular disease	[57]
2010	Fundamental research	T cells can prevent AS by blocking TCR-dependent antigen recognition.	[58]

2017	Clinical research	Canakinumab can reduce CRP protein level without reducing LDL level	[25]
2019	Clinical research	In patients with AS, low-dose methotrexate did not reduce the level of IL-1β, IL-6 or CRP, and did not cause fewer cardiovascular events compared with placebo	[59]
2020	Clinical research	The anti-inflammatory effect of colchicine can be used for the treatment of cardiovascular diseases	[60]
2020	Fundamental research	Pro-inflammatory factors and anti-macrophages are present in plaque	[61]
2022	Fundamental research	IL-10 signaling impairs lipid and tissue homeostasis to accelerate AS	[26]

2. Mechanisms Underlying the Development and Progression of Atherosclerosis

The development and progression of atherosclerosis (AS) result from the complex interplay of multiple factors, including lipid infiltration, endothelial injury, formation of smooth muscle cell–derived foam cells, and chronic inflammation. Each of these pathological processes plays a crucial role in different stages of AS.

Under the influence of various risk stimuli—such as dysregulated glucose and lipid metabolism, chronic inflammation, smoking, and elevated low-density lipoprotein (LDL) levels—vascular endothelial cells undergo damage and degeneration, leading to increased permeability and compromised barrier function. As a consequence, plasma lipoproteins, particularly LDL, infiltrate the intimal layer of the arterial wall. These retained lipoproteins undergo oxidative modification, transforming into oxidized LDL (oxLDL). Meanwhile, the damaged endothelium recruits circulating monocytes, which migrate into the intima and engulf oxLDL, differentiating into foam cells of monocytic origin.

Simultaneously, endothelial injury induces the activation of platelets, triggering their adhesion, aggregation, and the release of platelet-derived factors. The accumulation of foam cells, along with the migration and proliferation of vascular smooth muscle cells (VSMCs), contributes to the formation of fibrous plaques and

necrotic lipid cores—hallmarks of advanced atherosclerotic lesions.

These pathological changes can lead to a range of severe complications, including intraplaque hemorrhage, plaque rupture, thrombus formation, calcification, aneurysm development, and luminal narrowing. Moreover, atherosclerosis-related complications may result in a spectrum of cardiovascular disorders, such as heart failure, cardiogenic shock, coronary artery disease (CAD), and arrhythmias.

A comprehensive understanding of these mechanisms is essential for the prevention and targeted treatment of AS. An overview of the mechanistic progression of AS is illustrated in **Figure 3** [1].

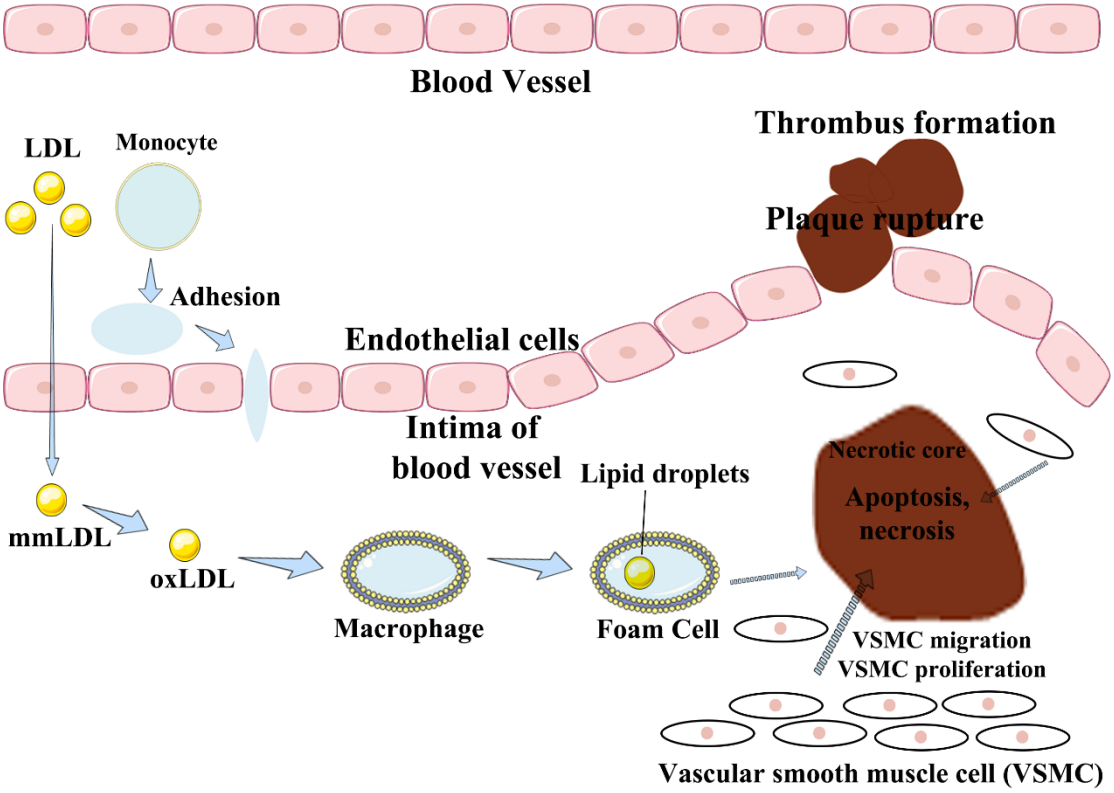

Figure 3. Mechanism of the occurrence and development of AS

3. Animal Models of Atherosclerosis (AS)

Animal models of atherosclerosis (AS) play a crucial role in AS pathology research, basic pharmacological studies, and preclinical therapeutic investigations.

These models are used to simulate the development, diagnosis, and clinical treatment of the disease, and to investigate the effects of environmental and genetic factors on AS pathogenesis and their underlying mechanisms. This review provides a comprehensive overview of the characteristics of AS animal models to facilitate anti-AS therapy research, focusing on the use of rodents, rabbits, dogs, pigs, and primates, along with insights from transgenic and gene-editing technologies.

Mice, as commonly used model organisms, are cost-effective, have short reproductive cycles, and benefit from well-established genetic modification techniques. However, they also exhibit differences in lipid metabolism compared to humans, and the use of high-fat diets for AS modeling can sometimes fail. Despite these limitations, mouse models of AS are well-established and widely used in basic AS research. Antisense oligonucleotides (ASOs), which inhibit gene expression through specific binding to DNA or mRNA sequences, have been employed to create animal models by knocking down LDL receptor (LDLR) expression in mice. Blood tests reveal increased total cholesterol (TC) levels, while En-face imaging has demonstrated the development of lesions in the aortic root, aortic arch, and brachiocephalic arteries. Furthermore, this technique also highlights the regression of advanced AS plaques in later stages of the disease [61]. Additionally, using AAV-CRISPR/Cas9 for LDLR knock-in mice via subcutaneous injection has shown reductions in TC, triglycerides (TG), and LDL cholesterol (LDL-C) levels, with a decrease in macrophage infiltration and improved AS phenotypes, underscoring the role of LDLR in AS progression [62]. Similarly, targeted gene replacement of the ApoE gene in mouse embryonic stem cells has demonstrated increased TC and TG levels, and the appearance of AS plaques, further confirming the role of ApoE in AS [63].

