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Review

Interaction between lipid metabolism and macrophage polarization in atherosclerosis

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SUMMARY

Atherosclerosis (AS) is a chronic inflammatory condition associated with lipid deposition. The interaction between abnormal lipid metabolism and the inflammatory response has been identified as the underlying cause of AS. Lipid metabolism disorders are considered the basis of atherosclerotic lesion formation and macrophages are involved in the entire process of AS formation. Macrophages have a high degree of plasticity, and the change of their polarization direction can determine the progress or regression of AS. The disturbances in bioactive lipid metabolism affect the polarization of different phenotypes of macrophages, thus, affecting lipid metabolism and the expression of key signal factors. Therefore, understanding the interaction between lipid metabolism and macrophages as well as their key targets is important for preventing and treating AS and developing new drugs. Recent studies have shown that traditional Chinese medicines play a positive role in the prevention and treatment of AS, providing a basis for clinical individualized treatment.

INTRODUCTION

Atherosclerosis (AS) is a disease in which lipid plaque-like deposits (atheromatous plaques or atherosclerotic plaques) form in the walls of medium or large arteries, resulting in reduced blood flow or blockage of blood outflow, and is a chronic inflammatory response lesion.[1–3] Impaired lipid metabolism is believed to be the root cause of AS. When lipid metabolism is compromised, lipids accumulate in the plasma and then accumulate in large amounts on the inner walls of the blood vessels, forming plaques. In contrast to unstable atherosclerotic plaques, stable plaques develop at a slower rate and are less likely to result in vascular embolisms. Although statins can reduce lipid levels, they do not reduce AS-associated morbidity because the "residual risk" caused by long-term inflammation has not been eliminated, suggesting that treatment of AS cannot simply regulate lipids but should be combined with anti-inflammatory effects, so there are strategies to prevent and control AS by the interaction of lipid metabolism and inflammation.[4]

In complex lesions such as AS, macrophages participate in the initiation, growth, rupture, and final healing stages of arterial plaque formation. Macrophages in plaques are highly heterogeneous and plastic, enabling them to alter their phenotype and function in response to changes in the plaque microenvironment.[5–7] The two main phenotypes associated with AS are M1 and M2. M1 macrophages are mainly involved in immune and inflammatory responses, increasing the expression of inflammatory factors and exacerbating AS progression, whereas M2 macrophages are mainly involved in the repair and regeneration processes and produce anti-inflammatory factors to delay AS progression.[8–11] The M1/M2 phenotypes of macrophages are highly correlated with the inflammatory response; thus, the inter-transformation of M1 and M2 is a potential target for clinically resolving AS. Although previous studies demonstrated the influence of lipids and macrophages on AS, the relationship between lipid metabolism and macrophages, as well as the mechanism whereby their interactions affect AS, is very complex, and the relevant comprehensive elaboration still lacks. Therefore, this study describes how the interaction between lipid metabolism and macrophages influences the occurrence, development, and outcome of AS to provide direction for in-depth studies.

According to traditional Chinese medicine, the core etiology and pathogenesis of AS is "phlegm-blood stasis mutual damage/co-existence," stimulation of blood vessels to induce toxicity, and toxic damage to the veins and channels. In a sense, the phlegm described in traditional Chinese medicine is similar to the accumulation of abnormal lipids caused by disordered lipid metabolism in Western medicine, which continuously develops into stasis deposited in the blood vessels to form plaques; this process is similar to the pathogenesis of lipid dysregulation

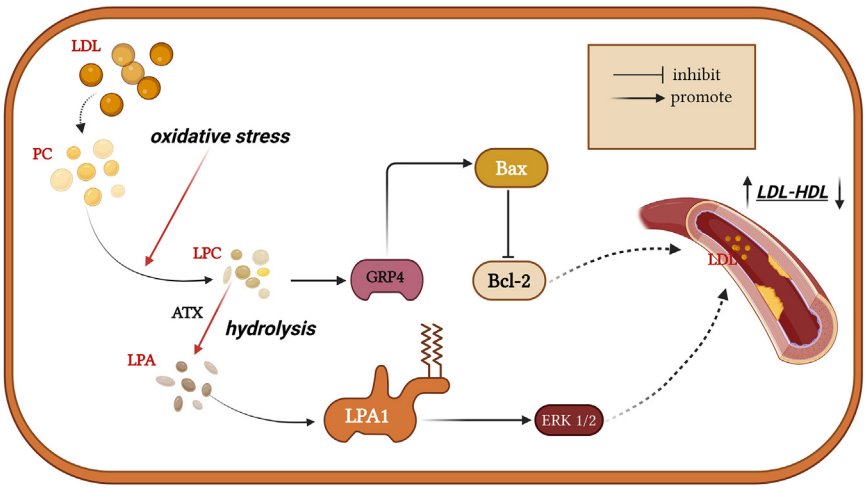

Figure 1. Low-density lipoprotein (LDL)-associated lipids promote atherosclerotic lesions

① Main constituent of LDL, phosphatidylcholine (PC), is oxidized and converted to lysophosphatidylcholine (LPC), which regulates the expression of Bax and Bcl-2 through activation of GPR4, inducing apoptosis of vascular endothelial cells, and promoting atherosclerosis; ② LPC is hydrolyzed to lysophosphatidic acid (LPA) by autotaxin (ATX). LPA activates the extracellular signal-regulated kinase ½ (ERK1/2) pathway by stimulating lysophosphatidic acid receptor 1 (LPA1), promoting the proliferation and migration of vascular smooth muscle cells, and contributing to atherosclerosis.

leading to inflammatory reactions in modern medicine.[12–14] In the process of preventing and controlling the occurrence and development of AS, we should combine the theory of formulae under the guidance of traditional Chinese medicine's diagnosis and treatment with the symptomatic treatment of pathogenesis and fully utilize the multi-target and multi-pathway characteristics of Chinese medicine.[15] Clinical studies have proven that the combination of activating blood stasis and clearing heat and detoxification preparations cannot only reduce blood lipid levels but also control inflammation and induce changes in the direction of macrophage polarization, which can effectively control the development of AS.[16] The discriminative thinking of Chinese medicine, in the modern medical environment that advocates individualized treatment, is able to combine the holistic concepts of Chinese medicine to give play to its characteristics.

LIPID METABOLISM AND AS

Lipids that promote the development of AS

Previous studies showed that the serum total cholesterol level is closely correlated with AS and can be used as a basis for risk stratification for a long time. Excessive accumulation and blocked efflux of cholesterol are important factors that promote AS; most lipids that contribute to AS are related to cholesterol.[17–19] When lipid metabolism is disrupted, the body consumes excessive amounts of lipids. The liver synthesizes high levels of very low-density lipoproteins (VLDL), which are then converted into low-density lipoproteins (LDL). LDL is a cholesterol-rich lipoprotein that carries cholesterol into cells of the peripheral tissue. An increase in the LDL concentration in the blood leads to the accumulation of excess cholesterol in the blood vessels, indicating a state of inflammation characterized by high LDL and low high-density lipoprotein (HDL) levels in the body. This condition gradually leads to the formation of atherosclerotic plaques.[20–22] The prevalent lipids that influence AS include LDL and its oxidation-related derivatives, as well as ceramide, among others.

