

# Research Advances on the Role of Immune Cells and Inflammatory Mediators in Atherosclerosis

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**Abstract:** *Atherosclerosis is a chronic inflammatory disease driven by dynamic interactions between lipid metabolism and immune responses. Its initiation and progression are co-regulated by innate and adaptive immunity. Innate immune cells are central to early plaque development. Neutrophils release pro-inflammatory mediators, including myeloperoxidase (MPO) and neutrophil extracellular traps (NETs), which contribute to endothelial dysfunction and tissue injury. Circulating monocytes infiltrate the arterial intima and differentiate into macrophages. These macrophages can polarize into distinct phenotypes, typically categorized as pro-inflammatory M1 or anti-inflammatory M2; an imbalance between these states exacerbates plaque inflammation. A pivotal early event is the uptake of modified lipoproteins—such as oxidized low-density lipoprotein (oxLDL)—via scavenger receptors (e.g., SR-A1 and CD36), leading to the formation of lipid-laden foam cells, a hallmark of early lesions. Adaptive immune responses also shape disease progression and plaque stability. Among CD4+ T helper subsets, Th1 cells promote atherosclerosis by secreting interferon- $\gamma$  (IFN- $\gamma$ ), whereas Th17 cells and their signature cytokine interleukin-17 (IL-17) are often associated with disease amplification. In contrast, regulatory T cells (Tregs) exert atheroprotective effects by suppressing immune activation and producing anti-inflammatory cytokines such as interleukin-10 (IL-10). B cells also contribute: B1 cells are generally protective, in part through natural IgM production, whereas B2 cells may be pro-atherogenic. Key inflammatory pathways sustain the chronic inflammatory milieu within plaques. The NLRP3 inflammasome, activated by damage-associated molecular patterns (DAMPs) such as cholesterol crystals, induces caspase-1 activation, which cleaves pro-IL-1 $\beta$  and pro-IL-18 into their bioactive forms. Cytokines including IL-1 $\beta$  and IL-6 are major drivers of inflammation; IL-1 $\beta$  upregulates endothelial adhesion molecules, whereas IL-6 promotes the hepatic production of acute-phase reactants. The association between systemic inflammatory diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis) and accelerated atherosclerosis further underscores the importance of shared immune pathways. This review synthesizes these interactions to provide a framework for understanding atherosclerosis pathogenesis.*

**Keywords:** Atherosclerosis, Inflammation, Immune Cells, Cytokines, Macrophages, Plaque Instability, NLRP3 Inflammasome.

## 1. Introduction

Atherosclerosis is a leading contributor to cardiovascular morbidity and mortality worldwide. According to the World Health Organization, an estimated 19.8 million people died from cardiovascular diseases in 2022, accounting for approximately 32% of all global deaths. Atherosclerosis is widely regarded as a lifestyle-associated disorder, alongside obesity, diabetes, and hypertension, because its prevalence is strongly linked to modifiable behaviors such as diet, physical activity, psychosocial stress, smoking, and alcohol consumption [1]. Beyond metabolic risk, atherosclerosis is a chronic inflammatory disease [2]; plaque destabilization and rupture, as well as progressive vascular stenosis or occlusion driven by platelet aggregation and thrombosis, can precipitate acute cardiovascular events [3]. Inflammation is a fundamental host response to tissue injury and is central to atherogenesis. Dysregulation of innate and adaptive immunity contributes to disease initiation and progression and is a key determinant of plaque instability.

## 2. Immune Cells in Atherosclerosis

Multiple immune cell infiltrates are present within AS plaques, accompanied by a series of complex alterations in the local microenvironment, suggesting that AS is closely associated with abnormal changes in both innate and adaptive immunity. Inflammation has been identified as a driving force in the progression of cardiovascular disease (CVD), through the synergistic interaction of innate and adaptive immune responses. Innate immune cells (e.g., neutrophils, monocytes/macrophages, dendritic cells, and mast cells)

initiate and amplify vascular inflammation, whereas adaptive immune cells (T and B lymphocytes) shape the chronicity of inflammation and influence plaque stability [4].

