Review

NLRP3 Inflammasome: A Potential Therapeutic Target for Atherosclerosis

Mengqi Wang [1,†], Jun Cheng [2,†], Fen Feng [3,*], and Linxi Chen [1,*]

[1] Institute of Pharmacy and Pharmacology, School of Pharmaceutical Science, Hengyang Medical College, University of South China, Hengyang 421001, China
[2] The First People's Hospital of Changde City, Changde Hospital Affiliated to Xiangya School of Medicine, Central South University, Changde 415000, China
[3] The School of Pharmacy, Shaoyang University, Shaoyang 422000, China
* Correspondence: fengfen20040141@126.com (F.F.); 1995001765@usc.edu.cn (L.C.)
† These authors contributed equally to this work.
Received: 6 August 2025; Revised: 17 September 2025; Accepted: 13 November 2025; Published: 7 April 2026

Abstract: Atherosclerosis is a vascular disease characterized by dysfunction of vascular endothelial cells, infiltration of macrophages, formation of foam cells, and proliferation and migration of vascular smooth muscle cells. Current studies have shown that the NLRP3 inflammasome plays a key regulatory role in the cellular pathological process of atherosclerosis. This review systematically summarizes the role and underlying mechanism of the NLRP3 inflammasome in the cellular pathological processes of atherosclerosis: various risk factors activate this inflammasome to exacerbate cell damage, while many endogenous factors exert protective effects by inhibiting its activity. In addition, the article reviews intervention strategies ranging from specific chemical drugs to multi-target natural products, and discusses emerging new technologies such as nano-targeted delivery, providing a theoretical basis for anti-inflammatory therapeutic strategies. Significance statement: This study focuses on NLRP3 inflammasome, whose key role in the process of atherosclerosis is becoming increasingly clear. These findings suggest that targeting the NLRP3 inflammasome may represent a potential direction for developing new therapeutic strategies, although most agents remain at the preclinical stage and require further validation.

Keywords: NLRP3 inflammasome; atherosclerosis; endothelial dysfunction; macrophage infiltration; the proliferation and migration of vascular smooth muscle cells

1. Introduction

Atherosclerosis (AS) is a chronic progressive disease that primarily affects the intima of the aorta or coronary arteries [1,2]. The cytopathological basis of this disease includes endothelial cells (ECs) injury, the migration and differentiation of immune cells such as monocytes/macrophages into foam cells with subsequent release of inflammatory factors, and the proliferation and migration of vascular smooth muscle cells (VSMCs) to form new plaques [3]. Among these processes, the role of the NLRP3 inflammasome has attracted widespread attention. Despite significant advances in modern medicine, AS remains one of the leading causes of cardiovascular diseases and mortality worldwide [4]. Therefore, targeted therapies against NLRP3 are regarded as an important direction for AS treatment.

As a key molecular complex in the inflammatory response, the NLRP3 inflammasome is composed of various proteins such as NLRP3 protein, apoptosis-associated speck-like protein (ASC), and pro-caspase-1 precursor. It is an important "signal hub" in the body's innate immune response. Its core mechanism lies in the following: When stimulated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the NLRP3 inflammasome is activated and recruits ASC and pro-caspase-1. Through protein interactions, it promotes the cleavage of pro-caspase-1 into active caspase-1; activated caspase-1 can specifically cleave pro-interleukin-1β (pro-IL-1β) and pro-interleukin-18 (pro-IL-18) to generate mature IL-1β and IL-18 and release them into the extracellular space, triggering a cascade of inflammatory responses; at the same time, it can cleave gasdermin D (GSDMD) to form a membrane pore, causing cell pyroptosis, which further amplifies the inflammatory effect. A large number of studies have confirmed that in the pathological process of AS, the NLRP3 inflammasome can be activated by cholesterol crystals deposited in the vascular wall, oxidized low-density

lipoprotein (ox-LDL), and other substances. Through the above mechanisms, it continuously regulates the release of inflammatory factors and cell pyroptosis, not only promoting the aggravation of endothelial damage, foam cell formation, and abnormal proliferation of VSMCs, but also accelerating the expansion of the lipid core in the plaque, thinning of the fibrous cap, promoting the development of the plaque to an unstable state, and ultimately inducing plaque rupture, thrombosis, and other serious complications [5]. The inflammatory response mediated by the NLRP3 inflammasome is a key molecular bridge connecting the pathological links and disease progression of AS.

Based on this, this article aims to systematically elaborate on how the NLRP3 inflammasome participates in the cellular pathophysiological process of AS, focusing on analyzing the molecular mechanisms by which it regulates the functions of key cells such as ECs, Monocytes/macrophages and VSMCs after activation; at the same time, it further reviews the latest progress in the development of drugs targeting the NLRP3 inflammasome, including the action targets and research status of different types of candidate drugs such as chemical drugs, natural extracts, and traditional Chinese medicine compound formulas, with the aim of providing new strategies targeting the inflammasome for the prevention and treatment of AS, and providing new insights for clinical intervention of this disease.

2. NLRP3

2.1. Inflammasome Structure and Expression

The NLRP3 inflammasome is currently the most fully characterized inflammasome and consists of the NLRP3 scaffold, the ASC adaptor (apoptosis-associated speck-like protein containing a caspase recruitment domain), and the effector enzyme pro-caspase-1 [6]. The NLRP3 inflammasome scaffold, a trivalent protein, comprises three distinct components: the pyrin domain (PYD) at the N-terminus, the nucleotide-binding and oligomerization (NACHT, also referred to as NOD) domain in the middle, and the leucine-rich repeat (LRR) domain at the C-terminus. ASC features two protein interaction domains: an amino-terminal PYD and a carboxy-terminal CARD. Meanwhile, pro-caspase-1 has an amino-terminal CARD along with two catalytic structural domains of varying sizes, namely p20 and p10. Through homotypic interactions between the NACHT domains, NLRP3 self-oligomerizes upon stimulation. After self-oligomerization, NLRP3 recruits ASCs via homotypic PYD-PYD interactions, leading to the assembly of ASCs into large speckled structures [7]. By means of CARD-CARD interactions, the clustered ASCs recruit pro-caspase-1. This recruitment promotes the autocatalytic activation of caspase-1. Activated caspase-1 regulates the maturation of pro-inflammatory cytokines pro-interleukin-1β and pro-interleukin-18 by directly cleaving them [8]. Furthermore, once caspase-1 is activated, it cleaves GSDMD, which then leads to both cellular lysis and pyroptosis [9,10]. The NLRP3 inflammasome shows a high level of expression in innate immune cells, such as macrophages and neutrophils. Additionally, it has expression in non-immune cells, encompassing endothelial cells, cardiomyocytes, fibroblasts, and epithelial cells [11] (Figure 1).

NLRP3 inflammasome is composed of the sensor NLRP3, the adaptor ASC, and the effector enzyme pro-caspase-1. NLRP3 contains LRR domain, NACHT domain, and PYD. ASC contains PYD and CARD. Pro-caspase-1 contains CARD and catalytic domains (p20/p10 subunits). Once NLRP3 senses DAMPs or PAMPs, it is activated through conformational changes and recruits ASC via PYD-PYD homotypic interactions. ASC then recruits pro-caspase-1 through CARD-CARD homotypic interactions, assembling into the NLRP3 inflammasome complex.

2.2. NLRP3 Inflammasome Priming and Activation

In these processes, the activation of the NLRP3 inflammasome necessitates two signals. The initial signal, typically termed “priming”, pertains to the initiation of NLRP3 transcription. Ordinarily, the intracellular levels of NLRP3 are insufficient to form an inflammasome without an up-regulation of NLRP3 transcription. The classical approach to enhance NLRP3 transcription involves activating the nuclear factor-κB (NF-κB) pathway. This pathway is triggered by the binding of specific ligands, including lipopolysaccharide (LPS), ox-LDL and cholesterol crystals, to Toll-like receptors (TLRs) and cytokine receptors. Examples of these cytokine receptors are tumor necrosis factor receptors and interleukin-1 receptors. Once activated, NF-κB translocates into the nucleus. Here, it not only promotes NLRP3 gene transcription but also facilitates the synthesis of pro-IL-1β and pro-IL-18. These processes prime subsequent inflammasome activation and cytokine maturation [12,13].

Pathogen-associated molecular patterns (PAMPs), such as LPS, or damage-associated molecular patterns (DAMPs), like adenosine triphosphate (ATP), can trigger the human immune response and accelerate the “activation” process of the inflammasome. They set off a series of upstream signaling events. Potassium (K^+) efflux, the formation of mitochondrial reactive oxygen species (mtROS), and lysosomal release of cathepsin constitute the main components of these signaling events [14–16]. Earlier research demonstrated that NLRP3 activators, for instance, extracellular ATP can promote K^+ efflux pathway via recognition by P2X7 receptor, thereby triggering NLRP3 inflammasome activation [17]. Research findings demonstrated that serine/threonine

kinase Nek7, a novel upstream regulator of the NLRP3 inflammasome [18], directly interacts with the NACHT and LRR domains of NLRP3. This interaction enables Nek7 to participate in inflammasome assembly and function at the downstream stage of K^+ efflux. As a result, it promoted the activation of NLRP3 [19]. Mitochondrial homeostasis is key to inflammasome activation. Subsequent to mitochondrial damage, the liberation of mtROS and mitochondrial DNA (mtDNA) directly instigates the activation of NLRP3. Therefore, mtROS are particularly critical in the activation of the NLRP3 inflammasome [20–22]. Moreover, cardiolipin, which is situated in mitochondria, also acts as an activator of NLRP3 [23]. Additionally, LPS can enhance mtDNA replication by upregulating the key enzyme UMP-CMPK2 for mitochondrial DNA synthesis, thereby promoting NLRP3 activation [24]. The activation of the NLRP3 inflammasome is significantly regulated by autophagy. Autophagy can inhibit NLRP3 activation by degrading damaged mitochondria with Parkin protein involved in clearing damaged mitochondria [25]. If the autophagy-related proteins are absent, mitochondrial homeostasis is disrupted, and the release of mtDNA will trigger the activation of the NLRP3 inflammasome [26]. Another cellular event that can trigger the activation of the NLRP3 inflammasome is the release of cathepsin from damaged lysosomes. When cholesterol crystals and other particulate substances are engulfed by macrophages, they are normally broken down in lysosomes. However, if the lysosomes are unstable such as being damaged, the tissue proteinase B (Cathepsin B) will leak from the lysosomes into the cytoplasm, triggering the activation of the NLRP3 inflammasome [27].

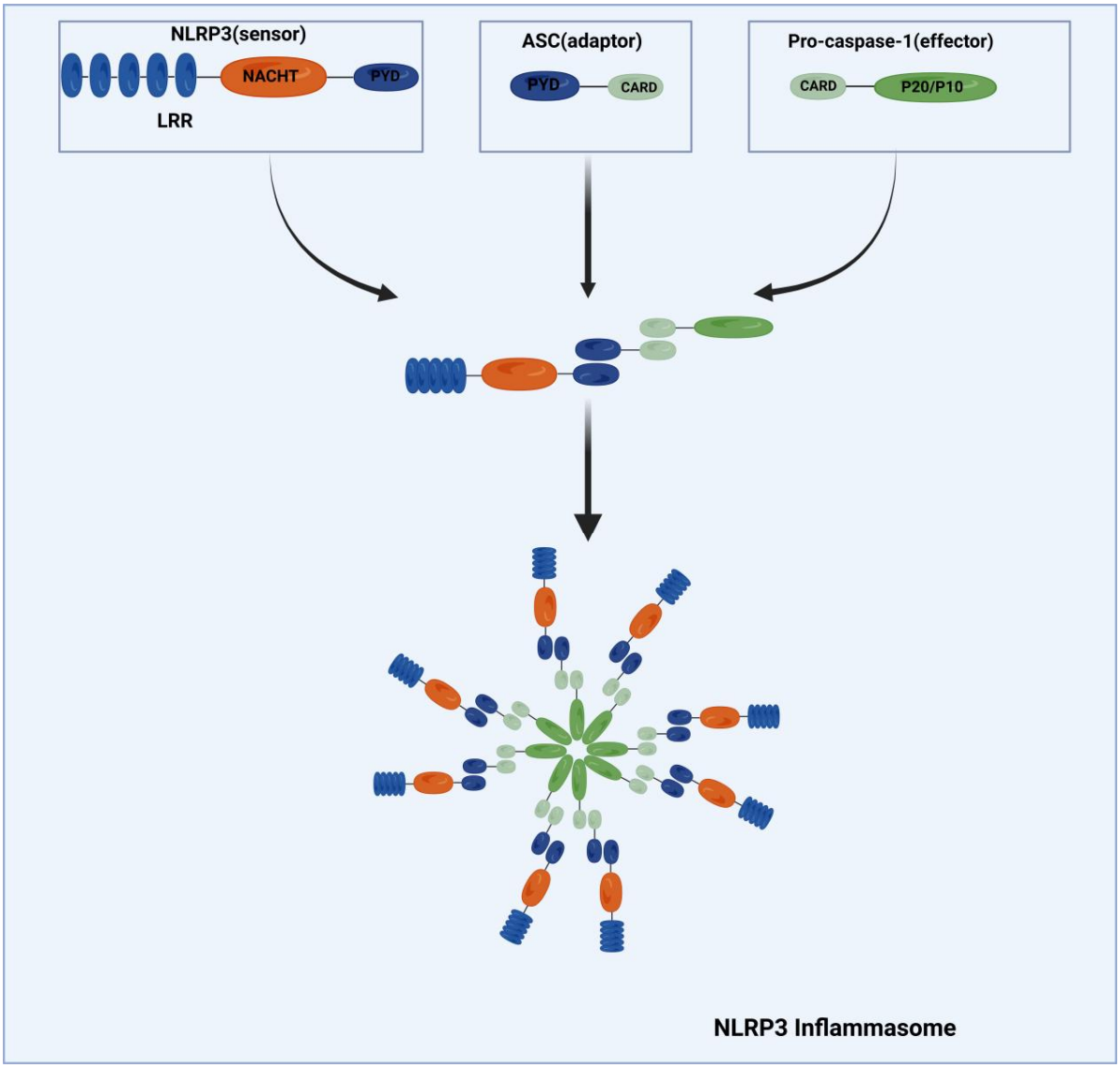

Figure 1. Components and assembly of NLRP3 inflammasome. The NLRP3 inflammasome is a key cytosolic multiprotein complex consisting of NLRP3, ASC, and pro-caspase-1.

Recent scientific investigations uncovered a novel mechanism. In this mechanism, the NLRP3 activator was demonstrated to initiate the disintegration process of the trans-Golgi network. This process caused the trans-Golgi

network to break down into a decentralized trans-Golgi network, and this decentralized structure acted as the place where the NLRP3 inflammasome assembled and got activated [28]. The result is that after the NLRP3 inflammasome is assembled and activated, it activates Caspase-1. Activated Caspase-1 will cleave the precursors of IL-1β and IL-18, generating mature IL-1β and IL-18 and releasing them, triggering the inflammatory response; at the same time, it cleaves Gasdermin D, and the resulting GSDMD fragments will form pores on the cell membrane, causing the cells to undergo pyroptosis [29].

