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The Inflammatory Basis of Atherosclerosis: Current Understanding and Future Therapeutic Directions

Asezebhobor Eseosa[1] & Aluyor Abraham[2]
[1]Mudiame University, Irrua, Nigeria; [2]Edo State University Iyamho, Nigeria
eseosa@mudiameuniversity.edu.ng; aluyor.abraham@edouniversity.edu.ng

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Abstract

Although atherosclerosis has increasingly been recognized as a chronic inflammatory disease, comprehensive reviews that integrate the inflammatory mechanisms underlying atherosclerotic progression remain limited. This review aims to synthesize current knowledge on inflammation-driven pathways in atherosclerotic lesion development and evaluate the clinical relevance of targeting these pathways. A narrative review approach was employed through examination of experimental studies, pathological evidence, and clinical trials identified from PubMed, Scopus, Web of Science, and Google Scholar, with literature selected based on its relevance to inflammatory mechanisms in atherosclerosis. The findings indicate that endothelial inflammatory responses initiate lesion development by promoting immune cell infiltration into the vessel wall, while persistent immune activity accelerates plaque growth and disease progression. Clinical evidence further shows that targeted anti-inflammatory therapies, particularly IL-1β inhibition and colchicine, can significantly reduce cardiovascular events, although therapeutic responses vary across patient populations. These findings support the evolving paradigm of atherosclerosis as an immune-mediated disease and clarify the interplay between inflammation, lipid metabolism, and vascular pathology. The review

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concludes that inflammation represents a central and therapeutically relevant mechanism in atherosclerosis. Its contribution lies in advancing cardiovascular immunology literature while offering practical implications for clinicians and policymakers to prioritize inflammation assessment and consider anti-inflammatory strategies in high-risk populations. Future research should further examine context-specific inflammatory phenotypes, optimal intervention timing, plaque-specific biomarkers, and the integration of anti-inflammatory approaches with existing cardiovascular therapies.

Keywords: Atherosclerosis; Inflammation; Endothelial Dysfunction; Immune Mechanisms; Anti-Inflammatory Therapy

Introduction

Atherosclerosis remains a leading cause of cardiovascular morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually according to the World Health Organization (WHO, 2021). Globally, atherosclerotic cardiovascular disease represents the primary contributor to myocardial infarction, stroke, and peripheral arterial disease (Ajoolabady *et al.*, 2024; Libby, 2002; Nedkoff *et al.*, 2023; 2025; Xu et al., 2025).). In both developed and developing nations, the burden of atherosclerosis continues to escalate despite advances in lipid-lowering therapies, reflecting the multifactorial nature of the disease and the presence of residual cardiovascular risk even among optimally treated patients (Bashir et al., 2024; Luo and Peng, 2023; Mach et al., 2024) This persistent disease burden underscores the urgent need to identify and therapeutically address mechanisms beyond traditional lipid management.

In response to these challenges, researchers and clinicians have increasingly recognized atherosclerosis as a chronic inflammatory disease rather than a disorder driven solely by lipid accumulation (Ajoolabady et al., 2024; Kong et al., 2022; Spindler and Henning, 2026). Leading experts in cardiovascular immunology argue that inflammatory processes are not secondary consequences but fundamental drivers of atherogenesis, influencing lesion initiation, progression, and clinical complications such as plaque rupture and thrombosis (Libby *et al.*, 2002; Ajoolabady et al., 2024). This paradigm shift has opened new avenues for therapeutic intervention, with clinical trials demonstrating that targeting specific inflammatory pathways can reduce cardiovascular events independent of lipid lowering (Buckley, 2024 Nidorf et al., 2020; Ridker et al., 2017). Such findings support the

position that inflammation represents a central and modifiable mechanism in atherosclerotic disease.

