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Review Article

Cytokines associated with immune response in atherosclerosis

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Abstract: Inflammation is an essential mechanism of immune response that involves a large number of different immune cells. Atherosclerosis is essentially an inflammatory disease caused by inappropriate activities of immune cells. During this process, various cytokines activate immune cells, regulate and transmit immune cell signals, and stimulate a local inflammatory environment. In this study, we reviewed the cytokines associated with immune activity in atherosclerosis, including their roles in immune cell activation and mediating immune cell chemotaxis. The findings give important insights into inflammatory immune microenvironment, including basic mechanisms and interactions, providing new ideas and options for clinical detection and treatment of this disease.

Keywords: Atherosclerosis, cytokine, immunity

Introduction

Atherosclerosis, a vascular disease strongly associated with high lipid levels, was first identified by Rudolf Virchow in the 1850s. As our understanding of its pathogenesis improved, it was established that atherosclerosis is not only due to lipid accumulation within the arterial wall, but also inappropriate body response to vascular damage. The disease involves a sequence of pathological events. First, substantial fibrous and lipid masses accumulate in the subendothelial layer of the artery, wrapping around the circulating cells to form plaques. This narrows or even occludes the blood vessels, obstructing blood flow and hypoxia, which may progress and develop myocardial infarction and stroke.

Several studies have shown that specific cytokines participate in different stages of immune cell activation, such as chemotaxis, differentiation, recruitment, and infiltration. Cytokines also regulate internal and external lipid flow and are essential chemical mediators in various pathophysiological processes, such as intercellular signal transduction. Experimental studies based on animal and patient samples have implicated cytokines in the development of atherosclerosis. In the past two decades, monoclonal antibodies against cytokines have become a standard treatment for chronic inflammatory diseases such as rheumatoid arthritis. Therefore, since atherosclerosis, is also inflammatory disease, similar treatment approaches are currently being explored as novel therapeutics for this disease. More than 20 clinical trials on the treatment of atherosclerosis by targeting immune-associated cytokines were included in ClinicalTrial.gov (**Tables 1** and **2**).

This review will summarize the different cytokines involved in the immune response during atherosclerosis, focusing on their mechanisms and interactions, and updating recent advances in targeted drug research.

Cytokines is involved in immune cell activation

Atherosclerosis is mainly caused by endothelial damage and high lipid levels in the arteries, which activate multiple immune cells that promote lesion formation. Increased infiltration

Table 1. Summary of clinical trials of drugs targeted cytokines involved in immune cell activation

Target	Drug	Disease	Phase	Outcome	NCT number	Status
TNF-α	Infliximab	Psoriasis Atherosclerosis	Unknown	No results posted	NCT01356758	Completed [65]
	Adalimumab	Psoriasis Vascular Inflammation Coronary Atherosclerosis	IV	Modest increase in vascular inflammation in carotids	NCT01722214	Completed [66]
	Adalimumab	Psoriasis Vascular Inflammation Coronary Atherosclerosis	IV	Reduce vascular inflammation in patients with moderate to severe psoriasis	NCT00940862	Completed [67]
	Etanercept	Atherosclerosis in Psoriasis Patients Study	Unknown	No results posted	NCT01522742	Terminated
IL-1β	Canakinumab	Atherosclerosis	III	Decreased hsCRP level and incidence of the primary endpoint	NCT01327846	Completed [68]
IL-12/IL-23	Ustekinumab	Psoriasis Atopic Dermatitis Atherosclerosis	Unknown	No effect on MACE	NCT01356758	Completed
Multiple	Methotrexate	Coronary Artery Disease	II	CRP, IL-6 levels ↓	NCT02366091	Completed
	Colchicine	Coronary Artery Disease Myocardial Infarction	III	MACE ↓	NCT02551094	Completed
		Coronary Artery Disease	IV	Attenuated the increase in interleukin-6 and hsCRP concentrations but did not lower the risk of PCI-related myocardial injury	NCT01709981	Active, not recruiting
		Atherosclerotic Vascular Disease	II	No results posted	NCT02162303	Completed

Table 2. Summary of clinical trials of drugs targeted cytokines mediating immune cell chemotaxis

Target	Drug	Type	Disease	Phase	Outcome	Status	NCT number
CCR2	MLN1202	humanized monoclonal antibody	atherosclerosis	II	CRP level ↓	Completed [129]	NCT00715169
CCR5	Maraviroc	Small-molecule receptor antagonist	STROKE	II	No results posted	Not yet recruiting	NCT04789616
	Maraviroc	Small-molecule receptor antagonist	atherosclerosis	IV	significant improvements in several markers for cardiovascular risk, endothelial dysfunction, arterial stiffness, and early carotid atherosclerosis	Completed [130]	NCT03402815
CCL2	Bindarit	Selective inhibitor	Coronary restenosis	II	in-stent late loss↓	Completed [131]	NCT01269242
CXCL12	JVS-100	nonviral DNA plasmid (transient CXCL12 expression)	Ischemic heart failure	II	Failed to demonstrate its primary endpoint of improved composite score at 4 months after treatment	Completed [132]	NCT01643590
	JVS-100	nonviral DNA plasmid (transient CXCL12 expression)	Ischemic heart failure	I/II	No results posted	Unknown	NCT01961726
	JVS-100	nonviral DNA plasmid (transient CXCL12 expression)	Critical limb ischemia	II	No results posted	Completed	NCT01410331
	JVS-100	nonviral DNA plasmid (transient CXCL12 expression)	Peripheral arterial disease	II	Failed to improve outcomes in CLTI at 6 months	Completed [133]	NCT02544204
	ACRX-100	nonviral DNA plasmid (transient CXCL12 expression)	heart failure	I	No results posted	Completed	NCT01082094
CXCR2	AZD5069	Small-molecule receptor antagonist	Coronary heart disease	II	No results posted	Ongoing	EudraCT 2016-000775-24
CXCR4	POL6326	Peptidic receptor antagonist	Large reperfused ST-elevation myocardial infarction	II	No results posted	Completed	NCT01905475
	PF-06747143	CXCR4 IgG1 antibody	Acute Myeloid Leukemia	I	No results posted	Terminated	NCT02954653
	BMS-936564	CXCR4 antagonist	chronic lymphocytic leukemia (CLL)	I	No results posted	Completed	NCT01359657
MIF	BAX69	MIF Antibody	Metastatic Adenocarcinoma of the Colon or Rectum Malignant Solid Tumors	I	Safety evaluation	Completed [99]	NCT01765790

