



Long-chain Fatty Acids in Atherosclerosis: Focus on Metabolites and Mechanisms*

PAN Jin-Qian^{1)**}, LIU Wang^{2)**}, LI Zhao-Bing^{1)**}, LIU Shi-Yang³⁾, ZHOU Qin-Yi^{1,4)***}

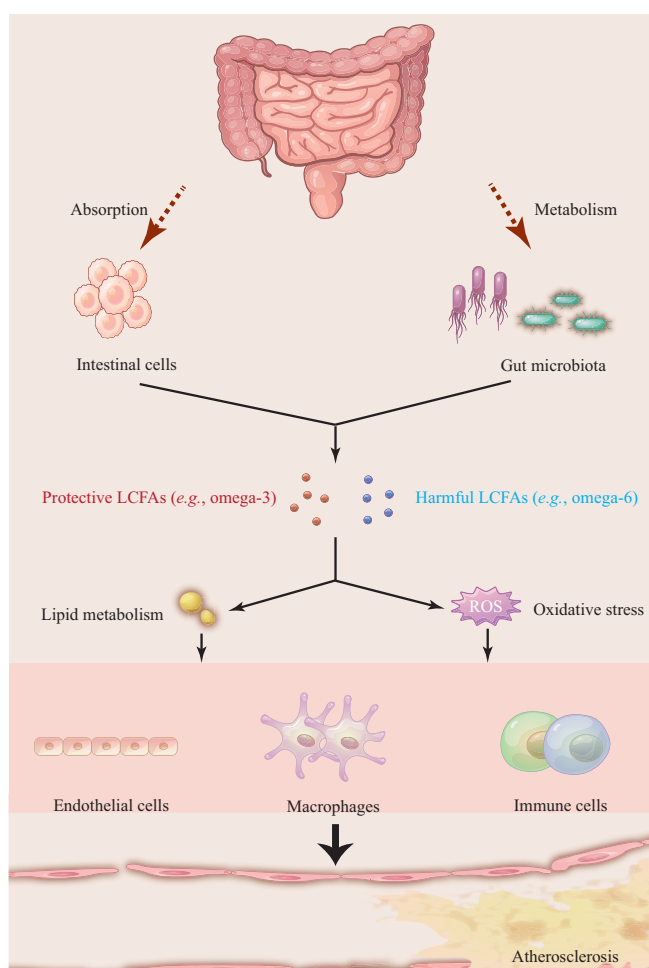
¹⁾Department of Cardiology, The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang 421002, China;

²⁾Department of General Surgery, The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang 421002, China;

³⁾Department of Neurology, The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang 421002, China;

⁴⁾Key Laboratory for Arteriosclerosis of Hunan Province, Institute of Cardiovascular Disease, Hengyang Medical School, University of South China, Hengyang 421002, China)

Graphical abstract



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** These authors contributed equally to this work.

*** Corresponding author.

Tel: 86-734-8358300, E-mail: 945134835@qq.com

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Abstract Atherosclerosis (AS) remains the core pathological basis underlying the high incidence and high rates of mortality and disability associated with cardiovascular disease (CVD) worldwide. Its essence is not merely lipid deposition, but rather an immune-mediated disease of the vascular wall characterized by an interplay of lipid metabolism disorders and chronic inflammation, with damage to vascular endothelial cells serving as the initiating event. As the disease progresses, it involves complex synergistic interactions among various cellular components, including endothelial cells, macrophages, and inflammatory cells, ultimately leading to plaque formation, instability, and even fatal thrombotic events. In recent years, the central driving role of lipid metabolic reprogramming in the progression of AS has garnered increasing attention from the scientific community. Among the vast array of lipid molecules, long-chain fatty acids (LCFAs) have become a primary focus of research due to their exceptional physiological functions. Traditional views have primarily emphasized the basic physiological functions of LCFAs: serving as highly efficient energy substrates through mitochondrial β -oxidation and acting as key structural components of cellular phospholipid membranes. However, emerging evidence clearly indicates that the functions of LCFAs extend far beyond those of mere metabolic fuel. They also act as potent bioactive signaling molecules, playing an indispensable multidimensional role in the pathogenesis of AS. Equally noteworthy and representing a paradigm shift in cardiovascular research is the emerging theory of the “gut-heart axis”. This theoretical framework views the human gut microbiota—comprising trillions of microorganisms—as a critical and metabolically active “bioreactor”. A wealth of clinical and multi-cohort epidemiological studies have conclusively demonstrated that imbalances in the composition and function of the gut microbiota are highly correlated with the clinical risk and severity of AS. Within this axis, the gut microbiota serves as the primary processing hub for dietary lipids. It actively participates in the digestion and biochemical remodeling of LCFAs, thereby altering their saturation and chemical structure and generating a wide variety of gut microbial metabolites. The effects of these gut-derived lipid metabolites extend far beyond the local intestinal microenvironment. Upon entering the bloodstream, these circulating microbiota metabolites act as endocrine signals. Given the extreme complexity of the underlying mechanisms, a comprehensive elucidation of the synergistic and bidirectional interactions between LCFAs and the gut microbiota in vascular pathology is particularly urgent. Therefore, this article aims to provide a systematic review of the multidimensional regulatory mechanisms of LCFAs and their associated gut microbiota metabolites in the onset, progression, and clinical manifestations of AS. By thoroughly exploring the interaction patterns within the “LCFAs-gut microbiota-AS” triad, this review seeks to fundamentally expand our understanding of the pathogenesis of CVDs. More importantly, translating these mechanistic insights into clinical practice holds tremendous promise. We hope to provide a solid theoretical foundation for the future development of novel AS prevention and treatment strategies based on non-traditional approaches. These include precision nutritional interventions (*i. e.*, dietary lipid intake plans tailored to an individual’s unique microbiome profile) and targeted microbiome modulation therapies (such as next-generation probiotics, prebiotics, or specific metabolite supplements). Targeting the gut as a “reactor” to treat vascular wall lesions represents a promising direction for future cardiovascular medicine.

Key words long-chain fatty acid, atherosclerosis, gut microbiota, metabolite

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Cardiovascular disease (CVD) has emerged as a significant public health threat and is characterized by rising morbidity and mortality rates^[1]. Consequently, research and practice aimed at preventing and treating CVD require urgent enhancement to address these escalating public health challenges. Atherosclerosis (AS) is the most prevalent pathology underlying CVD^[2]. Currently, the clinical management of CVD primarily relies on pharmacological interventions; however, the efficacy of these treatments is often limited, and they are often associated with side effects^[3]. Therefore, the pathogenesis of AS, along with the development of preventive and therapeutic measures, warrants thorough investigation to alleviate the burden of CVD.

AS is a chronic inflammatory disease that begins with endothelial cell dysfunction and is frequently accompanied by abnormalities in lipid metabolism, resulting in arterial lumen narrowing and impaired blood flow^[4]. AS progression is a complex biological process influenced by multiple factors, including genetic predisposition, environmental factors, and

lifestyle choices. Dyslipidemia, diabetes mellitus, and obesity are significant risk factors of AS^[5-7]. In recent years, evidence that the gut microbiota and their metabolites play crucial roles in AS development has increased^[8-10].

Long-chain fatty acids (LCFAs) are essential for energy metabolism and cellular functions. Disruptions in LCFA metabolism are implicated in various diseases, particularly those affecting cardiovascular health^[11-13]. Recent studies have revealed a complex relationship between LCFAs and AS, indicating that LCFAs contribute to the development of AS by influencing lipid metabolism, endothelial cell function, and inflammatory responses. Moreover, the interaction between LCFAs and the gut microbiota has recently gained significant attention in the research community. Thus, understanding the mechanisms by which LCFAs and their associated intestinal metabolites affect AS is vital for elucidating the pathological processes underlying CVD and identifying new therapeutic strategies.

This review aims to comprehensively examine

the relationship between LCFAs, intestinal metabolites related to LCFAs, and AS. It also analyzes the latest research advancements and proposes future research directions for this field. This exploration provides a theoretical foundation for the prevention and management of AS, ultimately aiding in the development of more effective and accessible interventions and treatments.

1 Overview of LCFAs

LCFAs are a class of fatty acids characterized by long carbon chains typically consisting of 12–22 carbon atoms. Based on their degree of saturation, LCFAs are classified as saturated or unsaturated. Saturated fatty acids lack double bonds in their carbon chains, whereas unsaturated fatty acids have one or more double bonds. Palmitic acid (PA) is a common saturated fatty acid widely found in vegetable oils and animal fats, such as palm oil and lard, and plays a significant role in CVD and metabolic syndrome^[14–15]. Unsaturated fatty acids can be further classified into mono-unsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs)^[16]. Among MUFAs, palmitoleic acid (POA) and oleic acid (OA) are prevalent and play important roles in cardiovascular health^[17–18]. POA is abundant in sea buckthorn oil, whereas OA is commonly found in olive oil. PUFAs are categorized based on their omega designation into omega-3 and omega-6 fatty acids. Omega-3 fatty acids include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α -linolenic acid (ALA), whereas omega-6 fatty acids primarily consist of linoleic acid (LA) and arachidonic acid (AA)^[19]. EPA and DHA are primarily derived from fat-rich fish and certain algae^[20]. ALA is widely present in vegetable oils, fruits, and leafy greens^[21]. LA is commonly found in vegetable oils, such as soybean oil^[22]. AA is primarily present in eggs and meat^[23]. In mammals, fatty acids are primarily synthesized in the liver, adipose tissue, mammary glands, lungs, and immune tissues^[24–26]. The metabolism of LCFAs in the body involves four steps: intestinal absorption and cellular production, transportation and storage, cellular uptake, and intracellular metabolism.