LDL and its oxidation-associated lipids

Oxidation of LDL is a complex process. Oxidative stress in the subendothelium induces oxidative modification of LDL, which increases the affinity of LDL for macrophage scavenger receptors, such as class A (SR-A1 and SR-A2) and class B (CD36) receptors, allowing the accumulation of oxidized LDL (ox-LDL) in macrophages and triggering a pro-inflammatory macrophage response. This process is thought to be a key step in AS lesion formation and progression.[23–25] Ox-LDL is more readily taken up by macrophages via scavenger receptors, generating foam cells, in the process largely mediated by the action of oxidized phospholipids (ox-PL). This finding was validated in a transgenic mouse assay which demonstrated that ox-PL promotes inflammation and AS.[26–29] Ox-PL can also interact with specific receptors on vascular cells (CD36, TLR2, and TLR4) to upregulate the expression of pro-inflammatory factors, such as interleukin (IL)-1β, IL-6, and IL-8, thereby triggering AS pathology.[30–32] Furthermore, ox-LDL acts as an important proinflammatory factor that elicits an inflammatory response through the lysophosphatidylcholine (LPC)-autotaxin-lysophosphatidic acid (LPA) pathway.[33] In addition, other lipids involved in LDL oxidation all affect AS, under oxidative stress, phosphatidylcholine (PC) in LDL molecules is converted to LPC, which activates G protein-coupled receptor 4 (GPR4) to regulate the expression of Bax and Bcl-2. Bcl-2 is an oncogene that inhibits apoptosis, and Bax is the most important apoptotic gene in the body. Bax can form heterodimers with Bcl-2 to inhibit Bcl-2 and induce apoptosis of vascular endothelial cells. In addition, LPC can increase vascular endothelial permeability and stimulate the expression of pro-inflammatory molecules, such as adhesion molecules and cytokines, demonstrating pro-atherogenic effects.[33,34] Zhaowei Cai et al. analyzed the correlation between common lipids and atherosclerotic parameters. They found that LPC was positively correlated with serum cholesterol levels, intima-media areas, and plaque areas.[35] Autotaxin hydrolyzes LPC to LPA, which activates the G-protein-coupled lysophosphatidic acid receptor 1 (LPA1) on the membrane of the vascular smooth muscle. This activation triggers the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, promoting smooth vascular muscle cell proliferation and migration. Ultimately, AS is induced (Figure 1).[33]

Ceramides

It is worthwhile for us to explore. In addition to common lipids such as cholesterol and LDL, which promote AS, research

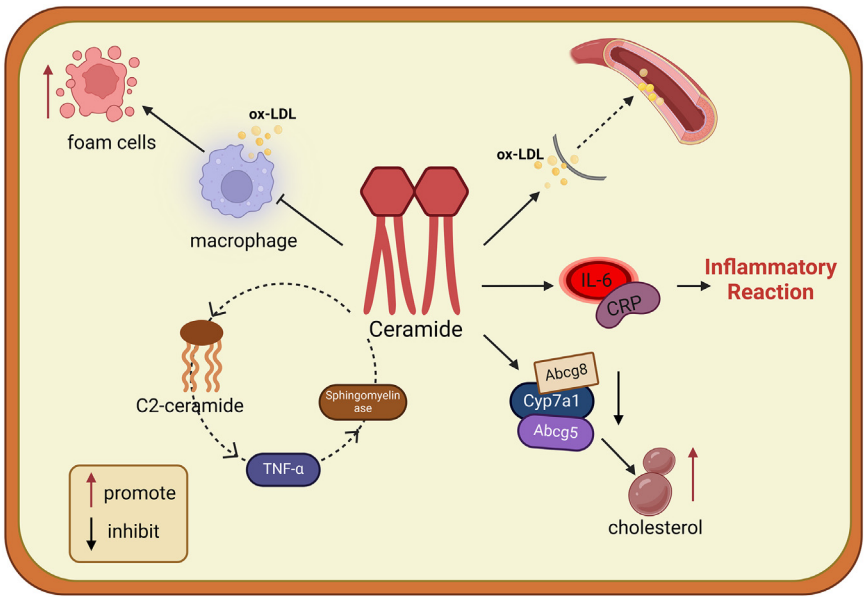

Figure 2. Pathway whereby ceramides promote atherosclerosis (AS) development

① Tumor necrosis factor (TNF)-α stimulates ceramide formation by activating neutral and acidic sphingomyelinase, and C2-ceramide, in turn, stimulates the expression of TNF-α by venous endothelial cells. TNF-α and ceramide may form a vicious cycle; ② ceramides exacerbate AS lesions by increasing cholesterol levels by downregulating the expression of the cholesterol elimination genes Cyp7a1, Abcg5, and Abcg8; ③ promoting foam cell formation by inhibiting macrophage digestion of oxidized low-density lipoprotein (ox-LDL), exacerbating AS; ④ by promoting *trans*-intimal transport of ox-LDL, ox-LDL is retained in the vascular endothelium, exacerbating AS; ⑤ by promoting the production of interleukin (IL)-6 and C-reactive protein (CRP), it exerts a pro-inflammatory effect and aggravates AS.

indicates that ceramide, a key component of sphingolipids, is regarded as a potential risk factor for cardiovascular disease and is involved in various physiological processes linked to AS.[35–40] The concentration of ceramide was notably increased in arterial plaques and showed a positive correlation with total cholesterol, triglyceride, and ox-LDL levels. This finding reveals a correlation between ceramide and AS development.[37,41,42] Ceramide exacerbates AS dyslipidemia by downregulating genes involved in cholesterol elimination, such as cholesterol 7α-hydroxylase (Cyp7a1), ATP-binding cassette subfamily G member 5 (Abcg5), and ATP-binding cassette subfamily G member 8 (Abcg8).[43] It retains ox-LDL in the vascular endothelium by facilitating its translocation across the endothelium or promotes foam cell formation by impairing macrophage-digestion of aggregated LDL.[44,45] Furthermore, tumor necrosis factor-α (TNF-α) stimulates ceramide formation by activating neutral and acidic sphingomyelinases. C2-ceramide stimulates human umbilical vein endothelial cells to express TNF-α. Ceramide and TNF-α form a vicious circle to enhance inflammation or promote production of inflammatory factors IL-6 and C-reactive protein, which in turn affects AS (Figure 2).[37,46–48]

Lipids that protect against the development of AS

HDL

Among the lipids that cause AS, LDL, as an important subject of study, is commonly referred to as the "bad lipid," whereas HDL, as the "good lipid," is on the opposite side. However, recent studies have demonstrated that viewing HDL simply as a "good lipid" is overly simplistic.

