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Targeting the NLRP3 Inflammasome in Cardiovascular Diseases

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Abstract

The NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD)-containing protein 3 (NLRP3) inflammasome is an intracellular sensing protein complex that plays a major role in innate immunity. Following tissue injury, activation of the NLRP3 inflammasome results in cytokine production, primarily interleukin(IL)-1β and IL-18, and, eventually, inflammatory cell death – pyroptosis. While a balanced inflammatory response favors damage resolution and tissue healing, excessive NLRP3 activation causes detrimental effects. A key involvement of the

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NLRP3 inflammasome has been reported across a wide range of cardiovascular diseases (CVDs). Several pharmacological agents selectively targeting the NLRP3 inflammasome system have been developed and tested in animals and early phase human studies with overall promising results. While the NLRP3 inhibitors are in clinical development, multiple randomized trials have demonstrated the safety and efficacy of IL-1 blockade in atherothrombosis, heart failure and recurrent pericarditis. Furthermore, the non-selective NLRP3 inhibitor colchicine has been recently shown to significantly reduce cardiovascular events in patients with chronic coronary disease. In this review, we will outline the mechanisms driving NLRP3 assembly and activation, and discuss the pathogenetic role of the NLRP3 inflammasome in CVDs, providing an overview of the current and future therapeutic approaches targeting the NLRP3 inflammasome.

Keywords

NLRP3; interleukin-1; interleukin-18; inflammation; cardiovascular diseases; thrombosis; heart failure; pericarditis; COVID-19

1. Introduction

Innate immunity is a conserved stereotyped response that is necessary for the prompt identification of infectious pathogens [1]. The innate immune response is largely based on pattern recognition. Infectious pathogens share a variety of molecules, called pathogen-associated molecular patterns (PAMPs), that possess similar chemical properties. A large variety of pathogens can be recognized by a small set of pattern recognition receptors (PRRs) [1]. Activation of PRRs induces a rapid and robust local and systemic inflammatory response resulting in production of several pro-inflammatory cytokines including interleukin (IL)-1β, IL-6 and IL-18. While lymphoid-mediated acquired immunity prepares antibody- and cell-mediated defenses during the first days of infection, these cytokines crucially activate myeloid-mediated innate immunity. Adequate cooperation of the innate and acquired immune responses, finely orchestrated by cytokines, ultimately leads to confinement and eradicatation of the pathogen [2].

PRRs also recognize self-derived molecules, defined as damage-associated molecular patterns (DAMPs) (Figure 1) [1-2]. DAMPs are released following tissue stress or injury, and serve as ‘alarmins’ to boost the inflammatory process, clear dead cells and initiate tissue healing [3]. DAMPs thus enable differential innate immune responses to commensal and non-commensal organisms [2,3].

This primordial innate immune response is considered an essential first-line defense to infections. Indeed, invididuals with inherited or acquired defects in the innate immunity are subject to deadly infections [1]. On the other hand, an exaggerated innate immune response exacerbates tissue damage and worsens prognosis [1]. In recent times, this adverse consequence has been evident in coronavirus disease 19 (COVID-19), in which hyperinflammation secondary to severe acute respiratory syndrome (SARS-CoV-2) infection significantly contributes to worse disease manifestations [4].

In the setting of chronic degenerative diseases, overactivation of PRRs drives chronic inflammation, which aggravates disease progression and outcomes. While it is well-established that inflammation plays a causal role in rheumatic disorders, the contribution of dysregulated innate immunity is now recognized in the development and progression of a wide range of non-rheumatic diseases such as cardiovascular, onco-hematological and neurodegenerative conditions [5-10].

The nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are PRRs that recognize a wide range of pathogens and danger-associated products [8]. The different members of the NLR family form multimolecular complexes named inflammasomes [8]. An inflammasome is a multiprotein complex that leads to the activation of a pro-inflammatory caspase (e.g. caspase-1) and promotes the release of cytokines of the IL-1β family [8]. The NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD)-containing protein 3 (NLRP3) is the most extensively studied inflammasome, and its involvement has been demonstrated in several rheumatic and non-rheumatic diseases [9]. Besides the NLRP3 inflammasome, several other inflammasomes, including NLRP1, NLRC4 and AIM2, have been well characterized, and their role in health and disease has been reviewed elsewhere [8]. Within the cardiovascular field, recent clinical trials have validated the inflammatory hypothesis of atherosclerosis, and ongoing work has elucidated a role of the NLRP3 inflammasome following ischemic and non-ischemic, acute and chronic insults to the cardiovascular system [10]. In this review, we outline the processes beyond NLRP3 inflammasome formation and activation, and discuss the role of the NLRP3 in cardiovascular diseases (CVDs). In this context, current and future therapeutic approaches targeting the NLRP3 inflammasome will be also discussed.

2. The NLRP3 Inflammasome

NLRP3 acts as a receptor for immune/damage surveillance [8,9]. Activation of the NLRP3 inflammasome transforms the cell into a powerhouse for the production and release of inflammatory cytokines belonging to the IL-1 family. NLRP3 activity also determines cell fate, by potentially inducing, through the formation of gasdermin D (GSDMD) channels in the membrane, pyroptosis, an inflammatory cell death.

NLRP3 is a multi-domain protein. It has a leucine-rich repeats (LRRs) domain at the C-terminus, that is the “sensing” component for PAMPs and DAMPs. It also possesses a nucleotide-binding and oligomerization domain (NOD, also known as NACHT), which contains the active ATPase site through the Walker A motif (ATP-binding site) and the Walker B motif (ATPase activity). Once activated, the LRR domain induces NLRP3 to oligomerize through their NACHT domain (Figure 2) [10-24]. The effector pyrin domain (PYD) at the N-terminus is responsible for the downstream pro-inflammatory effects, binding to the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain or CARD) through a PYD-PYD interaction [10,25-27]. This central oligomeric structure catalizes the polymerization of ASC into filamentous structures [25-27]. ASC then binds to the CARD of pro-caspase-1 to form the inflammasome [25-27]. Pro-caspase-1 auto-cleavage releases active caspase-1, which in turn activates pro-IL-1β, IL-18 and GSDMD. While IL-1β and IL-18 exert classical pro-inflammatory effects, the

activated N-terminal GSDMD (NT-GSDMD) forms membrane pores that facilitate the extracellular release of IL-1β and IL-18 as well as inflammatory cell death - pyroptosis [10,28-30].

Two independent but concomitant signals are required to induce inflammasome formation (Figure 2). This represents a mechanism of control, in order to regulate the potent inflammatory and pyroptotic consequences of NLRP3 activation [31-34]. A 'priming' signal is necessary to induce the transcription of the components of the inflammasome (NLRP3, pro-IL-1β and pro-IL-18). A 'triggering' signal, instead, leads to the structural changes in NLRP3 domains necessary for the assembly of the inflammasome. An additional regulatory level of NLRP3 activity is provided by post-translational modifications such as ubiquitination and phosphorylation of inflammasome proteins, as outlined below [35-38].

The priming signal can be induced by PRRs, including toll-like receptors (TLRs) and NOD2, by cytokine receptors, inducing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated transcriptional upregulation of the inflammasome components and substrates, as well as by pathways involved in cardiovascular regulation, such as the angiotensin receptor type 1 (AT1) or adrenergic receptors (Figure 2) [15,20,21,35].

The activation of the NLRP3 inflammasome signaling pathway is finely modulated by complex regulatory networks that include post-translational and post-transcriptional modifications. Numerous microRNAs (miRs) and long non-coding RNAs (lncRNAs) have been found to control the post-translational expression of the NLRP3 inflammasome proteins and substrates, by either reducing (miRs) or increasing (lncRNAs) NLRP3 expression [8,9,24,25]. Among these, miR22 reduces NLRP3 mRNA expression in rat coronary artery endothelial cells, whereas the lncRNA MALAT1 was shown to increase NLRP3 expression in the setting of acute myocardial infarction (AMI) [39,40]. Protein phosphorylation and ubiquitination also regulate post-translational priming and triggering of the NLRP3 inflammasome [41]. Cell experiments have shown that NLRP3, ASC and caspase-1 are targets of several kinases, phosphatases and ubiquitin ligases [41,42], although the role of these modifications in development and progression of CVDs has not been thoroughly investigated.

