Heliyon 9 (2023) e22005

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Exploring the mechanism of atherosclerosis and the intervention of traditional Chinese medicine combined with mesenchymal stem cells based on inflammatory targets

Shibiao Sun [a], Feixiang Liu [b], Feiyan Fan [a], Na Chen [a], Xiaolong Pan [a], Zhihui Wei [a], Yunke Zhang [a,b,*]

[a] Henan University of Chinese Medicine, Zhengzhou 450000, China
[b] The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, China

ARTICLE INFO

Keywords:
Immunity
Inflammation
Atherosclerosis
Traditional Chinese medicine
Mesenchymal stem cells

ABSTRACT

Atherosclerosis (AS) is a chronic inflammatory vascular disease, which is the common pathological basis of cardiovascular and cerebrovascular diseases. The immune inflammatory response throughout the course of AS has been evidenced by studies, in which a large number of immune cells and inflammatory factors play a crucial role in the pathogenesis of AS. The inflammation related to AS is mainly mediated by inflammatory cytokines (IL-1β, IL-6, IL-18, TNF-α, hs-CRP, SAA), inflammatory enzymes (Lp-PLA2, sPLA2-IIA, MMPs), and inflammatory signaling pathways (P38 MAPK signaling pathway, NF-κB signaling pathway, TLR2/4 signaling pathway). It is involved in the pathophysiological process of AS, and the degree of inflammation measured by it can be used to evaluate the risk of progression of AS plaque instability. In recent years, traditional Chinese medicine (TCM) has shown the advantage of minimal side effects in immune regulation and has made some progress in the prevention and treatment of AS. Mesenchymal stem cells (MSCs), as self-renewal, highly differentiated, and pluripotent stem cells with anti-inflammatory properties and immune regulation, have been widely used for AS treatment. They also play an important inflammation-immune regulatory function in AS. Notably, in terms of regulating immune cells and inflammatory factors, compared with TCM and its compound, the combination therapy has obvious anti-inflammatory advantages over the use of MSCs alone. It is an important means to further improve the efficacy of AS and provides a new way for the prevention and treatment of AS.

1. Introduction

Atherosclerosis (AS) is a chronic progressive disease with an extremely long incubation period and is the most common potential lesion of cerebrovascular disease, coronary artery disease, and peripheral artery disease, thus becoming a major global disease burden [1]. At present, the pathogenesis of AS mainly involves endothelial injury, immune inflammation, lipid infiltration, and other theories

* Corresponding author. Engaged in the research of prevention and treatment of cerebrovascular diseases with traditional Chinese medicine, 19 Renmin Road, Jinshui District, Zhengzhou City, Henan Province, China.

E-mail addresses: 2322456051@qq.com (S. Sun), spiritofwestlfx@126.com (F. Liu), 1065843457@qq.com (F. Fan), 13837195874@163.com (N. Chen), 2909630489@qq.com (X. Pan), 1306784953@qq.com (Z. Wei), henanzyk@126.com (Y. Zhang).

https://doi.org/10.1016/j.heliyon.2023.e22005
Received 2 March 2023; Received in revised form 1 November 2023; Accepted 1 November 2023
Available online 9 November 2023

[2], among which the immune inflammation theory plays an important role in all stages of its occurrence and development, plaque rupture, and thrombosis [3]. Long-term clinical observation has found that the biological manifestations of AS are observed earlier than imaging. Therefore, inflammatory markers can be used as prominent indicators for predicting and evaluating the degree of inflammation or the risk of plaque progression in AS. The biological response of chronic inflammation starting from vascular endothelial dysfunction mainly causes the occurrence and development of AS [4], and a recent anti-inflammatory thrombosis outcome study on canakinumab (IL-1β monoclonal antibody, CANTOS) has confirmed the effectiveness of anti-inflammatory therapy for AS treatment [5]. Therefore, in addition to existing lipid-lowering therapies, targeting immune inflammatory pathways is a novel approach to prevent and treat AS [6].

Mesenchymal stem cells (MSCs), which are multipotent stem cells with anti-inflammatory and immunosuppressive properties, can be isolated from various tissues such as bone marrow, peripheral blood, fat, placenta, and other tissues, and play an important inflammation-immune regulatory function in the field of cardiovascular and cerebrovascular, especially in the process of AS [7]. Traditional Chinese medicine (TCM) can affect the occurrence and development of AS through multiple ways and targets and has been effective in the prevention and treatment of AS. TCM has the advantage of minimal side effects in immune regulation, which can promote the proliferation, differentiation, and other physiological activities of various stem cells in vivo and in vitro, regulate the homing and colonization of MSCs, and improve the survival rate of MSCs after transplantation [8,9]. Therefore, the incorporation of the unique advantages of TCM in MSC treatment will further improve the efficacy of AS. As a result, based on the theory of immune inflammation, the role of relevant inflammatory targets in the pathogenesis of AS was expounded, while the anti-inflammatory mechanism of the combination of TCM with MSCs in the treatment of atherosclerotic diseases (e.g., major atherosclerotic cerebral infarction and coronary atherosclerotic heart disease) was discussed through the regulation of immune cells and inflammatory factors. This paper aims to further study and summarize the existing research results in order to provide reference for future clinical and experimental research.

2. Immune inflammation theory

Immune response is a defense response that maintains the stability of the internal environment, including innate and adaptive immunity, while inflammatory response is an important part of biology, which has defects in function and regulation in addition to structural defects [10]. The theory of immune inflammation was first proposed by Professor Virchow in 1856, and Professor Peter Libby finally introduced this theory into the pathogenesis of AS through a large number of experimental studies and summaries. The cells involved in the formation of AS mainly include monocytes (MCs), macrophages (Mφs), smooth muscle cells (SMCs), endothelial cells (ECs), lymphocytes (LYs), and dendritic cells (DCs). Amid the development of AS, the innate immune response begins with the deposition of low-density lipoprotein (LDL) in the arterial wall through the binding of apolipoprotein B and proteoglycan to penetrate the endothelial barrier and deposit in the extracellular matrix of the subendothelial space, causing ECs damage and dysfunction, and MC migration, adhesion, and infiltration to ECs damage. After subendothelial LDL is oxidized by vascular cells, ECs and vascular SMCs can be stimulated to produce monocyte chemoattractant protein-1 (MCP-1) and macrophage colony stimulating factor (M-CSF). Under

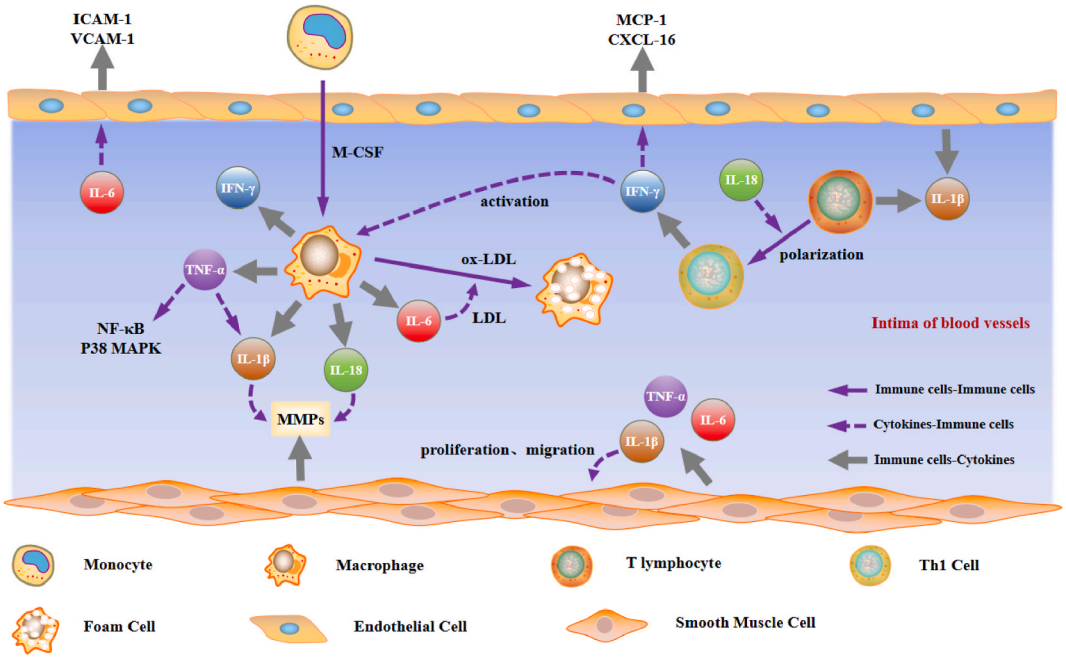

Fig. 1. Immune-inflammatory microenvironment in atherosclerosis.

the induction of M-CSF, MCs are transformed into Mφs and activated to release many inflammatory factors [11]. (Fig. 1). At the same time, Mφ can phagocytose oxidized low-density lipoprotein (ox-LDL) to form foam cells, and the accumulation of foam cells forms lipid streaks and plaques, leading to the formation of atherosclerotic plaques. Subsequently, when DC presents a series of potential antigens to LY, adaptive immune response rapidly occurs rapidly, which further aggravate local inflammation and plaque formation. In addition, SMC in the middle layer proliferates and migrates to the intima, thus promoting monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), matrix metalloproteinase (MMP), and other pro-inflammatory factors were significantly increased. Moreover, Mφs recruitment and the uptake of lipids lead to plaque progression and rupture [12].

