

Review

Inflammasomes in Atherosclerosis and Atherothrombosis

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Abstract

Atherosclerotic cardiovascular disease and its thrombotic complications, particularly myocardial infarction and ischemic stroke, remain leading causes of morbidity and mortality worldwide. Atherosclerosis was historically considered primarily a lipid accumulation disorder; however, it is now well recognized as a chronic inflammatory disease driven in large part by innate immune signaling. Inflammasomes, particularly NOD-like receptor protein 3 (NLRP3) and absent in melanoma 2 (AIM2), play important role in this process, linking vascular inflammation, plaque progression, and thrombosis through caspase-1 activation, interleukin-1 beta (IL-1 β) and IL-18 release, and gasdermin-mediated pyroptosis. In this narrative review we integrate mechanistic and translational evidence defining inflammasome activity across the continuum of atherosclerosis and atherothrombosis. We highlight inflammasome signaling in endothelial cells, macrophages, vascular smooth muscle cells, platelets, neutrophils, and perivascular adipose tissue, and discuss how these pathways contribute to early inflammation, necrotic core expansion, fibrous cap destabilization, and ultimately to acute thrombus formation. Emerging data on AIM2 activation, clonal hematopoiesis, platelet inflammasomes, and cell-free deoxyribonucleic acid (DNA) further expand current paradigms beyond macrophage focused models on macrophages. We also review single-cell and spatial transcriptomics, circulating biomarkers, and advanced vascular imaging approaches that may enable the identification of inflammasome-high atherothrombotic phenotypes. Finally, we appraise therapeutic strategies targeting inflammasomes and downstream pathways. These include IL-1 β and IL-6 inhibition, colchicine, direct NLRP3 inhibition, and cardiometabolic therapies with indirect effects on inflammasome activity. By examining the role of inflammasomes in linking plaque pathogenesis to thrombosis, this review outlines key translational opportunities and challenges for the precision prevention of atherothrombosis.

Keywords: inflammasomes; atherosclerosis; atherothrombosis; atherosclerotic cardiovascular disease; NLRP3; AIM2; pyroptosis

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading global cause of mortality and morbidity due to the acute atherothrombotic events it creates, such as myocardial infarction (MI) and ischemic stroke [1,2,3]. ASCVD has historically been described as a cholesterol storage disease, in which plaque formation is the result of cholesterol deposition. As our knowledge of the pathogenesis of atherosclerosis has expanded, it has been shown that this view reflects only part of a more complex biological process [3]. Indeed, ASCVD is now widely considered a chronic, maladaptive inflammatory disease in which dysregulated innate immune signals orchestrate vascular injury, plaque progression, plaque destabilization, and acute thrombosis [4].

Inflammasomes, cytosolic multiprotein sensing platforms such as NOD-like receptor protein 3 (NLRP3), absent in melanoma 2 (AIM2), and related complexes, have emerged as central regulators of this process [5]. By controlling the activation of caspase-1, inflammasomes govern the maturation of interleukin-1 beta (IL-1 β) and IL-18, and induce pyroptosis, a lytic, pro-inflammatory form of cell death [6]. Within the atherosclerotic plaque, inflammasome activation contributes to endothelial dysfunction, foam-cell formation, smooth muscle cell phenotypic switching, and extracellular matrix degradation, thereby weakening the fibrous cap and priming lesions for rupture [5]. Beyond the arterial wall, inflammasomes, when activated, seem to induce acute thrombosis. Indeed, pyroptotic cell remnants promote coagulation, IL-1 β -driven signaling ampli-



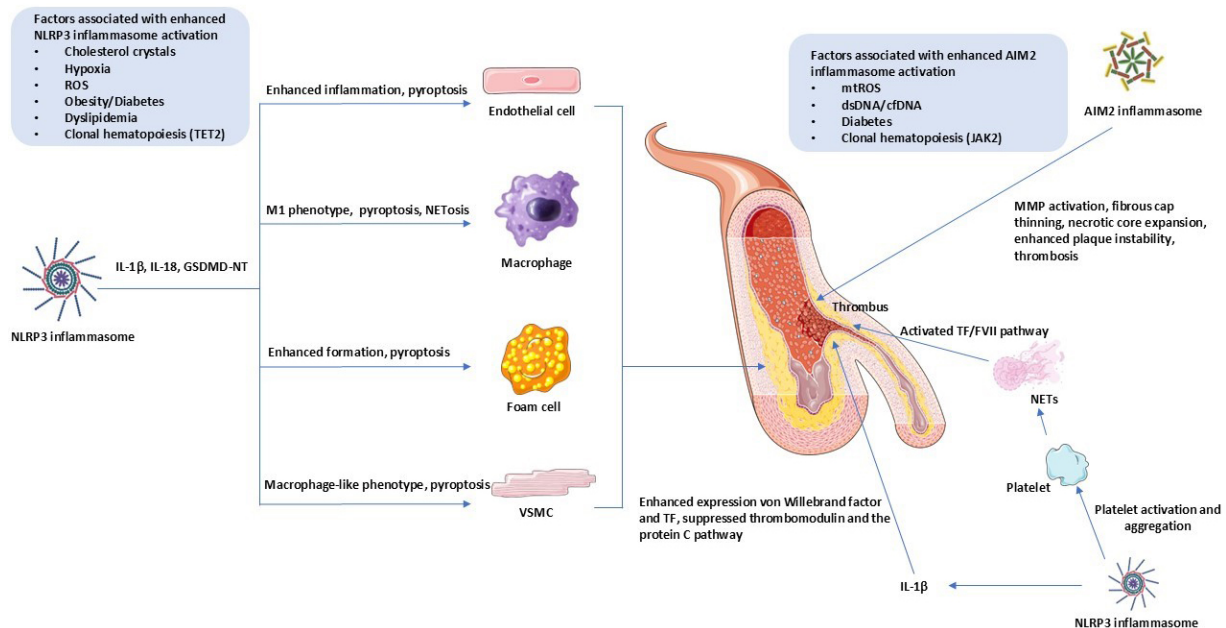


Fig. 1. The figure illustrates how cell- and compartment-specific activation of the NLRP3 and AIM2 inflammasomes links inflammatory signaling to atherosclerotic plaque progression and atherothrombosis. Cardiovascular risk factors promote inflammasome activation in endothelial cells, macrophages, VSMCs, platelets, and neutrophils, driving IL-1 β /IL-18 release, pyroptosis, NETosis, and endothelial dysfunction. These processes accelerate foam cell formation, VSMC phenotypic switching, necrotic core expansion, and fibrous cap weakening. Concurrently, inflammasome signaling enhances platelet activation, NET-mediated coagulation, and pro-thrombotic factor activation, thereby predisposing to thrombus formation. NLRP3, NOD-like receptor containing pyrin domain 3; ROS, reactive oxygen species; IL-1 β , interleukin-1 β ; IL-18, interleukin-18; N-GSDMD, gasdermin D N-terminal fragment; NETs, neutrophil extracellular traps; VSMCs, vascular smooth muscle cells; AIM2, absent in melanoma 2; mtROS, mitochondrial reactive oxygen species; dsDNA, double-stranded deoxyribonucleic acid; cfDNA, cell-free deoxyribonucleic acid; MMPs, Matrix metalloproteinases; TF, tissue factor; FVII, factor VII.

fies leukocyte-platelet crosstalk, and pro-thrombotic mediators surge at sites of plaque disruption [7,8] (Fig. 1).

Existing literature has primarily emphasized plaque biology, often investigating inflammasome-driven inflammation in isolation rather than within the broader atherothrombotic continuum which links innate immunity and clot formation. Recent advances are reshaping this landscape. New findings underlie cytosolic deoxyribonucleic acid (DNA) sensing, neutrophil extracellular traps (NETs)-related inflammation, and inflammasome activity within the platelets as important mediators of the atherothrombotic process [9,10,11,12]. Moreover, the development of selective NLRP3 inhibitors and early clinical testing signal the arrival of a new therapeutic era, yet efficacy, safety, and patient selection remain unresolved.

In this review, we aim to integrate cell-type-specific inflammasome biology across the lifespan of atherosclerotic plaque development and thrombus formation, and to synthesize mechanistic insights and clinical trial evidence to clarify the therapeutic promise, limitations, and risks of immune modulation in ASCVD.

2. The Inflammasome Landscape in Atherosclerosis and Atherothrombosis

2.1 Canonical Inflammasomes in Vascular Disease

Inflammasomes are intracellular multiprotein complexes that serve as important components of the innate immune system. They sense pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) and are activated in response to these signals to preserve tissue homeostasis [13,14]. Although initially linked to immune cells such as macrophages and dendritic cells, inflammasomes are also present in epithelial and endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and platelets, highlighting their broader biological significance [15,16,17,18].

Over the years, several inflammasome sensors have been identified, including interferon-gamma-inducible protein 16 (IFI16), AIM2, caspase recruitment domain (CARD)-containing protein 4 (NLRC4), and members of the nucleotide-binding (nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1 [NACHT]) and leucine-rich repeat (LRR)-containing (NLR) family [19,20]. Among these, the NLRP3 inflammasome is the most extensively studied, owing to its ability to sense a remarkable broad

range of pathogenic and sterile danger signals and its well-established involvement in numerous inflammatory and metabolic diseases [6]. Like most other inflammasomes, the NLRP3 inflammasome is composed of a sensor (NLRP3), an adaptor (apoptosis-associated speck-like protein containing CARD, ASC), and an effector (pro-caspase-1), with interactions between pyrin domains (PYD) and CARD enabling complex assembly and activation [21]. Its activation has been linked to various cardiovascular disorders, including heart failure (HF), atherosclerosis, abdominal aortic aneurysm (AAA), and atrial fibrillation (AF) [8,22].

NLRP3 inflammasome activation can occur through three pathways, canonical, non-canonical, and alternative [21]. The canonical pathway involves a two-step process of priming and activation. During priming, toll-like receptors (TLRs) detect PAMPs or DAMPs, activating nuclear factor kappa-light-chain-enhancer of activated B cells (nuclear factor- κ B [NF- κ B]), which in turn induces the transcription of NLRP3 inflammasome components and the proinflammatory cytokines, pro-IL-1 β and pro-IL-18 [23,24]. In the activation step, NLRP3 assembles with ASC and pro-caspase-1, forming a complex that activates caspase-1. Active caspase-1 then converts pro-IL-1 β and pro-IL-18 into their mature and active forms, and cleaves gasdermin D (GSDMD), leading to pyroptosis, a form of inflammatory cell death [24,25].

The non-canonical pathway is typically triggered by bacterial infection. In this pathway, cytosolic lipopolysaccharide (LPS) directly activates murine caspase-11 or human caspase-4 and -5, resulting in GSDMD cleavage and pyroptosis [26]. Moreover, the decreased level of intracellular potassium ions (K^+) can act as a second signal to stimulate the activation of the NLRP3 inflammasome and further induce IL-1 β secretion [27].

The alternative NLRP3 inflammasome activation pathway is distinct from both the classical and non-canonical pathways. Here, antigen stimulation occurs through the TLR4–TRIF–RIPK1–FADD–caspase-8 signaling axis. Then, NLRP3 is activated and contributes to IL-1 β release through an unknown trigger that does not rely on K^+ efflux. Note that caspase-8 replace caspase-1 in this alternative pathway [21].

2.2 Priming and Activation in the Atherogenic Milieu

The NLRP3 inflammasome seems to have an important role in the pathogenesis of atherosclerosis. Aberrant NLRP3 inflammasome activation contributes to plaque progression because it affects the key cell types involved in this process, including ECs, VSMCs, macrophages, and foam cells [28,29,30]. Several *stimuli* within the atherosclerotic microenvironment can initiate the priming and activation of the NLRP3 inflammasome and these include hypoxia, cholesterol crystals (CCs), oxidized low-density lipoprotein (oxLDL), NETs, and somatic TET2 mutations [31].

The oxidative hypothesis postulates that LDL oxidation in the endothelial wall is an event that occurs early in atherosclerosis [32]. OxLDL contributes to plaque development through multiple complementary mechanisms. It promotes endothelial dysfunction, enhances the formation of foam cells, stimulates smooth muscle cell migration and proliferation, and induces platelet adhesion and aggregation [33,34]. As atherosclerosis progresses, macrophages engulf oxLDL and become lipid-laden foam cells. This excessive cholesterol accumulation eventually leads to the formation of CCs [35]. Both oxLDL and CCs stimulate inflammation, which results in cellular stress and death. The subsequent release of DAMPs, such as adenosine triphosphate (ATP), mitochondrial DNA (mtDNA), and reactive oxygen species (ROS), together with CCs, can activate the NLRP3 inflammasome [31]. The exact mechanism by which CCs induce atherosclerosis remains unclear. It is thought to be phagocytosed and accumulate in lysosomes, an event that causes lysosomal membrane destabilization and rupture. This releases lysosomal cathepsins, especially cathepsin B, which can directly or indirectly promote NLRP3 activation, through mitochondrial dysfunction and ROS production [31]. Once activated, the NLRP3 inflammasome exacerbates lysosomal dysfunction, establishing a feed-forward cycle that accelerates atherosclerotic progression. Experimental studies in macrophages show that NLRP3 activation promotes lysosomal lipid retention and disrupts intracellular cholesterol trafficking, whereas genetic or pharmacologic inhibition of NLRP3 reduces lipid accumulation and restores lysosomal function. These findings support a causal role for inflammasome signaling in impaired lysosomal processing within foam cells [36].

Furthermore, oxLDL binding to cluster of differentiation 36 (CD36) primes NLRP3 activation through TLR4/6 heterodimer formation and induces mitochondrial ROS (mtROS) production, partly through translocation of the cytosolic enzyme pyruvate kinase muscle isoform 2 (PKM2) to the mitochondria [37,38]. A relatively recent study demonstrated that in LPS-stimulated macrophages, mtROS generated via reverse electron transport (RET) is a key regulator of IL-1 β release following NLRP3 inflammasome activation [39].

Atherosclerosis is associated with significant DNA damage, which starts in the earliest stages of the disease, becomes more pronounced in advanced lesions, and contributes substantially to the development of atheroma [40,41]. The NLRP3 inflammasome cannot directly detect double-stranded DNA (dsDNA) fragments that arise after cellular injury and death. In contrast, the AIM2 inflammasome acts as a direct cytosolic sensor of intracellular dsDNA and circulating cell-free DNA (cfDNA), an ability that reinforces its role in ASCVD [41,42]. cfDNA derived from NETs activates the AIM2 inflammasome and triggers an inflammatory cascade that enhances plaque vulnerability

through matrix metalloproteinase (MMP) activation. This process contributes to atherothrombosis and recurrent ischemic events [9].

In summary, lipid accumulation, oxidative stress, lysosomal dysfunction, and inflammasome activation interact to form a self-reinforcing cycle of oxidation and inflammation that promotes foam cell formation and accelerates plaque progression.

2.3 Downstream Effector Pathways

After activation, NLRP3 engages the adaptor protein ASC via homotypic interactions between their PYD domains. ASC then recruits pro-caspase-1 through CARD–CARD interactions, leading to assembly of the NLRP3 inflammasome complex and autoproteolytic activation of caspase-1 [15,31]. Activated caspase-1 processes pro-IL-1 β and pro-IL-18 into their mature forms and cleaves GS-DMD to generate the N-terminal fragment (gasdermin D N-terminal fragment [N-GSDMD]), which forms membrane pores that induce cell swelling and lysis with release of IL-1 β , IL-18, and other proinflammatory intracellular contents [24,42]. These cytokines promote recruitment and activation of additional immune cells, sustaining inflammation within the plaque and exerting strong pro-atherosclerotic effects, while infiltrating monocytes and T-cells contribute to necrotic core formation and fibrous cap thinning, thereby increasing plaque vulnerability to rupture and thrombosis [15]. Pyroptosis further promotes endothelial dysfunction in early lesions, enhances foam cell formation and necrotic core expansion in advanced plaques, and destabilizes plaques through fibrous cap thinning and procoagulant release, ultimately accelerating atherosclerosis progression and increasing the risk of atherothrombotic events [43].

In addition, NF- κ B responds to oxidative stress and inflammatory signals, such as mtROS and TLR activation, playing a central role in the development and progression of diseases linked to pyroptosis and apoptosis [44,45,46]. Risk factors such as smoking, obesity, and dyslipidemia exacerbate oxidative stress, thereby promoting the pathogenesis of these conditions [47].

3. Cell- and Compartment-Specific Inflammasome Signaling in Atherosclerotic Plaques

3.1 Endothelial Cells

ECs regulate vital function such as vascular tone, wound repair, oxidative balance, shear stress responses, inflammation, and play an important role in processes relevant to atherosclerosis and CAD [48]. ECs express several inflammasome components, including NLRP3 and AIM2, after activation by a variety of pathological conditions and external stimuli [49].

Disturbed blood flow can activate the NLRP3 inflammasome and promote vascular remodeling as ECs are highly responsive to hemodynamic changes [50]. Dis-

turbed flow activates the transcription factor sterol regulatory element-binding protein 2 (SREBP2), which up-regulates NLRP3 and NADPH-oxidase 2 (NOX2) expression, promoting lipid accumulation and atherogenesis. SREBP2 also transactivates Tumor necrosis factor alpha (TNF- α) receptor-associated factor-interacting protein with a forkhead-associated domain (TIFA), enhancing NF- κ B-mediated NLRP3 expression, and induces microRNA-92a, which suppresses Sirtuin 1 (SIRT1), Krüppel-like factor 2 (KLF2), and KLF4, further amplifying NLRP3 inflammasome activation [49,51].

Hyperglycemia directly impairs endothelial function, leading to the characteristic type 2 diabetes mellitus (T2DM) phenotype of microvascular and macrovascular complications [52]. Patients with T2DM exhibit increased circulating levels of IL-1 β and IL-18, indicating heightened inflammasome activity [53]. In EC cultures, high glucose levels further increase microtubule affinity-regulating kinase 4 (MARK4) expression and promote signaling through TLRs and NF- κ B, leading to NLRP3 activation [50]. Additionally, hyperglycemia induces ROS production in ECs, promoting atherogenesis, indicating a link to the NLRP3 inflammasome [54].

3.2 Monocytes/Macrophages and Foam Cells

Oxidative stress promotes oxidation of LDL in the subendothelial space and is a key driver of atherosclerosis. OxLDL contributes to foam cell formation by interacting with scavenger receptors, modulating miRNA signaling, and activating the NLRP3 inflammasome [55]. These processes exacerbate endothelial injury and stimulate ECs and macrophages, recruit leukocytes and collectively promote plaque initiation and progression. Exposure of VSMCs to modified LDLs triggers the release of chemokines promoting monocyte recruitment to the vessel wall. Recruited monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF) and secrete proinflammatory cytokines including IL-1 β , IL-18, TNF- α , and interferon-gamma (IFN- γ). These cytokines, along with TLR signaling, drive macrophages near the lipid core toward a proinflammatory M1 phenotype, reinforcing local inflammation, contributing to plaque vulnerability, and advancing atherosclerosis [7]. Macrophage death, largely driven by pyroptosis, further promotes necrotic core formation, weakens plaque stability, and accelerates thrombosis in atherosclerosis [56]. In atherosclerotic plaques, pyroptosis also promotes inflammation, foam cell formation, and the recruitment of macrophages and smooth muscle cells, with oxLDL and CCs activating the NLRP3 inflammasome and IL-1 β /IL-18 release, while AIM2 inflammasome activation further drives necrotic core formation and disease progression [57].