Previous research has extensively documented the cellular and molecular basis of inflammation in atherosclerosis. Studies have shown that endothelial dysfunction, triggered by cardiovascular risk factors, leads to upregulation of adhesion molecules and recruitment of circulating monocytes into the arterial wall

(Gimbrone & García-Cardeña, 2016; Ley *et al.*, 2007). Once in the subendothelial space, monocytes differentiate into macrophages, internalize modified lipoproteins to become foam cells, and secrete pro-inflammatory cytokines that amplify local inflammation (Moore & Tabas, 2011; Tabas & Glass, 2013). Furthermore, clinical trials such as CANTOS and COLCOT have confirmed that pharmacological inhibition of interleukin-1β and NLRP3 inflammasome signaling reduces recurrent cardiovascular events in high-risk populations (Ridker *et al.*, 2017; Tardif *et al.*, 2019). However, despite these advances, significant gaps remain in our understanding of how inflammatory mechanisms vary across different patient populations, disease stages, and plaque phenotypes. Moreover, the optimal timing of anti-inflammatory intervention, the identification of patients most likely to benefit, and the integration of anti-inflammatory strategies with existing cardiovascular therapies have not been comprehensively addressed in prior reviews.

The focus of this review is to provide a comprehensive synthesis of current evidence on inflammation-driven mechanisms in atherosclerosis, with particular emphasis on the molecular and cellular pathways underlying lesion development, the role of endothelial inflammation as an initiating event, immune cell-mediated plaque progression, and the therapeutic potential of targeting inflammatory pathways. Additionally, this review critically evaluates variability in clinical responses to anti-inflammatory therapies and identifies unresolved questions that require further investigation. Ultimately, the objective is to inform the development of more precise, inflammation-targeted therapeutic strategies that can reduce residual cardiovascular risk and improve long-term outcomes in patients with atherosclerotic disease.

Materials and Methods

This study employed a qualitative systematic review approach to synthesize existing evidence on inflammation-driven mechanisms in atherosclerosis and the clinical efficacy of

anti-inflammatory interventions. A qualitative review methodology was selected because it allows for comprehensive integration of diverse study types, including experimental research, pathological observations, and clinical trial data, enabling the identification of patterns, mechanisms, and gaps in current knowledge (Creswell & Creswell, 2018; Whittemore & Knafl, 2005). The study utilized a narrative review design involving systematic identification, critical appraisal, and thematic synthesis of relevant literature (Green *et al.*, 2006). This design was chosen to provide a comprehensive overview of inflammatory mechanisms across multiple levels of evidence, from molecular and cellular studies to large-scale randomized controlled trials. Compared to previous reviews that focused exclusively on either mechanistic pathways or clinical outcomes, this study integrates both domains to illustrate the translational relevance of targeting inflammation in atherosclerosis.

A comprehensive and systematic literature search was conducted across four major electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. The search strategy incorporated Boolean operators and combinations of keywords including atherosclerosis, inflammation, immune pathways, endothelial dysfunction, cytokines, NLRP3 inflammasome, interleukin-1β, interleukin-6, colchicine, and anti-inflammatory therapy. The search was supplemented by manual screening of reference lists from key articles and recent systematic reviews to identify additional relevant studies, a technique recommended for comprehensive literature retrieval (Greenhalgh & Peacock, 2005; Liberati *et al.*, 2009). No date restrictions were applied to capture both foundational and contemporary research. Data extraction focused on study objectives, methodologies, key findings related to inflammatory mechanisms, therapeutic interventions, and clinical outcomes.

Evidence Linking Inflammation to Atherosclerosis Development

Substantial evidence from basic science, clinical observations, and translational research supports the concept that inflammation is an integral driver of atherosclerosis. Historically, atherosclerosis was viewed primarily as a consequence of lipid accumulation within arterial walls. However, identification of immune cell infiltration and chronic inflammatory signaling within plaques has fundamentally reshaped this understanding, establishing inflammation as central to disease pathogenesis. At the cellular level, both

innate and adaptive immune responses contribute to atherogenesis (Hansson, 2001; Hansson & Hermansson, 2011; Libby *et al.*, 2002). Arterial endothelial cells, when exposed to disturbed blood flow and risk factors such as oxidized lipoproteins, express adhesion molecules that facilitate the recruitment of circulating monocytes and lymphocytes into the vessel wall (Gimbrone & García-Cardeña, 2016; Li & Mehta, 2000). These immune cells accumulate in the subendothelial space, where monocytes differentiate into macrophages and ingest modified lipids, forming foam cells that are hallmarks of early lesions. Within the developing plaque, macrophages secrete pro-inflammatory cytokines and chemokines that amplify local inflammation and recruit additional immune cells, sustaining a chronic inflammatory environment (Moore & Tabas, 2011; Moore *et al.*, 2013; Swirski & Nahrendorf, 2013; Tabas & Bornfeldt, 2016).