Multiple mechanisms regulate the expression and activity of the NLRP3 inflammasome, including post-translational modifications of proteins such as ubiquitination and endogenous regulatory factors such as non-coding RNAs: miRNAs, lncRNAs; proteins: COPs, etc.; small molecules: ATP, ROS [11]. The NLRP3 inflammasome can be activated by various stimuli such as mechanical/oxidative stress, infection, and nutritional changes. The activation pattern varies depending on the cell type and the environment. The molecular interaction mechanism is not yet fully understood. To better explore the occurrence of related diseases, further in-depth research on its regulatory mechanism is needed (Figure 2).

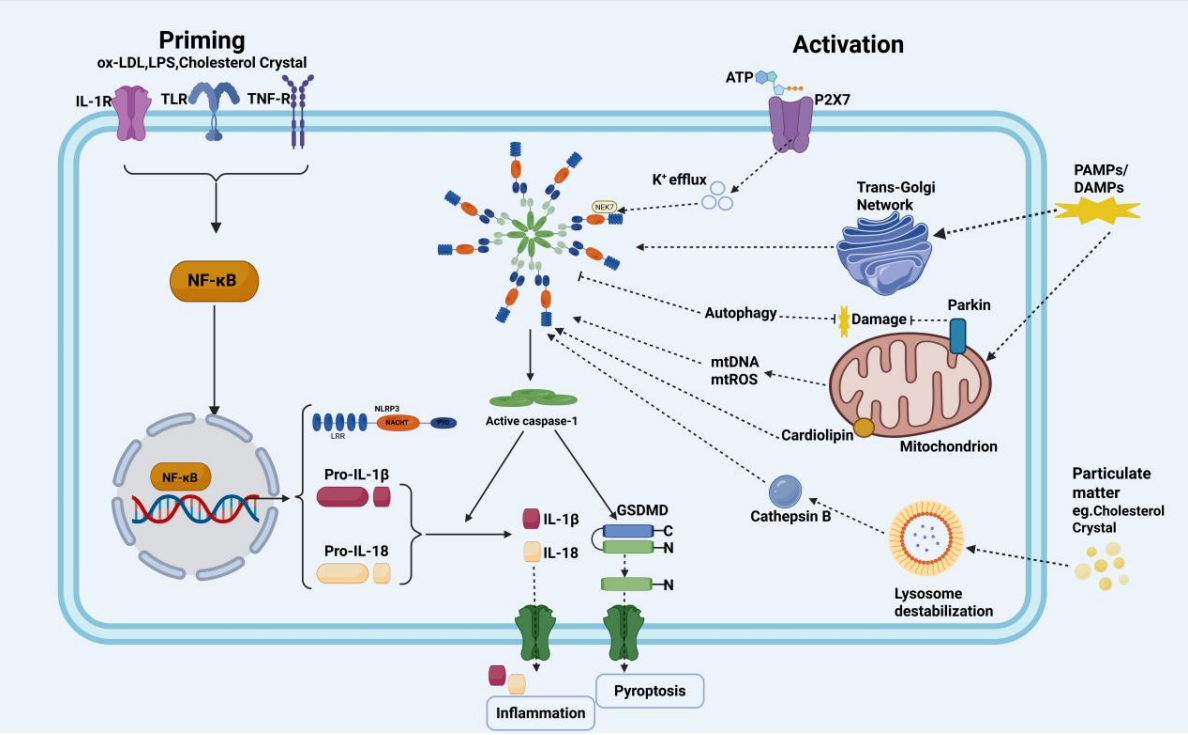

Figure 2. Two signals of NLRP3 inflammasome activation. NLRP3 inflammasome activation requires two sequential signals: a priming signal triggered by stimuli such as ox-LDL, LPS, and cholesterol crystals, which activates NF-κB to drive the transcription of NLRP3 and pro-inflammatory cytokines (pro-IL-1β, pro-IL-18); and an activation signal initiated by PAMPs/DAMPs, particulate matter, or ATP-induced K^+ efflux, with mitochondrial dysfunction and lysosomal destabilization further promoting inflammasome assembly. Active caspase-1 cleaves pro-IL-1β/pro-IL-18 into mature cytokines and cleaves GSDMD to induce pyroptosis, ultimately driving inflammation and vascular damage in atherosclerosis.

3. The Effects of the NLRP3 Inflammasome on atherosclerosis

3.1. Endothelial Cell Dysfunction

Vascular ECs act as the barrier and regulatory core of the vascular wall. Their dysfunction is the initial stage of AS occurrence. The pyroptosis of ECs mediated by the activation of the NLRP3 inflammasome is a key molecular event connecting EC damage and the progression of AS [30]. Various risk factors such as low shear stress, nicotine, environmental pollutants and endognous regulatory factors such as miRNAs, proteins, lncRNAs can affect the pyroptosis of ECs and the inflammatory response by regulating the activity of the NLRP3 inflammasome, ultimately promoting or inhibiting the development of AS.

3.1.1. Risk Factors for Activating AS: Activation of the NLRP3 Inflammasome in ECs

Physical Factor

Low shear stress (LSS) could promote ECs pyroptosis, which was one of the physical factors leading to the early occurrence of AS [31]. However, the mechanism of ECs pyroptosis induced by LSS remains unclear. Recent investigations conducted by Lv et al. have demonstrated that LSS gives rise to ECs pyroptosis as well as the phosphorylation of IKKε. Knocking down IKKε not only cut down on the atherosclerotic lesions in the aortic arch of high-cholesterol-fed (HCD) ApoE$^{-/-}$ mice a lot. Logically, it also greatly lessened the ECs pyroptosis and the expression of NLRP3, which was a direct result of the LSS. In further exploration of the mechanism, it had been demonstrated that IKKε had activated STAT1 to boost NLRP3 expression, and then STAT1 had bound to the NLRP3 promoter region. These findings implied that LSS exerted a pro-atherosclerotic effect by facilitating ECs pyroptosis via the IKKε/STAT1/NLRP3 pathway [32]. provides novel insights into the pathogenesis of AS. Oscillatory shear stress (OSS), intriguingly, represses Klf2 expression in the endothelium, which in turn down-regulates Foxp1 expression. As a consequence, the activation of the endothelial inflammasome was promoted, ultimately resulting in the formation of atherosclerotic lesions [33].

Chemical/Metabolic Factors

Studies have found that exposure of ECs to nicotine led to the NLRP3-ASC inflammasome activation and subsequent pyroptosis. The logical proof of this was the cleavage of caspase-1 and the generation of downstream IL-1β and IL-18. Subsequent experimental investigations disclosed that the nicotine-NLRP3-ASC-pyroptosis pathway was triggered by ROS. This conclusion was drawn because the ROS scavenger, N-acetyl-cysteine (NAC), was capable of averting ECs pyroptosis [34]. Therefore, during the development of nicotine-promoted AS, the ROS-mediated activation of NLRP3 inflammasome leading to ECs pyroptosis was an important mechanism further inducing the progression of AS. Moreover, there were studies to prove that the NLRP3-ASC inflammasome activation and the manifestation of nicotine's pro-atherosclerotic property, the signaling mediated by α1-nicotinic acetylcholine receptor(α1-nAchR) through lipid raft was indispensable [35]. Trimethylamine-N-oxide (TMAO), a metabolite of gut microbiota, has been closely associated with AS. Chen et al. found that TMAO could induce ECs pyroptosis through the ROS-NLRP3-caspase-1-GSDMD pathway, promoting vascular inflammation and neointimal formation [36]. Nuclear factor of activated T cells 5 (NFAT5) has been determined to be a critically important transcription factor. It plays a pivotal role in coordinating cellular defense mechanisms against osmotic stress specifically within the kidney [37]. Additionally, NFAT5 serves as a mediator in innate immune responses, highlighting the interconnectedness between its functions in inflammation and immunity [38]. Here, the research results vividly illustrated that due to hypertonic stress, which triggered the activation of NLRP3 inflammasome-mediated innate immunity by means of NFAT5 and the process of AS formation was accelerated. Particularly, high-salt-induced NFAT5 bound to the promoters of NLRP3 and IL-1β to exert control over their transcription, subsequently giving rise to the activation of the NLRP3 inflammasome and the onset of endothelial inflammation. The findings of this study reveal a groundbreaking mechanism underlying endothelial inflammation and the development of atherosclerotic lesions [39].

Environmental/Biology Factor

As a definite risk factor for AS, PM2.5 can activate the NLRP3 inflammasome in ECs, causing endothelial dysfunction and indirectly promoting the progression of AS [40]. Seroepidemiological investigation has shown that the Cytotoxin-related gene A (CagA) of Helicobacter pylori(H. pylori) has a positive correlation with the occurrence and development of AS [41]. However, Li et al.'s study found that the prevalence of CagA-positive strains in patients exhibited a significant positive correlation with the occurrence of AS, but not H. pylori. Research has shown that CagA exerts its influence in a way that it actively promotes inflammation within the aortic endothelium. This promotion of inflammation then acts as a driving force for accelerating the development of AS. The underlying mechanism operates through the NLRP3/caspase-1/IL-1β axis [42]. Research also proposed NLRP3 as a potential therapeutic target for CagA-positive H. pylori infection-related AS.

Proteins

Mixed lineage kinase domain-like (MLKL) was considered to be a key regulatory protein of necroptosis [43]. Wu et al. further found that ox-LDL induced an elevation in the expression of MLKL protein in ECs, the overexpression of MLKL significantly exacerbated the increases in the levels of caspase-1, IL-1β and lactate dehydrogenase (LDH) that were induced by ox-LDL. Remarkably, the effects of MLKL-induced caspase-1

activation and IL-1β maturation were abrogated by the NLRP3-specific inhibitor MCC950. It is demonstrated that MLKL promotes ox-LDL-induced pyroptosis and inflammation by activating the NLRP3 inflammasome [44]. This finding indicates that MLKL could be a highly targeted and promising therapeutic target for the mitigation of atherosclerotic-associated disorders. Moreover, it has been discovered that nuclear receptor subfamily 3 group C member 2 (NR3C2) is implicated in inflammatory pathways across various diseases [45,46]. Chen et al. Studies have shown that NR3C2 and NLRP3 levels had been elevated in the serum of coronary artery disease patients. Ox-LDL treatment had elevated NR3C2 levels, triggering ECs apoptosis, inflammation, and reducing cell viability. NR3C2 downregulation had enhanced ECs viability and mitigated ox-LDL-induced apoptosis and inflammation in ECs. The levels of NR3C2 had exhibited a positive correlation with NLRP3. Specifically, NR3C2 had upregulated the expression of NLRP3 at the transcriptional level [47]. This paper revealed the mechanism by which NR3C2 promoted the transcription of NLRP3 to induce inflammation in ECs treated with ox-LDL, thereby leading to ECs dysfunction. Reports have demonstrated that elevated levels of C-reactive protein (CRP) were closely associated with the initiation of AS. The underlying mechanism lay in its ability to directly enhance the transcytosis of LDL across ECs [48]. The work of Bian et al. elucidated the role of CRP in mediating the activation of the NLRP3 inflammasome. The underlying mechanisms involved the binding of CRP to CD32 and CD64, activation of NF-κB, upregulation of ROS levels, purinergic receptor signaling, and increased cysteine protease activity. Notably, this study revealed that the NLRP3 inflammasome played a role in the CRP-induced LDL transcytosis across ECs [49].

IncRNA

Besides, lncRNAs played a significant role in participating in the progression of ECs pyroptosis. Research has shown that the newly identified lncRNA, Gastric adenocarcinoma associated, positive CD44 regulator (Gaplinc), has the ability to interact with Specificity Protein 1(SP1). This interaction empowers the Gaplinc-SP1 complex with the capacity to bind to the NLRP3 promoter. As a direct consequence of this binding, the increased expression of target genes regulated by NLRP3, further leading to pyroptosis of ECs [50]. The results revealed the underlying mechanism of the lncRNA Gaplinc /SP1/NLRP3 axis in ECs pyroptosis, which may provide new potential targets for the treatment of AS.

3.1.2. Anti-as Endogenous Regulatory Factors: Inhibit the NLRP3 Inflammasome in ECs

MicroRNA (miRNA)

Hou et al.'s research results showed that LPS enhanced the expression of pro-inflammatory cytokines in a dose-dependent fashion. Additionally, it notably elevated the expression levels of phosphorylated NF-κB, NLRP3, and Caspase-1. Upon transfection of ECs with a miR-146a-5p mimic, a down-regulation of the mRNA and protein levels of NF-κB, NLRP3 and its downstream factors were observed. in addition, the expression of Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF6) and Interleukin-1 Receptor Associated Kinase 1(IRAK1) in these cells was down-regulated. As a result, MicroRNA-146a-5p, which acts as a modulator of TRAF6 and IRAK1, mitigates LPS-induced NLRP3 inflammasome and related inflammatory factors the generation and expression in ECs by precisely regulating the functions of TRAF6 and IRAK1 [51]. Therefore, it can be inferred that miR-146a-5p may be a new target for AS therapy. Meanwhile, the study by Bai et al. also found that miR-302c-3p exerted anti-pyroptotic effects both *in vitro* and *in vivo* by directly targeting NLRP3, thereby alleviating AS [52]. It is suggested that miR-302c-3p might be a powerful target for alleviating AS by inhibiting endothelial inflammation and pyroptosis. Also, it's interesting that research by Li et al. found that Sleep deprivation promoted endothelial inflammation and the occurrence of AS through reducing exosomal miR-182-5p, and via the myeloid differentiation factor 88 (MYD88)-NF-κB-NLRP3 pathway [53]. The interaction between sleep disorders and cardiovascular diseases is also expected to be further explored.

Protein/Cytokines

The transcriptional repressors Forkhead Box Protein P1 (FOXP1) was known as the gatekeeper of ECs inflammation [54]. To evaluate the role of Foxp1 in the development of AS, researchers conducted a study that included in-depth analysis of Foxp1 expression in human coronary arteries and mouse arteries. Notably, it was discovered that there existed a marked down-regulation of Foxp1 in the endothelium that was either atherosclerotic or prone to AS. In the hyperlipidemia model mice with endothelial-specific Foxp1 deficiency, the formation of atherosclerotic lesions at the aortic root significantly increased, monocyte adhesion was enhanced, and their migration and infiltration into the vessel wall were also augmented. In contrast, in the model mice with endothelial-

specific Foxp1 over-expression, the formation of atherosclerotic lesions decreased. Fibroblast growth factor 21 (FGF21) functions as an endocrine cytokine with a remarkable ability to specifically act on inflammation and AS [55]. Research carried out by Zeng et al. demonstrates that when ApoE$^{-/-}$ mice were treated exogenously with FGF21, there was a significant decline in the plaque area within the aortic sinus and a notable improvement in dyslipidemia. In both in-vivo and in-vitro models, FGF21 effectively mitigated the expression of pyroptosis-related proteins. FGF21 can also attenuate NLRP3-related pyroptosis by maintaining mitochondrial dynamics and function, reducing the production of ROS. Simultaneously, FGF21 inhibited endoplasmic reticulum stress in vascular ECs. The combined impact of these processes culminates in the manifestation of its anti-atherosclerotic properties [56] (Figure 3).