HDL has a complex composition, including proteins, lipids, and their regulatory factors and indicating that HDL affects AS through multiple pathways. HDL is considered a "lipid scavenger" because of its ability to take up excess cholesterol from the vascular wall and achieve reverse cholesterol transport. The final step of reverse cholesterol transport is selective lipid uptake of HDL-C, which is mediated by the type I class B scavenger receptor (SR-BI), which exerts a protective effect against AS.[49–52] Apolipoprotein A1 (APOA1), the most abundant apolipoprotein in HDL, helps maintain the structure of HDL and removes excess cellular cholesterol using ATP-binding cassette transporter 1 (ABCA1).[53] Additionally, APOA1 competes with LDL to bind to SR-BI, thereby limiting SR-BI-mediated LDL deposition in the subarterial lumen and delaying AS.[54] HDL participates in the reverse transportation of ox-LDL, reduces damage caused by ox-LDL, inhibits the proliferation of vascular smooth muscle cells induced by growth factors, and prevents AS.[55]

Nevertheless, despite the well-established anti-atherosclerotic properties of HDL, the additional mechanisms and impacts of its intricate constituents have not been extensively explored. In recent years, several studies have begun to revisit the structure of HDL and found that HDL is a rather complex family that undergoes constant remodeling processes in circulation. HDL has anti-inflammatory, antioxidant, anti-aggregation, and anti-clotting functions in addition to its role in reversing cholesterol.[56–59] Its complexity is also gradually revealing that HDL has not only anti-AS properties but sometimes the opposite. Early studies focused on the anti-inflammatory effects of HDL,[60–65] but in recent years, investigations shows that HDL and APOA1 also have pro-inflammatory functions. HDL exerts pro-inflammatory effects by enhancing protein kinase C activation in response to Toll-like receptor (TLR) ligands. It also activates inositol-requiring enzyme 1α (IRE1α)/apoptosis signal-regulating kinase-1 (ASK1)/p38 MAPK signaling due to excessive cellular cholesterol depletion, leading to pro-inflammatory endoplasmic reticulum stress responses to exert pro-inflammatory effects[63,66,67](Figure 3). These findings may reveal the singularity and limitations in our search for therapeutic targets for AS. Simultaneously, they may offer new ideas for exploring targets that are more appropriate and effective for preventing and treating AS.

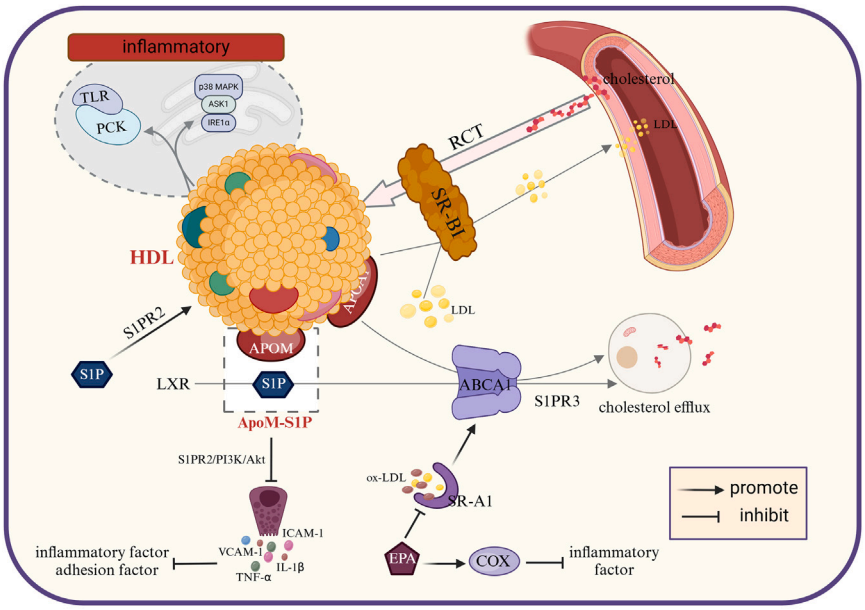

Figure 3. Role of high-density lipoprotein (HDL) and related lipids in atherosclerosis

① HDL ingests excess cholesterol from the vessel wall, enabling reverse cholesterol transport (RCT); ② APOA1, the most abundant apolipoprotein on HDL, removes excess cellular cholesterol via ATP-binding cassette transporter ABCA1; ③ APOA1 competes with LDL for SR-BI binding and limits SR-B1-mediated low-density lipoprotein (LDL) deposition in the subarterial lumen; ④ HDL responds to Toll-like receptor (TLR) ligands to enhance PCK activation exerting pro-inflammatory effects; ⑤ activation of the IRE1α/ASK1/p38 MAPK signaling pathway leads to a pro-inflammatory endoplasmic reticulum stress response, resulting in pro-inflammatory effects; ⑥ ApoM-S1P inhibits the secretion of IL-1β, TNF-α, ICAM-1, and VCAM-1from human umbilical vein endothelial cells (HUVECs) through the S1PR2/PI3K/Akt signaling pathway and downregulates the expression of inflammatory and adhesion factors; ⑦ S1P loading enhances the anti-inflammatory effect of HDL via S1PR2; ⑧ S1P regulates cholesterol outflow in a positive feedback manner dependent on S1PR3 via ABCA1 outputs; ⑨ EPA has many functions, including inhibiting the expression of inflammatory factors through cyclooxygenase (COX), decreasing the gene expression of the scavenger receptor SR-A1, reducing the phagocytosis of ox-LDL, and further increasing ABCA1 expression, thereby promoting cholesterol and phospholipid output.

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P), a lipid closely related to HDL, is produced by two isotypes of sphingosine kinase, namely SphK-1 and SphK-2. S1P functions as a signaling molecule in cell membrane signal transduction pathways. Both S1P and ceramide are called "bioactive sphingolipids," but their functions in the development of atherosclerosis are antagonistic.[68,69] S1P binds to apolipoprotein M (apoM), one of the essential components of HDL. ApoM-S1P protects endothelial cells by inhibiting ox-LDL-induced secretion of IL-1β, TNF-α, ICAM-1, and VCAM-1 from human umbilical vein endothelial cells (HUVECs) through the S1PR2/PI3K/Akt signaling pathway. This inhibition significantly downregulates the expression of inflammatory and adhesion factors.[70,71] Therapeutic S1P loading via S1PR2 enhances the anti-inflammatory effects of HDL. S1P is also previously identified as an unidentified intermediate in the liver X receptors (LXR)-stimulated ABCA1-mediated cholesterol efflux and can delay AS progression by being exported from macrophages via ABCA1 and regulating cholesterol efflux in a positive feedback manner dependent on S1PR3[72–74] (Figure 3). Furthermore, research has demonstrated that S1P possesses various roles pertinent to macrophage physiology and is capable of inhibiting the activation of inflammatory macrophages through multiple mechanisms. For example, S1P selectively weakens Toll-like receptor 2 signal transduction through negative crosstalk of S1PR1/2 and Toll-like receptor 2 signal transduction pathways in macrophages, thereby preventing inflammatory macrophage activation.[75] Mitigate inflammation through the suppression of nuclear factor kappa B (NF-kB) activity in macrophages.[76] The activation of S1P elicited a Th2 response, which resulted in a substantial decrease in macrophage populations due to the knockout of SphK1.[77] In light of the aforementioned experimental findings, it would be reasonable to investigate the relationship between S1P and diseases associated with M2 anti-inflammatory macrophages, such as AS.