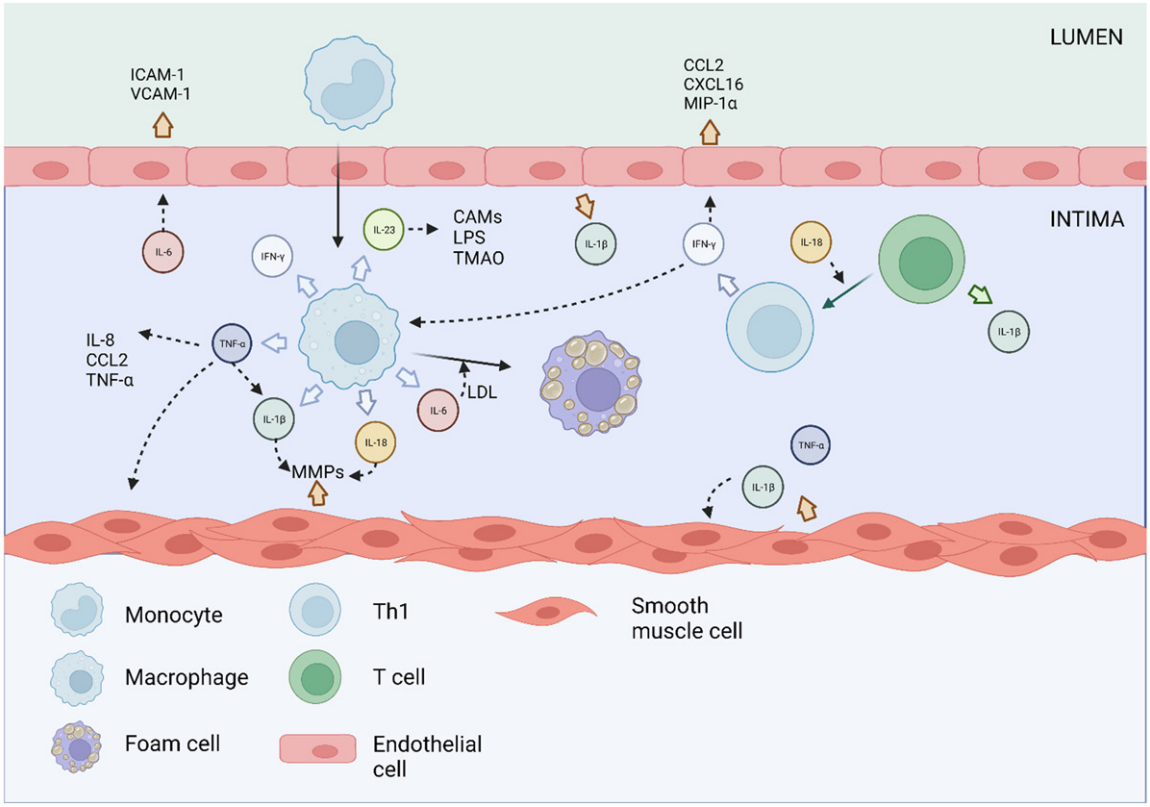

Figure 1. Schematic overview of cytokines involved in immune cell activation during atherosclerosis. Cytokines can be expressed in almost all types of cells in this environment, especially macrophages. Some of them, like TNF-α and IFN-γ, act as critical roles in this network, promoting the expression of other cytokines including IL-6, IL-8, CCL2, CXCL16, etc. IL-18 drives T cell polarization and induces MMP expression in vascular smooth muscle cells. IL-23 is mainly expressed by macrophages, causing subsequent inflammatory factors reaction. IL-1β has multiple pro-inflammatory functions, other than inducing MMPs and other cytokines, it can also affect the proliferation and migration of vascular smooth muscle cells. IL-6, also known as a key cytokine with diverse functions, can promote low-density lipoprotein uptake in macrophages and stimulate endothelial cells to secret adhesion molecules. More details are offered in the text. IL: interleukin; IFN-γ: interferon-γ; CCL2: C-C motif chemokine ligand 2; CXCL16: C-X-C motif chemokine ligand 16; MIP-1α: macrophage inflammatory protein-1α; CAMs: cell adhesion molecules; LPS: lipopolysaccharide; TMAO: trimetlylamine oxide; TNF-α: tumor necrosis factor-α; MMPs: matrix metalloproteinases. Figure was created using BioRender.com.

of immune cells such as monocytes, macrophages, T lymphocytes (T cells), B lymphocytes (B cells), and dendritic cells (DCs), in lesion sites, especially the plaque. These cells are part of the body's self-defense system, but play a role in atherosclerosis development. Some pro-inflammatory cytokines regulate genes that promote inflammation and activate immune cells and disrupt this self-defense system. Partial activities and interactions of these cytokines are represented in **Figure 1**.

Tumor necrosis factor-α (TNF-α)

TNF-α, which mainly secreted by monocytes/macrophages, is one of the most important cytokines in atherosclerosis. TNF-α promotes the expression of multiple pro-inflammatory genes. In atherosclerosis, TNF-α produced by immune cells or endothelial cells increase expression levels of several key genes involved in inflammation and cell proliferation by activating nuclear factor-κb (NF-κB), p38 mitogen-activated protein kinase (MAPK), janus kinase (JAK), and other signaling pathways. The target proteins include different pro-inflammatory cytokines, cell adhesion molecules (CAMs) and chemokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), C-C motif chemokine ligand 2 (CCL2). Increased TNF-α self-expression recruits more T cells and macrophages to the lesion site, accelerates the inflammatory cascade response, contributing to disease progression [1]. In addition, TNF-α

causes increased leukocyte infiltration into blood vessels, which is an essential first step in plaque formation [2]. TNF-α chronically stimulates macrophages through a MAPK-dependent pathway, downregulates scavenger receptor gene expression, and reduces the effect on the reverse cholesterol pathway, which exacerbates atherosclerosis [3]. In addition to regulating the activation and recruitment of various immune cells, TNF-α has a pro-inflammatory effect on vascular smooth muscle cells. It stimulates the production of matrix metalloproteinases (MMPs), thrombogenic proteins and tissue factor, causing reduced plaque stability and even rupture [4]. TNF-α also regulates phenotypic transition where contractile vascular smooth muscle cells progress to a secretory function, facilitating monocyte migration [5] and contributing to atherosclerosis development.