Mφs can be differentiated into two major functional phenotypes, M1 and M2, depending on the influence of the local microenvironment of blood vessels. M1 polarization produces tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and other pro-inflammatory factors, which further aggravates the occurrence and development of AS. However, M2 polarization leads to the secretion of anti-inflammatory factors such as IL-10 and transforming growth factor-β (TGF-β), which have a protective effect on AS [13].

3. Inflammatory markers in the pathogenesis and clinical diagnosis of AS

Inflammation mainly causes the pathogenesis of AS. Therefore, the degree of inflammation measured by inflammatory markers can evaluate the risk of progression of AS plaque instability. AS-related inflammation is mainly mediated by inflammatory cytokines, enzymes, and signaling pathways and participates in the pathological process of AS.

3.1. IL-1β、IL-6 and IL-18

IL-1β has a high biological activity in the IL-1 family and is mainly produced by MC, Mφ, and DC [14]. The inflammatory characteristics of IL-1 family are dominated by innate immunity, but Il-1β and IL-6 can play a role in adaptive immunity [15]. IL-1β is dependent on the activation of NLRP3 inflammasome and requires processing to exert its biological effects, while local stimulation in plaques is conducive to the production of active IL-1β through the molecular assembly of NLRP3 [16,17]. In addition, IL-1β can be induced by TNF-α and then stimulate the secretion of varied cytokines and adhesion molecules through local paracrine and autocrine signaling, resulting in immune cell extravasation and persistent local inflammation [18]. Also, the proliferation and migration of vascular SMCs can be promoted and MMP can be induced to accelerate the degradation of the fibrous skeleton of AS plaques [19]. Studies have shown that the activation of IL-1β can increase the expression of its downstream factor IL-6, which in turn increases the production of CRP in the liver to promote the recruitment of white blood cells, leading to endothelial dysfunction and systemically inducing the inflammatory cascade [20,21]. However, IL-6 can make SMC in the media migrate to the subintima, proliferate, and carry out phenotypic transformation. It can also promote MC aggregation and infiltration, and the local expression of IL-6 increases in unstable plaques [22]. In the CANTOS study, the effect of canakinumab was significantly associated with a reduction in IL-6 levels [23], indicating a synergistic effect of IL-1β and IL-6, and its predicting AS function was also observed in another study [24]. IL-18 is a noticeable factor in the inflammatory network, which functions synergistically with many cytokines involved in the development of AS, such as IL-6, IL-12, and IFN-γ [25] and amplifies the inflammatory response in lesions. Several studies have shown that serum IL-18 level was elevated in patients with coronary artery diseases, while IL-18 and its receptors were overexpressed in different immune cells in AS plaques, such as Mφs, T cells, ECs, and SMCs [26], indicating a correlation between IL-18 and AS lesions. Moreover, IL-18 has also been found to be associated with the risk of substantial residual inflammation in canakinumab-treated patients [27]. Therefore, IL-1β, IL-6 and IL-18 can be used as potential markers for predicting the risk of AS and plaque instability.

3.2. TNF-α

TNF-α is an inflammatory and immunomodulatory factor that is mainly secreted by MC/Mφ. Clinical studies have found that TNF-α can recruit T cells and Mφ to the lesions of AS but not in normal tissues, thus direct confirming that TNF-α participates in the inflammatory response of AS [28]. Dudeck [29] has shown that TNF-α can increase the expression levels of the key genes involved in inflammation and cell proliferation by activating NF-κB, P38 MAPK, JAK, and other signaling pathways, leading to disease progression. In addition, TNF-α leads to increased leukocyte infiltration into blood vessels, which is also a key step in plaque formation. In TNF-α ApoE double knockout mice, the AS lesion area is reduced by more than 50 %, and plaque necrosis and apoptosis are increased, which have been evidenced by a study [30]. Also, a study has confirmed that TNF-α levels are significantly associated with early carotid AS [31]. In conclusion, TNF-α can activate multiple pathways and recruit various immune cells with multidirectional proinflammatory effects, is a potent modulator of inflammation in AS, and can be used as an effective clinical marker of early AS.

3.3. Hypersensitive C-reactive protein and serum amyloid A

Hypersensitive C-reactive protein (hs-CRP) and serum amyloid A (SAA) are both acute phase response proteins that are synthesized by the liver under the stimulation of pro-inflammatory factors. Both SAA and hs-CRP levels can be detected in AS lesions, and the association of SAA is higher than that of hs-CRP [32]. The short-term continuous increase and maintenance of high levels of hs-CRP can predict the presence of carotid plaque and the instability of plaque on MR imaging (low signal in T1-weighted image), and high levels of hs-CRP are significantly correlated with more new brain lesions detected by MR diffusion-weighted imaging during carotid artery

stenting [33]. SAA can also stimulate the secretion of MMPs, thereby accelerating the degradation of matrix and matrix proteins [32]. Comprehensive analysis of relevant studies showed that hs-CRP and SAA, as sensitive inflammatory markers, can effectively evaluate AS and predict plaque rupture and potential cardiovascular and cerebrovascular diseases.

3.4. Lipoprotein-associated phospholipase A2 and secretory phospholipase A2 of group IIA

Lipoprotein-associated phospholipase A2 (Lp-PLA2), which mainly circulates a complex of LDL and HDL in the blood AS, can hydrolyze oxidized phospholipids in ox-LDL to produce pro-inflammatory lipids, and then produce various AS-causing effects. It also promotes the production of related cytokines [34–36]. However, Lp-PLA2 expression was upregulated in AS plaques, and its expression was enhanced in the Mφ of fibrous caps of vulnerable plaques [37]. Secretory phospholipase A2 of group IIA (sPLA2-IIA), an inflammatory protein, is activated through the PI3K/Akt pathway to increase ox-LDL-induced MCP-1 expression. It can also selectively activate the proinflammatory function in human aortic SMC, thereby exerting its AS effect [38–40]. In summary, PLA2 family members modify phospholipids to produce pro-inflammatory lipids that cause AS, and Lp-PLA2 and sPLA2-IIA are novel inflammatory markers for predicting and evaluating plaque instability in AS.

3.5. MMPs

MMPs are a superfamily of proteases secreted by Mφs, ECs, and LYs, which are responsible for tissue remodeling and extracellular matrix protein degradation and are involved in different stages of plaque progression in AS [41]. However, inflammatory cytokines are involved in ROS production and affect the expression and activity of MMPs. Tan C et al. [42] examined the association of MMP-9 and MCP-1 concentrations with the severity of carotid AS, as measured by carotid plaque and intima-media thickness (IMT), and found that an elevated serum MMP-9 concentration was independently associated with high total carotid plaque score, plaque instability, and increased IMT value. Nevertheless, MCP-1 concentration was independently associated with IMT rather than plaque morphology. Analysis of the corresponding changes in the APOE-deficient mouse model indicated that the increased expression of MMP-13 was due to the activation of the P38 mitogen-activated protein kinase (P38 MAPK) signaling pathway [43]. Increased MMP-7 activity may be associated with VSMC apoptosis and plaque instability within the fibrous cap [44]. Seifert et al. [45] confirmed that MMP-2 and MMP-9 activities were significantly higher in ApoE−/− models with unstable AS plaques compared to more stable plaque phenotypes downstream. In addition, MMPs, which were enhanced by the expression of MMP-9 under the stimulation of TNF-α, can promote VSMC proliferation and migration [46]. In the late stage of AS, MMPs can be regulated by TLR4/NF-κB and RAGE/NF-κB signaling, and the upregulation of MMPs mediated by NLRP3 inflammasomes is prone to plaque rupture [47,48]. In summary, MMPs play a key role in all stages of AS through vascular inflammation, VSMC migration, and plaque activation and rupture.