Other lipids

In addition to the two lipids mentioned previously, it is more noteworthy that polyunsaturated fatty acids act together from multiple species and pathways.[78] Omega-3 polyunsaturated fatty acid (PUFA), an important group of polyunsaturated fatty acids, delays AS progression by reducing the expression of inflammatory molecules, decreasing fat synthesis, and promoting lipolysis.[79] For instance, EPA inhibits the expression of inflammatory factors by producing anti-inflammatory products via cyclooxygenase (COX) and reduces the formation of AS by decreasing the gene expression of scavenger receptors (SR-A1 and CD36), lowering the phagocytosis of ox-LDL, and further increasing the expression of ABCA1 to enhance the efflux of cholesterol and phospholipids[79–81](Figure 3). In addition, lipids, such as nitro-oleic acid (NO2-OA), oxysterols, and conjugated linoleic acid (CLA) exert anti-AS effects by reducing lipid accumulation, increasing cholesterol efflux, and decreasing pro-inflammatory factor production. These effects have been demonstrated in numerous experiments.[82–85] In a word, lipid metabolism disorder, as the basis of AS, makes lipid play a dual role in regulating AS. However, it cannot be ignored that in the case of complex lesions such as AS, macrophages participate in the whole process and also have multiple regulatory effects on the development of AS, especially the different phenotypes under the high plasticity of macrophages.

MACROPHAGE POLARIZATION

Macrophage polarization under classical pathways

Macrophages can be transformed into M1 macrophages through the JAK1/2- signal transduction and transcriptional

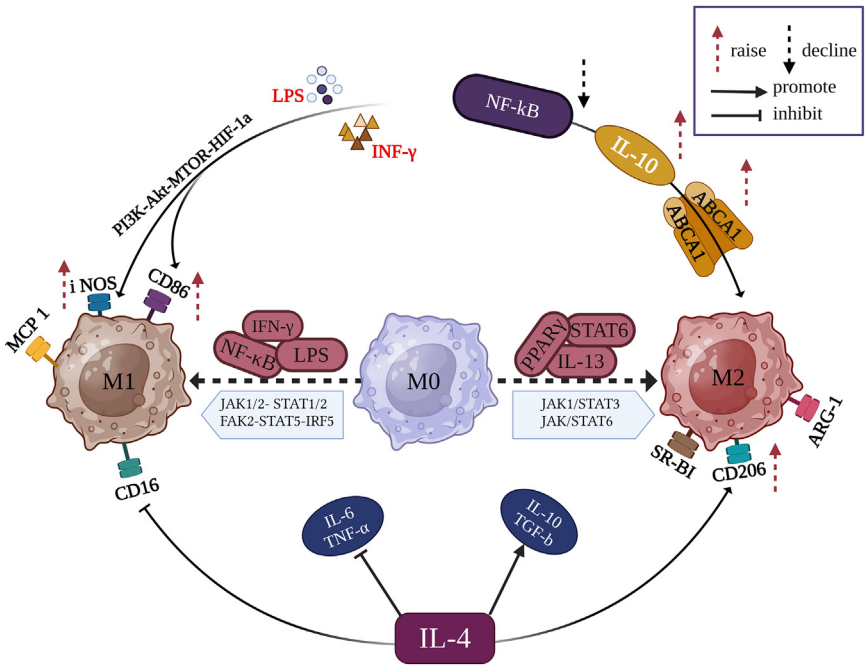

Figure 4. Summary of the polarization environment of macrophages

activator (STAT)1/2 and FAK2-STAT5-IRF5 pathways in the presence of lipopolysaccharide (LPS), IFN-γ, and NF-κB. In the presence of IL-4, PPARγ, STAT3, STAT6, interferon regulatory factor 4 (IRF4), and a hypoxic environment, macrophages transform into M2 macrophages through the JAK1/STAT3 signaling pathway and JAK/STAT6 signaling pathway.[86] Macrophages treated with LPS/IFN-γ showed elevated expression of iNOS and CD86. LPS induced macrophage polarization toward the M1 phenotype through the PI3K-Akt-MTOR-HIF-1α signaling pathway, which was further enhanced by IFN-γ. In IL-4-treated cells and mice, the expression of JAK1 and STAT6 was significantly elevated, promoting macrophage polarization toward the M2 subtype by activating Wnt-β-catenin signaling through enhanced nuclear translocation of β-catenin[87–90] (Figure 4).

Macrophage polarization under non-classical pathway

In addition to the classical pathway, macrophage phenotypes also undergo specific shifts in the context of autophagy and glycolysis. Impaired autophagy has been shown to facilitate the polarization of macrophages toward the M1 phenotype.[91] Conversely, enhancing autophagic flux in macrophages through the action of ubiquitin-specific protease 19 (USP 19) or through the administration of small molecule compounds that stimulate autophagy can drive macrophage polarization toward the M2 phenotype. In the regulation of autophagy, mTOR and NF-κB are involved. Inhibiting the mTOR pathway and stimulating macrophages to polarize toward M1. The induction of NF-κB p65 cytoplasmic ubiquitination leads to its degradation by p62-mediated autophagy. At the same time, inhibition of NF-κB activity saved by autophagy drives macrophages to shift to the M2 phenotype.[92,93] CCL2 and IL-6, which are effective factors for macrophages to induce autophagy, can also trigger the M2 phenotype.[94] In addition, the glycolytic pathway is a metabolic signaling pathway, and the lactate it produces is a key mediator of macrophage polarization. An increase in lactate levels activates hypoxia-inducible factor (HIF)-1α and HIF-2α, promoting M1 macrophages and M2 macrophages, respectively.[95] Lactate produced by endothelial cell glycolysis can also reverse M2 macrophage polarization through monocarboxylate transporter-1-dependent signal transduction.[96]