3. Mechanisms of Cardiac NLRP3 activation

Multiple alarmins and DAMPs can contribute to the priming phase in the heart. During AMI, the ischemic insult promotes the release of cellular debris and alarmins. In addition, chronic conditions such as obesity, hypertension or diabetes promote the priming through metabolites and neurohormonal activation (e.g. angiotensin II, fatty acids and glucose) [43-48]. For example, diabetic mice display basally increased levels of NLRP3 inflammasome components compared to their normoglycemic counterparts, and this exacerbates tissue damage in case of insults such as ischemia-reperfusion [49]. Numerous intracellular and extracellular signals activate NLRP3 [10]. These signals are unrelated and include intracellular pathways (e.g. reactive oxygen species [ROS], mitochondrial

dysfunction, lysosome rupture) and extracellular signals (e.g. ATP-mediated activation of the purinergic-type 2 receptor X7 [P2X7], potassium efflux and calcium influx) (Figure 2).

3.1. ATP and K^+ efflux

Extracellular ATP has been described as one of the signals capable of inducing NLRP3 activation [50,51]. The binding of ATP to the P2X7 opens the channel pore causing K^+ efflux that leads to conformational changes of NLRP3, allowing the interaction with ASC (Figure 2) [50]. During ischemia, P2X7 activation is one of the main mechanisms driving the formation of the NLRP3 inflammasome in cardiomyocytes [52]. Bacterial toxins like nigericin form membrane pores, allowing K^+ efflux independent of P2X7 activation [50,52]. The mitotic serine/threonine kinase NEK7, a member of the mammal NIMA-related kinases (NEK proteins) family, acts downstream of K^+ efflux, and directly binds NLRP3, thereby regulating its oligomerization and activation (Figure 2) [53]. NEK7 is highly expressed in the heart, making this protein a possible target to inhibit NLRP3 inflammasome activity [54].

3.2. Ca^{2+} mobilization

Different stimuli as extracellular ATP, nigericin and particulates can induce Ca^{2+} mobilization from the endoplasmic reticulum (ER) or the extracellular space, leading to mitochondrial damage and subsequent NLRP3 activation [55]. One of the sensors of extracellular Ca^{2+} is the calcium-sensing receptor (CaSR), that seems to mediate the increase in intracellular Ca^{2+} and the decrease in cellular cyclic AMP (cAMP). Both events are associated with NLRP3 activation [56]. In rats, CaSR mediates NLRP3 activation in the setting of hypertension and AMI [57,58].

3.3. Lysosomal rupture

Cytoplasmatic leak of lysosomal content has been shown to activate NLRP3 [59]. Incomplete phagocytosis of crystals causes lysosome swelling and instability, leading to lysosomal rupture with release the of cathepsin B, a lysosomal enzyme able to activate NLRP3 (Figure 2) [59-63]. This mechanism is common to different inflammasome-activating stressors, such as monosodium urate crystals, calcium phosphate crystals and cholesterol crystals [59-63]. In particular, these last two have been correlated with the development of atherosclerotic plaques [63].

3.4. Autophagy

Autophagy comprises several cellular pathways that synergistically lead to compartmentalization and digestion of cellular protein and/or organelles [64]. In cells in culture, abrogation of the physiological autophagy, either by deletion of autophagy-inducer proteins (e.g. microtubule-associated proteins 1A/1B light chain 3B [LC3B], beclin 1, autophagy related [ATG] 5, ATG7) or treatment with autophagy inhibitors (e.g. 3-Methyladenine), is associated with induction of the NLRP3 inflammasome [65]. On the contrary, in cells already expressing the inflammasome, induction of autophagy through rapamycin or starvation results in reduced NLRP3-mediated signaling [65]. In acute myocardial infarction, autophagy limits cardiac damage, while its suppression can

worsen cardiac remodeling [66,67]. In diabetic rats, induction of autophagy with rapamycin reduces the expression of the NLRP3 inflammasome components, which parallels with reduced infarct size after myocardial ischemia-reperfusion [68]. In vitro, exposure of rat cardiac myocytes H9C2 to high glucose or hypoxia induces the NLRP3 inflammasome, which is reduced by rapamycin treatement. In rats lacking NLRP3, experimental ischemia-reperfusion stimulates the autophagic flux together with reduced myocardial damage and infarct size [69].

Saturated fatty acids also promote inflammasome activation through autophagy and increase ROS production [70].

3.5. Reactive oxygen species and mitochondrial dysfunction

Mitochondria are the major source of DAMPS, including ROS, and are involved in the control of different types of cell death (necrosis/necroptosis, apoptosis as well as pyroptosis) [71]. Mitochondrial dysfunction and impaired mitochondrial autophagy (i.e. mitophagy) can cause increased ROS generation and cytosolic accumulation of dysfunctional mitochondria or mitochondrial DNA (mtDNA) leakage, which are potent NLRP3 activators (Figure 2) [71-74]. Other mitochondrial-derived molecules can mediate the activation of NLRP3. Among these, cardiolipin can directly bind NLRP3 through its LRR domain allowing its activation [75]. Also MAVS, a mitochondrial adaptor protein activated by ATP and nigericin, promotes NLRP3 oligomerization and ASC recruitment [76,77]. Mitochondrial dysfunction seems to play an important role in atherosclerosis, ischemia-reperfusion injury and pressure overload [78-80]. In addition, thioredoxin-interacting protein (TXNIP) plays a critical role in cellular redox control by binding to the oxidoreductase thioredoxin (TRX) [81]. In the setting of hyperglycemia and hypercholesterolemia, excessive ROS production and the presence of unfolded proteins can cause the dissociation of TXINP from TRX [81-83]. In this state, TXINP can bind and activate NLRP3 [84]. TXINP inhibition by siRNA has been shown to protect the heart after ischemia-reperfusion [85].

4. The NLRP3 inflammasome in cardiovascular diseases

Activation of the NLRP3 inflammasome has been importantly implicated in several CVDs. The dynamics of NLRP3 activation differs also between acute and chronic injury. Acute injury is associated with rapid and robust upregulation of the NLRP3 inflammasome [10,12,29,34]. In this setting, the therapeutic window to target the inflammasome tends to be narrower (i.e. hours-days) depending on the nature of the injury. On the contrary, in chronic conditions such as atherosclerosis, hypertension, diabetes, obesity, heart failure [HF], where low-grade basal activation of the NLRP3 inflammasome contributes to the disease progression, inhibition of NLRP3 inflammasome at different stages may alleviate worsening of the chronic condition, the therapeutic window is significantly wider (i.e. days-months-years)[10,12,29]. The impact may also be different in acute versus chronic setting. In the acute conditions, the inhibition of the NLRP3 inflammasome activity may lead to the rescue of viable tissue and provide ensuing large beneficial effects, but the efficacy will depend also by the nature of the injury and the time of the intervention [10,12,29]. In chronic conditions, the inhibition of the NLRP3 inflammasome can change the rate of

progression of the degenerative illness, and the efficacy may depend also by the activity of the NLRP3 inflammasome as compared with the chronic nature of the condition and injury already performed, and the ability of the treatment to ameliorate and change trajectory of conditions that are likely to progress and/or recur over time [12,15,29]. We herein provide an overview of the potential role of NLRP3 in CVDs including atherosclerosis, ischemic heart disease, diabetic cardiomyopathy, hypertensive cardiomyopathy, dilated cardiomyopathy, drug-induced cardiotoxicity, myocarditis, cardiac sarcoidosis, pericarditis, venous thromboembolism and COVID-19.