Compared to LDLR-deficient mice, ABCG1-deficient/LDLR-deficient double knockout (DK) mice exhibit elevated TC, VLDL-C, and LDL-C levels, with more severe lesion development and disruption of lipid metabolism, indicating ABCG1 as a potential protective factor in early AS damage and a promising model optimization for AS studies [64]. The antibody to ADAMTS7, a disintegrin and metalloproteinase

with thrombospondin 7, plays an essential role in the early stages of vascular matrix remodeling in AS, promoting smooth muscle cell migration and intimal thickening. Knockout models (Adamts7-/- mice, ApoE-/-/Adamts7-/- mice, and LDLR-/-/Adamts7-/- mice) have shown reduced neointima formation and less AS-related cellular migration and matrix modulation after injury [65].

In ApoAII knockout mice, targeted gene disruption via embryonic stem cells has resulted in reduced HDL, TC, TG, non-HDL-C, free fatty acids, insulin, and blood glucose levels. These changes suggest a complex role of ApoAII in lipid metabolism and AS progression, as well as its involvement in metabolic processes like insulin resistance and blood glucose regulation [66]. The angiotensin II type 1 receptor (AT1R) is crucial in vasoconstriction and neurohumoral activation, and its role in oxidative stress in cardiovascular diseases is well-documented. AT1R-deficient mice show reduced vascular oxidative stress, endothelial dysfunction, and AS lesions [67]. Angiotensin-converting enzyme 2 (ACE2), a key factor in hypertension, cardiovascular diseases, and diseases like SARS-CoV-2, has been found to play a potentially protective role in AS. In ApoE-/-/ACE2-/- DK mice, adhesion molecules and inflammatory cytokines such as TNF-α, IL-6, MCP-1, VCAM, JAM-A, MMP2, and MMP9 were elevated, leading to increased aortic plaque area and accumulation, highlighting ACE2's potential in reducing AS [68].

Chemokine receptors, central to oxidative stress and inflammation, mediate AS formation. The CX3C chemokine fractalkine receptor 1 (CX3CR1) has been linked to AS. CX3CR1-deficient mice exhibit reduced lipid staining lesions in the thoracic aorta, decreased aortic sinus AS development, and less macrophage aggregation [69]. In ApoE-/-/eNOS-/- knockout mice, peripheral coronary artery AS and myocardial fibrosis are observed. eNOS knockout changes the conventional AS knockout model and improves AS research, particularly in coronary heart disease (CHD) studies [70]. IL-10, an anti-inflammatory cytokine, has protective effects in AS. In ApoE-/-/IL-10-/- DK mice, elevated levels of LDL-C, T-helper cell 1 responses, lesion size, matrix metalloproteinases, tissue factor activity, and systemic coagulation markers were observed. In contrast, VLDL levels decreased, and early-stage AS lesions increased,

while late-stage lesions exhibited enhanced proteolysis and procoagulant activity, suggesting IL-10's role in preventing AS and stabilizing plaques [71]. Similarly, in ApoE-/-/IL-18-/- knockout mice, although IL-18 promotes AS, knocking it out resulted in reduced lesion size, elevated TC and TG levels, and decreased lesion severity, offering evidence for AS inflammation treatment and further validating inflammation models in AS research [72].

Lipocalin-type prostaglandin D synthase (L-PGDS) is highly expressed in the vascular endothelium and central nervous system. It protects the vascular wall through regulation of cell proliferation, differentiation, and apoptosis. In L-PGDS-deficient mice, increased body weight, TC, TG, LDL-C, and AS-related plaques are observed, along with reduced HDL-C levels, suggesting that L-PGDS plays a crucial role in inflammation and AS [73]. Endothelial nitric oxide synthase 3 (NOS3) promotes vasodilation and regulates angiogenesis. Dysregulation of NOS3 expression leads to unstable NO production, vascular endothelial damage, and AS, contributing to conditions such as hypertension. In ApoE-/-/NOS3-/- DK mice, elevated TC and LDL levels, liver steatosis, and aortic atherosclerotic lesions were observed, making this model a useful tool for hypertension and AS research [74]. In ApoE-/-/FGF2lmw- mice, AS progression was mitigated, with reduced aortic plaque, macrophage infiltration, and oxidative stress. These results reveal that low-molecular-weight FGF2 exacerbates inflammation in AS [75].

Chemokine receptor 7 (CCR7) plays a key role in inflammatory immunity. In CCR7-/-/LDLR-/- DK mice, reduced AS plaques were observed alongside increased inflammation, particularly in the AS plaques, where T cell responses and dendritic cell and T cell infiltration were enhanced. This suggests that inflammation and lipid metabolism may act as independent but interconnected risk factors for AS, offering new perspectives for future anti-AS research [76]. G-protein-coupled receptor G2A (G2A) mediates macrophage stimulation and T cell chemotaxis in AS, with G2A-deficient/LDLR-deficient DK mice showing anti-AS effects, reducing macrophage accumulation at atherosclerotic lesion sites and increasing blood HDL-C levels, demonstrating its role in promoting AS development [77].

Hepatic lipase (HL) hydrolyzes phospholipids and triglycerides in lipoproteins. In LP-/- mice, elevated HDL and TC levels were observed. While the study primarily focused on HL's role in lipid metabolism, further investigation is needed to understand its role in AS pathogenesis and as a cardiovascular disease model [78].

Transgenic mice with overexpressed paraoxonase-3 (PNO3) have demonstrated protective effects against AS and obesity, whereas PON3-deficient mice exhibited AS-related phenotypes such as increased lesion size, TC, TG, bile acids, VLDL/IDL/LDL cholesterol, and mitochondrial superoxide levels, along with impaired mitochondrial respiration. These findings highlight the role of PON3 in AS and obesity pathogenesis and provide a new knockout site for AS animal models [79].

Scavenger receptor class B, type I (SR-BI) mediates lipid transfer and is involved in cardiovascular diseases through interactions with AS and hypertension. SR-BI-/-/LDLR-/- DK mice exhibited more severe aortic and coronary artery AS compared to conventional models, with increased platelet aggregation, myocardial fibrosis, and circulating cytokine levels. This provides a new model for AS and coronary heart disease (CHD) research [80].

ApoE-deficient mice, which exhibit elevated TC and TG levels and reduced HDL, form foam cell deposits and severe occlusions in the proximal aorta, making them a useful model for studying atherosclerosis [81]. Studies on ApoE in lipid metabolism and its role in the formation and degradation of lipoproteins highlight its importance in AS, as demonstrated in ApoE-/-/ApoAI-/- DK mice, which exhibit increased aortic plaque area and coronary artery AS. These findings emphasize the advantages of multi-gene knockout models in simulating multifactorial disease development [82].

