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Review Article

Progress in macrophage immune regulation of atherosclerosis

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Abstract: Atherosclerosis is a chronic inflammatory disease that contributes to cardiovascular conditions, including coronary artery disease and stroke. Macrophages are central to its pathogenesis, accumulating in arterial walls, engulfing oxidized low-density lipoprotein (oxLDL), and forming foam cells that exacerbate inflammation. These macrophages can polarize into two main subsets: M1 macrophages, which promote inflammation, and M2 macrophages, which resolve inflammation and support tissue repair. The balance between these subsets is crucial for plaque progression and stability. Recent studies have elucidated the immune regulatory functions of macrophages in modulating atherosclerotic plaque formation and vulnerability. Understanding the mechanisms governing macrophage activation, polarization, and immune interactions presents promising therapeutic targets aimed at stabilizing plaques and preventing cardiovascular events. This review summarizes current research on the role of macrophages in atherosclerosis and discusses potential therapies targeting macrophage immune regulation.

Keywords: Macrophage immune, atherosclerosis, progress

Introduction

Atherosclerosis is a multifactorial, chronic inflammatory disease characterized by the gradual accumulation of lipids, inflammatory cells, and extracellular matrix within the arterial walls, leading to plaque formation [1]. These plaques, primarily composed of foam cells, smooth muscle cells, collagen, and lipids, progressively narrow the blood vessel lumen, impairing blood flow [2, 3]. This pathological process is a key cause of several cardiovascular diseases (CVDs), including coronary artery disease (CAD), stroke, and peripheral arterial disease (PAD), all of which are major contributors to global morbidity and mortality [4-8]. While traditionally viewed as a lipid-driven disorder, atherosclerosis also involves a complex interplay between lipid accumulation and immune responses [9]. Recent advances in immunology have revealed that the immune system plays a critical role in the initiation, progression, and complications of atherosclerosis [10]. Among the various immune cells involved, macrophages are central to the disease's pathogenesis [11], contributing to both inflammatory and reparative responses in the arterial wall, significantly influencing plaque development and stability.

Macrophages are versatile immune cells that constantly survey tissues for pathogens and cellular debris [12]. In atherosclerosis, they are recruited to sites of lipid accumulation, particularly where endothelial injury or dysfunction occurs. Upon arrival, macrophages engulf oxidized low-density lipoprotein (oxLDL) particles, transforming into foam cells [13-15]. These foam cells not only mark early atherosclerotic lesions but also serve as the primary source of pro-inflammatory cytokines that perpetuate the inflammatory cycle [16]. As foam cells accumulate, they contribute to the formation of fatty streaks, which serve as precursors to more advanced plaques. Macrophage polarization is crucial in determining the outcome of atherosclerotic lesions. Macrophages can adopt two major functional states: classically

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activated (M1) and alternatively activated (M2) phenotypes. M1 macrophages, induced by inflammatory stimuli such as interferon-gamma (IFN-γ) and lipopolysaccharide (LPS), are pro-inflammatory and contribute to tissue damage through the release of cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and reactive oxygen species (ROS). In contrast, M2 macrophages are generally anti-inflammatory and promote tissue repair, lipid clearance, and plaque stability [17-20]. This balance between M1 and M2 macrophages is crucial for regulating the pro-inflammatory and reparative processes in atherosclerotic plaques. The dynamics of macrophage polarization are influenced by factors such as local cytokine environments, lipid profiles, and the activation of specific signaling pathways. Atherogenic factors like hyperlipidemia, endothelial dysfunction, and oxidative stress promote M1 macrophage activation, which exacerbates plaque formation and instability [21, 22]. In contrast, M2 macrophages facilitate plaque resolution and regression by clearing apoptotic cells and promoting extracellular matrix production [23, 24].