4.1. Atherosclerosis

Atherosclerosis is a chronic inflammatory disorder and a well-known cause of several CVDs [86]. Macrophage infiltration in the vascular wall is the main characteristic of atherosclerosis [87]. In macrophages, cholesterol and calcium phosphate crystals lead to lysosomal instability causing cathepsin B release that, in turn, activates the NLRP3 inflammasome with IL-1β release [62,63]. The importance of NLRP3 inflammasome has been highlighted in several animal models of atherosclerosis. Decreased atherosclerosis was demonstrated in low density lipoprotein receptor knock-out mice ($Ldlr^{-/-}$) transplanted with bone marrow from $Nlrp3^{-/-}$, $Asc^{-/-}$ and $Il\text{-}1\beta^{-/-}$ mice [63]. These pieces of evidence make the NLPR3 inflammasome a promising therapeutic target for atherosclerosis.

4.2. Ischemic heart disease.

The inhibition of NLRP3 and other inflammasome components in animal model of ischemic cardiac injury showed beneficial effects in terms of reduced infarct size and improved cardiac function [52,85,88]. NLRP3 activation after ischemia is a time-dependent mechanism [89]. DAMPs and alarmins released from cells damaged by ischemia strongly stimulate the inflammatory response, with recruitment of highly active inflammatory cells at the site of injury. This feed-forward mechanism exacerbates the initial ischemic damage [90,91]. In experimental models of reperfused and non-reperfused AMI, peak NLRP3 inflammasome activation occurs respectively 1 and 3 days after ischemia [52,85,91]. NLRP3 inflammasome specks can be detected in leukocytes, endothelial cells, fibroblasts and cardiomyocytes after AMI [52,85,88]. However, when the healing phase starts, ASC aggregates prevalently localize in fibroblasts and cardiomyocytes [52,85,88], The response to inflammasome activation seems to be cell-type specific. Leukocytes, fibroblasts and endothelial cells mainly respond with IL-1β production. In cardiomyocytes, NLRP3 activation tend to result in caspase-1 activation and culminate with pyroptotic cell death [92]. After ischemia-reperfusion in mice, genetic or pharmacological inhibition of the NLRP3 inflammasome reduces infarct size and preserves cardiac function. This is recapitulated in studies with mice lacking caspase-1 or ASC (reviewed below) [52,85,88,93].

4.3. Dilated cardiomyopathy

Several pieces of evidence suggest an important inflammatory component in the pathogenesis of dilatated cardiomyopathy. Circulating levels of NLRP3 inflammasome seem to clinically correlate with cardiac function, NT-pro BNP levels and cumulative rehospitalization rate at 6 months [94]. At autopsy, markedly increased pyroptotic cell death was demonstrated in the hearts of patients with dilatated cardiomyopathy [95].

4.4. Hypertensive heart disease

Hypertensive cardiac damage promotes myocardial hypertrophy and fibrosis leading to left ventricular remodeling and development of HF. Cardiac upregulation of NLRP3 and IL-1β has been found in two different mouse models of hypertension: transverse aortic constriction, a pressure overload model inducing myocardial fibrosis and remodeling, and the hypertensive angiotensin II-infusion model [96-100]. In both models, inhibition or deletion of NLRP3 ameliorated cardiac remodeling, reducing inflammation and fibrosis [96,97]. However, the mechanisms of inflammasome activation in absence of ischemic damage and cell death are not completely elucidated. A recent study indicates that, in response to pressure overload, priming and activation of cardiac NLRP3 is mediated by Ca^{2+}/calmodulin-dependent protein kinase II δ (CaMKIIδ) [100].

4.5. Cancer therapy-associated cardiac injury

Several therapies employed to treat different types of cancer (i.e. radiation therapy and chemotherapy) are associated with the development of cardiomyopathy both in animals and humans. Mice injected with doxorubicin develop left ventricular dilatation, reduced cardiac function and increased cardiac fibrosis [101,102]. The decline in cardiac function parallels with increased cardiomyocyte expression of NLRP3, caspase-1, IL-1β and IL-18, and abudant pyroptosis [95,103]. Blocking NLRP3 by pharmacological inhibition or gene deletion attenuates cardiac dysfunction and myocardial damage induced by pyroptosis [95,104]. Given the beneficial effects of IL-1β and IL-18 blockade in radiation-induced cardiomyopathy, a direct involvement of the NLRP3 inflammasome in the initiation and progression of radiation-induced cardiac damage has been proposed [105-107].

4.6. Metabolic disorders and diabetic cardiomyopathy

In the context of cardiometabolic disorders, IL-1β and IL-18 are key mediators of the detrimental effects of obesity and aging [108,109]. Adipose tissue actively contributes to the systemic pro-inflammatory state, characterized by increased plasma levels of pro-inflammatory cytokines [110]. Upregulation of the NLRP3 inflammasome was reported in the adipose tissue of obese patients and animals [47,110-113]. In animal models of aging and obesity, NLRP3 inhibition was associated with improved metabolic profile [111-113]. Sustained metabolic abnormalities may lead to diabetic cardiomyopathy [114], in which cardiac NLRP3 directly contributes to organ dysfunction [115,116]. Cardiomyocyte death seems to be the first step in initiating the structural remodeling leading to diabetic cardiomyopathy [117]. Glucotoxicity and lipotoxicity represent potent stimuli for the NLRP3 inflammasome [118-120]. In particular, in several cell types, high glucose levels induce ROS production and subsequent activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and TXNIP, thereby acting as priming and triggering signals to the inflammasome [118-121].

4.7. Pericarditis

Acute pericarditis is characterized by an intense inflammatory response due to an acute injury of the mesothelial cells in the pericardium [122-124]. A key role of NLRP3 in pericarditis has been attested in several pre-clinical and clinical studies

[122,123]. Furthermore, the efficacy of colchicine, an anti-inflammatory agent with NLRP3 inflammasome inhibitory activity (reviewed below), in the treatment of acute pericarditis further supports a direct role of NLRP3 in this condition [122,123]. A recent study revealed the presence of inflammasome components (NLRP3, ASC and caspase-1) in pericardial samples of patients with chronic pericarditis experiencing an acute flare [123]. Consistent findings were obtained in a novel mouse model in which pericarditis was induced by zymosan intrapericardial injection [123]. In this model, inhibition of the inflammasome or IL-1α/β reduced pericardial effusion and thickening [123]. These observations are in line with the clinical efficacy of rilonacept, which inhibits both IL-1α and IL-1β, in patients with recurrent pericarditis [124,125]. In the phase III, RHAPSODY trial, rilonacept monotherapy was associated with a 96% reduction in recurrences as compared with placebo [125]. Similar benefits had been seen in the smaller AIRTRIP trial with anakinra, a recombinant IL-1 receptor antagonist, in patients with recurrent pericarditis resistant to colchicine [126]. IL-1 blockers are now considered standard of care for the treatment of recurrent pericarditis in patients who failed initial therapy. A potential role for interleukin-1 blockade in acute pericarditis is under investigation [127].

4.8. Myocarditis

The presence of the NLRP3 inflammasome has been shown in endomyocardial biopsies of patients with acute myocarditis [128]. Infection with coxsackievirus B3 (CVB3), one of the most common viruses causing myocarditis, is associated with enhanced NLRP3 activation together with increased ASC, caspase-1 and IL-1β expression observed within 7 days from the infection in mice [129]. Inhibition of caspase-1 or IL-1β ameliorates cardiac function and reduces the release of myocardial enzymes [129]. Of note, in experimental CVB3-induced myocarditis, inflammasome activation and subsequent pyroptosis seem to be mediated by cathepsin B [130]. A peculiar form of myocarditis, namely cardiac sarcoidosis, is characterized by the formation of giant cell granulomas in the heart, which progressively lead to cardiac failure and arrhythmias [131]. Recently, intense expression of the NLRP3 inflammasome and its products in the granulomas has been described [132]. A clinical trial with anakinra in cardiac sarcoidosis is currently ongoing [133].

4.9. Venous thromboembolism

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is the third leading cause of cardiovascular mortality worldwide [134]. In addition, post-thrombotic syndrome (PTS), a chronic inflammatory condition complicating VTE, accounts for considerable morbidity, affecting 20-40% of patients following VTE [134].