3.6. P38 MAPK signaling pathway

P38 mitogen activated protein kinase (P38 MAPK) is a member of the MAPK family, which includes extracellular signal-regulated kinases (ERKs) and c-Jun N-terminal kinases (JNKs). The p38 MAPK signaling pathway can be activated in response to various intracellular and extracellular stimuli, including oxidative stress, cytokines, and growth factors, which are abundant in AS lesions, while p38 MAPKs can be activated by ox-LDL stimulation in Mφ [49,50]. MAPK phosphorylation in the blood can yield abundant ROS, promote the MAPK signaling pathway to induce the accumulation of MCs in the arterial wall, and reduce the secretion of collagen and other matrixes by vascular SMCs, finally triggering cytotoxicity [51] and causing foam cell necrosis in vascular plaques and AS plaque fragmentation. Activation of MAPK is driven by inflammation, and stimulation of intermittent hypoxia/reoxygenation (IHR) can activate the MAPK pathway in ECs and induce the expression of proinflammatory cytokines, such as TNF-α, IL-1, and IL-6 [52]. Therefore, p38 MAPK may facilitate the progression of AS by promoting oxidative stress and chronic inflammation. Furthermore, interventions in MAPK signaling can also modulate the degree of intimal proliferation, platelet activation, and apoptosis [53], all of which are key influencing factors in AS formation.

3.7. NF-κB signaling pathway

Nuclear factor-kappa B (NF-κB) is a critical nuclear transcription factor in the Rel family, including Rel (p65), NF-κB1 (p50), NF-κB2 (p52), RelB, and c-Rel. The activation of the IκB kinase (IKK) complex can initiate the NF-κB signaling pathway [54,55]. The NF-κB-mediated signaling pathway can not only accelerate the growth of lipid plaques and promote the inflammatory response by regulating the expression of proinflammatory factors, such as IL-1β, TNF-α, and INF-γ [56] but also regulate the invasion and colonization of inflammatory cells in the vascular wall, change the composition of the extracellular matrix, and promote the migration of SMCs [57]. Thus, it participates in the occurrence and development of AS. Endothelial dysfunction AS the initial event in the development of AS is induced by the production of NF-κB and downstream inflammatory mediators, and NF-κB-induced NLRP3 inflammasome contributes to the development of AS. Induced chemokines attract LY and trigger endothelial inflammation. It can also promote the recruitment and differentiation of MC by increasing the levels of adhesion factors and M-CSF in EC [58]. In conclusion, the activation of the NF-κB pathway can significantly increase the levels of its downstream proinflammatory factors and also increase the expression of its chemokines and adhesion factors, which directly leads to inflammatory and proapoptotic responses in vascular endothelial cells, and thereby motivate the progression of AS [59,60].

3.8. Toll-like receptor 2/4 signaling pathway

Toll-like receptors (TLR) are transmembrane proteins that are widely expressed in immune and vascular cells [61]. The signaling pathways mediated by TLR are mainly divided into myd88-and TRIF-dependent pathway. MyD88 can mediate the signaling of all TLR and IL-1 receptor family members, except TLR3, and activate the NF-κB and MAPK signaling pathways and the expression of inflammatory cytokines [62]. TLR2 induced VSMC migration in an IL-6-dependent manner. TLR2 also interacted with Nox 1 to induce ROS production, pro-inflammatory cytokine production, and MMP-2 secretion. TLR4 expression is necessary for Mφ to differentiate into foam cells, which can activate the MyD88/NF-κB signaling pathway, and ox-LDL can increase TLR4 expression without affecting TLR2 expression [63]. Lipopolysaccharide (LPS) can upregulate the expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) through the TLR1 signaling pathway, which promotes Mφs to phagocytose oxidized lipids and converts them into foam cells, aggregating and increasing the plaque area [64]. In addition, ox-LDL can upregulate MMP-9 through the TLR9 signaling pathway, which promotes Mφs to express a series of inflammatory factors and accelerates plaque rupture [65]. Therefore, TLR2 and TLR4 are highly expressed in AS plaques of patients and play an important role in the initiation and progression of AS [66].

4. Study on the mechanism of Chinese medicine combined with MSCs in the treatment of as

AS is an inflammatory disease mediated by innate and adaptive immunity under pathological conditions, and it mainly causes ischemic stroke or myocardial infarction. Therefore, many anti-inflammatory strategies have become potential treatments for AS. The combination of TCM with MSCs has broad prospects and great potential in atherosclerotic diseases by targeting immune inflammatory pathways.

4.1. TCM combined with MSCs can regulate immune cells and inhibit inflammatory response

MC/Mφ is the main driver of the pathogenesis of AS and the main source of inflammatory cytokines in AS plaques, leading to innate immune response. T/B lymphocytes mainly recognize the presented antigen and release antibodies, leading to the occurrence of adaptive immune response in AS.

Arctium lappa root extract can reduce the vascular endothelial MC infiltration induced by TNF-α and the expression levels of IL-1β, IL-6, TNF-α, and MCP-1 in mouse aorta, indicating that it can directly or indirectly change the expression of inflammatory factors, reduce the infiltration of white blood cells into vascular endothelium, and participate in the treatment of AS [67]. Ginsenoside Rg3 can promote the transformation of Mφ into M2 type through peroxisome proliferator-activated receptor-γ-dependent mechanism, reduce inflammatory response, reduce the burden of AS plaque, and increase the stability of plaque [68,69]. In addition, Poria cocos polysaccharides [70] and icariin [71] can also induce the differentiation of M1-type Mφ into M2 type. Quercetin can inhibit the maturation of DCS by upregulating the domain antibody and then downregulate the Src/PI3K/Akt–NF–κB inflammatory pathway, thereby reducing the expression of DC surface markers CD80, CD86, MHC-II, IL-6, and IL-12 and inhibiting the inflammatory response in AS lesions [72]. Buyang-huanwu decoction can increase the number of Treg cells in the spleen and peripheral blood of ApoE−/−AS mice, increase the proportion of Treg cells in $CD4^+$ T cells, and regulate the levels of inflammatory factors [73]. Angong Niuhuang pill can reduce the expression level of Th17 cells and transcription factor RORγt and increase the expression level of Treg cells and transcription factor FOXP3, confirming that Angong Niuhuang Pill can inhibit chronic inflammation by regulating the balance of Th17/Treg [74]. Agarwood extract (phenethyl chromonone derivative GYF-21) can inhibit the survival, activation, proliferation, and differentiation of B cells mainly by blocking the signaling pathway activated by B cell activating factor and cause the apoptosis of B2 cells and a small increase in the proportion of B1 cells [75].

MSCs are natural immune privileged cells; hence, when the immune system is overactivated, MSCs can show anti-inflammatory effects to avoid excessive self-attack [76]. MSCs can regulate the polarization of Mφ by secreting prostaglandin E2 (PGE2), thereby reducing the secretion of inflammatory factors by changing the balance of M1/M2 [77]. Human amniotic MSCs can inhibit the inflammatory stimulation of Mφ induced by oxLDL by regulating the NF-κB pathway, inhibit the proliferation of Mφ, downregulate the levels of phosphorylated p65 and IκBα, remarkably reduce the expression of TNF-α, and increase the expression of IL-10 in order to achieve the anti-inflammatory effect on mice blood vessels and reduce the formation of plaque [78]. Human umbilical cord MSCs can participate in immune regulation and exert immunosuppressive effects by inhibiting the proliferation of T cells, downregulating Th1/Th17, and upregulating Treg cells [79]. BMSCs can inhibit the expression of p50 and p65 and affect the activation of NF-κB pathway through the overexpression of miR-23b, thereby inhibiting the maturation and differentiation of DC [80]. Tonsil derived MSCs inhibit the phytohemagglutinin-induced proliferation of peripheral blood MC, while the co-culture of tonsil derived MSCs significantly reduce the production of interferon-γ and IL-4, indicating their immunomodulatory effects on T cell proliferation and Th1 and Th2 specific cytokines [81].

The effect of the combination of asarone and MSCs on immune regulation has been evaluated by some studies [82] through in vitro and in vivo experiments. These research results have confirmed that asarone with umbilical cord MSCs can inhibit the proliferation of $CD4^+$ or $CD8^+$ T lymphocytes, downregulate Th1 cytokines, upregulate Th2 cytokines, and change the Th1/Th2 balance to a Th2 anti-inflammatory direction, thus inhibiting the inflammatory response. Zhao et al. [83] observed the immunogenicity and immunomodulation function of hMSCs after differentiation into neural-like cells induced by TCM herbs. Therefore, astragalus, gastrodiae, and ginseng, as TCM herbs, were selected to induce the differentiation of hMSCs into neural-like cells in vitro, and the one-way mixed lymphocyte reaction of differentiated cells was observed. The proliferation of lymphocytes in the experimental group was significantly lower than that in the control group. However, limited studies have focused on the regulation of immune cells by TCM combined with

MSC therapy, and many studies are still needed to confirm this finding (Table 1).