### 2.1 The Role of Innate Immune Cells in Atherosclerosis Formation

Multiple innate immune cell types are recruited to sites of arterial injury and lipid deposition, where they play pivotal roles in initiating and propelling atherosclerotic plaque development. This section details the specific functions of key innate immune cells—including neutrophils, monocytes / macrophages, dendritic cells, and mast cells—in this process.

#### 2.1.1 Neutrophils

Neutrophils are the first responders of the innate immune system, rapidly releasing pro-inflammatory mediators to neutralize threats following tissue injury or infection [5]. If inflammation persists, they continue to accumulate and release granules rich in substances such as myeloperoxidase (MPO), cathepsin 3, and matrix metalloproteinase-9 (MMP-9), leading to tissue damage and chronic inflammation [6]. Additionally, neutrophils can release neutrophil extracellular traps (NETs) composed of DNA, histones, and elastase through the process of NETosis to capture pathogens [6]. Accumulating evidence suggests that neutrophils are directly involved in atherosclerosis development and contribute to plaque instability in the setting of hyperlipidemia [7]. Consistent with this, clinical studies report that neutrophil-derived indices (such as the neutrophil-to-lymphocyte ratio) are associated with the

severity of coronary artery damage [8,9]. Neutrophils are a rich source of proinflammatory cytokines (such as TNF- $\alpha$ , IL-1, IL-6, IL-8, GM-CSF) and matrix metalloproteinases (MMP-8, MMP-9), which exacerbate plaque inflammation [10].

### 2.1.2 Macrophage

Monocytes, monocyte-derived macrophages, and foam cells are the most abundant myeloid cell types within atherosclerotic plaques. In the context of atherosclerosis, circulating monocytes adhere to and migrate across the activated endothelium, infiltrating the arterial intima where they differentiate into macrophages [8]. The primary functions of macrophages include phagocytosing pathogens and cellular debris, removing senescent, damaged, or apoptotic cells, and clearing immune complexes to maintain tissue homeostasis [11]. In a more recent study highlighting the crucial role of monocytes in the early stages of lesion formation, depletion of monocytes and macrophages during the initial phase of atherosclerosis reduced macrophage activity and abundance within plaques. This intervention attenuated early lesion progression and remodeled plaque composition, with reduced collagen content and necrotic core formation; however, depletion of monocytes and macrophages at later stages did not produce these effects [12]. Macrophages migrating into the vascular intima can polarize into M1 and M2 phenotypes. Highly oxidized LDL and cholesterol esters also induce M1 polarization by activating TLR-4 or NF- $\kappa$ B signaling pathways. M1 macrophages promote inflammatory responses within plaques via macrophage-derived inflammatory cytokines or inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO), whereas M2 macrophages exert anti-inflammatory effects by clearing locally apoptotic cells and suppressing persistent immune cell recruitment [13].

## 2.2 The Role of Adaptive Immune Cells in the Development of Atherosclerosis

The adaptive immune response is highly specialized. Antigen-presenting cells—primarily dendritic cells and macrophages—initiate adaptive immunity by processing antigens and presenting peptide-MHC (Major Histocompatibility Complex) class I or class II complexes to T cells, while concurrently delivering co-stimulatory signals. The local cytokine milieu at the priming site (in secondary lymphoid organs, i.e., draining lymph nodes and spleen, as well as in local atherosclerotic lesions, including arterial tertiary lymphoid organs [ATLOs]) further instructs T-cell fate decisions. Together, these cues drive the activation of naïve CD8 or CD4 T cells and their differentiation into distinct effector, memory, and regulatory subsets [14].