In addition to contributing to the local inflammatory environment, macrophages exert immune regulatory effects that influence the broader immune response. They interact with other immune cells, such as T lymphocytes, dendritic cells, and B cells, to modulate atherosclerosis progression [25-28]. For instance, macrophages can present antigens to T cells, initiating adaptive immune responses that amplify inflammation. This immune activation can create a pro-inflammatory environment that accelerates the development of complex, unstable plaques prone to rupture [29, 30]. Moreover, macrophages contribute to inflammation resolution in atherosclerosis by promoting efferocytosis (clearance of apoptotic cells) and secreting anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) [31-33]. These actions help mitigate excessive inflammation and restore homeostasis within the arterial wall. Recent studies have highlighted that macrophages influence the balance between plaque stability and vulnerability [34-37]. Stable plaques are typically characterized by a thicker fibrous cap and a lower inflammatory burden, whereas unstable plaques have a thinner fibrous cap and are rich in inflammatory cells, especially M1 macrophages [38, 39]. Unstable plaques are more prone to rupture, which can lead to thrombosis and acute cardiovascular events, such as myocardial infarction and ischemic stroke.

Understanding the immune regulatory role of macrophages in atherosclerosis is crucial as it opens new avenues for therapeutic intervention. Recent research has shifted focus from traditional lipid-lowering therapies to targeted immunomodulatory approaches aimed at modulating macrophage behavior within plaques [40]. Enhancing the resolution of inflammation and promoting M2 macrophage polarization could stabilize plaques and reduce the risk of cardiovascular events. Therapeutic strategies targeting macrophage polarization, signaling pathways, and macrophage interactions with other immune cells hold promise for altering the course of atherosclerosis [41, 42]. Additionally, identifying biomarkers that reflect macrophage activity within plaques could provide valuable diagnostic tools for assessing disease progression and therapeutic responses [43, 44].

This review provides a detailed analysis of current knowledge on macrophage immune regulation in atherosclerosis, including the molecular mechanisms behind macrophage polarization, their interactions with other immune cells, and their contribution to plaque stability. We will also explore the potential for therapeutic targeting of macrophages in atherosclerosis, highlighting recent advancements in pharmacological interventions and novel technologies aimed at modulating macrophage function.

Macrophage biology and polarization

Macrophages are essential immune cells that originate from hematopoietic stem cells in bone marrow. They are versatile and dynamic players in both innate and adaptive immune responses [45, 46], found in almost all tissues where they maintain homeostasis, promote tissue repair, and defend against pathogens [47]. In atherosclerosis, macrophages play critical roles in disease initiation, progression, and resolution, primarily due to their ability to modulate inflammation and lipid metabolism [48, 49].

Macrophages are derived from circulating monocytes, a type of white blood cells. Upon encountering signals from inflamed tissues, such as those found in atherosclerosis, monocytes differentiate into tissue-resident macrophages [50]. These macrophages can be categorized into two main types based on their functional roles: resident macrophages and inflammatory macrophages [51, 52]. Macrophages exhibit remarkable plasticity, meaning they can alter their phenotype and function in response to the local microenvironment, which is essential for their role in atherosclerosis and other diseases.

A key feature of macrophage biology is their ability to adopt different functional phenotypes in response to various signals. Macrophage polarization refers to the process by which macrophages shift their functional state toward specific activation programs. The two most studied macrophage phenotypes are M1 and M2. M1 macrophages are typically activated by pro-inflammatory cytokines, such as IFN-γ, or pathogen-associated molecular patterns (PAMPs) like LPS [53-55]. These stimuli activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and other pro-inflammatory pathways. M1 macrophages are characterized by the production of pro-inflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), interleukin-6 (IL-6), and ROS [56-58], which promote inflammation, recruit immune cells, and contribute to tissue damage. In atherosclerosis, M1 macrophages exacerbate the disease by driving plaque formation and increasing the risk of plaque rupture [59, 60]. They destabilize atherosclerotic plaques by secreting matrix-degrading enzymes like matrix metalloproteinases (MMPs), and cytokines that promote endothelial dysfunction and inflammation.

In contrast, M2 macrophages are induced by anti-inflammatory cytokines such as IL-4 and IL-13 [61, 62]. These cytokines activate the STAT family of transcription factors, particularly STAT6, driving macrophage polarization toward the M2 phenotype. M2 macrophages are involved in tissue repair, resolution of inflammation, and the maintenance of homeostasis. They produce anti-inflammatory cytokines like IL-10 and TGF-β, which promote wound healing and tissue repair [63, 64]. M2 macrophages also play key roles in lipid metabolism and the clearance of apoptotic cells, preventing excessive inflammation. In atherosclerosis, M2 macrophages help stabilize plaques by producing extracellular matrix components like collagen and supporting tissue repair. They also contribute to plaque regression by removing foam cells and reducing the inflammatory environment.