In humans, LCFAs are acquired primarily through intestinal absorption, followed by cellular production. In the intestine, pancreatic lipase hydrolyzes triglycerides (TGs) to free fatty acids and monoacylglycerols^[27]. These hydrolysis products enter the intestinal epithelium through passive diffusion or protein-mediated transport^[28]. Endogenous LCFAs are synthesized through two

primary biosynthetic pathways. The first pathway uses acetyl-CoA as a substrate and is catalyzed by acetyl-CoA carboxylase to produce malonyl-CoA. This process ultimately leads to LCFA synthesis in the presence of fatty acid synthase (FASN) and nicotinamide adenine dinucleotide phosphate (NADPH)^[26]. The second pathway uses synthesized fatty acids as substrates to create LCFAs through the action of elongase enzymes^[29]. Additionally, fatty acids can be converted to PUFAs by desaturase enzymes^[30]. Although the body can synthesize certain PUFAs, such as omega-3 and omega-6 fatty acids, their precursors—ALA and LA—are typically obtained from dietary sources^[31]. Because the conversion of ALA and LA to their omega-3 and omega-6 counterparts is inefficient, it is generally recommended that these fatty acids be acquired directly through diet^[32].

Once fatty acids are absorbed in the intestine, they are resynthesized into TGs by the intestinal epithelial cells and packaged into chylomicrons for entry into the bloodstream. The TGs within these chylomicrons are subsequently hydrolyzed by lipoprotein lipase (LPL) located on the surface of the capillaries, releasing free fatty acids^[28]. Some of these fatty acids are absorbed by tissue cells, whereas others are bound to albumin for transport in the circulation^[33]. Tissue cells facilitate fatty acid uptake through various proteins, including plasma membrane-associated fatty acid-binding proteins (FABPs), fatty acid transport proteins (FATPs), CD36, and Caveolin-1^[13]. FABPs are highly expressed in tissues with significant fatty acid metabolism, including the intestines, liver, adipose tissue, and muscle tissue^[34]. FATPs are predominantly expressed in the brain, skeletal muscle, heart, adipose tissue, and kidneys^[35]. CD36 is commonly expressed in platelets, immune cells, myocytes, intestinal epithelial cells, and microvascular endothelial cells^[36]. It should be noted that the level of CD36-mediated LCFA uptake in CVD is central to maintaining metabolic homeostasis^[37]. The Caveolin family is abundant in adipocytes, myocytes, endothelial cells, and epithelial cells^[13]. Once inside the cell, fatty acids combine with glycerol to form TGs, which serve as the primary storage form of fatty acids^[38].

The biological effects of LCFAs exhibit distinct multi-target and transmembrane characteristics. Primarily, LCFAs serve as extracellular signaling molecules that trigger downstream pathways by binding to surface receptors, such as free fatty acid receptor (FFAR) 1, FFAR4, and CD36. This regulates fundamental cellular functions, including

proliferation, differentiation, migration, and secretion. Specifically, all three are involved in regulating blood glucose levels. Additionally, FFAR4 participates in processes such as anti-inflammatory responses and thermogenesis, while CD36 possesses unique substance transport capabilities^[12]. Upon entering the cell, LCFAs specifically bind to cytosolic FABPs, which mediate their targeted transport to various biological sites to carry out physiological processes such as lipid synthesis, β -oxidation. They also activate the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway to sense nutritional status^[12]. At the functional level, LCFAs serve not only as core components for biofilm construction and vital substrates for energy metabolism, but also function as signaling precursor molecules extensively involved in lipid communication^[11]. Notably, LCFAs act as signaling molecules that can regulate key traits of bacterial pathogens, such as biofilm formation and virulence^[39]. Furthermore, LCFAs achieve profound

cellular functional remodeling at the levels of gene transcription and immune response by modulating metabolic enzyme activity, membrane protein function, and transcription factor expression^[12] (Figure 1). FFAR1 and FFAR4 are the primary receptors in FFARs that respond to LCFAs. FFAR1 is highly expressed in taste bud cells, pancreatic β -cells, intestinal L- and K-cells, immune cells, and the central nervous system, whereas FFAR4 has a broader expression across various tissues and cell types, particularly in taste bud cells, intestinal cells, immune cells, and adipocytes^[24]. The activation of both FFAR1 and FFAR4 has protective effects in diabetes; for instance, FFAR1 activation enhances glucose-dependent insulin release, whereas FFAR4 activation improves insulin sensitivity^[40]. The levels of circulating LCFAs have been linked to several diseases, including CVDs and cancer^[41]. In the context of CVDs, particularly AS, LCFAs influence disease progression both directly and indirectly. A

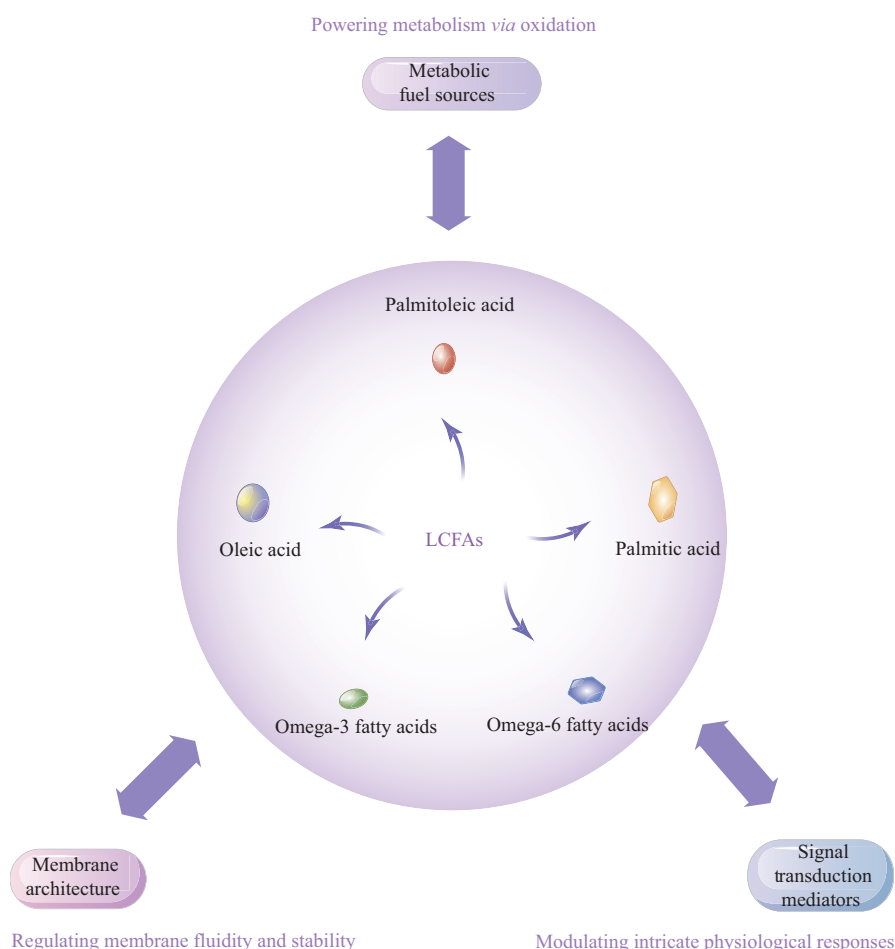


Fig. 1 The tripartite physiological roles of LCFAs in cellular homeostasis

LCFAs, encompassing saturated (*e.g.*, palmitic acid), monounsaturated (*e.g.*, oleic and palmitoleic acid), and polyunsaturated fatty acids (*e.g.*, omega-3 and omega-6), serve as fundamental determinants of cellular function through three primary modalities: metabolic fuel sources *via* oxidation; membrane architecture, by regulating fluidity and stability; and signal transduction mediators, by modulating intricate physiological responses. LCFAs, long-chain fatty acids.

clear association has been identified between omega-3 and omega-6 fatty acids and AS^[42]. Among numerous LCFAs, AA stands as a representative omega-6 fatty acid whose metabolic homeostasis is crucial for vascular health. AA primarily generates differentiated metabolites through COX-2 and 5-LOX pathways, thereby precisely regulating the pathological progression of AS^[23]. These bioactive metabolites encompass key components such as prostaglandins, thromboxane A₂, and leukotrienes (LTs)^[43]. As key products of the 5-LOX pathway, LTs are potent pro-inflammatory mediators. In the chronic inflammatory process of AS, LTs directly influence plaque thickness and stability by amplifying the inflammatory response^[44]. It is noteworthy that the role of AA-LTs extends beyond chronic lipid deposition; in acute cardiovascular events such as myocardial infarction, persistently elevated LT levels also serve as a key driver of myocardial injury and remodeling^[45]. The PA, POA, and OA also play significant roles in AS progression^[46-48]. Furthermore, LCFAs can indirectly affect the development of AS-related risk factors, such as dyslipidemia, diabetes, and obesity, by influencing metabolic processes, such as insulin resistance, inflammation, and fat storage, ultimately impacting AS progression^[49].