Biochemical mechanisms drive these inflammatory responses through several interconnected steps. Oxidized cholesterol particles in the blood, known as oxidized low-density lipoproteins (oxLDL), act as the primary triggers that start vascular inflammation (Tabas & Bornfeldt, 2016; Xu *et al.*, 2022). These damaged cholesterol particles are recognized by specialized sensors on the surface of endothelial cells and macrophages called Toll-like receptors, specifically TLR2 and TLR4 (Chavez-Sanchez *et al.*, 2010; Miller *et al.*, 2011; Roshan *et al.*, 2016). When these sensors detect oxLDL, they activate a chain reaction inside the cell. This activation triggers a series of enzyme reactions that ultimately free a master control protein called nuclear factor-ϰB (NF-ϰB), which is normally kept inactive in the cell's fluid interior. Once released, NF-ϰB moves into the cell's control center, the nucleus, where it acts like a switch to turn on genes that produce inflammatory chemicals (Baker *et al.*, 2011; Kawai & Akira, 2007; Roshan *et al.*, 2016). These inflammatory chemicals include signaling molecules such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which amplify inflammation, as well as adhesion molecules like VCAM-1 and ICAM-1, which help immune cells stick to and enter the blood vessel wall (Brasier *et al.*, 2010; De Winther *et al.*, 2005; Libby *et al.*, 2002).

At the molecular level, inflammatory signaling molecules create biochemical links between traditional cardiovascular risk factors and blood vessel damage. Once NF-ϰB is activated, cells produce chemical messengers called chemokines, particularly monocyte chemoattractant protein-1 (MCP-1), which act like homing signals to attract circulating monocytes to the damaged area of the artery (Li *et al.*, 2022; Singh *et al.*, 2021). These chemokines bind to specific receivers called CCR2 receptors on the surface of monocytes,

directing them to migrate into the inner layer of the arterial wall (Han *et al.*, 1998). Once monocytes enter the vessel wall and transform into macrophages, they increase production of specialized uptake receptors on their surface, including CD36 and SR-A1, which function like vacuum cleaners that continuously absorb oxidized cholesterol particles without any built-in shutoff mechanism (Kunjathoor *et al.*, 2002; Moore & Tabas, 2011; Park, 2014). This uncontrolled cholesterol uptake leads to massive accumulation of cholesterol inside the macrophages, transforming them into bloated foam cells that are characteristic of early atherosclerotic lesions (Moore & Tabas, 2011; Moore *et al.*, 2013; Steinberg & Witztum, 2010). The excessive cholesterol overload creates biochemical stress within the cell, damaging the cell's internal protein-folding machinery and energy-producing structures, which in turn generates harmful oxygen molecules called reactive oxygen species (ROS) (Feng *et al.*, 2003; Tabas, 2010; Tabas & Bornfeldt, 2016). These reactive oxygen molecules not only further activate inflammatory signaling pathways but also trigger programmed cell death, adding to the growing damage within the vessel wall (Li *et al.*, 2005; Tabas, 2010; Timmins *et al.*, 2009). Moreover, the oxidized cholesterol particles themselves can directly activate additional inflammatory sensors, including TLR receptors and another receptor called LOX-1, creating a self-sustaining cycle where inflammation continuously amplifies itself through repeated activation of NF-$\varkappa$B and related control proteins (Cominacini *et al.*, 2000; Li & Mehta, 2000; Mehta *et al.*, 2006; Miller *et al.*, 2011).

Additionally, the body produces fat-derived signaling molecules called eicosanoids that contribute to the inflammatory environment in atherosclerosis. An enzyme called phospholipase A2 releases a fatty acid called arachidonic acid from cell membranes, and this arachidonic acid is then converted by other enzymes, COX-2 and lipoxygenases, into inflammatory molecules including prostaglandins, thromboxanes, and leukotrienes (Balsinde *et al.*, 2002; Funk, 2001; Wang & Dubois, 2010). These inflammatory molecules affect multiple processes in the blood vessel, including regulating vessel constriction and relaxation, promoting blood clotting through platelet activation, and attracting more immune cells to the inflamed area (Badimon *et al.*, 2021; Mitchell & Kirkby, 2019; Yamaguchi *et al.*, 2022). On the other hand, the body also produces natural anti-inflammatory molecules called specialized pro-resolving mediators, which are made from omega-3 fatty acids found in fish oil. These beneficial molecules, including resolvins and lipoxins, work to calm inflammation by preventing white blood cells called neutrophils