CRISPR/Cas9 and zinc-finger nucleases (ZFNs) are increasingly employed for gene knockout applications, offering optimized methods for gene disruption. CRISPR/Cas9 systems have been used to model ApoE-/-/LDLR-/- DK mice, showing atherosclerotic lesions, pancreatic islet damage, and hyperlipidemia-associated inflammation [83]. Furthermore, gene-targeted ApoE-/-/LDLR-/- DK mice, generated

via homologous recombination in embryonic stem cells, show increased AS lesion size and greater atherosclerotic risk, highlighting CRISPR/Cas9 and ZFN methods as powerful tools for AS research [84].。

Table 2 Animal models related to AS genetic engineering

Number	Animal Type	Model	Target	Main Method	Main Feature	Reference
1	Mouse	Knock-down	LDLR	LDLR knock-down mice were injected intraperitoneally in C57BL/6 mice for antisense oligonucleotides (ASO)	Increased TC levels; The development of lesions in the aortic root, aortic arch, and brachiocephalic artery.	[61]
2	Mouse	Knock-in	LDLR	LDLR-E208X point mutation mice by AAV-CRISPR/Cas9 and subcutaneous injection.	Decreased TC, TG, LDL-C levels and the degree of macrophage infiltration; Improve AS phenotype.	[62]
3	Mouse	Knock-in	APOE2	Targeted gene replacementin embryonic stem cells to generate human APOE*2 KI mice.	Increased TC, TG, F10 levels in KI mice.	[63]
4	Mouse	Knock-out	ABCG1, LDLR	$ABCG1^{-/-}/LDLR^{-/-}$ C57BL/6 DK mice were generated by cross-bred.	Increased TC, VLDL-C, LDL-C levels and F10 in $ABCG1^{-/-}/LDLR^{-/-}$ DK mice compared to $ABCG1+/+/LDLR^{-/-}$ mice.	[64]
5	Mouse	Knock-out	Adamts7, ApoE, LDLR	$Adamts7^{-/-}$ KO mice cross-bred with $ApoE^{-/-}$ mice and $LDLR^{-/-}$ mice to generate $ApoE^{-/-}/Adamts7^{-/-}$ mice and $LDLR^{-/-}/Adamts7^{-/-}$ mice.	Decreased neointimal formation after femoral wire injury; Decrease AS in modulation of vascular cell migration and matrix.	[65]
6	Mouse	Knock-out	ApoAII	ApoAII knockout mice were generated by Targeting disruption of the mouse ApoAII in embryonicstem cells.	Decreased HDL, TC, TG, Glucose, Free fatty acid, insulin, and Non HDL-C levels.	[66]

7	Mouse	Knock-out	ApoE, AT1R	AT1R$^{-/-}$ C57BL/6J mice and ApoE$^{-/-}$ C57BL/6J mice were backcrossed to generate ApoE$^{-/-}$ /AT1R$^{-/-}$ DK mice.	Inhibition of vascular oxidative stress, endothelial dysfunction, and atherosclerotic lesion formation.	[67]
8	Mouse	Knock-out	ApoE, ACE2	ApoE$^{-/-}$/ACE2$^{-/-}$ DK C57Bl6 mice were generated by cross-bred from ApoE$^{-/-}$ mice and ACE2$^{-/-}$ mice.	Increased adhesion molecules and inflammatory cytokines such as TNF-α, IL-6, MCP-1, VCAM, JAM-A, MMP2 and MMP9 levels, increased aortic plaque area and plaue accumulation.	[68]
9	Mouse	Knock-out	ApoE, CX3CR1	CX3CR1$^{-/-}$ C57BL/6 KO mice were generated by targeted gene disruption, CX3CR1$^{-/-}$/ApoE$^{-/-}$ C57BL/6 mice were generated by crossbred.	Decreased lipid-stained lesions in the thoracic aorta, the development AS in the aortic sinus, and macrophage accumulation.	[69]
10	Mouse	Knock-out	ApoE, eNOS	ApoE$^{-/-}$/eNOS$^{-/-}$ DK C57BL/6J mice were generated by crossbred.	Increased AS in lesion area; mice develop peripheral coronary AS, perivascular and myocardial fibrosis.	[70]
11	Mouse	Knock-out	ApoE, IL-10	ApoE$^{-/-}$/IL-10$^{-/-}$ C57BL/6 DK mice were generated by crossbred.	Increased LDL-C, T-helper 1 responses, lesion size, matrix metalloproteinases and tissue factor activities, markers of systemic coagulation levels, decreased VLDL levels.	[71]
12	Mouse	Knock-out	ApoE, IL-18	ApoE$^{-/-}$/IL-18$^{-/-}$ C57BL/6J DK mice were generated by crossbred.	Reduced lesion size, Increased α-SM actin levels, TC, TG levels though the proatherogenic role for IL-18 in ApoE$^{-/-}$ /IL-18$^{-/-}$ C57BL/6J DK mice .	[72]
13	Mouse	Knock-out	ApoE, L-PGDS	L-PGDS$^{-/-}$ C57BL/6 mice were generated by gene targeting, DK mice were generated by crossbred.	Increased body weight, TC, LDL-C, TG, and atherosclerotic plaque levels ;Decreased HDL-C levels.	[73]

14	Mouse	Knock-out	ApoE, NOS3	$ApoE^{-/-}/NOS3^{-/-}$ mice were obtained through genotype identification and screening.	Increased TC, LDL levels, steatosis was found in liver and atherosclerotic lesions were observed in the aortic vessels cell in DK mice.	[74]
15	Mouse	Knock-out	FGF2	$ApoE^{-/-}$ FGF2lmw- mice were obtained by crossbred.	Improve AS; decreased aortic plaques, macrophage infiltration and oxidative stress.	[75]
16	Mouse	Knock-out	LDLR, CCR7	$CCR7^{-/-}/LDLR^{-/-}$ C57BL/6 mice were obtained by crossbred.	Reduced atherosclerotic plaque development; Increased Infiltration of dendritic cells and T cells in Atherosclerotic Plaques.	[76]
17	Mouse	Knock-out	LDLR, G2A	$G2A^{-/-}/LDLR^{-/-}$ C57BL/6J mice were generated by crossbred.	Increased HDL-C levels, decreased macrophage accumulation at lesion of the aorta, suppresses atherosclerotic lesion progression.	[77]
18	Mouse	Knock-out	LP	$LP^{-/-}$ mice were obtained by targeting gene in Embryonic stem cell.	Increased TC, and HDL levels.	[78]
19	Mouse	Knock-out	PON3	$PON3^{-/-}$ C57BL/6J mice were obtained using classic gene targeting.	Increased atherosclerotic lesion size, TC, TG, Bile acids, VLDL/IDL/LDL cholesterol and mitochondrial superoxide levels; impaired mitochondrial respiration.	[79]
20	Mouse	Knock-out	SR-BI, LDLR	$SR\text{-}BI^{-/-}/LDLR^{-/-}$ C57BL/6:129 DK mice were generated crossbred.	Aortic sinus AS, coronary artery AS; Increased platelets in coronary artery atherosclerotic plaques, substantial myocardial fibrosis, and circulating cytokine levels.	[80]