2 Regulatory factors of LCFAs

LCFA metabolism is regulated by various factors, including diet, signaling molecules, gut microbiota, individual genetics, and physiological conditions. The types of LCFA and their contents vary among different foods^[50]. Similarly, the absorption efficiency of LCFA varies under different dietary conditions, such as high-fat and low-fat diets^[51]. Furthermore, LCFAs can interact with each other. For example, omega-3 and omega-6 fatty acids share the same enzymes for intracellular synthesis, which leads to competition between the two classes^[52]. Specifically, a higher ratio of LA to ALA inhibited the synthesis of EPA and DHA from ALA. EPA and DHA are known to interact with each other^[53]. Insulin plays a significant role in regulating LCFAs by increasing the activity of LPL, which stimulates the hydrolysis of circulating TG bound to albumin and chylomicrons, thereby facilitating the entry of free fatty acids into cells^[54]. Insulin stimulates CD36, resulting in the enhanced cellular uptake of LCFA^[55]. Insulin promotes cellular lipogenesis^[56]. Additionally, butyrate inhibits lipid accumulation by activating the AMP-activated protein kinase (AMPK)/ peroxisome

proliferator-activated receptor α (PPAR α) pathway, which reduces the expression of lipid synthesis-related factors, such as FASN, and enhances fatty acid oxidation (FAO)^[57]. Thyroid hormones facilitate LCFA uptake and promote their β -oxidation^[58]. The entry of LCFAs into mitochondria and their subsequent oxidation—the process primarily involving β -oxidation—are regulated by various enzymes, including long-chain acyl-CoA synthetase 1 (ACSL1), carnitine, and acyl-CoA dehydrogenase^[1,59]. Mutations in nuclear genes encoding mitochondrial enzymes can impair LCFA oxidation^[60]. Additionally, vitamin D metabolites, such as lactone-vitamin D₃, influence FAO by affecting carnitine synthesis^[61]. Furthermore, interferon (IFN) type I can promote ACSL1 expression, which in turn affects β -oxidation^[59].

Numerous studies have established a close relationship between the gut microbiota and LCFAs, a relationship that affects the course of various diseases. Specifically, the gut microbiota converts LCFAs into acetyl-CoA through β -oxidation. In this process, different bacteria reshape the microbial community structure by utilizing their enzymatic diversity and energy utilization efficiency^[62]. The gut microbiota regulates LCFA. The composition and abundance of the gut microbiota are closely correlated with blood levels of LCFAs^[63]. Research indicates that the degree of saturation in dietary fatty acids is a key determinant of gut microbiota abundance and diversity. For instance, consumption of a high-fat diet rich in saturated fatty acids leads to a significant decline in microbial species diversity within the ileum and colon, while inducing abnormal expansion of the Firmicutes phylum^[64]. The gut microbiota can directly or indirectly affect the absorption and biotransformation of LCFAs. For instance, bifidobacterium can degrade OA by expressing oleate hydratase, thereby inhibiting tumour metastasis^[65]. The bacterium *Clostridia* employs thioesterase 1/protease 1/lysophospholipase L1 and acyl-ACP thioesterase to secrete stearic acid, thereby hindering the progression of colorectal cancer^[66]. *Escherichia coli* Nissle 1917 and *Dysosmobacter welbionis* J115T modulate colitis by affecting the levels of 3-hydroxyoctadecaenoic acid (C18-3OH), a metabolite of LCFAs^[67-68]. Our research group found that the gut microbiota-derived LCFA metabolite C18-3OH inhibits the progression of AS by regulating ABCA1-mediated cholesterol efflux^[69]. *Fusimonas intestini* promotes obesity development by producing increased levels of trans-OA through overexpression

of the fatty acid metabolism regulator fadR^[70]. *Enterococcus faecalis* can influence the development of obesity by affecting the myristoleic acid (MA)^[71]. Additionally, *Lactobacillus*, *Megasphaera*, and *Butyrivibrio* species produce different isomers of conjugated linoleic acid (CLA), which have varying effects on AS^[72]. Additionally, the farnesoid X receptor promotes intestinal ceramide synthesis by inducing its target gene sphingomyelin phosphodiesterase 3, thereby leveraging this key long-chain lipid metabolite to drive the pathological progression of AS^[73]. Moreover, oleoylethanolamide, as a key endogenous intestinal LCFA derivative, serves as a central molecule in regulating lipid homeostasis and the progression of obesity^[74]. Metabolites produced by gut microbiota also influence LCFAs. Takei *et al.*^[75] have recently indicated that the gut microbiota can regulate the binding of LCFAs to secondary bile acids, influencing cholesterol gallstone formation, and modulating immune responses. Furthermore, LCFA intake can affect the gut microbiota composition, influencing the abundance of strains, such as *Lactocaseibacillus rhamnosus*, *Lactocaseibacillus fermentum*, and *Lactocaseibacillus paracasei*^[76]. This interplay alters the production of gut microbiota metabolites, thereby influencing the composition and function of the gut microbiome, which in turn impacts overall physiological health^[77].

Individual differences in the physiological levels of LCFAs may result from genetic variation. For example, the production of long-chain PUFA is influenced by the fatty acid desaturase (FADS) and the elongation of very long-chain fatty acid (ELOVL) genes. Variants in the ELOVL and FADS genes can cause variations in endogenous long-chain PUFA synthesis^[78-79]. Genetic variations in CD36 can affect the cellular uptake of LCFAs^[80]. Physiological states can also affect the metabolism of LCFAs. For example, during fasting, the body preferentially utilizes LCFAs over glucose for energy^[81]. Sarcoidosis is associated with reduced serum omega-3 fatty acid levels^[82].

In conclusion, LCFA homeostasis in the body is maintained through a complex interplay between dietary sources, signaling molecules, gut microbiota, gene expression, and physiological states. Understanding these multifaceted interactions is essential for developing targeted interventions to address metabolic disorders and other health issues associated with LCFAs.

3 Impact of LCFAs on atherosclerosis

3.1 Cellular crosstalk: from vasculature to immunity

3.1.1 LCFAs and endothelial cells

Endothelial dysfunction is an early pathological manifestation of AS^[83]. Following endothelial cell injury, metabolic disturbances, such as the uncoupling of endothelial nitric oxide synthase (eNOS), can occur, resulting in dysfunction marked by excessive production of reactive oxygen species (ROS) and loss of nitric oxide (NO)-dependent vasodilation^[84]. Under normal conditions, endothelial cells function as barriers, recruit immune cells, maintain vascular tone, and regulate coagulation^[85]. The primary energy sources for endothelial cells are glucose and fatty acids^[86]. During mitochondrial FAO, FAO supports oxidative phosphorylation and maintains calcium ion (Ca^{2+}) homeostasis, which is essential for preserving the barrier function of endothelial cells^[87]. Additionally, FAO can inhibit transforming growth factor β signaling and endothelial-to-mesenchymal transition by increasing acetyl-CoA levels^[88]. LCFAs are involved in endothelial cell metabolism, nucleotide synthesis, and proliferation^[89]. Conversely, FASN inhibition reduces endothelial cell proliferation and downregulates the expression of vascular endothelial growth factor receptor 2^[90].

PA promotes endothelial cell damage by inducing endoplasmic reticulum (ER) stress, which subsequently increases the expression of LOX-1, leading to endothelial cell lipotoxicity^[91]. PA induces endothelial cell senescence by inhibiting autophagy^[92]. PA can inhibit the endothelial cell AMPK/PI3K/Akt/eNOS signaling pathway, thereby promoting endothelial cell injury^[93]. PA can promote endothelial cell injury by inhibiting the endothelial cell PI3K/Akt/eNOS signaling pathway, subsequently inducing the nuclear factor kappa B (NF- κ B) activation and elevated intracellular Ca^{2+} ^[94]. Additionally, PA promotes endothelial-mesenchymal transition by increasing mitochondrial DNA (mtDNA) content in the cytoplasm of endothelial cells. It also activates the cytosolic DNA-sensing cyclic GMP-AMP synthase-stimulator interferon gene (cGAS-STING) pathway^[95]. In contrast, OA has a protective effect on endothelial cells by inhibiting the response to proinflammatory factors, which reduces the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and monocyte

chemoattractant protein-1, while also increasing eNOS expression^[96]. Numerous studies have indicated that omega-6 fatty acids may contribute to endothelial cell injury by promoting the activation of NF- κ B and other inflammatory pathways^[97]. By contrast, omega-3 fatty acids influence endothelial cell function through various mechanisms. They modulate membrane fluidity, peroxidation sensitivity, and Na⁺/K⁺-ATPase activity in a concentration-dependent manner, leading to diverse effects on endothelial function^[98]. Omega-3 fatty acids promote the proliferation and migration of endothelial progenitor cells^[99]. Specifically, omega-3 fatty acids, particularly DHA, can reduce the

expression of tumor necrosis factor alpha (TNF- α)-induced adhesion molecules (*e. g.*, ICAM-1) and proinflammatory molecules (*e. g.*, IL-6) by inhibiting the NF- κ B pathway and activating the PPAR pathway, thereby helping maintain normal endothelial cell function^[100]. Omega-3 fatty acids and OA enhance endothelial cell function and integrity, whereas omega-6 fatty acids and PA promote endothelial damage (Figure 2). Thus, increasing the levels of omega-3 fatty acids and OA, while inhibiting omega-6 fatty acids and PA, may protect endothelial cells and represent a potential therapeutic strategy to inhibit AS progression.