from entering the damaged tissue and by helping macrophages clean up dead cells more efficiently (Serhan & Levy, 2018; Serhan & Savill, 2005; Serhan *et al.*, 2008; Tabas & Bornfeldt, 2016). This represents the body's natural defense mechanism to limit and resolve inflammatory damage, though in atherosclerosis this protective system is often overwhelmed by the ongoing inflammatory triggers.

Epidemiological and clinical data strongly reinforce these mechanistic and biochemical insights. Multiple epidemiological studies have linked elevated levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) with increased risk of atherosclerotic cardiovascular disease events, independent of traditional lipid measures (Ballantyne *et al.*, 2024; Ridker, 2001; Toth *et al.*, 2020). Similarly, higher circulating levels of interleukin-6 (IL-6) are consistently associated with increased risk of cardiovascular death, major adverse cardiovascular events, myocardial infarction, and stroke across a wide range of study populations (Khan *et al.*, 2024; Ridker *et al.*, 2000; Mehta *et al.*, 2024). In the Cardiovascular Inflammation Reduction Trial, elevated baseline levels of both IL-6 and hsCRP independently predicted major recurrent cardiovascular events in patients with prior myocardial infarction already receiving aggressive contemporary secondary prevention therapy, with adjusted hazard ratios increasing progressively across quartiles of both biomarkers (Ridker *et al.*, 2020).

Beyond serving as risk biomarkers, these inflammatory proteins may also actively participate in atherosclerotic disease progression. C-reactive protein, an acute-phase reactant primarily synthesized in the liver in response to inflammatory cytokines, is not merely a passive biomarker but actively contributes to atherogenesis through multiple mechanisms. Specifically, CRP suppresses the production of protective nitric oxide by endothelial nitric oxide synthase (eNOS), thereby impairing the normal vasodilatory and anti-inflammatory functions of the vascular endothelium. Additionally, CRP upregulates the expression of endothelial cell adhesion molecules and promotes the recruitment of circulating monocytes into the developing plaque, collectively accelerating the progression of atherosclerotic lesions (Devaraj *et al.*, 2002; Molins *et al.*, 2017; Verma *et al.*, 2002). These findings collectively provide further support for the important role of systemic inflammation in the pathogenesis of cardiovascular disease, confirming that inflammatory biomarkers independently predict cardiovascular outcomes beyond traditional risk factors.

Collectively, a robust body of evidence from cellular, biochemical, and clinical studies demonstrates that inflammation is not a secondary phenomenon in atherosclerosis, but a driving force that interacts with metabolic and hemodynamic factors to promote lesion initiation and progression.

Endothelial Inflammation and Early Lesion Formation

Endothelial cells form a dynamic barrier between the blood and the vascular wall, regulating vascular tone, permeability, and homeostasis. Under physiological conditions, they maintain an anti-inflammatory, anticoagulant state by producing nitric oxide (NO) and other protective factors (Cyr *et al.*, 2020; Rajendran *et al.*, 2013; Gimbrone & García-Cardeña, 2016). However, exposure to cardiovascular risk factors such as oxidized low-density lipoproteins (ox-LDL), hyperglycemia, hypertension, and disturbed blood flow can trigger endothelial dysfunction, which is a critical initiating event in atherogenesis (Gimbrone & García-Cardeña, 2016; Pirillo *et al.*, 2013; Xu *et al.*, 2022).

At the biochemical level, endothelial dysfunction involves three key changes in the vessel lining. First, the endothelium produces less nitric oxide, the protective molecule that keeps blood vessels relaxed and healthy. Second, harmful oxygen molecules called reactive oxygen species accumulate, creating oxidative stress that damages cells. Third, the endothelial cells increase production of sticky proteins on their surface, including molecules called VCAM-1, ICAM-1, and E-selectin, which act as binding sites to capture passing immune cells from the bloodstream (De Caterina *et al.*, 1995; Gimbrone & García-Cardeña, 2016; Verma *et al.*, 2002). These proteins facilitate the adhesion and migration of circulating monocytes and T-lymphocytes into the subendothelial space. Once recruited, monocytes differentiate into macrophages and internalize modified lipoproteins, forming foam cells, the hallmark of early atherosclerotic lesions (Gimbrone & García-Cardeña, 2016; Moore & Tabas, 2011; Ramji & Davies, 2015).