21	Mouse	Knock-out	ApoE	Targeting to inactivate the ApoE gene to generate $ApoE^{-/-}$ mice.	Increased TC, TG and decreased HDL levels in ApoE-deficient mice; developed foam cell-rich depositions in proximal aortas; severe occlusion of the coronary artery ostium.	[81]
22	Mouse	Knock-out	ApoE, ApoAI	$ApoE^{-/-}$/$ApoAI^{-/-}$ DK C57Bl/6J mice .	Increased plaque extent at the aortic sinus and Coronary Atherosclerosis; Causing Skin Xanthomas, and Worsening of Inflammation.	[82]
23	Mouse	Knock-out	ApoE, LDLR	$ApoE^{-/-}$/$LDLR^{-/-}$ non-obese diabetic mice were generated by CRISPR/Cas9 system and microinjection.	Development atherosclerotic plaques in the aorta, and destruction of pancreatic islets and an inflammatory response to hyperlipidemia.	[83]
24	Mouse	Knock-out	ApoE, LDLR	$ApoE^{-/-}$/$LDLR^{-/-}$ DK mice were created by homologous recombination in embryonic stem cell.	Increased TC, atherosclerotic lesions levels in DK mice.	[84]
25	Mouse	Knock-out	ApoE, LDLR	$ApoE^{-/-}$/$LDLR^{-/-}$ C57BL/J6 DK mice by target gene disruption.	Increased TC, VLDL, and LDL levels in mice.	[85]
26	Mouse	Knock-out	GPx1, ApoE	$ApoE^{-/-}$/$GPx1^{-/-}$ C57BL/J6 DK mice.	Increased clerotic lesions in the aortic sinusregion, arch, thoracic, abdominal lesions, and proinflammatory and profibrotic factors.	[86]
27	Mouse	Knock-out	Klkb1	$Klkb1^{-/-}$/$ApoE^{-/-}$ DK mice were generated by crossbred.	Decreased atherosclerotic plaque development and increased hepatic LDLR protein, TC, and TG levels.	[87]
28	Mouse	Knock-out	LCAT	$LCAT^{-/-}$ KO mice model were generated by targeting disruption of the LCAT gene in mice embryonic stem cells.	Decreased TC, PL, CE, HDL-C, ApoAI levels, increased TG levels.	[88]

29	Mouse	Knock-out	LDLR	Homologous recombination in embryonic stem cells to produce $LDLR^{-/-}$ KO mice.	Increased TC, IDL, LDL levels without a significant change in HDL.	[89]
30	Mouse	Knock-out	LDLR	Targeting the Ldlr gene for C57BL/6J $LDLR^{-/-}$ KO mice by AAV-CRISPR/Cas9 injection.	Severe hypercholesterolemia, increased TC levels and atherosclerotic lesions in the aorta.	[90]
31	Mouse	Knock-out	PCSK9	$PCSK9^{-/-}$ KO mice were generated by new nanocarrier-delivered CRISPR/Cas9 system.	Decreased LDL-C levels.	[91]
32	Mouse	Knock-out	Pggt1b	Pggt1b Δ/Δ conditional knockout mice were generated by CRISPR/Cas9 system.	Attenuated diabetes-accelerated AS.	[92]
33	Mouse	Knock-out	SR-BI	Targeted disruption of the SR-BI to generate $SR\text{-}BI^{-/-}$ KO mice.	Increased TC levels, atherosclerotic lesions, and vascular calcification in mice.	[93]
34	Mouse	Mutant	PCSK9	AAV mutant C57BL/6J mice were generated by pAAV/D377Y-mPCSK9 and single tail vein injection.	Increased TC, PCSK9 levels, atherosclerotic lesions, and vascular calcification in mice; Inducing macrophage accumulation.	[94]
35	Mouse	Transgene	ApoAI	Transgenic C57BL/6 mice expressing human ApoAI.	Increased HDL-C levels, decresed aortic sinus foam-cell lesion area.	[95]
36	Mouse	Transgene	ApoAII	Transgenic C57BL/6J mice overexpressing ApoAII.	Increased aortic lesions, TC, HDL-C levels.	[96]
37	Mouse	Transgene	ApoB	Transgenic C57BL/6 mice expressing human ApoB with a high fat diet.	Increased human apoB, TC, non-HDL cholesterol levels, atherosclerotic lesions in transgenic mice with a high diet.	[97]
38	Mouse	Transgene	ApoCIII	Transgenic C57BL/6 mice expressing human ApoCIII.	Increased TG levels, ApoCIII overexpression can cause hypertriglyceridemia but lack of protection in ApoCIII knock-out mice.	[22]

39	Mouse	Transgene	ApoE, CETP	Transgenic mice expressing both ApoE*3-Leiden and CETP.	Compared with ApoE$^{-/-}$ mice, atherosclerotic plaques are graded, including 0/I/II/III/IV/V.	[98]
40	Mouse	Transgene	CETP, LCAT	LCAT*CETP-tg mice were generated by crossbred.	Accumulation of dysfunctional HDL, impaired reverse cholesterol transport and AS.	[99]
41	Mouse	Transgene	IDOL	IDOL transgenic C57BL/6J mice expressing human IDOL from the liver-specific albumin promoter.	Increased LDL-C levels, decreased hepatic LDLR protein, developed marked atherosclerotic lesions.	[100]
42	Mouse	Transgene and Knock-out	APP, ApoE	APP Transgenic mice and ApoE$^{-/-}$ /APPTg mice.	Increased vascular inflammation, arterial wall thickness and AS in APP transgenic mice and ApoE$^{-/-}$ /APPTg mice.	[101]
43	Mouse	Transgene and Knock-out	LDLR, ApoB 100	LDLR$^{-/-}$ /ApoB100Tg mice were crossbred.	Increased TC, AS lesion area levels.	[102]
44	Rat	Knock-out	ApoE	ApoE$^{-/-}$ Sprague Dawley rats were obtained by TALEN-mediated gene targeting.	Increased TC, TG, LDL-C, and HDL-C levels without obvious atherosclerotic lesion.	[103]
45	Rat	Knock-out	ApoE	ApoE$^{-/-}$ rats were generayed by TALENs targeting.	Increased TC levels, development of mild aortic AS with severe coronary AS, lipid, macrophages and collagen fibers in coronary atherosclerosis plaques.	[104]
46	Rat	Knock-out	ApoE, LDLR	ApoE$^{-/-}$/LDLR$^{-/-}$ DK rats were generated by CRISPR/Cas9 system.	Severe dyslipidemia and liver steatosis; mononuclear cell infiltration in atherosclerotic plaques and macrophage accumulation in lesions.	[105]
47	Rat	Knock-out	ApoE, LDLR	ApoE$^{-/-}$/LDLR$^{-/-}$ DK rats were generated by CRISPR-Cpf1.	Hyperlipidemia and aortic lesions.	[106]