### 2.2.1 T cell

T cells are present in the outer layer of healthy arteries in wild-type mice [15] and in the arteries of mouse models susceptible to atherosclerosis [16]. scRNA-seq studies have detected aortic T cells at all stages of atherosclerotic disease. T cells produce proinflammatory cytokines and adhesion molecules, leading to the migration of monocytes into the subendothelial layer of the intima [17]. Research confirms

that Th1 cells promote AS by releasing interferon (IFN)- $\gamma$ , interleukin (IL)-2, and IL-12. Transcripts of Th2-associated cytokines such as IL-4, IL-5, and IL-13 are expressed in mouse plaques. The role of IL-4 in atherosclerosis appears to be variable, whereas IL-5 and IL-13 exert protective effects against atherosclerosis [18]. Th17 cells belong to the CD4+ T cell subset and can secrete multiple cytokines, primarily IL-17A, IL-17F, and IL-22 [19]. Th17 cells and the cytokine IL-17 they secrete are positively correlated with the pathological progression of atherosclerosis [20]. Regulatory T cells (Treg) constitute a subset of T cells that control the body's autoimmune responses. Within the body, Treg suppress the activation of various immune cells, including CD4+ T cells, CD8+ T cells, B cells, and natural killer T cells (NKT cells). Research has confirmed that the recruitment and functional suppression of Treg in animal models significantly accelerates the progression of atherosclerosis [21].

### 2.2.2 B cell

B cells can secrete antibodies in both T cell-dependent and T cell-independent ways. On one hand, B1 cells located in serosal cavities (such as the peritoneum, pleura, and pericardium) secrete native IgM antibodies, which provide protection against atherosclerosis in mice [22]. On the other hand, B2 cells can be categorized into protective marginal zone B cells (MZB) and pro-atherogenic follicular B cells [23]. B cells can be classified into three distinct subpopulations based on their surface markers: B1 cells, B2 cells, and marginal zone B cells. B1 cells recognize the autoantigen ox-LDL to produce anti-AS immunoglobulin M (IgM) antibodies, thereby clearing apoptotic cells and ox-LDL. This process inhibits the release of inflammatory mediators and prevents foam cell formation, exerting an anti-AS effect [24]. B2 cells increase plaque vulnerability by inducing inflammation and cell death. They present antigens to CD4+ T cells that can cause AS, activating these T cells and further exacerbating atherosclerosis [25].

## 3. Key Role of Cytokines and Inflammasomes in Atherosclerosis Development

Inflammation has been demonstrated to play a crucial role in the initiation and progression of atherosclerotic plaques. In early atherosclerosis, the aetiology of atherosclerosis involves endothelial injury, abnormal lipid metabolism, and hemodynamic injury; the atherosclerotic process is believed to be accompanied by flow-mediated inflammatory changes in endothelial cells (ECs) [26].

### 3.1 IL-6

IL-6, as a secondary proinflammatory cytokine, is secreted by multiple cell types including macrophages, monocytes, fibroblasts, and endothelial cells. When IL-6 interacts with its specific receptor or soluble IL-6 receptor, it forms a complex that binds to the gp130 protein, triggering signaling pathways that produce acute-phase reactants such as C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor-1. These reactants are essential for the progression of atherosclerotic thrombosis [27].

### 3.2 IL-1 $\beta$

IL-1 $\beta$  is primarily synthesized by monocytes, macrophages, and dendritic cells. It stimulates endothelial cells to produce adhesion molecules and chemokines, thereby promoting the expression of multiple inflammatory mediators including IL-6. The activation of IL-1 $\beta$  from its precursor form is facilitated by the NLRP3 inflammasome. The NLRP3 inflammasome functions as an intracellular sensor in innate immune cells, recognizing diverse pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including cholesterol crystals [27] and oxLDL [28]. This recognition activates caspase-1, which subsequently cleaves the proinflammatory cytokines IL-1 $\beta$  and IL-18 into their active forms [29].

### 3.3 NLRP3

Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) is a crucial immunoregulatory protein. As a cytoplasmic NLR family receptor, it primarily initiates inflammatory responses by forming a multimolecular complex known as the inflammasome [30]. The canonical activation of NLRP3 inflammasome involves two processes: initiation and activation. The initiation step is induced by TLR and cytokine receptors (such as TNF receptors or IL-1 receptors), followed by NF- $\kappa$ B activation and transcriptional upregulation of NLRP3 and pro-IL-1 $\beta$ , which promotes NLRP3 inflammasome assembly. The activation step involves NLRP3 oligomerization and recruitment of the adaptor ASC, which in turn recruits procaspase-1 and promotes its autocatalytic activation to caspase-1; activated caspase-1 then cleaves pro-IL-1 $\beta$  and pro-IL-18 into their mature, bioactive forms [13]. NLRP3 inflammasomes are activated by intracellular or extracellular signals, secreting IL-1 $\beta$  and IL-18 to further promote the inflammatory process. This enhances vascular smooth muscle cell (VSMC) phenotypic transformation and migration, leading to intimal hyperplasia and stenosis [31].