Endothelial cells also actively fuel local inflammation by releasing chemical signals such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8. These chemical messengers act like distress signals that attract more white blood cells to the area and keep the inflammatory response going within the blood vessel wall (Deng, 2021; Li *et al.*, 2022; Shaito *et al.*, 2022). These interactions create a self-reinforcing cycle: inflammation promotes endothelial activation, and activated endothelium further drives inflammatory cell

accumulation. This cycle not only initiates lesion formation but also sets the stage for plaque progression and instability (Libby *et al.*, 2024; Poston, 2019; Singh *et al.*, 2024). This self-perpetuating inflammatory process leads to the formation of early atherosclerotic lesions called fatty streaks, which appear as yellowish deposits in the artery wall. These fatty streaks consist primarily of foam cells derived from macrophages and vascular smooth muscle cells, along with T-lymphocytes, accumulated beneath a layer of activated endothelial cells. Although fatty streaks cause no symptoms and do not obstruct blood flow, they represent the first visible manifestation of atherosclerosis and serve as the foundation from which more dangerous, advanced plaques eventually develop (Gui *et al.*, 2022; Watanabe & Fan, 2025; Xu *et al.*, 2024). When inflammation in the blood vessel lining continues, the constant arrival of immune cells and buildup of fats cause the plaque to grow larger, change the surrounding tissue structure, and eventually become unstable. Understanding these mechanisms is essential to appreciating how inflammation contributes to both lesion initiation and the progression of atherosclerosis.

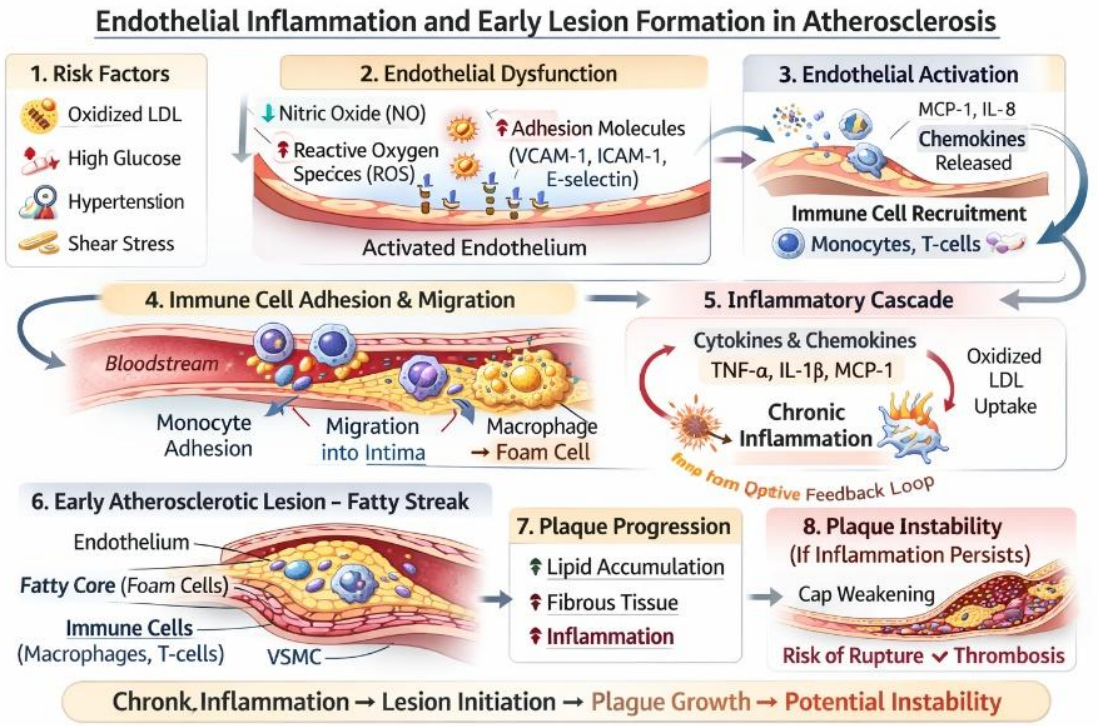

Figure 1. Role of inflammation in early lesion formation in Atherosclerosis

Immune Cell Mediated Plaque Progression and Lesion Development

Following endothelial inflammation, immune cells are central to the progression of atherosclerotic plaques. Once the endothelium becomes activated, monocytes adhere to the