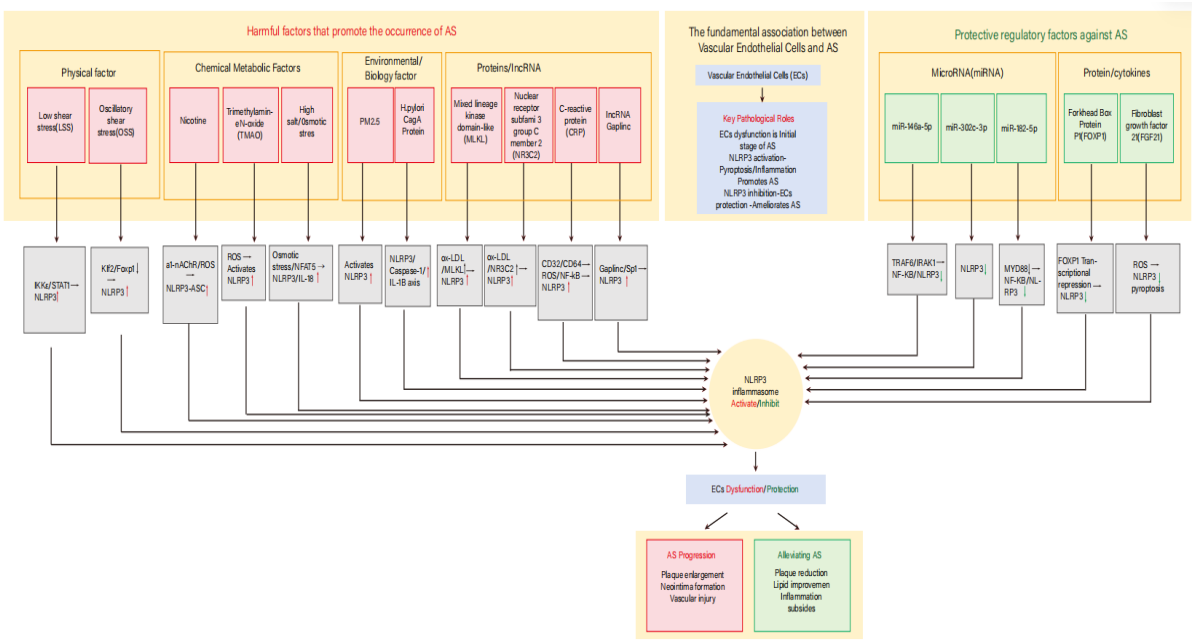

Figure 3. Regulation of endothelial NLRP3 inflammasome signaling in atherosclerosis. Harmful factors (physical, chemical/metabolic, environmental/biological, and protein/lncRNA) activate the NLRP3 inflammasome, trigger endothelial cell (EC) dysfunction, and drive atherosclerotic plaque progression. Conversely, protective factors (miRNAs, proteins, cytokines) inhibit inflammasome activation, maintain endothelial function, and mitigate atherosclerotic vascular injury.

3.2. Monocyte/Macrophage Infiltration, Macrophage Inflammation, and Foam Cell Formation

As a crucial component of the immune system, monocytes/macrophages had a significant impact on the development and exacerbation of AS. Mechanistically, the uptake of excess ox-LDL was accompanied by the infiltration of monocytes and the conversion of monocytes to macrophages to engulf ox-LDL and the formation of lipid-rich macrophages, namely foam cells, leading to the formation of early plaques called fat streaks [57]. In this process, the activation of monocytes/macrophage NLRP3 inflammasome was the key event that drives AS. The following elaborates on the specific mechanisms from four major aspects: harmful factors induction, protective regulatory factors, non-coding RNA regulation, and metabolites/lipid regulation.

3.2.1. Harmful Factors Promoting AS

Smoking-Related Components

Studies showed that the levels of transcription and translation of NLRP3 inflammasome assembly markers in all cell stages of THP-1 cells exposed to cigarette smoke condensate were increased, and the levels of downstream proinflammatory cytokines were significantly increased, confirming their activation of the inflammasome NLRP3. It was also suggested that cigarette smoke condensate exposure induced the transition of monocytes into macrophages and may also involve the activation of the NLRP3 inflammasome [58]. Nicotine, an active ingredient in cigarettes, has been demonstrated to promote the development of AS through the regulation of the autophagy-lysosomal pathway [59]. Studies have shown that NLRP3 inflammatory mediated macrophage pyroptosis was a key link in the development of AS [60,61]. However, whether nicotine, as an inflammatory stimulant, can cause macrophage pyroptosis and what is the mechanism? Therefore, *in vitro* studies by Xu et al.

have demonstrated the role of Histone deacetylase 6 (HDAC6) triggered by nicotine in the pyroptosis of macrophages. Nicotine upregulated histone deacetylase 6 (HDAC6) expression; this upregulation induced p65 deacetylation, enhanced p65 nuclear translocation, and thereby supported NLRP3 transcription, as p65 functions as a mediator for NLRP3 transcription. The transcription of NLRP3 ultimately led to macrophage pyroptosis. At the same time, *in vivo* studies showed that nicotine triggered a series of cellular events. For example, by directly acting on macrophages, nicotine triggered pyroptosis, ultimately speeding up the progression of AS [62].

Other Pro-Inflammatory/Pro-Oxidative Factors

Recently, it was reported that Golgi phosphoprotein 73 (GP73), a novel protein highly associated with inflammation and disruption of lipid metabolism, enhanced ox-LDL-induced THP-1-derived macrophage inflammation by influencing NLRP3 inflammasome signaling [63]. Furthermore, Oncostatin M also promoted the ox-LDL-induced activation of NLRP3 inflammasome via the NF-κB pathway in THP-1 macrophages and promoted the progression of AS [64]. In addition, some receptor proteins and channel proteins could also affect the development of AS by affecting the macrophage inflammasome NLRP3. Orecchioni et al. identified a role for the olfactory receptor Olfr2 and its human ortholog olfactory receptor OR6A2 in AS. Olfr2 on vascular macrophages bound octanol, a product of lipid peroxidation, and activated the NLRP3 inflammasome and IL-1β secretion, driving AS pathology. Inhibitors of OR6A2 might represent a promising therapy for AS [65]. Poly-(ADP-ribose) polymerases (PARPs) were also proteases. The activation of PARP was intimately associated with the onset and progression of numerous chronic inflammatory diseases, and it was anticipated that the suppression of PARP activity has emerged as a potential therapeutic target for the treatment of these kinds of diseases [66,67]. Thus, the latest study demonstrated that olaparib inhibition of PARP in THP-1 monocytes attenuates the expression of the protein of the NLRP3 inflammasome component induced by oxidation of ox-LDL as well as the IL-1β and IL-18 proteins. Olaparib inhibition of PARP also decreased NF-κB and NLRP3 inflammasome activity, monocyte adhesion and macrophage foam cell formation. Thus, the data from this study suggested that PARP inhibition inhibited NF-κB-induced NLRP3 inflammasome activity and mononuclear/macrophage oxidative stress. These results indicated that PARP inhibitor combined with immunomodulator has a certain effect on AS [68].

Liang et al. demonstrated that ox-LDL treatment significantly induced pyroptosis in THP-1 macrophages, accompanied by increased secretion of pro-inflammatory cytokines. Transfection with long intergenic non-coding RNA 00657 (linc00657) siRNA significantly alleviated these effects, while linc00657 overexpression exacerbated them. Mechanistically, high expression of linc00657 competitively bound to miR-106b-5p, releasing its inhibition on thioredoxin-interacting protein (TXNIP), thereby enhancing TXNIP-mediated NLRP3 inflammasome activation. Additionally, the study found that in the aortas of $ApoE^{-/-}$ mice fed a HFD, linc00657 overexpression significantly increased the expression of pyroptosis-related factors and decreased miR-106b-5p levels. These findings indicate that linc00657 promotes macrophage pyroptosis and exacerbates the progression of AS through the miR-106b-5p/TXNIP/NLRP3 pathway. Therefore, focusing on linc00657 in macrophages may open up a new prevention and treatment path for coronary atherosclerotic heart disease and provide a highly promising direction for the intervention strategy of this disease [69].

3.2.2. Protective Regulatory Factors against AS

Protein Regulatory Factors

Studies have investigated that How Sirtuin3 (SIRT3) may influence the intake of lipid substances and the conversion process of macrophages to foam cells when they are triggered via the action of ox-LDL. Research found that when compared to wild-type (WT) mice, SIRT3-deficient mice exhibited a more significant increase in foam cell formation and the accumulation of cellular cholesterol. Additionally, oxidative stress was exacerbated, the mitochondrial permeability potential was impaired, and NLRP3 was further activated in SIRT3-deficient mice. Treatment with Dihydromyricetin (DMY) increased the expression of SIRT3, and macrophages stimulated by ox-LDL markedly suppressed the aoxidative stress and diminished the activation level of NLRP3. In addition, in macrophages of SIRT3 knockout mice, DMY failed to exert the above-mentioned protective effect. Combining the results of various studies, this study clearly verified the positive role of SIRT3 in resisting oxidative stress and restraining the NLRP3 inflammasome from being activated, and also revealed its key protective effect on cholesterol accumulation and foam cell formation in macrophages under the ox-LDL stimulation environment. This research is significant for the formulation of prevention and treatment strategies for AS, and may provide a theoretical basis for the development of new prevention and treatment methods [70].

Other proteins, such as SUMO-specific protease 3 (SENP3)—a member of the SENPs family—also participate in this regulatory network. Although little had been reported about the role of SENP3 in vascular

disease, the latest research proved that in ox-LDL-stimulated macrophages, SENP3 inhibited cholesterol uptake, CD36 expression, and NLRP3 inflammasome activation [71].

Sestrins (SESNs) were a family of proteins that played an important role in cellular stress responses and metabolic regulation [72]. Researchers studied SESN1 and discovered its expression and function in macrophages. High expression of SESN1 was found in aortic macrophages of atherosclerotic mice. When SESN1 was overexpressed in macrophages, NLRP3 activation was inhibited, and the formation of the ASC-NLRP3 complex and the activation of caspase-1 and the production of mature IL-1β were reduced. Further studies found that SESN1 suppressed the NF-κB signaling pathway in macrophages that were stimulated by ox-LDL. SESN1 also restrained the activation of the NLRP3 inflammasome and the formation of foam cells triggered by cholesterol crystals. Adoptive transfer of macrophages overexpressed SESN1 decreased macrophage infiltration and proinflammatory cytokine expression, while knockdown of SESN1 did the opposite. In conclusion, SESN1 could reduce the development of AS by inhibiting NLRP3 inflammasome activation, foam cell formation, and macrophage inflammation [73].

Yuan et al. further identified the nuclear receptor Nur77 as a negative regulator of NLRP3. They found that Nur77 can directly bind to the promoter region of the NLRP3 gene, thereby inhibiting its transcriptional activity. In Nur77-deficient mice, macrophage-mediated inflammation driven by the NLRP3 inflammasome was significantly intensified, and the progression of AS was accelerated—highlighting Nur77's protective role in restraining NLRP3-dependent atherogenesis [74].

Beyond proteins involved in enzymatic or transcriptional regulation, ion channels also contribute to AS pathogenesis. As an important chloride ion channel, Voltage-gated chloride channel 2 (ClC-2) was involved in various pathophysiological processes. Previous studies had reported that the change of intracellular chloride ion concentration was related to the formation of macrophage foam cells [75]. However, recent studies by Ding et al. further demonstrated that the mechanism of CLC-2 was through suppressing the activation of the NLRP3 inflammasome. However, knockdown of ClC-2 exacerbated macrophage foam cell generation and inflammation [76].

MicroRNA (miRNA)

Research by Xu et al. indicated that miR-223-3p was downregulated in the serum of patients with AS and in THP-1 cells stimulated by ox-LDL. Overexpression of miR-223-3p could inhibit the activation of the NLRP3 inflammasome and inflammation in THP-1 cells induced by ox-LDL. Moreover, studies have demonstrated that NLRP3 and Forkhead Box Protein O3(FOXO3) were the two direct targets of miR-223-3p in THP-1 cells, and miR-223-3p inhibited the activation of NLRP3 inflammasome mediated by ox-LDL by directly targeting NLRP3 and FOXO3 [77]. miR-181a was also considered to participate in the progression of AS. Earlier studies demonstrated that the expression of miR-181a was down-regulated in carotid artery and ox-LDL-stimulated THP-1 macrophages in atherosclerotic mice. When miR-181a was overexpressed exogenously, it suppressed the activation of the MEK/ERK/NF-κB pathway. Moreover, it reduced the expression of proteins such as NLRP3, caspase-1, IL-18, and IL-1β [78]. Enhanced autophagy can inhibit the development of AS. Wang et al. showed that miR-99a-5p inhibited the activation of NLRP3 inflammasome by targeting mTOR and promoted macrophage autophagy and relieved AS [79].

Metabolites and Lipids

Yi et al. studied that SCFAs, including sodium acetate, sodium propionate, and sodium butyrate, were able to suppress the inflammation of macrophages triggered by ox-LDL. Moreover, it exerted its anti-inflammatory functions along the NF-κB/NLRP3 signaling pathway. The three SCFAs might have suppressed inflammation by impacting sphingolipid metabolism pathways in macrophages. The findings of this research offered a theoretical foundation for the utilization of lactic acid bacteria products or SCFAs and other therapies to prevent AS and adjuvant therapy [80]. Previous studies have shown that activation of inflammasome in proinflammatory macrophages requires fatty acid oxidation [81]. Studies by Hohensinner et al. have shown that pharmacological inhibition of fatty acid oxidation can slow down the advancement of AS by suppressing the process of NLRP3 inflammasome becoming active in macrophages [82] (Figure 4).

3.3. Apoptosis, Proliferation, Migration, and Phenotypic Transformation of Vascular Smooth Muscle Cells

The abnormal and excessive proliferation, the overly active migration, and the abnormal phenotypic transformation of VSMCs were considered to be important triggers of AS vascular inflammatory injury [83]. A variety of regulatory factors such as nicotine, long-chain RNA, enzymes and proteins can affect the AS process through two pathways: On one hand, these factors can activate the NLRP3 inflammasome, thereby promoting

excessive proliferation, abnormal migration, phenotypic transformation and apoptosis of VSMCs, and ultimately promoting the development of AS; on the other hand, some factors can also regulate the function of vascular smooth muscle by inhibiting the activation of the NLRP3 inflammasome, thereby exerting protective effects on AS.