The balance between M1 and M2 macrophages is crucial in determining the outcome of atherosclerotic lesions. When M1 macrophages dominate, inflammation and tissue damage are exacerbated, leading to the formation of unstable plaques that are more likely to rupture and cause thrombotic events, such as heart attacks and strokes [65]. In contrast, a shift toward M2 polarization can promote plaque stability and regression by suppressing inflammation and supporting tissue repair. M1 macrophages are more prevalent in the early stages of plaque formation, driving inflammatory processes that lead to foam cell formation, lipid accumulation, and secretion of pro-inflammatory cytokines. These macrophages can also promote the expansion of the necrotic core, which is associated with plaque instability [66]. M2 macrophages help stabilize plaques by promoting collagen deposition and fibrous cap formation, reducing inflammation, and facilitating the clearance of apoptotic cells. A balance between M1 and M2 macrophages within the plaque is essential for preventing plaque rupture and maintaining vascular health [67].

Macrophages in atherosclerosis

Macrophages play a central role in atherosclerosis, beginning with their recruitment to the endothelial layer of the arterial wall in response to endothelial injury and lipid accumulation. In healthy arteries, endothelial cells form a barrier between the bloodstream and the vascular smooth muscle cells of the arterial wall [68]. However, in atherosclerosis, risk factors such as high cholesterol, hypertension, smoking, and diabetes induce endothelial dysfunction, allowing low-density lipoproteins (LDL) to infiltrate the vessel wall. Once in the subendothelial space, LDL particles undergo oxidation to form oxidized LDL (oxLDL), which is highly atherogenic and triggers inflammatory responses

through interactions with specific receptors on macrophages, such as scavenger receptors (e.g., CD36, LOX-1) [69]. These interactions facilitate the uptake of oxLDL by macrophages, leading to foam cell formation. Foam cells are lipid-laden macrophages resulting from the excessive accumulation of lipids, especially cholesterol, in the cytoplasm. Foam cells contribute to the early stages of atherosclerotic plaque formation, and their accumulation forms fatty streaks in the arterial intima, which serve as the foundation for more advanced plaques.

Chawla et al. [70] showed that lipid metabolism in macrophages is tightly regulated by transcription factors like liver X receptors (LXRs) and peroxisome proliferator-activated receptors (PPARs), which control the expression of genes involved in cholesterol efflux and lipid handling. Dysregulated lipid metabolism in macrophages can lead to foam cell formation and the progression of atherosclerosis. Targeting macrophage metabolism is a promising strategy for mitigating plaque development. However, foam cells can also promote disease progression by secreting pro-inflammatory cytokines and matrix-degrading enzymes that further contribute to plaque development.

Macrophages are key determinants of plaque stability. The balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages influences plaque vulnerability [71]. In atherosclerotic plaques, the accumulation of M1 macrophages is often associated with plaque instability, while M2 macrophages contribute to plaque stabilization. M1 macrophages are highly pro-inflammatory and produce cytokines and enzymes that degrade the extracellular matrix, weakening the fibrous cap of the plaque and increasing the likelihood of plaque rupture. Rupture exposes the lipid-rich core of the plaque to the bloodstream, triggering thrombosis and leading to acute cardiovascular events, such as heart attacks and strokes. In contrast, M2 macrophages, which are involved in tissue repair and inflammation resolution [72], produce anti-inflammatory cytokines like IL-10 and TGF-β. These cytokines help stabilize the plaque by promoting collagen deposition and extracellular matrix production, reinforcing the fibrous cap and reducing the risk of rupture.

Gordon et al. [73] demonstrated that M1 macrophages, activated by pro-inflammatory cytokines such as IFN-γ, promote plaque instability by releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and matrix-degrading enzymes. Conversely, M2 macrophages, induced by IL-4 and IL-13, play a protective role by promoting tissue repair, collagen synthesis, and plaque stabilization. This shift in macrophage polarization presents a potential therapeutic target, as restoring the M2 phenotype in plaques may reduce inflammation and promote plaque regression, as suggested by Korc et al. [74]. Moore et al. [75] highlighted the central role of macrophage-derived foam cells in plaque formation and progression by contributing to lipid accumulation and inflammatory cytokine production. This process accelerates the growth of fatty streaks and the development of mature atherosclerotic plaques. Additionally, macrophages contribute to the expansion of the necrotic core, a key feature of plaque vulnerability.