3.3 Vascular Smooth Muscle Cells

The arterial media is primarily composed of VSMCs that normally maintain a contractile phenotype to regulate vascular tone. However, VSMCs are highly plastic and can switch to alternative phenotypes in response to vascular stress. This phenotypic switching contributes to atherosclerosis, as dedifferentiated VSMCs accumulate within plaques and drive vascular remodeling through the production of extracellular matrix (ECM) components and proteases [58]. Note that VSMCs are also the main cellular constituents of the fibrous cap [59]. The NLRP3 inflammasome contributes to VSMC phenotypic switching and increases the likelihood of plaque rupture. Burger et al. [59] in an *in vitro* study, showed that monocytes and hyperlipidemia drive VSMCs toward a macrophage-like phenotype by activating the NLRP3 inflammasome. This process collectively promotes cholesterol accumulation, necrotic core formation, and plaque destabilization through *Oct-4* expression, increased KLF4 levels, enhanced IL-1 β secretion, and induction of pyroptosis [59]. NLRP3 activation also induces cleavage of contractile proteins, including tropomyosin and myosin heavy chain, impairing VSMC contractility. Clinical evidence from patients with AAAs further shows elevated NLRP3 and IL-1 β in VSMCs, highlighting the central role of inflammasome-driven inflammation and pyroptosis in VSMC dysfunction and vascular disease progression [60].

3.4 Adventitia, Vasa Vasorum and Perivascular Adipose

Atherosclerosis is a chronic inflammatory disease and involves complex interactions among multiple cell types across all layers of the vascular wall [61]. The tunica adventitia represents an important but incompletely characterized compartment in atherosclerosis and includes a heterogeneous population of cells, including fibroblasts, macrophages, T cells, dendritic cells, mast cells, and ganglionic cells [61,62]. Adventitial inflammation is characterized by the accumulation and activation of macrophages and T-cells. This process has a key role in early coronary atherogenesis and may communicate with the intima before visible lesions develop [63]. The activation of the NLRP3 inflammasome in adventitial macrophages is mediated by mtROS and serves as a driver of vascular inflammation and contributes to the formation of AAAs [64]. This indicates how inflammasome activity in adventitial immune cells serves as a fundamental mechanism linking inflammation and vascular disease progression.

The perivascular adipose tissue (PVAT) that is located outside the adventitia also plays a significant role in atherogenesis [65]. PVAT is considered to be the fourth layer of the blood vessel wall, also known as the tunica adiposa, and secretes adipokines, vasoactive molecules, cytokines, and growth factors, including leptin, adiponectin, and resistin, which contribute to the regulation of vascular tone and maintenance of vascular homeostasis [61,65].

PVAT is expanded in both obesity and diabetes, exhibiting a proinflammatory phenotype which is marked by reduced anti-inflammatory adipokine production, increased oxidative stress, and vascular dysfunction, contributing to vascular inflammation and atherosclerosis development [66]. Among the proinflammatory mediators produced by PVAT, IL-1 β and IL-18 are dependent on NLRP3 inflammasome activation. In an experimental model using Zucker diabetic fatty rats, glucagon-like peptide 1 (GLP-1) attenuated NLRP3 inflammasome activation in perivascular adipose tissue, with NF- κ B signaling implicated as a key mechanism mediating this regulatory effect [67]. Smoking has also been shown to exacerbate PVAT inflammation by increasing the expression and activity of the P2X7 receptor-inflammasome complex [68].

4. Inflammasomes and Plaque Evolution: From Initiation to Vulnerability

4.1 Early Lesion Formation

Atherosclerosis is a complex process initiated by endothelial dysfunction, which promotes LDL retention and modification within the intima. Atherogenic *stimuli* such as smoking and diabetes together with oxLDLs, activate ECs and promote monocyte recruitment into the vessel wall. Within the intima, monocytes and VSMCs internalize oxLDLs via scavenger receptors, giving rise to foam cells. These events drive fatty streak formation, which is the earliest detectable atherosclerotic lesion and is characterized by intracellular and extracellular lipid accumulation, which facilitates the formation of CCs [69]. Fatty streaks can develop from childhood, particularly in regions of disturbed blood flow where adaptive intimal thickening and NF- κ B-mediated inflammatory signaling predominate [70]. NF- κ B activation results in its nuclear translocation and binding to NF- κ B-responsive promoters, inducing the transcription of pro-inflammatory target genes, including NLRP3 [71]. CCs, although usually associated with advanced plaques, are also present at early stages of atherosclerosis, where they trigger NLRP3 inflammasome activation in macrophages and amplify pro-inflammatory signaling [72].

Furthermore, activation of the NLRP3 inflammasome appears to serve as a key mediator of the disruption of reverse cholesterol transport (RCT) within the arterial wall. Inflammasome assembly promotes the maturation of IL-1 β , initiating a signaling cascade that suppresses the liver X receptor alpha (LXR α) pathway [73]. This can lead to downregulation of key cholesterol efflux transporters, ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1), as well as the selective high-density lipoprotein (HDL) receptor scavenger receptor class B type 1 (SR-B1), thereby promoting atherosclerotic progression [74]. The pathological relevance of RCT impairment is further supported by a recent study demonstrating that apolipoprotein A-I (ApoA1) deficiency, asso-

ciated with reduced HDL levels, induces apoptosis through a B-cell lymphoma 2 (Bcl-2)–interacting mediator of cell death (Bim)–dependent pathway, significantly contributing to necrotic core formation and plaque advancement [75].

4.2 Growth of the Necrotic Core, Fibrous Cap Thinning, and Intraplaque Hemorrhage

In atherosclerosis, necrosis gives rise to a large region called the necrotic core, which is depleted of viable cells and filled with cellular debris [76]. Multiple forms of regulated necrosis drive lesion complexity and instability in the progression of the atherosclerotic plaques [77]. A known mechanism is necroptotic cell death, after the macrophage exposure to oxLDLs elevates ROS, leading to increased expression of receptor-interacting protein kinase (RIPK)-3 and mixed lineage kinase domain-like protein (MLKL) [78,79,80]. In parallel, ferroptosis is triggered within plaques as hypoxia stimulates neovascularization [81,82]. Ferroptosis is an iron-dependent form of regulated cell death characterized by intracellular iron overload and redox imbalance, and it is closely linked to NLRP3 inflammasome activation [83]. The newly formed intraplaque microvessels are often fragile and permeable, allowing infiltration of inflammatory blood cells leading to intraplaque hemorrhage (IPH) [84]. These hemorrhagic areas are surrounded by erythrocytes through erythrophagocytosis, which activates heme oxygenase-1 (HMOX-1), increases intracellular heme and iron accumulation, and predisposes cells to ferroptotic death [77]. Although apoptosis occurs, impaired efferocytosis in advanced lesions leads to the accumulation of apoptotic bodies that progress to secondary necrosis and may trigger inflammasome activation [85,86]. Additionally, pyroptosis is induced when CCs within plaques disrupt lysosomal membranes, activating NLRP3 inflammasome [74]. Of note, apoptosis and pyroptosis share several hallmark features; however, despite these similarities, pyroptosis differs fundamentally from apoptosis in that it rapidly and irreversibly disrupts plasma membrane integrity. Both processes are characterized by chromatin condensation; however, nuclear structure is preserved during apoptosis [87].

A plaque is defined as vulnerable after persistent exposure to a pro-atherogenic environment leads to an extensive necrotic core, a thin fibrous cap, and heightened inflammatory activity [88]. The fibrous cap isolates the highly thrombogenic necrotic core from circulating platelets and coagulation components, and its thickness is closely linked to plaque stability [89]. Loss of VSMCs leads to diminished ECM synthesis, while the release of MMPs increases matrix degradation, collectively resulting in weakening of the fibrous cap [69]. Inflammation contributes significantly to the vulnerability of atherosclerotic lesions. Inflammatory mediators commonly detected in atheromatous plaques, including NLRP3-related cytokines such as IL-1 β and IL-18, as well as TNF- α , have been shown *in vitro* to upregulate

MMP expression in VSMCs [69,90]. This inflammatory response is usually seen within the fibrous cap and plaque shoulders rather than being evenly distributed throughout the lesion [69].

IPH is a key driver of plaque progression. It leads to a rapid increase in plaque volume and contributes to plaque destabilization [91]. IPH is most commonly observed within or near the necrotic core and is believed to arise from the leakage of erythrocytes from dysfunctional microvessels, followed by the accumulation of local inflammatory cells, including macrophages [92]. The accumulation of erythrocyte membranes within atheromas as a result of IPH serves as a major source of lipids for the necrotic core and promotes the formation of CCs [93]. As previously mentioned, these crystals can activate NLRP3 inflammasomes by causing phagolysosomal disruption and the release of cytosolic cathepsins, leading to IL-1 β secretion into the extracellular space. Consequently, elevated cholesterol content in the arterial wall is closely linked to the development of arterial thrombosis [91].

Collectively, these interconnected mechanisms contribute to the enlargement of the necrotic core, amplifying inflammation, weakening the fibrous cap, promoting plaque destabilization, and increasing the risk of rupture and thrombus formation [77].

4.3 “Mixed Picture” and Counter-Evidence

Studies using mouse models of atherosclerosis, most commonly LDL receptor-deficient (*LDLr*–/–) and apolipoprotein E-deficient (*ApoE*–/–) mice, support a causal role for inflammasome activation and IL-1 β in the development and progression of atherosclerosis [93,94]. In particular, experimental work has implicated the NLRP3 inflammasome in lesion formation in cholesterol-rich diet-fed *Ldlr*–/– mice, where genetic deletion of key inflammasome components attenuates early plaque development [93,95]. However, the contribution of inflammasome signaling appears to be highly context dependent, as several studies have reported minimal or no effects of inflammasome deficiency or IL-1 β inhibition in *ApoE*–/– or *Ldlr*–/– mice fed cholesterol-rich diets. These divergent findings may be influenced by factors such as sex, stage of lesion progression, microbiome composition, or other experimental variables [96,97]. Collectively, the evidence suggests that basal inflammasome activity is relatively modest in standard mouse models, but becomes more pronounced in the presence of additional pro-inflammatory or metabolic stressors, including impaired cholesterol efflux, defective DNA repair, clonal hematopoiesis, or diabetes [93]. Importantly, although a similar pattern is observed, human cells appear to be more sensitive to NLRP3 inflammasome activation, potentially amplifying the impact of chronic disease [98].

An important unresolved issue is whether inflammasome activation directly interacts with lipid metabolism.

In *LDLR*^{-/-} and *ApoE*^{-/-} models, interpretation is complicated by defects in LDL receptor- or ApoE-mediated clearance. It therefore remains unclear whether NLRP3-driven IL-1 β signaling modulates hepatic LDL receptor expression, peripheral ApoE-dependent uptake, or circulating LDL cholesterol levels under conditions of intact lipoprotein metabolism. Emerging evidence indicates bidirectional crosstalk between proprotein convertase subtilisin/kexin type 9 (PCSK9) and the NLRP3 inflammasome. In particular, NLRP3-driven IL-1 β may increase PCSK9 expression, while PCSK9 can trigger caspase-1-dependent pyroptosis via mitochondrial DNA damage and NLRP3 activation. The mechanisms linking this interaction to atherosclerosis remain unclear [99]. Further studies are therefore needed to clarify whether inflammasome activation primarily affects vascular inflammation or also intersects with core components of the lipid hypothesis.

5. Inflammasomes at the Atherothrombotic Interface

5.1 Platelet Inflammasomes

Platelets have a central role in atherothrombosis that emerges from a tightly interwoven network of inflammatory and thrombotic pathways [100]. Platelets are now recognized as active inflammatory effectors that propagate vascular inflammation, and the NLRP3 inflammasome has attracted considerable attention as a potential molecular hub linking platelet activation to atherothrombotic disease [12].

Emerging evidence supports the presence of a functional NLRP3 inflammasome in platelets [12]. Platelets retain inflammasome-related transcripts and low-abundance protein components, including ASC and GSDMD, and can exhibit caspase-1 activity under inflammatory or thrombotic stress [12,101,102,103]. Megakaryocytes appear to play a critical role, shaping a pro-inflammatory platelet proteome in response to systemic cues such as hyperlipidemia, infection, or myocardial injury [97,104,105,106,107]. This megakaryocyte–platelet axis may explain how inflammasome competence is selectively enhanced in disease states while remaining difficult to detect in platelets from healthy individuals [12]. Functionally, platelet NLRP3 inflammasome activation converges on the production and release of IL-1 β . Platelet-derived IL-1 β exerts potent autocrine effects that amplify platelet activation and acts on ECs and leukocytes, thereby promoting endothelial activation, leukocyte recruitment, and NETs formation [108,109,110,111].

At the clinical level, dysregulated platelet inflammasome activity has been linked to atherothrombotic disease and venous thrombosis [112,113]. In acute coronary syndromes (ACS), platelet NLRP3 inflammasome expression was found to be markedly increased and associated with disease severity, adverse cardiac function, and poor clinical outcomes, serving as an independent predictor of adverse cardiovascular events following percutaneous coronary in-

tervention (PCI) [112]. Similarly, a more recent mouse study of deep vein thrombosis (DVT) demonstrated that NLRP3 inflammasome activity specifically within platelets regulates intrathrombus IL-1 β levels, thereby promoting NETs formation and driving venous thrombus development [113].

Collectively, these findings position platelet inflammasomes as critical modulators at the atherothrombotic interface, integrating inflammatory danger signals with thrombotic responses. While controversies remain regarding the precise composition and activation requirements of the platelet NLRP3 inflammasome, its functional consequences—particularly IL-1-mediated autocrine and paracrine signaling—are increasingly difficult to ignore. Targeting platelet inflammasome pathways, either directly or through upstream megakaryocyte programming, may therefore represent a novel therapeutic avenue to attenuate residual inflammatory risk in atherothrombotic disease without compromising essential hemostatic function.

5.2 Neutrophil Extracellular Traps and the Inflammasome–NETosis Axis

NLRP3 inflammasome signaling promotes neutrophil recruitment into atherosclerotic plaques, where CCs trigger NETosis. This is a distinct form of cell death characterized by the release of NETs, which aims to eliminate pathogens and appears to promote the progression of atherosclerosis [11,114,115,116]. Indeed, CCs can react with free radicals, leading to the production of ROS that activate peptidyl arginine deiminase 4 (PADI4), which catalyzes arginine citrullination and promotes chromatin relaxation from histones. Concurrently, myeloperoxidase (MPO) and neutrophil elastase (NE) contribute to nuclear membrane disruption and further chromatin decondensation. The loosened chromatin forms NETs embedded with granule-derived and cytosolic proteins, released upon neutrophil membrane rupture, causing cell death [117]. The released NETs enhance the expression of pro-IL-1 β , thereby amplifying inflammasome-mediated inflammatory responses [114]. Additionally, NETs provide dsDNA that can trigger activation of the AIM2 inflammasome [118].

NETosis is also involved in thrombus formation and contributes substantially to prothrombotic signaling by inducing ROS generation, promoting endothelial dysfunction and apoptosis, triggering LDL oxidation, enhancing platelet aggregation, and facilitating the accumulation of von Willebrand factor and fibrinogen [117,119]. Moreover, in an experimental animal model of DVT, NETs were shown to form a DNA-based scaffold that incorporates red blood cells, von Willebrand factor, fibronectin, and fibrinogen, thereby promoting thrombus development [120]. In a stenosis-induced mouse model of DVT, sterile NLRP3 inflammasome activation triggered NETosis and enhanced venous thrombosis, whereas genetic or pharmacological inhibition of NLRP3 reduced both NET formation and throm-

bus size [121]. Similarly, in an experimental model of acute MI, NLRP3 activation exacerbated myocardial injury by promoting NET-mediated microvascular blockage and tissue damage. These NETs obstruct capillaries and release proteases and proinflammatory molecules, amplifying local thrombo-inflammation and immune cell recruitment [122].

5.3 Coagulation and Fibrinolysis

The coagulation system functions as part of innate host defense. LPS induces tissue factor (TF) expression in circulating monocytes through TLR4 signaling and both canonical and noncanonical inflammasome pathways, culminating in GSDMD activation. Subsequent pyroptosis, along with increased intracellular calcium and phosphatidylserine exposure, amplifies the coagulation cascade [123]. In addition to activating coagulation, LPS stimulation reduces fibrous cap thickness and increases macrophage accumulation, inflammatory cytokine production, and MMP expression, thereby promoting plaque vulnerability and increasing the risk of thrombosis [124].

The complement system has also been implicated in thrombosis. Elevated complement C3 levels in the general population are associated with increased risk of DVT, and complement activation correlates with thrombotic complications in infectious diseases [125]. Complement can elicit the secretion of IL-1 β and IL-18 both *in vitro* and *in vivo* via the NLRP3 inflammasome, providing a mechanistic link between complement activation, inflammation, and thrombosis [126].

IL-1 links inflammation and thrombosis through its effects on ECs and coagulation pathways [127]. IL-1 α (IL-1 α) and IL-1 β act in autocrine and paracrine fashion to promote a prothrombotic endothelial phenotype characterized by increased expression of adhesion molecules, including P-selectin, ICAM-1, and VCAM-1, which facilitate leukocyte and platelet recruitment. Concurrently, IL-1 β enhances the expression of procoagulant factors such as von Willebrand factor and TF, while suppressing endogenous anticoagulant mechanisms, including thrombomodulin and the protein C pathway [127,128,129].

IL-1 β also contributes to thrombus formation through interactions with NETs. In concert with NET-associated proteases such as cathepsin G, IL-1 α induces TF expression and activity on the endothelium, thereby amplifying local coagulation and promoting thrombo-inflammation [130]. This process is reinforced by a feed-forward loop in which TF generation and fibrin deposition further enhance IL-1 β -mediated endothelial activation, sustaining both inflammation and thrombosis [127].

IL-18 also contributes to thrombo-inflammation through direct effects on ECs by promoting endothelial activation, which is characterized by increased von Willebrand factor expression and suppression of tissue plasminogen activator, thereby favoring a prothrombotic and antifibrinolytic state. In venous thrombosis, IL-18-

mediated activation of NF- κ B induces abnormalities in EC growth and function and plays an important role in the development of DVT [131].

5.4 Clinical Contexts of Inflammasome-Driven Atherothrombosis

Arterial thrombosis is primarily caused by the rupture of an atherosclerotic plaque, which leads to the exposure of the subendothelial extracellular matrix and triggers extensive release of TF [132]. This process plays a significant role in the pathogenesis of ACS and ischemic stroke (IS), where the coordinated interplay between platelets, thrombotic factors, and the inflammasome axis critically drives thrombus formation and activation. Analysis of aspirated intracoronary thrombi from patients with ST-elevation myocardial infarction (STEMI) demonstrated increased expression of inflammasome-related genes, including TLR4, NLRP3, and IL-6 receptor, which correlated with myocardial injury assessed by troponin T, indicating active inflammasome signaling [133]. Consistently, the same group reported a strong association between NLRP3 inflammasome activity within coronary thrombi and elevated circulating levels of phosphatidylserine positive (PS⁺) microvesicles in STEMI patients. In contrast, phosphatidylserine negative (PS⁻) microvesicles were inversely associated with inflammasome gene expression, suggesting a potential immunomodulatory or protective role that requires further investigation [134].

Furthermore, acute IS (AIS) or MI can promote destabilization of distant atherosclerotic plaques. In a rupture-prone mouse model, both conditions triggered plaque instability and recurrent ischemic events through NET-derived cell-free DNA-mediated activation of the AIM2 inflammasome, leading to MMP activation and atherothrombosis. Similar inflammatory mechanisms were observed in human carotid plaques shortly after stroke, and targeting this pathway reduced recurrent ischemic events in experimental models [9]. Finally, recent evidence in AIS further links inflammasome activity to thrombus biology and clinical outcome. NETs were identified within AIS thrombi and were found to colocalize with inflammasome components, including caspase-1 and ASC. Levels of caspase-1, ASC, and IL-1 β were significantly elevated in thrombi compared with plasma and healthy controls, and higher intrathrombus inflammasome signaling was associated with prolonged and less effective mechanical thrombectomy, indicating that inflammasome-enriched NETs contribute to thrombus resistance and worse procedural outcomes in AIS [135].