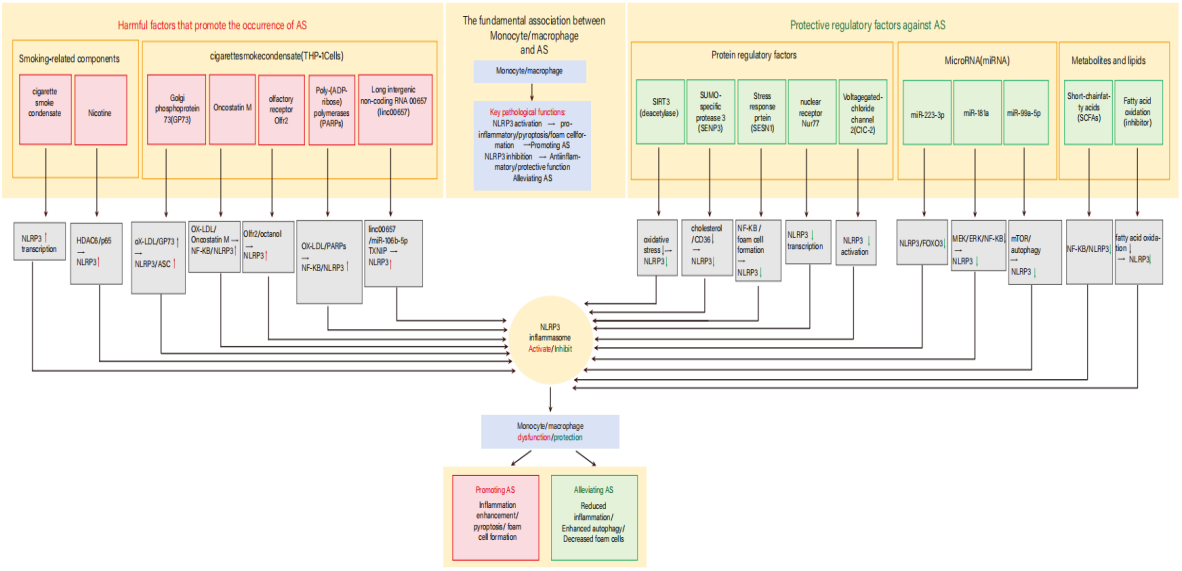

Figure 4. Regulation of NLRP3 inflammasome signaling in monocyte/macrophage dysfunction during atherosclerosis. Harmful factors (smoking-related components and cigarette smoke condensate-associated molecules) activate the NLRP3 inflammasome, promote inflammation, pyroptosis, and foam cell formation, driving atherosclerotic progression. Conversely, protective factors (proteins, miRNAs, metabolites, and lipids) inhibit inflammasome activation, reduce inflammation, enhance autophagy, and decrease foam cells, mitigating atherosclerosis.

3.3.1. Harmful Factors that Promote the Occurrence of AS

Chemical/Environmental Factors

New research showed that besides causing endothelial dysfunction, nicotine advanced the fragility of atherosclerotic plaques by triggering the functionality of the NLRP3 inflammasome in VSMCs, a process regulated by lysosomal dysfunction [84]. Tetrachlorobisphenol A (TCBPA), an organic compound widely used in industrial production, is also an environmental toxin that can cause oxidative stress and inflammation when it enters the body. Similarly, studies indicated that TCBPA could also affect VSMCs, prompting changes in them, and thus had an adverse effect on the development of AS. The research by Qiao and his colleagues further pointed out the possible toxicological effects of TCBPA on VSMCs. The molecular mechanism was that TCBPA promoted the proliferation of VSMCs and the occurrence and progression of AS through the ROS/NF-κB/NLRP3 signaling cascade [85].

Proteins

Ubiquitin carboxyl-terminal hydrolase L5 (UCHL5), as a deubiquitinating enzyme, promotes phenotype transformation of VSMCs and promote the process of becoming atherosclerotic. For example, Yang et al. showed that UCHL5 was significantly up-regulated in serum of VSMCs in atherosclerotic patients. Subsequent experiments showed that knockdown of UCHL5 not only inhibited the formation of plaques, vascular remodeling, and inflammatory responses induced by a HFD, but also inhibited the proliferation, migration, inflammation, and phenotypic transformation of VSMCs affected by ox-LDL. From the mechanism, for the initial time, This research revealed that the METTL14/YTHDF1 axis promoted UCHL5 expression by enhancing the m6A methylation level of UCHL5 mRNA, thereby activating the NLRP3 inflammasome, promoting the proliferation, migration, inflammation and phenotype transformation of VSMCs, and promoting the progression of AS [86]. Cathepsin B (CTSB) is widely expressed in humans and has a causal relationship with the development of AS. Li et al. investigated the effects and mechanisms of CTSB overexpression and knockdown on AS by feeding HFD to ApoE$^{-/-}$ mice, and explored the specific functions of CTSB in VSMCs *in vitro*. The study showed that CTSB increased the lesion area of AS plaques, and pyroptosis was observed in AS plaques, particularly in VSMCs. *In vitro* experiments revealed that ox-LDL upregulated CTSB expression, and CTSB promoted ox-LDL-induced pyroptosis in VSMCs. Additionally, CTSB activated the NLRP3 inflammasome and increased NLRP3 expression through the NF-κB/NLRP3 signaling pathway, thereby exacerbating AS in ApoE$^{-/-}$ mice [87].

3.3.2. Protective Regulatory Factors against AS

Ling et al. confirmed through a range of in-vivo and in-vitro experimental trials that mitochondrial dynamics related lncRNA (MDRL) regulated NLRP3 inflammasome activation and apoptosis of VSMCs, and played an anti-atherosclerotic role. The study showed that MDRL could alleviate AS by sponging miR-361, relieving its inhibitory effect on the p62 protein gene (SQSTM1), thereby suppressing NLRP3 inflammasome activation and apoptosis. This suggested that MDRL might be a potential therapeutic target for AS-related diseases [88]. Furthermore, the study by Zhang et al. elucidated that the C1q tumor necrosis factor associated protein 9 (CTRP9) exerted its protective effect against AS by regulating inflammation and the functions of VSMCs through the CTRP9-AMPK-NLRP3 inflammasome pathway [89] (Figure 5).

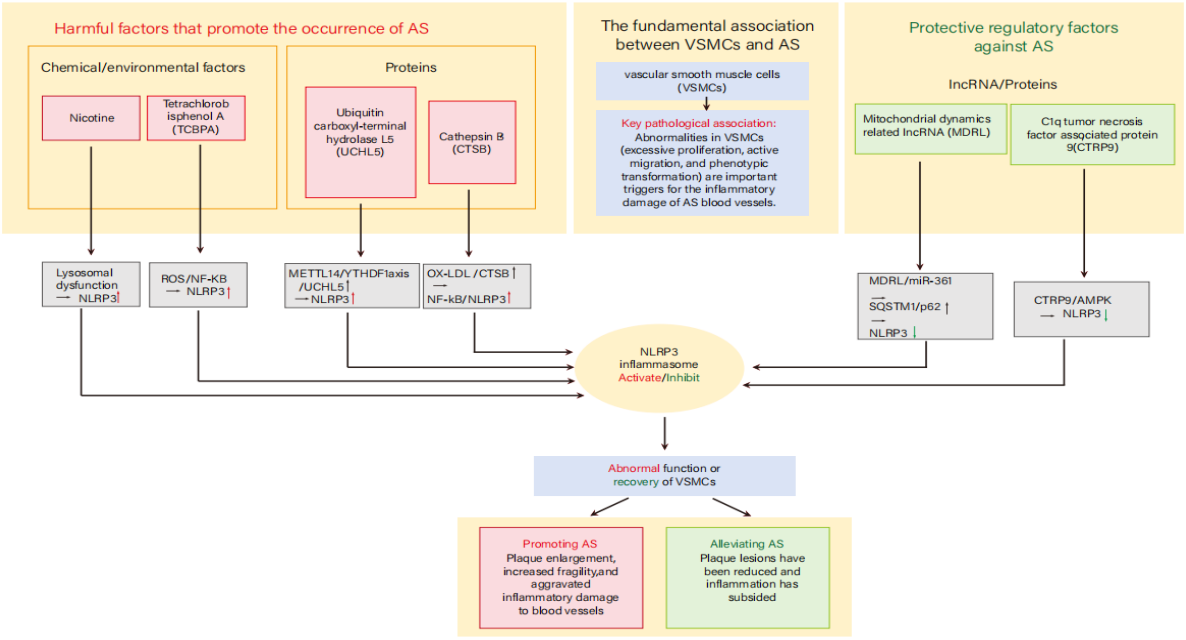

Figure 5. Regulation of NLRP3 inflammasome signaling in vascular smooth muscle cells (VSMCs) during atherosclerosis. Harmful factors (chemical/environmental agents and specific proteins) activate the NLRP3 inflammasome, trigger VSMC dysfunction, and promote plaque enlargement, fragility, and vascular inflammation. Conversely, protective factors (specific lncRNAs and proteins) inhibit inflammasome activation, restore VSMC function, reduce plaque lesions, and alleviate inflammation.

4.Roles of Other Inflammasomes in Atherosclerosis

At present, there is no report on whether other inflammasomes are involved in the occurrence and development of AS except NLRP1 and NLRC4. Previous studies have found that in 60 patients with atherosclerotic lesions and normal individuals, NLRP1 and NLRC4 gene expression levels in patients with atherosclerotic lesions were significantly higher than normal controls [90]. As far as NLRP1 is concerned, the study of Bleda et al. showcased that, in the setting of increased triglycerides and very-low-density lipoprotein (VLDL)concentrations, there is an increased expression of NLRP1 inflammasome in human arterial ECs [91]. Such expression is associated with the severity of endothelial dysfunction [92]. Ge, Ji-Yong et al. found that LINC00346 can inhibit NLRP1-mediated pyroptosis and autophagy activation by binding with microRNA-637, thereby reducing vascular damage [93].

5. Targeting the NLRP3 Inflammasome for the Treatment of AS

Given the central role of the NLRP3 inflammasome in the occurrence and development of AS, targeting the NLRP3 signaling pathway has become a highly promising therapeutic strategy. Currently, drug development for this pathway mainly focuses on four key aspects: inhibiting inflammasome assembly, blocking upstream activating signals, intercepting the release of downstream inflammatory factors, and regulating the gene expression and protein synthesis of NLRP3. As shown in the table below, these inhibitors include not only synthetic drugs with clear mechanisms of action, but also numerous active ingredients derived from natural products and traditional Chinese medicines. These traditional Chinese medicines-derived active ingredients and compound preparations

complement modern synthetic drugs and together form a rich drug resource library targeting NLRP3, providing an important basis for the development of more distinctive and effective anti-atherosclerotic drugs (Table 1).

Table 1. Classification, mechanisms, and representative drugs targeting the NLRP3 inflammasome in atherosclerosis.

Drug Category	Mechanism of Action	Representative Drugs	Source/Type	References
NLRP3 assembly inhibitor	Block the binding of NLRP3 to ASC/pro-caspase-1 and inhibit the assembly of inflammasome	MCC950	Pharmaceutical chemical	[94–98]
		VX-765		
		Tranilast		
		Impavido (Miltefosine)		
		GSK461364		
		Oridonin	Natural product	[99–110]
		Artesunate		
		Baicalin		
		Tanshinone IIA		
		Juglone		
		Colchicine		
		Quercetin		
		Curcumin		
		Paeoniol		
		Sorbremnoids A and B		
		Dehydrocostus Lactone		
		Resibufogenin (RBG)		
		preparation-Biejiajian pill	Herbal formula	[111,112]
		preparation-Xinmaikang Tablet		
NLRP3 activation signal blocker	It inhibits upstream activation signals (such as potassium efflux, mtROS, and lysosomal rupture), indirectly inhibiting NLRP3 activation	IL-36RN	Pharmaceutical chemical	[113,114]
		Small molecule mitochondrial uncouplers-Nitazoxanid		
		Polydatin	Natural product	[103,104,115–121]
		Andrographolide		
		Juglone		
		Colchicine		
		Apigenin		
		Fucoidan		
		Fisetin		
		Licorice		
		Methylberberine		
		Tongxinluo	Herbal formula	[122]
Inhibitor of inflammatory factor release	Inhibit the activity of caspase-1 or the secretion of IL-1β/IL-18 to block the downstream effect of NLRP3	The Novel Bispecific Antibody InflamAb	Pharmaceutical chemical	[123]
		Apple polyphenol extract	Natural product	[103,124]
		Juglone		
NLRP3 transcriptional/ translation regulator	Down-regulate the expression of the NLRP3 gene (such as targeting NF-κB and miRNA) or inhibit the translation of the NLRP3 protein	Salvianolic acid A and Salvianolic Acid B	Natural product	[100,102,115,116, 125–129]
		Polydatin		
		Apigenin		
		Rutaecarpine		
		Artesunate		
		Andrographolide		
		Tanshinone IIA		
		Phenethyl isothiocyanate (PEITC)		
		preparation-Biejiajian pill	Herbal formula	[111,112,130,131]
		preparation-Xinmaikang Tablet		

Note: Many natural products and herbal compounds exhibit multi-target effects. In this table, they are categorized according to their principal reported mechanism of action in the context of NLRP3 inflammasome regulation in atherosclerosis.

Regarding the mechanism of action, the mechanism of chemical drugs is clear and specific. The mechanism of traditional natural drugs/traditional Chinese medicines is relatively complex and mostly involves multi-target regulation. For example, some traditional Chinese medicines such as Polydatin, Andrographolide, and Artesunate inhibit the activation of NLRP3 by down-regulating the expression of NLRP3-related genes or by inhibiting upstream activating signals such as potassium efflux, mtROS, and lysosomal rupture. From the perspective of components and structure, the components of chemical drugs are single, mostly being artificial synthetic small molecule compounds such as MCC950, VX-765 or biological products, with clear structures. Traditional natural drugs/traditional Chinese medicines have complex and diverse components, containing various types of natural products such as alkaloids, flavonoids, and polyphenols, and are mixtures of multiple components. Taking

compound traditional Chinese medicine preparations as an example, they may contain several or even dozens of herbs, and each herb contains multiple active components.

Therefore, the advantage of chemical drugs lies in clear target points, clear mechanisms, rapid efficacy, and strong predictability, which facilitate the conduct of precision medical research. The limitations are the potential off-target effects, the possibility of developing drug resistance with long-term use, and the relatively obvious side effects of some chemical drugs, such as potential damage to liver and kidney functions. MCC950 was discontinued in clinical trials for rheumatoid arthritis due to liver toxicity issues, highlighting its potential off-target effects or mechanism-related toxicity. However, through reasonable drug design and dose optimization, these risks can be reduced to a certain extent.

The advantages of traditional natural drugs/traditional Chinese medicines are multi-component and multi-target synergy, overall regulation of the body's state. Traditional Chinese medicines mostly come from natural sources, and the body has a better tolerance to them, with relatively smaller toxic side effects. They may have an advantage in chronic inflammatory diseases and other conditions that require long-term adjustment. Traditional Chinese medicine generally has a long history of clinical use: many traditional Chinese medicines such as Polydatin, Andrographolide are used in traditional medicine to treat modern inflammatory diseases, and a large amount of clinical experience has been accumulated, suggesting its effectiveness and certain safety recognition. However, it should be noted that some components of traditional Chinese medicines may have potential toxicity, and the complex components of traditional Chinese medicine may interact with other drugs, and caution should be exercised when using in combination. Limitations are unclear mechanisms, difficult quality control, unstable efficacy, and difficulty in meeting the "precision" requirements of modern drug development.

Although the aforementioned small-molecule chemical drugs and natural Chinese medicine components have demonstrated clear potential in inhibiting the NLRP3 inflammasome, their clinical application is often challenged by low bioavailability, poor targeting, and potential off-target effects. Beyond the direct inhibition by traditional drugs, the current research focuses on in achieving precise and controllable NLRP3 intervention. Nanotechnology-based targeted therapy and combined medication strategies are the concentrated manifestations of progress in this direction. Among these, nanoscale targeted delivery systems represent the most prominent emerging technology, with research primarily focusing on utilizing nanotechnology to achieve specific accumulation of drugs at lesion sites and cell-specific delivery, especially to macrophages, while integrating cutting-edge strategies such as gene silencing, gene editing, and immunomodulation.

