

Inflammation and Oxidative Stress in Atherosclerosis: Molecular Mechanisms and Novel Treatment Strategies

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Abstract. Atherosclerosis (AS) is a leading global cause of death due to its role in cardiovascular diseases. In the pathogenesis of AS, inflammation has a pivotal role: pro-inflammatory molecules such as cytokines (e.g., TNF- α , IL-6) and immune cells like monocytes, macrophages and T cells are involved. Oxidative stress also contributes significantly, where low-density lipoprotein (LDL) is oxidized into oxidized LDL (ox-LDL), and vascular smooth muscle cells' phenotype are altered, promoting plaque formation and eventual rupture. Recent studies indicate a variety of therapeutic strategies targeting inflammation and oxidative stress in the pathogenesis of AS, including the use of anti-inflammatory agents and antioxidants. Combination therapies targeting multiple pathways have also been developed for the treatment of atherosclerosis. These strategies are expected to serve as key interventions in the therapeutic landscape of the disease, significantly contributing to its effective management and mitigation.

Keywords: atherosclerosis, inflammation, oxidative stress, novel treatment strategy

1. Introduction

World Health Organization reports that approximately 17.9 million lives are claimed by cardiovascular diseases (CVD) annually, accounting for 32% of global mortality [1]. Arteriosclerosis, marked by arterial thickening due to the accumulation of plaques beneath the endothelium—comprising fatty acids, cholesterol, calcium, fibrin, cellular debris, and metabolic waste—is a vital determinant in the onset and progression of various CVDs [2]. Given that AS frequently leads to multifarious potentially life-threatening complications, for example, myocardial infarction and stroke, it remains one of the leading causes of mortality in both industrialized and emerging nations, significantly contributing to global health burdens [3, 4]. Therefore, a thorough and precise comprehension of the underlying mechanisms driving AS is quite indispensable for advancing efficacious therapeutic strategies nowadays.

Decades ago, arteriosclerosis was considered a disease caused by dyslipidemia [5]. However, currently, a growing number of experimental studies indicate that AS should be recognized as a persistent immune-inflammatory disease rather than merely a lipid metabolism disorder [2, 6]. Besides, oxidative stress also has a strong influence on the development of AS [7]. This review begins by offering a concise summary of the pathological progression of AS, outlining its key developmental stages. Then, it further investigates a detailed overview of the molecular basis of

inflammation and oxidative stress in the progression of AS. Finally, this review delves into potential therapeutic strategies for AS from the perspectives of inflammation and oxidative stress while also providing an outlook on future therapeutic approaches.

2. Pathophysiological mechanism of atherosclerosis

Low-density lipoprotein (LDL), generally known as "bad cholesterol," is an important contributor to arterial plaque formation. In the early stages of AS, LDL progressively builds up within the intimal layer [8]. And owing to its susceptibility to oxidative modification, a portion of this accumulated LDL will transform into oxidized LDL (ox-LDL) [9]. The lodgment of LDL within the subendothelial space and its oxidative modification serves as a critical trigger for endothelial activation. For instance, this process stimulates endothelial cells (ECs) to upregulate adhesion molecule expression and enhance chemokine secretion [10]. These chemotactic signals, in turn, recruit circulating monocytes, which migrate toward the developing atherosclerotic lesion and penetrate the intimal layer [11]. Once inside the intima, monocytes differentiate into macrophages, which act as pivotal mediators in the progression of AS. On one hand, they can release cytokines to amplify inflammatory responses. On the other hand, they ingest ox-LDL and other debris, transforming into foam cells. These foam cells further emit pro-inflammatory cytokines, intensifying inflammation and facilitating plaque expansion [2, 12]. As the disease develops, smooth muscle cells (SMCs) infiltrate the subintimal zone and begin to multiply and synthesize extracellular matrix substances, such as collagen (Fig.1). These substances further accumulate and form a fibrous cap, encapsulating lipid deposits and creating a 'fibrofatty plaque'. At the same time, some plaques may undergo calcification, making the arterial wall stiffer and leading to the loss of vascular elasticity, causing gradual arterial hardening [4, 13].