Histopathological analyses of cerebral thrombi show variable proportions of platelets, leukocytes, and red blood cells, and this compositional heterogeneity is believed to reflect differences in thrombus origin [136]. In the thrombectomy era, growing interest has focused on ischemic stroke thrombus composition, although only a limited number of

studies have explored the thrombus inflammatory milieu in relation to stroke etiology. In this context, analysis of ischemic stroke thrombi demonstrated that cardioembolic strokes, particularly those associated with AF, contain significantly higher numbers of CD11b⁺ myeloid cells compared with thrombi from large artery atherosclerosis, with cryptogenic stroke thrombi showing a similar inflammatory profile. These findings suggest that CD11b-driven atrial inflammation contributes to thrombus formation and support the concept that a substantial proportion of cryptogenic strokes may arise from subsequent AF [137]. Note that inflammasome signaling contributes to AF pathogenesis [138].

6. Multiscale Evidence: From Genetics and Omics to Human Biomarkers

6.1 Human Genetic and Clonal Hematopoiesis Data

Emerging data suggest that genetic variants in components of the NLRP3 and AIM2 inflammasomes influence susceptibility to CVD. Mutations in the NLRP3 gene that drive excessive IL-1 β production cause rare hereditary autoinflammatory syndromes, such as cryopyrin-associated periodic syndromes, while more common NLRP3 variants are linked to polygenic inflammatory disorders, including celiac disease, rheumatoid arthritis, Crohn's disease, and abdominal aortic aneurysms [138,139,140,141,142,143]. Extending these observations to cardiovascular pathology, a recent study identified the intronic NLRP3 variant rs10754555 as a functional expression quantitative trait locus associated with enhanced NLRP3 transcription, elevated IL-18 plasma levels, augmented ASC formation, and increased inflammasome activation in human monocyte-enriched peripheral blood mononuclear cells (PBMCs) [144]. Functionally, this variant impaired re-endothelialization in experimental models and increased the risk of CAD in individuals younger than 60 years, indicating an age-dependent genetic effect. Across multiple validation cohorts, including patients with prevalent CAD and general population samples, rs10754555 was consistently associated with higher cardiovascular mortality [143]. In addition, the NLRP3 rs35829419 variant is a gain-of-function polymorphism that increases IL-1 β production and has been associated with a higher long-term risk of macrovascular complications, particularly MI, in patients with T2DM [145,146]. Finally, the NLRP3 rs4612666 polymorphism may be associated with the occurrence of large artery atherosclerotic ischemic stroke and microembolic signals, suggesting that this variant increases susceptibility to ischemic stroke by influencing plaque vulnerability [147]. Regarding the AIM2 inflammasome, a recent study interestingly showed that the rs2793845 T allele and GT/TT genotypes were highly frequent in males with periodontal disease and CAD [148].

Recent studies indicate that clonal hematopoiesis of indeterminate potential (CHIP), an age-related expansion

of hematopoietic stem cells carrying somatic mutations in genes such as TET2, DNMT3A, and ASXL1, promotes a pro-inflammatory macrophage phenotype with increased inflammasome activity and cytokine release, which progresses atherosclerosis and plaque instability, thereby increasing cardiovascular risk and mortality [149,150]. Carriers of the TET2 mutation display atherosclerotic lesions with larger necrotic cores and increased inflammation, which contribute to plaque vulnerability. Multi-omics analyses further showed that TET2-mutant macrophages had increased LDL receptor and inflammasome gene expression [149]. JAK2 CHIP is associated with an approximately 12-fold increased risk of ischemic cardiovascular events, including MI and stroke [151]. In murine models, the JAK2 V617F mutation induces atherosclerotic lesion formation and NET release due to the activation of the AIM2 inflammasome, a process that is also seen in venous thrombosis [152]. UK Biobank data have demonstrated strong associations between JAK2 mutations and incident venous thromboembolic events, underscoring the broad cardiovascular impact of JAK2 CHIP [150,153].

6.2 Single-Cell and Spatial Transcriptomics of Human Plaques

Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) offer high-resolution analysis of cellular heterogeneity and signaling within diseased vessels, which gives us the opportunity to expand our understanding of atherosclerosis [154]. By keeping the spatial context of cells within their native tissue structure, ST complements scRNA-seq to show not only which cells are present, but also where they are located and how they interact [154,155]. These approaches have revealed distinct ECs, macrophages, foam cells, and VSMCs subpopulations with enhanced inflammasome-related gene expression patterns.

A recent study using scRNA-seq revealed that the IL1Bhi macrophage subpopulation exhibits increased inflammasome activation within atherosclerotic plaques [156]. Furthermore, scRNA-seq has shown that foam cells in atherosclerotic plaques express triggering receptor on myeloid cells 2 (TREM2), which is a lipid receptor on tissue macrophages that promotes cell survival, proliferation, efferocytosis, and has anti-inflammatory functions [157,158]. In atherosclerosis-prone *Ldlr*^{-/-} mice, the activation of TREM2 with the agonist AL002a stabilized plaques by enhancing cholesterol efflux and collagen deposition [158]. It is important to note that TREM2 knockdown has also been reported to promote NLRP3 inflammasome activation and pyroptosis in neurodegenerative diseases, findings that underscore its role in other inflammasome-related disorders [159].

Spatial transcriptomic analyses of human plaques have shown that macrophage subpopulations with increased inflammasome activity, including TREM2hi and

Mac TREM2hi CCL18 cells, are predominantly localized in rupture-prone shoulder regions and adjacent to necrotic cores. C1Q+ and HMOX1+ macrophages accumulate in subluminal positions [160]. A gradual transdifferentiation of subluminal inflammatory HMOX1+ macrophages into a lipid-handling TREM2+ phenotype within border zones of the fibrous cap and necrotic core is observed during atherosclerotic progress, highlighting a spatial organization that links inflammasome activity to plaque vulnerability, local inflammation, and matrix remodeling [160].

6.3 Circulating and Tissue Biomarkers

Elevated plasma indicators of inflammasome-related systemic inflammation can be used as prognostic markers for atherosclerosis. IL-1 β and TNF- α are central mediators of endothelial dysfunction, which is considered the earliest event in atherogenesis [161]. IL-1 β promotes vascular pathology because it causes oxidative stress and induces EC death. TNF- α signaling further exacerbates endothelial dysfunction as it triggers endothelial apoptosis and upregulates adhesion molecule expression [162,163,164]. A recent study demonstrated that IL-1 β is a strong predictor of atherogenic risk in individuals with prediabetes. This study showed a robust association between IL-1 β and an elevated atherogenic index of plasma (AIP) and underscores its potential as an early cardiovascular risk biomarker. In contrast, TNF- α signaling and C-reactive protein (CRP) provided limited additional predictive value. However, the small sample size limits the generalizability of these findings [165].

Despite their clinical relevance, IL-1 β and TNF- α have some limitations as potential biomarkers. Both of them have short half-lives, predominantly localized tissue activity, and require highly sensitive assays that are not routinely available. Consequently, other markers of NLRP3 inflammasome activation may offer more practical and reliable tools for clinical risk stratification [166]. IL-1 β appears to connect the NLRP3 inflammasome with the IL-6 pathway by promoting IL-6 production [148]. IL-6 has emerged as a clinically relevant inflammatory biomarker for cardiovascular risk prediction because it has shown strong associations with future vascular events in primary and secondary prevention settings, supporting its important role in the development of ASCVD [167,168,169]. Emerging evidence suggests that elevated CRP levels are associated with NLRP3 inflammasome activation, highlighting a potential link to atherosclerosis [170,171]. High-sensitivity CRP (hsCRP) is a well-established biomarker for cardiovascular risk, particularly in advanced CVD and secondary prevention, where residual risk remains substantial despite modern interventions [166]. While hsCRP reliably predicts future cardiovascular events, evidence supporting a direct causal role in atherogenesis is limited and inconsistent. Studies in animals suggest that CRP may contribute to endothelial dysfunction. However, interventions which

aimed to reduce CRP, including antisense oligonucleotides (ASOs) and CRP apheresis, have showed mixed results, and clinical evidence in humans is limited [166,172,173,174]. Based on current data, it seems that CRP serves primarily as a prognostic marker rather than a proven pathogenic driver of CVD.

Caspase-1, a central mediator of pyroptosis and activator of IL-1 β and IL-18, plays a significant role in the progression of CVD such as ischemia/reperfusion (I/R) injury, HF, and arrhythmias. Elevated plasma caspase-1 levels have been associated with increased cardiovascular risk, partially influenced by metabolic syndrome [175]. Caspase-1 promotes atherosclerosis by amplifying inflammation within the lesion, likely through activation of lesion-associated immune cells and upregulation of IFN- γ expression [176]. As discussed in the current review, NLRP3 inflammasome activation promotes neutrophil infiltration into atherosclerotic plaques and NET formation. Accordingly, NET-derived biomarkers have gained attention in CVD. MPO-DNA complexes and citrullinated histones serve as key biomarkers for assessing NET involvement in CVD. The MPO-DNA complex serves as a predictive marker for both the presence of atherosclerotic coronary arteries and major adverse cardiovascular events (MACEs) and higher MPO-DNA levels are associated with increased plaque fragility in patients with carotid stenosis [177,178]. In addition, NET-associated citrullinated histones have been shown to promote LDL aggregation and foam cell formation *in vitro*, highlighting their potential as a biomarker of atherosclerosis [179].

6.4 Imaging Techniques of Plaque Vulnerability

Refining the risk assessment in individuals at elevated risk of atherothrombosis have led to development of non-invasive and invasive imaging modalities that enable early identification of vulnerable, rupture-prone plaques before the development of fatal thrombotic events [180]. Noninvasive modalities such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are increasingly explored for their ability to identify imaging markers associated with plaque instability and future cardiovascular events [181]. Coronary computed tomography angiography (CCTA) is the most widely used non-invasive method for coronary artery disease evaluation and provides detailed visualization of both the vessel lumen and plaque morphology. CCTA can identify high-risk plaque features, including positive remodeling, low-attenuation plaques, spotty calcification, high perivascular fat attenuation index, and the napkin-ring sign, that have been linked to adverse clinical outcomes [182,183]. MRI can quantify plaque burden and assess tissue composition without patient exposure to ionizing radiation. However, the MRI utility in assessment of the coronary anatomy is constrained by limited spatial resolution, sensitivity to

cardiac motion, and prolonged acquisition times, which hinder reliable identification of thin-cap fibroatheromas [184]. PET provides complementary functional information by detecting metabolically active plaques, reflecting inflammatory cell activity and microcalcification [185]. Although NLRP3 plays a critical role in the progression of atherosclerosis, it has proven to be a challenging imaging target because of its limited abundance and restricted cellular distribution. However, recent advances have led to the development of a candidate PET imaging agent targeting NLRP3, based on the aminopyridazine derivative (R)-2-(6-((1-cyclopropylpiperidin-3-yl)amino)pyridazin-3-yl)-5-fluoro-3-methylphenol (17b), which fulfills key preclinical criteria for a successful imaging tracer and is currently being explored in the central nervous system [186]. Such approaches may eventually enable the identification of regions with high macrophage infiltration and active NLRP3 inflammasome signaling.

Invasive coronary imaging modalities, including intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS), provide high-resolution and offer unique insights into plaque instability caused by inflammation [166,181]. IVUS allows accurate quantification of plaque burden and lumen dimensions, features associated with adverse outcomes. However, this imaging technique has limited spatial resolution and this restricts direct visualization of thin fibrous caps and inflammatory cell infiltration [187]. OCT provides near-histologic resolution and enables precise measurement of fibrous-cap thickness, identification of plaque rupture or erosion, and detailed characterization of lipid-rich plaques and microstructures [188,189]. Importantly, OCT can also indirectly detect macrophage accumulation through regions of high signal backscatter and attenuation allowing to link inflammatory activity to cap thinning and plaque vulnerability [166,190]. Given that macrophage infiltration is often driven by inflammasome activation and IL-1 β signaling, OCT may also serve as an indirect marker of inflammasome-driven inflammatory processes within plaques. A thin-cap fibroatheroma, defined by a cap thickness of ≤ 65 μ m, is strongly associated with increased rupture risk and thrombosis [191]. While NIRS primarily detects lipid-core burden, a feature closely related to inflammatory plaque biology, it does not provide detailed morphologic information on its own [166]. Although NIRS cannot directly capture inflammasome activity, its ability to identify lipid-rich areas offers valuable insights into the local inflammatory environment, which is often linked to NLRP3 activation.

7. Therapeutic Targeting of Inflammasomes and Downstream Pathways

7.1 IL-1 Axis Inhibition

IL-1 β is a central proinflammatory cytokine generated downstream of NLRP3 inflammasome activation and rep-

resents an important therapeutic target in inflammasome-driven disease [192]. Inhibition of IL-1 signaling at the receptor level lacks specificity because many IL-1 receptors are not directly linked to inflammasome activity. Clinically available IL-1-targeted agents include anakinra, a recombinant IL-1 receptor antagonist that blocks both IL-1 α and IL-1 β , canakinumab, a long-acting monoclonal antibody that selectively neutralizes IL-1 β , and rilonacept, a soluble decoy receptor active against both IL-1 α and IL-1 β [193].

Anakinra has been widely evaluated in CVD. In HF with preserved ejection fraction (HFpEF), it reduces systemic inflammation, reflected by lower CRP levels, though functional benefits have been inconsistent [194,195]. In HF with reduced ejection fraction (HFrEF), anakinra lowers CRP and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and improves exercise capacity [196]. In ACS, outcomes have varied. In patients with non-ST-segment elevation MI (NSTEMI), the MRC-ILA Heart Study found that anakinra produced a transient reduction in inflammatory markers such as CRP and IL-6, but was unexpectedly associated with higher rates of MACEs at one year [197]. In contrast, in patients with STEMI enrolled in the VCU-ART3 trial, anakinra reduced the incidence of death and new-onset HF, as well as the composite outcome of death or hospitalization for HF, compared with placebo [198].

Canakinumab is a monoclonal antibody targeting IL-1 β that is approved for the treatment of several inflammasome-mediated conditions, including rheumatoid arthritis, acute gout, and atherosclerosis [199,200]. In the CANTOS trial, IL-1 β inhibition with canakinumab significantly lowered the incidence of cardiovascular events in patients with prior MI and residual inflammatory risk, as reflected by elevated CRP levels. Treatment was associated with reductions in CRP and IL-6, alongside increases in total cholesterol and triglycerides, providing compelling clinical evidence that targeting inflammation can improve cardiovascular outcomes independently of lipid lowering [199]. Beyond vascular events, a prespecified secondary analysis of CANTOS suggested that treatment with the 150-mg dose improved left ventricular ejection fraction and exercise capacity in patients with HFrEF [201]. In another study, canakinumab reduced the incidence and mortality of lung cancer in patients with a history of MI, particularly in those who received the highest dose, a finding that highlights the role of IL-1 β -mediated inflammation in disease pathogenesis [202]. These benefits were linked with an increased risk of fatal infections, which limits the broader clinical application of canakinumab [200,203].

Rilonacept has shown anti-inflammatory effects in early cardiovascular studies, including small trials in atherosclerosis and recurrent pericarditis, but robust evidence in broader cardiovascular populations is still lacking [204,205].

7.2 Colchicine as an Indirect Inflammasome Modulator

Colchicine, a naturally derived alkaloid traditionally used for gout and pericarditis, has emerged as a potential therapy for atherosclerotic cardiovascular disease. It exerts anti-inflammatory effects by disrupting microtubule assembly, which inhibits neutrophil chemotaxis, adhesion, and activation, and reduces proliferation of vascular smooth muscle cells and fibroblasts. Importantly, colchicine suppresses NLRP3 inflammasome activity by preventing the assembly and subcellular trafficking of ASC and NLRP3 [206]. It also mitigates platelet–leukocyte interactions and dampens TNF- α -mediated macrophage activation, contributing to its cardiovascular protective effects [207].

A recent meta-analysis evaluated the long-term efficacy and safety of colchicine for secondary prevention in patients with ASCVD [208]. The analysis included six randomized controlled trials (RCTs) with a total of 21,800 patients (colchicine $n = 10,871$; placebo $n = 10,929$), encompassing post-MI (COLCOT, CLEAR-SYNERGY), post-stroke (CONVINCE), stable CAD (LoDoCo, LoDoCo2), and ACS (COPS) populations [208,209,210,211,212,213]. Over follow-up periods ranging from 12 to 34 months, colchicine significantly reduced the incidence of MACEs, including MI, ischemic stroke, and urgent coronary revascularization (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.56–0.93). Safety outcomes, including non-cardiovascular mortality, were comparable between colchicine and placebo groups [208]. These findings support colchicine as an effective and well-tolerated anti-inflammatory therapy for reducing recurrent cardiovascular events in secondary prevention across diverse atherosclerotic populations. Similarly, a recent meta-analysis of 30,659 patients (colchicine $n = 15,255$; no colchicine $n = 15,404$) with prior CAD or stroke showed that colchicine reduced the composite risk of cardiovascular death, MI, or stroke by 12% in secondary prevention. The study also reported a 35% increase in hospitalizations for gastrointestinal events with colchicine, while no increase was observed for pneumonia, newly diagnosed cancers, or non-cardiovascular death [214].

7.3 IL-6 Pathway Targeting

IL-1 β strongly induces IL-6 in various cell types, including intrinsic vascular cells, creating an additional amplification step. IL-6 is the primary driver of the acute-phase response in hepatocytes, leading to the production of acute-phase reactants such as C-reactive protein (CRP), fibrinogen, the precursor of clots, and plasminogen activator inhibitor-1, a key inhibitor of endogenous thrombolysis, collectively promoting thrombus formation and accumulation [215].

Elevated circulating IL-6 is consistently linked to adverse cardiovascular outcomes and all-cause mortality, highlighting the need for therapies that specifically target

IL-6 to reduce cardiovascular risk and HF [216]. In line with targeting IL-6, the RESCUE-2 phase 2 trial evaluated ziltivekimab, a fully human monoclonal antibody against the IL-6 ligand, in Japanese patients with chronic kidney disease and elevated hsCRP. Over 12 weeks, ziltivekimab at 15 mg and 30 mg doses markedly reduced hsCRP by over 90% compared with placebo, along with significant reductions in serum amyloid A and fibrinogen. The treatment was well tolerated and only minor increases in triglyceride levels and no adverse effects on cholesterol ratios were noted. These findings support ziltivekimab as a promising strategy to lower residual inflammatory risk in high-risk atherosclerotic patients [217]. In addition, a phase 2b study investigated clazakizumab, a monoclonal antibody targeting the IL-6 ligand, in adults with CVD and/or diabetes receiving maintenance dialysis with elevated hsCRP. Patients were randomized to clazakizumab (2.5 mg, 5 mg, or 10 mg) or placebo every four weeks. After 12 weeks, clazakizumab significantly reduced hsCRP by 86–92% compared with placebo, achieving the primary endpoint. Secondary outcomes showed reductions in fibrinogen, serum amyloid A, secretory phospholipase A2, and lipoprotein(a), along with increased albumin levels. Most patients in the treatment groups achieved hsCRP <2 mg/L, whereas none in the placebo group did. Safety was generally acceptable, with no severe thrombocytopenia or neutropenia and comparable serious infection rates across groups, although slightly higher in the 10 mg dose. These findings demonstrate that clazakizumab effectively lowers IL-6-driven inflammation in high-risk cardiovascular patients on dialysis [218].