Firstly, the most fundamental approach in nanoscale targeted delivery is antibody-based targeting. For instance, Luo, Qiang et al. employed anti-CD47 antibodies to target plaque macrophages; their nanoparticles simultaneously achieve "intracellular NLRP3 inhibition + extracellular macrophage function repair", restoring the cholesterol clearance capacity of macrophages to synergistically alleviate AS [132]. Similarly, Jia, Xiong et al. used VCAM-1-binding peptides to target ECs in atherosclerotic plaques; the liposomes concurrently realize "intracellular NLRP3 gene silencing + extracellular LDL transport regulation". By silencing NLRP3, they inhibit inflammatory responses within plaques, while regulating the transcytosis of LDL to reduce lipid deposition in vascular walls, thereby exerting a dual synergistic effect in alleviating AS [133]. Research also involves direct intervention on the NLRP3 gene, which represents a cutting-edge therapeutic strategy for AS treatment at the genetic level.

Another category encompasses smart responsive nanocarriers that release drugs under stimulation from the lesion microenvironment, such as high levels of ROS. To achieve on-demand drug delivery. For example, Ni, Huaner et al. developed ROS-responsive nanoparticles loaded with small interfering ribonucleic acid (siRNA) targeting olfactory receptor 2. These nanoparticles can target lesion areas in atherosclerotic plaques where ROS levels are significantly elevated, using ROS as a signal for targeted response and drug release. They simultaneously achieve "intracellular olfactory receptor 2 gene silencing + atherosclerotic theranostics synergy": the siRNA silences the Olfr2 gene to regulate related inflammatory or lipid metabolism pathways, while the nanoparticles' properties assist in AS diagnosis, enabling dual synergistic intervention in AS [134]. This approach also integrates cutting-edge gene silencing strategies with nanoscale targeting. Additionally, Ni, Huaner, et al. conducted another study, which utilized a type of smart responsive nanomedicine based on dual-gas synergistic metal-organic supramolecular cages. While delivering NLRP3 inhibitors in a targeted manner, these nanomedicines release therapeutic gases, such as NO and CO. To regulate vascular relaxation, inhibit inflammation, and enhance the anti-atherosclerotic efficacy [135].

Furthermore, research by Anghelache, Maria et al. integrated more advanced immunomodulatory therapeutic strategies with nanotechnology. Moving beyond direct inhibition of NLRP3 itself, either upstream or downstream, this research shifts toward more advanced immune homeostasis reconstruction. They investigated nanoparticles loaded with pro-resolving lipid mediators, which actively initiate the "termination program" of inflammation rather

than merely inhibiting it. These biomimetic nanocarriers loaded with specialized pro-resolving lipid mediators can target atherosclerotic lesion areas and simultaneously achieve "intracellular inflammatory resolution regulation + extracellular plaque microenvironment improvement". By releasing specialized pro-resolving lipid mediators, they promote the active resolution of AS-related inflammation, instead of simple inflammation inhibition and improve the local plaque microenvironment, such as reducing inflammatory cell infiltration and promoting damage repair, thereby exerting a dual synergistic effect in alleviating AS and enhancing plaque stability [136].

The latest research by Yu, Wenfei et al. demonstrated the combined use of the antioxidant idebenone and the lipid-lowering drug rosuvastatin, which simultaneously achieves "intracellular NLRP3 inflammasome activation inhibition + extracellular lipid metabolism regulation" [137]. This dual effect synergistically prevents AS, embodying the latest efficient combined medication strategy for treating AS targeting NLRP3.

Beyond pharmaceutical therapeutic strategies, research by Wu, Tong et al. indicated that whole-grain highland barley alleviates AS in ApoE$^{-/-}$ mice through dual mechanisms: regulating the NLRP3 inflammation pathway and improving the gut microbiota, such as increasing the abundance of beneficial bacteria and reducing endotoxin release. This research not only provides a new dietary option for the prevention and treatment of AS but also lays a foundation for advancing studies on the "drug-food combination" therapeutic strategy for AS treatment via targeting NLRP3. Meanwhile, studies have suggested that aerobic exercise can also treat AS through targeting NLRP3, confirming that aerobic exercise is a safe, non-pharmaceutical approach for regulating the NLRP3 inflammation [138]. In terms of the clinical application of drugs, although the current enthusiasm for drug research in this field is high, most candidate drugs still remain at the preclinical stage. In the clinical treatment of atherosclerotic cardiovascular diseases, low-dose colchicine is the only standard treatment drug that has been verified by large-scale randomized controlled trials (RCTs) and widely recognized. Its clear anti-inflammatory effect includes the inhibition of NLRP3 [139,140]. In the field of traditional Chinese medicine, there have also been breakthroughs. A recent high-quality RCT has confirmed that Tongxinluo Capsules can significantly benefit patients with acute myocardial infarction [141]. This further confirms the potential of traditional Chinese medicine compound preparations to intervene in AS by regulating multiple targets, among which the NLRP3 signaling pathway may be one of the key targets. Additionally, natural extracts such as curcumin and quercetin, although there are small-scale clinical studies suggesting that they can improve AS risk factors, still require more clinical trials with hard endpoints to verify their efficacy.

6. Summary and Prospect

This study systematically reviewed the core role of the NLRP3 inflammasome in the pathogenesis of AS and the progress of targeted therapeutic approaches. At the mechanistic level, studies have clearly confirmed that the NLRP3 inflammasome serves as a key regulatory node in the cellular pathological process of AS, and its core role runs through the entire occurrence and development of AS. Specifically, this role is reflected in the regulation of three core pathological links: mediating pyroptosis of vascular ECs, promoting the infiltration of monocytes/macrophages and the formation of foam cells, and regulating the abnormal proliferation and migration of VSMCs. Atherosclerotic risk factors such as low shear stress, nicotine, and PM2.5 can exacerbate the damage to vascular ECs, macrophages, and VSMCs by activating the NLRP3 inflammasome, thereby accelerating the pathological progression of AS. In contrast, endogenous protective factors including miR-146a-5p and deacetylase SIRT3 can inhibit the activation or function of the NLRP3 inflammasome, thereby alleviating cellular damage and inflammatory responses and exerting anti-atherosclerotic effects. At the therapeutic strategy level, it summarized targeted chemical drugs such as MCC950, natural products such as baicalin, and the traditional Chinese medicine compound Tongxinluo Capsule, as well as frontier technologies such as anti-CD47 antibody-conjugated nanoparticles, ROS-responsive carriers, and combination therapy such as the combination of idebenone and rosuvastatin. These provide multiple options for precise intervention in AS. Although current research has clearly identified the importance of the NLRP3 inflammasome in AS, several areas require further investigation: firstly, the inflammasome family members are numerous. Besides NLRP3, the roles of other inflammasomes such as NLRP1 and NLRC4 in AS and their synergistic or antagonistic relationships with NLRP3 have not been clearly defined, and their cell-specific functions need to be further explored; secondly, the existing targeted NLRP3 drugs are mostly at the basic research or early clinical stage. Some chemical drugs such as MCC950 have safety issues such as hepatotoxicity, and the mechanisms of action of natural drugs and traditional Chinese medicine compound need more precise molecular target validation to solve clinical translation bottlenecks such as low bioavailability and difficult quality control; thirdly, the long circulation stability *in vivo*, immunogenicity of the nanosystem, and dose optimization of combination therapy of the nanosystem, as well as issues such as the stability of the nanosystem and the immune response, still need to be improved through more rigorous animal experiments and preclinical studies. In

the future, in-depth exploration can be carried out around the regulatory network of the NLRP3 inflammasome, the development of new targeted drugs, and the combined intervention of multiple technologies,which may provide new theoretical breakthroughs and clinical solutions for the prevention and treatment of AS, and promote the development of precise diagnosis and treatment of cardiovascular diseases.

Author Contributions: M.W.: data curation, writing—original draft preparation; J.C.: conceptualization, methodology, software; F.F.: investigation, supervision; L.C.: validation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the grants from the National Natural Science Foundation of China (Grant numbers: 82173813) and the Hunan Provincial Natural Science Foundation of China (Grant numbers: 2022JJ50173) and Hunan Provincial Natural Science Foundation Science and Health Joint Project (Grant numbers: 2023JJ60006) and Chenzhou National Sustainable Development Agenda Innovation Demonstration Areas Construction Provincial Special Funding (Grant numbers:2023sfq05).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies: No AI-assisted technologies were used in the preparation of this manuscript.

References

1. Emini Veseli, B.; Perrotta, P.; De Meyer, G.R.A.; Roth, L.; Van der Donckt, C.; Martinet, W.; De Meyer, G.R.Y. Animal models of atherosclerosis. *Eur. J. Pharmacol.* **2017**, *816*, 3–13. https://doi.org/10.1016/j.ejphar.2017.05.010.
2. Miao, J.; Zang, X.; Cui, X.; Zhang, J. Autophagy, Hyperlipidemia, and Atherosclerosis. *Adv. Exp. Med. Biol.* **2020**, *1207*, 237–264. https://doi.org/10.1007/978-981-15-4272-5_18.
3. Tall, A.R.; Yvan-Charvet, L. Cholesterol, inflammation and innate immunity. *Nat. Rev. Immunol.* **2015**, *15*, 104–116. https://doi.org/10.1038/nri3793.
4. Ezzati, M.; Obermeyer, Z.; Tzoulaki, I.; Mayosi, B.M.; Elliott, P.; Leon, D.A. Contributions of risk factors and medical care to cardiovascular mortality trends. *Nat. Rev. Cardiol.* **2015**, *12*, 508–530. https://doi.org/10.1038/nrcardio.2015.82.
5. Tsioufis, P.; Theofilis, P.; Tsioufis, K.; Tousoulis, D. The Impact of Cytokines in Coronary Atherosclerotic Plaque: Current Therapeutic Approaches. *Int. J. Mol. Sci.* **2022**, *23*, 15937. https://doi.org/10.3390/ijms232415937.
6. Schroder, K.; Tschopp, J. The inflammasomes. *Cell* **2010**, *140*, 821–832. https://doi.org/10.1016/j.cell.2010.01.040.
7. Cai, X.; Chen, J.; Xu, H.; Liu, S.; Jiang, Q.X.; Halfmann, R.; Chen, Z.J. Prion-like polymerization underlies signal transduction in antiviral immune defense and inflammasome activation. *Cell* **2014**, *156*, 1207–1222. https://doi.org/10.1016/j.cell.2014.01.063.
8. Li, Y.; Fu, T.M.; Lu, A.; Witt, K.; Ruan, J.; Shen, C.; Wu, H. Cryo-EM structures of ASC and NLRC4 CARD filaments reveal a unified mechanism of nucleation and activation of caspase-1. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 10845–10852. https://doi.org/10.1073/pnas.1810524115.
9. Shi, J.; Zhao, Y.; Wang, K.; Shi, X.; Wang, Y.; Huang, H.; Zhuang, Y.; Cai, T.; Wang, F.; Shao, F. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* **2015**, *526*, 660–665. https://doi.org/10.1038/nature15514.
10. Kesavardhana, S.; Kanneganti, T.D. Mechanisms governing inflammasome activation, assembly and pyroptosis induction. *Int. Immunol.* **2017**, *29*, 201–210. https://doi.org/10.1093/intimm/dxx018.
11. Takahashi, M. NLRP3 inflammasome as a key driver of vascular disease. *Cardiovasc. Res.* **2022**, *118*, 372–385. https://doi.org/10.1093/cvr/cvab010.
12. Christgen, S.; Place, D.E.; Kanneganti, T.D. Toward targeting inflammasomes: Insights into their regulation and activation. *Cell Res* **2020**, *30*, 315–327. https://doi.org/10.1038/s41422-020-0295-8.
13. Christgen, S.; Kanneganti, T.D. Inflammasomes and the fine line between defense and disease. *Curr. Opin. Immunol.* **2020**, *62*, 39–44. https://doi.org/10.1016/j.coi.2019.11.007.
14. Kelley, N.; Jeltema, D.; Duan, Y.; He, Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *Int. J. Mol. Sci.* **2019**, *20*, 3328. https://doi.org/10.3390/ijms20133328.
15. Takahashi, M. Cell-Specific Roles of NLRP3 Inflammasome in Myocardial Infarction. *J. Cardiovasc. Pharmacol.* **2019**, *74*, 188–193. https://doi.org/10.1097/fjc.0000000000000709.
16. McKee, C.M.; Coll, R.C. NLRP3 inflammasome priming: A riddle wrapped in a mystery inside an enigma. *J. Leukoc. Biol.* **2020**, *108*, 937–952. https://doi.org/10.1002/jlb.3mr0720-513r.
17. Di Virgilio, F.; Dal Ben, D.; Sarti, A.C.; Giuliani, A.L.; Falzoni, S. The P2X7 Receptor in Infection and Inflammation. *Immunity* **2017**, *47*, 15–31. https://doi.org/10.1016/j.immuni.2017.06.020.