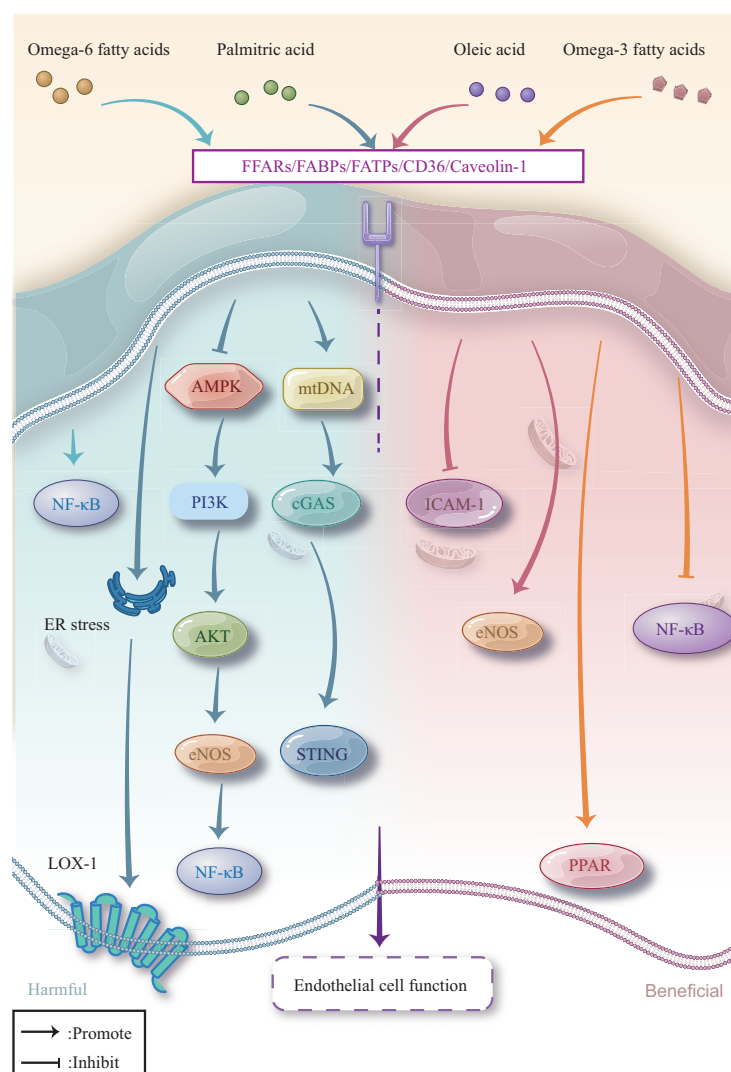


Fig. 2 Impact of LCFAs and their metabolites on endothelial cell injury

For endothelial cells, omega-6 fatty acids and palmitic acid promote endothelial cell damage through various mechanisms, whereas omega-3 fatty acids and oleic acid help maintain normal endothelial cell function through multiple pathways. These LCFAs exert a potential role in atherosclerosis by influencing endothelial cell health. AKT, v-akt murine thymoma viral oncogene homolog; AMPK, AMP-activated protein kinase; cGAS, cyclic GMP-AMP synthase; eNOS, endothelial nitric oxide synthase; ER stress, endoplasmic reticulum stress; FABP, fatty acid-binding protein; FATP, fatty acid transport protein; FFAR, free fatty acid receptor; ICAM-1, intercellular adhesion molecule-1; LCFA, long-chain fatty acid; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; mtDNA, mitochondrial DNA; NF- κ B, nuclear factor kappa B; PPAR, peroxisome proliferator-activated receptor; PI3K, phosphatidylinositol-3 kinase; STING, stimulator interferon gene.

3.1.2 LCFAs and macrophages

AS is a progressive inflammatory disease characterized by significant infiltration of foam cells, which primarily originate from macrophages. During the development of AS, macrophages play a critical role in lipid metabolism, inflammatory modulation, changes in polarization status, and stability of atherosclerotic plaques. Macrophages can be categorized into two main functional types: M1 and M2. M1 macrophages are generally associated with pro-inflammatory responses and secrete various inflammatory factors, such as tumor necrosis factor (TNF) and IFN. By contrast, M2 macrophages are associated with anti-inflammatory responses, participate in tissue repair, and secrete anti-inflammatory factors, such as interleukin-10 (IL-10)^[101].

PA promotes foam cell formation by activating the macrophage ROS-p38 pathway and promoting lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) expression, which in turn drives oxidized low-density lipoprotein (ox-LDL) uptake^[102]. PA promotes the release of miR-3064-5p-containing exosomes from macrophages, which can be taken up by macrophages and subsequently target nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitors α (IkB α) to activate NF- κ B signaling pathway, which in turn promotes inflammation^[103]. However, PA has recently been observed to inhibit the expression of proinflammatory genes, thereby suppressing inflammation by inducing the production of the macrophage lncRNA PARAIL, which promotes PARAIL's interaction with ELAV-like RNA binding protein1 (ELAVL1)^[104]. POA acts independently of PPAR α , PPAR γ , and AMPK to suppress inflammation-associated factors, such as NF- κ B, ultimately favoring M2 macrophage polarization^[105]. PA can promote macrophage Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) expression through a TNF- α -independent mechanism, which drives macrophage polarization toward the M1-type^[106]. By contrast, OA can inhibit this proinflammatory effect of PA by suppressing the TLR4-NF- κ B signaling pathway^[107]. Nitro-OA inhibits foam cell formation by binding to macrophage CD36, which reduces the uptake of modified LDL (mLDL)^[108]. Omega-3 fatty acids enhance the expression of Kruppel-like factor 4 (KLF4) by activating the p38 MAPK signaling pathway, which promotes M2 macrophage polarization^[109]. Additionally, omega-3 fatty acids can inhibit the effects of PA by reducing macrophage expression of endothelial lipase (EL), leading to decreased production of proinflammatory molecules

and increased production of anti-inflammatory molecules^[110]. Omega-3 fatty acids exert potential anti-inflammatory effects by inhibiting TLR4-regulated NF- κ B in macrophages^[111]. Interestingly, different omega-3 fatty acids exert varying effects on macrophage lipolysis. For example, DHA promotes macrophage lipolysis and inhibits their differentiation into foam cells, whereas EPA counteracts this protective effect^[112]. The omega-3 fatty acid metabolite 12-hydroxyeicosapentaenoic acid (12-HEPE) also inhibits foam cell formation *via* PPAR γ activation^[113]. By contrast, omega-6 fatty acids have complex effects on macrophages, producing both proinflammatory and anti-inflammatory mediators^[114]. Therefore, LCFAs significantly affect the onset and progression of AS by modulating macrophage polarization, regulating inflammatory responses, and altering foam cell formation (Figure 3). Understanding these mechanisms may provide new insights into therapeutic strategies for managing AS and related CVDs.

3.1.3 LCFAs and immunity

The immune system plays a complex and multifaceted role in the development of AS. In addition to macrophages, other immune cells, such as lymphocytes (including T and B cells) and dendritic cells (DCs), contribute significantly to the inflammatory response associated with AS^[115]. The interaction between these inflammatory cells is initiated by the release of adhesion molecules owing to endothelial damage, which triggers an innate immune response primarily involving macrophages and monocytes. Subsequently, DCs and macrophages activate lymphocytes through antigen presentation, leading to an adaptive immune response predominantly mediated by lymphocytes^[116]. In AS, the levels of T cells and DC notably increased, and their subtype proportions significantly changed^[115]. Among the various T cell subtypes, CD4⁺ T cells, such as T helper 1 (Th1) and regulatory T (Treg) cells, are particularly influential in AS progression^[117]. Th1 cells secrete proinflammatory cytokines, such as IFN- γ , contributing to proatherogenic effects. In contrast, Treg cells help maintain immune homeostasis by suppressing Th1-mediated inflammatory responses and downregulating antigen presentation by DCs, thereby exerting anti-atherogenic effects^[118]. Based on their functions and phenotypes, B cells are categorized into several subpopulations, including B1, B2, and regulatory B (Breg) cells. Using IgM antibodies, B1 cells play a protective role in AS by reducing the number of apoptotic cells, decreasing the size of necrotic cores,