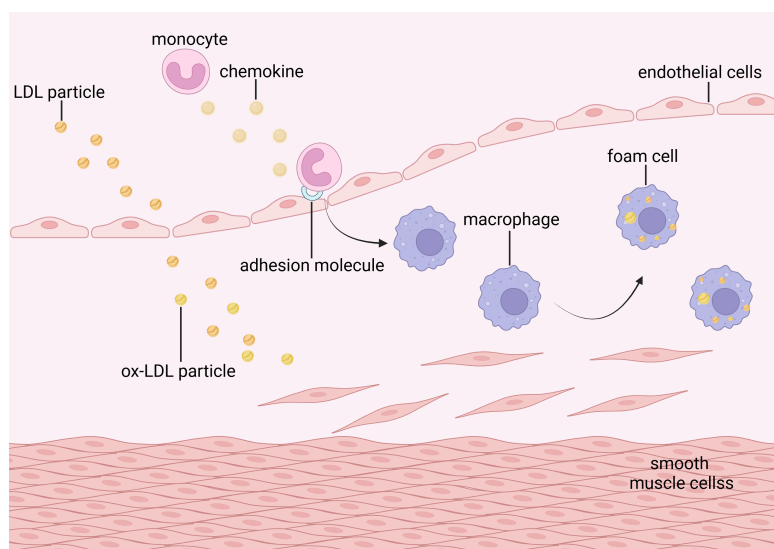


Figure 1. Onset and advancement of AS

If the atherosclerotic plaque is unstable, the fibrous cap may rupture, precipitating thrombus formation. When the thrombus is formed, it may further obstruct the vessel lumen, leading to restricted blood flow in the affected area. In severe instances, this may lead to critical outcomes, including myocardial infarction or stroke [14]. Additionally, as the plaque enlarges and calcifies, the arterial lumen narrows, restricting blood flow. This further impedes the delivery of oxygen and nutrients, resulting in organ dysfunction and potentially escalating to life-threatening complications.

3. Inflammation and atherosclerosis

3.1. The role of cytokines in atherosclerosis

Cytokines, a class of small secreted proteins typically less than 40 kDa in size, are instrumental in inflammation. They encompass a diverse spectrum of molecules, including interleukins (ILs), tumor necrosis factor (TNF), interferons (IFN), transforming growth factor (TGF), colony-stimulating factors (CSF), and an array of chemokines [15]. These cytokines are involved in regulating immune cell function, promoting inflammation, and facilitating the communication between different cell types within the immune system. Driven by inflammation and various stimuli, T cells, monocytes, macrophages, and platelets, along with ECs, SMC, and adipocytes, actively secrete cytokines, collectively facilitating the progression of atherosclerosis through multiple pathways [16].

Tumor Necrosis Factor- α (TNF- α) serves as a critical cytokine in orchestrating systemic inflammation and immune regulation, having a multifaceted influence on the evolution and advancement of AS [17]. TNF- α stimulates ECs to upregulate the production of adhesion molecules. In detail, TNF- α initiates the downstream Rac1-ROS signaling pathway, contributing to the degradation of I κ B α . This process promotes the nuclear translocation and activation of nuclear factor kappa-B (NF- κ B), which subsequently drives the upregulation of intercellular adhesion molecule-1 (ICAM-1) [18]. The increasing adhesion molecules can help recruit monocytes, laying the foundation for the subsequent migration of monocytes, conversion into macrophages, and eventual transformation of foam cells [19]. Therefore, it is a critical event in the early stage of AS. Moreover, NF- κ B activation promotes the discharge of additional pro-inflammatory cytokines [20]. These cytokines subsequently stimulate adhesion molecule expression in ECs, activate immune cells, and drive smooth muscle cell proliferation, collectively accelerating the onset and progression of AS [21]. Notably, the presence of interferon-gamma (IFN γ) amplifies the efficiency of TNF- α -mediated NF- κ B activation. This occurs as IFN- γ signaling facilitates the nuclear translocation of STAT1 α , which interferes with its recruitment to the TNFR1 complex. Eventually, this disruption further augments TNF- α -induced NF- κ B activation [22].