More than 50% reduction in atherosclerotic lesion area and increased plaque necrosis and apoptosis have been found in TNF-$\alpha^{-/-}$Apoe$^{-/-}$ double knockout mice [6]. In a study of patients with psoriatic arthritis, the use of TNF-α inhibitors slowed the progression of atherosclerosis and improved vascular inflammation [7]. Therefore, it might be concluded that TNF-α is essential for atherosclerosis. It activates multiple pathways and recruits various immune cells with polydirectional pro-inflammatory effects, hence an ideal potential target for the treatment of atherosclerosis. Studies have also established that TNF-α level is significantly correlated with early carotid atherosclerosis [8]. This suggests that TNF-α can be used as an effective clinical marker for early atherosclerosis.

However, TNF-α as a potential therapeutic target for atherosclerosis has been well studied clinically. This may be due to the negative effects it has shown in some clinical trials, such as exacerbated heart failure and changes in lipidogram, which requires further safety tests [9].

Interestingly, a study showed that loss of p55, a TNF-α receptor, also known as TNF-α R1, appeared to promote the atherosclerosis process [10]. However, the opposite outcomes have been reported in recent studies: it has been found that TNF-α R1 promoted atherosclerosis in low-density lipoprotein receptor knock-out mice [11]. Brusatol was confirmed to inhibit the development of atherosclerosis by suppressing TNF-α R1 [12]. It seems the pro-atherogenic role of TNF-α R1 has been generally revealed.

Interleukin-1β (IL-1β)

IL-1β is a pro-inflammatory cytokine that is expressed mostly in macrophages, endothelial cells and vascular smooth muscle cells. It is induced by TNF-α and subsequently acts as a local paracrine and autocrine stimulator. Accordingly, IL-1β stimulates the secretion of multiple cytokines and CAMs, leading to immune cell extravasation and persistent local inflammation [13]. IL-1β also promotes the proliferation and migration of vascular smooth muscle cells and induces MMPs to accelerate degradation of atherosclerotic plaque fibrous skeleton [14]. This remodels and transforms the extracellular matrix, affecting plaque stability [15].

In animal models, IL-1β suppression can effectively slow down the development of atherosclerosis. Injection of IL-1β-induced receptors in Apoe$^{-/-}$ mice reduced the fatty streak area in arteries [16]. Under similar conditions, IL-1β$^{-/-}$ Apoe$^{-/-}$ double knockout mice had 30% less lesion area than the control group [17].

In the CANTOS (Canakinuub Anti-inflammatory Thrombosis Outcomes Study) study, patients treated with Canakinnub (a monoclonal antibody to IL-1β) had a significantly lower incidence of clinical outcomes such as atherosclerosis-related myocardial infarction and stroke than the placebo group [18]. The CANTOS trial also confirms the inflammatory hypothesis of atherosclerosis and provides further evidence that targeting inflammation offers an independent pathway for the atherosclerosis treatment. Additionally, the study lays the foundation for the development of additional inflammation-targeted drugs.

Apart from IL-1β, NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory vesicles upstream of IL-1β is another possible target. Drugs, such as colchicine in the LODOCO (low-dose colchicine) study, have been shown to reduce IL-1β production by inhibiting NLRP3 inflammatory vesicle activity, with a lower risk of adverse cardiovascular events [19]. This finding was confirmed by the

more comprehensive LODOCO2 study [20]. A new NLRP3 inhibitor, MCC950, which is currently under trial [21], might serve as a potentially effective treatment for atherosclerosis.

On the other hand, IL-1β facilitated the formation of fibrous cap and increased plaque stability in the late stages of lesion development. Conversely, plaque stability decreased in atherosclerotic mice knocked out of IL-1 receptors or treated with IL-1β antibodies. This suggests that plaque stability and subsequent possible cardiovascular events should be considered when administering IL-1β-related drugs, especially to patients with advanced atherosclerosis [22].

Interleukin-6 (IL-6)

IL-6 is mostly secreted by macrophages as well as other cell types including fibroblasts and endothelial cells. It is a multifunctional cytokine, which plays an important role in the inflammatory response of atherosclerosis. IL-6 promoted leukocyte recruitment by increasing the production of C-reactive protein (CRP) from liver, resulting in endothelial dysfunction [23]. It can promote low density lipoprotein (LDL) uptake and cytokines expression in macrophages [24]. Activate endothelial cells can express adhesion molecules and chemokines, which stimulated migration and proliferation of smooth muscle cells [25]. A recent study showed that age-associated mitochondrial dysfunction induced by IL-6 contributed to atherosclerosis formation [26].

In mice atherosclerosis models, exogenous IL-6 enhanced the development of early atherosclerosis lesions [27] and destabilized atherosclerosis plaques [28]. However, another study has shown that $Apoe^{-/-}IL\text{-}6^{-/-}$ mice had the tendency to gain atherosclerosis more easily, which suggested the dual-modulatory function of IL-6 [29].

IL-6 is known to be involved in several signaling pathways. It can bind to the membrane-bound IL-6 receptor (IL-6R) on leucocytes and endothelial cells, or bind to gp130 with a compound of IL-6 and soluble IL-6R, then activate intracellular signaling in cells that can't express IL-6R. The third way was trans-presentation through interaction between dendritic cells and receiver T cells [30]. The therapeutic targets for IL-6 pathways usually included IL-6, IL-6R, gp130 and downstream molecules of the janus kinase-signal transducer and activators of transcription pathway (JAK-STAT pathway). Now multiple antibody drugs for some inflammatory diseases targeting IL-6 related pathways have been studied in some clinical trials [31, 32]. However, only Sarilumab was under recruitment for its phase IV clinical trial (NCT04350216). Notably, in the CANTOS study, the effect of canakinumab was significantly associated with the decreased level of IL-6 [33], suggesting the synergism of IL-1β and IL-6. Additionally, its role in predicting atherosclerosis was also observed in another study [34]. Therefore, IL-6 may work as a marker of atherosclerosis in the clinical setting.

Interleukin-18 (IL-18)

IL-18 was originally known as an interferon-γ (IFN-γ)-inducible factor because it induces IFN-γ expression. However, IL-18 is now known to be a multifunctional cytokine in various cells, including macrophages and endothelial cells, where its inactive precursors promote signaling through NF-κB pathway [35]. Its receptors occur on macrophages, endothelial cells and vascular smooth muscle cells and mediate interaction between immune cells and blood vessels [36]. It polarizes T cells to Th1 cells [37], the "war hawk" of helper T cells that promotes the development of inflammation. In addition, it amplifies MMPs in monocytes and vascular endothelial cells, which affects plaque stability [36]. IL-18 is a member of the IL-1 cytokine superfamily that also includes IL-1β, which is activated and released downstream of NLRP3 inflammatory vesicles to promote the development of atherosclerosis [38].