## 4. Systemic Inflammatory Diseases and Atherosclerosis

### 4.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease. Patients with SLE face a markedly elevated risk of accelerated atherosclerosis. An early study demonstrated that premenopausal women with SLE had a greater than 50-fold increased risk of myocardial infarction compared to age-matched controls [32]. This stark clinical association is further supported by imaging studies revealing a significantly higher prevalence of carotid plaques in SLE patients. The underlying link extends beyond traditional risk factors and is strongly driven by SLE-specific immune dysregulation (e.g., autoantibody production, aberrant T-cell responses), which exacerbates the shared inflammatory pathways fundamental to atherosclerosis. A study of premenopausal female SLE patients showed a carotid plaque detection rate of 14.4%, whereas no plaque was detected in the healthy control group [33]. SLE-associated atherosclerosis results from the combined effects of traditional and non-traditional risk factors, with immune dysfunction also recognized as a significant contributor to cardiovascular disease risk in SLE. Notably, recent studies indicate that abnormalities in serum lipid

profiles, autoantibodies, and T lymphocyte responses to lipids may play a role in the development of atherosclerosis [34].

### 4.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disease and the most common form of autoimmune arthritis, affecting up to 1% of the population [35]. Rheumatoid arthritis is recognized as an independent cardiovascular risk factor in the European Society of Cardiology guidelines [36]. Compared to non-RA patients, RA patients face a higher risk of developing coronary artery plaques. The increased incidence of coronary atherosclerosis doubles the likelihood of silent acute myocardial infarction in rheumatoid arthritis patients [37]. RA and atherosclerotic cardiovascular disease share proinflammatory pathways, including the IL-1 and IL-6 pathways [38].

### 4.3 Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disease. The associated inflammation may extend beyond the skin. The increased risk of ischemic cardiovascular events in psoriasis patients appears to be associated with heightened disease activity [39]. Within psoriatic plaques, activated plasmacytoid dendritic cells (pDCs) promote the maturation of myeloid dendritic cells (mDCs) and produce TNF- $\alpha$ , IL-12, and IL-23. This leads to the activation of Th1 and Th17 cells, which subsequently secrete inflammatory cytokines such as TNF- $\alpha$ , IL-17, IL-21, and IL-22 [40]. The pathophysiological mechanisms of atherosclerosis and psoriasis share commonalities. Both atherosclerosis and coronary artery disease are chronic inflammatory conditions involving immune cells, including Th1 and Th17 cells, with inflammatory cytokine infiltration observed throughout all stages of the diseases [41].

## 5. Conclusions

Atherosclerosis is essentially a chronic inflammatory disease driven by both innate and adaptive immune responses. Innate immune cells, such as neutrophils, initiate and exacerbate plaque inflammation by releasing MPO and NETs, while macrophages contribute through M1/M2 polarization imbalance and foam cell formation. Adaptive immune cells, particularly different subsets of T cells (such as pro-inflammatory Th1 and Th17 cells and protective Treg cells) and B cells, regulate disease progression and plaque stability through a complex network of cytokines. Key inflammatory signaling pathways, such as the NLRP3 inflammasome activating caspase-1 to promote the secretion of mature pro-inflammatory factors like IL-1 $\beta$  and IL-18, play a central role in maintaining the chronic inflammatory environment of AS. Moreover, the significant association between systemic inflammatory diseases (such as systemic lupus erythematosus and rheumatoid arthritis) and AS risk further underscores the central role of immune system dysregulation in the pathophysiology of AS. This review systematically summarizes the complex interactions between immune cells and inflammatory mediators in AS, providing a solid theoretical framework for a deeper understanding of the immune-inflammatory mechanisms underlying this disease.

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