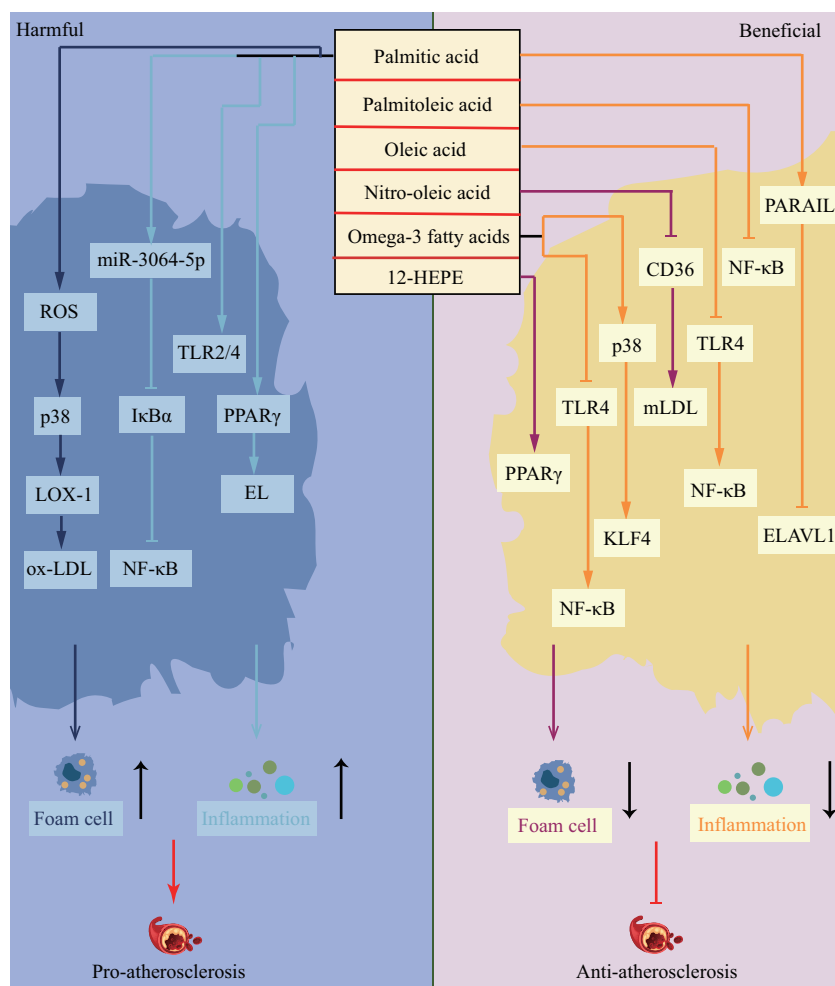


Fig. 3 Impact of LCFAs and their metabolites on foam cell formation and inflammation

PA promotes foam cell formation and inflammation. POA, OA, and omega-3 fatty acids inhibit inflammation. Nitro-OA and 12-hydroxyeicosapentaenoic acid (12-HEPE) can suppress foam cell formation. PA, POA, OA, and omega-3 fatty acids primarily influence inflammation by regulating nuclear factor kappa B. Meanwhile, PA, nitro-OA, and 12-HEPE mainly affect foam cell formation by modulating low-density lipoprotein uptake. Thus, LCFAs impact inflammation and foam cell formation through multiple mechanisms, potentially playing a role in atherosclerosis development. EL, endothelial lipase; ELAVL1, ELAV-like RNA binding protein1; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitors α; KLF4, Kruppel-like factor 4; LCFA, long-chain fatty acid; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; mLDL, modified LDL; NF-κB, nuclear factor kappa B; OA, oleic acid; ox-LDL, oxidized low-density lipoprotein; PA, palmitic acid; POA, palmitoleic acid; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; 12-HEPE, 12-hydroxyeicosapentaenoic acid.

and blocking the uptake of ox-LDL by macrophages^[118]. Conversely, B2 cells can contribute to AS progression by activating M1-type macrophages via the production of antibodies and TNF-α^[119-120]. Breg cells inhibit AS progression by producing the anti-inflammatory cytokine IL-10, which suppresses vascular inflammation and helps mitigate AS development^[118]. Meanwhile, DCs promote AS progression by enhancing T cell activation and the secretion of proinflammatory cytokines, such as TNF-α and IFN-γ^[121]. Thus, dysregulation of the immune response significantly accelerates the progression of AS.

LCFAs influence the immune response through multiple mechanisms. First, LCFAs act as signaling molecules that regulate various immune cell types. Second, they serve as essential substrates for energy metabolism, which is critical for immune cell function. For instance, PA reduces the number of CD3⁺ T cells, which are precursors of CD4⁺ T cells^[122]. In addition, low concentrations of PA stimulate T cell proliferation, whereas high concentrations exhibit cytotoxic effects on T cells^[40]. PA also promotes inflammatory responses by modulating the expression of lymphocyte activation molecule family member 3 in T cells and activating

the classical MAPK and v-akt murine thymoma viral oncogene homolog (Akt) signaling pathways in Jurkat T cells^[40]. Furthermore, OA deficiency enhances the differentiation of CD4⁺ T cells into Treg cells^[123]. OA enhances the proliferation of CD4⁺ T cells by incorporating into membrane lipids^[124]. Moreover, OA influences CD4⁺ T cell differentiation toward proatherogenic subtypes by regulating their metabolism^[125]. Nitro-OA inhibits the transcription of nuclear factors in activated T cells by modulating calcineurin phosphatase activity in T cells, which, in turn, reduces T cell proliferation, activation, and the release of proinflammatory factors^[126]. Omega-3 fatty acids inhibit T-cell migration, proliferation, and activation^[40]. However, a deficiency in omega-3 fatty acids may lead to increased activation of Th1 cells^[127]. Different isomers of omega-6 fatty acids can also affect T cell differentiation and alter subtype distribution within the lymphocyte population^[128]. In B cells, particularly germinal center B cells, various fatty acids, such as PA, are utilized in FAO, providing a substantial energy source for rapid proliferation^[129]. Omega-3 fatty acids activate B-cells and increase IgM levels in the body^[130]. In addition, different isomers of omega-6 fatty acids influence antibody secretion by B cells and their representation in lymphocyte population^[128]. Omega-6 fatty acid metabolites

regulate Ca²⁺ channels in B cells, affecting Ca²⁺ influx and enhancing B cell responses to adhesion molecules, such as ICAM-1 and vascular cell adhesion molecule-1, thereby promoting B cell adhesion^[131]. Saturated fatty acids promote the maturation and activation of DCs, leading to the release of proinflammatory factors, whereas unsaturated fatty acids generally exert the opposite effect^[132]. PA enhances the interaction between DCs and T cells by acting on the PPARs gene in DCs, promoting the expression of proinflammatory factors and facilitating their migration^[133]. Omega-3 fatty acids can inhibit dendritic cell activation, phagocytosis, and antigen presentation capabilities^[134]. However, contradictory findings suggest that OA, along with omega-3 and omega-6 fatty acids, may promote the expression of the DC co-stimulatory molecule CD86^[135]. Moreover, both omega-3 and omega-6 fatty acids enhance DC maturation, inhibit the proliferation of co-cultured T cells, and promote T cell differentiation toward Treg cells^[136]. In conclusion, LCFAs significantly influence the immune response by regulating the function, proliferation, and differentiation of various immune cells, indicating their importance in the development and progression of AS (Table 1).

Table 1 Regulation of immunity by long-chain fatty acids and their metabolites

Immune cells	LCFAs	Results	Reference
T cells	Palmitic acid	Reduces the number of CD3 ⁺ T cells; induces T cell proliferation at low concentrations, while exhibiting cytotoxicity at high concentrations; promotes inflammatory responses	[40, 122]
	Oleic acid	Influences the differentiation of Treg cells and proatherogenic subtypes; stimulates the proliferation of CD4 ⁺ T cells	[123-125]
	Nitro-oleic acid	Inhibits T cell proliferation, activation, and the release of proinflammatory factors	[126]
	Omega-3 fatty acids	Inhibits T cell migration, proliferation, and activation; in the absence, it promotes the activation of Th1 cells	[40, 127]
	Omega-6 fatty acids	Different isomers influence T cell differentiation and regulate the proportion of T cell subtypes	[128]
B cells	Palmitic acid	Promotes the rapid proliferation of germinal center B cells	[129]
	Omega-3 fatty acids	Activates B cells and increases IgM levels	[130]
	Omega-6 fatty acids	Different isomers influence the secretion of antibodies by B cells and their proportion among lymphocytes; their metabolic products promote B cell adhesion	[128, 131]
DC cells	Saturated fatty acids	Promotes the maturation and activation of DC cells, leading to the release of pro-inflammatory factors	[132]
	Unsaturated fatty acids	Inhibits the maturation and activation of DC cells, thereby suppressing the release of pro-inflammatory factors	[132]

Continued to Table 1

Immune cells	LCFAs	Results	Reference
	Palmitic acid	Promotes the expression of proinflammatory factors in DC cells; enhances the interaction between DC cells and T cells	[133]
	Oleic acid	Promotes the expression of the co-stimulatory molecule CD86 in DC cells	[135]
	Omega-3 fatty acids	Promotes the expression of the co-stimulatory molecule CD86 in DC cells; inhibits the activation, phagocytosis, and antigen-presenting functions of DC cells; promotes the maturation of DC cells, suppresses the proliferation of T cells co-cultured with DC cells, and facilitates the differentiation of T cells into Treg cells	[134-136]
	Omega-6 fatty acids	Promotes the expression of the co-stimulatory molecule CD86 in DC cells; facilitates the maturation of DC cells, inhibits the proliferation of T cells co-cultured with DC cells, and promotes the differentiation of T cells into Treg cells	[135-136]

Palmitic acid, oleic acid, nitro-oleic acid, omega-3 fatty acids, and omega-6 fatty acids can influence immune responses by regulating the function, proliferation, and differentiation of T cells, B cells, and DCs, thereby potentially playing a role in atherosclerosis.