In one study, serum IL-18 was elevated in patients with coronary artery disease whereas IL-18 and its receptors were overexpressed in several immune cells, including macrophages, T cells, endothelial cells, and vascular smooth muscle cells in atherosclerotic plaques [39]. This suggested an association between IL-18 and atherosclerotic lesions.

A lower incidence of atherosclerosis was found in $IL\text{-}18^{-/-}Apoe^{-/-}$ double knockout mice than in the control group [40]. Treatment with IL-18 inhibitors not only prevented plaque formation, but also transformed it into a more stable

plaque phenotype [41]. Apoe$^{-/-}$ mice injected with IL-18 exhibited increased plaque burden [42]. Notably, IFN-γ$^{-/-}$Apoe$^{-/-}$ double knockout mice were less lesioned than Apoe$^{-/-}$ mice injected with recombinant IL-18, suggesting a synergistic relationship between IL-18 and IFN-γ [40].

IL-18 is an important node in the inflammatory network. It synergizes with many cytokines involved in atherogenesis, such as IL-6, IL-12, and IFN-γ [43], amplifying inflammatory response in the lesion. A study found that IL-18 was related to substantial residual inflammatory risk among the patients who took canakinumab (IL-1β inhibitor) therapy [44]. Therefore, block IL-18 in drugs such as IL-18Bpa (an IL-18 neutralizing antibody), or upstream caspase-1 inhibitors may inhibit multiple pro-inflammatory cascades to attenuate lesion development. However, further research in this area is needed. Inhibition of upstream NLRP3 inflammatory vesicles may also inhibit IL-18 release, as described in section IL-1β above.

Interleukin-23 (IL-23)

Macrophages express both IL-23 and IL-23 receptors, which induces various cells to express Interleukin-17 (IL-17), Interleukin-22 (IL-22), and TNF-α pro-inflammatory factors [45]. The inactivation of IL-23-IL-22 axis signaling causes the intestinal barrier deterioration and ecological dysregulation, increasing systemic pro-atherogenic metabolites such as lipopolysaccharide (LPS) and oxidized trimethylamine and causing atherosclerosis progression [46].

IL-23 has been detected in both mice and human atherosclerotic plaques. Plasma levels of IL-23 were significantly higher in patients with atherosclerosis compared to healthy controls. Follow-up data showed that high plasma levels of IL-23 were correlated with mortality risk [47]. Notably, IL-23 and IL-23 receptor genes were highly expressed in carotid plaques compared to healthy vessels. Levels of IL-17 and TNF-α secreted were higher in monocytes from patients with carotid atherosclerosis treated with IL-23/LPS combination than in monocytes from healthy controls [47].

Briakinumab and ustekinumab, antibodies that target IL-23 subunit p40, have been shown to increase major adverse cardiovascular events (MACE) to different degrees in several clinical trials [48, 49]. Other studies did not show exacerbated MACE rates, but this risk cannot be ignored. In addition, monoclonal antibodies Guselkumab, Tildrakizumab, and Risankizumab, which selectively inhibit IL-23 subunit p19, have been studied in clinical trials for psoriasis treatment, but the sample sizes were not sufficient to describe the effects of these drugs on atherosclerosis and subsequent cardiovascular events [50].

Interferon-γ (IFN-γ)

IFN-γ belongs to type II interferon family and is expressed by multiple immune cells, including natural killer cells (NK cells), T cells, and macrophages. It is a widely studied cytokine that regulates multiple human genes mainly through the JAK-STAT pathway [51]. It has a potent prolipidogenic effect on atherosclerosis: it induces macrophages to further secrete pro-inflammatory factors [52]. IFN-γ also induces the release of chemokines that attract monocytes and T lymphocytes, such as monocyte chemotactic protein-1, CXC (C-X-C motif) ligand 16 (CXCL16), and macrophage inflammatory protein 1α (MIP-1) and promotes monocyte differentiation into macrophages [53]. In addition, IFN-γ promotes uptake of oxidized low-density lipoprotein (ox-LDL) by macrophages and vascular smooth muscle cells, reduces cholesterol efflux, and contributes to the development of foam cells [54], which lay the foundation for plaque formation.

Injecting IFN-γ into Apoe$^{-/-}$ mice increased plaque deposition and reduced vascular smooth muscle proliferation and collagen deposits in the plaque cap, suggesting that IFN-γ may also impair plaque stability [55]. In contrast, in IFN-γ$^{-/-}$Apoe$^{-/-}$ double knockout mice, plaque shrinkage was observed [56]. IFN-γ is essential in all stages of atherosclerosis progression, from immune cell recruitment, LDL accumulation, to plaque development and stabilization.

Some lipid-lowering drugs such as statins and PCSK-9 inhibitors decrease IFN-γ [57, 58] level in addition to their cholesterol lowering effect. Currently, new therapies targeting IFN-γ are being investigated. Neutralizing IFN-γ antibodies were used to reduce atherosclerosis in the grafted vessels and aorta in Apoe$^{-/-}$ mice undergoing heart transplantation [59]. Bioinforma-

tics data analysis supported the ability of specific long-stranded non-coding RNAs (lncRNAs) to promote atherosclerosis by affecting the IFN-γ pathway [60]. Another study showed that microRNA miR-155, which is highly expressed in atherosclerotic plaques, also induces IFN-γ expression [61, 62]. In systemic lupus erythematosus patients, using type I anifrolumab could reduce neutrophil extracellular trap formation and interleukin-10 (IL-10) levels [63]. However, it is important to note that restricted expression of IFN-γ may lead to immunosuppression and increase the incidence of infection [64]. Therefore, it is important to treat opportunistic infections when administering lipid-lowering drugs in the long term.

Cytokines mediate immune cell chemotaxis

Chemokines were originally named after their function of directing white blood cells to inflammation sites. However, recent advances in research have led to the discovery that they perform other functions besides immune cell recruitment, including keeping cellular homeostasis and activating different cell functions. Chemokines are highly active in inflammation sites and regulate various inflammatory cellular processes. As an inflammatory disease, atherosclerosis development and progression is driven by chemokines. Therefore, understanding the mechanism of atherosclerosis-related chemokines will inform the development of effective treatments to control atherosclerotic lessions.