In conclusion, the activation of immune cells is characterized by the adhesion and aggregation of MCs, the formation of foam cells, the differentiation of M1/M2 Mφs, the maturation of DCs, and the differentiation of lymphocytes in the pathogenesis of AS. Among them, the main biological mechanisms of TCM herbs and MSCs in the treatment of AS by immune cells are comprised of inhibiting the adhesion, aggregation, infiltration and differentiation of MCs, inhibiting the polarization of M1 Mφs or promoting M2 Mφ polarization, inhibiting the maturation and differentiation of DCs as well as the proliferation of MCs and T cells, increasing the proportion of Treg cells, regulating the balance of Th1/Th17/Treg cells, and regulating the function of B cells, all of which can slow the process of AS. The combination of TCM with MSC has an obvious inhibitory effect on immune regulation, but limited studies have focused on this method. The combination of stem cells with immune cell therapy can effectively reduce the inflammatory response of AS, but MSCs do not have complete immune privileges in the allogeneic host with normal immune function, and how to reduce the immunogenicity of MSCs in allogeneic transplantation needs to be considered. Therefore, TCM can play a better role in the treatment of stem cells combined with immune cells, and the research of stem cell immunity combined with traditional Chinese and western medicine may also be the trend of future development.

4.2. TCM combined with MSCs can regulate inflammatory factors and inhibit inflammatory response

Cytokines are protein mediators of inflammation and immunity, which can act through autocrine, paracrine, or endocrine pathways. Inflammatory signaling pathways also play an important role in the inflammatory response.

Tanshinone IIA can inhibit the NF-κB or TLR4/NF-κB pathway, downregulate the levels of adhesion molecules ICAM-1 and VCAM-1, and inhibit the migration of Mφ, thus playing an immunomodulatory and anti-inflammatory role [84,85]. Baicalin inhibits the NF-κB and p38 MAPK signaling pathways in a dose-dependent manner, thereby reducing the increase of IL-6, TNF-α, and soluble vascular endothelial cadherin (SVE-cadherin) induced by AS [86]. Berberine can regulate the NLRP3/NF-κB pathway and reduce the expression of pro-IL-1β and other inflammatory factors [87]. Matrine can inhibit the NF-κB/MAPK signaling pathway and ROS production in hASMC, reduce the expression of inflammatory TNF-α, and inhibit the agES-induced M1 polarization of macrophages by inhibiting the RAGE-induced oxidative stress-mediated TLR4/STAT1 signaling pathway [88,89]. Andrographolide can inhibit the proliferation of VEC and relieve inflammation by inhibiting PI3K/Akt pathway and reducing TNF-α induced ICAM-1 expression [90]. Qingxin-jieyu decoction can reduce the levels of serum hs-CRP, IL-6, MMP-9, sCD40L, and other inflammatory factors in patients with CHD through the NLRP3/IL-1β pathway [91].

Human induced pluripotent stem cell-derived MSCs can inhibit the inflammatory response by reducing the expression levels of TNF-α and IL-6 or by reducing the expression of Notch1 gene in plaques [92]. The transplantation of skin-derived MSCs can significantly reduce the plaque area of AS mice, and skin-derived MSCS can inhibit the expression of TNF-α and enhance the expression of IL-10 in the plaque by regulating the NF-κB pathway in vivo and in vitro [93]. Human placenta-derived MSCs attenuate the NF-κB pathway by regulating the expression of TLR4 and the phosphorylation of IκBα and p65, thereby reducing the release of inflammatory factors and reducing the level of inflammation [94].

Table 1
Related studies on the mechanism of TCM/stem cells regulating immune cells to suppress inflammatory responses.

TCM Active Ingredients/MSCs	Mechanism of Action	Targets of Action	The Literature
Arctium lappa root extract	Inhibition of MC adhesion and aggregation	MC infiltration to the vascular endothelium ↓; IL-1β ↓、IL-6 ↓、TNF-α ↓、MCP-1 ↓	[67]
Ginsenoside Rg3	Regulation of Mφ polarization	Activity of M1 ↓ , Activity of M2 ↑; Mφ of type M1 differentiated into Mφ of type M2	[68,69] [70] [71]
Poria cocos polysaccharides、icariin			
Quercetin	Inhibition of DC maturation	Domain specific antibody ↑、Src/PI3K/Akt–NF–κB ↓; CD80/86、MHC-II、IL-6、IL-12 ↓	[72]
Buyang-huanwu decoction	Regulation of Th17/Treg balance	Number of Treg ↑, proportion of Treg in $CD4^+$ T ↑	[73]
Angong Niuhuang pill		Th17 cells ↓、RORγt ↓; Treg cells ↑、FOXP3 ↑	[74]
Agarwood extracts (GYF-21)	Regulation of B cell function	B cell survival, activation, proliferation and differentiation ↓; The number of B2 cells ↓ and the proportion of B1 cells ↑	[75]
MSCs	Regulation of the M1/M2 balance	Activity of M1 ↓ , Activity of M2 ↑	[77]
hAMSCs	Inhibition of Mφ proliferation	NF-κB signaling pathway ↓ , The number of Mφ ↓; TNF-α、Phosphorylated p65 ↓、IκBα ↓ , IL-10 ↑	[78]
hUC-MSCs	Regulation of Th1/Th17/Treg balance	Proliferation of T cells、Th1、Th17 ↓; Treg cell ↑	[79]
BMSCs	Inhibition of DC maturation and differentiation	Overexpression of miR-23b、NF-κB signaling pathway ↓	[80]
T-MSCs	Inhibition of peripheral blood MC and T cell proliferation	Interferon-γ in Th1 and IL-4 in Th2 ↓	[81]
Asarone combined with hUC-MSCs	Inhibition of proliferation of $CD4^+$ or $CD8^+$ T cells	Th1 cytokines ↓, Th2 cytokines ↑	[82]
Astragalus, gastrodin, and ginseng/hMSCs	Inhibition of T cell proliferation	The number of T cell proliferation ↓	[83]

Note: ↑ indicates increase, upregulation, activation; ↓ means decrease, down regulation, inhibition.

Zhang et al. [95] found that after 4 weeks of combined treatment with isoglycyrrhiza and BMSCs, the levels of TNF-α and IL-1β were and the level of IL-10 was higher than that those of the with monotherapy with isoglycyrrhiza and BMSCs, indicating the combined treatment can significantly inhibit inflammatory response and delay nerve tissue damage compared with the two alone treatment. Jiang [96] found that Xionggui prescription combined with BMSC-derived exosomes could reduce the mRNA expression levels of TNF-α and iNOS and the surface markers of M1-type MG compared with the control group. M2-type MG decreased the mRNA expression of pro-inflammatory factors IL-1β and IL-6, increased the mRNA expression of surface markers TGF-β and Arg-1, and increased the mRNA expression of anti-inflammatory factor IL-13. Liu [97] found that after lateral ventricle injection, neural-like cells co-cultured with *Dendrobium officinale* polysaccharide (DOP) and BMSCs could further reduce the levels of TNF-α, IL-1β, and IL-6 in the brain tissue of rats with cerebral ischemia, reduce neuroinflammation, and reduce cerebellar infarction volume compared with BMSCs alone. Li et al. [98] showed that the combination of Danshen Tongluo Jiedu decoction with BMSC transplantation could significantly improve myocardial injury in AMI model rats by regulating the NF-κB pathway, reduce the levels of TNF-α and IL-6, inhibit inflammatory response, and repair ischemic myocardium. Zhang et al. [99] found that the combination of Buyang-Huanwu decoction with BMSCs can synergize with TIMP-1 to reduce the expression of serum MMP-9 and MMP-2 in MCAO rats, inhibit the degradation of extracellular matrix caused by it, repair the blood–brain barrier, inhibit the inflammatory response, and thus reduce the formation of brain edema after ischemia (Table 2).