7.4 Direct NLRP3 Inhibitors

MCC950 is a selective inhibitor of the NLRP3 inflammasome that targets its NACHT domain and has shown cardioprotective effects in preclinical studies [219]. In both mouse and human macrophages, MCC950 inhibited canonical and non-canonical NLRP3 inflammasome activation and suppressed IL-1 β production by preventing ASC oligomerization [220]. MCC950 has shown promise as an anti-atherosclerotic agent by reducing plaque size, enhancing plaque stability, improving vascular function, and decreasing intraplaque macrophage content in experimental models [221,222]. In another study using *ApoE* $^{-/-}$ mice and oxLDL-stimulated THP-1-derived macrophages, MCC950 reduced plaque size and intraplaque macrophage content without affecting serum lipid levels. Mechanistic analyses showed that it suppressed macrophage pyroptosis and IL-1 β /IL-18 production by inhibiting the NLRP3/ASC/Caspase-1/GSDMD-N pathway, while leaving TLR4 expression and NLRP3 priming unchanged, indicating that its anti-atherosclerotic effects stem from blocking inflammasome assembly and activation rather than transcriptional priming [223]. In addition, NLRP3 inhibition with MCC950 can reverse the accelerated atherosclerosis associated with Tet2-mutant clonal hematopoiesis, high-

lighting the interplay between epigenetic dysregulation and inflammasome signaling in disease progression [10,96].

Oridonin, a herbal medicinal product, demonstrates protective effects against atherosclerosis in ApoE^{-/-} mice by reducing plaque progression, stabilizing lesions, and decreasing macrophage infiltration. This agent mitigates NLRP3-mediated inflammation, stabilizes nuclear factor erythroid 2-related factor 2 (Nrf2), suppresses oxidative stress, and prevents the formation of foam cells through modulation of lipid uptake and efflux in macrophages. All of these findings suggest oridonin as a potential therapeutic agent for atherosclerosis [224]. CY-09 binds directly to the ATP-binding site of the NACHT domain of NLRP3. In preclinical diabetic ischemic stroke models, CY-09 alleviates disease symptoms and helps preserve cardiac function [225]. BAY 11-7082, an NF- κ B inhibitor that also strongly suppresses NLRP3 inflammasome activity by inhibiting NLRP3 adenosine triphosphatase (ATPase) function, has shown significant cardioprotective effects [226,227,228]. In preclinical ischemia/reperfusion models, it reduced infarct size, myocardial apoptosis, fibrosis, and inflammation, while preserving cardiac function and limiting pyroptosis [226,227].

7.5 Targeting, ASC, Caspase-1, and Gasdermin-D

ASC functions as a central adaptor of the NLRP3 inflammasome. It facilitates caspase-1 recruitment, making it an attractive but technically challenging therapeutic target [229]. OLT1177, an orally available β -sulfonyl nitrile compound, selectively interferes with ASC oligomerization while sparing other inflammasomes such as AIM2 and NLRC4 [38]. In a mouse model of myocardial ischemia/reperfusion (I/R) injury, OLT1177, when administered at reperfusion, significantly reduced infarct size and preserved left ventricular systolic function in a dose-dependent manner. Note that this cardioprotective effect was maintained even when treatment was delayed up to 60 minutes after reperfusion, a finding that underscores the potential of NLRP3 inhibition to limit post-ischemic myocardial injury [230]. In humans, a phase 1B randomized trial that enrolled stable patients with HFrEF showed that short-term oral OLT1177 was not only safe and well tolerated, but also improved left ventricular ejection fraction and exercise capacity. Hence, this study supported the translational potential of NLRP3 inhibition in HF [231].

VX-765 and VX-740 are peptidomimetic inhibitors of caspase-1, which are metabolized *in vivo* into their active forms [232,233]. In preclinical I/R studies, VX-765 demonstrated cardioprotective effects, as it limits myocardial injury and attenuates atherosclerotic disease development [234,235]. Despite these promising results, the clinical development of caspase-1 inhibitors was discontinued because of concerns about liver toxicity and a higher risk of infections [236].

Targeting GSDMD-dependent pyroptosis is another promising approach to limit inflammasome-mediated atherosclerosis. Several pharmacologic inhibitors of GSDMD are currently under investigation for cardiovascular and other inflammatory conditions [237]. Among them, disulfiram has been shown to attenuate aortic root atherosclerosis in hyperlipidemic mouse models, an effect attributed to enhanced autophagy, improved efferocytosis, and favorable alterations in gut microbiota composition [238]. Disulfiram has also demonstrated promise in cardiometabolic disease models, where it reduces obesity and ameliorates steatohepatitis in preclinical studies [239,240].

More recently, GI-Y1 has been identified as a selective small-molecule inhibitor of GSDMD. Preclinical evidence indicates that GI-Y1 suppresses cardiomyocyte pyroptosis, limits myocardial ischemia–reperfusion injury, and reduces pathological cardiac remodeling by inhibiting GSDMD-N pore formation, highlighting its potential as a therapeutic candidate for GSDMD-mediated cardiac disorders [241].

7.6 Modulating Upstream Metabolic Drivers

Sodium–glucose cotransporter 2 inhibitors (SGLT2is), originally developed for glycemic control, are now well established as therapies that confer substantial cardiovascular and renal protection through multiple pleiotropic mechanisms. These agents exert anti-inflammatory, antifibrotic, and antioxidant effects, many of which are linked to inhibition of NLRP3 inflammasome signaling [242]. SGLT2is directly reduce oxidative stress, suppress NF- κ B signaling, and enhance autophagy, thereby limiting IL-1 β and IL-18 production and mitigating atherosclerotic progression. They also increase β -hydroxybutyrate (β -OHB), a metabolite that inhibits NLRP3 activation in monocytes, contributing further to plaque stabilization [243]. Preclinical studies in diabetic models confirm that SGLT2is improve vascular function, reduce inflammation and oxidative stress, and protect against endothelial dysfunction and atherosclerosis [244]. Clinically, SGLT2is modestly lower all-cause mortality and reduce atherosclerotic cardiovascular events, with the greatest benefits observed in patients with T2DM and chronic kidney disease or established ASCVD [245,246]. While SGLT2is may increase erythrocytosis compared with dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists (GLP-1RAs), this does not appear to increase thrombotic risk [247]. Interestingly, dual SGLT1/2 inhibition with sotagliflozin shows enhanced anti-platelet and antithrombotic effects compared with selective SGLT2 inhibition. This is largely mediated by SGLT1 inhibition and suggests that SGLT1/2 inhibitors may provide increased cardiovascular benefit in high-risk patients [248].

GLP-1RAs are widely used for the treatment of T2DM, obesity, and CVD, owing to their strong metabolic effects and comprehensive cardio–renal–metabolic bene-

Table 1. Summary of therapeutic candidates and emerging agents targeting inflammasome-related pathways in atherosclerosis and atherothrombosis.

Compound	Target	Proposed mechanism of action	Major effects
Anti-inflammatory compounds			
Anakinra	IL-1 α , IL-1 β	Recombinant human IL-1R antagonist.	Reduces systemic inflammation (ICRP/IL-6). Improves exercise capacity and lowers NT-proBNP in HFrEF. Limited functional benefit in HFpEF. Mixed effects in ACS, higher 1-year MACEs in NSTEMI, but reduced mortality and HF events in STEMI [194,195,196,197,198].
Canakinumab	IL-1 β	Monoclonal IL-1 β neutralising antibody.	Lowers residual inflammation (ICRP, IL-6) and reduces recurrent cardiovascular events after MI, independent of lipid lowering, despite modest increases in cholesterol and triglycerides. Improves LVEF and exercise capacity in HFrEF (secondary analysis). Increased risk of fatal infections limits widespread use and requires careful risk–benefit assessment [199,200,201,202,203].
Rilonacept	IL-1 α , IL-1 β	Fusion protein active against IL-1 α and IL-1 β .	Demonstrates anti-inflammatory activity in atherosclerosis and recurrent pericarditis, but clinical evidence in broader cardiovascular populations remains limited [204,205].
Colchicine	Chemotaxis, VSMCs, fibroblasts, NLRP3 inflammasome	Inhibits tubulin polymerization into microtubules, prevents the assembly and subcellular trafficking of ASC and NLRP3.	Reduces recurrent cardiovascular events in secondary prevention across diverse ASCVD populations, with an acceptable safety profile; gastrointestinal adverse events are increased, but no excess in non-cardiovascular mortality, cancer, or pneumonia has been observed [208,209,210,211,212,213,214].
Ziltivekimab	IL-6	Fully human monoclonal antibody against the IL-6 ligand.	Potently lowers hsCRP, serum amyloid A, and fibrinogen in high-risk atherosclerotic patients, with good tolerability and minimal lipid changes, supporting its potential to reduce residual inflammatory risk [217].
Clazakizumab	IL-6	Monoclonal antibody targeting the IL-6 ligand.	Lowers hsCRP, fibrinogen, serum amyloid A, secretory phospholipase A2, and lipoprotein(a), while increasing albumin, in high-risk cardiovascular patients on dialysis, with generally acceptable safety [218].
MCC950	NLRP3 inflammasome	Specifically inhibits the NLRP3 inflammasome by targeting its NACHT domain.	Inhibits both canonical and non-canonical NLRP3 inflammasome activation, suppressing IL-1 β and IL-18 production, reducing macrophage pyroptosis, decreasing plaque size and intraplaque macrophages, and improving plaque stability and vascular function, without altering serum lipid levels [220,221,222,223].
Oridonin	NLRP3 inflammasome	Creates a covalent bond with cysteine (Cys)279 in the NACHT domain.	Reduces plaque progression and macrophage infiltration, stabilizes lesions, and inhibits NLRP3-driven inflammation, oxidative stress, and foam cell formation [199].
CY-09	NLRP3 inflammasome	Blocks NLRP3 assembly via NACHT ATPase binding.	In preclinical diabetic ischemic stroke models, it reduces disease severity and may protect against cardiac dysfunction [224].
BAY 11-7082	NF- κ B/NLRP3 inflammasome	Inhibitor of NF- κ B activation and NLRP3 ATPase activity.	In preclinical ischemia/reperfusion models, it decreased infarct size, apoptosis, fibrosis, and inflammation, preserved cardiac function, and limited pyroptosis [226,227,228].
OLT1177	NLRP3 inflammasome	A beta-sulfonyl nitrile molecule that blocks ASC oligomerization.	Demonstrates cardioprotective effects across preclinical and human studies by reducing infarct size, limiting myocardial injury and inflammation, preserving left ventricular function, and improving exercise capacity, with good safety and tolerability [230,231].

Table 1. Continued.

Compound	Target	Proposed mechanism of action	Major effects
VX-765 and VX-740	Caspase-1	Peptidomimetic inhibitors of caspase-1.	VX-765 reduces myocardial injury and atherosclerosis in pre-clinical studies, but clinical development was limited by liver toxicity and increased infection risk [234,235,236].
Disulfiram	GSDMD	Inhibitor of GSDMD-mediated pyroptosis.	Reduces aortic atherosclerosis, improves autophagy and efferocytosis, modulates gut microbiota, and ameliorates obesity and steatohepatitis in preclinical cardiometabolic models [238,239,240].
GI-Y1	GSDMD	Selective inhibitor of GSDMD.	Inhibits GSDMD-mediated pyroptosis, reduces myocardial ischemia–reperfusion injury, and limits pathological cardiac remodeling in preclinical models [241].
Upstream metabolic modulators			
SGLT2 inhibitors	in- SGLT2 protein/NLRP3 inflammasome	Exert anti-inflammatory, antifibrotic, and antioxidant effects.	Reduce inflammation and oxidative stress, improve endothelial and vascular function, protect against atherosclerosis, lower all-cause mortality and ASCVD events (especially in T2DM with CKD or established ASCVD) [242,243,244,245,246].
GLP-1 RAs	Glucagon-like peptide-1 receptor/NLRP3 inflammasome	Exert antifibrotic, anti-inflammatory, antioxidant effects, improve mitochondrial function.	Exert anti-inflammatory and anti-atherosclerotic effects by inhibiting NLRP3 inflammasome activation, reducing lesion infiltration, promoting mitophagy, lowering mitochondrial ROS, and shifting macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotype [250,251,252,253,254].
Statins	HMG-CoA/NLRP3 inflammasome	Blocks the activation of the NLRP3 inflammasome by inhibiting the mevalonate/isoprenoid pathway. Pleiotropic effects.	Statins reduce atheroma progression and thrombotic events, inhibit NLRP3 inflammasome-driven inflammation, and decrease platelet activation and thrombin generation, though inflammasome activation may occur in some contexts [255,256,257].

IL-1 β , interleukin-1 β ; IL-1R, interleukin-1 receptor; CRP, C-reactive protein; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACS, acute coronary syndrome; MACES, major adverse cardiac events; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; IL-1 α , interleukin-1 α ; VSMCs, vascular smooth muscle cells, NLRP3, NOD-like receptor containing pyrin domain 3; ASCVD, atherosclerotic cardiovascular disease; hsCRP, high sensitivity CRP; IL-18, interleukin-18; ATPase, adenosine triphosphatase; NF- κ B, nuclear factor- κ B; ASC, apoptosis-associated speck-like protein; GSDMD, gasdermin D; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; ROS, reactive oxygen species; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; NACHT, nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1.

fits [249]. These agents have notable anti-inflammatory and antifibrotic properties, while also improving cardiac energy metabolism and reducing oxidative stress [250,251,252,253]. Part of their anti-inflammatory effect appears to stem from inhibition of the NLRP3 inflammasome that leads to reduced NLRP3-mediated inflammatory cell infiltration within atherosclerotic lesions. Mechanistically, GLP-1RAs suppress NLRP3 activation by promoting mitophagy, reducing mtROS production, and driving macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 state [254].

Statins inhibit NLRP3 inflammasome activation by blocking the mevalonate/isoprenoid pathway, preventing small GTPase prenylation, reducing NF- κ B-mediated IL-1 β and IL-18 transcription, and lowering ROS generation, thereby limiting inflammasome assembly and cytokine re-

lease [255]. In certain metabolic contexts, however, statins may paradoxically enhance NLRP3 activation, which has been associated with impaired insulin signaling, a modest increase in new-onset diabetes, and statin-associated myopathy [256,257].

Beyond lipid lowering, statins reduce atheroma progression and thrombotic risk through decreased platelet activation, modulation of fibrinolysis, and inhibition of thrombin generation via suppression of isoprenoid-dependent tissue factor/factor VII signaling, although effects on fibrinogen and factor VII levels remain inconsistent [258].

Table 1 (Ref. [194,195,196,197,198,199,200,201,202,203,204,205,208,209,210,211,212,213,214,217,218,220,221,222,223,224,226,227,228,230,231,234,235,236,238,239,240,241,242,243,244,245,246,250,251,252,253,254,

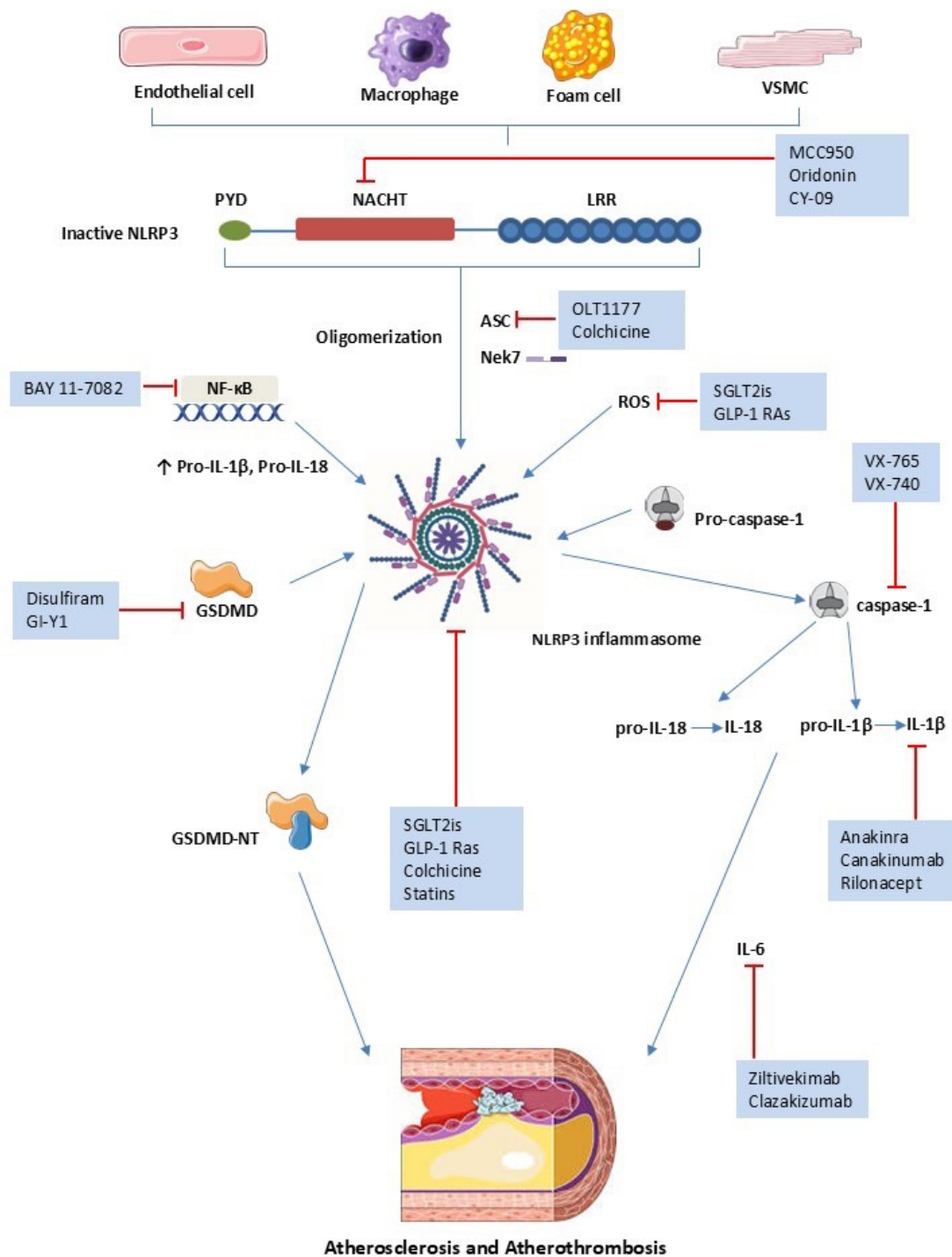


Fig. 2. Graphical representation of therapeutic strategies targeting the NLRP3 inflammasome and its downstream pathways contributing to atherogenesis and thrombotic complications. VSMC, vascular smooth muscle cells; PYD, pyrin domain; NACHT, nucleotide-binding domain, Apaf-1, CIITA, HET-E, TP1; LRR, leucine-rich repeat; ASC, apoptosis-associated speck-like protein containing a CARD; NF- κ B, nuclear factor- κ B; Nek7, NIMA-related kinase 7; SGLT2is, sodium-glucose cotransporter 2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; ROS, reactive oxygen species; pro-IL-1 β , pro-interleukin-1 β ; pro-IL-18, pro-interleukin-18; IL-1 β , interleukin-1 β ; IL-18, interleukin-18; IL-6, interleukin-6; GSDMD, gasdermin D; GSDMD-NT, gasdermin D N-terminal fragment; NLRP3, NOD-like receptor containing pyrin domain 3.

255,256,257]) summarizes therapeutic agents and their potential roles in the treatment of inflammasome-mediated atherosclerosis. Fig. 2 provides a schematic overview of

current pharmacological strategies targeting the NLRP3 inflammasome and its downstream signaling pathways in atherosclerosis and atherothrombosis.