The clinical therapeutic targeting of macrophages in atherosclerosis was summarized in **Table 1**.

In conclusion, the balance between M1 and M2 macrophages within plaques is critical for plaque stability and the risk of acute events. Predominant M1 macrophage presence is associated with increased plaque rupture and thrombosis, while M2 macrophages contribute to plaque stabilization and potential regression.

Immune regulation by macrophages

Macrophages are highly versatile cells that perform a variety of functions depending on the signals they receive from their environment. They are central to both the initiation and resolution of inflammation, with their actions being tightly regulated by various cytokines, growth factors, and signaling pathways. Macrophages release a wide range of cytokines, small signaling molecules that modulate immune responses. These cytokines can have either pro-inflammatory or anti-inflammatory effects, depending on the type of activation the macrophages undergo. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are produced during immune activation and promote the recruitment of additional immune cells to sites of

Table 1. The therapeutic targeting of macrophages in atherosclerosis

Therapeutic Target	Mechanism of Action	Clinical Application	Current Status
Statins	Inhibit cholesterol synthesis and reduce inflammation in macrophages	Used to reduce plaque formation and inflammation in atherosclerosis	Approved for clinical use
PCSK9 Inhibitors	Inhibit PCSK9 to increase LDL receptor activity, reducing LDL cholesterol levels	Used for patients with high LDL cholesterol and atherosclerosis	Approved for clinical use
Anti-TNF-α	Block TNF-α signaling, which is involved in inflammation and macrophage activation	Reduce inflammation and macrophage-driven plaque formation	In clinical trials
IL-1β Inhibitors	Inhibit IL-1β signaling, reducing inflammatory responses in macrophages	Potential for reducing inflammation in atherosclerotic plaques	In clinical trials
M2 Macrophage Polarization	Promote polarization of macrophages toward an anti-inflammatory phenotype (M2)	Potential therapeutic approach to reduce plaque instability and inflammation	Preclinical studies
Targeting TLRs (Toll-Like Receptors)	Modulate macrophage activation by targeting TLRs involved in innate immunity	Potential to reduce macrophage-driven inflammation and plaque progression	Preclinical studies
Apolipoprotein E (ApoE) Modulation	Modulate macrophage cholesterol uptake and efflux via ApoE	Modulating ApoE in macrophages could reduce foam cell formation and atherosclerosis	Preclinical studies
NLRP3 Inflammasome Inhibitors	Inhibit the NLRP3 inflammasome pathway in macrophages, reducing IL-1β production	Potential to reduce inflammation and plaque rupture	Preclinical studies

LDL: Low-density lipoprotein.

infection or injury. In contrast, anti-inflammatory cytokines like IL-10 and TGF-β help resolve inflammation and restore tissue homeostasis.

Macrophages are also critical in antigen presentation. They capture and process pathogens or debris and present these antigens to T cells, thereby activating adaptive immunity [76]. By expressing major histocompatibility complex class II molecules, macrophages can activate CD4+ T cells, which are essential for orchestrating immune responses [77]. Additionally, macrophages can influence the differentiation of T cells into various subtypes, such as Th1, Th2, or regulatory T cells (Tregs), which significantly affect the immune response in diseases like atherosclerosis.

Macrophages play a pivotal role in clearing pathogens, dead cells, and cellular debris from tissues [78]. Tabas et al. [79] demonstrated that M1 macrophages contribute to plaque rupture and thrombosis by secreting MMPs that degrade the extracellular matrix and destabilize the fibrous cap of the plaque. In contrast, M2 macrophages help stabilize plaques by promoting extracellular matrix production and resolving inflammation. The ability to manipulate this macrophage polarization balance holds therapeutic potential for preventing plaque rupture and reducing the risk of heart attacks and strokes.

Phagocytosis, the process by which macrophages remove pathogens and debris, is essential for maintaining tissue integrity and preventing excessive inflammation. Additionally, the clearance of apoptotic cells by macrophages (efferocytosis) is crucial for resolving inflammation. Failure in this process can lead to the persistence of inflammatory signals and tissue damage, as seen in atherosclerosis.