vessel wall and migrate into the intima. There, they differentiate into macrophages, which normally help clear debris and pathogens (Moore *et al.*, 2013; Murphy & Tall, 2016; Tabas & Bornfeldt, 2020). In atherosclerosis, macrophages take up oxidized low-density lipoprotein (oxLDL), transforming into foam cells. These foam cells accumulate within the plaque and release inflammatory molecules that attract additional immune cells, perpetuating chronic inflammation (Bekkering *et al.*, 2014; Lee *et al.*, 2020; Moore & Tabas, 2011).

Foam cells and activated macrophages secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which recruit more immune cells and amplify local inflammation (Li *et al.*, 2005; Newby, 2008; Shaito *et al.*, 2022). They also release enzymes like matrix metalloproteinases (MMPs) that degrade components of the fibrous cap, weakening the plaque's structure and increasing the risk of rupture (Newby, 2008; Samah *et al.*, 2023). Adaptive immune cells further influence plaque progression. CD4+ T cells recognize antigens from modified lipoproteins and become activated, producing interferon-gamma (IFN-γ) and other cytokines that stimulate macrophage inflammation and suppress repair mechanisms (Hansson, 2001; Hansson & Hermansson, 2011; McLaren *et al.*, 2011). Other T cell subsets and B cells can either promote or limit inflammation depending on the plaque microenvironment (Hansson & Hermansson, 2011; Saigusa *et al.*, 2020).

Dendritic cells and neutrophils also contribute to the inflammatory environment. Dendritic cells present antigens to T cells, reinforcing adaptive immune responses (Bobryshev, 2010; Sage *et al.*, 2015; Sun *et al.*, 2020), while neutrophils release neutrophil extracellular traps (NETs) that damage vascular tissue and further increase inflammation (Döring *et al.*, 2017; Qi *et al.*, 2017; Wang *et al.*, 2024).

The ongoing activity of these immune cells creates a continuous cycle of inflammation within the artery wall, causing the plaque's fatty core to expand, the protective cap to weaken, and the overall structure to become increasingly unstable and prone to rupture, regardless of the blood cholesterol levels.