In conclusion, both TCM and MSC transplantation can increase the expression of anti-inflammatory cytokines (e.g., IL-10 and TGF-β) through the TLR4/NF-κB, p38 MAPK/NF-κB, and NLRP3/IL-1β signaling pathways. The expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, NF-κB, and MCP-1) decreased. In terms of regulating inflammatory factors, the effect of TCM combined with MSCs transplantation is more significant than that of single treatment. However, only animal experimental studies of TCM combined with MSCs transplantation have been conducted for the treatment of AS, and clinical trials of TCM combined with MSC transplantation remain lacking. In addition, AS is a chronic condition that is secondary to *turbidness, phlegm, stasis, and toxicity* in TCM based on the therapy including the stagnation of meridians or deficiency of meridians and the uncured disease for a long time, which leads to unfavorable channels and dysfunction of viscera organs. The main functions of the aforementioned TCM treatment are invigorating qi and activating blood circulation, removing blood stasis and dredging collaterals, and clearing heat and detoxifying, which are related to the pathological changes and clinical manifestations of AS. Meanwhile, TCM functions of nourishing qi and activating blood circulation, and removing blood stasis and dredging collaterals can make the body's qi carry blood with nutrition to reach all organs and tissues, which can improve pathological conditions, such as lipid deposition. TCM functions of heat-clearing and detoxifying can remove toxic factors, improve the vascular microenvironment, and inhibit the inflammatory response. Therefore, according to the mechanism of AS, the unique advantages of TCM, and the anti-inflammatory properties of stem cells, the combination of TCM and stem cells may effectively inhibit the inflammatory response of AS.

5. Summary and prospect

The concept of inflammation, as a driver of AS, has met considerable resistance in the past. However, inflammation provides a

Table 2
Related studies on the mechanism of TCM/stem cells regulating inflammatory factors and inhibiting inflammatory responses.

TCM Active Ingredients/MSCs	Pathways of action	Targets of Action	The Literature
Tanshinone IIA	NF-κB signaling pathway、TLR4/NF-κB signaling pathway	ICAM-1 ↓、VCAM-1 ↓	[84,85]
Baicalin	NF-κB signaling pathway、p38 MAPK signaling pathway	IL-6 ↓、TNF-α ↓、SVE-cadherin ↑	[86]
Berberine	NLRP3/NF-κB signaling pathway	pro-IL-1β ↓	[87]
Matrine	NF-κB/MAPK signaling pathway、TLR4/STAT1 signaling pathway	TNF-α ↓; Polarization of M1-type Mφ	[88,89]
Andrographolide	PI3K/Akt signaling pathway	TNF-α ↓、ICAM-1 ↓	[90]
Qingxin-jieyu Decoction	NLRP3/IL-1β signaling pathway	hs-CRP ↓、IL-6 ↓、MMP-9 ↓、sCD40L ↓	[91]
iPSC-MSC	–	IL-6 ↓、TNF-α ↓; Gene expression of Notch1↓	[92]
Skin-derived MSCs	NF-κB signaling pathway	TNF-α ↓、IL-10 ↑	[93]
HPMSCs	TLR4/NF-κB signaling pathway	Phosphorylated IκBα、p65 ↓	[94]
Isoglycyrrhiza combined with BMSCs	–	IL-1β ↓、TNF-α ↓	[95]
Xionggui prescription combined with BMSCs-exos	–	Expression of TNF-α and iNOS mRNA ↓、Expression of TGF-β and Arg-1 mRNA ↑; Expression of IL-1β and IL-6 mRNA ↓、Expression of IL-13 mRNA ↑	[96]
DOP combined with BMSCs	–	TNF-α ↓、IL-1β ↓、IL-6 ↓	[97]
Danshen Tongluo Jiedu decoction combined with BMSCs	NF-κB signaling pathway	TNF-α ↓、IL-6 ↓	[98]
Buyang-Huanwu decoction combined with BMSCs	–	MMP-2 ↓、MMP-9 ↓	[99]

Note: ↑ indicates increase, upregulation, activation; ↓ means decrease, down regulation, inhibition.

means through which traditional risk factors can exert their pathogenic effects at the level of arterial wall cells. According to this review, immune inflammatory response was observed throughout the course of AS, among which proinflammatory cytokines such as IL-6, TNF-α, and hs-CRP and inflammatory enzymes such as Lp-PLA2, sPLA2-IIA, and MMPs can be used as important indicators for the diagnosis of AS and the prediction and evaluation of the risk of plaque progression. P38 MAPK, NF-κB, and TLR2/4 signaling pathways play an important role in the pathogenesis of this disease. In terms of inhibiting inflammation by regulating immune cells and inflammatory factors, the effect of TCM combined with MSCs is more significant than that of single treatment.

In recent years, an increasing number of clinical studies has made new attempts into anti-AS treatment based on anti-inflammation and immune regulation. In addition to the success of the CANTOS clinical trial to establish anti-cytokine therapy, several large-scale RCTS are in progress, including ENTRACTE, COLCOT, and CIRT, which target IL-6, TNF-α, and neutrophils with methotrexate, etanercept, and colchicine, respectively. These studies aim to develop better therapeutic drugs for immune anti-inflammatory therapy of AS. A recent trial was conducted in China to evaluate the effect of optimal medical treatment of low-dose colchicine (0.5 mg/day) on cardiovascular outcomes in stroke patients with evidence of persistent coronary inflammation (based on hs-CRP). The theory of immune inflammation has become a new breakthrough in the prevention and treatment of AS, and inflammation in AS has developed from a theory to an established reality [100]. Aspirin is a classic nonsteroidal anti-inflammatory drug that can directly inhibit the formation of proinflammatory eicosanoids (PGI2 and PGE2) in endothelial cells. In contrast, the administration of aspirin will increase proresolved LXA4 formation, when COX-2 expression is induced in cells with Il-1β, thus supporting a beneficial anti-inflammatory and proresolved function of low-dose aspirin [101]. In addition, ox-LDL has significantly to do with the occurrence, development, and eventually thrombosis of AS. Therefore, the treatment of natural antioxidants, such as glutathione, is theoretically effective; Indeed this theoretical inference is not sufficient, and more relevant evidence-based medical evidence is needed. To date, in some international multicenter large-scale studies, natural antioxidants have shown negative results, which prove that natural antioxidants cannot achieve the ideal effect. However, some synthetic antioxidants, such as probucol, have shown positive effects. A series of clinical studies with small sample sizes in China and Japan have shown that probucol has preliminary results of reversing plaque, preventing vascular events, and changing the properties of plaque to a certain extent. In addition, the peripheral nervous system establishes a polysynaptic artery–brain–nerve circuit through the interaction of adventitial immune cells with atherosclerotic plaque, which is involved in the control of cardiovascular homeostasis and AS [102]. This study confirms for the first time that AS plaque is directly regulated by the nervous system. The results provide a new idea for the formation and development of AS.

Mediators produced and released by MSCs in AS lesions contribute to the regulation of inflammation and can improve impaired endothelial function. At present, many in vitro experiments and animal studies support the application of MSCs in the treatment of AS. Long-term beneficial effects of MSCs can be achieved through the engineering of MSCs to selectively deliver immunosuppressive and anti-angiogenic agents and thus reduce the development of AS lesions. Endothelial-to-mesenchymal transition (EndMT) may be a new direct source of MSCs, that dedifferentiation into MSCs by EC occurs in AS lesions, indicating that MSCs derived from EndMT are easily obtained, and MSCs need not be injected into the recipient as with traditional treatment methods [103,104]. Moreover, this method has a high safety and no graft rejection. However, many problems still need to be solved with MSCs. Among them, the two biggest challenges are the translation of in vitro and animal studies of MSCs to patients with atherosclerotic plaques and the use of MSCs to target the specific pathways involved in the development of AS and retention of MSCs at the site of action without affecting other regions and other mechanisms. Furthermore, the formation of AS is the result of the comprehensive action of many mechanisms, especially the immune inflammation always being involved in its pathological progression. TCM possess unique advantages in the prevention and treatment of AS; however, most researches on AS models are still in their infancy, and the upstream and downstream molecules in some drug target pathways have not been specifically studied. Therefore, the action mechanism of TCM and its compounds in the treatment of AS need to be discovered and verified by more researchers in the future. Considering that AS is a multi-target chronic vascular disease driven by inflammation, its treatment will require long-term administration. Therefore, AS treatment drugs require highly safe and multi-target anti-inflammatory drugs, and TCM will be a potential source of drug research in the future. Ultimately, and TCM combined with MSCs will also be an important direction of future research.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81974564) ; the National Natural Science Foundation of China (No. 82104730) ; Zhongyuan talent plan–leading talent project for scientific and technological innovation (No. 224200510027) ; and The Traditional Chinese Medicine Scientific Research Project of "Double first-class" establishment discipline in Henan Province (HSRP-DFCTCM-2023-1-04) . All the authors declare that financial support did not influence the opinion of the article or the statistical analysis and reporting of the objective results of the study data.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article. Shibiao Sun conceived the content, drafted the manuscript, and approved the final version to be submitted. Feixiang Liu, Feiyan Fan, and Na Chen helped in writing the manuscript, revised it critically for important intellectual content, and approved the final version to be submitted. Xiaolong Pan and Zhihui Wei helped in writing the manuscript and approved the final version to be submitted. Yunke Zhang conceived the content, revised it critically for important intellectual content, and approved the final version to be submitted.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Glossary