48	Rat	Knock-out	LDLR	$LDLR^{-/-}$ KO rats were generated by the zinc finger technology.	Increased TC, TG, weight, glucose intolerant PCSK9, and leptin levels.	[107]
49	Rat	Transgene	CETP	A new line of CETP-transgenic Fisher rats.	Decreased HDL-C concentration in CETPtg rats; Different private feed composition affects the development of diseases.	[108]
50	Hamster	Knock-out	ABCA1	$ABCA1^{-/-}$ KO hamsters were generated by CRISPR/CAS9 technology.	Increased IL-6, TNF-α, ICAM, COX, CD36, TG and CRP levels; Decreased HDL-C levels.	[113]
51	Hamster	Knock-out	ApoC2	$ApoC2^{-/-}$ KO golden Syrian hamsters were generated by CRISPR/CAS9 technology and microinjections.	Increased TG, TC, NEFA, atherosclerotic lesion size levels, decreased HDL-C, glucose, lipolysis capacity and insulin levels.	[39]
52	Hamster	Knock-out	Klkb1	$Klkb1^{-/-}/ApoE^{-/-}$ DK mice were generated by crossbred.	Increased hepatic LDLR levels, decreased circulating cholesterol levels.	[87]
53	Hamster	Knock-out	LCAT	LCAT mutant Syrian Golden hamsters were generated by CRISPR/CAS9 system.	Decreased CETP, and HDL-C levels; Increased TC, TG, non-HDL-C, free cholesterol, and atherosclerotic lesion levels.	[44]
54	Hamster	Knock-out	LDLR	$LDLR^{-/-}$ hamsters were obtained by CRISPR/Cas9 system and microinjections.	Increased TC, TG levels and atherosclerotic lesion size; with coronary AS.	[115]
55	Hamster	Knock-out	LDLR	$LDLR^{-/-}$ hamsters were obtained by CRISPR/Cas9 system and microinjections.	Different animal models show different effects in AS, $LDLR^{-/-}$ hamsters for AS are better than mice and rats.	[116]
56	Hamster	Knock-out	ApoCIII	$ApoCIII^{-/-}$ in hamster using CRISPR/Cas9 system.	Protect against AS; Decreased TG, and TC levels; Increased HDL-C levels.	[24]
57	Hamster	Knock-out	LDLR, APOCIII	$LDLR^{-/-}/ApoCIII^{-/-}$ hamsters were generated by CRISPR/Cas9 system.	Increased atherosclerotic lesion size, accelerate As development.	[117]

58	Hamster	Knock-out	Idol	Idol$^{-/-}$ hamsters were generated by CRISPR/Cas9 system.	Decreased TC, and TG levels; Protect against spontaneous atherosclerotic lesion.	[118]
59	Hamster	Knock-out	IL10	IL10$^{-/-}$ hamsters were generated by CRISPR/Cas9 system.	Decreased TG, HDL-C levels; Increased atherosclerotic lesion size; alter microbiome homeostasis.	[26]
60	Rabbit	Knock-in	ApoAII	New Zealand White ApoAII KI rabbits were generated by TALEN-mediated homologous recombination.	Decreased TG and aortic AS levels, Increased HDL-C levels.	[119]
61	Rabbit	Knock-out	ApoCIII	ApoCIII$^{-/-}$ KO rabbits were generated by zinc finger nucleases.	Decreased TG, TC levels.	[23]
62	Rabbit	Knock-out	ApoE	ApoCIII$^{-/-}$ KO rabbits were generated by ZFN/CRISPR/Cas9.	Increased TC, AS lesion area levels.	[120]
63	Rabbit	Knock-out	LDLR	LDLR$^{-/-}$ KO rabbits were generated by CRISPR/Cas9 system.	Increased TC, LDL-C, TG and aortic/coronary artery AS lesions; Decreased HDL-C levels.	[121]
64	Rabbit	Knock-out	LDLR, APOE	LDLR$^{-/-}$/APOE$^{-/-}$DK New Zealand White rabbits were generated by CRISPR/Cas9 system.	Increased TC, TG, and LDL-C levels, decreased HDL-C levels and the accumulation of atherosclerotic lesions.	[122]
65	Rabbit	Knock-out	CETP	CETP$^{-/-}$ KO rabbits were generated by ZFN.	Increased TC, and HDL-C levels; Decreased aortic and coronary AS.	[123]
66	Rabbit	Knock-out	Lp-PLA2	Lp-PLA2 knockout rabbits were generated by CRISPR/Cas9 system.	Decreased SREBP2, HMGCR protein levels; Reduced hypercholesterolemia and aortic atherosclerosis lesions.	[124]
67	Rabbit	Transgene	Apo (a)	Transgenic rabbits expressing human apo(a).	Increased atherosclerotic lesions for the aorta, the iliac artery, and the carotid artery.	[125]
68	Rabbit	Transgene	ApoB-100	Human ApoB transgenic rabbit.	Increased TG, and TC levels; Decreased HDL-C levels.	[126]

69	Rabbit	Transgene	ApoCIII	ApoCIIITg Japanese white rabbits were generated by microinjection.	Increased TG levels, decreased LPL activity.	[127]
70	Rabbit	Transgene	ApoE3	New Zealand White rabbits expressing human ApoE3.	Increased LDL-C, VLDL; Stimulating VLDL production, enhancing VLDL clearance, and inhibiting VLDL lipolysis.	[128]
71	Rabbit	Transgene	ApoAI	New Zealand White rabbits transgenic for human apo A-I.	Increased HDL-C levels; Decreased thoracic aorta lesions.	[129]
72	Rabbit	Transgene	ApoAII	Transgenic (Tg) Japanese white rabbits expressing the human apo A-II.	Decreased macrophages and smooth muscle cells, decreased CRP and blood leukocytes levels.	[130]
73	Rabbit	Transgene	CETP	Japanese white rabbits expressing human CETP.	Increased TG and aortic AS lesions levels; Decreased HDL-C levels.	[131]
74	Rabbit	Transgene	LCAT	Transgenic (Tg) rabbits expressing LCAT.	Development of aortic AS; Increased HDL-C and non-HDL-C levels.	[132]
75	Rabbit	Transgene	MMP-9	Tg rabbits expressing human MMP-9 by microinjection.	Increased AS aortic lesions.	[133]
76	Rabbit	Transgene	PLTP	New Zealand White PLTP transgenic rabbits expressing human PLTP.	Increased TC levels; Developmeng of aortic fatty streaks.	[134]
77	Rabbit	Transgene	EL	Transgenic (Tg) rabbits expressing EL.	Less AS and hypercholesterolemia; reduced lesion area; fewer macrophages and smooth muscle cells; decreased TC, TG, HDL-C, and PL levels.	[135]
78	Swine	Knock-out	ApoE	$ApoE^{-/-}$ KO Bama miniature pigs were generated by CRISPR/Cas9 system.	Increased TC, TG, LDL-C, and HDL-C levels; Increased atherosclerotic lesions.	[136]
79	Swine	Knock-out	LDLR	$LDLR^{-/-}$ pigs were generated by targeted deletion.	Accelerate coronary plaques; Increased TC levels.	[137]

80	Swine	Knock-out	LDLR, ApoE	$LDLR^{-/-}/ApoE^{-/-}$ pigs were generated by CRISPR/Cas9 system.	Increased LDL-C and TC levels.	[138]
81	Dog	Knock-out	ApoE	$ApoE^{-/-}$ dogs were generated by CRISPR/Cas9 system.	Shows hypercholesterolemia and severe extensive AS, characterized by arterial stenosis and occlusion, as well as clinical manifestations of stroke and gangrene.	[139]

3. Emerging Research Targets in Atherosclerosis

As research on traditional lipid disorders and inflammatory metabolic targets for atherosclerosis (AS) progresses, new emerging targets related to AS have revealed novel mechanisms in its pathology and treatment, providing further insights into therapeutic strategies and animal models for AS research. One such innovation is the development of a novel vaccine targeting metallopeptidase-containing platelet-activating protein 7, which offers an anti-AS effect independent of lipid-lowering mechanisms. This approach avoids the usual clinical risks associated with thrombosis, offering a new chronic vaccination treatment strategy distinct from conventional therapies [140]. Aldehyde dehydrogenase 4 family member A1 (ALDH4A1) has been identified as both a biomarker and a target for AS. Studies utilizing high-throughput quantitative proteomics and metabolomics methods in LDLR-/- mice have identified A12 and its corresponding antigen ALDH4A1 as associated with AS. Injection of A12 antibodies delayed plaque formation, reduced circulating free cholesterol and LDL levels, and effectively slowed AS progression, positioning it as a potential target for anti-AS and other cardiovascular diseases [141].