8. Knowledge Gaps, Controversies and Future Directions

In recent years, there have been significant advances in the understanding of how inflammasome signaling contributes to atherothrombosis and how it can be regulated therapeutically. However, several important questions remain. To begin with, the available data cannot fully clarify whether the risk of atherosclerosis is driven primarily by inflammasomes, by downstream inflammatory cytokines such as IL-1 β and IL-6, or by pyroptosis. We know that inhibition of IL-1 β improves outcomes related to atherosclerosis, but we are still uncertain whether directly inhibiting inflammasomes will provide additional or distinct benefits compared with cytokine blockade alone. In order to address these issues, we should develop new therapeutic strategies that selectively modulate inflammasome activity in relevant vascular or immune cell populations.

Another issue we have to address is the optimal timing of treatment. Currently, it is unclear when anti-inflammasome agents should be given in order to be most effective against atherothrombosis. Future research should focus on determining whether they should be administered during early, subclinical atherosclerosis to prevent or slow atherogenesis, when plaques are vulnerable, or after ACS.

Precision medicine approaches may help us deal with these uncertainties. It would be helpful if we could identify patients with increased inflammasome activity who are expected to benefit the most from anti-inflammatory medicines. In line with this, using circulating biomarkers, such as IL-1 β and CRP, plaque imaging, or multi-omics profiling could enable targeted treatment of individuals, resulting in improved clinical outcomes. However, clinically practical biomarkers are still lacking.

Safety is another important concern. It is logical to assume that chronic suppression of inflammasomes could increase the risk of infections and malignancy. Last but not least, future research should explore rational combination strategies. The integration of therapies that target inflammasomes with lipid-lowering drugs, antithrombotics, and emerging cardiometabolic agents represents an exciting area of future research for improving cardiovascular outcomes.

9. Conclusion

Inflammasomes, particularly NLRP3 and AIM2, represent a critical mechanistic link between vascular inflammation and the transition to acute atherothrombotic events. Growing evidence suggests that targeting inflammasome pathways could be beneficial. However, many issues remain to be addressed, including safety and the optimal timing at which anti-inflammasome therapies should be initiated. In addition to clinical considerations, there is a pressing need for further fundamental studies to elucidate the molecular regulation of the NLRP3 inflammasome and its role in atherogenesis. Therefore, future efforts should fo-

cus on mechanistic research, refined patient stratification, and correctly designed clinical trials in order to translate our knowledge about inflammasome pathophysiology into effective strategies for atherothrombotic prevention.

Author Contributions

KG: Conceptualization, Methodology, Investigation, Visualization, Project administration, Writing—original draft, Writing—review & editing, Designed the research study, Prepared figures/tables, Searched references. APA: Writing—original draft, Writing—review & editing, Designed the research study, Prepared figures/tables, Searched references. VL: Writing—review & editing, Prepared tables, Searched references. NK: Writing—review & editing, Prepared tables, Searched references. PT: Writing—review & editing, Prepared figures/tables, Searched references. PI: Writing—review & editing, Prepared tables, Searched references. PKV: Writing—review & editing, Prepared tables, Searched references. AA: Writing—review & editing, Prepared tables, Searched references. BF: Writing—review & editing, Prepared figures/tables, Searched references. EK: Writing—review & editing, Prepared tables, Searched references. NF: Writing—review & editing, Supervision, Designed the research study. PK: Conceptualization, Methodology, Investigation, Writing—review & editing, Validation, Supervision, Designed the research study. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Nedkoff L, Briffa T, Zemedikun D, Herrington S, Wright FL. Global Trends in Atherosclerotic Cardiovascular Disease. *Clinical Therapeutics*. 2023; 45: 1087–1091. <https://doi.org/10.1016/j.clinthera.2023.09.020>
- [2] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics—2021 Update: A Report From the American Heart Association. *Circulation*. 2021; 143: e254–e743. <https://doi.org/10.1161/CIR.0000000000000950>

- [3] Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. *Nature Reviews. Disease Primers*. 2019; 5: 56. <https://doi.org/10.1038/s41572-019-0106-z>
- [4] Mensah GA, Arnold N, Prabhu SD, Ridker PM, Welty FK. Inflammation and Cardiovascular Disease: 2025 ACC Scientific Statement: A Report of the American College of Cardiology. *Journal of the American College of Cardiology*. 2026; 87: 1381–1404. <https://doi.org/10.1016/j.jacc.2025.08.047>
- [5] Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D. Inflammation in Atherosclerosis-From Pathophysiology to Treatment. *Pharmaceuticals (Basel, Switzerland)*. 2023; 16: 1211. <https://doi.org/10.3390/ph16091211>
- [6] Guo H, Callaway JB, Ting JPY. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nature Medicine*. 2015; 21: 677–687. <https://doi.org/10.1038/nm.3893>
- [7] Tanase DM, Valasciuc E, Gosav EM, Ouatu A, Buliga-Finis ON, Floria M, et al. Portrayal of NLRP3 Inflammasome in Atherosclerosis: Current Knowledge and Therapeutic Targets. *International Journal of Molecular Sciences*. 2023; 24: 8162. <https://doi.org/10.3390/ijms24098162>
- [8] Caldarelli M, Franza L, Cutrupi S, Menegolo M, Franceschi F, Gasbarrini A, et al. Inflammasomes in Cardiovascular Diseases: Current Knowledge and Future Perspectives. *International Journal of Molecular Sciences*. 2025; 26: 5439. <https://doi.org/10.3390/ijms26125439>
- [9] Cao J, Roth S, Zhang S, Kopczak A, Mami S, Asare Y, et al. DNA-sensing inflammasomes cause recurrent atherosclerotic stroke. *Nature*. 2024; 633: 433–441. <https://doi.org/10.1038/s41586-024-07803-4>
- [10] Yalcinkaya M, Tall AR. Genetic and epigenetic regulation of inflammasomes: Role in atherosclerosis. *Atherosclerosis*. 2024; 396: 118541. <https://doi.org/10.1016/j.atherosclerosis.2024.118541>
- [11] Karasawa T, Takahashi M. Inflammasome Activation and Neutrophil Extracellular Traps in Atherosclerosis. *Journal of Atherosclerosis and Thrombosis*. 2025; 32: 535–549. <https://doi.org/10.5551/jat.RV22033>
- [12] Hindle MS, Berger M, Naseem KM. The NLRP3 inflammasome in platelets - form, functions, and future of the complex. *Platelets*. 2025; 36: 2562267. <https://doi.org/10.1080/09537104.2025.2562267>
- [13] Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL- β . *Molecular Cell*. 2002; 10: 417–426. [https://doi.org/10.1016/s1097-2765\(02\)00599-3](https://doi.org/10.1016/s1097-2765(02)00599-3)
- [14] Abderrazak A, Syrovets T, Couchie D, El Hadri K, Friguet B, Simmet T, et al. NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. *Redox Biology*. 2015; 4: 296–307. <https://doi.org/10.1016/j.redox.2015.01.008>
- [15] Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, et al. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines*. 2021; 9: 781. <https://doi.org/10.3390/biomedicines9070781>
- [16] Frising UC, Ribo S, Doglio MG, Malissen B, van Loo G, Wullaert A. Nlrp3 inflammasome activation in macrophages suffices for inducing autoinflammation in mice. *EMBO Reports*. 2022; 23: e54339. <https://doi.org/10.15252/embr.202154339>
- [17] Ferreira I, Liberal J, Martins JD, Silva A, Neves BM, Cruz MT. Inflammasome in Dendritic Cells Immunobiology: Implications to Diseases and Therapeutic Strategies. *Current Drug Targets*. 2017; 18: 1003–1018. <https://doi.org/10.2174/1389450117666160921144830>
- [18] Santana PT, Martel J, Lai HC, Perfettini JL, Kanellopoulos JM, Young JD, et al. Is the inflammasome relevant for epithelial cell function? *Microbes and Infection*. 2016; 18: 93–101. <https://doi.org/10.1016/j.micinf.2015.10.007>
- [19] Swanson KV, Deng M, Ting JPY. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nature Reviews. Immunology*. 2019; 19: 477–489. <https://doi.org/10.1038/s41577-019-0165-0>
- [20] Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature*. 2012; 481: 278–286. <https://doi.org/10.1038/nature10759>
- [21] Chen P, Li X. NLRP3 inflammasome in atherosclerosis: Mechanisms and targeted therapies. *Frontiers in Pharmacology*. 2024; 15: 1430236. <https://doi.org/10.3389/fphar.2024.1430236>
- [22] González-Moro A, Valencia I, Shamoon L, Sánchez-Ferrer CF, Peiró C, de la Cuesta F. NLRP3 Inflammasome in Vascular Disease: A Recurrent Villain to Combat Pharmacologically. *Antioxidants (Basel, Switzerland)*. 2022; 11: 269. <https://doi.org/10.3390/antiox11020269>
- [23] Ma Q. Pharmacological Inhibition of the NLRP3 Inflammasome: Structure, Molecular Activation, and Inhibitor-NLRP3 Interaction. *Pharmacological Reviews*. 2023; 75: 487–520. <https://doi.org/10.1124/pharmrev.122.000629>
- [24] Kanneganti TD. The inflammasome: firing up innate immunity. *Immunological Reviews*. 2015; 265: 1–5. <https://doi.org/10.1111/imr.12297>
- [25] Olsen MB, Gregersen I, Sandanger Ø, Yang K, Sokolova M, Halvorsen BE, et al. Targeting the Inflammasome in Cardiovascular Disease. *JACC. Basic to Translational Science*. 2021; 7: 84–98. <https://doi.org/10.1016/j.jacbts.2021.08.006>
- [26] Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death & Disease*. 2019; 10: 128. <https://doi.org/10.1038/s41419-019-1413-8>
- [27] Muñoz-Planillo R, Kuffa P, Martínez-Colón G, Smith BL, Rajendiran TM, Núñez G. K⁺ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity*. 2013; 38: 1142–1153. <https://doi.org/10.1016/j.immuni.2013.05.016>
- [28] Meyers AK, Zhu X. The NLRP3 Inflammasome: Metabolic Regulation and Contribution to Inflammation. *Cells*. 2020; 9: 1808. <https://doi.org/10.3390/cells9081808>
- [29] Paramel Varghese G, Folkersen L, Strawbridge RJ, Halvorsen B, Yndestad A, Ranheim T, et al. NLRP3 Inflammasome Expression and Activation in Human Atherosclerosis. *Journal of the American Heart Association*. 2016; 5: e003031. <https://doi.org/10.1161/JAHA.115.003031>
- [30] Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nature Reviews. Immunology*. 2016; 16: 407–420. <https://doi.org/10.1038/nri.2016.58>
- [31] Jin Y, Fu J. Novel Insights Into the NLRP3 Inflammasome in Atherosclerosis. *Journal of the American Heart Association*. 2019; 8: e012219. <https://doi.org/10.1161/JAHA.119.012219>
- [32] Stocker R, Keaney JF, Jr. Role of oxidative modifications in atherosclerosis. *Physiological Reviews*. 2004; 84: 1381–1478. <https://doi.org/10.1152/physrev.00047.2003>
- [33] Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis. *Mediators of Inflammation*. 2013; 2013: 152786. <https://doi.org/10.1155/2013/152786>
- [34] Magwenzi S, Woodward C, Wraith KS, Aburima A, Raslan Z, Jones H, et al. Oxidized LDL activates blood platelets through CD36/NOX2-mediated inhibition of the cGMP/protein kinase G signaling cascade. *Blood*. 2015; 125: 2693–2703. <https://doi.org/10.1182/blood-2014-05-574491>
- [35] Janoudi A, Shamoun FE, Kalavakunta JK, Abela GS. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. *European Heart Journal*. 2016; 37: 1959–1967. <https://doi.org/10.1093/eurheartj/ehv653>

- [36] Li X, Zhang Y, Xia M, Gulbins E, Boini KM, Li PL. Activation of Nlrp3 inflammasomes enhances macrophage lipid-deposition and migration: implication of a novel role of inflammasome in atherogenesis. *PloS One*. 2014; 9: e87552. <https://doi.org/10.1371/journal.pone.0087552>
- [37] Zhang J, Chang J, Chen V, Beg MA, Huang W, Vick L, et al. Oxidized LDL stimulates PKM2-mediated mtROS production and phagocytosis. *Journal of Lipid Research*. 2025; 66: 100809. <https://doi.org/10.1016/j.jlr.2025.100809>
- [38] Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhalawon B, Carpenter SB, et al. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nature Immunology*. 2013; 14: 812–820. <https://doi.org/10.1038/ni.2639>
- [39] Casey AM, Ryan DG, Prag HA, Chowdhury SR, Marques E, Turner K, et al. Pro-inflammatory macrophages produce mitochondria-derived superoxide by reverse electron transport at complex I that regulates IL-1 β release during NLRP3 inflammasome activation. *Nature Metabolism*. 2025; 7: 493–507. <https://doi.org/10.1038/s42255-025-01224-x>
- [40] Mahmoudi M, Gorenne I, Mercer J, Figg N, Littlewood T, Bennett M. Statins use a novel Nijmegen breakage syndrome-1-dependent pathway to accelerate DNA repair in vascular smooth muscle cells. *Circulation Research*. 2008; 103: 717–725. <https://doi.org/10.1161/CIRCRESAHA.108.182899>
- [41] Lin J, Wang J, Fang J, Li M, Xu S, Little PJ, et al. The cytoplasmic sensor, the AIM2 inflammasome: A precise therapeutic target in vascular and metabolic diseases. *British Journal of Pharmacology*. 2024; 181: 1695–1719. <https://doi.org/10.1111/bph.16355>
- [42] Shi J, Gao W, Shao F. Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death. *Trends in Biochemical Sciences*. 2017; 42: 245–254. <https://doi.org/10.1016/j.tibs.2016.10.004>
- [43] Qian Z, Zhao Y, Wan C, Deng Y, Zhuang Y, Xu Y, et al. Pyroptosis in the Initiation and Progression of Atherosclerosis. *Frontiers in Pharmacology*. 2021; 12: 652963. <https://doi.org/10.3389/fphar.2021.652963>
- [44] Mitchell S, Vargas J, Hoffmann A. Signaling via the NF κ B system. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine*. 2016; 8: 227–241. <https://doi.org/10.1002/wsbm.1331>
- [45] Wang YM, Ji R, Chen WW, Huang SW, Zheng YJ, Yang ZT, et al. Paclitaxel alleviated sepsis-induced acute lung injury by activating MUC1 and suppressing TLR-4/NF- κ B pathway. *Drug Design, Development and Therapy*. 2019; 13: 3391–3404. <https://doi.org/10.2147/DDDT.S222296>
- [46] Song D, Li M, Yu X, Wang Y, Fan J, Yang W, et al. The Molecular Pathways of Pyroptosis in Atherosclerosis. *Frontiers in Cell and Developmental Biology*. 2022; 10: 824165. <https://doi.org/10.3389/fcell.2022.824165>
- [47] Lei Q, Yi T, Chen C. NF- κ B-Gasdermin D (GSDMD) Axis Couples Oxidative Stress and NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3) Inflammasome-Mediated Cardiomyocyte Pyroptosis Following Myocardial Infarction. *Medical Science Monitor*. 2018; 24: 6044–6052. <https://doi.org/10.12659/MSM.908529>
- [48] Pepin ME, Gupta RM. The Role of Endothelial Cells in Atherosclerosis: Insights from Genetic Association Studies. *The American Journal of Pathology*. 2024; 194: 499–509. <https://doi.org/10.1016/j.ajpath.2023.09.012>
- [49] Wu J, Shyy M, Shyy JYJ, Xiao H. Role of inflammasomes in endothelial dysfunction. *British Journal of Pharmacology*. 2024; 181: 4958–4972. <https://doi.org/10.1111/bph.16479>
- [50] Penna C, Pagliaro P. Endothelial Dysfunction: Redox Imbalance, NLRP3 Inflammasome, and Inflammatory Responses in Cardiovascular Diseases. *Antioxidants (Basel, Switzerland)*. 2025; 14: 256. <https://doi.org/10.3390/antiox14030256>
- [51] Xiao H, Lu M, Lin TY, Chen Z, Chen G, Wang WC, et al. Sterol regulatory element binding protein 2 activation of NLRP3 inflammasome in endothelium mediates hemodynamic-induced atherosclerosis susceptibility. *Circulation*. 2013; 128: 632–642. <https://doi.org/10.1161/CIRCULATIONAHA.113.002714>
- [52] Luo X, Hu Y, He S, Ye Q, Lv Z, Liu J, et al. Dulaglutide inhibits high glucose-induced endothelial dysfunction and NLRP3 inflammasome activation. *Archives of Biochemistry and Biophysics*. 2019; 671: 203–209. <https://doi.org/10.1016/j.abb.2019.07.008>
- [53] Milan KL, Megha B, Ramkumar KM. Role of inflammasomes in diabetes mellitus: mechanisms, complications, and therapeutic potential. *Molecular Biology Reports*. 2025; 52: 621. <https://doi.org/10.1007/s11033-025-10719-5>
- [54] Yin Y, Zhou Z, Liu W, Chang Q, Sun G, Dai Y. Vascular endothelial cells senescence is associated with NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation via reactive oxygen species (ROS)/thioredoxin-interacting protein (TXNIP) pathway. *The International Journal of Biochemistry & Cell Biology*. 2017; 84: 22–34. <https://doi.org/10.1016/j.biocel.2017.01.001>
- [55] Poznyak AV, Nikiforov NG, Markin AM, Kashirskikh DA, Myasoedova VA, Gerasimova EV, et al. Overview of OxLDL and Its Impact on Cardiovascular Health: Focus on Atherosclerosis. *Frontiers in Pharmacology*. 2021; 11: 613780. <https://doi.org/10.3389/fphar.2020.613780>
- [56] Martinet W, Coornaert I, Puylaert P, De Meyer GRY. Macrophage Death as a Pharmacological Target in Atherosclerosis. *Frontiers in Pharmacology*. 2019; 10: 306. <https://doi.org/10.3389/fphar.2019.00306>
- [57] Zeng X, Liu D, Huo X, Wu Y, Liu C, Sun Q. Pyroptosis in NLRP3 inflammasome-related atherosclerosis. *Cell Stress*. 2022; 6: 79–88. <https://doi.org/10.15698/cst2022.10.272>
- [58] Chen R, McVey DG, Shen D, Huang X, Ye S. Phenotypic Switching of Vascular Smooth Muscle Cells in Atherosclerosis. *Journal of the American Heart Association*. 2023; 12: e031121. <https://doi.org/10.1161/JAHA.123.031121>
- [59] Burger F, Baptista D, Roth A, da Silva RF, Montecucco F, Mach F, et al. NLRP3 Inflammasome Activation Controls Vascular Smooth Muscle Cells Phenotypic Switch in Atherosclerosis. *International Journal of Molecular Sciences*. 2021; 23: 340. <https://doi.org/10.3390/ijms23010340>
- [60] Pi S, Xiong S, Yuan Y, Deng H. The Role of Inflammasome in Abdominal Aortic Aneurysm and Its Potential Drugs. *International Journal of Molecular Sciences*. 2024; 25: 5001. <https://doi.org/10.3390/ijms25095001>
- [61] Xu S, Lyu QR, Ilyas I, Tian XY, Weng J. Vascular homeostasis in atherosclerosis: A holistic overview. *Frontiers in Immunology*. 2022; 13: 976722. <https://doi.org/10.3389/fimmu.2022.976722>
- [62] Tesfamariam B. Periadventitial local drug delivery to target restenosis. *Vascular Pharmacology*. 2017. <https://doi.org/10.1016/j.vph.2017.12.062> (online ahead of print)
- [63] Kortelainen ML, Porvari K. Adventitial macrophage and lymphocyte accumulation accompanying early stages of human coronary atherogenesis. *Cardiovascular Pathology*. 2014; 23: 193–197. <https://doi.org/10.1016/j.carpath.2014.03.001>
- [64] Usui F, Shirasuna K, Kimura H, Tatsumi K, Kawashima A, Karasawa T, et al. Inflammasome activation by mitochondrial oxidative stress in macrophages leads to the development of angiotensin II-induced aortic aneurysm. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015; 35: 127–136. <https://doi.org/10.1161/ATVBAHA.114.303763>
- [65] Hillock-Watling C, Gotlieb AI. The pathobiology of perivascular adipose tissue (PVAT), the fourth layer of the blood vessel wall. *Cardiovascular Pathology*. 2022; 61: 107459. <https://doi.org/10.1016/j.carpath.2022.107459>