Macrophage polarization in AS

In the case of complex AS lesions, the plasticity of macrophages significantly affect AS progression.[97,98] M1-type polarization, also known as pro-inflammatory polarization, releases pro-inflammatory factors TNF-α and IL-1β. It exhibits a low cholesterol scavenging capacity, destabilizes plaques, and promotes the development of AS. In contrast, M2 polarization has an anti-inflammatory effect; these cells secret cytokines such as those found in inflammatory zone 1 (Fizz1), arginase 1 (Arg-1), and IL-10. M2 polarization also leads to low foam cell formation. These cells exhibit high phagocytic activity, an increased ability to clear apoptotic cells, and can produce anti-inflammatory factors that inhibit the development of AS.[10,99] Furthermore, IL-1β, MCP1, and iNOS can be used as M1-type cell markers, while ARG1, IL-10, IL-4, and CD206 can be used as M2-type cell markers. The levels of M1 and M2 markers reflect the transformation of M1-and M2-type macrophages, respectively. Altering the environment in which the two macrophages are located is a viable strategy for achieving from M1 to M2 polarization. This transformation from M1 to M2 in AS has gradually become a research goal that we are pursuing. Notably, macrophage plasticity is not purely M1 and M2 polarization; with advances in technology, more phenotypes of macrophages have been identified and recognized. The M2 phenotype alone can be categorized as M2a, M2b, M2c, and M2d; normally, M2 macrophages exhibit anti-inflammatory effects, yet M2b macrophages deviate from this anti-inflammatory mode as they maintain high levels of inflammatory cytokine production.[100] In addition to the M1 and M2 phenotypes, the M(Hb), Mhem, Mox, and M4 phenotypes have also been detected, and it is precisely because of the diversity of macrophage phenotypes that the complete reflection of the *in vivo* situation by the M1/M2 phenotypes has become more complex and difficult,[6] but most current studies still classify macrophages into the M1 and M2 classes to evaluate their properties and functions; therefore working on finding a complete pathway from M1 to M2 is also more conducive to realizing a true reflection of the *in vivo* situation by M1/M2.[101]

NF-κB plays a crucial role in the development of AS. Inhibiting the NF-κB regulatory pathway reduces aortic stiffness, mitigates inflammation, enhances IL-10 secretion, upregulates ABCA1 expression to facilitate cholesterol efflux from foam cells, and triggers the transformation of macrophages into the M2 type.[8] For instance, rutin and hirudin He-D inhibit macrophage migration by targeting IKα and IKγ in the NF-κB signaling pathway; n-Butyric acid (NBA) mediated by GPR43-β-receptorstatin-2 and lipoxin A4 (LXA4) inhibits IRF5 activity and promotes interferon regulatory factor 4 (IRF4) activation via FPR2-mediated inhibition. These processes downregulate p-NF-κB p65 activity, reducing M1 marker expression and increasing the mRNA levels of M2 markers, facilitating the transformation of macrophages from the M1 phenotype to the M2 phenotype, thereby improving the inflammatory response of macrophages. Consequently, NF-κB plays a role in AS.[102–105] With the current technological advancements, M1 to M2 conversion is no longer limited to drug research. New technologies and therapies have emerged that show potential for use in treating AS, including sonodynamic therapy (SDT), a treatment developed from photodynamic therapy.[106–108] Previous studies,[109] showed that SDT narrowed and stabilized advanced AS plaques by modulating M1 to M2 macrophage polarization. It enhanced anti-AS effects and had an earlier onset of action than statins, achieving M1 to M2 conversion at a technical level. In conclusion, the discovery of more target pathways for M1 to M2 conversion in AS is expected to reverse AS progression and prevent AS-related acute events.

LIPID METABOLISM AND MACROPHAGE POLARIZATION

In the complex lesions of AS, lipid-lowering through lipid metabolism alone or the anti-inflammatory actions of macrophages is effective treatment that has been extensively studied. Previously, we described inflammatory lipids such as ox-LDL and ox-PL promote the development of AS. In contrast, anti-inflammatory lipids, such as HDL, S1P, and EPA delay AS development. Additionally, distinct macrophage phenotypes are known to have differential impacts on the course of AS progression, which further complicates the understanding of this multifactorial disease. However, whether lipid metabolism and macrophages interact with each other to affect AS has not been systematically reported. Therefore, herein, we focused on their interactions and related mechanisms to explore whether lipid metabolism and macrophage interactions can serve as potentially effective targets for the clinical treatment of AS, and provide more information for new drug research and development in the treatment of AS.

Interaction between lipid metabolism and macrophage polarization

In AS lesions, macrophages are exposed to accumulated lipids and their derivatives. Lipid metabolism plays a crucial and indispensable role in modulating the function of macrophages, with particular emphasis on fatty acids. Metabolic discrepancies in fatty acid biosynthesis (FA) and fatty acid oxidation (FAO) induce distinct phenotypes of macrophages.[110] Research indicates that microRNA-33 (miR-33) facilitates the development of the inflammatory M1-like macrophage phenotype, which is linked to metabolic disorders. Conversely, the suppression of miR-33 has been shown to metabolically reprogram macrophages toward the M2 phenotype by enhancing FAO. It is posited that miR-33 plays a regulatory role in the polarization of macrophages between the M1 and M2 phenotypes by modulating the equilibrium between cellular glycolysis and FAO.[111] At the same time, as phagocytes, macrophages take up different forms of lipids, such as LDL, VLDL, and oxidized lipoproteins, from phagocytosed dying cells and the microenvironment through phagocytosis, macropinocytosis, and scavenger receptor-mediated pathways. The ingested lipids are processed by acid lipases in lysosomes, resulting in the production of free fatty acids and cholesterol. And the generation of M2 macrophages is partly dependent on fatty acid uptake and oxidation, and one of the sources of fatty acids is through lysosomal lipolysis uptake mediated by lysosomal acid lipases.[112,113] In macrophages, sterol regulatory element-binding proteins (SREBPs) and LXRs are expressed at high levels, exerting influence on the transcriptional regulation of lipid metabolism and modulating the release of cytokines. LPS treatment augments the activity of macrophage SREBP-1a via NF-κB, and macrophages with SREBP-1a deficiency are unable to generate inflammatory factors subsequent to LPS stimulation, thereby indicating that lipid metabolism in M1 macrophages is correlated with inflammasome activation.[114] In contrast, M2 macrophages are distinguished by the activation of LXR, which regulates cholesterol homeostasis and lipid synthesis. Overexpression or activation of LXRα is capable of suppressing the M1 response and inflammation through the inhibition of NF-κB activity.[115]

In general, these findings elucidate the interaction between lipid metabolism and macrophage polarization, thereby providing significant support for the research on metabolic diseases, particularly AS. Subsequently, we will discuss the relationship between specific macrophage phenotypes and lipid metabolism, as well as their influence on AS.

Lipid metabolism and macrophage polarization in AS

Lipid metabolism and M1 macrophages in AS

In the preceding text, we have discussed the impact of ox-LDL on the occurrence of AS through the accumulation of foam cells. Herein, we will first conduct a further exploration of the relationship between ox-LDL and macrophage polarization and investigate its influence on AS. Ox-LDL is capable of promoting the signal transduction of the PI3K/Akt/mTOR pathway and blocking the autophagic process of macrophages, resulting in an increase in p62 expression.[116] The accumulated p62 activates NF-κB through the phosphorylation of inhibitor of κB kinase (IKK), leading to the nuclear translocation of NF-κB, thereby facilitating the transcription of inflammatory factors and inducing M1 polarization. Additionally, ox-LDL binds to the receptor CD36, causing the uptake of long-chain fatty acids (LCFAs). In macrophages stimulated by ox-LDL, the expression of fatty acid-binding protein 4 (FABP 4) and acyl-CoA synthetase 1 (ASCL 1) is upregulated,[117,118] and after processing the LCFA, it is transported to the mitochondrial matrix through carnitine palmitoyl transferase CPTI and CPTII.[119,120] Consequently, LCFA accumulates in mitochondria, leading to the downregulation of FAO and mitochondrial oxidative phosphorylation (OXPHOS), thereby promoting