Initiation and propagation of venous thrombosis is a multifactorial process involving a complex sequence of events, in which inflammation directly promotes activation of the coagulation system and the endothelium, as well as the recruitment of leukocytes and platelets forming aggregates and aggravating thrombosis [135,136]. Several lines of evidence indicate that the NLRP3 inflammasome is implicated in the regulation of these events [135-141]. Blood flow restriction and hypoxia following experimental venous thrombosis have been shown to induce the NLRP3, caspase-1 and IL-1β [137-139]. In mice,

genetic deletion of the NLRP3 inflammasome and pharmacological inhibition of caspase-1 or IL-1β significantly ameliorate venous thrombosis [137-139]. Recently, deficiency of caspase-1 or GSDMD has been shown to protect against experimental venous thrombosis [140]. Furthermore, tissue factor released from monocytes and macrophages following NLRP3 activation trigger the coagulation cascade [141]. In patients with VTE, elevated NRLP3 activity, as measured by high concentrations of caspase-1, IL-1β, IL-6 or C-reactive protein, were found from days to months after the index event, and correlated with thrombus extent and incomplete thrombus resolution [137,142]. Surrogate biomarkers of NLRP3 inflammasome activation seemed to predict the development PTS, as well as the recurrence of thrombotic events [143,144]. Other studies have also found an association between basal levels of inflammation and the occurrence of a first event of VTE [145]. Despite no clinical trial specifically addressing inflammation in VTE exists, althogether, these data may allow to speculate that strategies selectively targeting the NLRP3 inflammasome may lead to the development of novel therapeutics against VTE, which may maximize the benefits of anticoagulation.

4.10. COVID-19

Viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have the ability to trigger the NLRP3 inflammasome [146]. In recent times, a role of the NLRP3 inflammasome has been demonstrated in the pathophysiology of COVID-19. Severe forms of COVID-19 are characterized by systemic hyperinflammation which contributes to diffuse organ damage, including the lungs, heart and vasculature, and worsens clinical outcomes [4]. Upon autopsy, abundant presence of NLRP3, ASC and caspase-1 were found in the lungs of patients with fatal COVID-19 [147,148]. Analysis of circulating myeloid cells isolated from COVID-19 patients indicated that NLRP3 and caspase-1 are highly active and produce large amounts of mature IL-1β [148-150]. In addition, higher concentrations of inflammasome-derived products such as caspase-1 and IL-18 in the sera of patients with COVID-19 correlated with disease severity and predicted worse evolution [148-150]. Mechanistic in vitro studies have consistently demonstrated that the interaction of SARS-CoV-2 spike protein with the virus receptor entry angiotensin-converting enzyme 2 induces abundant cytokine release including IL-1β, IL-6, IL-8 and IL-18, through activation of NLRP3 and caspase-1 [151-153]. Of note, abrogation of NLRP3-mediated signaling with different selective NLRP3 inhibitors resulted in significantly reduced cytokine production in cultured peripheral blood mononuclear cells (PBMCs) exposed to recombinant SARS-CoV-2 spike protein [152]. It has been hypothesized that IL-1β and IL-18 resulting from NLRP3 signaling activate monocytes, which in turn produce several other cytokines such as IL-6, IL-8 and tumor necrosis factor (TNF) responsible for hyperinflammation and, through multiple mechanisms, subsequent local (i.e. in the lungs) and systemic damage associated with severe forms of COVID-19 [4,148-150]. These mechanisms include abundant recruitment of neutrophils to the lungs, generation of neutrophil extracellular traps (NETs) through GSDMD and ROS, as well as cell death (e.g. through pyroptosis) [147-152]. NETs recruit platelets, facilitate tissue factor release from pyroptotic monocytes and promote the hypercoagulable state associated with COVID-19. In addition, multiple cytokines such as IL-1α, IL-1β and IL-6 increase

vascular permeability and activate the endothelium, which further predispose to thrombosis [135,153].

Besides regulating the activation of leukocytes, platelets, endothelial cells and the coagulation cascade following SARS-CoV-2 infection, the NLRP3 inflammasome has been found in hematopoietic stem cells, opening to the possibility that SARS-CoV-2, by means of NLRP3, may also remotely affect tissue proliferation and regeneration [154]. Altogether, these observations indicated that hyperactivation of the NLRP3 inflammasome contributes in initiating and propagating hyperinflammation associated with COVID-19, and suggested that selectively targeting of the NLRP3 inflammasome may represent a promising therapeutic strategy in COVID-19. This has led to the initiation of a phase II randomized trial with dapansutrile, an oral NLRP3 inhibitor (NCT04540120). Nevertheless, IL-1 inhibition with anakinra or canakinumab has been already evaluated in multiple observational studies with overall encouraging results [155-157]. In the SAVE-MORE double-blind, randomized controlled trial of anakinra, IL-1 receptor antagonist, in 594 patients with COVID-19 pneumonia, significantly reduced the risk as compared with placebo of clinical worsening and reduced twenty-eight-day mortality [158]. In the phase III CAN-COVID trial randomizing 454 patients with severe COVID-19 pneumonia and systemic hyperinflammation, treatment with canakinumab was safe and associated with a trend towards improved survival without invasive mechanical ventilation and COVID-19-related mortality at day 29 compared to placebo [159]. Although results were not statistically significant for the primary endpoint, early treatment with canakinumab was associated with a reduction of death, need for invasive mechanical ventilation or use of other IL-1/IL-6 blockers for worsening disease [159]. The efficacy of anti-cytokine treatments in COVID-19 has been proven for strategies targeting IL-6, a potent pleiotropic cytokine induced by the NLRP3 inflammasome [160]. During the early phases of the pandemic, different IL-6 antagonists including tocilizumab, sarilumab and siltuximab, already approved for rheumatic and oncological diseases, have been repurposed for COVID-19 [160]. After initial promising experiences with tocilizumab, several randomized trials were launched worldwide [156,161-165]. A meta-analysis including 10,930 hospitalized COVID-19 patients from 27 randomized controlled trials, found that administration of either tocilizumab or sarilumab, two monoclonal antibodies directed against the IL-6 receptor, significantly reduced 28-day all-cause-mortality compared to standard of care or placebo [166]. Early administration of tocilizumab in combination with dexamethasone has become standard-of-care in hospitalized COVID-19 patients exhibiting rapid respiratory decompensation [167,168].

5. Pharmacological targeting of the NLRP3 inflammasome

Due to the broad role of the NLRP3 inflammasome in several types of diseases as well as the direct and indirect evidences showing the benefits of NLRP3 blockade, several NLRP3 inflammasome inhibitors are in preclinical and clinical development (Table 1). While some of these selectively block the NLRP3 inflammasome, others have broader effects which indirectly result in NLRP3-mediated signaling inhibition (Figure 3). This review will focus on the NLRP3 inhibitors that have been tested in CVDs.

5.1. Glyburide derivates

Glyburide is an oral sulfonylurea used in the treatment of type 2 diabetes mellitus. It promotes insulin release from pancreatic β-cells through a cyclohexylurea moiety [169]. It was the first drug shown to inhibit NLRP3 at high doses in vitro [170]. Nevertheless, high-dose glyduride induce severe hypoglycemia in vivo [169,170]. For this reason, a glyburide derivative, named 16673-34-0, which lacks the cyclohexylurea moiety but retains the inhibitory activity against NLRP3, was developed [171]. The 16673-34-0, at a dose of 100 mg/Kg, inhibited cardiac caspase-1 activity, and reduced infarct size in mice subjected to myocardial ischemia followed by 24 hours reperfusion [89,171]. Comparable beneficial effects were obtained even when treatment with 16673-34-0 was administered in a clinically relevant scenario (i.e. 60 minutes after reperfusion) [89,171]. The 16673-34-0 improved cardiac function also in a model of permanent coronary artery ligation, independently from infarct size reduction [104]. In rats in which circulatory death was induced through, pre-treatment with 16673-34-0 before cardiac arrest or addition of 16673-34-0 to the buffer used for ex-vivo reanimation of the heart limited the ischemic damage and improved contractility [172]. In a rat model of donation after circulator death (DCD), consisting of heterotopic heart transplantation to a recipient rat after circulatory death of the donor is induced, the 16673-34-0 was administered with cardioplegia to the donor rat heart at the moment of heart procurement as well as to the recipient rat one hour before heart transplantation. After 24 hours, the transplanted heart displayed reduced myocardial ASC staining and improved contractility [173]. In mice with experimental pericarditis, 16673-34-0 reduced pericardial effusion and thickening [123]. In mouse models of doxorubicin-induced or Western diet-induced cardiomyopathy, 16673-34-0 improved cardiac function and reduced interstitial fibrosis [104,174]. JC-124, a compound derived from 16673-34-0 developed at Virginia Commonwealth University, was shown to be more powerful than 16673-34-0 in inhibiting the inflammasome and reducing infarct size in a mouse model of ischemia-reperfusion [175]. Similarly to 16673-34-0, JC-124 is specific for NLRP3 and shows no inhibitory activity on the NLRP1 or NLRC4 inflammasomes, while it remains active against NLRP3 mutants associated with genetic forms of cryopyrin-associated diseases [104,175].