acronym	
AS	atherosclerosis
MSCs	mesenchymal stem cells
MC	monocyte
Mφ	macrophage
SMC	smooth muscle cell
EC	endothelial cell
LY	lymphocyte
DC	dendritic cell
LDL	low-density lipoprotein
M-CSF	macrophage colony stimulating factor
ox-LDL	oxidized low density lipoprotein
MCP-1	monocyte chemoattractant protein-1
VCAM-1	vascular cell adhesion molecule-1
ICAM-1	intercellular adhesion molecule-1
MMP	matrix metalloproteinase
TNF-α	tumor necrosis factor-α
IL-1	interleukin-1
TGF-β	transforming growth factor-β
hs-CRP	hypersensitive C-reactive protein
SAA	serum amyloid A
Lp-PLA2	lipoprotein-associated phospholipase A2
sPLA2-IIA	secretory phospholipase A2 of group IIA
P38 MAPK	P38 mitogen activated protein kinase
NF-κB	nuclear factor-kappa B
TLR	Toll-like receptors
PGE2	prostaglandin E2
BMSCs	bone marrow mesenchymal stem cells
BMSCs-exos	BMSCs-derived exosomes
EndMT	endothelial-to-mesenchymal transition

References

[1] P. Libby, The changing landscape of atherosclerosis[J], Nature 592 (7855) (2021) 524–533.
[2] D.Q. Pu, Z. Liu, C. Zhou, Visual analysis of research hotspots in the pathogenesis of atherosclerosis in the past 10 years[J], World Science and Technology-Chinese Medicine Modernization 23 (7) (2021) 2276–2284.
[3] J. Pedro-Botet, E. Climent, D. Benaiges, Atherosclerosis and inflammation. New therapeutic approaches[J], Med. Clínica 155 (6) (2020) 256–262.
[4] Y. Higashi, Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease[J], 2022, Antioxidants 11 (10) (1958).
[5] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease[J], N. Engl. J. Med. 377 (12) (2017) 1119–1131.
[6] O. Soehnlein, P. Libby, Targeting inflammation in atherosclerosis - from experimental insights to the clinic[J], Nat. Rev. Drug Discov. 20 (8) (2021) 589–610.
[7] A. Mahdavi Gorabi, M. Banach, Ž. Reiner, et al., The role of mesenchymal stem cells in atherosclerosis: prospects for therapy via the modulation of inflammatory milieu[J], J. Clin. Med. 8 (9) (2019) 1413.
[8] Z.Y. Liang, C.W. Qian, T.H. Lan, et al., Regulatory T cells: a new target of Chinese medicine in treatment of atherosclerosis[J], Chin. J. Integr. Med. 27 (11) (2021) 867–873.
[9] Y.H. Zhao, Essential role of Chinese medicines in mesenchymal stem cells transplantation for treatment of ischemic stroke[J], Chin. J. Integr. Med. 25 (10) (2019) 723–727.
[10] R. Medzhitov, The spectrum of inflammatory responses[J], Science 374 (6571) (2021) 1070–1075.
[11] R.A. van Dijk, K. Rijs, A. Wezel, et al., Systematic evaluation of the cellular innate immune response during the process of human atherosclerosis[J], J. Am. Heart Assoc. 5 (6) (2016), e002860.
[12] M.T. Nguyen, S. Fernando, N. Schwarz, et al., Inflammation as a therapeutic target in atherosclerosis[J], J. Clin. Med. 8 (8) (2019) 1109.
[13] M. Mehu, C.A. Narasimhulu, D.K. Singla, Inflammatory cells in atherosclerosis[J], Antioxidants 11 (2) (2022) 233.