Chemokines are a family of structurally similar cytokines. Most chemokines are secreted proteins with a molecular weight of about 10 kda. Each chemokine consists of a carboxy-terminal alpha helix structure that preferentially binds proteoglycans and extracellular matrix proteins on vascular endothelial cells. It also includes four cysteines at highly conserved positions. Based on the distribution of cysteine N-terminal residues, chemokines are classified into four subclasses: CC, CXC, CX3C, and XC. Chemokines bind to G protein-coupled receptors, initiate the dissociation of G protein subunits α, β, and γ, subsequently activate MAPK, phosphatidylinositol 3-kinase (PI3K) and phospholipase C (PLC) pathways. In addition, such binding increases intracellular calcium levels, causing cell polarization, adhesion and migration. G protein-coupled receptors are also known as conventional chemokine receptors (CKRs). Another type of receptors, the atypical chemokine receptors (ACKRs), are mainly considered as scavenger receptors. They act independently from the G protein signaling pathway, indirectly control the interaction between chemokines and CKRs by regulating the localization and function of chemokines. Usually, many chemokines from the same family bind to several different receptors and a specific receptor may have multiple chemokine ligands. Therefore, chemokines and their receptors together form a large network with complex interactions that need further mechanistic exploration. Partial activities and interactions of these chemokines are represented in **Figure 2**.

C-C motif chemokine ligand 2 (CCL2)

CCL2 is the best known CC chemokine that was first recognized as a monocyte chemotactic factor. Studies have shown that the CCL2-CCR2 axis is required for monocytes to migrate from bone marrow to peripheral circulation [69]. However, CCL2 has recently been found to to promote tumor progression and immune surveillance. CCR2 is a CCL2 receptor that is expressed on the surface of monocytes after exposure to inflammatory stimuli. CCL2 is typically expressed in endothelial cells, monocytes/macrophages, smooth muscle cells, and T cells. It causes monocytes to aggregate due to inflammation or injury through downstream signaling pathways such as JAK-STAT pathway, MAPK pathway, and PI3K pathway [70]. Its expression is induced mainly by cytokines such as IL-1, interleukin-4 (IL-4), TNF-α, and IFN-γ, various growth factors, lipopolysaccharides, reactive oxygen species (ROS), oxLDLs and immune complexes [71]. CCL2 is a monocyte efflux signal that activates G protein-coupled receptors to mediate cellular trafficking, which subsequently directs monocytes along a chemokine gradient to the site of injury. It is associated with various diseases, including rheumatoid arthritis, atherosclerosis, diabetes, certain cancers (breast cancer, prostate cancer, pancreatic cancer, etc.). This article focuses on monocyte migration in atherosclerosis.

In addition to chemotaxis, CCL2 is important in cell polarization and survival. Its ability to direct macrophage polarization toward M1 via granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony-stimulating