5.2. MCC950 (CP-456,773 or CRID3)

MCC95 is a small-molecule that non-covalently binds near the Walker B motif and blocks NLRP3 ATPase activity, potently inhibiting NLRP3 both in vivo and in vitro [176-182]. MCC950 specifically targets NLRP3 and lacks inhibitory effects againts NLRP1, NLRC4 or AIM2 inflammasome activity [176-182]. In pigs, a 7-day treatment of MCC950, at a dose of 3-6 mg/Kg, reduced neutrophil infiltration and myocardial IL-1β expression, and reduced infarct size and cardiac dysfunction [183]. Similar results have been shown in mice [184,185]. Additionaly, in a rat model of cardiac arrest and cardiopulmonary resuscitation, MCC950 reduced cardiac troponin I release and reduced mitochondrial damage, ameliorating cardiac function [186]. MCC950 also possesses cardioprotective benefits in non-ischemic cardiomyopathy, as evidenced by reductions in myocardial fibrosis and IL-1β levels in angiotensin II-induced hypertension [96]. When administered for 8 weeks (10 mg/kg, 3 times/week) in a mouse model of post-menopausal heart disease, MCC950 limited hypertrophic remodeling, improved systolic and diastolic function and reduced cardiac ANF and BNP mRNA levels [187]. The long-term use of MCC950 (20

mg/kg/daily) for 15 weeks improved autophagy flux and reduced cardiac apoptosis [188]. Mice with cardiomyocyte-specific expression of constitutively active NLRP3 spontaneously develop premature atrial contractions and are particularly prone to atrial fibrillation. These NLRP3-induced arrhytomogenic effects were attenuated by MCC950 [189]. MCC950 prevents atherosclerotic plaque development by decreasing the expression of adhesion molecules in the plaque and the number of infiltrating macrophages [182]. Twenty-five days of MCC950 treatment (10 mg/kg) can reduce blood pressure and renal inflammation in hypertensive mice [190]. In mice fed with high-fat, high-cholesterol diet or treated with angiotensin II, MCC950 inhibited the dilatation of the aorta, the dissection and rupture of aortic segments in the thoracic and abdominal tract [191].

5.3. Bay 11-7082

The synthetic kappa B kinase β (IKKβ) inhibitor, Bay 11-7082, structurally related to vinyl sulfone, alkylates the cysteine residues in the NLRP3 ATPase region, thus leading to NF-κB pathway inhibition [192]. However, independently from its IKKβ inhibitory activity, Bay 11-7082 can specifically block the NLRP3 inflammasome, without affecting other inflammasome receptors (NLRP1 and NLRC4) [192]. In experimental myocardial ischemia-reperfusion in the mouse, administration of Bay 11-7082 10 minutes before coronary artery reperfusion reduces leukocyte infiltration in the infarcted area and improves cardiomyocyte apoptosis and infarct size [193]. Likewise, pre-treatment with Bay 11-7082 alleviates myocardial damage, preserves contractility and limits ensuing fibrosis [194]. In diabetic rats undergoing cardiac ischemia-repurfusion, Bay 11-7082 attenuated NLRP3 activation, caspase-1 and IL-1β expression and pyroptosis [49]. Overall, these findings indicate that Bay 11-7082 exerts cardioprotective effects and inhibit NLRP3-mediated signaling inflammasome in multiple rodent models of ischemia-reperfusion injury. Nevertheless, since Bay 11-7082 inhibits both IKKβ and NLRP3, it remains unclear whether its beneficial effects are due to the inhibiton of NF-κB-dependent signaling or the blockade of the NLRP3 inflammasome.

5.4. OLT1177

OLT1177, is an orally available beta-sulfonyl nitrile small molecule that specifically inhibits NLRP3 by blocking its ATPase activity (Figure 3) [195-198]. Notably, OLT1177 demonstrates efficacy against constitutively active mutants of NLRP3 such as those observed in patients with cryopyrin-associated periodic syndrome [195]. In an animal models of myocardial ischemia-reperfusion, OLT1177 dose-dependently reduced the infarct size and preserved cardiac function at 24 hours and 7 days after reperfusion [199]. In permanent coronary artery occlusion models, OLT1177 preserved left ventricular contractile reserve and end diastolic pressure [200]. Importantly, OLT1177 is effective when administered up to 60 minutes after reperfusion, a scenario which resembles clinical practice in which patients receive treatment with a delay after reperfusion [199]. OLT1177 was safe and effective in reducing target joint pain in patients with gout enrolled in an open-label phase 2A study [201]. In a phase 1B, double-blind trial in patients with heart failure with reduced ejection fraction (HFrEF), 14-day treatment with OLT1177 was safe. Interestingly, in the cohort receiving the highest dose tested, an increase in the left ventricular ejection fraction and treadmill exercise time was observed (Table 1) [202].

5.5. Colchicine

Colchicine is a tricyclic alkaloid used in the treatment of gout, familial mediterranean fever, and acute and recurrent pericarditis [203,204]. Colchicine concentrates in circulating leukocytes where it interferes with NLRP3 and ASC approximation through microtubule disruption, among other effects [205]. Colchicine also inhibits neutrophil chemotaxis and diapedesis, possibly by inducing hepatic synthesis of growth differentiation factor 15 (GDF-15) without directly interfering with leukocyte function [206]. Colchicine improved survival and preserved left ventricular systolic function in mice at 4 weeks after permanent coronary artery ligation, and reduced myocardial mRNA of NLRP3 inflammasome components [207]. Among the NLRP3 inflammasome inhibitors, colchicine is the one that has been most investigated. Data from multiple clinical trials have consistently suggested that colchicine reduces the risk of ischemic cardiovascular events in patients with acute or chronic coronary artery disease (Table 1) [208-215]. Among 5522 patients with chronic coronary disease randomized to colchicine at a dose of 0.5 mg once daily or placebo, colchicine significantly reduced adverse cardiovascular events [210]. When initiated in-hospital in patients with acute coronary syndromes, colchicine may reduce the risk of recurrent coronary events - [209]. An earlier study with colchicine in patients with ST-segment elevation myocardial infarction had shown a reduction in infarct size measured with plasma biomarkers [211]. A recent randomized clinical trial of 192 patients with ST-segment elevation myocardial infarction colchicine failed to meet the primary endpoint of infarct size reduction measured at cardiac magnetic resonance [212]. While colchicine in patients with stable or chronic coronary disease has been thoroughly explored in clinical trials, further investigation is warranted to establish the effects of colchicine in the acute setting. In addition to its beneficial effects on coronary artery disease, colchicine reduces the risk of recurrence in adults with acute or recurrent pericarditis, possibly through NLRP3 inflammasome inhibition [123,216,217].