Interleukin-6 (IL-6) is a multifaceted cytokine that is able to exhibit both pro-inflammatory and anti-inflammatory properties. Its specific effects vary based on the type of tissue damage, as well as the organs and cell types involved in the response [23, 24]. In AS, IL-6 activates the JAK/STAT signaling pathway, resulting in the upregulation of ICAM-1 in ECs and stimulating the proliferation of vascular smooth muscle cells (VSMCs), ultimately contributing to plaque expansion [25, 26]. Besides, it can also induce platelet activation, leading to the thrombus formation. In cases where an atherosclerotic plaque ruptures, this process can significantly heighten the risk of life-threatening complications [27, 28]. In addition, IL-6 induces the synthesis of acute-phase proteins, including β 2-fibrinogen, C-reactive protein (CRP), haptoglobin, amyloid protein, and hemoglobin, which serves as a vital factor in AS [29]. For example, among them, CRP can be used as an inflammatory marker and is clinically effective in predicting the occurrence of AS [30]. Serum amyloid A (SAA) can trigger inflammation by activating the NLRP3 inflammasome in macrophages, then inducing localized inflammation and further promoting the progression of AS. Together, these mechanisms synergistically drive the advancement of AS. However, on the flip hand, IL-6 can lower plasma LDL levels by upregulating the number of LDL receptors on hepatocytes, thereby providing a protective effect for the body [31]. Therefore, the effect of IL-6 on AS is complex, and the ultimate outcome it exerts can vary depending on the different states of the body.

3.2. The role of immune cells in atherosclerosis

Apart from cytokines, diversified immune cells—chiefly monocytes, macrophages, and T cells—have a momentous influence on driving the continuous progression of atherosclerotic plaques.

Derived from hematopoietic stem cells (HSCs), monocytes are continuously generated throughout the lifespan of both humans and mice [11]. In healthy arteries, monocytes are rarely found. However, when AS begins to develop, elevated chemokine levels drive monocyte recruitment to the vascular wall, mediated C-X₃-C motif chemokine receptor 1 (CX₃CR1) by and C-C motif chemokine receptor 2 (CCR2) [32, 33]. The next step is the adhesion of monocytes. Selectins, a class of cell-surface proteins, bind to glycoprotein ligands, facilitating the initial, transient, and low-affinity adhesion of monocytes to ECs that have been activated by cytokines [34]. Throughout the adhesion process, circulating monocytes utilize L-selectin (CD62L) to recognize and bind specific fucosylated mucin-like glycoproteins displayed on vascular endothelial cells. Concurrently, P-selectin glycoprotein ligand-1 (PSGL-1) on monocytes interacts with P-selectin (CD62P) and E-selectin (CD62E), both of which are upregulated on inflamed endothelial cells [35, 36]. This adhesive interaction decelerates monocyte rolling, creating an opportunity for these cells to engage with chemokines bound to ECs. After chemokines engaging with the G protein-coupled receptors (GPCRs) on monocytes, they induce the activation of integrins. And the activated β 2-integrins (LFA1) and α 4-integrins (VLA4) then interact with ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) expressed on ECs, ultimately facilitating monocyte arrest and firm adhesion [37]. The tenacious adhesion of monocytes to the endothelial layer triggers morphological and phenotypic changes, a transformation known as polarization [38]. Following polarization, activated integrins and chemokine receptors become concentrated at the cell's leading edge. Monocytes then move toward endothelial junctions, where tight junction proteins of the JAM family interact with integrins, guiding their transmigration [37]. Finally, monocyte migration is completed through homophilic interactions of platelet/endothelial cell adhesion molecule-1 (PECAM-1) and CD99, as well as endothelial retraction induced by vascular endothelial cadherin (VE-cadherin) [39, 40].