The proliferation-inducing ligand (APRIL), encoded by the Tnfsf13 gene and produced by myeloid and stromal cells, is highly present in arterial tissues. Clinical studies have shown an increase in APRIL levels in coronary heart disease (CHD) patients. In Tnfsf13 knockout LDLR-/- mice, increased arterial plaque damage and accelerated AS progression were observed. Research suggests that non-canonical

forms of APRIL may serve as a predictive factor for cardiovascular disease mortality, with APRIL's protective mechanism in AS being through its interaction with heparan sulfate proteoglycans, which restricts AS progression [142]. The asialoglycoprotein receptor 1 (ASGR1) is linked to cholesterol metabolism. Deficiency in ASGR1 is associated with lower cholesterol levels and a reduced risk of cardiovascular diseases. Research has demonstrated that ASGR1 deficiency promotes cholesterol efflux into bile, lowering both blood and liver lipid levels. RNA-Seq analysis revealed that ASGR1 deficiency affects the LXR pathway, increasing LXR protein levels, which in turn upregulate target genes such as ABCG5 and ABCG8. This suggests ASGR1 as a new lipid-lowering target and a potential treatment focus for cardiovascular diseases like AS [143].

Genetic studies in humans and mouse models have shown that the regulation of Beta-1,4-galactosyltransferase 1 (B4GALT1) expression is associated with a reduced risk of coronary artery disease, offering a multi-faceted potential for heart protection [144]. Expression of the transcription factor Bach1 has been linked to AS and coronary artery disease. Endothelial cell-specific Bach1 knockout reduced turbulence-induced blood flow, AS lesions, macrophage content in plaques, and the expression of endothelial adhesion molecules. It also lowered plasma levels of TNF-α and IL-1β, positioning Bach1 as a potential target for AS and coronary artery disease [145].

The absence of Casein kinase 2-interacting protein 1 (CKIP-1) in mice leads to increased lipoprotein uptake and foam cell formation, exacerbating AS damage and increasing plaque area. This indicates that CKIP-1 may attenuate AS by reducing foam cell formation, with its mechanism involving REGγ-mediated Oct-1 degradation [146]. Research utilizing CRISPR genome-wide screening has identified Cold shock domain-containing protein E1 (CSDE1) as a modulator of LDLR degradation. CSDE1 silencing in mice results in lipid abnormalities similar to those caused by PCSK9, suggesting that targeting CSDE1 could regulate post-transcriptional LDLR mRNA processing and offer new strategies for preventing cardiovascular diseases [147].

Brown adipose tissue (BAT) plays a key role in energy expenditure and cardiovascular health. Metabolomics-based research by Alexander Pfeifer's team

discovered that adenosine treatment in mice increased BAT-dependent energy metabolism. Additionally, ENT1 regulates inosine levels in BAT, and modulation of ENT1 can enhance BAT activity, thus improving diet-induced obesity and influencing obesity-related cardiovascular diseases [148].

A genome-wide association study (GWAS) revealed that mutations in the GPR75 gene can prevent obesity. In genetically engineered mice, the deletion of GPR75 led to weight loss and improved insulin sensitivity, offering a new approach for obesity treatment and providing new insights for research into obesity-related diseases, such as cardiovascular diseases [149].

Inflammation is closely linked to obesity, AS, and other diseases. Serum IL-27 levels were significantly reduced in obese populations, while mouse models showed that IL-27 could promote energy expenditure through adipocyte thermogenesis. Recombinant IL-27 reduced weight and fat levels in mice, positioning IL-27 as a novel target for lipid metabolism disorders and cardiovascular disease prevention and treatment [150].

Analysis of over 360,000 sequenced samples from the UK Biobank revealed that loss of INHBE function offers protection against abdominal obesity. INHBE mutations are associated with adjusted waist-to-hip ratios and have causal links to diseases like diabetes and coronary heart disease (CHD). Targeting INHBE could significantly reduce abdominal obesity, alleviating complications related to obesity [151].

Studies have identified Insulin inhibitory receptor (IIR), which interacts with the INSR-IGF1R signaling complex in β-cells, inhibiting insulin signaling. In Inceptor knockout mice, this resulted in upregulated signaling pathways and increased β-cell proliferation, improving glucose metabolism tolerance. These findings uncover new mechanisms related to insulin resistance and type 2 diabetes and offer novel therapeutic targets for preventing diabetes and its cardiovascular complications [152].

La Ribonucleoprotein 7 (LARP7) is a protein regulating DNA damage response and cellular senescence. LARP7 deficiency in mice results in premature aging and

AS-related phenotypes, possibly through decreased SIRT1 activity, leading to vascular aging and plaque damage. The ATM-LARP7-SIRT1 pathway is essential for AS regulation, making LARP7 a critical protein for vascular aging and cardiovascular diseases [153].

The Mitochondrial open reading frame of the 12S rRNA type-c (MOTS-c) has immunomodulatory effects, preventing β-cell destruction in autoimmune diabetes. MOTS-c regulates T-cell differentiation through FOXP3 and IFNG expression, modulating immune activation via the mTORC1 pathway. MOTS-c shows promise as a treatment for autoimmune diabetes and related complications, such as diabetic foot, vascular disease, and AS [154].

Neuregulin 4 (Nrg4) plays a crucial role in vascular regulation, improving lipid metabolism disorders and inhibiting pro-inflammatory cytokine expression. It offers endothelial protection and anti-AS effects. In Nrg4-/-/ApoE-/- mice, AS damage worsened, with increased pro-inflammatory cytokine expression, suggesting that Nrg4 could be a potential target for cardiovascular protection and AS treatment [155].

Olfactory receptor 2 (OLFR2), part of the G-protein-coupled receptor family, plays an important role in taste and smell. In ApoE-/- KO mice, OLFR2 protein expression was found to be associated with lipid peroxidation and macrophage secretion of inflammatory factors. Activation of OLFR2 by hexenal enhanced AS features, while OLFR2 knockout mice exhibited reduced AS plaques and less damage. Thus, OLFR2 could be targeted for AS prevention and treatment [156].