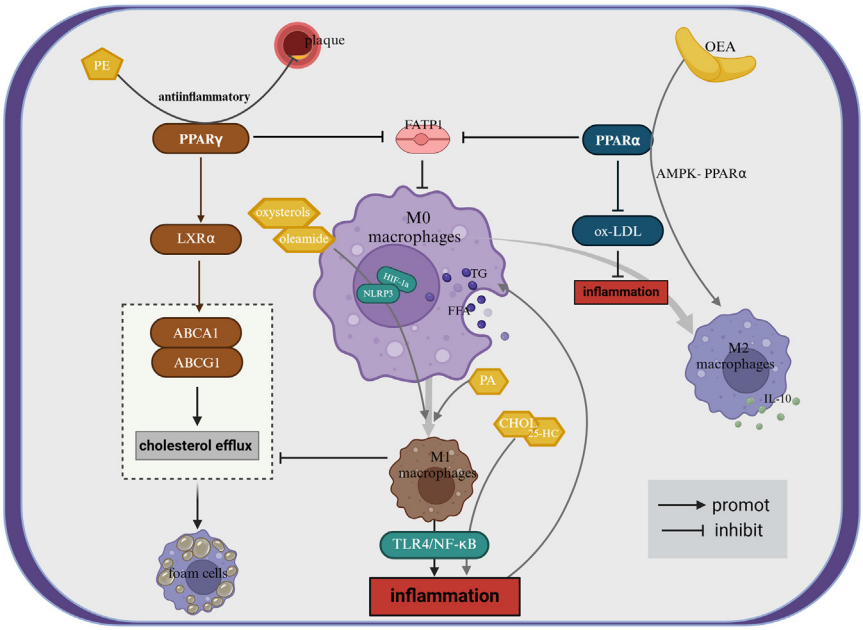

Figure 5. Mechanisms associated with "lipid-inflammatory" interactions in atherosclerosis (AS)

① Palmitic acid (PA) converts macrophages to the M1 type, which exacerbate the inflammatory response by upregulating the TLR4/NF-κB signaling pathway; ② excess free cholesterol and 25-hydroxycholesterol (25-HC) promote NF-κB-mediated inflammatory responses through the TLR4 pathway; ③ oxysterols and oleamide polarize macrophages toward the M1 type by activating HIF-1α or NLRP3 inflammatory vesicles in macrophages; ④ activation of PPARα and PPARγ attenuates free fatty acid (FFA) and TG accumulation in macrophages by inhibiting FATP1; ⑤ activation of PPARα and PPARγ attenuates FFA and TG accumulation in macrophages by inhibiting FATP1; ⑥ macrophages accelerate the conversion to foam cells by reducing the expression of ABCA1 and ABCG1 expression; ⑦ phosphatidylethanolamine (PE) improves AS plaque stability through PPARγ-mediated anti-inflammatory properties; ⑧ oleoyl ethanol amide (OEA) activates PPARα, which, inhibits ox-LDL production and reverses the inflammatory response; it promotes M2 macrophage polarization via the AMPK-PPARα pathway.

macrophage M1 polarization and exacerbating AS lesions. Furthermore, within macrophages, the TLR/NF-κB pathway is a significant player associated with inflammation, and more lipids exert the macrophage polarization effect under the classical pathway through this signaling. The saturated fatty acid palmitic acid (PA), which converts macrophages to the M1 type, induces M1 macrophages, and exacerbates the inflammatory response by upregulating the TLR4/NF-κB signaling pathway. This, in turn, promotes lipid synthesis in cells. Excess free cholesterol and 25-hydroxycholesterol (25-HC) increase susceptibility to apoptosis by activating the p38 mitogen-activated protein kinase (p38MAPK) signaling pathway or promoting NF-κB-mediated expression of pro-inflammatory genes via the Toll-like receptor 4 (TLR4) pathway. These steps enhance inflammatory responses in lipid-hyperlipidemic macrophages, thereby exacerbating AS plaque instability[121,122]; the same is true for oxidized lipoproteins and cholesterol linoleic acid (Figure 5).[123–125] It is worth noting that in the relationship between lipid metabolism and macrophage polarization, some lipids directly affect M1 polarization through inflammatory factors. For example, oxysterol and oleamide promote the production of the pro-inflammatory factor IL-1β by activating HIF-1a or NLRP3 inflammasome in macrophages, creating an environment conducive to the polarization of M1 macrophages.[126,127] Specifically, ox-PL upregulates the expression of activating transcription factor 4 (ATF4) directly through the PERK/eIF2α axis, thereby promoting M1-type macrophage.[128] In contrast, M1-type macrophages, as pro-inflammatory macrophages, release several pro-inflammatory factors, such as TNF-α, IL-1β, and IL-6, which influence lipid efflux and, thus, AS development. M1-type macrophages downregulate cholesterol efflux, develop pathological processes such as vascular endothelial cell damage, platelet aggregation, and vascular smooth muscle cell proliferation. Therefore, decreasing the expression of scavenger receptors and cholesterol efflux transporter proteins, thereby decreasing the ability to remove lipids from plaques, promoting the accumulation of lipids within the lesion, and accelerating the transformation of macrophages into foam cells; the released TNF-α also triggers the adipocyte' inflammatory response, exacerbating the release of inflammatory free fatty acids (FAA) from adipocytes, while secreting MCP-1, leading to the further infiltration of monocytes from the bloodstream.[129–132] In summary, lipids and M1 macrophages can interact through multiple pathways, exacerbating the formation of AS plaques (Table 1).

Lipid metabolism and M2 macrophages in AS

The relationship between M2 polarization and lipids in macrophages is somewhat simpler compared to that of M1 polarization. Most physiologically active lipids inhibit the production of inflammatory factors and promote the secretion of M2 macrophage markers, placing macrophages in an environment that favors M2 polarization, which in turn promotes macrophage polarization toward M2-type macrophages. Phosphatidyl serine liposome (PSL) stimulation reduces the expression of pro-inflammatory cytokines IL-1α, IL-1β, IL-12, IL-6, and TNF-α; enhances the secretion of IL-10 and TGF-β and the expression of the M2 macrophage biomarker CD206; and provides an environment conducive to the differentiation of macrophages toward M2, thus phosphatidylserine (PS) significantly enhances the M2-like polarization of macrophages via the PSRS-STAT3-JMJD3 pathway.[133] Phosphatidyl ethanolamine (PE) decreases the expression of inflammatory factors NOS, CCL2, ICAM-1, and VCAM-1; increases the aortic expression of SR-BI, a phenotypic marker of M2 macrophages; and promotes the transformation of macrophages into an anti-inflammatory M2 type. The same is true of the polyunsaturated fatty acid docosahexaenoic acid (DHA).[134] Moreover, a certain degree of M2 polarization is