5.6. H_2S, CY-09 and IFN4E

Endogenous hydrogen sulfide (H_2S) is a gasotransmitter that exerts important physiological functions [218]. In vivo, administration of H_2S protects the cardiovascular system in several models of disease [219]. Na_2S, a H_2S donor, reduces NLRP3-dependent caspase-1 activation and pyroptosis in primary cardiomyocytes, and reduces caspase-1 activity and infarct size in mice undergoing ischemia-reperfusion injury [220]. H_2S appears to reduce inflammasome activity by acting both on the priming and trigger signals [221,222], CY-09, binds directly to the ATP-binding motif of the NLRP3 NACHT domain [223]. In mice, Cy-09 was able to protect from cardiac dysfunction associated with diabetic ischemic stroke [223]. In ex-vivo experiments using Langendorff-perfused rat hearts subjected ischemia-reperfusion, pre-treatment with IFN4E reduced infarct size and improved left ventricular pressure. Furthermore, IFN4E treatment of these hearts reduced expression of NLRP3 system components and concomitantly activated the protective RISK pathway and improved mitochondrial function [224,225]. Other structurally similar compounds have been developed but not yet tested in models of CVDs [226].

6. The role of the other inflammasome components in myocardial damage

Inhibition of the other components of the inflammasome machinery (i.e. ASC, caspase-1, IL-1β and IL-18) can block NLRP3 activation. However, since these components and substrates are shared by different inflammasomes, their inhibition may result in less specific but wider effects due to potential inhibition of the activity of other inflammasomes.

6.1. Specific role of ASC, caspase-1, and GSDMD in cardiovascular diseases

ASC knock-out mice are protected from ischemia-reperfusion injury, and display reduced levels of IL-1β [88]. ASC-deficient mice display attenuated neointimal formation after vascular injury [227]. ASC and caspase-1 knock-out mice are protected from the development of atherosclerosis, however, the reproducibility of these effects seems dependent on the atherosclerosis model used [228,229]. In humans, methylation of the *Asc* gene affects the ASC protein expression. The degree of methylated of CpG sites in the promoter region of exon 1 of *Asc* is inversely proportional to the ASC mRNA and protein expression [230]. In patients with HF (NYHA class II and III), the levels of *Asc* methylation measured in PBMCs were inversely correlated to the levels of plasma IL-1β (i.e. higher degrees of methylation corresponded to higher IL-1β levels), and directly correlated with peak VO_2 [230]. In HF patients, physical exercise increased the methylation of ASC in PBMCs, and this was associated with a significant decrease in IL-1β [231].

The clinical effects of ASC inhibition on the cardiovascular system have not been tested yet. IC100 is a monoclonal antibody of the IgG4 class that inhibits ASC polymerization in cell extracts, resulting in inhibition of the inflammasome pathway. Since the monoclonal antibody needs to cross the cell membrane to exert its inhibitory activity on ASC, IC100 efficacy should be carefully examined when used in vivo. The data from a mouse model of multiple sclerosis suggested that IC100 reduced disease severity, and the number of CD4+, CD8+ and active myeloid cells [232]. Nevertheless, since IgG4 antibodies themselves have immunomodulatory effects [233], the absence of a non-IgG4 antibody control together with the lack of direct evidence ASC/inflammasome inhibition limit the findings of the this study [232].

Cell specific overexpression of active caspase-1 in cardiomyocytes is sufficient to induce a heart failure in the mouse. In fact, caspase-1 transgenic mice develop dilated cardiomyopathy, increased ventricular fibrosis and increased expression of genes associated with cardiac failure [234]. In accordance with the observations in NLRP3- and ASC-deficient mice, caspase-1 knock-out mice display reduced levels of IL-1β and are protected from ischemia-reperfusion injury [88]. In vitro, caspase-1 inhibition on myocardial tissue strips exposed to hypoxic conditions, improves tissue contractility compared to controls [235]. Another caspase-1 inhibitor, VX795, protected rat hearts from ex-vivo ischemia-reperfusion injury [236,237].

GSDMD is responsible for forming pores into the cell membrane necessary for the release of the active IL-1β and IL-18 and then mediating inflammatory cell death [28]. There are two distinct pathways responsible for GSDMD activation, one through the NLRP3/caspase-1 pathway and one through the toll-like receptor/caspase-4 pathway (caspase-11 in the mouse)

[28,238]. In mice, cardiomyocyte-restricted conditional deletion of GSDMD significantly ameliorates infarct size and cardiac function [238]. Targeting of GSDMD may therefore represent another prominisg approach to counteract excessive inflammasome activation.

6.2. Role of IL-1β in atherosclerosis, myocardial damage and heart failure

The role of IL-1 in the development of atherosclerosis and plaque instability is well substantiated. Deletion of the IL-1 receptor type I (IL-1RI), as well as deletion of IL-1β and IL-1α, reduces the size of the plaque in mice [63]. Vromann and colleagues elegantly showed that, while IL-1α determines arterial remodeling during early experimental atherogenesis, IL-1β regulates progression of atheromas [239]. In the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) pilot trial, canakinumab, a monoclonal antibody against IL-1β, was shown to blunt inflammation without affecting low-densitiy lipoprotein cholesterol or high-density lipoprotein cholesterol [240]. These preliminary findings were confirmed by the CANTOS trial, in which canakinumab compared to placebo significantly reduced the rate of atherothrombotic events among 10061 patients with established atherosclerotic disease (Table 1) [241,242].

Modulation of IL-1 signaling following permanent coronary artery occlusion modulates the process of scar formation and ventricular remodeling. IL-1RI-deficient mice display attenuated infarct scarring and more favorable ventricular remodeling compared to wild-type mice [243]. On the other hand, deletion of IL-1 receptor antagonist (IL-1Ra), an endogenous antagonist of IL-1 signaling, worsens post-ischemic ventricular remodeling and produces a dysfunctional scar [243]. Treatment with anakinra, a recombinant form of the human IL-1Ra, or with IL-1 trap, a chimeric protein that neutralizes bot IL-1α and IL-β, reduces the myocardial remodeling in mice undergoing permanent coronary artery ligation [244-246]. Anakinra also exerts cardioprotective effects in reperfused mouse models of AMI [247]. Follow-up studies demonstrated that while the selective IL-1β inhibition using a antibody reduces the infarct size in mice that undergo ischemia-reperfusion injury, the inhibition of IL-1α has no effect on infarct size in the same model [248,249]. However, IL-1β inhibition using two different monoclonal antibodies reduces adverse remodeling and improves left ventricular contractility following permanent coronary ligation [250-252]. Three sequential double-blinded placebo-controlled phase II clinical studies (The VCUART-Virginia Commonwealth University Anakinra Remodeling Trials) tested the efficacy of anakinra in patients with ST-segment elevation myocardial infarction, and proved that the anakinra is safe and blunts the acute inflammatory response following AMI, thereby reducing the rate of new onset HF and HF hospitalization when compared to placebo [253-256]. In the MRC-ILA-Heart study, however, patients with smaller non-ST-segment elevation myocardial infarction, anakinra also reduced the acute systemic inflammatory response during AMI, but it did not result in improved clinical outcomes (Table 1) [257].

One potential advantage of using anakinra as a therapeutic strategy is the blockade of both IL-1β and IL-1α [258]. IL-1α is a member of the IL-1 family that shares high homology with IL-1β but lacks the cleavage domain for caspase-1 and therefore is not activated in the inflammasome [258]. IL-1α is active however already in its pro-form inducing a pro-inflammatory signal through the IL-1 type I receptor, and priming the cell for the

formation of the inflammasome and as such it functions as an alarmin [258]. Strategies targeting specifically IL-1α reduce inflammatory injury and infarct size [248]. IL-1α is also expressed on the cell membrane of leukocytes and regulates the systemic inflammatory response after ischemic injury [259].