Molecular mechanisms of macrophage immune regulation

Macrophages are dynamic and versatile cells that play a central role in immune regulation. They are involved in both initiating and resolving inflammation through cytokine production, interactions with other immune cells, and modulation of local tissue environments. The molecular mechanisms underlying macrophage immune regulation are complex, involving a wide array of signaling pathways, transcription factors, and epigenetic modifications. A key study by Bäck et al. [80] found that macrophage-derived cytokines, such as TNF-α and IL-1β, recruit additional immune cells, including T cells and neutrophils, to the site of plaque formation. This recruitment amplifies the inflammatory response, driving plaque progression and instability. Conversely, macrophage-derived IL-10 and TGF-β contribute to inflammation resolution, highlighting the dual role macrophages play in maintaining immune homeostasis in the plaque. These mechanisms allow macrophages to respond appropriately to various stimuli, such as pathogen invasion, tissue injury, or lipid accumulation in atherosclerosis. Understanding these molecular mechanisms is crucial for developing strategies to modulate macrophage function in diseases like atherosclerosis, where immune regulation plays a pivotal role in disease progression and plaque stability.

Macrophages sense and respond to various environmental signals through a variety of receptor-mediated signaling pathways. These pathways are integral to macrophage activation and polarization, determining whether macrophages promote inflammation (M1) or resolve it (M2). The primary signaling pathways involved in macrophage immune regulation include the NF-κB, JAK/STAT, and PI3K/Akt pathways.

NF-κB pathway

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a critical transcription factor in immune cells, especially macrophages. It plays a crucial role in the inflammatory responses by controlling the expression of genes involved in immune cell activation, cytokine production, and cell survival [81]. Upon activation by inflammatory stimuli, such as TNF-α, IL-1β, or PAMPs through receptors like TNF receptors and Toll-like receptors (TLRs), NF-κB translocates to the nucleus, where it activates the transcription of pro-inflammatory genes. In atherosclerosis, NF-κB signaling is crucial for macrophage activation and the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which drive plaque formation and destabilization [82]. Wang et al. [83] demonstrated that the NF-κB axis in macrophages is a potential therapeutic target for atherosclerosis-related diseases.

Persistent activation of NF-κB in macrophages contributes to chronic inflammation in atherosclerotic plaques, promoting disease progression and increasing the risk of plaque rupture.

JAK/STAT pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is another critical regulator of macrophage function, particularly in the polarization process. This pathway is activated by various cytokines, including IL-4, IL-13, IFN-γ, and IL-6, which bind to specific cytokine receptors on the macrophage surface [84, 85]. The binding of cytokines to their receptors activates JAKs, which phosphorylate STATs (e.g., STAT1, STAT6), leading to their translocation into the nucleus and the initiation of gene transcription. In M1 macrophages, IFN-γ activates STAT1, promoting the expression of pro-inflammatory genes. In contrast, IL-4 and IL-13 activate STAT6 in M2 macrophages, leading to the expression of genes involved in tissue repair, anti-inflammatory responses, and the resolution of inflammation [86]. The balance between STAT1 and STAT6 signaling is crucial in determining whether macrophages adopt a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype. In atherosclerosis, the JAK/STAT pathway regulates macrophage polarization within plaques. Pro-inflammatory cytokines, such as IFN-γ, promote M1 polarization, while IL-4 and IL-13 drive M2 polarization [87]. Modulating this pathway may provide a therapeutic strategy for stabilizing atherosclerotic plaques and reducing inflammation.

PI3K/Akt pathway

The phosphoinositide 3-kinase (PI3K)/Akt pathway is a key signaling pathway that regulates cell survival, metabolism, and inflammation [88]. In macrophages, activation of the PI3K/Akt signaling pathway contributes to several processes, including immune cell migration, cytokine production, and phagocytosis. The PI3K/Akt pathway is involved in macrophage survival and function. It is activated by several receptor systems, including those responsive to cytokines (e.g., IL-4, IL-10) and growth factors [89, 90]. Upon activation, PI3K phosphorylates inositol lipids, which in turn activate Akt, triggering downstream signaling pathways that regulate cell proliferation, migration, and survival [91, 92]. In the context of atherosclerosis, the PI3K/Akt pathway regulates macrophage responses to inflammatory stimuli. It also plays a role in macrophage migration to the plaque formation site and modulates the immune response by influencing cytokine production [93]. Moreover, PI3K/Akt signaling helps regulate macrophage polarization, with activated Akt promoting an anti-inflammatory M2 phenotype that counterbalances the pro-inflammatory M1 polarization in atherosclerotic plaques.