Table 1. The interaction between lipid metabolism and macrophage polarization

Polarization pathway	Mode of action	Lipids	Lipid impact macrophage signaling pathways	Direction of polarization	Macrophages influence lipid metabolic pathways
Classical pathway	Indirect	Saturated fatty acid palmitic acid	/	M1	TLR4/NF-κB
		Cholesterol/25-hydroxycholestero	TLR4/p38MAPK/NF-κB	M1	Increased susceptibility to apoptosis
		Oxidized lipoproteins	TLR4/NF-κB	M1	Activate the inflammation factor
		Cholesterol linoleic acid	TLR4/NF-κB	M1	Activate the inflammation factor
		Phosphatidylserine	PSRS-STAT3-JMJD	M2	Raised cholesterol efflux gene
	Direct	Oxysterol	Activate HIF-1a/NLRP3 and promote IL-1b production	M1	Decrease the expression of scavenger receptor and cholesterol efflux transporter
		Oleamide	Activate HIF-1a/NLRP3 and promote IL-1b production	M1	Decrease the expression of scavenger receptor and cholesterol efflux transporter
		ox-PL	Upregulation of ATF4 through PERK/eIF2α axis	M1	Decrease the expression of scavenger receptor and cholesterol efflux transporter
		Phosphatidyl serine liposome	Reduce proinflammatory cytokines, enhance CD206 expression	M2	Raised cholesterol efflux gene
		Phosphatidyl ethanolamine	Reduce inflammation factor expression, increase SR - B expression	M2	Raised cholesterol efflux gene
		Polyunsaturated fatty acid docosahexaenoic acid	Anti-inflammation	M2	Raised cholesterol efflux gene
Non-classical pathway	Autophagy	ox-LDL	Block macrophage autophagy, increase P62 expression, and activate NF-κB via IKK	M1	Inflammatory cytokines produced
	Metabolic reprogramming	ox-LDL	Downregulation of FAO and OXPHOS	M1	Lipid accumulation
		Fatty acid	Biosynthesis	M1	Activate the inflammasome
		Fatty acid	Uptake and oxidation	M2	Pathways mediated by phagocytosis, macropinocytosis, and scavenger receptors

reliant on the uptake and oxidation of fatty acids, and it promotes wound-healing processes via IL-4 and IL-13 signal transduction (Table 1). Polarized M2 macrophages enhance the production of anti-inflammatory substances, have anti-inflammatory, repair, and regenerative functions, affect the accumulation and efflux of lipids, clear lipid deposits and cell debris in blood vessels, promote the repair of vascular endothelial cells and the remodeling of blood vessel walls, downregulate the expression of SR and the uptake of cholesterol genes, and upregulate the efflux genes of cholesterol through the secretion of IL-10. These processes reduce the uptake of lipids, increase the exclusion of lipids, reduce the accumulation of lipids in cells, and then delay the development of AS.[135,136] However, not all lipids are involved in M2 polarization impede AS development, as a ''bioactive sphingolipid'', S1P induces polarization of M2-type macrophages through IL-4 secretion and signal transduction, thereby upregulating cholesterol efferent genes and downregulating cholesterol uptake genes, reducing cholesterol accumulation, and inhibiting apoptosis signals, namely the activation of caspase 3 and 8, thereby enhancing the stability of AS plaques. However, by inhibiting S1P lyase, a long-term increase in endogenous S1P levels promotes AS,[135,137] contradicting the results of previous studies and may lead to an exciting new area of research. In conclusion, this review elaborates on the impact of the interaction between lipid metabolism and macrophage polarization on AS, which may offer new insights for the development of individualized clinical treatment regimens involving combined lipid-inflammation medications. Furthermore, in-depth exploration of the interaction mechanism between the two will also contribute to the discovery of new drugs and new therapeutic targets for AS treatment.

"Lipid-inflammatory" interaction mechanism between lipid metabolism and macrophage polarization

In the foregoing content, we delved into the intricate relationship between lipid metabolism and macrophage polarization within the context of AS. Our exploration revealed that the reciprocal influence between these two elements predominantly converges on the ''lipid-inflammatory'' interplay. Beyond the well-established

TLR/NF-κB canonical pathway, the peroxisome proliferator-activated receptor (PPAR) emerges as a pivotal target that demands meticulous consideration. Previous studies showed that activation of PPARα and PPARγ attenuates accumulation of total FFAs and triglycerides in macrophages by inhibiting fatty acid transporter 1 (FATP1).[138] PPARγ participates in the regulation of adipocyte differentiation and lipid metabolism, regulates the expression of cholesterol efflux genes including ABCA1 and ABCG1 by activating LXRα, inhibits cholesterol outflow by blocking the PPARγ-LXRα-ABCA1/ABCG1 pathway, thus regulating lipid accumulation in AS plaques.[139–142] Furthermore, activation of PPARγ effectively suppresses macrophage inflammation and likely facilitates the conversion of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages. In contrast, inhibition of PPARγ is associated with a decreased M1/M2 ratio of macrophages. This evidence suggests that PPARγ co-regulates AS through lipid-lowering and anti-inflammatory mechanisms.[143,144] For instance, phosphatidylethanolamine (PE), a multifunctional phospholipid rich in cells, improves the stability of AS plaques through PPARγ-mediated anti-inflammatory properties; oleoyl ethanol amide (OEA), an endogenous PPARα ligand, activates PPAR α and then inhibits the production of ox-LDL in mouse macrophages, reversing the ox-LDL-induced pathological effects in AS animals, including AS plaque formation and inflammation. Additionally, it promotes M2 macrophage polarization and inhibits M1 macrophage polarization through the AMPK-PPAR α pathway (Figure 5).[134,145–147] Overall, these lipids affect the direction of macrophage polarization through the anti-inflammatory and lipid-regulating effects of PPAR, thus affecting AS. PPAR may become a very important research target to identify the interaction between lipid metabolism and macrophage polarization and its effects on AS.

THE STRATEGY OF TRADITIONAL CHINESE MEDICINE TO PREVENT AND CONTROL AS BY REGULATING BLOOD LIPID AND ANTI-INFLAMMATION

For AS, the most widely used lipid-lowering drugs in the clinic in Western countries include niacin, phenoxy aromatic acids, and statins.[148] Statins, the most widely studied drugs, can slow AS by reducing lipid levels[149–151] but are associated with side effects such as AS muscle pain, liver injury, and increased diabetes risk.[152] Therefore, clinical research on alternative AS drugs has increased.