3.2 Molecular cascades: lipid metabolism and oxidative stress

3.2.1 LCFAs and lipid metabolism

Disorders of lipid metabolism are significant risk factors for AS^[137]. Lipid metabolism plays a crucial role in maintaining energy homeostasis and the structural integrity of organisms. The key lipid species involved include TG, lipoproteins such as LDL, high-density lipoprotein (HDL), and apolipoproteins^[138]. Current AS research has focused primarily on the roles of TG, LDL, and HDL. However, the European AS Society has suggested that lipoprotein(a) may promote AS through its proinflammatory effects^[139]. ox-LDL is particularly noteworthy because it promotes endothelial dysfunction, stimulates vascular smooth muscle cell and fibroblast proliferation and migration, facilitates foam cell formation, and contributes to plaque instability and thrombosis^[140]. Conversely, HDL is involved in reverse cholesterol transport and exhibits antioxidant, anti-inflammatory, antithrombotic, and anti-apoptotic properties^[141]. TG promotes proatherosclerotic effects by altering LDL and HDL structure and function^[142]. Clinical studies have shown that increased LDL and TG concentrations can elevate the risk of AS^[143-144]. However, elevated HDL levels are protective against AS^[145].

LCFAs indirectly influence AS development by regulating lipid levels. For example, PA elevates the LDL levels^[146]. By contrast, POA is associated with reduced TG and LDL levels, and elevated HDL levels^[17]. Similarly, OA reduces TG levels and increases HDL levels^[147]. Omega-3 fatty acids lower both LDL and TG levels^[148-149]. Similarly, omega-6 fatty acids reduce LDL and TG levels^[150-151]. At the cellular level, omega-3 fatty acids, such as EPA, play a critical role in maintaining membrane stability and

inhibiting lipid oxidation, including LDL oxidation and the formation of cholesterol-rich domains^[152]. Omega-3 fatty acids also enhance HDL function, promote HDL-mediated cholesterol efflux, and have antioxidant effects^[153]. Moreover, omega-3 fatty acids can regulate transcription factors, such as peroxisome PPAR α , thereby influencing lipid metabolism^[154]. Activation of the PPAR γ -LXR α signaling pathway by omega-3 fatty acids leads to the upregulation of cholesterol-efflux transporter proteins, such as ATP-binding cassette transporter A1 and ATP-binding cassette transporter G1, which collectively help reduce lipid accumulation^[17]. In addition, the omega-3 fatty acid metabolite 8-hydroxyeicosapentaenoic acid (8-HEPE) promotes the expression of PPARs, further regulating lipid metabolism^[155]. Therefore, LCFAs affect the levels and functions of TG, LDL, HDL, and other lipids through multiple pathways, thereby influencing AS progression (Figure 4). Understanding these interactions is crucial for developing therapeutic strategies aimed at improving lipid profiles and reducing AS risk.

3.2.2 LCFAs and oxidative stress

Oxidative stress is a crucial factor in all the stages of AS and contributes to altered lipid metabolism, endothelial cell damage, and inflammation. Oxidative stress refers to an imbalance between ROS production and scavenging in the body, leading to cellular and tissue damage. ROS are a group of oxygen-containing free radicals and nonradical molecules, primarily superoxide anions, hydrogen peroxide, and hydroxyl radicals^[156]. The primary source of ROS in the body is cellular metabolism^[157]. ROS are generated at several cellular sites, including the cytoplasm, ER, mitochondria, and peroxisome^[158]. The major enzymatic sources of ROS include NADPH oxidase, NO synthase, xanthine

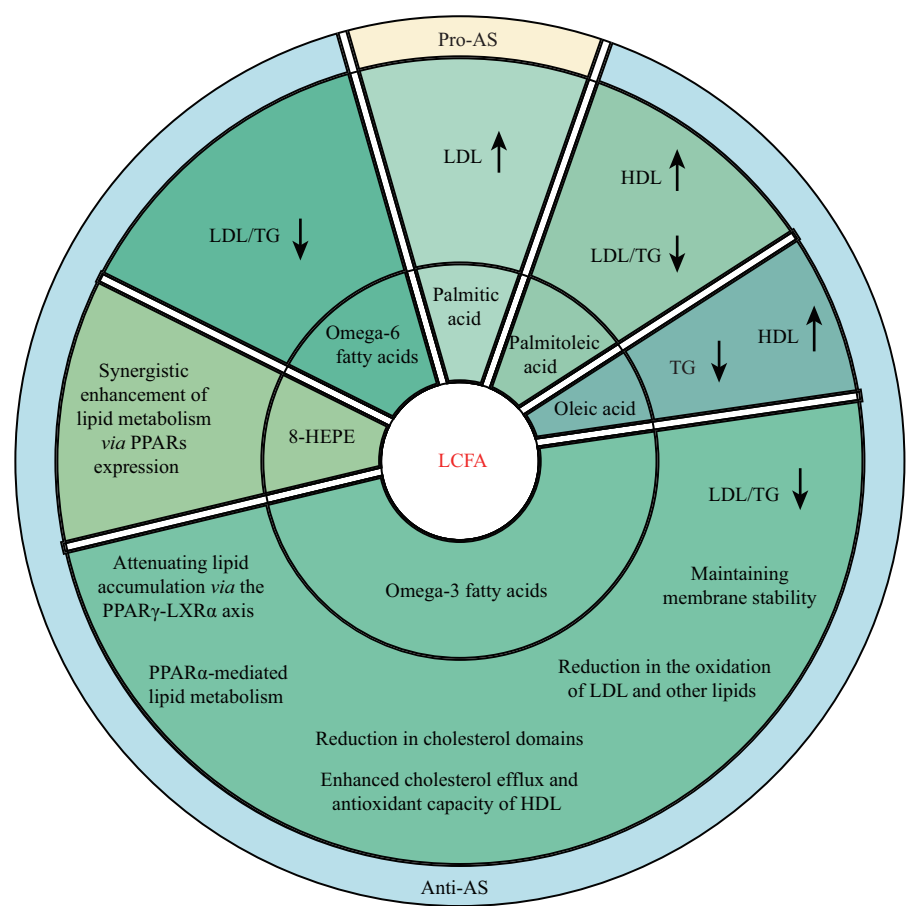


Fig. 4 LCFAs and their metabolites in lipid metabolism

In lipid metabolism, palmitic acid promotes AS, whereas palmitoleic acid, oleic acid, omega-3 fatty acids, 8-HEPE, and omega-6 fatty acids exert inhibit AS. This influence is primarily achieved through the regulation of triglycerides, low-density lipoprotein, and high-density lipoprotein. AS, atherosclerosis; HDL, high-density lipoprotein; LCFA, long-chain fatty acid; LDL, low-density lipoprotein; LXRα, liver X receptor α; PPAR, peroxisome proliferator-activated receptor; TG, triglyceride; 8-HEPE, 8-hydroxyeicosapentaenoic acid.

oxidase, and the mitochondrial electron transport chain^[156]. Under normal physiological conditions, the body employs various antioxidant mechanisms to scavenge ROS, including superoxide dismutase (SOD) and glutathione peroxidase (GPX)^[159-160]. However, when ROS production exceeds the body's scavenging capacity, leading to elevated ROS levels, oxidative stress occurs and promotes the onset and progression of AS. Oxidative stress not only initiates endothelial imbalance but also, by mediating lipid peroxidation, triggers a macrophage activation cascade that subsequently amplifies vascular inflammation through a cascade amplification mechanism^[161-162]. Furthermore, oxidative stress and inflammation interact; oxidative stress can activate inflammatory signaling pathways, while inflammation can, in turn, exacerbate oxidative stress^[19].

The regulation of oxidative stress by LCFAs

occurs through three main mechanisms, which are modulation of ROS and related oxidation product generation, regulation of antioxidant capacity, and alteration of cellular responsiveness to oxidants. PA promotes ROS generation in endothelial cells, while decreasing the levels of the antioxidant glutathione (GSH), thereby driving endothelial cell senescence^[163]. Although OA may exhibit some pro-oxidant effects under specific conditions, such as transiently increasing ROS production, its more significant role is to enhance the body's antioxidant capacity. This is achieved by increasing the expression and activity of antioxidant enzymes, such as SOD and GPX, ultimately resulting in pronounced antioxidant effects^[164]. Omega-3 fatty acids elevate the levels of antioxidant enzymes, such as serum SOD and GPX, *in vivo*^[165]. Omega-3 fatty acids inhibit ROS production in endothelial cells^[166]. Additionally,

omega-3 fatty acids can reduce ox-LDL levels by incorporating EPA into the cell membranes to scavenge free radicals^[153]. By contrast, omega-6 fatty acids tend to elevate ox-LDL levels and increase the susceptibility of LDL to oxidative stress, while interfering with the incorporation of EPA into cell membranes^[167]. Unsaturated fatty acids are particularly susceptible to oxidation and their oxidative metabolites, such as malondialdehyde and

other reactive carbonyl compounds, exacerbate oxidative stress by promoting the generation of additional free radicals through chain reactions^[167].

Different LCFAs play distinct roles in the regulation of oxidative stress. In summary, PA and omega-6 fatty acids promote oxidative stress within an organism, whereas OA and omega-3 fatty acids exhibit inhibitory effects, highlighting their potential roles in AS development and progression (Table 2).