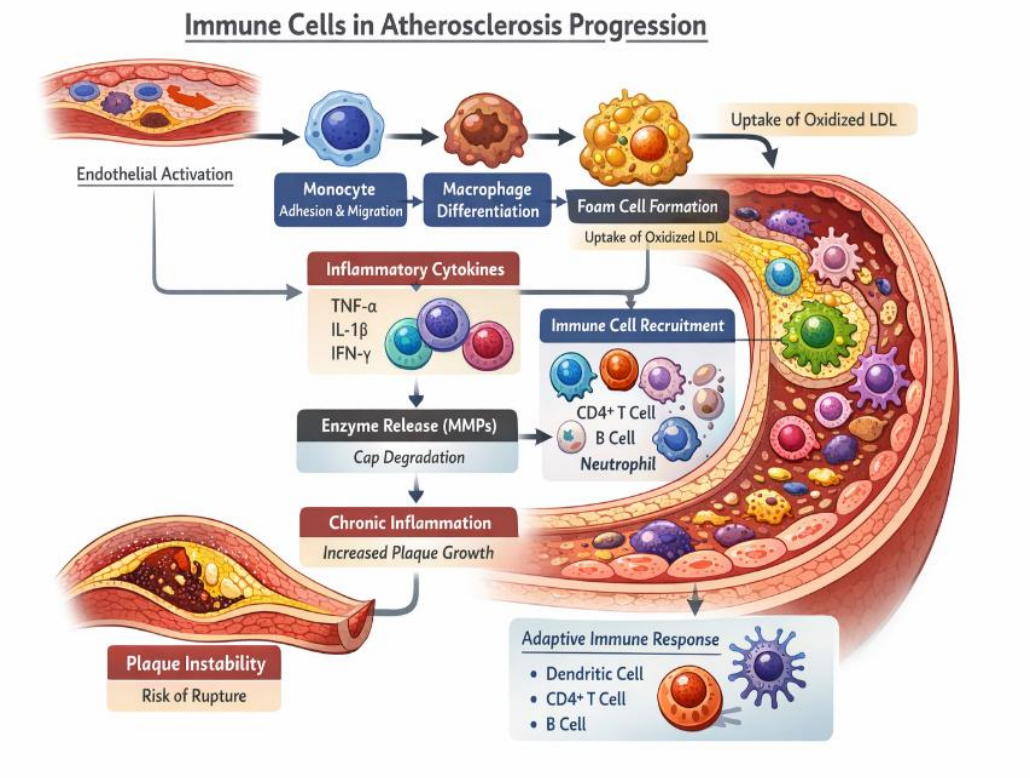

Figure 2. Role of immune cells in atherosclerosis progression

Clinical Evidence from Anti-Inflammatory Interventions

Emerging clinical evidence has substantiated the hypothesis that residual inflammatory risk contributes to the development and progression of atherosclerotic cardiovascular disease (ASCVD) beyond traditional lipid-lowering strategies. Key randomized clinical trials have evaluated pharmacologic agents targeting inflammatory pathways, providing the first direct evidence that modulation of inflammation can alter cardiovascular outcomes in patients with established disease.

IL-1β Inhibition: The CANTOS Trial

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) was a landmark Phase III randomized, placebo-controlled trial that tested **canakinumab**, a human monoclonal antibody targeting interleukin-1β (IL-1β), in patients with a history of myocardial infarction (MI) and persistently elevated high-sensitivity C-reactive protein (hs-CRP ≥2 mg/L) despite optimal secondary prevention therapy ((Ridker et al., 2017). Canakinumab significantly reduced the composite endpoint of major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal MI, and nonfatal

stroke, compared with placebo, with an approximate 15% relative reduction in MACE ((Zubirán et al., 2024; Ridker et al., 2017). These findings provided the first proof of concept that targeting inflammation independently of lipid lowering could confer cardiovascular benefit in ASCVDH. However, the CANTOS trial also revealed an increased incidence of fatal infections in the canakinumab group, underscoring the importance of safety considerations with systemic cytokine blockade (Harrington et al., 2017; Libby, 2021; Ridker et al., 2017).

Colchicine in Atherosclerotic Cardiovascular Disease (ASCVD): COLCOT, LoDoCo and LoDoCo2 Trials

Colchicine, a broad-spectrum anti-inflammatory agent with inhibitory effects on the NLRP3 inflammasome, has demonstrated consistent cardiovascular benefits in multiple large clinical trials. In the Colchicine Cardiovascular Outcomes Trial (COLCOT), low-dose colchicine (0.5 mg daily) initiated soon after a recent MI reduced the risk of recurrent cardiovascular events compared with placebo, including reductions in cardiovascular death, MI, stroke, and urgent hospitalizations for angina (Tardif et al., 2019). Similarly, the LoDoCo2 trial in patients with stable coronary artery disease documented significant reductions in MACE including cardiovascular death, nonfatal MI, ischemic stroke, and revascularization (Nidorf et al., 2020). Across these trials, the hazard ratios favored colchicine over placebo, generally in the range of a 23–31% relative reduction in composite cardiovascular endpoints, reinforcing its role as a clinically effective anti-inflammatory strategy in secondary prevention (Tardif et al., 2019; Nidorf et al., 2020). Recent meta-analytic evidence strengthens the case for colchicine by demonstrating that colchicine at doses ≤0.5 mg daily significantly reduces the risk of MI, coronary revascularization, stroke, and cardiovascular hospitalizations in patients with stable CAD (Ahmed et al., 2025). These findings have contributed to guideline recommendations that consider low-dose colchicine as an adjunctive therapy to standard care in selected high-risk patients with established ASCVD.