//doi.org/10.1016/j.carpath.2022.107459

- [66] Alkhalil M, Edmond E, Edgar L, Digby JE, Omar O, Robson MD, et al. The relationship of perivascular adipose tissue and atherosclerosis in the aorta and carotid arteries, determined by magnetic resonance imaging. *Diabetes & Vascular Disease Research*. 2018; 15: 286–293. <https://doi.org/10.1177/1479164118757923>
- [67] Chen X, Huang Q, Feng J, Xiao Z, Zhang X, Zhao L. GLP-1 alleviates NLRP3 inflammasome-dependent inflammation in perivascular adipose tissue by inhibiting the NF- κ B signalling pathway. *The Journal of International Medical Research*. 2021; 49: 300060521992981. <https://doi.org/10.1177/0300060521992981>
- [68] Rossi C, Santini E, Chiarugi M, Salvati A, Comassi M, Vitolo E, et al. The complex P2X7 receptor/inflammasome in perivascular fat tissue of heavy smokers. *European Journal of Clinical Investigation*. 2014; 44: 295–302. <https://doi.org/10.1111/eci.12232>
- [69] Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of Atherosclerosis. *International Journal of Molecular Sciences*. 2022; 23: 3346. <https://doi.org/10.3390/ijms23063346>
- [70] Pahwa R, Jialal I. Atherosclerosis. StatPearls Publishing: Treasure Island (FL). 2023.
- [71] Tasouli-Drakou V, Ogurek I, Shaikh T, Ringor M, DiCaro MV, Lei K. Atherosclerosis: A Comprehensive Review of Molecular Factors and Mechanisms. *International Journal of Molecular Sciences*. 2025; 26: 1364. <https://doi.org/10.3390/ijms26031364>
- [72] Abela GS. Cholesterol crystals piercing the arterial plaque and intima trigger local and systemic inflammation. *Journal of Clinical Lipidology*. 2010; 4: 156–164. <https://doi.org/10.1016/j.jacl.2010.03.003>
- [73] Fessler MB. Liver X Receptor: Crosstalk Node for the Signaling of Lipid Metabolism, Carbohydrate Metabolism, and Innate Immunity. *Current Signal Transduction Therapy*. 2008; 3: 75–81. <https://doi.org/10.2174/157436208784223170>
- [74] Zhou L, Li C, Gao L, Wang A. High-density lipoprotein synthesis and metabolism (Review). *Molecular Medicine Reports*. 2015; 12: 4015–4021. <https://doi.org/10.3892/mmr.2015.3930>
- [75] Qian AS, Kluck GEG, Yu P, Gonzalez L, Balint E, Trigatti BL. Apolipoprotein A1 deficiency increases macrophage apoptosis and necrotic core development in atherosclerotic plaques in a Bim-dependent manner. *Journal of Lipid Research*. 2025; 66: 100782. <https://doi.org/10.1016/j.jlr.2025.100782>
- [76] Tabas I. Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005; 25: 2255–2264. <https://doi.org/10.1161/01.ATV.0000184783.04864.9f>
- [77] Puylaert P, Zurek M, Rayner KJ, De Meyer GRY, Martinet W. Regulated Necrosis in Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2022; 42: 1283–1306. <https://doi.org/10.1161/ATVBAHA.122.318177>
- [78] Degterev A, Hitomi J, Germscheid M, Ch'en IL, Korkina O, Teng X, et al. Identification of RIP1 kinase as a specific cellular target of necrostatins. *Nature Chemical Biology*. 2008; 4: 313–321. <https://doi.org/10.1038/nchembio.83>
- [79] Zhang DW, Shao J, Lin J, Zhang N, Lu BJ, Lin SC, et al. RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. *Science (New York, N.Y.)*. 2009; 325: 332–336. <https://doi.org/10.1126/science.1172308>
- [80] He S, Wang L, Miao L, Wang T, Du F, Zhao L, et al. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF- α . *Cell*. 2009; 137: 1100–1111. <https://doi.org/10.1016/j.cell.2009.05.021>
- [81] Tarbell J, Mahmoud M, Corti A, Cardoso L, Caro C. The role of oxygen transport in atherosclerosis and vascular disease. *Journal of the Royal Society, Interface*. 2020; 17: 20190732. <https://doi.org/10.1098/rsif.2019.0732>
- [82] Zheng X, Liang Y, Zhang C. Ferroptosis Regulated by Hypoxia in Cells. *Cells*. 2023; 12: 1050. <https://doi.org/10.3390/cells12071050>
- [83] Chen Y, Fang ZM, Yi X, Wei X, Jiang DS. The interaction between ferroptosis and inflammatory signaling pathways. *Cell Death & Disease*. 2023; 14: 205. <https://doi.org/10.1038/s41419-023-05716-0>
- [84] Chistiakov DA, Orekhov AN, Bobryshev YV. Contribution of neovascularization and intraplaque haemorrhage to atherosclerotic plaque progression and instability. *Acta Physiologica (Oxford, England)*. 2015; 213: 539–553. <https://doi.org/10.1111/apha.12438>
- [85] Kojima Y, Weissman IL, Leeper NJ. The Role of Efferocytosis in Atherosclerosis. *Circulation*. 2017; 135: 476–489. <https://doi.org/10.1161/CIRCULATIONAHA.116.025684>
- [86] Pagliaro P, Penna C. Inhibitors of NLRP3 Inflammasome in Ischemic Heart Disease: Focus on Functional and Redox Aspects. *Antioxidants (Basel, Switzerland)*. 2023; 12: 1396. <https://doi.org/10.3390/antiox12071396>
- [87] Li C, Yang Y, Zhou F, Jiang Q, Jiang Y, Huang X, et al. Efferocytosis in Health and Disease. *MedComm*. 2025; 6: e70546. <https://doi.org/10.1002/mco2.70546>
- [88] Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *Journal of the American Heart Association*. 2017; 6: e005543. <https://doi.org/10.1161/JAHA.117.005543>
- [89] Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *European Heart Journal. Acute Cardiovascular Care*. 2012; 1: 60–74. <https://doi.org/10.1177/2048872612441582>
- [90] Mallat Z, Corbaz A, Scoazec A, Besnard S, Lesèche G, Chvatchko Y, et al. Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability. *Circulation*. 2001; 104: 1598–1603. <https://doi.org/10.1161/hc3901.096721>
- [91] Sakamoto A, Suwa K, Kawakami R, Finn AV, Maekawa Y, Virmani R, et al. Significance of Intra-plaque Hemorrhage for the Development of High-Risk Vulnerable Plaque: Current Understanding from Basic to Clinical Points of View. *International Journal of Molecular Sciences*. 2023; 24: 13298. <https://doi.org/10.3390/ijms241713298>
- [92] Michel JB, Virmani R, Arbustini E, Pasterkamp G. Intraplaque haemorrhages as the trigger of plaque vulnerability. *European Heart Journal*. 2011; 32: 1977–1985c. <https://doi.org/10.1093/eurheartj/ehr054>
- [93] Tall AR, Bornfeldt KE. Inflammasomes and Atherosclerosis: a Mixed Picture. *Circulation Research*. 2023; 132: 1505–1520. <https://doi.org/10.1161/CIRCRESAHA.123.321637>
- [94] Silvis MJM, Demkes EJ, Fiolet ATL, Dekker M, Bosch L, van Hout GPJ, et al. Immunomodulation of the NLRP3 Inflammasome in Atherosclerosis, Coronary Artery Disease, and Acute Myocardial Infarction. *Journal of Cardiovascular Translational Research*. 2021; 14: 23–34. <https://doi.org/10.1007/s12265-020-10049-w>
- [95] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*. 2010; 464: 1357–1361. <https://doi.org/10.1038/nature08938> Erratum in: *Nature*. 2010; 466: 652
- [96] Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science (New York, N.Y.)*. 2017; 355: 842–847.

<https://doi.org/10.1126/science.aag1381>

- [97] Chen S, Markman JL, Shimada K, Crother TR, Lane M, Abol-hesn A, et al. Sex-Specific Effects of the Nlrp3 Inflammasome on Atherogenesis in LDL Receptor-Deficient Mice. *JACC. Basic to Translational Science*. 2020; 5: 582–598. <https://doi.org/10.1016/j.jacbts.2020.03.016>
- [98] Wang H, Mao L, Meng G. The NLRP3 inflammasome activation in human or mouse cells, sensitivity causes puzzle. *Protein & Cell*. 2013; 4: 565–568. <https://doi.org/10.1007/s13238-013-3905-0>
- [99] Wang Y, Fang D, Yang Q, You J, Wang L, Wu J, et al. Interactions between PCSK9 and NLRP3 inflammasome signaling in atherosclerosis. *Frontiers in Immunology*. 2023; 14: 1126823. <https://doi.org/10.3389/fimmu.2023.1126823>
- [100] Spronk HMH, Padro T, Siland JE, Prochaska JH, Winters J, van der Wal AC, et al. Atherothrombosis and Thromboembolism: Position Paper from the Second Maastricht Consensus Conference on Thrombosis. *Thrombosis and Haemostasis*. 2018; 118: 229–250. <https://doi.org/10.1160/TH17-07-0492>
- [101] Burkhardt JM, Vaudel M, Gambaryan S, Radau S, Walter U, Martens L, et al. The first comprehensive and quantitative analysis of human platelet protein composition allows the comparative analysis of structural and functional pathways. *Blood*. 2012; 120: e73–e82. <https://doi.org/10.1182/blood-2012-04-416594>
- [102] Rowley JW, Oler AJ, Tolley ND, Hunter BN, Low EN, Nix DA, et al. Genome-wide RNA-seq analysis of human and mouse platelet transcriptomes. *Blood*. 2011; 118: e101–e111. <https://doi.org/10.1182/blood-2011-03-339705>
- [103] Zeiler M, Moser M, Mann M. Copy number analysis of the murine platelet proteome spanning the complete abundance range. *Molecular & Cellular Proteomics*. 2014; 13: 3435–3445. <https://doi.org/10.1074/mcp.M114.038513>
- [104] Heffron SP, Marier C, Parikh M, Fisher EA, Berger JS. Severe obesity and bariatric surgery alter the platelet mRNA profile. *Platelets*. 2019; 30: 967–974. <https://doi.org/10.1080/09537104.2018.1536261>
- [105] Trugilho MRDO, Hottz ED, Brunoro GVF, Teixeira-Ferreira A, Carvalho PC, Salazar GA, et al. Platelet proteome reveals novel pathways of platelet activation and platelet-mediated immunoregulation in dengue. *PLoS Pathogens*. 2017; 13: e1006385. <https://doi.org/10.1371/journal.ppat.1006385>
- [106] Bourne JH, Campos J, Hopkin SJ, Whitworth K, Palis J, Senis YA, et al. Megakaryocyte NLRP3 hyperactivation induces mild anemia and potentiates inflammatory response in mice. *Frontiers in Immunology*. 2023; 14: 1226196. <https://doi.org/10.3389/fimmu.2023.1226196>
- [107] Wang Y, Jiang H, Hu X, Fu W. Bone marrow NLRP3 inflammasome-IL-1 β signal regulates post-myocardial infarction megakaryocyte development and platelet production. *Biochemical and Biophysical Research Communications*. 2021; 585: 96–102. <https://doi.org/10.1016/j.bbrc.2021.11.031>
- [108] Brown GT, Narayanan P, Li W, Silverstein RL, McIntyre TM. Lipopolysaccharide stimulates platelets through an IL-1 β autocrine loop. *Journal of Immunology (Baltimore, Md.: 1950)*. 2013; 191: 5196–5203. <https://doi.org/10.4049/jimmunol.1300354>
- [109] Beaulieu LM, Lin E, Mick E, Koupenova M, Weinberg EO, Kramer CD, et al. Interleukin 1 receptor 1 and interleukin 1 β regulate megakaryocyte maturation, platelet activation, and transcript profile during inflammation in mice and humans. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014; 34: 552–564. <https://doi.org/10.1161/ATVBAHA.113.302700>
- [110] Nhek S, Clancy R, Lee KA, Allen NM, Barrett TJ, Marcantoni E, et al. Activated Platelets Induce Endothelial Cell Activation via an Interleukin-1 β Pathway in Systemic Lupus Erythematosus. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2017; 37: 707–716. <https://doi.org/10.1161/ATVBAHA.116.308126>
- [111] Meher AK, Spinoza M, Davis JP, Pope N, Laubach VE, Su G, et al. Novel Role of IL (Interleukin)-1 β in Neutrophil Extracellular Trap Formation and Abdominal Aortic Aneurysms. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018; 38: 843–853. <https://doi.org/10.1161/ATVBAHA.117.309897>
- [112] Peng H, Wu H, Zhang G, Zhang W, Guo Y, Chang L, et al. Expression and Clinical Prognostic Value of Platelet NLRP3 in Acute Coronary Syndrome. *International Journal of General Medicine*. 2020; 13: 791–802. <https://doi.org/10.2147/IJGM.S275481>
- [113] Zhang J, Zhu H, Dai Y, Jiang H, Li Y, Chen S, et al. A predominant role of platelet NLRP3 in deep vein thrombosis in mice. *Journal of Thrombosis and Haemostasis*. 2025; 23: 2890–2902. <https://doi.org/10.1016/j.jtha.2025.05.031>
- [114] Döring Y, Soehnlein O, Weber C. Neutrophil Extracellular Traps in Atherosclerosis and Atherothrombosis. *Circulation Research*. 2017; 120: 736–743. <https://doi.org/10.1161/CIRCRESAHA.116.309692>
- [115] Knight JS, Luo W, O'Dell AA, Yalavarthi S, Zhao W, Subramanian V, et al. Peptidylarginine deiminase inhibition reduces vascular damage and modulates innate immune responses in murine models of atherosclerosis. *Circulation Research*. 2014; 114: 947–956. <https://doi.org/10.1161/CIRCRESAHA.114.303312>
- [116] Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. *Science (New York, N.Y.)*. 2015; 349: 316–320. <https://doi.org/10.1126/science.aag8064>
- [117] Singh P, Kumar N, Singh M, Kaur M, Singh G, Narang A, et al. Neutrophil Extracellular Traps and NLRP3 Inflammasome: A Disturbing Duo in Atherosclerosis, Inflammation and Atherothrombosis. *Vaccines*. 2023; 11: 261. <https://doi.org/10.3390/vaccines11020261>
- [118] Paulin N, Viola JR, Maas SL, de Jong R, Fernandes-Alnemri T, Weber C, et al. Double-Strand DNA Sensing Aim2 Inflammasome Regulates Atherosclerotic Plaque Vulnerability. *Circulation*. 2018; 138: 321–323. <https://doi.org/10.1161/CIRCULATIONAHA.117.033098>
- [119] Moschonas IC, Tselepis AD. The pathway of neutrophil extracellular traps towards atherosclerosis and thrombosis. *Atherosclerosis*. 2019; 288: 9–16. <https://doi.org/10.1016/j.atherosclerosis.2019.06.919>
- [120] Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD, Jr, et al. Extracellular DNA traps promote thrombosis. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107: 15880–15885. <https://doi.org/10.1073/pnas.1005743107>
- [121] Münzer P, Negro R, Fukui S, di Meglio L, Aymonnier K, Chu L, et al. NLRP3 Inflammasome Assembly in Neutrophils Is Supported by PAD4 and Promotes NETosis Under Sterile Conditions. *Frontiers in Immunology*. 2021; 12: 683803. <https://doi.org/10.3389/fimmu.2021.683803>
- [122] Heger LA, Schommer N, Van Bruggen S, Sheehy CE, Chan W, Wagner DD. Neutrophil NLRP3 promotes cardiac injury following acute myocardial infarction through IL-1 β production, VWF release and NET deposition in the myocardium. *Scientific Reports*. 2024; 14: 14524. <https://doi.org/10.1038/s41598-024-64710-4>
- [123] Sachetto ATA, Mackman N. Monocyte Tissue Factor Expression: Lipopolysaccharide Induction and Roles in Pathological Activation of Coagulation. *Thrombosis and Haemostasis*. 2023; 123: 1017–1033. <https://doi.org/10.1055/a-2091-7006>
- [124] Ni M, Wang Y, Zhang M, Zhang PF, Ding SF, Liu CX, et al. Atherosclerotic plaque disruption induced by stress and