[14] A. Abbate, S. Toldo, C. Marchetti, et al., Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease[J], Circ. Res. 126 (9) (2020) 1260–1280.
[15] C.A. Dinarello, Overview of the IL-1 family in innate inflammation and acquired immunity[J], Immunol. Rev. 281 (1) (2018) 8–27.
[16] P. Libby, Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond[J], J. Am. Coll. Cardiol. 70 (18) (2017) 2278–2289.
[17] M. Takahashi, NLRP3 inflammasome as a key driver of vascular disease[J], Cardiovasc. Res. 118 (2) (2022) 372–385.
[18] X. Wang, G.Z. Feuerstein, J.L. Gu, et al., Interleukin-1 beta induces expression of adhesion molecules in human vascular smooth muscle cells and enhances adhesion of leukocytes to smooth muscle cells[J], Atherosclerosis 115 (1995) 89–98.
[19] J.J. Kaden, C.E. Dempfle, R. Grobholz, et al., Interleukin-1 beta promotes matrix metalloproteinase expression and cell proliferation in calcific aortic valve stenosis, Atherosclerosis 170 (2003) 205–211.
[20] P.M. Ridker, Targeting interleukin-1 and interleukin-6: the time has come to aggressively address residual inflammatory risk[J], J. Am. Coll. Cardiol. 76 (15) (2020) 1774–1776.
[21] J.R. Souza, R.T. Oliveira, M.H. Blotta, et al., Serum levels of interleukin-6 (Il-6), interleukin-18 (Il-18) and C-reactive protein (CRP) in patients with type-2 diabetes and acute coronary syndrome without ST-segment elevation[J], Arq. Bras. Cardiol. 90 (2008) 86–90.
[22] L. Hermus, J.D. Lefrandt, R.A. Tio, et al., Carotid plaque formation and serum biomarkers[J], Atherosclerosis 213 (1) (2010) 21–29.
[23] P.M. Ridker, P. Libby, J.G. MacFadyen, et al., Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)[J], Eur. Heart J. 39 (38) (2018) 3499–3507.
[24] A. Eltoft, K.A. Arntzen, T. Wilsgaard, et al., Interleukin-6 is an independent predictor of progressive atherosclerosis in the carotid artery: the Tromsø study, Atherosclerosis 271 (2018) 1–8.
[25] A. Bahrami, T. Sathyapalan, A. Sahebkar, The role of interleukin-18 in the development and progression of atherosclerosis[J], Curr. Med. Chem. 28 (9) (2021) 1757–1774.
[26] S. Blankenberg, L. Tiret, C. Bickel, et al., Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina[J], Circulation 106 (2002) 24–30.
[27] P.M. Ridker, J.G. MacFadyen, T. Thuren, et al., Residual inflammatory risk associated with interleukin-18 and interleukin-6 after successful interleukin-1β inhibition with canakinumab: further rationale for the development of targeted anti-cytokine therapies for the treatment of atherothrombosis[J], Eur. Heart J. 41 (23) (2020) 2153–2163.
[28] J. Ma, J. Luo, Y. Sun, et al., Cytokines associated with immune response in atherosclerosis[J], Am J Transl Res 14 (9) (2022) 6424–6444.
[29] J. Dudeck, J. Kotrba, R. Immler, et al., Directional mast cell degranulation of tumor necrosis factor into blood vessels primes neutrophil extravasation[J], Immunity 54 (3) (2021) 468–483.
[30] L. Brånén, L. Hovgaard, M. Nitulescu, E. Bengtsson, J. Nilsson, S. Jovinge, Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein E knockout mice[J], Arterioscler. Thromb. Vasc. Biol. 24 (2004) 2137–2142.
[31] T. Skoog, W. Dichtl, S. Boquist, et al., Plasma tumour necrosis factor-alpha and early carotid atherosclerosis in healthy middle-aged men[J], Eur. Heart J. 23 (2002) 376–383.
[32] J. Zhang, Clinical application of serum SAA combined with hypersensitive C-reactive protein in the diagnosis of atherosclerosis[J], Primary Medicine Forum 26 (1) (2022) 98–100.
[33] E. Martinez, J. Martorell, V. Riambau, Review of serum biomarkers in carotid atherosclerosis[J], J. Vasc. Surg. 71 (1) (2020) 329–341.
[34] F. Huang, K. Wang, J. Shen, Lipoprotein-associated phospholipase A2: the story continues[J], Med. Res. Rev. 40 (1) (2020) 79–134.
[35] T. Heriansyah, N. Nafisatuzzamrudah, F.N. Aini, et al., Reduction in vasa vasorum angiogenesis by lp-PLA2 selective inhibitor through the HIF-1α and VEGF expression under dyslipidemic conditions in atherosclerosis pathogenesis[J], Cardiovasc. Hematol. Agents Med. Chem. 16 (2) (2018) 114–119.
[36] C.J. English, H.L. Mayr, A.E. Lohning, et al., The association between dietary patterns and the novel inflammatory markers platelet-activating factor and lipoprotein-associated phospholipase A2: a systematic review[J], Nutr. Rev. 80 (6) (2022) 1371–1391.
[37] Z. Fras, J. Tršan, M. Banach, On the present and future role of Lp-PLA2 in atherosclerosis-related cardiovascular risk prediction and management[J], Arch. Med. Sci. 17 (4) (2020) 954–964.
[38] M.I. Khan, G. Hariprasad, Human secretary phospholipase A2 mutations and their clinical implications[J], J. Inflamm. Res. 13 (2020) 551–561.
[39] Y. Guo, B. Li, X. Xu, et al., sPLA2-IIA augments oxidized LDL-induced MCP-1 expression in vitro through activation of akt[J], Cell. Physiol. Biochem. 37 (4) (2015) 1345–1354.
[40] K. El Hadri, C. Denoyelle, L. Ravaux, et al., AMPK signaling involvement for the repression of the IL-1β-induced group IIA secretory phospholipase A2 expression in VSMCs, PLoS One 10 (7) (2015), e0132498.
[41] P.K. Shah, Biomarkers of plaque instability, Curr. Cardiol. Rep. 16 (12) (2014) 547.
[42] C. Tan, Y. Liu, W. Li, et al., Associations of matrix metalloproteinase-9 and monocyte chemoattractant protein-1 concentrations with carotid atherosclerosis, based on measurements of plaque and intima-media thickness[J], Atherosclerosis 232 (1) (2014) 199–203.
[43] H.S. Lee, J.Y. Noh, O.S. Shin, et al., Matrix metalloproteinase-13 in atherosclerotic plaque is increased by influenza A virus infection[J], J. Infect. Dis. 221 (2) (2020) 256–266.
[44] B. Levkau, R.D. Kenagy, A. Karsan, et al., Activation of metalloproteinases and their association with integrins: an auxiliary apoptotic pathway in human endothelial cells[J], Cell Death Differ. 9 (2002) 1360–1367.
[45] R. Seifert, M.T. Kuhlmann, S. Eligehausen, et al., Molecular imaging of MMP activity discriminates unstable from stable plaque phenotypes in shear-stress induced murine atherosclerosis[J], PLoS One 13 (2018), e0204305.
[46] J.W. Jeong, J.W. Kim, S.K. Ku, et al., Essential oils purified from Schisandrae semen inhibits tumor necrosis factor-alpha-induced matrix metalloproteinase-9 activation and migration of human aortic smooth muscle cells[J], BMC Complement Altern Med 15 (2015) 7.
[47] N. Wang, X. Zhang, Z. Ma, et al., Combination of tanshinone IIA and astragaloside IV attenuate atherosclerotic plaque vulnerability in ApoE(-/-) mice by activating PI3K/AKT signaling and suppressing TRL4/NF-κB signaling[J], Biomed. Pharmacother. 123 (2020), 109729.
[48] L. Park, K.G. Raman, K.J. Lee, et al., Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts, Nat Med 4 (9) (1998) 1025–1031.
[49] A. Reustle, M. Torzewski, Role of p38 MAPK in atherosclerosis and aortic valve sclerosis[J], Int. J. Mol. Sci. 19 (12) (2018) 3761.
[50] S. Wang, H. Zhou, T. Feng, et al., beta-Glucan attenuates inflammatory responses in oxidized LDL-induced THP-1 cells via the p38 MAPK pathway[J], Nutr. Metabol. Cardiovasc. Dis. 24 (3) (2014) 248–255.
[51] L. Gong, Y. Lei, Y. Liu, et al., Vaccarin prevents ox-LDL-induced HUVEC EndMT, inflammation and apoptosis by suppressing ROS/p38 MAPK signaling[J], Am J Transl Res 11 (4) (2019) 2140–2154.
[52] S. Ryan, W.T. McNicholas, C.T. Taylor, A critical role for p38 map kinase in NF-kappaB signaling during intermittent hypoxia/reoxygenation[J], Biochem. Biophys. Res. Commun. 355 (3) (2007) 728–733.
[53] B.R. Jeon, M. Irfan, S.E. Lee, et al., Rumex acetosella inhibits platelet function via impaired MAPK and phosphoinositide 3-kinase signaling[J], Chin. J. Integr. Med. 28 (9) (2022) 802–808.
[54] M.C. Mulero, T. Huxford, G. Ghosh, NF-κB, IκB, and IKK: integral components of immune system signaling[J], Adv. Exp. Med. Biol. 1172 (2019) 207–226.
[55] P. Poma, NF-κB and disease[J], Int. J. Mol. Sci. 21 (23) (2020) 9181.
[56] S. Chen, J. Ye, X. Chen, et al., Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-κB pathway dependent of HDAC3 [J], J. Neuroinflammation 15 (1) (2018) 150.
[57] Q. Zhang, J. Liu, H. Duan, et al., Activation of Nrf2/HO-1 signaling: an important molecular mechanism of herbal medicine in the treatment of atherosclerosis via the protection of vascular endothelial cells from oxidative stress[J], J. Adv. Res. 34 (2021) 43–63.
[58] W. Li, K. Jin, J. Luo, et al., NF-κB and its crosstalk with endoplasmic reticulum stress in atherosclerosis[J], Front Cardiovasc Med 9 (2022), 988266.