18. He, Y.; Zeng, M.Y.; Yang, D.; Motro, B.; Núñez, G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature* **2016**, *530*, 354–357. https://doi.org/10.1038/nature16959.
19. Sharif, H.; Wang, L.; Wang, W.L.; Magupalli, V.G.; Andreeva, L.; Qiao, Q.; Hauenstein, A.V.; Wu, Z.; Núñez, G.; Mao, Y.; et al. Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. *Nature* **2019**, *570*, 338–343. https://doi.org/10.1038/s41586-019-1295-z.
20. Zhou, R.; Yazdi, A.S.; Menu, P.; Tschopp, J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* **2011**, *469*, 221–225. https://doi.org/10.1038/nature09663.
21. Shimada, K.; Crother, T.R.; Karlin, J.; Dagvadorj, J.; Chiba, N.; Chen, S.; Ramanujan, V.K.; Wolf, A.J.; Vergnes, L.; Ojcius, D.M.; et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity* **2012**, *36*, 401–414. https://doi.org/10.1016/j.immuni.2012.01.009.
22. Próchnicki, T.; Latz, E. Inflammasomes on the Crossroads of Innate Immune Recognition and Metabolic Control. *Cell Metab.* **2017**, *26*, 71–93. https://doi.org/10.1016/j.cmet.2017.06.018.
23. Iyer, S.S.; He, Q.; Janczy, J.R.; Elliott, E.I.; Zhong, Z.; Olivier, A.K.; Sadler, J.J.; Knepper-Adrian, V.; Han, R.; Qiao, L.; et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. *Immunity* **2013**, *39*, 311–323. https://doi.org/10.1016/j.immuni.2013.08.001.
24. Zhong, Z.; Liang, S.; Sanchez-Lopez, E.; He, F.; Shalapour, S.; Lin, X.J.; Wong, J.; Ding, S.; Seki, E.; Schnabl, B.; et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature* **2018**, *560*, 198–203. https://doi.org/10.1038/s41586-018-0372-z.
25. Zhong, Z.; Umemura, A.; Sanchez-Lopez, E.; Liang, S.; Shalapour, S.; Wong, J.; He, F.; Boassa, D.; Perkins, G.; Ali, S.R.; et al. NF-κB Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. *Cell* **2016**, *164*, 896–910. https://doi.org/10.1016/j.cell.2015.12.057.
26. Nakahira, K.; Haspel, J.A.; Rathinam, V.A.; Lee, S.J.; Dolinay, T.; Lam, H.C.; Englert, J.A.; Rabinovitch, M.; Cernadas, M.; Kim, H.P.; et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat. Immunol.* **2011**, *12*, 222–230. https://doi.org/10.1038/ni.1980.
27. Rajamäki, K.; Lappalainen, J.; Oörni, K.; Välimäki, E.; Matikainen, S.; Kovanen, P.T.; Eklund, K.K. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: A novel link between cholesterol metabolism and inflammation. *PLoS ONE* **2010**, *5*, e11765. https://doi.org/10.1371/journal.pone.0011765.
28. Chen, J.; Chen, Z.J. PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation. *Nature* **2018**, *564*, 71–76. https://doi.org/10.1038/s41586-018-0761-3.
29. Jiang, C.; Xie, S.; Yang, G.; Wang, N. Spotlight on NLRP3 Inflammasome: Role in Pathogenesis and Therapies of Atherosclerosis. *J. Inflamm. Res.* **2021**, *14*, 7143–7172. https://doi.org/10.2147/jir.s344730.
30. Theofilis, P.; Oikonomou, E.; Chasikidis, C.; Tsioufis, K.; Tousoulis, D. Inflammasomes in Atherosclerosis-From Pathophysiology to Treatment. *Pharmaceuticals* **2023**, *16*, 1211. https://doi.org/10.3390/ph16091211.
31. He, L.; Zhang, C.L.; Chen, Q.; Wang, L.; Huang, Y. Endothelial shear stress signal transduction and atherogenesis: From mechanisms to therapeutics. *Pharmacol. Ther.* **2022**, *235*, 108152. https://doi.org/10.1016/j.pharmthera.2022.108152.
32. Lv, Y.; Jiang, Z.; Zhou, W.; Yang, H.; Jin, G.; Wang, D.; Kong, C.; Qian, Z.; Gu, Y.; Chen, S.; et al. Low-Shear Stress Promotes Atherosclerosis via Inducing Endothelial Cell Pyroptosis Mediated by IKKepsilon/STAT1/NLRP3 Pathway. *Inflammation* **2024**, *47*, 1053–1066. https://doi.org/10.1007/s10753-023-01960-w.
33. Zhuang, T.; Liu, J.; Chen, X.; Zhang, L.; Pi, J.; Sun, H.; Li, L.; Bauer, R.; Wang, H.; Yu, Z.; et al. Endothelial Foxp1 Suppresses Atherosclerosis via Modulation of Nlrp3 Inflammasome Activation. *Circ. Res.* **2019**, *125*, 590–605. https://doi.org/10.1161/circresaha.118.314402.
34. Wu, X.; Zhang, H.; Qi, W.; Zhang, Y.; Li, J.; Li, Z.; Lin, Y.; Bai, X.; Liu, X.; Chen, X.; et al. Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis. *Cell Death Dis.* **2018**, *9*, 171. https://doi.org/10.1038/s41419-017-0257-3.
35. Duan, F.; Zeng, C.; Liu, S.; Gong, J.; Hu, J.; Li, H.; Tan, H. α1-nAchR-Mediated Signaling Through Lipid Raft Is Required for Nicotine-Induced NLRP3 Inflammasome Activation and Nicotine-Accelerated Atherosclerosis. *Front. Cell Dev. Biol.* **2021**, *9*, 724699. https://doi.org/10.3389/fcell.2021.724699.
36. Chen, C.Y.; Leu, H.B.; Wang, S.C.; Tsai, S.H.; Chou, R.H.; Lu, Y.W.; Tsai, Y.L.; Kuo, C.S.; Huang, P.H.; Chen, J.W.; et al. Inhibition of Trimethylamine N-Oxide Attenuates Neointimal Formation Through Reduction of Inflammasome and Oxidative Stress in a Mouse Model of Carotid Artery Ligation. *Antioxid. Redox Signal.* **2023**, *38*, 215–233. https://doi.org/10.1089/ars.2021.0115.
37. Miyakawa, H.; Woo, S.K.; Dahl, S.C.; Handler, J.S.; Kwon, H.M. Tonicity-responsive enhancer binding protein, a rel-like protein that stimulates transcription in response to hypertonicity. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 2538–2542. https://doi.org/10.1073/pnas.96.5.2538.

38. Boland, B.S.; Widjaja, C.E.; Banno, A.; Zhang, B.; Kim, S.H.; Stoven, S.; Peterson, M.R.; Jones, M.C.; Su, H.I.; Crowe, S.E.; et al. Immunodeficiency and autoimmune enterocolopathy linked to NFAT5 haploinsufficiency. *J. Immunol.* **2015**, *194*, 2551–2560. https://doi.org/10.4049/jimmunol.1401463.
39. Ma, P.; Zha, S.; Shen, X.; Zhao, Y.; Li, L.; Yang, L.; Lei, M.; Liu, W. NFAT5 mediates hypertonic stress-induced atherosclerosis via activating NLRP3 inflammasome in endothelium. *Cell Commun. Signal.* **2019**, *17*, 102. https://doi.org/10.1186/s12964-019-0406-7.
40. Hu, T.; Zhu, P.; Liu, Y.; Zhu, H.; Geng, J.; Wang, B.; Yuan, G.; Peng, Y.; Xu, B. PM2.5 induces endothelial dysfunction via activating NLRP3 inflammasome. *Environ. Toxicol.* **2021**, *36*, 1886–1893. https://doi.org/10.1002/tox.23309.
41. Mendall, M.A.; Goggin, P.M.; Molineaux, N.; Levy, J.; Toosy, T.; Strachan, D.; Camm, A.J.; Northfield, T.C. Relation of Helicobacter pylori infection and coronary heart disease. *Br. Heart J.* **1994**, *71*, 437–439. https://doi.org/10.1136/hrt.71.5.437.
42. Li, B.W.; Liu, Y.; Zhang, L.; Guo, X.Q.; Wen, C.; Zhang, F.; Luo, X.Y.; Xia, Y.P. Cytotoxin-associated gene A (CagA) promotes aortic endothelial inflammation and accelerates atherosclerosis through the NLRP3/caspase-1/IL-1β axis. *FASEB J.* **2021**, *35*, e21942. https://doi.org/10.1096/fj.202100695RR.
43. Quarato, G.; Guy, C.S.; Grace, C.R.; Llambi, F.; Nourse, A.; Rodriguez, D.A.; Wakefield, R.; Frase, S.; Moldoveanu, T.; Green, D.R. Sequential Engagement of Distinct MLKL Phosphatidylinositol-Binding Sites Executes Necroptosis. *Mol. Cell* **2016**, *61*, 589–601. https://doi.org/10.1016/j.molcel.2016.01.011.
44. Wu, Q.; He, X.; Wu, L.M.; Zhang, R.Y.; Li, L.M.; Wu, C.M.; Lu, Y.B.; Hu, B.; Shi, C.; Lu, Z.F.; et al. MLKL Aggravates Ox-LDL-Induced Cell Pyroptosis via Activation of NLRP3 Inflammasome in Human Umbilical Vein Endothelial Cells. *Inflammation* **2020**, *43*, 2222–2231. https://doi.org/10.1007/s10753-020-01289-8.
45. Huang, Y.; Wang, Y.; Ouyang, Y. Elevated microRNA-135b-5p relieves neuronal injury and inflammation in post-stroke cognitive impairment by targeting NR3C2. *Int. J. Neurosci.* **2022**, *132*, 58–66. https://doi.org/10.1080/00207454.2020.1802265.
46. Wang, C.; Hu, F. Long noncoding RNA SOX2OT silencing alleviates cerebral ischemia-reperfusion injury via miR-135a-5p-mediated NR3C2 inhibition. *Brain Res. Bull.* **2021**, *173*, 193–202. https://doi.org/10.1016/j.brainresbull.2021.05.018.
47. Chen, X.; Li, W.; Chang, C. NR3C2 mediates oxidised low-density lipoprotein-induced human coronary endothelial cells dysfunction via modulation of NLRP3 inflammasome activation. *Autoimmunity* **2023**, *56*, 2189135. https://doi.org/10.1080/08916934.2023.2189135.
48. Bian, F.; Yang, X.; Zhou, F.; Wu, P.H.; Xing, S.; Xu, G.; Li, W.; Chi, J.; Ouyang, C.; Zhang, Y.; et al. C-reactive protein promotes atherosclerosis by increasing LDL transcytosis across endothelial cells. *Br. J. Pharmacol.* **2014**, *171*, 2671–2684. https://doi.org/10.1111/bph.12616.
49. Bian, F.; Yang, X.Y.; Xu, G.; Zheng, T.; Jin, S. CRP-Induced NLRP3 Inflammasome Activation Increases LDL Transcytosis Across Endothelial Cells. *Front. Pharmacol.* **2019**, *10*, 40. https://doi.org/10.3389/fphar.2019.00040.
50. Tang, Y.; Yan, J.H.; Ge, Z.W.; Fei, A.H.; Zhang, Y.C. LncRNA Gaplinc promotes the pyroptosis of vascular endothelial cells through SP1 binding to enhance NLRP3 transcription in atherosclerosis. *Cell. Signal.* **2022**, *99*, 110420. https://doi.org/10.1016/j.cellsig.2022.110420.
51. Hou, J.; Deng, Q.; Deng, X.; Zhong, W.; Liu, S.; Zhong, Z. MicroRNA-146a-5p alleviates lipopolysaccharide-induced NLRP3 inflammasome injury and pro-inflammatory cytokine production via the regulation of TRAF6 and IRAK1 in human umbilical vein endothelial cells (HUVECs). *Ann. Transl. Med.* **2021**, *9*, 1433. https://doi.org/10.21037/atm-21-3903.
52. Bai, B.; Yang, Y.; Ji, S.; Wang, S.; Peng, X.; Tian, C.; Sun, R.C.; Yu, T.; Chu, X.M. MicroRNA-302c-3p inhibits endothelial cell pyroptosis via directly targeting NOD-, LRR- and pyrin domain-containing protein 3 in atherosclerosis. *J. Cell. Mol. Med.* **2021**, *25*, 4373–4386. https://doi.org/10.1111/jcmm.16500.
53. Li, X.; Cao, Y.; Xu, X.; Wang, C.; Ni, Q.; Lv, X.; Yang, C.; Zhang, Z.; Qi, X.; Song, G. Sleep Deprivation Promotes Endothelial Inflammation and Atherogenesis by Reducing Exosomal miR-182-5p. *Arterioscler. Thromb. Vasc. Biol.* **2023**, *43*, 995–1014. https://doi.org/10.1161/atvbaha.123.319026.
54. Kanter, J.E. FOXP1: A Gatekeeper of Endothelial Cell Inflammation. *Circ. Res.* **2019**, *125*, 606–608. https://doi.org/10.1161/circresaha.119.315687.
55. Lin, Z.; Pan, X.; Wu, F.; Ye, D.; Zhang, Y.; Wang, Y.; Jin, L.; Lian, Q.; Huang, Y.; Ding, H.; et al. Fibroblast growth factor 21 prevents atherosclerosis by suppression of hepatic sterol regulatory element-binding protein-2 and induction of adiponectin in mice. *Circulation* **2015**, *131*, 1861–1871. https://doi.org/10.1161/circulationaha.115.015308.
56. Zeng, Z.; Zheng, Q.; Chen, J.; Tan, X.; Li, Q.; Ding, L.; Zhang, R.; Lin, X. FGF21 mitigates atherosclerosis via inhibition of NLRP3 inflammasome-mediated vascular endothelial cells pyroptosis. *Exp. Cell Res.* **2020**, *393*, 112108. https://doi.org/10.1016/j.yexcr.2020.112108.
57. Galkina, E.; Ley, K. Immune and inflammatory mechanisms of atherosclerosis (*). *Annu. Rev. Immunol.* **2009**, *27*, 165–197. https://doi.org/10.1146/annurev.immunol.021908.132620.