JUPITER Trial

The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial was a randomized, double-blind, placebo-controlled study that evaluated the effect of rosuvastatin 20 mg daily on cardiovascular outcomes in

17,802 apparently healthy men aged 50 and older and women aged 60 and older who had low to normal LDL cholesterol (<130 mg/dL) but elevated high-sensitivity C-reactive protein (hs-CRP ≥2 mg/L). Participants were randomly assigned to receive either rosuvastatin or placebo and followed for a median of 1.9 years (Ridker et al., 2008). The primary endpoint was the first occurrence of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death. The trial demonstrated a significant 44 percent relative reduction in the primary composite endpoint in the rosuvastatin group compared to placebo, with hazard ratio 0.56 (95 % CI, 0.46–0.69; P < 0.00001). Individual outcomes, including myocardial infarction, stroke, and revascularization, were also significantly reduced, and all-cause mortality decreased by approximately 20 percent (Ridker *et al.*, 2008; Ridker *et al.*, 2009; Ridker *et al.*, 2012). Rosuvastatin therapy lowered LDL cholesterol by about 50 percent and hs-CRP by 37 percent, supporting the notion that both lipid-lowering and anti-inflammatory effects contributed to cardiovascular risk reduction. (Ridker *et al.*, 2008; Ridker *et al.*, 2009; Shishehbor and Hazen, 2009. The JUPITER trial established that elevated inflammation, as measured by hs-CRP, identifies individuals at high cardiovascular risk even when LDL cholesterol is normal, and that targeting these patients with statin therapy can significantly reduce the risk of first cardiovascular events.

Emerging Targeted Therapies

Beyond IL-1β and colchicine, other anti-inflammatory strategies are under investigation. IL-6 inhibition with monoclonal antibodies such as ziltivekimab has demonstrated dose-dependent reductions in hs-CRP and fibrinogen in phase II studies, providing a rationale for ongoing phase III evaluation (Ridker *et al.*, 2021). These selective approaches target central mediators of the inflammatory cascade implicated in atherosclerosis, with the goal of improving outcomes while minimizing risks associated with broader cytokine inhibition.

Gaps in Current Knowledge and Future Directions

Clinical studies show that inflammation plays a key role in atherosclerosis and that reducing it can lower the risk of cardiovascular events. Despite these findings, there are still significant gaps that limit how anti-inflammatory treatments are used in everyday cardiovascular care.

One major question is when to start anti-inflammatory therapy. Most trials have studied patients who already have heart disease or have had a heart attack, when plaque buildup and vascular inflammation are advanced. While these studies show that inflammation can be targeted even at late stages, it is unclear whether starting treatment earlier, before plaques become unstable, could provide better or longer-lasting benefits. There is a lack of studies testing inflammation-lowering therapy in people who have not yet developed significant disease.

Another challenge is the complexity of inflammatory processes in atherosclerosis. IL-1β and IL-6 are important targets, but many immune pathways contribute to plaque development. It is not yet clear which pathways are most important at different stages of disease or in different types of patients. This raises the question of whether blocking a single pathway is enough or if multiple pathways need to be targeted together. Furthermore, how anti-inflammatory treatments fit with current therapies is also unclear. Most patients already receive cholesterol-lowering, antithrombotic, and metabolic medications. How these therapies interact, whether they work together, and the best way to combine or sequence them are questions that have not been fully studied. Biomarkers of inflammation also need improvement. Measures such as hsCRP and IL-6 reflect general inflammation in the body, but they may not accurately show inflammation inside plaques. Without biomarkers that directly indicate plaque-level inflammation, it is difficult to track how well treatments are working.

Future research should focus on when to intervene, how to identify the right patients, finding plaque-specific biomarkers, and testing new targeted therapies in outcome-driven trials. Filling these gaps is essential to move from proof-of-concept studies to precise and effective anti-inflammatory strategies in preventing and treating atherosclerotic cardiovascular disease.

Conclusion

Inflammation is a fundamental and modifiable driver of atherosclerosis, influencing both the development and progression of vascular lesions. Evidence from experimental and clinical studies demonstrates that targeting inflammatory pathways can reduce cardiovascular events, highlighting the therapeutic potential of this approach.

Key challenges remain in translating these insights into clinical practice, including determining the optimal timing of intervention, identifying patients most likely to benefit, and integrating anti-inflammatory strategies with existing therapies. Addressing these gaps through carefully designed research will be essential to realize the full potential of inflammation-targeted approaches in the prevention and management of atherosclerotic cardiovascular disease.

By focusing on these priorities, future strategies can move toward precision interventions that reduce residual inflammatory risk and improve long-term cardiovascular outcomes.

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