After infiltrating the arterial wall, monocytes differentiate into macrophages, adopting either the M1 or M2 phenotype. M1 macrophages primarily drive pro-inflammatory responses, while M2 macrophages aid anti-inflammatory processes. Research indicates that M1 macrophages are key contributors in AS. Firstly, it can recruit inflammatory cells and further amplify the inflammation. By releasing cytokines like TNF, IL-1, IL-6, and monocyte chemoattractant protein-1 (MCP-1), macrophages can amplify inflammation and recruit monocytes [41-43]. Following monocyte recruitment, pro-inflammatory macrophages release more chemokines, further exacerbating inflammation, accelerating atherosclerotic lesion progression, and creating a self-perpetuating feedback loop [43]. Secondly, macrophages are the precursors of foam cells. Macrophages harbor a variety of scavenger receptors (SR), such as SR-A1, CD36, and lectin-like ox-LDL receptor-1 (LOX-1), mediating interactions with lipoproteins. Several cholesterol transporters, such as ABCA1, ABCG1, and SR-BI, are also expressed on Macrophages to facilitate the reverse transport of cholesterol. During the development of AS, the expression of SR, especially LOX-1, is upregulated, whereas cholesterol transporter expression is suppressed. As a result, macrophages experience excessive cholesterol accumulation, ultimately undergoing transformation into foam cells [44]. Moreover, ox-LDL can upregulate the expression of the adhesion receptor CD146, thereby enhancing lipid internalization through CD36, which further drives macrophages transformation into foam cells [45]. Furthermore, macrophage activation leads to increased expression of hypoxia-inducible lipid droplet-associated protein (HILPDA), which in turn downregulates adipose

triglyceride lipase (ATGL) at the protein level. This leads to impaired triglyceride hydrolysis, causing lipid accumulation within macrophages and ultimately transforming macrophages into foam cells [46]. Finally, macrophages can promote plaque progression. In the early stage of AS, M2 macrophages facilitate the removal of apoptotic foam cells via efferocytosis, a critical process for maintaining cellular homeostasis. Nevertheless, when macrophages engulf an excessive number of apoptotic cells, endoplasmic reticulum stress (ERS) can be triggered, ultimately resulting in macrophage death and the subsequent liberation of intracellular components, including lipids and matrix metalloproteinases (MMPs). Among these factors, MMPs possess the enzymatic capability to break down the extracellular matrix (ECM) scaffold, including the overlying fibrous cap, ultimately contributing to plaque rupture [47]. With lesion progression, macrophages exhibit elevated levels of Ca^{2+} /calmodulin-dependent protein kinase γ (CaMKII γ), which then downregulates the expression of the phagocytic receptor c-Mer tyrosine kinase, thereby compromising their phagocytic capacity [48]. Moreover, the downregulation of calreticulin, a crucial "eat me" signal molecule, further impairs phagocytic activity, exacerbating the dysfunction in macrophage-mediated clearance. Consequently, in advanced stages of AS, the phagocytic capacity of anti-inflammatory macrophages is significantly compromised. This functional impairment leads to the progressive accretion of apoptotic macrophages and facilitates the generation of a highly inflammatory necrotic core [49]. The initiation and growth of the necrotic core destabilizes the atherosclerotic plaque, rendering it susceptible to rupture, which may ultimately precipitate acute thrombosis and trigger a myocardial infarction [50].