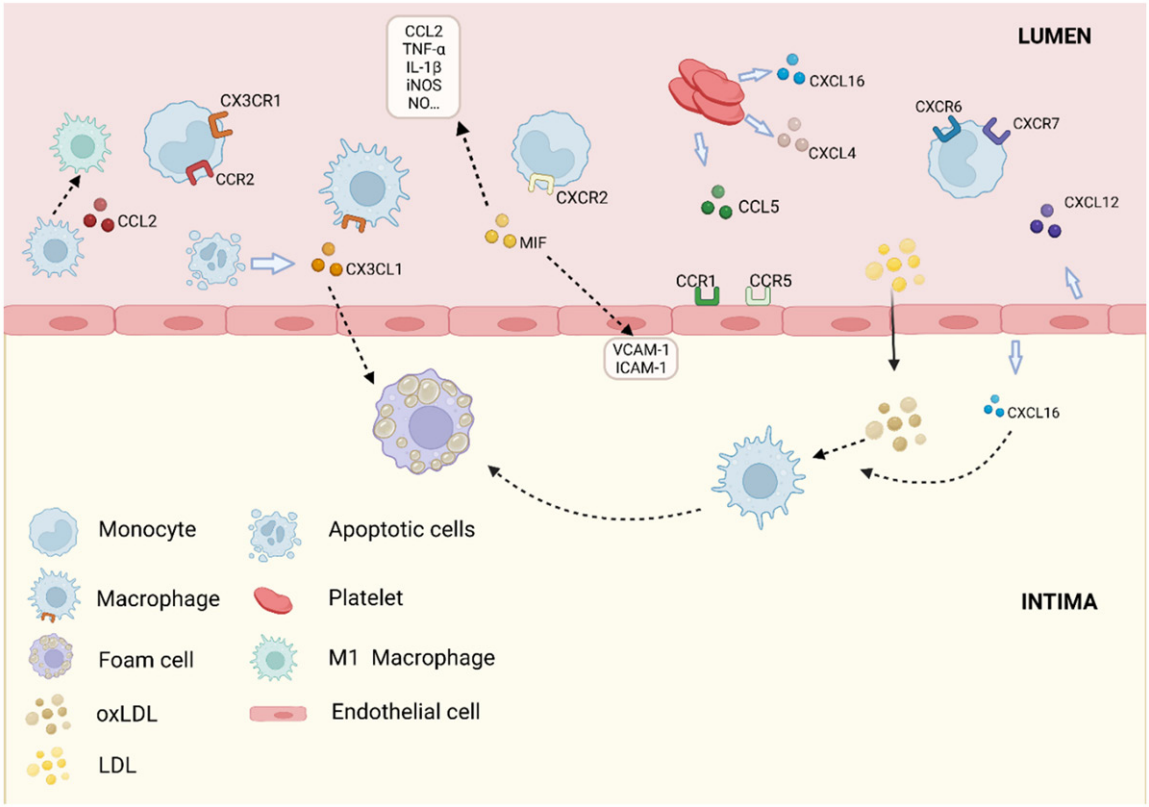

Figure 2. Schematic overview of cytokines mediating immune cell chemotaxis during atherosclerosis. CCL2 can attract monocytes to the lesion and drive them to differentiate into macrophages. CCL2 further promotes macrophages polarization to M1. CX3CL1 was released by apoptotic cells and then recruits macrophages to form foam cells. MIF is a multipotent atypical chemokine, it selectively recruits T cells, monocytes and leucocytes through different receptors. It also promotes the expression of other cytokines, VCAM-1 and ICAM-1. Platelets are the factory of several chemokines including CCL5, CXCL4 and CXCL16. CCL5 can stop leucocytes from moving through the CCR1 and CCR5 receptors and migrate leucocytes to the endothelium. CXCL4 can also bind to CCR1 and form a complex with CCL5, performing chemotaxis. CXCL16 promotes oxLDL uptake of macrophages other than its chemotactic function. CXCL12 exerts diverse effects including recruitment and promoting adhesion by binding to different receptors. More details are offered in the text. CCL2: C-C motif chemokine ligand 2; CCL5: C-C motif chemokine ligand 5; CCR1: C-C motif chemokine receptor 1; CCR2: C-C motif chemokine receptor 2; CCR5: C-C Motif Chemokine Receptor 5; CXCL4: C-X-C motif chemokine ligand 4; CXCL12: C-X-C motif chemokine ligand 12; CXCL16: C-X-C motif chemokine ligand 16; CXCR2: C-X-C motif chemokine receptor 2; CXCR6: C-X-C motif chemokine receptor 6; CXCR7: C-X-C motif chemokine receptor 7; CX3CL1: C-X3-C motif chemokine ligand 1; CX3CR1: C-X3-C motif chemokine receptor 1; TNF-α: tumor necrosis factor-α; IL: interleukin; MIF: macrophage migration inhibitory factor; iNOS: inducible nitric oxide synthase; NO: nitric oxide; LDL: low-density lipoprotein; oxLDL: oxidized low-density lipoprotein. Figure was created using BioRender.com.

factor (M-CSF) has been demonstrated in CCL2 knockout mice and CCR2-deficient mice [72]. In addition, CCL2 activates CCR2 and mediates inflammatory response to atherosclerosis via ERK-dependent downstream signaling of leukotriene liposomes in foam cells [73]. All these processes largely contribute to the development of atherosclerosis.

Studies in mice have yielded indisputable results. CCR2$^{-/-}$ knockout mice had significantly lowatherosclerosis but normal blood lipid and lipoprotein levels, demonstrating an association between CCL2 and atherosclerosis [74]. Further, treatment targeting CCL2-CCR2 axis effectively reduced lesion development and progression [75]. Clinical studies have also shown a significant correlation between CCL2 levels and atherosclerotic stroke in human patients [76].

Some anti-inflammatory and lipid-lowering drugs such as glucocorticoids [77] and statins [78] have been shown to have a non-selective inhibitory effect on CCL2. A recent study found the new effects of Colchicine to lower CCL2 lev-

els in patients with acute coronary syndrome (ACS) [79]. Various cancer drugs targeting CCL2-CCR2 axis have been clinically tested-with only a few of them showing positive results [80, 81]. This outcome is probably due to the complex non-unilinear function of chemokines. When one of the pathways is blocked, its function is maintained by the compensatory effect of other pathways. In addition, inhibiting the chemotactic effect of CCL2 may affect the organism itself, including causing abnormalities in damage response to inflammation, which are important side effects of CCL2.

C-X3-C motif chemokine ligand 1 (CX3CL1)

CX3CL1 is involved in the initiation step of atherosclerotic plaque formation. Its toxicity damages vascular endothelial cells, causing vascular injury, which later set offcascade reactions. Compared to other chemokines, CX3CL1 is unique because it is both soluble and membrane-adhesive [82]. It is also specific to CX3CR1 receptors. CX3CR1 is typically expressed on leukocytes and binds to membrane-bound CX-3CL1 of endothelial cells, activating lymphocytes and the release of lysis granules that destroy vascular endothelium [83]. Apoptotic cells also release CX3CL1 to recruit macrophages that remove apoptotic debris [84]. This clearance may be useful in early stages of lesion development. However, in advanced stage, CX3CL1-CX3CR1 axis signaling exacerbates the formation of foam cells [85], contributing to lesion progression. In addition, smooth muscle cells in atherosclerotic plaques also express CX3CR1 [86], which moves and converges CX3CL1 in near the lesion.

Platelets are actively involved in plaque formation, CX3CL1 promotes lesion development by activating platelets and through its adhesion to the endothelium [87]. Both the expression of CX3CR1 on platelets and its binding to CX3CL1 increase after hyperlipidemia, promoting platelet aggregation and monocyte recruitment [88]. The hemostatic and thrombogenic functions of platelets are highly correlated with atherosclerosis and the probability of subsequent plaque rupture. Platelet levels depend heavily on the regulation of chemokines, mainly CX3CL1, C-X3-C motif chemokine ligand 16 (CXCL16), C-X3-C motif chemokine ligand 12 (CXCL12), C-C motif chemokine ligand 12 (CCL12), and C-C motif chemokine ligand 22 (CCL22) [89].

In animal experiments, $Apoe^{-/-}$ and $Ldlr^{-/-}$ atherosclerotic mice were treated with F1, an amino-terminal modified CX3CR1 ligand with CX3CR1 antagonist activity. The results revealed that macrophages accumulated in the arteries, fewer monocytes were recruited, and atherosclerotic lesions were ameliorated [90]. This indicates that antagonizing CX3CR1 is a promising strategy for slowing the progression of atherosclerosis, but it needs to be tested clinically. Now clinical trials of specific CX3CL1 inhibitor is still blank, but colchicine showed a positive effect in inhibiting CX3CL1 in ACS patients [79].

Macrophage migration inhibitory factor (MIF)

MIF is a multipotent immunomodulatory cytokine with a unique structure. It was one of the first cytokines identified by Bloom and Bennett in 1966 when studying delayed hypersensitivity reaction.Its primary function is to inhibit random migration of macrophages from capillaries. Because it lacks the characteristic N-terminal cysteine of classical chemokines but exhibits chemokine-like functions and binds to classical chemokine receptors, MIF is classified as a novel atypical chemokine (ACKs). The expression level of MIF is low in normal vessels, but significantly high in inflammatory states. Two receptors bind to MIF: CXCR2 and CXCR4, which are predominantly expressed on the surface of monocytes and T cells, respectively. Both CXCR2 and CXCR4 are expressed on the surface of leukocytes, and by binding to both receptors, MIF promotes the recruitment of monocytes and T cells [91]. It also increases vascular cell adhesion molecule-1 (VCAM-1)/intercelluar adhesion molecule-1 (ICAM-1) expression and promotes leukocyte adhesion to vascular endothelium, CCL2 expression and macrophage activation [92]. MIF in plaques also promotes the release of other cytokines such as TNF-α and IL-1β, which exacerbate the local inflammatory environment. It promotes foam cell formation by stimulating enhanced oxLDL uptake and increases plaque instability by inducing matrix degradation through MMPs [93]. In additional experiments, MIF was found to affect plaque stability by inhibiting VSMC proliferation and regulating proteolytic activity and elastin and collagen breakdown [94]. It also inhibited p53 function, causing inhibition of apoptosis and promotion of inflammatory response, which contributed to lesion development [95].