Traditional Chinese medicines, characterized by minimal toxic and side effects, have the unique advantage of multi-target and multi-component synergy in disease management. They align closely with the treatment strategies for AS. Chinese medicine posits that herbs that promote blood circulation, alleviate blood stasis, and eliminate heat and toxins can greatly contribute to reducing inflammation, combating fat accumulation, providing antioxidant effects, and preventing thrombosis. In addition, these herbs are believed to play crucial roles in delaying AS progression.[153] Based on the specific categorization of effects, salidroside has been shown to significantly decrease levels of cholesterol, fatty acids, and other biosynthetic products, thereby stabilizing AS by downregulating the gene expression of sterol regulatory element binding proteins (Srebf1 and Srebf2). Ethyl acetate extract of Patrinia villosa (PVJEE) has an anti-AS effect by downregulating the LPC of glycerol phospholipid metabolic pathway and inhibiting the apoptosis of vascular endothelial cells. Gypenosides promote autophagy and affect LncTUG1/miR-26a to improve lipid deposition and prevent and treat atherosclerosis.[148,154,155] Curcumin upregulates the expression of PPARγ in M1 macrophages, which in turn promotes the expression of CD36 and ABCA1. By supporting cholesterol homeostasis, curcumin exerts an anti-atherosclerotic effect.[97] Secondly, in terms of anti-inflammation, ginsenoside Rb1 demonstrates its effects by inducing the production of anti-inflammatory cytokines such as IL-4 and IL-13, as well as by suppressing the synthesis of pro-inflammatory factors. Additionally, it facilitates the polarization of M2 macrophages through various signaling pathways, including JAK-STAT, PPARS, and AMPK, thereby contributing to the attenuation of AS.[156–158] Similarly, laminaran enhance the expression of genes associated with anti-inflammatory factors while inhibiting the expression of genes linked to inflammation. Furthermore, they promote autophagic activity in macrophages and encourage the polarization of these cells toward the M2 phenotype by modulating relevant signaling pathways, thus playing a role in the prevention and progression of AS.[159] Tanshinone II A has been shown to effectively inhibit the M1 polarization of macrophages induced by ox-LDL, with the underlying mechanism potentially involving the suppression of miR-375, which activates KLF4.[160] Furthermore, convallaria toxin (CNT), a naturally occurring cardioside, has been found to reduce the secretion of inflammatory cytokines, activate the PPARγ signaling pathway, and promote the M2 phenotype of macrophages, thereby contributing to the regulation of AS.[161] In addition to the previously discussed active monomer components, it is worth mentioning the role of traditional Chinese medicine compounds. Huang-Lian-Jie-Du decoction, recognized as a representative prescription for heat-clearing and detoxification in Chinese medicine, has been shown to reduce the expression of pro-inflammatory factors associated with M1 macrophage polarization. Simultaneously, it enhances the expression of CD163 and Arg1 markers linked to M2 polarization, thereby influencing the progression of AS by modulating macrophage polarization.[162] The Shenlian formula, an empirically derived clinical formulation for the treatment of AS, is supported by multiple lines of evidence demonstrating its efficacy in alleviating AS. This is achieved through mechanisms such as promoting LAL-LXRα-mediated cholesterol ester degradation and cholesterol efflux, modulating inflammatory responses, and improving blood flow and lipid profiles.[163–166] In conclusion, the results of these experiments indicate that both the active monomer components of traditional Chinese medicine and its composite compounds play a role in the prevention and management of AS through various mechanisms related to lipid metabolism and macrophage polarization (Table 2).

CONCLUSION AND OUTLOOK

AS pathogenesis is complex and abnormal lipid metabolism and inflammatory reactions occur throughout its occurrence and development. Many lipid components in the body are important for the maintenance of physiological functions. When the

Table 2. Monomer composition and compound prescription of traditional Chinese medicine regulating the development of AS

Type of action	lipids	Signaling pathways	Role purpose	Affect the AS
Reduce lipids	Salidroside	Downregulated Srebf1 and Srebf2 expression	Decrease of lipid synthesis	Stable AS plaque
	PVJEE	Downregulate the metabolic pathway of glycerol phospholipid	Inhibition of vascular endothelial cell apoptosis	Anti-as effect
	Gypenosides	Promote autophagy and affect Inctug1/mir-26a	Improve lipid deposition	Mitigate the occurrence of AS
	Curcumin	Raised pparγ expression, and promote the CD36/ABCA1 expression	Supports cholesterol homeostasis	Stable AS plaque
	Shenlian formula	LAL-lxrα	Cholesterol efflux	Mitigate the occurrence of AS
Anti-inflammation	Ginsenoside Rb1	JAK-STAT/PPARS/AMPK	Promote the M2 macrophage polarization	Anti-AS effect
	Laminaran	Inhibit the expression of inflammation-related cytokines	Promote the M2 macrophage polarization	Anti-AS effect
	Tanshinone II A	Inhibition of mir-375 activated KLF4	Prevent polarization of M1 macrophages	Anti-AS effect
	Convallaria toxin (CNT)	Activate the pparγ signaling pathway	Promote the M2 macrophage polarization	Anti-AS effect
	Huang-Lian-Jie-Du decoction	Decreased the expression of proinflammatory factor, increased the expression of CD 163 and Arg 1	Promote M1 polarization to M2	Anti-AS effect

composition, quantity, and proportion of lipids change, their metabolic balance in the body is disrupted; the number and proportion of oleamide, ceramide, lysophosphatidylcholine, and other pro-inflammatory lipids increase; and macrophages are stimulated to M1 type transformation via a series of signaling pathways. However, although lipid-lowering drugs used to treat AS can reduce blood lipid levels, they often fail to have the expected effect on AS development and incidence of cardiovascular and cerebrovascular diseases.[167] This leads the researchers to further study and find that improving the inflammatory response can also regulate lipid levels in AS plaques.[168,169] Lipids such as phosphatidylethanolamine, S1P, phosphatidyl serine, and ω-3 PUFA in plaques can promote the polarization of M2 macrophages and play an anti-inflammatory role. The proposal of ''lipid-inflammation'' interactions provides clues for the diagnosis and treatment idea for clinical treatment of AS. This review aims to expand the scope of drug targets for the clinical management of AS by elucidating the interrelationships, conditions, and pathways of reciprocal alterations between lipid metabolism and macrophage-mediated inflammatory responses. It suggests that it will become a trend to develop personalized treatment regimens for combined drug use, tailored to patients' lipid metabolism and macrophage polarization. Through syndrome differentiation and treatment and prescription compatibility, traditional Chinese medicine plays a role in regulating the occurrence and development of AS. However, further treatment based on syndrome differentiation and scientific compatibility will play a more important role in preventing and treating AS and reducing the incidence of cardiovascular and cerebrovascular diseases caused by lipid metabolism and macrophage polarization. At the same time, it can also prove that the prescription of traditional Chinese medicine is scientific and effective.

LIMITATIONS OF THE STUDY

With the development of technology, more and more phenotypes of macrophages are being identified, and only M2 phenotypes can be divided into M2a, M2b, M2c, and M2d. M2 macrophages usually show anti-inflammatory effects, but M2b macrophages deviate from this anti-inflammatory model because they maintain high levels of inflammatory cytokines. In this article we only study the general M2 phenotype, its more detailed classifications and functions have not been systematically reported, which will be included in our next research plan.

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AUTHOR CONTRIBUTIONS

X.W. and Z.X. contributed equally in this work; conceptualization, Y.D. and S.X.; writing—original draft preparation, X.W. and Z.X.; writing—review and editing, X.W., Z.X., J.Z., Y.C., and Q.L.; supervision, Q.Y.; project administration, X.C. and B.L. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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