[59] G.K. Dimitriadis, J. Kaur, R. Adya, et al., Chemerin induces endothelial cell inflammation:activation of nuclear factor-kappa beta and monocyte-endothelial adhesion, Oncotarget 9 (24) (2018) 16678–16690.
[60] M. Liu, P. Yu, H. Jiang, et al., The essential role of pin 1 via NF-kappa B signaling in vascular inflammation and atherosclerosis in Apo E-/-mice[J], Int. J. Mol. Sci. 18 (3) (2017) 644.
[61] Y. Wang, E. Song, B. Bai, et al., Toll-like receptors mediating vascular malfunction: lessons from receptor subtypes[J], Pharmacol. Ther. 158 (2016) 91–100.
[62] Y. Zhou, P.J. Little, L. Downey, et al., The role of toll-like receptors in atherothrombotic cardiovascular disease[J], ACS Pharmacol. Transl. Sci. 3 (3) (2020) 457–471.
[63] K. Koushki, S.K. Shahbaz, K. Mashayekhi, et al., Anti-inflammatory action of statins in cardiovascular disease: the role of inflammasome and toll-like receptor pathways[J], Clin. Rev. Allergy Immunol. 60 (2) (2021) 175–199.
[64] J. Jongstra-Bilen, C.X. Zhang, T. Wisnicki, et al., Oxidized low-density lipoprotein loading of macrophages downregulates TLR-induced proinflammatory responses in a gene-specific and temporal manner through transcriptional control[J], J. Immunol. 199 (6) (2017) 2149–2157.
[65] T. Li, X. Li, X. Liu, et al., The elevated expression of TLR4 and MMP9 in human abdominal aortic aneurysm tissues and its implication[J], BMC Cardiovasc. Disord. 21 (1) (2021) 378.
[66] P. Kong, Z.Y. Cui, X.F. Huang, et al., Inflammation and atherosclerosis: signaling pathways and therapeutic intervention[J], Signal Transduct Target Ther 7 (1) (2022) 131.
[67] J. Lee, S.J. Ha, J. Park, et al., Arctium lappa root extract containing L-arginine prevents TNF-alphainduced early atherosclerosis in vitro and in vivo[J], Nutr. Res. 77 (2020) 85–96.
[68] M. Guo, J. Xiao, X. Sheng, et al., Ginsenoside Rg3 mitigates atherosclerosis progression in diabetic apoE-/- mice by skewing macrophages to the M2 phenotype [J], Front. Pharmacol. (9) (2018) 464.
[69] S. Kang, S.J. Park, A.Y. Lee, et al., Ginsenoside Rg3 promotes inflammation resolution through M2 macrophage polarization[J], J Ginseng Res 42 (1) (2018) 68–74.
[70] H.F. Liao, X.L. Deng, X. Luo, et al., Effect of carboxymethyl-pachymaran on macrophage polarization[J], Chinese Journal of Experimental Pharmaceutics 22 (13) (2016) 122–126.
[71] W.P. Zhang, C.Y. Liu, J. Zhou, Effects of icariin on lipopolysaccharide induced M1/M2 inflammatory phenotype transformation of macrophage RAW264.7 cells [J], Chin J Traditional Chinese Medicine 31 (10) (2016) 4239–4242.
[72] W. Lin, W. Wang, D. Wang, et al., Quercetin protects against atherosclerosis by inhibiting dendritic cell activation[J], Mol. Nutr. Food Res. 61 (9) (2017), 1600031.
[73] S. Chen, Y. Wang, C. Liang, et al., Buyang Huanwu Decoction ameliorates atherosclerosis by regulating TGF-β/Smad 2 pathway to promote the differentiation of regulatory T cells[J], J. Ethnopharmacol. 269 (2021), 113724.
[74] Q. Fan, Y. Liu, J. Rao, et al., Anti-atherosclerosis effect of Angong Niuhuang pill via regulating Th17/treg immune balance and inhibiting chronic inflammatory on ApoE-/- mice model of early and mid-term atherosclerosis[J], Front. Pharmacol. 10 (2020) 1584.
[75] R. Guo, J. Li, Y. Gu, et al., GYF-21, an epoxide 2-(2-phenethyl)-chromone derivative, suppresses dysfunction of B cells mainly via inhibiting BAFF activated signaling pathways[J], Int Immunopharmacol 67 (2019) 473–482.
[76] W. Jiang, J. Xu, Immune modulation by mesenchymal stem cells[J], Cell Prolif. 53 (1) (2020), e12712.
[77] A.B. Vasandan, S. Jahnavi, C. Shashank, et al., Human mesenchymal stem cells program macrophage plasticity by altering their metabolic status via a PGE2-dependent mechanism[J], Sci. Rep. 6 (2016), 38308.
[78] X. Wei, G. Sun, X. Zhao, et al., Human amnion mesenchymal stem cells attenuate atherosclerosis by modulating macrophage function to reduce immune response[J], Int. J. Mol. Med. 44 (4) (2019) 1425–1435.
[79] L. Yang, H.Z. Lin, S.Y. Qian, et al., Human umbilical cord mesenchymal stem cells inhibit T cell immunity[J], Chin J Histochemistry & Cytochemistry 31 (4) (2022) 327–332+366.
[80] J. Wu, C. Ji, F. Cao, et al., Bone marrow mesenchymal stem cells inhibit dendritic cells differentiation and maturation by microRNA-23b[J], Biosci. Rep. 37 (2) (2017), BSR20160436.
[81] A. Baci'c, D. Prgomet, S. Janjanin, Tonsil-derived mesenchymal stem cells exert immunosuppressive effects on T cells[J], Croat. Med. J. 60 (1) (2019) 12–19.
[82] H. He, T. Yang, F. Li, et al., A novel study on the immunomodulatory effect of umbilical cord derived mesenchymal stem cells pretreated with traditional Chinese medicine Asarinin[J], Int Immunopharmacol 100 (2021), 108054.
[83] H.N. Zhao, Y. Wu, Immunoregulatory effects of traditional Chinese medicine on the differentiation of mesenchymal stem cells into neural cells, Modern Medicine and Health 4 (2010) 492–494.
[84] D. Zhao, L. Tong, L. Zhang, et al., Tanshinone II A stabilizes vulnerable plaques by suppressing RAGE signaling and NF-κB activation in apolipoprotein-E-deficient mice[J], Mol. Med. Rep. 14 (6) (2016) 4983–4990.
[85] Z. Chen, X. Gao, Y. Jiao, et al., Tanshinone IIA exerts anti-inflammatory and immune-regulating effects on vulnerable atherosclerotic plaque partially via the TLR4/MyD88/NF-κB signal pathway[J], Front. Pharmacol. 10 (2019) 850.
[86] Y. Wu, F. Wang, L. Fan, et al., Baicalin alleviates atherosclerosis by relieving oxidative stress and inflammatory responses via inactivating the NF-κB and p38 MAPK signaling pathways[J], Biomed. Pharmacother. 97 (2018) 1673–1679.
[87] Y. Jiang, K. Huang, X. Lin, et al., Berberine attenuates NLRP3 inflammasome activation in macrophages to reduce the secretion of interleukin-1β[J], Ann. Clin. Lab. Sci. 47 (6) (2017) 720–728.
[88] G. Wang, C. Ji, C. Wang, et al., Matrine ameliorates the inflammatory response and lipid metabolism in vascular smooth muscle cells through the NF-κB pathway[J], Exp. Ther. Med. 22 (5) (2021) 1309.
[89] Q. Cui, H. Du, Y. Ma, et al., Matrine inhibits advanced glycation end products-induced macrophage M1 polarization by reducing DNMT3a/b-mediated DNA methylation of GPX1 promoter[J], Eur. J. Pharmacol. 926 (2022), 175039.
[90] C.Y. Lu, Y.C. Yang, C.C. Li, et al., Andrographolide inhibits TNFα-induced ICAM-1 expression via suppression of NADPH oxidase activation and induction of HO-1 and GCLM expression through the PI3K/Akt/Nrf2 and PI3K/Akt/AP-1 pathways in human endothelial cells[J], Biochem. Pharmacol. 91 (1) (2014) 40–50.
[91] X. Gao, Clinical Study of Qingxin-Jiayu Decoction in Patients with Stable Coronary Heart Disease with Enhanced Inflammatory response[D], China Academy of Chinese Medical Sciences, Beijing, 2017.
[92] H. Shi, M. Liang, W. Chen, et al., Human induced pluripotent stem cell-derived mesenchymal stem cells alleviate atherosclerosis by modulating inflammatory responses[J], Mol. Med. Rep. 17 (1) (2018) 1461–1468.
[93] Q. Li, W. Sun, X. Wang, et al., Skin-derived mesenchymal stem cells alleviate atherosclerosis via modulating macrophage function[J], Stem Cells Transl Med 4 (11) (2015) 1294–1301.
[94] Y. Liu, X. Zhang, Y. Hu, et al., Human placental mesenchymal stem cells regulate inflammation via the NF-κB signaling pathway[J], Exp. Ther. Med. 24 (5) (2022) 654.
[95] P. Zhang, B.Q. Lu, J. Yang, Protective effect of isoglycyrrhizin combined with bone marrow mesenchymal stem cells in rats with cerebral infarction[J], Chin J Immunology 36 (3) (2020) 305–310.
[96] M.M. Jiang, Effects of Xionggui Decoction and BMSCs-Exosomes on Neuroinflammation in Stroke patients[D], Tianjin University of Traditional Chinese Medicine, 2021.
[97] X. Liu, Effects of Polysaccharides from Dendrobium Officinale on Differentiation of Bone Marrow Mesenchymal Stem Cells into Neural-like Cells and Prognosis of MCAO rats[D], Anhui Medical University, Hefei, 2020.
[98] Y.J. Li, X.H. Li, M.X. Huang, et al., Effect of Jiedu Huoxue Tongluo method on NF-κB-mediated inflammatory response in rats with acute myocardial infarction induced by bone marrow stem cells transplantation[C], in: Proceedings of the Third National Forum on Febrile Disease and Advanced Training Course on the Clinical Extension and Application of Treatment Based on Differentiation of Febrile Disease, 2016, pp. 201–208.

[99] Y.K. Zhang, J.Y. Song, Z.Q. Zhang, Mechanism of Buyang Huanwu decoction combined with bone marrow mesenchymal stem cells in the treatment of middle cerebral artery occlusion and reperfusion[J], Chinese Tissue Engineering Research 19 (50) (2015) 8120–8125.
[100] P. Libby, Targeting inflammatory pathways in cardiovascular disease: the inflammasome, interleukin-1, interleukin-6 and beyond[J], Cells 10 (4) (2021) 951.
[101] K.M. Rood, N. Patel, I.M. DeVengencie, et al., Aspirin modulates production of pro-inflammatory and pro-resolving mediators in endothelial cells[J], PLoS One 18 (4) (2023), e0283163.
[102] S.K. Mohanta, L. Peng, Y. Li, et al., Neuroimune cardiovascular interfaces control atherosclerosis[J], Nature 605 (7908) (2022) 152–159.
[103] S. Man, G. Sanchez Duffhues, P. Ten Dijke, et al., The therapeutic potential of targeting the endothelial-to-mesenchymal transition[J], Angiogenesis 22 (1) (2019) 3–13.
[104] X. Zhang, Z. Ren, Z. Jiang, EndMT-derived mesenchymal stem cells: a new therapeutic target to atherosclerosis treatment[J], Mol. Cell. Biochem. (2022) 1–11.