Table 3 Emerging research targets of AS

Target	Abbreviation	Disease	Discription	Source	Reference

A disintegrin and metalloproteinase with thrombospondin type 1 motif 7	ADAMTS-7	Atherosclerosis	Anti-atherosclerotic vaccine targeting ADAMTS-7.	Circulation	[140]
Aldehyde dehydrogenase 4 family member A1	ALDH4A1	Atherosclerosis	ALDH4A1 is a biomarker of AS; anti-ALDH4A1 antibodies can be used to delaye plaque formation and reduce circulating free cholesterol and LDL levels.	Nature	[141]
A proliferation-inducing ligand	APRIL	Atherosclerosis	APRIL limits and protects against AS by binding to heparan sulfate proteoglycans; Ldlr$^{-/-}$/Tnfsf13$^{-/-}$ mice shows increased aortic root plaques.	Nature	[142]
Asialoglycoprotein receptor 1	ASGR1	Atherosclerosis, Fatty liver	Inhibition of ASGR1 protein promotes cholesterol to be discharged into bile and further excreted from the body through feces, thus reducing the level of lipids.	Nature	[143]
Beta-1,4-galactosyltransferase 1	B4GALT1	Cardiovascular disease	B4GALT1, association with decreased coronary artery disease.	Science	[144]
BTB and CNC homology 1	BACH1	Atherosclerosis	Lack of BACH1 attenuates AS by reducing endothelial Inflammation.	Circulation Research	[145]
Caseinkinase 2-interacting protein-1	CKIP-1	Atherosclerosis	CKIP-1 attenuates AS and reduces foam cells.	Nature Communications	[146]
Cold Shock Domain-Containing Protein E1	CSDE1	Cardiovascular disease	Targeting CSDE1 to manipulate posttranscriptional regulation of LDLR mRNA to prevent cardiovascular disease.	Science Translational Medicine	[147]

Equilibrative nucleoside transporter 1	ENT1	Obesity	ENT1 can regulate the inosine level in BAT, and the pharmacological inhibition and elimination of ENT1 can enhance the activity of BAT and offset diet-induced obesity.	Nature	[148]
G protein–coupled receptors 75	GPR75	Obesity	Reduced GPR75 may be a therapeutic strategy for obesity.	Science	[149]
Interleukin-27	IL-27	Obesity, Obesity-related syndrome	IL-27 plays an important role in metabolic programs, and is a target for anti-obesity immunotherapy and obesity-related syndrome.	Nature	[150]
Inhibin beta E	INHBE	Obesity, Cardiovascular disease	Loss of function in INHBE protect from abdominal obesity.	Nature Communications	[151]
Insulin inhibitory receptor	Iir	Diabetes mellitus	Inceptor, a potential target for insulin signal sensitivity and diabetes treatment.	Nature	[152]
La Ribonucleoprotein 7	LARP7	Aging, Atherosclerosis	Redeuced ATM-LARP7-SIRT1-p53/p65 senescence axis alleviates senescence and AS.	Cell Reports	[153]
Mitochondrial open reading frame of the 12S rRNA type-c	MOTS-c	Diabetes mellitus	Mitochondrial encoded MOTS-c prevents islet destruction in autoimmune diabetes.	Cell Reports	[154]
Neuregulin 4	Nrg4	Atherosclerosis	Nrg4 protects aginst endothelial inflammation and AS.	Nature Metabolism	[155]
Olfactory receptor 2	OLFR2	Atherosclerosis	The decrease of AS-related plaque and the reduction of injury in OLFR2 function deficient mice.	Science	[156]

Programmed death-ligand 1	PD-L1	Obesity	PD-L1 reduces inflamation and obesity.	Science Translational Medicine	[157]
Gamma-secretase subunit PEN-2	PEN2	Diabetes mellitus	PEN2 is the direct target of metformin and the target of diabetes.	Nature	[158]
Prekallikrein	PK	Atherosclerosis	Decreases LDL-C by stabilizing LDLR and protects against AS.	Circulation	[87]
Prosaposin	PSAP	Atherosclerosis	PSAP is highly expressed in human AS plaque macrophages, which is related to the inflammatory activity.	Science Translational Medicine	[159]
Receptor-interacting serine/threonine-protein kinase 1	RIPK1	Obesity	Reduced RIPK1 expression improves glycolipid metabolism and RIPK1 is associated with obesity.	Nature Metabolism	[160]
Secreted isoform of endoplasmic reticulum membrane complex subunit 10	scEMC10	Obesity	EMC10, high expression in human obesity.	Nature Communications	[161]
Soluble urokinase plasminogen activator receptor	suPAR	Atherosclerosis	suPAR modulates monocyte function to reduce AS.	Journal of Clinical Investigation	[162]
Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1	SVEP1	Atherosclerosis	SVEP1 is associated with risk of coronary disease without the impact of plasma lipids.	Science Translational Medicine	[163]
Insulin-like growth factor-binding protein 3 receptor	TMEM219	Diabetes mellitus	IGFBP3/TMEM219 pathway regulates beta cell homeostasis.	Nature Communications	[164]

Thymic stromal lymphopoietin	TSLP	Obesity	TSLP protects against diet-induced obesity and glucose intolerance.	Science	[165]
Thioredoxin domain containing 5	TXNDC5	Atherosclerosis	TXNDC5 is high expressed in human and mouse atherosclerotic lesions.	Science Advances	[166]
Epsins	Epsins	Atherosclerosis	Epsins promote atherosclerosis of endothelial cells and macrophages.	Circulation	[167]
Growth factor receptor bound protein 10	Grb10	Obesity	Grb10 enhances leptin signaling and reduces obesity.	Nature Metabolism	[168]
Sarcoplasmic/endoplasmic reticulum calcium ATPase 2a	SERCA2a	Diabetic cardiomyopathy	SERCA2a phosphorylation affects myocardial insulin resistance and myocardial contractility.	Life Metabolism	[169]
Tripartite motif-containing 24	TRIM24	Diabetes mellitus	TRIM24 can regulate liver lipid metabolism and is an important target for the prevention and treatment of fatty liver.	Nature Communications	[170]
Transient receptor potential melastatin 2	TRPM2	Atherosclerosis	The macrophage inflammatory response mediated by CD36 and TRPM2 provides a new idea for the treatment of AS.	Nature Cardiovascular Research	[171]
Nuclear factor of activated T-cells, cytoplasmic 3	NFATc3	Atherosclerosis	NFATc3 prevents foam cell formation and AS.	European Heart Journal	[172]
Disruptor of telomeric silencing 1-like	DOT1L	Atherosclerosis	DOT1L regulates vascular smooth muscle cell-monocyte crosstalk.	European Heart Journal	[173]
Interleukin-1β	IL-1β	Atherosclerosis	IL-1β increase the stability of macrophages, and then promote the expression of chemokines, thus aggravating AS.	Cell Reports	[174]

This paper discusses atherosclerosis (AS) in relation to lipid metabolism disorders,

inflammation and immune response, pathological processes, genetic engineering, and emerging therapeutic targets. It systematically reviews the progress of AS research, providing a comprehensive summary of conventional lipid metabolism and inflammation-immune models for AS. Additionally, it offers new perspectives on the prevention and treatment of AS through emerging therapeutic targets. However, AS research faces several challenges. On one hand, the disease itself is becoming more prevalent among younger populations, women, and in developing countries, increasing the global burden. On the other hand, treatment challenges persist, as lipid metabolism-targeted therapies alone cannot fully control the progression of AS. The rise of research approaches such as inflammation and immune responses, metabolomics, gut microbiota, and the neuro-immune-vascular effects in AS provides new avenues for treatment. These strategies enable a deeper understanding of AS's pathological and genetic mechanisms, thereby contributing to a reduction in the incidence of cardiovascular diseases and promoting better human health.