The molecular mechanisms underlying macrophage immune regulation are intricate, involving multiple signaling pathways, transcription factors, and epigenetic modifications. Macrophages sense environmental signals through receptors such as TLRs, cytokine receptors, and lipid sensors, which activate key signaling pathways like NF-κB, JAK/STAT, and PI3K/Akt. These pathways regulate macrophage polarization, cytokine production, and interactions with other immune cells (**Figure 1**). Understanding these molecular mechanisms is crucial for developing targeted therapies to modulate macrophage function in diseases like atherosclerosis, where immune regulation plays a critical role in disease progression, plaque instability, and the risk of cardiovascular events.

Therapeutic targeting of macrophages in atherosclerosis

Atherosclerosis is a chronic inflammatory disease that significantly contributes to cardiovascular conditions such as heart attacks, strokes, and peripheral artery disease [94]. Macrophages play a central role in the development, progression, and instability of atherosclerotic plaques, making them a key target for therapeutic intervention. In atherosclerosis, macrophages are involved in multiple stages of the disease, including lipid accumulation, inflammation, plaque destabilization, and the resolution of inflammation. Given their pivotal role in both promoting and mitigating atherosclerosis, macrophages represent a promising target for stabilizing plaques, reducing inflammation, and preventing cardiovascular events. This section outlines current and emerging strategies for targeting macrophages in atherosclerosis treatment, including modulation of macrophage polarization, regulation of macro-

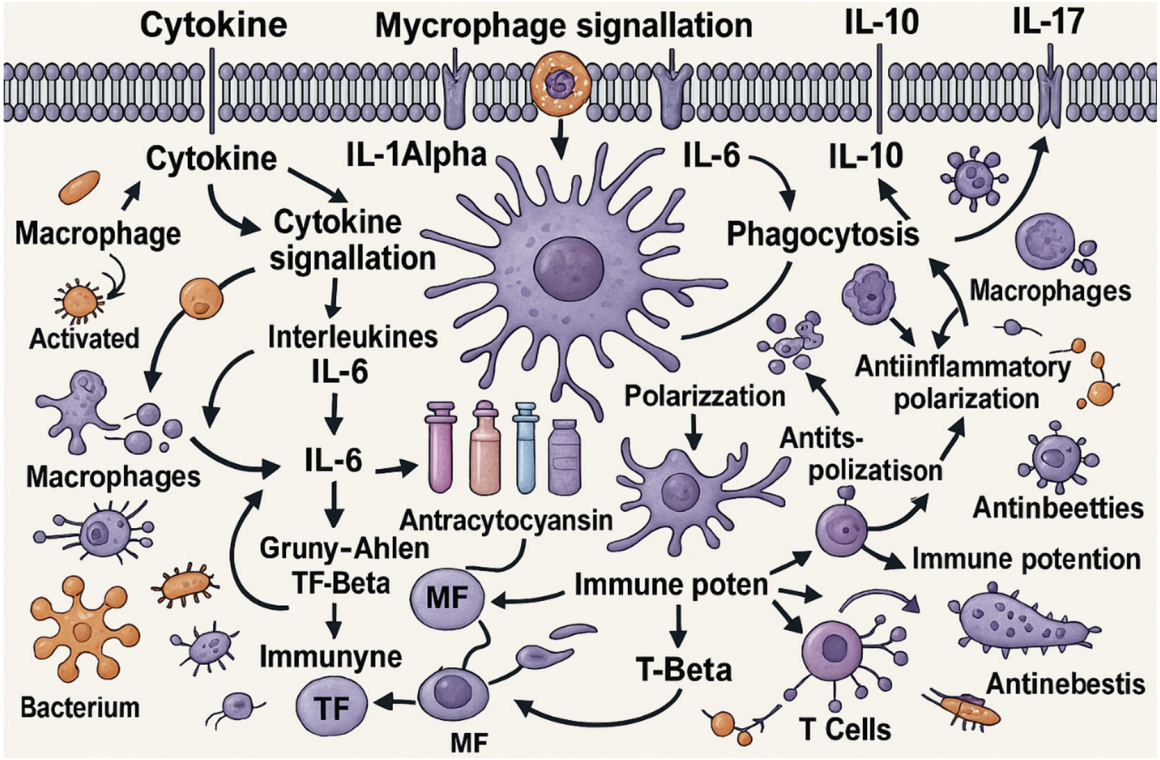

Figure 1. The molecular mechanisms of macrophage immune regulation.

phage-derived cytokines, and novel approaches involving nanotechnology and gene therapy.