In the MIF-deficient murine model, chronic inflammation developed later and more slowly in mice compared to controls, and plaque lesions were reduced [96]. Apoe$^{-/-}$ mice treated with MIF-neutralizing antibodies had significantly reduced inflammatory indices and aortic plaque area compared to the control group [97].

Drugs targeting MIF have been recently approved for use, such as Ibudilast for treating multiple sclerosis [98]. Other drugs like Imalumab [99] and IPG-1094 are under clinical trial, but the target diseases are still mainly limited to various types of tumors.

C-C motif chemokine ligand 5 (CCL5)

CCL5, also known as RANTES, is one of the chemokines that is highly expressed and released when platelets are activated at the lesion site. It is carried by platelets to activated endothelial cells and binds to CCR1 and CCR5, causing leukocytes to migrate to arterial intima [100]. It also promotes the recruitment of other platelets and immune cells [101]. The interaction between CCR5 and CCL5 mediates CD4+ T cell homing. Scientists have identified a specific subtype of CCR5+CD4+ T cells [102] capable of secreting IFN-γ, various interleukins and TNF-α. Some of these cytokines are pro-inflammatory cytokines that promote the development of atherosclerosis. CCL5 is known to form complexes with other chemokines such as C-X-C motif chemokine ligand 4 (CXCL4) and C-C motif chemokine Ligand17 (CCL17), which act in combination and carry each other to recruit immune cells that promote atherosclerosis [103].

CCL5 is highly expressed in atherosclerotic plaques. Mice treated with the CCL5 antagonist Met-RANTES had significantly low leukocyte infiltration levels and atherosclerotic lesions [104]. Atherosclerosis was also reduced in CCR5 knockout Apoe$^{-/-}$ mice compared to controls [105]. These experimental results validate that the crucial role of CCL5-CCR1-CCR5 axis in plaque formation. In samples of atherosclerotic patients, elevated circulating levels of RANTES were statistically associated with progression of acute coronary syndromes [106].

In addition, the role of CCL5-CCR5 axis has been studied in various diseases, including cancer, some inflammatory diseases, and AIDS. The drug Maraviroc (MVC), which targets CCR5 and is currently used as an antiviral drug for HIV treatment. MVC has been found to reduce the risk of atherosclerosis and alleviate advanced plaque progression in a mouse model [107]. MVC also affects carotid intima-media thickness and atherosclerotic plaques in HCV/HIV co-infected patients. Inhibition of CCR5 prevents the development of atherosclerosis in HCV/HIV co-infected patients, especially in the non-calcified phase [108]. A novel dual antagonist of CCR5 and CCR2, Cenicriviroc (CVC), which inhibits monocyte chemotaxis by reducing E-selectin expression, is a promising treatment for atherosclerosis [109]. However, further animal experiments and clinical trials are needed to identify suitable drug targets for atherosclerosis.

C-X-C motif chemokine ligand 4 (CXCL4)

CXCL4, also known as platelet factor 4 (PF4), exerts an anti-apoptotic effect on monocytes and stimulates their differentiation into macrophages [110]. Activated platelets synergistically act with chemokines to exacerbate the pathogenesis of atherosclerosis. Platelets secrete CXCL4, and the structural properties of its receptor CCR1 allow CXCL4 and CCL5 to interact, forming a complex that causes monocyte arrest on the endothelium at the site of inflammatory injury and consequently atherosclerotic lesions [103]. Also, immunohistochemical analysis of human carotid atherosclerotic lesion samples reveals co-localization of CXCL4 with ox-LDL. This confirms the hypothesis that CXCL4 binding to oxLDL subsequently mediates macrophage uptake and esterification, thereby promoting the formation of foam cells [111]. Additionally, a non-allelic variant isoform of CXCL4, CXCL4L1, exists, which has a distinct effect on monocyte, inhibiting chemotactic recruitment and angiogenesis as well as causing endothelial cell migration [112].

In vitro cell experiments indicate that CXCL4 promotes atherosclerosis by limiting apoptosis of neutrophils and monocytes under pro-inflammatory conditions and mediating T cell-platelet interactions with platelets [113]. Cell experiments on macrophages revealed that PF4 causes macrophage differentiation, resulting in the downregulation of the CD163 atherosclerotic protective receptor. Besides, analysis of human atherosclerotic plaque samples upregulated PF4 and downregulated CD163 expres-

sion [114]. In animal experiments, atherosclerotic plaque burden was reduced in both C57BL/6PF4$^{-/-}$ and Apoe$^{-/-}$ PF4$^{-/-}$ mice [115], which is similar to the effect of CX3CL1. Immunohistochemical analysis of atherosclerotic plaque samples from human carotid arteries identified the presence of PF4 in the endothelium and macrophages of the lesioned fraction, and the levels positively correlated with the severity of atherosclerosis [116].

Although the CXCL4-CCL5 complex affects atherosclerosis, targeting CCL5 alone caused a systemic immune response. Therefore, stable peptide inhibitors targeting the CCL5-CXCL4 complex structure have been designed to suppress atherosclerosis by reducing monocyte recruitment in mice models. For example, MKEY (a specifically designed compound to block CCL5-CXCR4 interaction) has demonstrated therapeutic benefit by inhibiting specific chemokines crucial for the development of atherosclerosis in mice [117].

C-X-C motif chemokine ligand 16 (CXCL16)

CXCL16 is a functionally diverse chemokine found in both membrane-binding type and secretory forms; On one hand, it protects against atherosclerosis and promotes it on the other hand. CXCL16 is expressed by dendritic cells, macrophages, B cells, T cells, smooth muscle cells, and endothelial cells. Membrane-binding CXCL16 act as an adhesion molecule for cells expressing the receptor CXCR6, promoting leukocyte aggregation and adhesion to the damaged vascular endothelium [118]. Nonetheless, macrophages in CXCL16$^{-/-}$ mice exhibit a reduced capacity to internalize LDL. CXCL16 also acts as a scavenger receptor for oxLDL, helping macrophages and smooth muscle cells absorb oxLDL, which protects against atherosclerosis in the early stage and promotes foam cell formation [119].