Experimental studies in vitro and in vivo have shown that IL-1β impairs myocardial relaxation and contractility and alters the response to β-adrenergic stimulation in mice, even in absence of AMI or other types of acute myocardial injury [258]. Compared to the placebo, anakinra reduced the acute inflammatory response and improved the ejection fraction in hospitalized patients hospitalized with acute decompensated systolic HF [260]. In a subgroup of patients enrolled in the CANTOS trial, canakinumab reduced the rate of hospitalizations for HF [261]. In the REDHART study (Recently Decompensated Heart Failure Anakinra Response Trial), anakinra improved cardiorespiratory fitness (peak oxygen consumption), reduced levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and increased the patient quality of life [262]. The REDHART2 study is currently ongoing [263]. In the D-HART (Diastolic Heart Failure Anakinra Response Trial), anakinra was administered to patients with heart failure with preserved ejection fraction (HFpEF) and promoted significant improvements in peak oxygen consumption [264]. The D-HART2 study, conducted in the same patient population, albeit with a higher degree of obesity, showed a significant increase in treadmill exercise time, lower plasma levels of NT-proBNP, and improved quality of life measures, in absence of a significant change in peak oxygen consumption (Table 1) [265].

Rheumatic diseases have been linked to an increased risk of developing HF [266]. In these diseases, the activity of the NLRP3 inflammasome in the site of inflammation is increased and, it is associated with a systemic increase of pro-inflammatory markers, including those of the IL-1 pathway [267]. Experimental induction of arthritis promotes, indeed, remodeling of the heart in mice [268,269]. A strong link between cardiac dysfunction and the pro-inflammatory effects of IL-1β has been found in patients with rheumatoid arthritis (RA) [270]. In this patient population, recombinant IL-1Ra improved cardiovascular function within three hours after the first dose, and the effects lasted for 30 days (Table 1) [270]. Besides, independent of the presence of coronary artery disease, RA patients treated with recombinant IL-1Ra had reduced oxidative stress and improved LV contractility and relaxation. These pieces of evidence point out that extra-cardiac (or systemic) inflammasome activation affects the heart as well as the inflammasome activation in cardiac cells [270,271]. This notion is of utmost importance since systemic upregulation of the NLRP3 inflammasome and its downstream cytokines observed in several chronic conditions such obesity, diabetes, hypertension or aging, may directly impact the heart structure and function with detrimental consequences.

6.3. Role of IL-18 in cardiovascular diseases

Together with IL-1, IL-18 is one of the main NLRP3-derived cytokines. IL-18 has been implicated in several cardiovascular diseases, in which elevated plasma levels of IL-18 are found, and correlate with disease severity [272]. Following AMI, circulating IL-18 concentrations increase and predict dire outcomes [272-274]. Decompensation of

HF is associated with increased levels of IL-18 [275]. In mouse models, pretreatment with a neutralizing antibody against IL-18 reduces the infarct size [276]. Recombinant IL-18 binding protein (IL-18BP) reduces myocardial damage and inflammation following ischemia-reperfusion in a mouse model of heterotopic heart transplantation [277]. IL-18BP improves the heart function and reduced myocardial damage in a mouse model of heart donation after circulatory death ex vivo [278]. Furthermore, IL-18BP improves cardiomyocyte contractility in cultured human heart strips exposed to ischemia in vitro [235]. IL-18BP also ameliorates right ventricular function in mice exposed to chronic hypoxia for 2 weeks [279]. In a mouse model of β-adrenergic receptor overstimulation induced by high-dose injections of isoproterenol, genetic deletion of IL-18 or neutralization through anti-IL-18 antibodies reduced damage to the heart, ameliorating cardiac function and remodeling [280]. Like IL-1, IL-18 is involved in the progression of atherosclerosis in multiple models of atherogenesis in mice [281-284]. In fact, IL-18 administration to atherosclerosis-prone mice accelerates plaque development, whereas deletion of IL-18 reduces plaque development [282,283]. In contrast with these observations, one study reported increased atherosclerotic lesions in proatherogenic lacking the IL-18 gene [284]. However, another study found that IL-18 deletion prevented the development of cardiomyopathy in mice fed with a high-fat and high-sugar diet [285].

IL-18 plays a crucial role in homeostasis. Even when fed with a regular diet, mice lacking IL-18 are hyperphagic and become diabetic and obese [285,286]. When fed with a high-fat and high-sugar diet, deficiency of IL-18 induces significant gain in body weight compared to wild-type mice [283,284]. In addition, IL-18 controls the appetite in the central nervous system and the NLRP1 inflammasome regulates IL-18 physiological production [286,287].

6.4. Role of IL-6 in cardiovascular diseases

IL-6 production is induced by IL-1β, therefore IL-6 is an indirect product of the NLRP3 inflammasome [160,288]. Nevertheless, several other cytokines can control IL-6 expression and secretion [160,288]. IL-6 has powerful pro-inflammatory and pro-thrombotic effects, strongly contributing to augment cardiovascular risk [160,288]. Increased IL-6 levels predict worse outcomes across health and disease, and several IL-6 inhibitors are clinically available [289,290]. The preclinical evidence supporting the beneficial effects of IL-6 blockade in ischemia-reperfusion provided the basis for the phase II trial with the IL-6 receptor inhibitor tocilizumab [291]. In the ASSAIL-MI trial, treatment with tocilizumab was associated with a significant reduction in the systemic inflammatory response and an improvement in the myocardial salvage index in patients with ST-segment elevation myocardial infarction [291]. The positive results of the recently completed phase II RESCUE trial with ziltivekimab, an anti-IL-6 antibody, prompted the launch of a larger cardiovascular outcome trial [292]. The ZEUS trial will test ziltivekimab in patients with low-grade chronic inflammation, established atherosclerotic disease and chronic renal disease (Table 1) [290]. IL-6 directly activates membrane-bound IL-6 receptors (classical signaling), but also can complex with soluble IL-6 receptors, which then bind membrane-bound gp130 to initiate IL-6 signaling (trans-signaling) [160,288,290]. Initial evidence suggests that trans-, but not classical, IL-6 signaling contributes to atherosclerosis [293]. Whether specific inhibitors of IL-6 trans-

signaling offer better efficacy or more targeted anti-inflammatory effects in humans remains unclear.

7. Cell-specific effects of the inflammasome in the myocardium

Circulating monocytes, in which the NLRP3 inflammasome is constitutively expressed at high levels, are proptly recruited in the heart following injury [32]. On the contrary, the most abundant cardiac resident cells, such as cardiomyocytes, fibroblasts and endothelial cells, display low basal expression of the inflammasome constituents, which are strongly upregulated after priming [10,30,33]. Activation of the NLRP3 inflammasome induces secretion of IL-1β in leukocytes, endothelial cells and fibroblasts. In cardiomyocytes, the inflammasome primarily activates caspase-1 leading to pyroptotic cell death [92]. GSDMD permits release of IL-1β and IL-18 from cells after activation of the inflammasome, and mediates pyroptosis independently from cytokine production [238]. The type of response to injury depends on the nature of insult, and it appears to be cell-type-specific in the heart [92]. In the heart of patients who died from AMI, ASC was expressed in infiltrating cells [88]. However, in animal models, NLRP3 inflammasome expression also localizes in cardiomyocytes, endothelial cells, and fibroblasts [88,93,84]. Activation of the inflammasome is responsible for the pyroptotic death in cardiomyocytes [52,104]. Endothelial cells and fibroblasts exposed to ischemia release IL-1β [92-94]. In these cells, the inflammasome promotes the production of active IL-1β and IL-18. IL-18 modulates myocardial contractility, collagen deposition by fibroblasts and endothelial function [92-94]. However, except for the production of IL-1β, the specific contribution of fibroblast and endothelial NLRP3 in the early phases following acute myocardial injury has not been fully elucidated yet.

8. Conclusions

The formation and activation of the NLRP3 inflammasome with the production of IL-1β and IL-18 and inflammatory cell death – pyroptosis - have a central role in the pathogenesis of acute and chronic cardiovascular diseases, ranging from atherosclerosis to acute myocardial infarction, heart failure to pericarditis. The recent development of specific NLRP3 inflammasome inhibitors has opened the way to testing the hypothesis that targeting the NLRP3 inflammasome may improve clinical outcomes. Early phase clinical trials with targeted NLRP3 inflammasome inhibitors show promising results awaiting validation. Phase II-III clinical trials targeting cytokines downstream of the inflammasome like IL-1β and IL-6 have shown efficacy across a variety of cardiovascular conditions, and are currently under further investigation. IL-1 inhibition with rilonacept has recently become standard-of-care for the treatment of recurrent pericarditis.