Kuwabara et al. [95] demonstrated that macrophages are responsible for the clearance of apoptotic cells (efferocytosis), which is essential for reducing inflammation and resolving atherosclerotic lesions. Impaired efferocytosis leads to the accumulation of dead cells and exacerbates the inflammatory response, contributing to plaque progression. Strategies that enhance efferocytosis or promote the phagocytic capacity of macrophages could help resolve inflammation and reduce plaque size, providing a potential therapeutic approach to atherosclerosis.

Macrophages exhibit functional plasticity, allowing them to switch between different phenotypic states depending on the local microenvironment [96]. In atherosclerosis, macrophages can polarize into pro-inflammatory M1 macrophages or anti-inflammatory M2 macrophages. The balance between these two phenotypes significantly impacts plaque development and stability. M1 macrophages are characterized by the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and their presence in atherosclerotic plaques promotes plaque instability, inflammation, and rupture. The use of cytokine inhibitors targeting key pro-inflammatory cytokines, such as TNF-α and IL-1β, has been explored to reduce M1 macrophage polarization and inflammation. For example, TNF-α inhibitors (e.g., infliximab, adalimumab) are used for inflammatory diseases like rheumatoid arthritis and Crohn's disease, and their potential application in atherosclerosis is under investigation [97]. Statins, commonly used to lower cholesterol, also possess anti-inflammatory effects by inhibiting M1 macrophage polarization [98]. These effects are mediated through the inhibition of the Rho GTPase pathway, reducing pro-inflammatory cytokine production and promoting macrophage polarization toward the M2 phenotype. Libby et al. [99] explored the potential of using anti-inflammatory therapies to modulate macrophage function in atherosclerosis. Statins, which are typically used for cholesterol lowering, have pleiotropic effects, including the modulation of macrophage polarization and reduction of plaque inflammation.

In contrast to M1 macrophages, M2 macrophages are involved in tissue repair, the resolution of inflammation, and the stabilization of atherosclerotic plaques [100]. Promoting macrophage polarization toward the M2 phenotype can mitigate chronic inflammation and stabilize plaques [101, 102]. The administration of cytokines such as IL-4 and IL-13 can promote M2 polarization by activating the STAT6 signaling pathway, inducing the expression of anti-inflammatory genes and tissue repair factors. IL-4 has shown promise in animal models for improving plaque stability and reducing inflammation [103]. Peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor, plays a key role in macrophage polarization toward the M2 phenotype. PPARγ activation has anti-inflammatory effects and promotes plaque stability by enhancing collagen production and extracellular matrix remodeling [104]. Thiazolidinediones, such as pioglitazone, are PPARγ agonists that have shown promise in preclinical studies for promoting M2 polarization in atherosclerosis [105]. Statins not only inhibit M1 polarization but can also promote M2 macrophage polarization by increasing the production of anti-inflammatory cytokines like IL-10. This dual effect makes statins a potential therapeutic option for stabilizing plaques by shifting the macrophage population toward a more reparative phenotype. Ridker et al. [106] demonstrated in the CANTOS trial that targeting IL-1β with the monoclonal antibody canakinumab significantly reduced the incidence of cardiovascular events in patients with high levels of inflammation, underscoring the importance of macrophage-driven inflammation in atherosclerosis.