Beyond the involvement of monocytes and macrophages, T cells also contribute to the progression of AS. Upon recognizing MHC proteins presented by antigen-presenting cells, T cells differentiate into a series of subtypes, such as CD4^+ T cells and CD8^+ T cells, each following distinct activation pathways [51]. Th1 cells, a subset of CD4^+ T helper cells, are considered to exhibit the strongest pro-atherogenic potential. After activation, Th1 cells markedly increase the cellular display of chemokine recognition molecules, including CCR5, CXCR3, and CXCR6. These interactions between chemokines and receptors then attract Th1 cells to the site of atherosclerotic plaques [52]. A broad spectrum of pro-inflammatory cytokines, including IFN- γ , TNF- α , IL-2, and lymphotoxin, can then be secreted by Th1 cells, thereby driving persistent inflammation and accelerating the advancement of AS [53]. Among these cytokines, IFN- γ exacerbates plaque instability by stimulating MMP secretion, suppressing smooth muscle cell proliferation, and downregulating collagen gene expression (collagen I and III). This ultimately heightens the likelihood of thrombosis and myocardial infarction [54]. Regulatory T cells (Tregs) are another distinct population within the T cell lineage. At the early phase of the disease, Tregs mediate their atheroprotective effects primarily through the emission of anti-inflammatory cytokines IL-10 and TGF- β , coupled with the inhibition of pro-inflammatory effector T cell proliferation [55]. However, during the advanced AS, the number of Treg cells decreases, and they lose their regulatory and protective functions. This results in uncontrolled immune responses, which promote plaque rupture [56].

4. Oxidative stress and atherosclerosis

Reactive oxygen species (ROS) encompass various oxygen-derived chemical entities within cells that readily interact with lipids, proteins, and DNA, including superoxide anion ($\text{O}_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) [57]. They serve as a crucial factor in modulating diverse cellular activities and physiological pathways [58]. In blood vessels, ROS primarily originate from sources such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and uncoupled endothelial nitric oxide synthase (eNOS). At the same time, there is an antioxidant system in the

vascular wall, which mainly includes superoxide dismutase (SOD), glutathione peroxidase, catalase, and nitric oxide (NO) [59]. When the yield of ROS increases and/or the antioxidant capacity is compromised, ROS levels rise, bringing about oxidative stress. During oxidative stress, ROS have multiple effects on the vascular system, collectively promoting the development of AS.

4.1. Lipid oxidation

During the formation of atherosclerosis, LDL accumulates in the vascular wall and is prone to becoming ox-LDL, a vital driver in AS, when ROS is overproduced. Firstly, ox-LDL can damage endothelial cells. Ox-LDL induces inflammatory responses in endothelial cells and facilitates leukocyte adhesion. ECs can internalize Ox-LDL via the ox-LDL receptor 1 (LOX-1), which subsequently upregulates the expression of endothelial adhesion molecules, including ICAM-1, VCAM-1, and E-selectin. This process facilitates monocyte adhesion and migration [60, 61]. Upon infiltrating into the intima layer, monocytes transform into macrophages, which, in turn, release pro-inflammatory cytokines and produce ROS. This perpetuates a self-amplifying cycle, progressively contributing to endothelial inflammation. Secondly, ox-LDL facilitates foam cell generation. Through CD36-mediated signaling, ox-LDL initiates NLRP3 inflammasome activation in macrophages, subsequently promoting the secretion of IL-1 β . The secreted IL-1 β further acts on macrophages, accelerating their uptake of ox-LDL, thus generating a reinforcing feedback mechanism. Ultimately, lipids continuously accumulate within macrophages, transforming them into foam cells [62]. Moreover, ox-LDL can also activate platelets. On the one hand, ox-LDL stimulates platelets via CD36, resulting in Src kinase-dependent activation of Syk and phospholipase C γ 2, which increases intracellular Ca²⁺ levels and activates myosin IIa kinase. On the other hand, Src kinase activation induces a downstream signaling pathway leading to RhoA activation, subsequently stimulating RhoA kinase while suppressing myosin IIa phosphatase activity. These processes culminate in the phosphorylation of myosin IIa, ultimately driving platelet activation [63]. Additionally, the PI3K/Akt signaling pathway activated by ox-LDL enhances osteopontin expression, then facilitating the proliferation and migration of VSMCs [64]. Collectively, these four mechanisms further drive the progression of AS, exacerbating its pathological development.