58. Mehta, S.; Dhawan, V. Exposure of cigarette smoke condensate activates NLRP3 inflammasome in THP-1 cells in a stage-specific manner: An underlying role of innate immunity in atherosclerosis. *Cell. Signal.* **2020**, *72*, 109645. https://doi.org/10.1016/j.cellsig.2020.109645.
59. Ni, H.; Xu, S.; Chen, H.; Dai, Q. Nicotine Modulates CTSS (Cathepsin S) Synthesis and Secretion Through Regulating the Autophagy-Lysosomal Machinery in Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 2054–2069. https://doi.org/10.1161/atvbaha.120.314053.
60. Martinet, W.; Coornaert, I.; Puylaert, P.; De Meyer, G.R.Y. Macrophage Death as a Pharmacological Target in Atherosclerosis. *Front. Pharmacol.* **2019**, *10*, 306. https://doi.org/10.3389/fphar.2019.00306.
61. Corrêa, R.; Silva, L.F.F.; Ribeiro, D.J.S.; Almeida, R.D.N.; Santos, I.O.; Corrêa, L.H.; de Sant'Ana, L.P.; Assunção, L.S.; Bozza, P.T.; Magalhães, K.G. Lysophosphatidylcholine Induces NLRP3 Inflammasome-Mediated Foam Cell Formation and Pyroptosis in Human Monocytes and Endothelial Cells. *Front. Immunol.* **2019**, *10*, 2927. https://doi.org/10.3389/fimmu.2019.02927.
62. Xu, S.; Chen, H.; Ni, H.; Dai, Q. Targeting HDAC6 attenuates nicotine-induced macrophage pyroptosis via NF-κB/NLRP3 pathway. *Atherosclerosis* **2021**, *317*, 1–9. https://doi.org/10.1016/j.atherosclerosis.2020.11.021.
63. Lin, Y.F.; Li, M.H.; Huang, R.H.; Zhang, S.Z.; Xu, X.F.; Zhou, H.M.; Liu, M.H.; Liao, X.X.; Liao, L.Z.; Guo, Y.; et al. GP73 enhances the ox-LDL-induced inflammatory response in THP-1 derived macrophages via affecting NLRP3 inflammasome signaling. *Int. J. Cardiol.* **2023**, *387*, 131109. https://doi.org/10.1016/j.ijcard.2023.05.059.
64. Liu, C.; Wu, J.; Jia, H.; Lu, C.; Liu, J.; Li, Y.; Guo, M. Oncostatin M promotes the ox-LDL-induced activation of NLRP3 inflammasomes via the NF-κB pathway in THP-1 macrophages and promotes the progression of atherosclerosis. *Ann. Transl. Med.* **2022**, *10*, 456. https://doi.org/10.21037/atm-22-560.
65. Wang, C.; Andreasson, K.I. Odorant receptors in macrophages: Potential targets for atherosclerosis. *Trends Immunol.* **2022**, *43*, 262–264. https://doi.org/10.1016/j.it.2022.02.006.
66. Pazzaglia, S.; Pioli, C. Multifaceted Role of PARP-1 in DNA Repair and Inflammation: Pathological and Therapeutic Implications in Cancer and Non-Cancer Diseases. *Cells* **2019**, *9*, 41. https://doi.org/10.3390/cells9010041.
67. Fehr, A.R.; Singh, S.A.; Kerr, C.M.; Mukai, S.; Higashi, H.; Aikawa, M. The impact of PARPs and ADP-ribosylation on inflammation and host-pathogen interactions. *Genes Dev.* **2020**, *34*, 341–359. https://doi.org/10.1101/gad.334425.119.
68. Mustafa, K.; Han, Y.; He, D.; Wang, Y.; Niu, N.; Jose, P.A.; Jiang, Y.; Kopp, J.B.; Lee, H.; Qu, P. Poly-(ADP-ribose) polymerases inhibition by olaparib attenuates activities of the NLRP3 inflammasome and of NF-κB in THP-1 monocytes. *PLoS ONE* **2024**, *19*, e0295837. https://doi.org/10.1371/journal.pone.0295837.
69. Liang, Y.; Xu, X.D.; Xu, X.; Cai, Y.B.; Zhu, Z.X.; Zhu, L.; Ren, K. Linc00657 promoted pyroptosis in THP-1-derived macrophages and exacerbated atherosclerosis via the miR-106b-5p/TXNIP/NLRP3 axis. *Int. J. Biol. Macromol.* **2023**, *253*, 126953. https://doi.org/10.1016/j.ijbiomac.2023.126953.
70. Ding, Y.; Gong, W.; Zhang, S.; Shen, J.; Liu, X.; Wang, Y.; Chen, Y.; Meng, G. Protective role of sirtuin3 against oxidative stress and NLRP3 inflammasome in cholesterol accumulation and foam cell formation of macrophages with ox-LDL-stimulation. *Biochem. Pharmacol.* **2021**, *192*, 114665. https://doi.org/10.1016/j.bcp.2021.114665.
71. Chen, J.; Sun, X.; Liu, Y.; Zhang, Y.; Zhao, M.; Shao, L. SENP3 attenuates foam cell formation by deSUMOylating NLRP3 in macrophages stimulated with ox-LDL. *Cell. Signal.* **2024**, *117*, 111092. https://doi.org/10.1016/j.cellsig.2024.111092.
72. Lee, J.H.; Budanov, A.V.; Karin, M. Sestrins orchestrate cellular metabolism to attenuate aging. *Cell Metab.* **2013**, *18*, 792–801. https://doi.org/10.1016/j.cmet.2013.08.018.
73. Keping, Y.; Yunfeng, S.; Pengzhuo, X.; Liang, L.; Chenhong, X.; Jinghua, M. Sestrin1 inhibits oxidized low-density lipoprotein-induced activation of NLRP3 inflammasome in macrophages in a murine atherosclerosis model. *Eur. J. Immunol.* **2020**, *50*, 1154–1166. https://doi.org/10.1002/eji.201948427.
74. Yuan, R.; Zhang, W.; Nie, P.; Lan, K.; Yang, X.; Yin, A.; Xiao, Q.; Shen, Y.; Xu, K.; Wang, X.; et al. Nur77 Deficiency Exacerbates Macrophage NLRP3 Inflammasome-Mediated Inflammation and Accelerates Atherosclerosis. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 2017815. https://doi.org/10.1155/2022/2017815.
75. Wu, Q.Q.; Liu, X.Y.; Xiong, L.X.; Shang, J.Y.; Mai, X.Y.; Pang, R.P.; Su, Y.X.; Yu, B.X.; Yuan, J.N.; Yang, C.; et al. Reduction of Intracellular Chloride Concentration Promotes Foam Cell Formation. *Circ. J.* **2016**, *80*, 1024–1033. https://doi.org/10.1253/circj.CJ-15-1209.
76. Ding, W.; Li, J.; Wang, L.; Zhang, M.; Zheng, F. ClC-2 inhibition prevents macrophage foam cell formation by suppressing Nlrp3 inflammasome activation. *Biosci. Biotechnol. Biochem.* **2020**, *84*, 2096–2103. https://doi.org/10.1080/09168451.2020.1793294.
77. Xu, W.; Qian, L.; Yuan, X.; Lu, Y. MicroRNA-223-3p inhibits oxidized low-density lipoprotein-mediated NLRP3 inflammasome activation via directly targeting NLRP3 and FOXO3. *Clin. Hemorheol. Microcirc.* **2022**, *81*, 241–253. https://doi.org/10.3233/ch-211232.

78. Song, J.; Yang, S.; Yin, R.; Xiao, Q.; Ma, A.; Pan, X. MicroRNA-181a regulates the activation of the NLRP3 inflammatory pathway by targeting MEK1 in THP-1 macrophages stimulated by ox-LDL. *J. Cell. Biochem.* **2019**, *120*, 13640–13650. https://doi.org/10.1002/jcb.28637.
79. Wang, G.; Jing, S.Y.; Liu, G.; Guo, X.J.; Zhao, W.; Jia, X.L.; Zheng, M.Q.; Tan, W.Y. miR-99a-5p: A Potential New Therapy for Atherosclerosis by Targeting mTOR and Then Inhibiting NLRP3 Inflammasome Activation and Promoting Macrophage Autophagy. *Dis. Markers* **2022**, *2022*, 7172583. https://doi.org/10.1155/2022/7172583.
80. Yi, C.; Sun, W.; Ding, L.; Yan, M.; Sun, C.; Qiu, C.; Wang, D.; Wu, L. Short-Chain Fatty Acids Weaken Ox-LDL-Induced Cell Inflammatory Injury by Inhibiting the NLRP3/Caspase-1 Pathway and Affecting Cellular Metabolism in THP-1 Cells. *Molecules* **2022**, *27*, 8801. https://doi.org/10.3390/molecules27248801.
81. Moon, J.S.; Nakahira, K.; Chung, K.P.; DeNicola, G.M.; Koo, M.J.; Pabón, M.A.; Rooney, K.T.; Yoon, J.H.; Ryter, S.W.; Stout-Delgado, H.; et al. NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages. *Nat. Med.* **2016**, *22*, 1002–1012. https://doi.org/10.1038/nm.4153.
82. Hohensinner, P.J.; Lenz, M.; Haider, P.; Mayer, J.; Richter, M.; Kaun, C.; Goederle, L.; Brekalo, M.; Salzmann, M.; Sharma, S.; et al. Pharmacological inhibition of fatty acid oxidation reduces atherosclerosis progression by suppression of macrophage NLRP3 inflammasome activation. *Biochem. Pharmacol.* **2021**, *190*, 114634. https://doi.org/10.1016/j.bcp.2021.114634.
83. Lu, Q.B.; Wan, M.Y.; Wang, P.Y.; Zhang, C.X.; Xu, D.Y.; Liao, X.; Sun, H.J. Chicoric acid prevents PDGF-BB-induced VSMC dedifferentiation, proliferation and migration by suppressing ROS/NFκB/mTOR/P70S6K signaling cascade. *Redox Biol.* **2018**, *14*, 656–668. https://doi.org/10.1016/j.redox.2017.11.012.
84. An, J.; Ouyang, L.; Yu, C.; Carr, S.M.; Ramprasath, T.; Liu, Z.; Song, P.; Zou, M.H.; Ding, Y. Nicotine exacerbates atherosclerosis and plaque instability via NLRP3 inflammasome activation in vascular smooth muscle cells. *Theranostics* **2023**, *13*, 2825–2842. https://doi.org/10.7150/thno.81388.
85. Qiao, H.; Yang, B.; Lv, X.; Liu, Y. Exposure to TCBPA stimulates the growth of arterial smooth muscle cells through the activation of the ROS/NF-κB/NLRP3 signaling pathway. *Toxicology* **2024**, *503*, 153759. https://doi.org/10.1016/j.tox.2024.153759.
86. Yang, X.; Wang, C.; Zhu, G.; Guo, Z.; Fan, L. METTL14/YTHDF1 axis-modified UCHL5 aggravates atherosclerosis by activating the NLRP3 inflammasome. *Exp. Cell Res.* **2023**, *427*, 113587. https://doi.org/10.1016/j.yexcr.2023.113587.
87. Li, H.; Zhao, Q.; Liu, D.; Zhou, B.; Liao, F.; Chen, L. Cathepsin B aggravates atherosclerosis in ApoE-deficient mice by modulating vascular smooth muscle cell pyroptosis through NF-κB / NLRP3 signaling pathway. *PLoS ONE* **2024**, *19*, e0294514. https://doi.org/10.1371/journal.pone.0294514.
88. You, L.; Zheng, Y.; Yang, J.; Hou, Q.; Wang, L.; Zhang, Y.; Zhao, C.; Xie, R. LncRNA MDRL Mitigates Atherosclerosis through miR-361/SQSTM1/NLRP3 Signaling. *Mediat. Inflamm.* **2022**, *2022*, 5463505. https://doi.org/10.1155/2022/5463505.
89. Zhang, H.; Gong, X.; Ni, S.; Wang, Y.; Zhu, L.; Ji, N. C1q/TNF-related protein-9 attenuates atherosclerosis through AMPK-NLRP3 inflammasome singling pathway. *Int. Immunopharmacol.* **2019**, *77*, 105934. https://doi.org/10.1016/j.intimp.2019.105934.
90. Borborema, M.E.A.; Crovella, S.; Oliveira, D.; de Azevêdo Silva, J. Inflammasome activation by NLRP1 and NLRC4 in patients with coronary stenosis. *Immunobiology* **2020**, *225*, 151940. https://doi.org/10.1016/j.imbio.2020.151940.
91. Bleda, S.; de Haro, J.; Varela, C.; Ferruelo, A.; Acin, F. Elevated levels of triglycerides and vldl-cholesterol provoke activation of nlrp1 inflammasome in endothelial cells. *Int. J. Cardiol.* **2016**, *220*, 52–55. https://doi.org/10.1016/j.ijcard.2016.06.193.
92. Bleda, S.; de Haro, J.; Varela, C.; Esparza, L.; Ferruelo, A.; Acin, F. NLRP1 inflammasome, and not NLRP3, is the key in the shift to proinflammatory state on endothelial cells in peripheral arterial disease. *Int. J. Cardiol.* **2014**, *172*, e282–e284. https://doi.org/10.1016/j.ijcard.2013.12.201.
93. Ge, J.Y.; Yan, X.J.; Yang, J.; Jin, H.; Sun, Z.K.; Guo, J.L.; Zhu, Y.; Wang, F.F. LINC00346 regulates NLRP1-mediated pyroptosis and autophagy via binding to microRNA-637 in vascular endothelium injury. *Cell. Signal.* **2023**, *109*, 110740. https://doi.org/10.1016/j.cellsig.2023.110740.
94. Zeng, W.; Wu, D.; Sun, Y.; Suo, Y.; Yu, Q.; Zeng, M.; Gao, Q.; Yu, B.; Jiang, X.; Wang, Y. The selective NLRP3 inhibitor MCC950 hinders atherosclerosis development by attenuating inflammation and pyroptosis in macrophages. *Sci. Rep.* **2021**, *11*, 19305. https://doi.org/10.1038/s41598-021-98437-3.
95. Tapia-Abellán, A.; Angosto-Bazarra, D.; Martínez-Banaclocha, H.; de Torre-Minguela, C.; Cerón-Carrasco, J.P.; Pérez-Sánchez, H.; Arostegui, J.I.; Pelegrin, P. MCC950 closes the active conformation of NLRP3 to an inactive state. *Nat. Chem. Biol.* **2019**, *15*, 560–564. https://doi.org/10.1038/s41589-019-0278-6.
96. Chen, S.; Wang, Y.; Pan, Y.; Liu, Y.; Zheng, S.; Ding, K.; Mu, K.; Yuan, Y.; Li, Z.; Song, H.; et al. Novel Role for Tranilast in Regulating NLRP3 Ubiquitination, Vascular Inflammation, and Atherosclerosis. *J. Am. Heart Assoc.* **2020**, *9*, e015513. https://doi.org/10.1161/jaha.119.015513.