Macrophages produce various cytokines and chemokines that contribute to the inflammatory environment of atherosclerotic plaques [107]. Modulating the production of these cytokines offers a potential therapeutic approach to reduce inflammation and stabilize plaques. TNF-α is a potent pro-inflammatory cytokine that drives macrophage activation and contributes to plaque formation [108]. Inhibition of TNF-α with monoclonal antibodies or soluble receptors has been studied for its potential to reduce macrophage-driven inflammation in atherosclerosis. IL-1β is another critical cytokine involved in atherosclerosis, and its inhibition has shown promise in reducing plaque inflammation and improving outcomes in animal models [109]. Canakinumab, a monoclonal antibody against IL-1β, has shown clinical efficacy in reducing cardiovascular events in patients with high levels of inflammation. IL-6, a cytokine that drives systemic inflammation, is also involved in the progression of atherosclerosis [110]. The use of IL-6 inhibitors, such as tocilizumab, is being investigated for its potential to reduce inflammation in atherosclerosis and other inflammatory diseases.

Nanotechnology is emerging as a promising tool for targeting macrophages in atherosclerosis. Nanoparticles can be engineered to specifically target macrophages and deliver drugs directly to the site of the atherosclerotic plaque, improving drug efficacy and reducing side effects [111]. Nanoparticles can deliver anti-inflammatory drugs, such as corticosteroids or specific cytokine inhibitors, directly to macrophages in the plaque [112]. This targeted approach reduces systemic inflammation and minimizes the potential side effects of these drugs. In addition to drug delivery, nanoparticles can also be used for imaging atherosclerotic plaques. By targeting macrophages, these nanoparticles allow non-invasive imaging of plaque inflammation, providing valuable information on plaque vulnerability and treatment efficacy.

Gene editing technologies, such as CRISPR/Cas9, are emerging as powerful tools for modifying macrophage function in atherosclerosis [113]. These technologies can be used to knock out specific genes involved in macrophage polarization, cytokine production, or lipid metabolism, with the goal of reducing inflammation or promoting plaque regression. Gene editing can be used to manipulate key transcription factors or signaling pathways that regulate macrophage polarization. For instance, targeting genes involved in M1 polarization, such as NF-κB, or enhancing M2 polarization through the activation of PPARγ, could shift the balance of macrophages in plaques, promoting a more anti-inflammatory and reparative environment [114, 115].

Macrophages exhibit significant functional and phenotypic heterogeneity depending on their location and the local microenvironment [116]. Targeting specific macrophage subtypes within

atherosclerotic plaques is challenging due to the complexity of macrophage polarization and plasticity. The long-term effects of macrophage-targeted therapies need thorough investigation, particularly in chronic diseases like atherosclerosis, where sustained therapeutic effects are required to prevent plaque rupture and thrombosis.

Future directions

Despite significant progress in understanding the role of macrophages in atherosclerosis, several challenges remain in translating these findings into effective therapies. Future research should focus on gaining a more precise understanding of macrophage polarization dynamics, particularly the factors that regulate the transition between pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages within atherosclerotic plaques. A deeper exploration of the molecular and epigenetic mechanisms that govern macrophage activation and plasticity is essential for developing therapies that specifically target macrophage function without compromising overall immune system integrity.

Another important direction is the identification of reliable biomarkers for macrophage activity in atherosclerosis, which would improve disease monitoring and enable personalized treatment strategies. Advances in imaging techniques, such as macrophage-targeted nanoparticles, may offer a non-invasive method for tracking plaque progression and macrophage infiltration in real time, providing valuable insights into disease dynamics.

Emerging therapeutic approaches, including gene editing and cell-based therapies, also hold promise for modulating macrophage function. Techniques like CRISPR/Cas9 could allow for the precise manipulation of macrophage polarization or inhibition of inflammatory pathways, potentially offering long-term solutions for stabilizing plaques and preventing rupture. Additionally, the development of more targeted macrophage-specific drug delivery systems using nanotechnology could enhance the efficacy of anti-inflammatory treatments while minimizing side effects.

By addressing these challenges, future research may lead to more effective and personalized therapies for atherosclerosis, ultimately reducing the burden of cardiovascular diseases.

Conclusion

Macrophages play a central role in the pathogenesis of atherosclerosis, influencing both the progression and stability of atherosclerotic plaques. Their involvement in foam cell formation, inflammatory cytokine production, and plaque instability makes them key drivers of disease progression. The balance between M1 and M2 macrophages within plaques determines the outcome of atherosclerosis, with M1 macrophages contributing to plaque rupture and thrombosis, while M2 macrophages promote plaque stability and regression. Understanding the mechanisms regulating macrophage function and polarization is crucial for developing novel therapeutic strategies aimed at stabilizing plaques and reducing the risk of cardiovascular events.

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