- lipopolysaccharide in apolipoprotein E knockout mice. *American Journal of Physiology. Heart and Circulatory Physiology*. 2009; 296: H1598–H1606. <https://doi.org/10.1152/ajpheart.01202.2008>
- [125] Stark K, Kilani B, Stockhausen S, Busse J, Schubert I, Tran TD, et al. Antibodies and complement are key drivers of thrombosis. *Immunity*. 2024; 57: 2140–2156.e10. <https://doi.org/10.1016/j.immuni.2024.08.007>
- [126] Laudisi F, Spreafico R, Evrard M, Hughes TR, Mandriani B, Kandasamy M, et al. Cutting edge: the NLRP3 inflammasome links complement-mediated inflammation and IL-1 β release. *Journal of Immunology* (Baltimore, Md.: 1950). 2013; 191: 1006–1010. <https://doi.org/10.4049/jimmunol.1300489>
- [127] Potere N, Abbate A, Kanthi Y, Carrier M, Toldo S, Porreca E, et al. Inflammasome Signaling, Thromboinflammation, and Venous Thromboembolism. *JACC. Basic to Translational Science*. 2023; 8: 1245–1261. <https://doi.org/10.1016/j.jacbs.2023.03.017>
- [128] Bevilacqua MP, Pober JS, Majeau GR, Cotran RS, Gimbrone MA, Jr. Interleukin 1 (IL-1) induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. *The Journal of Experimental Medicine*. 1984; 160: 618–623. <https://doi.org/10.1084/jem.160.2.618>
- [129] Nawroth PP, Handley DA, Esmon CT, Stern DM. Interleukin 1 induces endothelial cell procoagulant while suppressing cell-surface anticoagulant activity. *Proceedings of the National Academy of Sciences of the United States of America*. 1986; 83: 3460–3464. <https://doi.org/10.1073/pnas.83.10.3460>
- [130] Folco EJ, Mawson TL, Vromman A, Bernardes-Souza B, Franck G, Persson O, et al. Neutrophil Extracellular Traps Induce Endothelial Cell Activation and Tissue Factor Production Through Interleukin-1 α and Cathepsin G. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018; 38: 1901–1912. <https://doi.org/10.1161/ATVBAHA.118.311150>
- [131] Li G, Zhou R, Zhao X, Liu R, Ye C. Correlation between the expression of IL-18 and deep venous thrombosis. *International Journal of Molecular Medicine*. 2018; 42: 883. <https://doi.org/10.3892/ijmm.2018.3682> Erratum in: *International Journal of Molecular Medicine*. 2018; 42: 2972. <https://doi.org/10.3892/ijmm.2018.3843>
- [132] Jackson SP. Arterial thrombosis—insidious, unpredictable and deadly. *Nature Medicine*. 2011; 17: 1423–1436. <https://doi.org/10.1038/nm.2515>
- [133] Nordeng J, Schandiz H, Solheim S, Åkra S, Hoffman P, Roald B, et al. The Inflammasome Signaling Pathway Is Actively Regulated and Related to Myocardial Damage in Coronary Thrombi from Patients with STEMI. *Mediators of Inflammation*. 2021; 2021: 5525917. <https://doi.org/10.1155/2021/5525917>
- [134] Bratseth V, Nordeng J, Helseth R, Solheim S, Åkra S, Arnesen H, et al. Circulating Microvesicles in Association with the NLRP3 Inflammasome in Coronary Thrombi from STEMI Patients. *Biomedicines*. 2022; 10: 2196. <https://doi.org/10.3390/biomedicines10092196>
- [135] Chen SH, Scott XO, Ferrer Marcelo Y, Almeida VW, Blackwelder PL, Yavagal DR, et al. Netosis and Inflammasomes in Large Vessel Occlusion Thrombi. *Frontiers in Pharmacology*. 2021; 11: 607287. <https://doi.org/10.3389/fphar.2020.607287>
- [136] Brinjikji W, Duffy S, Burrows A, Hacke W, Liebeskind D, Majoie CBLM, et al. Correlation of imaging and histopathology of thrombi in acute ischemic stroke with etiology and outcome: a systematic review. *Journal of Neurointerventional Surgery*. 2017; 9: 529–534. <https://doi.org/10.1136/neurintsurg-2016-012391>
- [137] Finger C, Emara G, Chiu GS, Li K, Sheth S, Tan C, et al. Thrombi from stroke due to cardioembolic etiology have higher CD11b-positive cells compared to large artery atherosclerosis. *Journal of Thrombosis and Thrombolysis*. 2026; 59: 514–521. <https://doi.org/10.1007/s11239-025-03196-x>
- [138] Karakasis P, Pamporis K, Theofilis P, Milas N, Vlachakis PK, Grigoriou K, et al. Inflammasome Signaling in Cardiac Arrhythmias: Linking Inflammation, Fibrosis, and Electrical Remodeling. *International Journal of Molecular Sciences*. 2025; 26: 5954. <https://doi.org/10.3390/ijms26135954>
- [139] Yu JR, Leslie KS. Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response. *Current Allergy and Asthma Reports*. 2011; 11: 12–20. <https://doi.org/10.1007/s11882-010-0160-9>
- [140] Pontillo A, Vendramin A, Catamo E, Fabris A, Crovella S. The missense variation Q705K in CIAS1/NALP3/NLRP3 gene and an NLRP1 haplotype are associated with celiac disease. *The American Journal of Gastroenterology*. 2011; 106: 539–544. <https://doi.org/10.1038/ajg.2010.474>
- [141] Schoultz I, Verma D, Halfvarsson J, Törkvist L, Fredrikson M, Sjöqvist U, et al. Combined polymorphisms in genes encoding the inflammasome components NALP3 and CARD8 confer susceptibility to Crohn's disease in Swedish men. *The American Journal of Gastroenterology*. 2009; 104: 1180–1188. <https://doi.org/10.1038/ajg.2009.29>
- [142] Kastbom A, Verma D, Eriksson P, Skogh T, Wingren G, Söderkvist P. Genetic variation in proteins of the cryopyrin inflammasome influences susceptibility and severity of rheumatoid arthritis (the Swedish TIRA project). *Rheumatology* (Oxford, England). 2008; 47: 415–417. <https://doi.org/10.1093/rheumatology/kem372>
- [143] Roberts RL, Van Rij AM, Phillips LV, Young S, McCormick SPA, Merriman TR, et al. Interaction of the inflammasome genes CARD8 and NLRP3 in abdominal aortic aneurysms. *Atherosclerosis*. 2011; 218: 123–126. <https://doi.org/10.1016/j.atherosclerosis.2011.04.043>
- [144] Schunk SJ, Kleber ME, März W, Pang S, Zewinger S, Triem S, et al. Genetically determined NLRP3 inflammasome activation associates with systemic inflammation and cardiovascular mortality. *European Heart Journal*. 2021; 42: 1742–1756. <https://doi.org/10.1093/eurheartj/ehab107>
- [145] Verma D, Särndahl E, Andersson H, Eriksson P, Fredrikson M, Jönsson JJ, et al. The Q705K polymorphism in NLRP3 is a gain-of-function alteration leading to excessive interleukin-1 β and IL-18 production. *PloS One*. 2012; 7: e34977. <https://doi.org/10.1371/journal.pone.0034977>
- [146] Klen J, Goričar K, Janež A, Dolžan V. NLRP3 Inflammasome Polymorphism and Macrovascular Complications in Type 2 Diabetes Patients. *Journal of Diabetes Research*. 2015; 2015: 616747. <https://doi.org/10.1155/2015/616747>
- [147] Cheng L, Yin R, Yang S, Pan X, Ma A. Rs4612666 Polymorphism of the NLRP3 Gene Is Associated with the Occurrence of Large Artery Atherosclerotic Ischemic Strokes and Microembolic Signals. *BioMed Research International*. 2018; 2018: 6345805. <https://doi.org/10.1155/2018/6345805>
- [148] Daily ZA, Al-Ghurabi BH. Absent in Melanoma 2 Gene Associated Periodontitis and Coronary Heart Disease. *F1000Research*. 2025; 13: 810. <https://doi.org/10.12688/f1000research.151954.2>
- [149] von Scheidt M, Adkar SS, Krefting J, Hoermann G, Meggen-dorfer M, Bauer S, et al. Clonal haematopoiesis of indeterminate potential and mortality in coronary artery disease. *European Heart Journal*. 2026; 47: 453–469. <https://doi.org/10.1093/eurheartj/ehaf602>
- [150] Oren O, Small AM, Lin AE, Libby P. Managing Cardiovascular Risk in Clonal Hematopoiesis of Indeterminate Potential: JACC: CardioOncology Short-Form Primer. *JACC. CardioOncology*. 2025; 7: 496–500. <https://doi.org/10.1016/j.jacc.ao.2025.05.013>

- [151] Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *The New England Journal of Medicine*. 2017; 377: 111–121. <https://doi.org/10.1056/NEJMoa1701719>
- [152] Fidler TP, Xue C, Yalcinkaya M, Hardaway B, Abramowicz S, Xiao T, et al. The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis. *Nature*. 2021; 592: 296–301. <https://doi.org/10.1038/s41586-021-03341-5>
- [153] Zon RL, Sekar A, Clapham K, Oren O, Niroula A, Bick AG, et al. JAK2-mutant clonal hematopoiesis is associated with venous thromboembolism. *Blood*. 2024; 144: 2149–2154. <https://doi.org/10.1182/blood.2024024187>
- [154] Chen R, Zhang H, Tang B, Luo Y, Yang Y, Zhong X, et al. Macrophages in cardiovascular diseases: molecular mechanisms and therapeutic targets. *Signal Transduction and Targeted Therapy*. 2024; 9: 130. <https://doi.org/10.1038/s41392-024-01840-1>
- [155] Longo SK, Guo MG, Ji AL, Khavari PA. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. *Nature Reviews. Genetics*. 2021; 22: 627–644. <https://doi.org/10.1038/s41576-021-00370-8>
- [156] Bashore AC, Yan H, Xue C, Zhu LY, Kim E, Mawson T, et al. High-Dimensional Single-Cell Multimodal Landscape of Human Carotid Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2024; 44: 930–945. <https://doi.org/10.1161/ATVBAHA.123.320524>
- [157] Zernecke A, Winkels H, Cochain C, Williams JW, Wolf D, Soehnlein O, et al. Meta-Analysis of Leukocyte Diversity in Atherosclerotic Mouse Aortas. *Circulation Research*. 2020; 127: 402–426. <https://doi.org/10.1161/CIRCRESAHA.120.316903>
- [158] Patterson MT, Xu Y, Hillman H, Osinski V, Schrank PR, Kennedy AE, et al. Trem2 Agonist Reprograms Foamy Macrophages to Promote Atherosclerotic Plaque Stability-Brief Report. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2024; 44: 1646–1657. <https://doi.org/10.1161/ATVBAHA.124.320797>
- [159] Huang P, Zhang Z, Zhang P, Feng J, Xie J, Zheng Y, et al. TREM2 Deficiency Aggravates NLRP3 Inflammasome Activation and Pyroptosis in MPTP-Induced Parkinson's Disease Mice and LPS-Induced BV2 Cells. *Molecular Neurobiology*. 2024; 61: 2590–2605. <https://doi.org/10.1007/s12035-023-03713-0>
- [160] Pauli J, Garger D, Peymani F, Wettich J, Sachs N, Wirth J, et al. Single cell spatial transcriptomics integration deciphers the morphological heterogeneity of atherosclerotic carotid arteries. *Nature Communications*. 2025; 16: 11282. <https://doi.org/10.1038/s41467-025-67679-4>
- [161] Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF- κ B in biology and targeted therapy: new insights and translational implications. *Signal Transduction and Targeted Therapy*. 2024; 9: 53. <https://doi.org/10.1038/s41392-024-01757-9>
- [162] Libby P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond. *Journal of the American College of Cardiology*. 2017; 70: 2278–2289. <https://doi.org/10.1016/j.jacc.2017.09.028>
- [163] Kleinbongard P, Heusch G, Schulz R. TNF α in atherosclerosis, myocardial ischemia/reperfusion and heart failure. *Pharmacology & Therapeutics*. 2010; 127: 295–314. <https://doi.org/10.1016/j.pharmthera.2010.05.002>
- [164] Ono H, Ichiki T, Ohtsubo H, Fukuyama K, Imayama I, Iino N, et al. CAMP-response element-binding protein mediates tumor necrosis factor- α -induced vascular cell adhesion molecule-1 expression in endothelial cells. *Hypertension Research*. 2006; 29: 39–47. <https://doi.org/10.1291/hypres.29.39>
- [165] Ayash R, Kabalan Y, Chamaa S. Exploring the predictive potentials of IL-1 β and TNFR1 in prediabetes. *Scientific Reports*. 2025; 15: 37369. <https://doi.org/10.1038/s41598-025-12852-4>
- [166] Kim S, Jang Y. Inflammation in Atherosclerotic Cardiovascular Diseases: Biomarkers to Therapeutics in Clinical Settings. *Journal of Cardiovascular Intervention*. 2024; 3: 199–215. <https://doi.org/10.54912/jci.2024.0014>
- [167] Dimosiari A, Patoulas D, Kitas GD, Dimitroulas T. Do Interleukin-1 and Interleukin-6 Antagonists Hold Any Place in the Treatment of Atherosclerotic Cardiovascular Disease and Related Co-Morbidities? An Overview of Available Clinical Evidence. *Journal of Clinical Medicine*. 2023; 12: 1302. <https://doi.org/10.3390/jcm12041302>
- [168] Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. *Circulation Research*. 2016; 118: 145–156. <https://doi.org/10.1161/CIRCRESAHA.115.306656>
- [169] Altyar AE, Bhardwaj S, Ghaboura N, Kaushik P, Alenezi SK, Mantargi MJS, et al. Role of IL-2, IL-6, and TNF- α as Potential Biomarkers in Ischemic Heart Disease: A Comparative Study of Patients with CAD and Non-CAD. *Medical Sciences (Basel, Switzerland)*. 2025; 13: 40. <https://doi.org/10.3390/medsci13020040>
- [170] Bian F, Yang XY, Xu G, Zheng T, Jin S. CRP-Induced NLRP3 Inflammasome Activation Increases LDL Transcytosis Across Endothelial Cells. *Frontiers in Pharmacology*. 2019; 10: 40. <https://doi.org/10.3389/fphar.2019.00040>
- [171] Yao Y, Mao J, Xu S, Zhao L, Long L, Chen L, et al. Rosmarinic acid inhibits nicotine-induced C-reactive protein generation by inhibiting NLRP3 inflammasome activation in smooth muscle cells. *Journal of Cellular Physiology*. 2019; 234: 1758–1767. <https://doi.org/10.1002/jcp.27046>
- [172] Hein TW, Singh U, Vasquez-Vivar J, Devaraj S, Kuo L, Jialal I. Human C-reactive protein induces endothelial dysfunction and uncoupling of eNOS in vivo. *Atherosclerosis*. 2009; 206: 61–68. <https://doi.org/10.1016/j.atherosclerosis.2009.02.002>
- [173] Zaczekiewicz M, Zimmermann O, Torzewski J. A short review on CRP synthesis inhibition in cardiovascular disease. *Frontiers in Drug Discovery*. 2024; 4: 1338535. <https://doi.org/10.3389/fddsv.2024.1338535>
- [174] Torzewski J. C-reactive protein and atherogenesis: new insights from established animal models. *The American Journal of Pathology*. 2005; 167: 923–925. [https://doi.org/10.1016/S0002-9440\(10\)61182-0](https://doi.org/10.1016/S0002-9440(10)61182-0)
- [175] Zhang Y, Huang Y, Hu S, Liu G, Zeng T, Pan A, et al. Associations between plasma caspase-1 levels and cardiovascular disease, with the mediating role of metabolic syndrome. *Atherosclerosis*. 2025; 401: 119090. <https://doi.org/10.1016/j.atherosclerosis.2024.119090>
- [176] Gage J, Hasu M, Thabet M, Whitman SC. Caspase-1 deficiency decreases atherosclerosis in apolipoprotein E-null mice. *The Canadian Journal of Cardiology*. 2012; 28: 222–229. <https://doi.org/10.1016/j.cjca.2011.10.013>
- [177] Borissoff JJ, Joosen IA, Versteilen MO, Brill A, Fuchs TA, Savchenko AS, et al. Elevated levels of circulating DNA and chromatin are independently associated with severe coronary atherosclerosis and a prothrombotic state. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2013; 33: 2032–2040. <https://doi.org/10.1161/ATVBAHA.113.301627>
- [178] Vita JA, Brennan ML, Gokce N, Mann SA, Goormastic M, Shishehbor MH, et al. Serum myeloperoxidase levels independently predict endothelial dysfunction in humans. *Circulation*. 2004; 110: 1134–1139. <https://doi.org/10.1161/01.CIR.0000140262.20831.8F>
- [179] Haritha VH, George A, Shaji BV, Anie Y. NET-associated citrullinated histones promote LDL aggregation and foam cell formation in vitro. *Experimental Cell Research*. 2020; 396: 112320. <https://doi.org/10.1016/j.yexcr.2020.112320>

- [180] Vergallo R, Park SJ, Stone GW, Erlinge D, Porto I, Waksman R, et al. Vulnerable or High-Risk Plaque: A JACC: Cardiovascular Imaging Position Statement. *JACC: Cardiovascular Imaging*. 2025; 18: 709–740. <https://doi.org/10.1016/j.jcmg.2024.12.004>
- [181] Spagnolo M, Giaccopo D, Laudani C, Greco A, Finocchiaro S, Mauro MS, et al. Advances in the Detection and Management of Vulnerable Coronary Plaques. *Circulation: Cardiovascular Interventions*. 2025; 18: e015529. <https://doi.org/10.1161/CIRCINTEVENTIONS.125.015529>
- [182] Adamson PD, Newby DE. Non-invasive imaging of the coronary arteries. *European Heart Journal*. 2019; 40: 2444–2454. <https://doi.org/10.1093/eurheartj/ehy670>
- [183] Gaba P, Gersh BJ, Muller J, Narula J, Stone GW. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. *Nature Reviews: Cardiology*. 2023; 20: 181–196. <https://doi.org/10.1038/s41569-022-00769-8>
- [184] Dweck MR, Puntman V, Vesey AT, Fayad ZA, Nagel E. MR Imaging of Coronary Arteries and Plaques. *JACC: Cardiovascular Imaging*. 2016; 9: 306–316. <https://doi.org/10.1016/j.jcmg.2015.12.003>
- [185] Nensa F, Bamberg F, Rischpler C, Menezes L, Poeppel TD, la Fougère C, et al. Hybrid cardiac imaging using PET/MRI: a joint position statement by the European Society of Cardiovascular Radiology (ESCR) and the European Association of Nuclear Medicine (EANM). *European Radiology*. 2018; 28: 4086–4101. <https://doi.org/10.1007/s00330-017-5008-4>
- [186] Whitehead DM, Fischer C, Briard E, Farady CJ, Graveleau N, Karrer J, et al. [18F]NP3-627, a Candidate PET Imaging Agent Targeting the NLRP3 Inflammasome in the Central Nervous System. *ChemMedChem*. 2025; 20: e202400816. <https://doi.org/10.1002/cmdc.202400816>
- [187] Garcia-Garcia HM, Costa MA, Serruys PW. Imaging of coronary atherosclerosis: intravascular ultrasound. *European Heart Journal*. 2010; 31: 2456–2469. <https://doi.org/10.1093/eurheartj/ehq280>
- [188] Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation*. 2002; 106: 1640–1645. <https://doi.org/10.1161/01.cir.0000029927.92825.f6>
- [189] Araki M, Park SJ, Dauerman HL, Uemura S, Kim JS, Di Mario C, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. *Nature Reviews: Cardiology*. 2022; 19: 684–703. <https://doi.org/10.1038/s41569-022-00687-9> Erratum in: *Nature Reviews Cardiology*. 2024; 21: 348. <https://doi.org/10.1038/s41569-023-00982-z>
- [190] Moreno PR, Kini A. Resolution of inflammation, statins, and plaque regression. *JACC: Cardiovascular Imaging*. 2012; 5: 178–181. <https://doi.org/10.1016/j.jcmg.2012.01.002>
- [191] Liu X, He W, Hong X, Li D, Chen Z, Wang Y, et al. New insights into fibrous cap thickness of vulnerable plaques assessed by optical coherence tomography. *BMC Cardiovascular Disorders*. 2022; 22: 484. <https://doi.org/10.1186/s12872-022-02896-z>
- [192] Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. *Annual Review of Medicine*. 2014; 65: 223–244. <https://doi.org/10.1146/annurev-med-061512-150641>
- [193] Arnold DD, Yalamanoglu A, Boyman O. Systematic Review of Safety and Efficacy of IL-1-Targeted Biologics in Treating Immune-Mediated Disorders. *Frontiers in Immunology*. 2022; 13: 888392. <https://doi.org/10.3389/fimmu.2022.888392>
- [194] Van Tassell BW, Arena R, Biondi-Zoccai G, Canada JM, Oddi C, Abouzaki NA, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). *The American Journal of Cardiology*. 2014; 113: 321–327. <https://doi.org/10.1016/j.amjcard.2013.08.047>
- [195] Van Tassell BW, Trankle CR, Canada JM, Carbone S, Buckley L, Kadariya D, et al. IL-1 Blockade in Patients With Heart Failure With Preserved Ejection Fraction. *Circulation: Heart Failure*. 2018; 11: e005036. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.005036>
- [196] Van Tassell BW, Abouzaki NA, Oddi Erdle C, Carbone S, Trankle CR, Melchior RD, et al. Interleukin-1 Blockade in Acute Decompensated Heart Failure: A Randomized, Double-Blinded, Placebo-Controlled Pilot Study. *Journal of Cardiovascular Pharmacology*. 2016; 67: 544–551. <https://doi.org/10.1097/FJC.0000000000000378>
- [197] Morton AC, Rothman AMK, Greenwood JP, Gunn J, Chase A, Clarke B, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *European Heart Journal*. 2015; 36: 377–384. <https://doi.org/10.1093/eurheartj/ehu272>
- [198] Abbate A, Trankle CR, Buckley LF, Lipinski MJ, Appleton D, Kadariya D, et al. Interleukin-1 Blockade Inhibits the Acute Inflammatory Response in Patients With ST-Segment-Elevation Myocardial Infarction. *Journal of the American Heart Association*. 2020; 9: e014941. <https://doi.org/10.1161/JAHA.119.014941>
- [199] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *The New England Journal of Medicine*. 2017; 377: 1119–1131. <https://doi.org/10.1056/NEJMoa1707914>
- [200] Chakraborty A, Tannenbaum S, Rordorf C, Lowe PJ, Floch D, Gram H, et al. Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1 β monoclonal antibody. *Clinical Pharmacokinetics*. 2012; 51: e1–e18. <https://doi.org/10.2165/11599820-000000000-00000>
- [201] Trankle CR, Canada JM, Cei L, Abouzaki N, Oddi-Erdle C, Kadariya D, et al. Usefulness of Canakinumab to Improve Exercise Capacity in Patients With Long-Term Systolic Heart Failure and Elevated C-Reactive Protein. *The American Journal of Cardiology*. 2018; 122: 1366–1370. <https://doi.org/10.1016/j.amjcard.2018.07.002>
- [202] Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, et al. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2017; 390: 1833–1842. [https://doi.org/10.1016/S0140-6736\(17\)32247-X](https://doi.org/10.1016/S0140-6736(17)32247-X)
- [203] Rossi-Semerano L, Fautrel B, Wendling D, Hachulla E, Galeotti C, Semerano L, et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. *Orphanet Journal of Rare Diseases*. 2015; 10: 19. <https://doi.org/10.1186/s13023-015-0228-7>
- [204] Napoli C, Hayashi T, Cacciatore F, Casamassimi A, Casini C, Al-Omran M, et al. Endothelial progenitor cells as therapeutic agents in the microcirculation: an update. *Atherosclerosis*. 2011; 215: 9–22. <https://doi.org/10.1016/j.atherosclerosis.2010.10.039>
- [205] Klein AL, Imazio M, Brucato A, Cremer P, LeWinter M, Abbate A, et al. RHAPSODY: Rationale for and design of a pivotal Phase 3 trial to assess efficacy and safety of rilonacept, an interleukin-1 α and interleukin-1 β trap, in patients with recurrent pericarditis. *American Heart Journal*. 2020; 228: 81–90. <https://doi.org/10.1016/j.ahj.2020.07.004>
- [206] Mo B, Ding Y, Ji Q. NLRP3 inflammasome in cardiovascular diseases: an update. *Frontiers in Immunology*. 2025; 16: 1550226. <https://doi.org/10.3389/fimmu.2025.1550226>