Table 2 The effects of LCFAs and their metabolites on oxidative stress

LCFAs	Mechanisms	Affects	Reference
PA	Promote ROS; inhibit GSH	Promote oxidative stress.	[163]
OA	Promote ROS	Promote oxidative stress	[164]
	Promote antioxidant enzymes such as SOD and GPX	(weak) Inhibit oxidative stress (strong)	[164]
Omega-3 fatty acids	Inhibit ROS and ox-LDL; promote antioxidant enzymes such as SOD and GPX	Inhibit oxidative stress	[153, 165-166]
Omega-6 fatty acids	Elevate ox-LDL; increase the sensitivity of LDL to oxidative stress	Promote oxidative stress	[167]
Metabolites of unsaturated fatty acids (such as malondialdehyde)	Promote the generation of more free radicals through a chain reaction	Promote oxidative stress	[167]

PA, omega-6 fatty acids, and metabolites of unsaturated fatty acids, such as malondialdehyde, can promote oxidative stress. In contrast, OA and omega-3 fatty acids can inhibit oxidative stress. These LCFAs may play a potential role in the development of atherosclerosis by regulating oxidative stress. LCFAs, long chain fatty acids; GSH, glutathione; GPX, glutathione peroxidase; LDL, low-density lipoprotein; OA, oleic acid; ox-LDL, oxidized low-density lipoprotein; PA, palmitic acid; ROS, reactive oxygen species; SOD, superoxide dismutase.

4 Impact of gut microbiota metabolites on atherosclerosis

The gut microbiota plays a crucial role in regulating LCFA metabolism, and significantly influences AS progression *via* two primary mechanisms. First, gut microbes can directly synthesize LCFAs. Moreover, they metabolize LCFAs to produce various bioactive derivatives. These metabolites not only directly influence the progression of AS *via* multiple pathways but also indirectly influence its development by impacting major risk factors, including dyslipidemia, diabetes mellitus, and obesity. Current research indicates that LCFAs and their associated gut microbiota metabolites can modulate the development of these risk factors by affecting host inflammatory responses, lipid metabolism, and insulin sensitivity.

LCFAs influence the development of diabetes and obesity by altering lipid metabolism and insulin sensitivity. For instance, certain intestinal bacteria, such as *Lactobacillus*, *Megasphaera*, and *Butyrivibrio*, can produce CLA, with different CLA

isoforms having varying effects on human health^[72]. The c9,t11-CLA isoform activates insulin sensitivity and inhibits AS through the activation of PPAR γ , whereas the t10, c12-CLA isoform inhibits insulin sensitivity and promotes AS by inhibiting the expression of both PPAR γ and liver X receptor α (LXR α). Conversely, the t9,t11-CLA isoform inhibits AS by activating LXR α ^[72]. Patients with obesity and diabetes exhibit significant colonization by intestinal bacteria, such as *Fusimonas intestini*, which produce long-chain unsaturated fatty acid elaidate by metabolizing a high-fat diet, a process that can exacerbate obesity^[70]. In addition, *Enterococcus faecalis* reduces fat accumulation and inhibits the development of obesity by producing MA, which activates the brown adipose tissue and induces beige fat formation^[71]. Furthermore, LCFA metabolites from gut microbiota can influence obesity and diabetes development by modulating inflammatory responses and affecting lipid and glucose metabolism. For example, the abundance of Ruminococcaceae_UCG_009 has been associated with AA metabolites that influence AS-related inflammatory responses^[168]. *Lactobacilli* utilize PUFAs as substrates to produce

compounds, such as 10-hydroxy-cis-12-octadecenoic acid and 10-oxo-trans-12-octadecenoic acid, which can improve obesity outcomes^[169]. Additionally, the levels of 12-HETE are diminished in patients with diabetes, whereas oligofructose feeding promotes 12-HETE production by the gut microbiota, thereby enhancing glucose metabolism and lowering blood glucose levels^[170]. *Dysosmobacter welbionis* J115T, which is found in low abundance in type 2 diabetes, reduces weight and fat gain induced by a high-fat diet, while improving glucose tolerance and insulin resistance through its effects on various long-chain lipids associated with obesity and diabetes^[67]. Recognizing that LCFA-related metabolites produced by the gut microbiota are not the only factors involved in AS progression is important. Metabolites produced by other tissues, such as ceramides, can also contribute to insulin resistance^[171].

In this study, we explored the regulatory roles of LCFA-associated gut microbiota metabolites in glucose metabolism, lipid metabolism, and insulin resistance. Therefore, LCFA-associated gut microbiota metabolites may play a significant role in regulating AS. An in-depth study of these interactions will elucidate not only the important roles of LCFA and gut microbiota in cardiovascular health but also reveal the potential mechanisms of gut microbiota metabolites in AS development. These studies provide a theoretical basis for new preventive and therapeutic strategies for AS and novel directions for clinical intervention.

5 LCFAs modulate the core molecular network integrating atherosclerosis

Current evidence suggests a distinct functional dichotomy between LCFAs in the progression of AS. As illustrated in the signaling framework, PA and omega-6 fatty acids act as pro-inflammatory triggers by engaging surface receptors such as FFARs and CD36. This engagement induces the generation of ROS, which subsequently activates the NF- κ B pro-inflammatory cascade. Conversely, OA and Omega-3 fatty acids exert protective effects by modulating the TLR4 axis to suppress NF- κ B activation and simultaneously act as agonists for the nuclear receptors PPAR α and PPAR γ ^[172].

These divergent pathways establish a sophisticated “push-pull” regulatory network which converges in the pathogenesis of arteriosclerosis. The imbalance between these LCFA-mediated signals drives a systemic shift in lipid metabolism and oxidative stress, ultimately compromising the

functional integrity of endothelial cells, macrophages, and broader immune cell populations. This dysregulated microenvironment accelerates the transition from early lipid accumulation to advanced plaque formation and vascular destabilization (Figure 5).

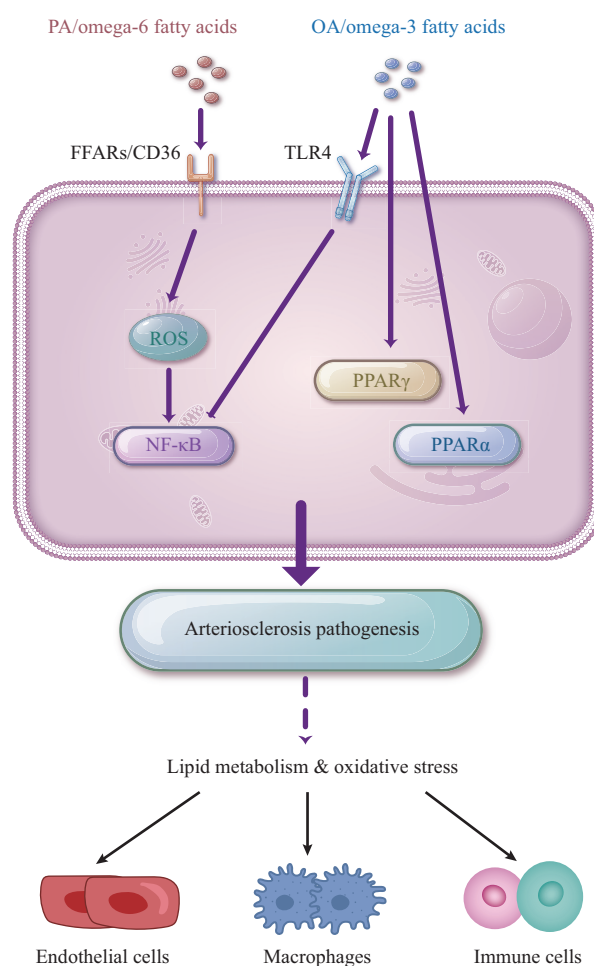


Fig. 5 LCFAs modulate the core molecular network integrating AS

The omega-3 fatty acids and OA primarily serve a protective function in the progression of AS. In contrast, the omega-6 fatty acids and PA have been demonstrated to have a detrimental effect on the progression of AS. AS, atherosclerosis; FFAR, free fatty acid receptor; LCFA, long-chain fatty acid; NF- κ B, nuclear factor kappa B; OA, oleic acid; PA, palmitic acid; PPAR α , peroxisome proliferator-activated receptor α ; PPAR γ , peroxisome proliferator-activated receptor γ ; ROS, reactive oxygen species; TLR4, Toll-like receptor 4.

6 Potential strategies for intervening with LCFAs in the prevention and treatment of atherosclerosis

Current preventive and therapeutic options for AS include aspirin, an antiplatelet agent, and statins,

which are lipid-lowering drugs^[173-174]. However, these treatments have certain side effects, highlighting the need for simpler and more effective methods to prevent and treat AS. Given the pivotal role of LCFAs in regulating endothelial function, macrophage activation, and immune inflammation, establishing a multi-tiered LCFAs-based intervention system holds significant clinical value. Potential intervention strategies targeting different populations include dietary modifications, nutritional supplements, and pharmacological approaches. These approaches may also involve precise interventions aimed at modifying the gut microbiota. As for population, the composition of dietary fatty acids is central to AS primary prevention. First, different foods contain varying types and proportions of LCFAs, which can significantly affect cardiovascular health. For example, deep-sea fish are rich in beneficial omega-3 fatty acids, whereas palm oil and lard contain primarily saturated fatty acids. Consuming foods high in monounsaturated and omega-3 fatty acids, while reducing intake of saturated fatty acids, can help lower the risk of AS. Thus, developing a rational dietary plan and selecting appropriate foods are crucial for intervening in LCFA metabolism and preventing AS. This lifestyle-based intervention holds broad applicability and serves as a foundational strategy for reducing the risk of AS onset within populations. For high-risk individuals or those already diagnosed, dietary intake alone often proves insufficient to achieve therapeutic plasma concentrations, necessitating an escalation of intervention strategies towards nutritional supplements and prescription-grade formulations. A variety of omega-3 fatty acid supplements (*e.g.*, fish oil capsules) are currently available on the market^[175]. These supplements can significantly improve AS^[176]. Pharmacological agents containing omega-3 fatty acids, such as Epanova and Icosapent ethyl, also help manage CVD^[177]. Pharmaceutical formulations can effectively modulate the types, ratios, and levels of LCFAs to target specific diseases and meet the individualized needs of diverse populations. Clinical studies have demonstrated cardiovascular benefits associated with LCFA intake and reduced CVD-related mortality. Clinical trials have shown that a high intake of omega-3 fatty acids has been linked to lower incidences of coronary artery disease and heart failure as well as decreased mortality among patients with myocardial infarction and heart failure^[177]. This is partly attributable to the fact that omega-3 fatty acids can enhance cardiac function in patients with heart failure^[178]. As a key upstream regulator of LCFA