Table 4 Abbreviated name table

Chinese Name	English Name	Abbreviation
CX3C 趋化因子受体 1	CX3C chemokine fractalkine Receptor 1	CX3CR1
3-羟基 3-甲基戊二酰辅酶 A 还原酶	3-hydroxy-3-methylglutaryl coenzyme A reductase	HMGCR
金属肽酶含血小板反应蛋白 7	A Disintegrin And Metalloproteinase With Thrombospondin 7	ADAMTS-7
血管紧张素 II 1 型受体	Activation of the angiotensin II type 1 receptor	AT1R
腺病毒相关病毒	Adeno-associated virus	AAV
淀粉样前体蛋白	Amyloid precursor protein	APP
血管紧张素 II 1 型受体	Angiotensin II type 1 receptor	AT1R
血管紧张素转化酶 2	Angiotensin-converting enzyme 2	ACE2
载脂蛋白	Apolipoprotein	Apo
载脂蛋白 B	Apolipoprotein B	APOB
载脂蛋白 C2	Apolipoprotein C2	ApoC2
载脂蛋白 C3	Apolipoprotein C3	ApoC3
载脂蛋白 E	Apolipoprotein E	ApoE
载脂蛋白	ApolipoproteinAI	ApoAI

去唾液酸糖蛋白受体 1	Asialoglycoprotein receptor 1	ASGR1
三磷酸腺苷结合盒亚家族 G1	ATP-binding cassette sub-family G member 1	ABCG1
ABC 转运蛋白	ATP-binding cassette transporter	ABCA1
β-1,4-半乳糖转移酶 1	beta-1,4-galactosyltransferase 1	B4GALT1
转录因子 Bach1	BTB and CNC homology 1	BACH1
酪蛋白酶 2-相互作用蛋白-1	Caseinkinase 2-interacting protein-1	CKIP-1
趋化因子受体 7	Chemokine receptor 7	CCR7
胆固醇酯	Cholesterol ester	CE
胆固醇酯转移蛋白	Cholesteryl ester transfer protein	CETP
乳糜微粒	Chylomicron	CM
规律成簇的间隔短回文重复/规律成簇的间隔短回文重复相关蛋白 9	Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR Associated Protein	CRISPR/Cas9
含 RNA 结合冷休克域蛋白 E1	Cold shock domain-containing protein E1	CSDE1
C 反应蛋白	C-reactive protein	CRP
CX3C 趋化因子配体 1	CX3C chemokine ligand 1	CX3CL1
端粒沉默阻断剂 1 类似物	Disruptor of telomeric silencing 1-like	DOT1L
内皮脂肪酶	Endothelial lipase	EL
内皮型一氧化氮合酶 3	Endothelial nitric oxide synthase 3	NOS3
成纤维细胞生长因子 2	Fibroblast growth factor 2	FGF2
G 蛋白耦联受体 G2A	G Protein Coupled Receptor G2A	G2A
G 蛋白偶联受体 75	G protein–coupled receptors 75	GPR75
谷胱甘肽过氧化物酶 -1	Glutathione peroxidase-1	GPx1
生长因子受体结合蛋白-10	Growth factor receptor bound protein 10	Grb10
肝脂酶	Hepatic lipase	HL
高密度脂蛋白	High-density lipoprotein	HDL
低密度脂蛋白受体的诱导降解蛋白	Inducible degrader of the low-density lipoprotein receptor	IDOL

抑制素 βE	Inhibin beta E	INHBE
胰岛素抑制受体	Insulin inhibitory receptor	Iir
白介素-1β	Interleukin-1β	IL-1β
白细胞介素-27	Interleukin-27	IL-27
白细胞介素-6	Interleukin-6	IL-6
细胞内粘附分子	Intra Cellular Adhesion Molecule	ICAM
连接黏附分子 A	Junctional adhesion molecule-A	JAM-A
基因敲除	Knock-out	KO
核糖核蛋白 7	La Ribonucleoprotein 7	LARP7
卵磷脂胆固醇脂酰转移酶	Lecithin-cholesterol acyltransferase	LCAT
脂质运载蛋白型前列腺素 D 合成酶	Lipocalin-type prostaglandin D synthase	L-PGDS
脂蛋白磷脂酶 A2	Lipoprotein-Associated Phospholipase A2	Lp-PLA2
低密度脂蛋白	Low-density lipoprotein	LDL
低密度脂蛋白胆固醇	Low-density lipoprotein cholesterol	LDL-C
低密度脂蛋白受体	Low-density lipoprotein receptor	LDLR
基质金属蛋白酶 12	Matrix metallopeptidase 12	MMP-12
基质金属蛋白酶 9	Matrix metallopeptidase 9	MMP9
基质金属蛋白酶 2	Matrix metalloproteinase 2	MMP2
线粒体开放阅读框 12S rRNA c	Mitochondrial open reading frame of the 12S rRNA type-c	MOTS-c
单核细胞趋化蛋白-1	Monocyte chemotactic protein-1	MCP-1
神经调节蛋白 4	Neuregulin 4	Nrg4
游离脂肪酸	Nonesterified fatty acid	NEFA
活化 T-细胞核因子 3	Nuclear factor of activated T-cells, cytoplasmic 3	NFATc3
嗅觉受体	Olfactory receptor 2	OLFR2
对氧磷酶 3	Paraoxonase-3	PNO3
磷脂	Phospholipids	PL
血浆激肽释放酶	Plasma kallikrein	Klkb1
血小板糖蛋白 4	Platelet glycoprotein 4	CD36
前激肽释放酶	Prekallikrein	PK
基质金属蛋白酶 12	Programmed death-ligand 1	PD-L1
前蛋白转化酶枯草杆菌蛋白酶 Kexin-9	Proprotein convertase subtilisin kexin 9	PCSK9
鞘脂激活蛋白原	Prosaposin	PSAP
香叶烯基转移酶 1β	Protein geranylgeranyl transferase type-1 subunit beta	PGGT1B
受体相互作用丝氨酸/苏氨酸蛋白激酶 1	Receptor-interacting serine/threonine-protein kinase 1	RIPK1
肌浆/内质网钙 ATP 酶 2a	Sarcoplasmic/endoplasmic reticulum calcium ATPase 2a	SERCA2a

B 类 I 型清道夫受体	Scavenger receptor class B, type I	SR-BI
内质网膜复合物亚基 10 的分泌同工型	Secreted isoform of endoplasmic reticulum membrane complex subunit 10	scEMC10
单导向 RNA	Single guide RNA	sgRNA
可溶性尿激酶型纤溶酶原激活物受体	Soluble urokinase plasminogen activator receptor	suPAR
固醇调节因子结合蛋白 2	Sterol regulatory element-binding protein 2	SREBP2
硫氧还蛋白 5	Thioredoxin domain containing 5	TXNDC5
胸腺基质淋巴细胞生成素	Thymic stromal lymphopoietin	TSLP
总胆固醇	Total cholesterol	TC
总甘油三酯	Total triglyceride	TG
转录激活样效应因子核酸酶	Transcription activator-like efector nucleases	TALEN
瞬时受体电位通道 M2	Transient receptor potential melastatin 2	TRPM2
含三联基元蛋白 24	Tripartite motif-containing 24	TRIM24
肿瘤坏死因子-α	Tumor necrosis factor-α	TNF-α
血管粘附分子	Vascular adhesion molecule	VCAM
血管细胞粘附分子	Vascular cell adhesion molecule	VCAM
血管平滑肌细胞	Vascular smooth muscle cell	VSMC
极低密度脂蛋白	Very low-density lipoprotein	VLDL
极低密度脂蛋白	Very low-density-lipoprotein cholesterol	VLDL-C
锌指核酸酶	Zinc finger nuclease	ZFN

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