- [207] Singh A, Sunder V, Cho L. Low-dose colchicine for management of coronary artery disease. *Cleveland Clinic Journal of Medicine*. 2025; 92: 609–618. <https://doi.org/10.3949/ccjm.92a.25005>
- [208] Samuel M, Berry C, Dubé MP, Koenig W, López-Sendón J, Maggioni AP, et al. Long-term trials of colchicine for secondary prevention of vascular events: a meta-analysis. *European Heart Journal*. 2025; 46: 2552–2563. <https://doi.org/10.1093/eurheartj/ehaf174>
- [209] Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *Journal of the American College of Cardiology*. 2013; 61: 404–410. <https://doi.org/10.1016/j.jacc.2012.10.027>
- [210] Jolly SS, d'Entremont MA, Lee SF, Mian R, Tyrwhitt J, Kedev S, et al. Colchicine in Acute Myocardial Infarction. *The New England Journal of Medicine*. 2025; 392: 633–642. <https://doi.org/10.1056/NEJMoa2405922>
- [211] Kelly P, Lemmens R, Weimar C, Walsh C, Purroy F, Barber M, et al. Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial. *Lancet (London, England)*. 2024; 404: 125–133. [https://doi.org/10.1016/S0140-6736\(24\)00968-1](https://doi.org/10.1016/S0140-6736(24)00968-1)
- [212] Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in Patients with Chronic Coronary Disease. *The New England Journal of Medicine*. 2020; 383: 1838–1847. <https://doi.org/10.1056/NEJMoa2021372>
- [213] Tong DC, Quinn S, Nasir A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. *Circulation*. 2020; 142: 1890–1900. <https://doi.org/10.1161/CIRCULATIONAHA.120.050771>
- [214] d'Entremont MA, Poorthuis MHF, Fiolet ATL, Amarenco P, Boczar KE, Buyschaert I, et al. Colchicine for secondary prevention of vascular events: a meta-analysis of trials. *European Heart Journal*. 2025; 46: 2564–2575. <https://doi.org/10.1093/eurheartj/ehaf210>
- [215] Ait-Oufella H, Libby P. Inflammation and Atherosclerosis: Prospects for Clinical Trials. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2024; 44: 1899–1905. <https://doi.org/10.1161/ATVBAHA.124.320155>
- [216] Khan MS, Talha KM, Maqsood MH, Rymer JA, Borlaug BA, Docherty KF, et al. Interleukin-6 and Cardiovascular Events in Healthy Adults: MESA. *JACC. Advances*. 2024; 3: 101063. <https://doi.org/10.1016/j.jacadv.2024.101063>
- [217] Wada Y, Jensen C, Meyer ASP, Zonoozi AAM, Honda H. Efficacy and safety of interleukin-6 inhibition with ziltivekimab in patients at high risk of atherosclerotic events in Japan (RESCUE-2): A randomized, double-blind, placebo-controlled, phase 2 trial. *Journal of Cardiology*. 2023; 82: 279–285. <https://doi.org/10.1016/j.jjcc.2023.05.006>
- [218] Chertow GM, Chang AM, Felker GM, Heise M, Velkoska E, Fellström B, et al. IL-6 inhibition with clazakizumab in patients receiving maintenance dialysis: a randomized phase 2b trial. *Nature Medicine*. 2024; 30: 2328–2336. <https://doi.org/10.1038/s41591-024-03043-1>
- [219] Wu D, Chen Y, Sun Y, Gao Q, Li H, Yang Z, et al. Target of MCC950 in Inhibition of NLRP3 Inflammasome Activation: a Literature Review. *Inflammation*. 2020; 43: 17–23. <https://doi.org/10.1007/s10753-019-01098-8>
- [220] Coll RC, Robertson AAB, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserra MC, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nature Medicine*. 2015; 21: 248–255. <https://doi.org/10.1038/nm.3806>
- [221] Sharma A, Choi JSY, Stefanovic N, Al-Sharea A, Simpson DS, Mukhamedova N, et al. Specific NLRP3 Inhibition Protects Against Diabetes-Associated Atherosclerosis. *Diabetes*. 2021; 70: 772–787. <https://doi.org/10.2337/db20-0357>
- [222] van der Heijden T, Kritikou E, Venema W, van Duijn J, van Santbrink PJ, Slütter B, et al. NLRP3 Inflammasome Inhibition by MCC950 Reduces Atherosclerotic Lesion Development in Apolipoprotein E-Deficient Mice-Brief Report. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2017; 37: 1457–1461. <https://doi.org/10.1161/ATVBAHA.117.309575>
- [223] Zeng W, Wu D, Sun Y, Suo Y, Yu Q, Zeng M, et al. The selective NLRP3 inhibitor MCC950 hinders atherosclerosis development by attenuating inflammation and pyroptosis in macrophages. *Scientific Reports*. 2021; 11: 19305. <https://doi.org/10.1038/s41598-021-98437-3>
- [224] Wang L, Zhao X, Ding J, Liu Y, Liu H, Zheng L, 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>
- [225] Lin HB, Wei GS, Li FX, Guo WJ, Hong P, Weng YQ, et al. Macrophage-NLRP3 Inflammasome Activation Exacerbates Cardiac Dysfunction after Ischemic Stroke in a Mouse Model of Diabetes. *Neuroscience Bulletin*. 2020; 36: 1035–1045. <https://doi.org/10.1007/s12264-020-00544-0>
- [226] Kim YS, Kim JS, Kwon JS, Jeong MH, Cho JG, Park JC, et al. BAY 11-7082, a nuclear factor- κ B inhibitor, reduces inflammation and apoptosis in a rat cardiac ischemia-reperfusion injury model. *International Heart Journal*. 2010; 51: 348–353. <https://doi.org/10.1536/ihj.51.348>
- [227] Qiu Z, Lei S, Zhao B, Wu Y, Su W, Liu M, et al. NLRP3 Inflammasome Activation-Mediated Pyroptosis Aggravates Myocardial Ischemia/Reperfusion Injury in Diabetic Rats. *Oxidative Medicine and Cellular Longevity*. 2017; 2017: 9743280. <https://doi.org/10.1155/2017/9743280>
- [228] Juliana C, Fernandes-Alnemri T, Wu J, Datta P, Solorzano L, Yu JW, et al. Anti-inflammatory compounds parthenolide and Bay 11-7082 are direct inhibitors of the inflammasome. *The Journal of Biological Chemistry*. 2010; 285: 9792–9802. <https://doi.org/10.1074/jbc.M109.082305>
- [229] Zhang X, Wang Z, Zheng Y, Yu Q, Zeng M, Bai L, et al. Inhibitors of the NLRP3 inflammasome pathway as promising therapeutic candidates for inflammatory diseases (Review). *International Journal of Molecular Medicine*. 2023; 51: 35. <https://doi.org/10.3892/ijmm.2023.5238>
- [230] Toldo S, Mauro AG, Cutter Z, Van Tassell BW, Mezzaroma E, Del Buono MG, et al. The NLRP3 Inflammasome Inhibitor, OLT1177 (Dapansutril), Reduces Infarct Size and Preserves Contractile Function After Ischemia Reperfusion Injury in the Mouse. *Journal of Cardiovascular Pharmacology*. 2019; 73: 215–222. <https://doi.org/10.1097/FJC.0000000000000658>
- [231] Wohlford GF, Van Tassell BW, Billingsley HE, Kadariya D, Canada JM, Carbone S, et al. Phase 1B, Randomized, Double-Blinded, Dose Escalation, Single-Center, Repeat Dose Safety and Pharmacodynamics Study of the Oral NLRP3 Inhibitor Dapansutril in Subjects With NYHA II-III Systolic Heart Failure. *Journal of Cardiovascular Pharmacology*. 2020; 77: 49–60. <https://doi.org/10.1097/FJC.0000000000000931>
- [232] Wannamaker W, Davies R, Namchuk M, Pollard J, Ford P, Ku G, et al. (S)-1-((S)-2-{[1-(4-amino-3-chloro-phenyl)-methanoyl]-amino}-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-amide (VX-765), an orally available selective interleukin (IL)-converting enzyme/caspase-1 inhibitor, exhibits potent anti-inflammatory activities by inhibiting the release of IL-1 β and IL-18. *The Journal of Pharmacology and Experimental Therapeutics*. 2007; 321: 509–516. <https://doi.org/10.1124/jpet.106.111344>

- [233] Boxer MB, Quinn AM, Shen M, Jadhav A, Leister W, Simeonov A, et al. A highly potent and selective caspase 1 inhibitor that utilizes a key 3-cyanopropanoic acid moiety. *ChemMedChem*. 2010; 5: 730–738. <https://doi.org/10.1002/cm.200900531>
- [234] Li Y, Niu X, Xu H, Li Q, Meng L, He M, et al. VX-765 attenuates atherosclerosis in ApoE deficient mice by modulating VSMCs pyroptosis. *Experimental Cell Research*. 2020; 389: 111847. <https://doi.org/10.1016/j.yexcr.2020.111847>
- [235] Do Carmo H, Arjun S, Petrucci O, Yellon DM, Davidson SM. The Caspase 1 Inhibitor VX-765 Protects the Isolated Rat Heart via the RISK Pathway. *Cardiovascular Drugs and Therapy*. 2018; 32: 165–168. <https://doi.org/10.1007/s10557-018-6781-2>
- [236] MacKenzie SH, Schipper JL, Clark AC. The potential for caspases in drug discovery. *Current Opinion in Drug Discovery & Development*. 2010; 13: 568–576.
- [237] Zhu C, Xu S, Jiang R, Yu Y, Bian J, Zou Z. The gasdermin family: emerging therapeutic targets in diseases. *Signal Transduction and Targeted Therapy*. 2024; 9: 87. <https://doi.org/10.1038/s41392-024-01801-8>
- [238] Traugher CA, Timinski K, Prince A, Bhandari N, Neupane K, Khan MR, et al. Disulfiram Reduces Atherosclerosis and Enhances Efferocytosis, Autophagy, and Atheroprotective Gut Microbiota in Hyperlipidemic Mice. *Journal of the American Heart Association*. 2024; 13: e033881. <https://doi.org/10.1161/JAHA.123.033881>
- [239] Bernier M, Mitchell SJ, Wahl D, Diaz A, Singh A, Seo W, et al. Disulfiram Treatment Normalizes Body Weight in Obese Mice. *Cell Metabolism*. 2020; 32: 203–214.e4. <https://doi.org/10.1016/j.cmet.2020.04.019>
- [240] Lei Y, Tang L, Chen Q, Wu L, He W, Tu D, et al. Disulfiram ameliorates nonalcoholic steatohepatitis by modulating the gut microbiota and bile acid metabolism. *Nature Communications*. 2022; 13: 6862. <https://doi.org/10.1038/s41467-022-34671-1>
- [241] Zhong L, Han J, Fan X, Huang Z, Su L, Cai X, et al. Novel GSDMD inhibitor GI-Y1 protects heart against pyroptosis and ischemia/reperfusion injury by blocking pyroptotic pore formation. *Basic Research in Cardiology*. 2023; 118: 40. <https://doi.org/10.1007/s00395-023-01010-4>
- [242] Hanke J, Romejko K, Niemczyk S. Sodium-Glucose Cotransporter-2 Inhibitors in Diabetes and Beyond: Mechanisms, Pleiotropic Benefits, and Clinical Use-Reviewing Protective Effects Exceeding Glycemic Control. *Molecules (Basel, Switzerland)*. 2025; 30: 4125. <https://doi.org/10.3390/molecules30204125>
- [243] Yang L, Zhang X, Wang Q. Effects and mechanisms of SGLT2 inhibitors on the NLRP3 inflammasome, with a focus on atherosclerosis. *Frontiers in Endocrinology*. 2022; 13: 992937. <https://doi.org/10.3389/fendo.2022.992937>
- [244] Rroji M, Spahia N, Figurek A, Spasovski G. Targeting Diabetic Atherosclerosis: The Role of GLP-1 Receptor Agonists, SGLT2 Inhibitors, and Nonsteroidal Mineralocorticoid Receptor Antagonists in Vascular Protection and Disease Modulation. *Biomedicines*. 2025; 13: 728. <https://doi.org/10.3390/biomedicines13030728>
- [245] Rahman H, Khan SU, Lone AN, Ghosh P, Kunduru M, Sharma S, et al. Sodium-Glucose Cotransporter-2 Inhibitors and Primary Prevention of Atherosclerotic Cardiovascular Disease: A Meta-Analysis of Randomized Trials and Systematic Review. *Journal of the American Heart Association*. 2023; 12: e030578. <https://doi.org/10.1161/JAHA.123.030578>
- [246] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet (London, England)*. 2019; 393: 31–39. [https://doi.org/10.1016/S0140-6736\(18\)32590-X](https://doi.org/10.1016/S0140-6736(18)32590-X) Erratum in: *Lancet*. 2019; 393: 30. [https://doi.org/10.1016/S0140-6736\(18\)33206-9](https://doi.org/10.1016/S0140-6736(18)33206-9)
- [247] Lewis M, Burrack N, Heymann A, Grossman A, Neuman T, Abuhasira R. Sodium-Glucose Cotransporter 2 Inhibitors, Erythrocytosis, and Thrombosis in Adults With Type 2 Diabetes. *JAMA Network Open*. 2025; 8: e2517086. <https://doi.org/10.1001/jamanetworkopen.2025.17086>
- [248] Stanger L, Yalavarthi P, Flores M, Creen D, Pitt B, Holinstat M. Comparison of the Anti-Platelet and Anti-Thrombotic Effects of the Dual SGLT1/2 Inhibitor Sotagliflozin to the Relatively Selective SGLT2 Inhibitor Empagliflozin. *Blood*. 2024; 144: 3933–3933. <https://doi.org/10.1182/blood-2024-202339>
- [249] Drucker DJ. GLP-1-based therapies for diabetes, obesity and beyond. *Nature Reviews. Drug Discovery*. 2025; 24: 631–650. <https://doi.org/10.1038/s41573-025-01183-8> Erratum in: *Nature Reviews. Drug Discovery*. 2025; 24: 570. <https://doi.org/10.1038/s41573-025-01231-3>
- [250] Mehdi SF, Pusapati S, Anwar MS, Lohana D, Kumar P, Nandula SA, et al. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. *Frontiers in Immunology*. 2023; 14: 1148209. <https://doi.org/10.3389/fimmu.2023.1148209>
- [251] Kim JH, Lee GY, Maeng HJ, Kim H, Bae JH, Kim KM, et al. Effects of Glucagon-Like Peptide-1 Analogue and Fibroblast Growth Factor 21 Combination on the Atherosclerosis-Related Process in a Type 2 Diabetes Mouse Model. *Endocrinology and Metabolism (Seoul, Korea)*. 2021; 36: 157–170. <https://doi.org/10.3803/EnM.2020.781>
- [252] Li Q, Lin Y, Wang S, Zhang L, Guo L. GLP-1 Inhibits High-Glucose-Induced Oxidative Injury of Vascular Endothelial Cells. *Scientific Reports*. 2017; 7: 8008. <https://doi.org/10.1038/s41598-017-06712-z>
- [253] Solomon SD, Ostrominski JW, Wang X, Shah SJ, Borlaug BA, Butler J, et al. Effect of Semaglutide on Cardiac Structure and Function in Patients With Obesity-Related Heart Failure. *Journal of the American College of Cardiology*. 2024; 84: 1587–1602. <https://doi.org/10.1016/j.jacc.2024.08.021> Erratum in: *Journal of the American College of Cardiology*. 2025; 85: 967–968. <https://doi.org/10.1016/j.jacc.2025.01.010>
- [254] Wang T, Ding J, Cheng X, Yang Q, Hu P. Glucagon-like peptide-1 receptor agonists: new strategies and therapeutic targets to treat atherosclerotic cardiovascular disease. *Frontiers in Pharmacology*. 2024; 15: 1396656. <https://doi.org/10.3389/fphar.2024.1396656>
- [255] Khan S, Huda B, Bhurka F, Patnaik R, Banerjee Y. Molecular and Immunomodulatory Mechanisms of Statins in Inflammation and Cancer Therapeutics with Emphasis on the NF- κ B, NLRP3 Inflammasome, and Cytokine Regulatory Axes. *International Journal of Molecular Sciences*. 2025; 26: 8429. <https://doi.org/10.3390/ijms26178429>
- [256] Henriksbo BD, Tamrakar AK, Phulka JS, Barra NG, Schertzer JD. Statins activate the NLRP3 inflammasome and impair insulin signaling via p38 and mTOR. *American Journal of Physiology. Endocrinology and Metabolism*. 2020; 319: E110–E116. <https://doi.org/10.1152/ajpendo.00125.2020>
- [257] Robin N, Barra N, Patoli D, Watt K, Nguyen K, Foley K, et al. Statins activate the NLRP3 inflammasome and inhibit the Hippo pathway to promote myopathy. *Physiology*. 2023; 38: 5732019. <https://doi.org/10.1152/physiol.2023.38.s1.5732019>
- [258] Colli S, Werba JP, Tremoli E. Statins in atherothrombosis. *Seminars in Vascular Medicine*. 2004; 4: 407–415. <https://doi.org/10.1055/s-2004-869598>