metabolism, the gut microbiota is emerging as a novel therapeutic target for the prevention and treatment of ankylosing spondylitis. Several probiotic products, such as VSL#3 and MCP® BCMC® strains, along with fecal microbiota transplantation, are currently available and have shown promise in improving conditions, such as nonalcoholic steatohepatitis^[179-180]. Therefore, strategies that supplement the gut microbiota to promote the production of beneficial metabolites—such as using probiotics or engineered bacteria expressing fatty acid isomerase—and target the reduction of proinflammatory flora through phage therapy could become important approaches for treating and preventing the progression of AS. Additionally, enhancing the absorption of nutrient products and optimizing the gut microbiota are essential for these interventions.

It needs to be acknowledged that each individual has a unique genome, metabolic profile, and lifestyle, which can lead to variability in response to diets, supplements, and medications. Future research should prioritize the exploration of personalized nutritional intervention strategies, such as tailored LCFA intake plans based on genomic data and lipid metabolic profiles of individuals. This personalized approach may improve the effectiveness of nutritional interventions and reduce the risk of AS.

7 Conclusion and future perspectives

LCFAs play a pivotal role in AS by regulating various aspects of lipid metabolism, endothelial function, inflammatory responses, and oxidative stress within the body. First, LCFAs' influence on lipid levels provides a significant biological foundation for their role in AS prevention and treatment. For instance, PA can increase the concentration of proatherogenic lipids in the body, thereby contributing to AS development. Conversely, POA, OA, omega-3 fatty acids, and omega-6 fatty acids can lower proatherogenic lipid levels and increase anti-atherogenic lipid levels, thus playing a protective role against AS. These findings highlight the potential of clinical nutritional interventions targeting LCFAs. Second, the effect of LCFAs on endothelial cells is a crucial aspect of their anti-AS mechanisms. PA and certain omega-6 fatty acids can induce endothelial cell injury; whereas OA and omega-3 fatty acids promote endothelial health and enhance barrier function, contributing to improved vasodilatory capacity. Lastly, LCFAs regulate AS progression by modulating inflammatory responses and oxidative stress. For example, omega-3 fatty acids possess anti-

inflammatory and antioxidant properties that mitigate vascular inflammation, whereas excessive intake of specific omega-6 fatty acids can exacerbate inflammation and oxidative processes, thereby accelerating AS progression.

Moreover, metabolites derived from LCFAs and associated with the gut microbiota play a significant role in the progression of AS by influencing critical risk factors, such as diabetes and obesity. Understanding the interactions between LCFAs and gut microbiota is essential for developing individualized gut microbiota intervention programs and assessing the safety and efficacy of long-term interventions, thereby ultimately providing novel strategies for the prevention and treatment of AS. EPA and DHA are crucial for the primary prevention of CVD. Additionally, examining how genetic background influences LCFA regulation in AS is essential. Methodologically, the key regulatory network of the LCFA-gut microbiota-AS axis was systematically explored using a multi-omics integrated analysis strategy that combines multidimensional data from metabolomics, metagenomics, and epigenetics. The development of probiotics that enhance the anti-AS effects of LCFAs is also of significant importance, especially when considering the “gut-heart axis” perspective. These studies clarify the biological functions of LCFAs in AS and provide a theoretical foundation for subsequent intervention strategies. Furthermore, precise nutritional intervention studies that account for variations in the gut microbiota can lead to the development of tailored LCFA supplementation programs based on different enterotypes. Future research should also focus on the effects of dietary interventions, such as the long-term intake of MUFAs and omega-3 fatty acids, while reducing saturated fatty acids and monitoring their enduring impact on cardiovascular health. Omega-3 fatty acid intake may affect the platelet function and increase the risk^[177]. Recent clinical studies have indicated that omega-3 fatty acids can have a dose-dependent effect on the occurrence of atrial fibrillation^[181]. Hence, future research should focus on interventions involving the long-term intake of MUFAs and omega-3 fatty acids, along with the reduction of saturated fatty acids, to monitor their long-term effects on cardiovascular health. A comprehensive assessment system based on multidimensional biomarkers, including lipid profiles and inflammatory markers, should also be established to objectively evaluate the effects of these interventions.

In recent years, our understanding of LCFAs,

particularly PA, has significantly evolved. Although PA has traditionally been considered detrimental to cardiovascular health, emerging research has suggested that palm oil-rich diets may confer certain health benefits. PA promotes endothelial ciliation by facilitating S-palmitoylation of ciliary proteins, such as ADP ribosylation factor-like GTPase 13B, thereby maintaining normal endothelial cell function. Conversely, OA may reduce the availability of PA within endothelial cells by promoting the formation of lipid droplets, which can lead to ciliary loss, ultimately resulting in endothelial cell damage^[182]. These findings highlight the potential benefits of PA and harmful effects of OA, indicating a significant shift in our understanding of the roles of LCFAs. To further elucidate the molecular mechanisms by which LCFAs influence AS, future studies should aim to identify key target genes involved in the action of LCFAs against AS. A deeper understanding of these mechanisms will provide a vital foundation for the development of novel targeted therapies. Currently, LCFAs are recognized as ligand molecules that bind to specific receptors and activate intracellular signaling pathways that regulate glucose and lipid metabolism. These are critical processes linked to the progression of AS, insulin resistance, glucose tolerance abnormalities, and hyperlipidemia. Drugs targeting PPARs, which serve as action sites for LCFAs, and FFARs, which are receptors for LCFAs, have demonstrated effectiveness in the treatment of metabolic diseases. Furthermore, employing a combination of multiple targeted drugs and developing multi-target medications represents a promising strategy to broaden the application of LCFA receptor-targeted therapies while minimizing adverse effects. As our understanding of LCFAs continues to deepen, intervention with LCFAs and their associated gut microbiota will yield new ideas and strategies for the primary prevention and clinical treatment of AS. This could facilitate the development of effective methods for preventing and treating CVD, ultimately alleviating the burden on the cardiovascular system and enhancing overall quality of life.

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长链脂肪酸在动脉粥样硬化中的作用： 聚焦代谢产物及其机制*

潘锦芊^{1)**} 刘旺^{2)**} 李招兵^{1)**} 刘诗洋³⁾ 周琴怡^{1,4)***}

⁽¹⁾ 南华大学衡阳医学院附属南华医院心内科, 衡阳 421002;

⁽²⁾ 南华大学衡阳医学院附属南华医院普通外科, 衡阳 421002;

⁽³⁾ 南华大学衡阳医学院附属南华医院神经内科, 衡阳 421002;

⁽⁴⁾ 南华大学衡阳医学院心血管病研究所, 湖南省动脉硬化病学重点实验室, 衡阳 421002)

摘要 动脉粥样硬化 (atherosclerosis, AS) 作为导致全球心血管疾病高死残率的核心病理基础, 其本质并非单纯的脂质堆积, 而是一种由血管内皮细胞损伤为始动环节、伴随脂质代谢紊乱与慢性炎症相互交织的血管壁免疫性疾病。近年来, 随着对 AS 研究的进展, 脂质代谢重编程在 AS 演进中的驱动作用日益受到重视。其中, 长链脂肪酸 (long-chain fatty acids, LCFAs) 不仅是机体重要的能量底物与细胞膜结构组分, 更作为关键的生物活性信号分子, 在 AS 的病理轨迹中扮演着至关重要的角色。更值得关注的是, 基于新兴的“肠道微生态-心血管轴 (gut microbiota-cardiovascular axis)”理论, 肠道菌群作为 LCFAs 代谢的关键“生物反应器”, 其群落组成与功能的稳态失衡与 AS 的发病风险高度相关。肠道菌群不仅直接参与宿主对膳食 LCFAs 的消化与重塑, 其利用特定脂质底物衍生出的微生态代谢物更可突破肠屏障进入体循环调节 AS 进展。本文旨在系统性综述 LCFAs 及其相关肠道菌群代谢物在 AS 发生、发展中的多维调控机制。通过深入探讨“LCFAs-肠道菌群-AS”三者间的相互作用规律, 期望不仅能进一步拓宽对 AS 发病机制的认知边界, 更期冀为未来开发基于精准营养干预及靶向微生态调节的新型 AS 防治策略提供坚实的理论支撑与潜在干预靶点。

关键词 长链脂肪酸, 动脉粥样硬化, 肠道微生物群, 代谢产物

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** 并列第一作者。

*** 通讯联系人。

Tel: 0734-8358300, E-mail: 945134835@qq.com

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