4.2. The impact on vascular smooth muscle

ROS, including superoxide (O₂⁻) and hydrogen peroxide (H₂O₂), contribute to the regulation of VSMCs by driving their proliferation, migration, and apoptosis. The phenotypic switching of VSMCs is predominantly governed by the NADPH oxidase family, with NOX1, NOX4, and NOX5 serving as the principal regulators [65]. When AS occurs, NOX1 is activated by angiotensin II to generate ROS, which then mediates the activation of p21-activated kinase 1 (PAK1). PAK1 not only promotes VSMCs migration by regulating cofilin and participating in cytoskeletal remodeling but also induces VSMCs proliferation, migration, and inflammation through several downstream molecular signaling networks, such as MAPK and NF- κ B pathways [66, 67]. NOX4 can similarly activate multiple upstream and downstream pathways by promoting ROS generation, thereby driving the release of inflammatory factors. Additionally, studies have found that NOX4 can enhance ROS production, further activating soluble epoxide hydrolase (sEH). sEH, through regulating the metabolism of epoxy fatty acids, then amplifies the inflammatory response triggered by homocysteine (Hcy), ultimately leading to functional changes in VSMCs [68]. NOX5 is an enzyme whose activity is regulated by intracellular Ca²⁺ concentrations [69]. In the late stages of AS, extracellular Ca²⁺ enters VSMCs via clathrin- and caveolin-mediated endocytosis of extracellular

vesicles (EVs), leading to an increase in cytoplasmic Ca^{2+} levels. As a result, Nox5 is activated, leading to an elevated generation of ROS. The increased ROS concentration enhance EV release while reducing EV phagocytosis, resulting in an elevated level of EVs within the extracellular matrix and ultimately promoting vascular calcification [70]. All of the above events can contribute to the exacerbation of atherosclerosis.

5. Novel treatment strategies

With continuous advancements in research, AS is now recognized as more than just a lipid-driven disorder. The development and progression of AS are also significantly influenced by inflammatory responses and oxidative stress. Therefore, developing new therapeutic strategies targeting inflammation and oxidative stress pathways has become a promising new approach for treating this pathology.

5.1. Anti-inflammatory therapy

Given its extensive involvement in inflammation and AS progression, TNF- α serves as a promising therapeutic target for treating the disease. Several anti-TNF- α agents like adalimumab, certolizumab, golimumab, and infliximab, which are monoclonal antibodies, have been designed and implemented for managing inflammatory and autoimmune disorders [71]. In an early clinical study, it was discovered that the proportion of first cardiovascular events in rheumatoid arthritis patients treated with infliximab, which is 14.0 cases per 1000 person per year, was markedly lower than in those not receiving the treatment, which is 35.4 cases per 1000 person per year [72]. At the same time, in another five-year clinical study conducted on psoriasis patients, results show that those treated with tumor necrosis factor inhibitors exhibited a markedly reduced prevalence of cardiovascular diseases relative to patients undergoing alternative therapies [73]. In addition to infliximab, various other monoclonal antibodies have demonstrated promising therapeutic efficacy in clinical trials targeting AS and other inflammatory disorders [74]. However, anti-TNF- α agents also have certain limitations. Clinical research has revealed that in individuals diagnosed with moderate to severe heart failure, a six-week course of infliximab treatment did not lead to any noticeable symptom improvement. Moreover, administering a high dose (10 mg/kg) could potentially elevate the risk of heart failure deterioration [75]. Additionally, anti-TNF- α drugs have shown inconsistent results in individuals with metabolic syndrome, obesity, lupus, or type 2 diabetes [76].

As a cytokine functioning as an essential component in AS, and whose expression level is intimately linked to the disease progression, IL-6 has also emerged as a prospective therapeutic target for AS treatment [77]. Tocilizumab (TCZ) is a monoclonal antibody that achieves its therapeutic effect through impeding the connection of IL-6 and IL-6R [78]. In a placebo-controlled and randomized trial conducted on individuals with rheumatoid arthritis, it was found that TCZ effectively reduced the levels of inflammation markers and altered the composition of HDL particles, leading to enhanced anti-inflammatory activity. These results suggest that TCZ can alleviate inflammation and thus exert an anti-atherosclerotic effect [79]. However, an increase in triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels has been witnessed in the course of TCZ treatment, which may lead to an unfavorable lipid profile [74]. Ziltivekimab also known as Zevacizumab, is a monoclonal antibody that is both highly selective and fully human in origin, with its development specifically aimed at treating AS. It has been engineered with the specific purpose of binding to the IL - 6 ligand [80]. In a Phase II trial that was double-blinded, randomized, and placebo-controlled, involving individuals suffering from chronic kidney

disease but without evident signs of inflammation, it was found that ziltivekimab effectively reduced biomarker levels related to atherosclerosis-associated inflammation and thrombosis. Moreover, it demonstrated superior clinical characteristics compared to TCZ [81].