97. Traughber, C.A.; Iacano, A.J.; Neupane, K.; Khan, M.R.; Opoku, E.; Nunn, T.; Prince, A.; Sangwan, N.; Hazen, S.L.; Smith, J.D.; et al. Impavido attenuates inflammation, reduces atherosclerosis, and alters gut microbiota in hyperlipidemic mice. *iScience* **2023**, *26*, 106453. https://doi.org/10.1016/j.isci.2023.106453.
98. Luo, R.; Ma, M.; Wang, D.; Luo, L.; Xu, X.; Huang, L.; Wang, F.; Kuang, G.; Liu, H.; Ni, R.; et al. GSK461364 Inhibits NLRP3 Inflammasome by Targeting NEK7 Phosphorylation. *Adv. Sci* **2025**, *12*, e04816. https://doi.org/10.1002/advs.202504816.
99. Wang, L.; Zhao, X.; Ding, J.; Liu, Y.; Liu, H.; Zheng, L.; Zhao, H.; Sun, Z.; Li, K.; Cai, J.; et al. Oridonin attenuates the progression of atherosclerosis by inhibiting NLRP3 and activating Nrf2 in apolipoprotein E-deficient mice. *Inflammopharmacology* **2023**, *31*, 1993–2005. https://doi.org/10.1007/s10787-023-01161-9.
100. Liu, P.; Wang, Y.; Tian, K.; Bai, X.; Wang, Y.; Wang, Y. Artesunate inhibits macrophage-like phenotype switching of vascular smooth muscle cells and attenuates vascular inflammatory injury in atherosclerosis via NLRP3. *Biomed. Pharmacother.* **2024**, *172*, 116255. https://doi.org/10.1016/j.biopha.2024.116255.
101. Zhao, J.; Wang, Z.; Yuan, Z.; Lv, S.; Su, Q. Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice. *Diabetes Vasc. Dis. Res.* **2020**, *17*, 1479164120977441. https://doi.org/10.1177/1479164120977441.
102. Wen, J.; Chang, Y.; Huo, S.; Li, W.; Huang, H.; Gao, Y.; Lin, H.; Zhang, J.; Zhang, Y.; Zuo, Y.; et al. Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation. *Aging* **2020**, *13*, 910–932. https://doi.org/10.18632/aging.202202.
103. Kim, N.H.; Kim, H.K.; Lee, J.H.; Jo, S.I.; Won, H.M.; Lee, G.S.; Lee, H.S.; Nam, K.W.; Kim, W.J.; Han, M.D. Juglone Suppresses LPS-induced Inflammatory Responses and NLRP3 Activation in Macrophages. *Molecules* **2020**, *25*, 3104. https://doi.org/10.3390/molecules25133104.
104. Li, Y.; Zhang, Y.; Lu, J.; Yin, Y.; Xie, J.; Xu, B. Anti-inflammatory mechanisms and research progress of colchicine in atherosclerotic therapy. *J. Cell. Mol. Med.* **2021**, *25*, 8087–8094. https://doi.org/10.1111/jcmm.16798.
105. Li, H.; Xiao, L.; He, H.; Zeng, H.; Liu, J.; Jiang, C.; Mei, G.; Yu, J.; Chen, H.; Yao, P.; et al. Quercetin Attenuates Atherosclerotic Inflammation by Inhibiting Galectin-3-NLRP3 Signaling Pathway. *Mol. Nutr. Food Res.* **2021**, *65*, e2000746. https://doi.org/10.1002/mnfr.202000746.
106. Ruan, H.; Zeng, X.; Shen, S. Mechanism of Curcumin Inhibiting NLRP3 Inflammatory Body and Improving Atherosclerotic Endothelial Cell Injury. *Discov. Med.* **2024**, *36*, 121–128. https://doi.org/10.24976/Discov.Med.202436180.11.
107. Liu, Y.; Wu, H.; Wang, T.; Shi, X.; He, H.; Huang, H.; Yang, Y.; Dai, M. Paeonol reduces microbial metabolite α-hydroxyisobutyric acid to alleviate the ROS/TXNIP/NLRP3 pathway-mediated endothelial inflammation in atherosclerosis mice. *Chin. J. Nat. Med.* **2023**, *21*, 759–774. https://doi.org/10.1016/s1875-5364(23)60506-0.
108. Zhang, K.; Liu, J.; Jiang, Y.; Sun, S.; Wang, R.; Sun, J.; Ma, C.; Chen, Y.; Wang, W.; Hou, X.; et al. Sorbremnoids A and B: NLRP3 Inflammasome Inhibitors Discovered from Spatially Restricted Crosstalk of Biosynthetic Pathways. *J. Am. Chem. Soc.* **2024**, *146*, 18172–18183. https://doi.org/10.1021/jacs.4c06538.
109. Lv, Q.; Zhang, Y.; Wang, J.; Lin, W.; Xie, Y.; Yang, H.; Yin, X.; Zhu, Z.; Cui, Y.; Hu, Y.; et al. Dehydrocostus Lactone Effectively Alleviates Inflammatory Diseases by Covalently and Irreversibly Targeting NLRP3. *MedComm* **2025**, *6*, e70367. https://doi.org/10.1002/mco2.70367.
110. Xiaoyang, C.; Yijun, C.; Chenguang, Z.; Wanying, D.; Zijun, C.; Jun, W.; Xuegong, X.; Wei, W.; Chun, L. Resibufogenin protects against atherosclerosis in ApoE(-/-) mice through blocking NLRP3 inflammasome assembly. *J. Adv. Res.* **2025**. https://doi.org/10.1016/j.jare.2025.04.029.
111. Fu, Y.; Yuan, J.; Sang, F.; Shao, M.; Yan, S.; Li, L.; Zhu, R.; Wang, Z. Biejiajian Pill Ameliorates Diabetes-Associated Atherosclerosis through Inhibition of the NLRP3 Inflammasome. *Evid. Based Complement. Altern. Med.* **2022**, *2022*, 9131178. https://doi.org/10.1155/2022/9131178.
112. Hou, C.; Jiang, X.; Sheng, W.; Zhang, Y.; Lin, Q.; Hong, S.; Zhao, J.; Wang, T.; Ye, X. Xinmaikang (XMK) tablets alleviate atherosclerosis by regulating the SREBP2-mediated NLRP3/ASC/Caspase-1 signaling pathway. *J. Ethnopharmacol.* **2024**, *319*, 117240. https://doi.org/10.1016/j.jep.2023.117240.
113. Tian, Y.; Ling, X.Y.; Chen, D.L.; Zhang, X.Q.; Qiu, C.M. Interleukin-36 receptor antagonist attenuates atherosclerosis development by inhibiting NLRP3 inflammasome. *J. Cell. Physiol.* **2020**, *235*, 9992–9996. https://doi.org/10.1002/jcp.29813.
114. Ma, M.H.; Li, F.F.; Li, W.F.; Zhao, H.; Jiang, M.; Yu, Y.Y.; Dong, Y.C.; Zhang, Y.X.; Li, P.; Bu, W.J.; et al. Repurposing nitazoxanide as a novel anti-atherosclerotic drug based on mitochondrial uncoupling mechanisms. *Br. J. Pharmacol.* **2023**, *180*, 62–79. https://doi.org/10.1111/bph.15949.
115. Zhang, X.; Wang, Z.; Li, X.; Chen, J.; Yu, Z.; Li, X.; Sun, C.; Hu, L.; Wu, M.; Liu, L. Polydatin protects against atherosclerosis by activating autophagy and inhibiting pyroptosis mediated by the NLRP3 inflammasome. *J. Ethnopharmacol.* **2023**, *309*, 116304. https://doi.org/10.1016/j.jep.2023.116304.

116. Chen, C.C.; Lii, C.K.; Liu, K.L.; Lin, Y.L.; Lo, C.W.; Li, C.C.; Yang, Y.C.; Chen, H.W. Andrographolide Attenuates Oxidized LDL-Induced Activation of the NLRP3 Inflammasome in Bone Marrow-Derived Macrophages and Mitigates HFCCD-Induced Atherosclerosis in Mice. *Am. J. Chin. Med.* **2023**, *51*, 2175–2193. https://doi.org/10.1142/s0192415x23500933.
117. Weng, X.; Luo, X.; Dai, X.; Lv, Y.; Zhang, S.; Bai, X.; Bao, X.; Wang, Y.; Zhao, C.; Zeng, M.; et al. Apigenin inhibits macrophage pyroptosis through regulation of oxidative stress and the NF-κB pathway and ameliorates atherosclerosis. *Phytother. Res.* **2023**, *37*, 5300–5314. https://doi.org/10.1002/ptr.7962.
118. Cheng, Y.; Pan, X.; Wang, J.; Li, X.; Yang, S.; Yin, R.; Ma, A.; Zhu, X. Fucoidan Inhibits NLRP3 Inflammasome Activation by Enhancing p62/SQSTM1-Dependent Selective Autophagy to Alleviate Atherosclerosis. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 3186306. https://doi.org/10.1155/2020/3186306.
119. Varghese, J.F.; Patel, R.; Singh, M.; Yadav, U.C.S. Fisetin Prevents Oxidized Low-density Lipoprotein-Induced Macrophage Foam Cell Formation. *J. Cardiovasc. Pharmacol.* **2021**, *78*, e729–e737. https://doi.org/10.1097/fjc.0000000000001096.
120. He, J.; Deng, Y.; Ren, L.; Jin, Z.; Yang, J.; Yao, F.; Liu, Y.; Zheng, Z.; Chen, D.; Wang, B.; et al. Isoliquiritigenin from licorice flavonoids attenuates NLRP3-mediated pyroptosis by SIRT6 in vascular endothelial cells. *J. Ethnopharmacol.* **2023**, *303*, 115952. https://doi.org/10.1016/j.jep.2022.115952.
121. Peng, Z.; Zhan, H.; Shao, Y.; Xiong, Y.; Zeng, L.; Zhang, C.; Liu, Z.; Huang, Z.; Su, H.; Yang, Z. 13-Methylberberine improves endothelial dysfunction by inhibiting NLRP3 inflammasome activation via autophagy induction in human umbilical vein endothelial cells. *Chin. Med.* **2020**, *15*, 8. https://doi.org/10.1186/s13020-020-0286-1.
122. Jiang, X.; Ma, C.; Gao, Y.; Cui, H.; Zheng, Y.; Li, J.; Zong, W.; Zhang, Q. Tongxinluo attenuates atherosclerosis by inhibiting ROS/NLRP3/caspase-1-mediated endothelial cell pyroptosis. *J. Ethnopharmacol.* **2023**, *304*, 116011. https://doi.org/10.1016/j.jep.2022.116011.
123. Delfos, L.; Depuydt, M.A.C.; Chemaly, M.; Coyle, S.; Schaftenaar, F.H.; van Santbrink, P.J.; Lindenbergh, P.P.; Bernabé Kleijn, M.N.A.; Costello, C.; Power, C.A.; et al. NLRP3 Inflammasome Inhibition by the Novel Bispecific Antibody InflamAb Attenuates Atherosclerosis in Apolipoprotein E-Deficient Mice. *JACC Basic Transl. Sci.* **2025**, *10*, 826–840. https://doi.org/10.1016/j.jacbts.2024.12.012.
124. Yang, H.; Song, R.; Xie, Y.; Qian, Q.; Wu, Z.; Han, S.; Li, X. Apple Polyphenol Extract Ameliorates Atherosclerosis and Associated Cognitive Impairment through Alleviating Neuroinflammation by Weakening TLR4 Signaling and NLRP3 Inflammasome in High-Fat/Cholesterol Diet-Fed LDLR(-/-) Male Mice. *J. Agric. Food Chem.* **2023**, *71*, 15506–15521. https://doi.org/10.1021/acs.jafc.3c01966.
125. Ma, Q.; Yang, Q.; Chen, J.; Yu, C.; Zhang, L.; Zhou, W.; Chen, M. Salvianolic Acid A Ameliorates Early-Stage Atherosclerosis Development by Inhibiting NLRP3 Inflammasome Activation in Zucker Diabetic Fatty Rats. *Molecules* **2020**, *25*, 1089. https://doi.org/10.3390/molecules25051089.
126. Zhang, Y.; Feng, X.; Du, M.; Ding, J.; Liu, P. Salvianolic acid B attenuates the inflammatory response in atherosclerosis by regulating MAPKs/ NF-κB signaling pathways in LDLR-/- mice and RAW264.7 cells. *Int. J. Immunopathol. Pharmacol.* **2022**, *36*, 3946320221079468. https://doi.org/10.1177/03946320221079468.
127. Lu, Z.; Liu, L.; Zhao, S.; Zhao, J.; Li, S.; Li, M. Apigenin attenuates atherosclerosis and non-alcoholic fatty liver disease through inhibition of NLRP3 inflammasome in mice. *Sci. Rep.* **2023**, *13*, 7996. https://doi.org/10.1038/s41598-023-34654-2.
128. Luo, J.; Wang, X.; Jiang, X.; Liu, C.; Li, Y.; Han, X.; Zuo, X.; Li, Y.; Li, N.; Xu, Y.; et al. Rutaecarpine derivative R3 attenuates atherosclerosis via inhibiting NLRP3 inflammasome-related inflammation and modulating cholesterol transport. *FASEB J.* **2020**, *34*, 1398–1411. https://doi.org/10.1096/fj.201900903RRR.
129. Jiang, X.; Li, Y.; Wang, W.; Han, X.; Han, J.; Chen, M.; Zhang, J.; Wang, C.; Li, S.; Luo, J.; et al. Nuclear Factor Erythroid 2 Related Factor 2 Activator JC-5411 Inhibits Atherosclerosis Through Suppression of Inflammation and Regulation of Lipid Metabolism. *Front. Pharmacol.* **2020**, *11*, 532568. https://doi.org/10.3389/fphar.2020.532568.
130. Liu, M.; Luo, G.; Liu, T.; Yang, T.; Wang, R.; Ren, W.; Liu, P.; Lai, X.; Zhou, H.; Yang, S. Zhilong Huoxue Tongyu Capsule Alleviated the Pyroptosis of Vascular Endothelial Cells Induced by ox-LDL through miR-30b-5p/NLRP3. *Evid. Based Complement. Altern. Med.* **2022**, *2022*, 3981350. https://doi.org/10.1155/2022/3981350.
131. Liu, M.; Wang, R.; Chen, M.; Hu, Z.; Han, M.; Mazhar, M.; Xue, J.; Zou, Y.; Wu, Q.; Yang, S. Zhilong Huoxue Tongyu capsule inhibits rabbit model of hyperlipidemia and atherosclerosis through NF-κB/NLRP3 signaling pathway. *Heliyon* **2023**, *9*, e20026. https://doi.org/10.1016/j.heliyon.2023.e20026.
132. Luo, Q.; Dai, L.; Li, J.; Chen, H.; Hao, Y.; Li, Q.; Pan, L.; Song, C.; Qian, Z.; Chen, M. Intracellular and extracellular synergistic therapy for restoring macrophage functions via anti-CD47 antibody-conjugated bifunctional nanoparticles in atherosclerosis. *Bioact. Mater.* **2024**, *34*, 326–337. https://doi.org/10.1016/j.bioactmat.2023.12.024.
133. Jia, X.; Bai, X.; Yang, X.; Wang, L.; Lu, Y.; Zhu, L.; Zhao, Y.; Cheng, W.; Shu, M.; Mei, Q.; et al. VCAM-1-binding peptide targeted cationic liposomes containing NLRP3 siRNA to modulate LDL transcytosis as a novel therapy for experimental atherosclerosis. *Metabolism* **2022**, *135*, 155274. https://doi.org/10.1016/j.metabol.2022.155274.

134. Ni, H.; Zhou, H.; Liang, X.; Ge, Y.; Chen, H.; Liu, J.; Wang, B.; Chen, H.; Zhang, Y.; Luo, S.; et al. Reactive Oxygen Species-Responsive Nanoparticle Delivery of Small Interfering Ribonucleic Acid Targeting Olfactory Receptor 2 for Atherosclerosis Theranostics. *ACS Nano* **2024**, *18*, 23599–23614. https://doi.org/10.1021/acsnano.4c07988.
135. Li, D.; Chen, J.; Lu, Y.; Yan, X.; Yang, X.; Zhang, F.; Tang, Y.; Cao, M.; Wang, J.; Pan, M.; et al. Codelivery of Dual Gases with Metal-Organic Supramolecular Cage-Based Microenvironment-Responsive Nanomedicine for Atherosclerosis Therapy. *Small* **2024**, *20*, e2402673. https://doi.org/10.1002/smll.202402673.
136. Anghelache, M.; Voicu, G.; Anton, R.; Safciuc, F.; Boteanu, D.; Deleanu, M.; Turtoi, M.; Simionescu, M.; Manduteanu, I.; Calin, M. Inflammation resolution-based treatment of atherosclerosis using biomimetic nanocarriers loaded with specialized pro-resolving lipid mediators. *Mater. Today Bio* **2025**, *32*, 101733. https://doi.org/10.1016/j.mtbio.2025.101733.
137. Yu, W.; Jiang, W.; Wu, W.; Wang, G.; Zhao, D.; Yan, C.; Lin, P. Combining idebenone and rosuvastatin prevents atherosclerosis by suppressing oxidative stress and NLRP3 inflammasome activation. *Eur. J. Pharmacol.* **2023**, *955*, 175911. https://doi.org/10.1016/j.ejphar.2023.175911.
138. Hu, S.; Wan, X.; Li, X.; Wang, X. Aerobic exercise alleviates pyroptosis-related diseases by regulating NLRP3 inflammasome. *Front. Physiol.* **2022**, *13*, 965366. https://doi.org/10.3389/fphys.2022.965366.
139. Tardif, J.C.; Kouz, S.; Waters, D.D.; Bertrand, O.F.; Diaz, R.; Maggioni, A.P.; Pinto, F.J.; Ibrahim, R.; Gamra, H.; Kiwan, G.S.; et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N. Engl. J. Med.* **2019**, *381*, 2497–2505. https://doi.org/10.1056/NEJMoa1912388.
140. Nidorf, S.M.; Fiolet, A.T.L.; Mosterd, A.; Eikelboom, J.W.; Schut, A.; Opstal, T.S.J.; The, S.H.K.; Xu, X.F.; Ireland, M.A.; Lenderink, T.; et al. Colchicine in Patients with Chronic Coronary Disease. *N. Engl. J. Med.* **2020**, *383*, 1838–1847. https://doi.org/10.1056/NEJMoa2021372.
141. Yang, Y.; Li, X.; Chen, G.; Xian, Y.; Zhang, H.; Wu, Y.; Yang, Y.; Wu, J.; Wang, C.; He, S.; et al. Traditional Chinese Medicine Compound (Tongxinluo) and Clinical Outcomes of Patients with Acute Myocardial Infarction: The CTS-AMI Randomized Clinical Trial. *JAMA* **2023**, *330*, 1534–1545. https://doi.org/10.1001/jama.2023.19524.