Furthermore, CXCL16 is secreted by platelets and also activates platelets by binding to CXCR6 on platelets, promoting platelet aggregation on the endothelium [120]. Its expression on platelets is associated with disease severity; platelets from patients with ACS exhibit enhanced CXCL16 expression than platelets from those with coronary artery disease [121].

HUNT study found that baseline levels of circulating CXCL16 were linked to a higher risk of death in patients with acute coronary syndromes [122]. A follow-up study also confirmed that CXCL16 is still useful for predicting atherosclerosis and subsequent cardiovascular events, either in plaque stability or in acute coronary syndromes, after excluding other contributing factors [123].

C-X-C motif chemokine ligand 12 (CXCL12)

The production of CXCL12, also known as stromal cell-derived factor 1 (SDF-1), is triggered by the endothelial cell-derived apoptotic vesicles via micro-126 during lesions [124]. Its ligands, including CXCR4 and CXCR7, and CXCL12, play different roles when bound to other ligands. CXCR7 acts as a negative regulator of CXCL12, internalizing CXCL12 and transmitting it to lysosomes for degradation, thereby regulating CXCL12/CXCR4 signaling. Besides, CXCR7 (also known as ACKR3) is involved in monocyte adhesion and survival [125]. Regardless of the receptor it binds, CXCL12 promotes macrophage differentiation, facilitating platelet phagocytosis, thereby causing foam cell formation [126].

In Apoe$^{-/-}$ mice, CXCL12 promotes lesion stabilization without affecting vessel diameter via smooth muscle cell mobilization, increased collagen content, and fibrous cap thickening [127], beneficial in advanced atherosclerosis.

CXCL12 antagonist LIT-927 in immunodeficient mice prone to lupus regulates the correction of immune changes, attenuates lymphocyte activity, and hence regulates inflammation. Its effect is better than that of CXCR4/CXCR7 antagonist AMD3100 [128]. This also suggests that controlling disease progression by antagonizing chemokines in the early stages of atherosclerosis yields a proactive preventive effect.

Anti-inflammatory cytokines in atherosclerosis

In addition to the pro-inflammatory cytokines mentioned above, anti-inflammatory cytokines should not be disregarded. IL-10 and transforming growth factor β (TGF-β) are the most representative anti-inflammatory cytokines. IL-10 was mainly produced by macrophages in plaque. The atheroprotective role of IL-10 was exemplified by lowering the expression of MMP and some pro-inflammatory cytokines (e.g. IL-1β, TNF-α, IL-8), promoting macrophages polarization towards the M2 phenotype and fur-

ther inhibited the progress of atherosclerosis [134]. Recent studies showed that using exosome-mediated IL-10 mRNA can effectively control atherosclerosis in Apoe$^{-/-}$ mice [135]. For rheumatoid arthritis treatments, antibody fragment F8-mediated IL-10 has been studied in clinical trials (NCT02076659, NCT02270632), which taking hope to IL-10 therapy in atherosclerosis. TGF-β was expressed in various cells such as leukocytes, macrophages, and VSMCs. It showed anti-inflammatory properties by inhibiting inflammatory cytokines including TNF-α, IL-1β, etc, subsequently suppressed the adhesion and activation of inflammatory cells [136]. Several experiments conducted in mice confirmed the effects on regulating TGF-β [137-139]. Notably, regulatory T cells (Tregs) were the common source of both IL-10 and TGF-β. Clinical data also indicated the relevance between Treg level and coronary artery disease (CAD) [140]. Thus, targeting Tregs may also be potential access, such as activating protective immunity of Tregs by administering antigens [141]. Patients who had influenza vaccination injection after myocardial infarction with a lower risk of all cause death and cardiovascular death [142], which added evidence to this possible treatment.

It has been noted that IL-2 was not normally regarded as an anti-inflammatory cytokine. However, it had a positive function in atheroprotection. Mice experiments showed that IL-2 could alleviate atherosclerosis by promoting Treg expansion [143, 144].

Aside from targeting pro-inflammatory cytokines, we needed to pay attention to anti-inflammatory cytokines and their potential avenues including increasing the level of anti-inflammatory cytokines or strengthening the cells which produce them. These studies and clinical trials of anti-inflammatory cytokines were relatively rare, probably due to the limited effects of enhancing anti-inflammatory function. Future treatment of atherosclerosis using potent anti-inflammatory agents or in combination with anti-inflammatory agents with pro-inflammatory cytokines inhibitors might be feasible.

Conclusion

Chemotaxis and activation of immune cells by cytokines are crucial mechanisms for the pathogenesis of atherosclerosis. Thus, investigating the role of cytokines is critical to unraveling the pathogenic mechanism of atherosclerosis and possible therapeutic interventions. The progression of atherosclerotic lesions can be effectively combatted by pinpointing key targets and making a global observation, as well as regulating the dynamic changes at the lesion site or even the inflammatory state of the whole organism. At present, research on the treatment of atherosclerosis by targeting cytokines is still ongoing, and some clinical effects are still uncertain. Combination of drug regimens have been proposed to address this, i.e., different cytokine inhibitors are combined to inhibit multiple inflammatory pathways; besides, cytokine inhibitors combined with lipid-lowering drugs are utilized to act on both cholesterol and inflammatory pathways. For instance, PCSK9 inhibitors (targeted cholesterol-lowering) alone can be used to treat atherosclerosis [145]. However, this also increases the risk of inflammation [146]. PCSK9 and cytokine antibodies might yield a 1+1>2 effect. Importantly, understanding the underlying mechanisms of the above cytokines can disclose the nature of the cytokine action network. To further combat atherosclerosis progression, critical nodes in the cytokine network can be targeted to limit immune cell chemotaxis, regulate immune cell activation, block signaling pathways including NF-*κB* and reduce the secretion of pro-inflammatory cytokines. This will facilitate efficient management of pathogenesis and mitigates or even prevents its development. Specifically, research should concentrate on multidirectional interactions and crosstalk of different cytokines and their receptors, their effects on normal tissues, and distinct or even opposite effects of a specific cytokine at each lesion stage so as to identify novel targets for therapeutic interventions.

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Disclosure of conflict of interest

None.

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