5.2. Antioxidant therapy

Fruits and vegetables contain many natural antioxidants, so using dietary antioxidant therapy seems to be a potential approach for treating atherosclerosis. However, the results of 78 randomized clinical trials indicate that dietary antioxidant therapy does not provide protective effects for cardiovascular health [82]. In another large-scale primary prevention trial, it was discovered that taking vitamin D supplements was unable to lower the frequency of cardiovascular events when compared to the placebo [83]. These results emphasize the unreliability of using antioxidant supplements as a treatment for AS.

In addition, synthetic antioxidants have also not shown good results in clinical settings. Febuxostat is a xanthine oxidase inhibitor that decreases the production of ROS by suppressing the activity of the enzyme. A clinical trial conducted on asymptomatic hyperuricemia patients showed that after 24 months of treatment with febuxostat, the alteration in carotid artery intima-media thickness observed in the treatment group closely paralleled that of the reference group. This finding indicates that the progression of AS is not attenuated by febuxostat treatment [84]. In conclusion, although antioxidants show strong therapeutic potential, there are still significant barriers to their clinical implementation.

5.3. Future: multi-pathway combination therapy

Inflammation and oxidative stress are key pathogenic factors in atherosclerosis. Therefore, developing drugs with combined anti-inflammatory and antioxidant effects for the treatment of atherosclerosis holds promising prospects. Epigallocatechin gallate (EGCG), the predominant constituent of green tea polyphenols, is highly concentrated in green tea leaves and is also present in large quantities in oolong and black tea leaves [85]. EGCG has multiple functions. On one hand, EGCG exerts anti-inflammatory properties via downregulating NF- κ B activation, therefore suppressing the gene expression of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , while simultaneously facilitating the macrophages to polarize in the direction of the M2 phenotype [86]. On the other hand, EGCG exhibits antioxidant activity by scavenging intracellular ROS, reducing the prevalence of oxidative stress [87]. In a particular study, a lipid nanoparticle (SE-LNP) was formulated with simvastatin (SIM) serving as the model drug, EGCG functioning as an anti-inflammatory and antioxidant agent, and distearoylphosphatidylcholine (DSPC) acting as the principal carrier. This formulation was administered to ApoE $^{-/-}$ atherosclerotic mice. The experimental results showed that the drug significantly reduced oxidative stress levels, encouraged the polarization of macrophages to the M2 phenotype and held back the inflammatory response generated by M1 macrophages, thereby exerting anti-atherosclerotic effects. Additionally, the lipid nanoparticle was able to target the atherosclerotic lesion area, providing localized therapeutic effects and reducing systemic side effects [88]. Although the drug has not yet entered clinical trials, its remarkable results suggest a promising future as a potent candidate for atherosclerosis treatment.

6. Conclusion

Growing evidence indicates that inflammation and oxidative stress are crucial contributors to the progression of AS. The interplay between inflammatory cytokines (TNF- α , IL-6) and immune cells (monocytes, macrophages, T cells) triggers and amplifies the inflammatory response, ultimately resulting in endothelial dysfunction, along with the multiplication and translocation of VSMCs, all of which expedite the progression of AS. During oxidative stress, ROS not only oxidizes LDL to form ox-LDL but also induces phenotypic changes in VSMCs, thereby contributing to AS from multiple angles. Many anti-inflammatory and antioxidant agents are continuously being devised for the cure of AS. And the combined use of multiple therapeutic pathways offers a promising future for treating AS.

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