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Abbreviations:

AMI	acute myocardial infarction
AT1	angiotensin receptor type 1
ATP	adenosine triphosphate
cAMP	cyclic AMP
CaMKIIδ	Ca^{2+}/calmodulin-dependent protein kinase II δ
CaSR	Ca^{2+} is the calcium-sensing receptor
COVID-19	coronavirus disease 19
CVB3	coxsackievirus B3
CVDs	cardiovascular diseases
DAMPs	damage-associated molecular patterns
DCD	donation after circulator death
ER	endoplasmic reticulum
GDF-15	growth differentiation factor 15
GSDMD	gasdermin D
HF	heart failure
HFpEF	preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
H_2S	hydrogen sulfide
IKKb	inhibitor of kappa B kinase b
IL	interleukin
IL-1Ra	IL-1 receptor antagonist
IL-18BP	IL-18 binding protein
lncRNAs	long non-coding RNAs
LRR	leucine-rich repeat
MAVS	Mitochondrial antiviral-signaling protein
MERS-CoV	Middle East respiratory syndrome coronavirus
miRs	microRNAs
mtDNA	mitochondrial DNA

NETs	neutrophil extracellular traps
NEK	NIMA-related kinases
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NLRs	nucleotide-binding oligomerization domain (NOD)-like receptors
NLRP3	NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD)-containing protein 3
NOD	nucleotide-binding oligomerization domain
NT-GSDMD	N-terminal GSDMD
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAMPs	pathogen-associated molecular patterns
PBMCs	peripheral blood mononuclear cells
PRRs	pattern recognition receptors
PYD	pyrin domain
PTS	post-thrombotic syndrome
P2X7	purinergic-type 2 receptor X7
RA	rheumatoid arthritis
ROS	reactive oxygen species
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome
TNF	tumor necrosis factor
TRX	thioredoxin
TXNIP	thioredoxin-interacting protein
VTE	venous thromboembolism

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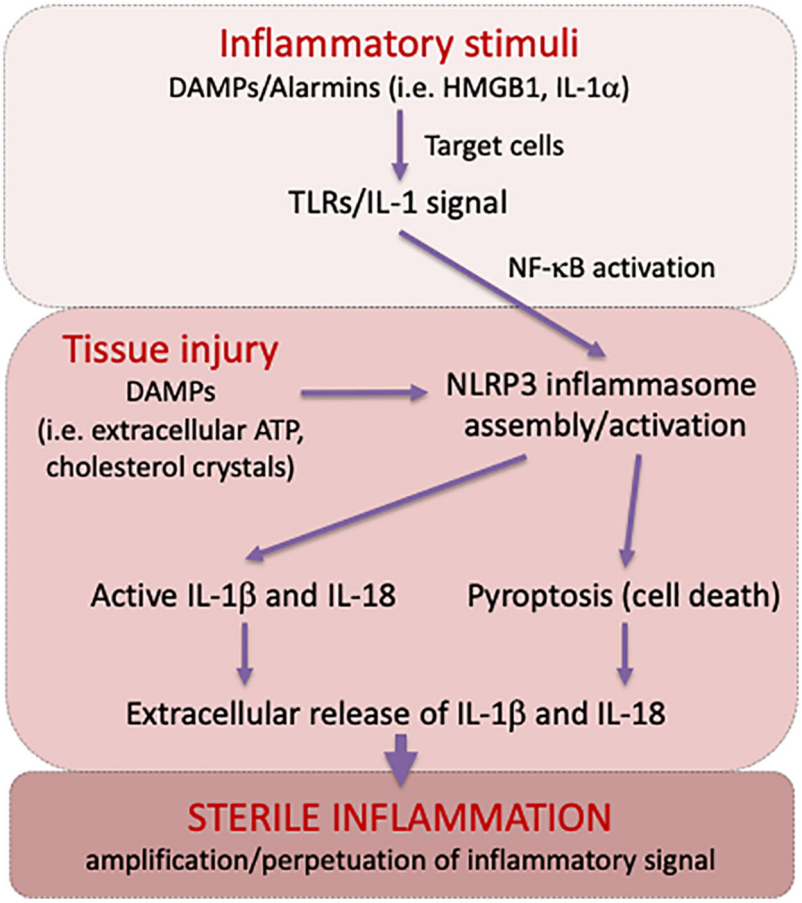

Figure 1.
Overview of the key molecular events driving the inflammatory response following tissue injury.

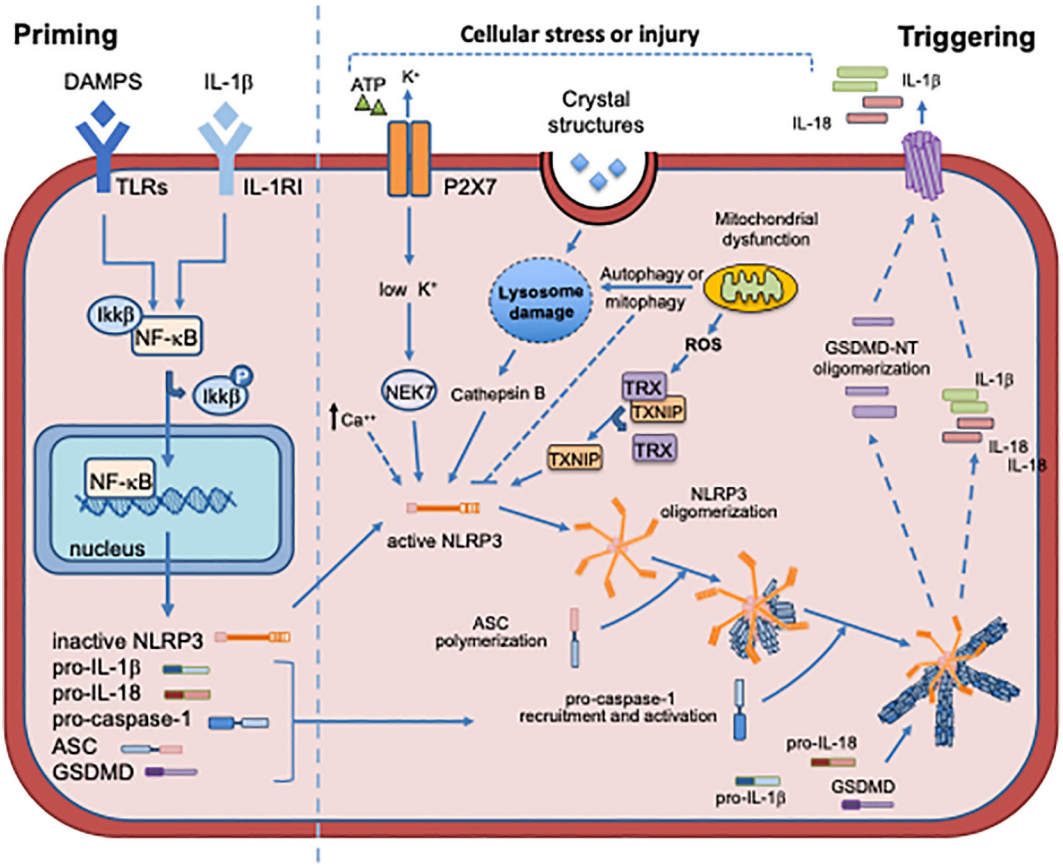

Figure 2.

Priming and triggering signals regulating the assembly and activation of the NLRP3 inflammasome. Primining signals result in the transcription, primarily through NF-κB, of the NLRP3 inflammasome components. Triggering signals result in: NLRP3 inflammasome assembly; caspase-1 activation: cleavage of pro-IL-1β and pro-IL-18 into the mature forms; cleavage of GSDMD which forms pores on the cell membrane, allowing secretion of active IL-1β and IL-18.

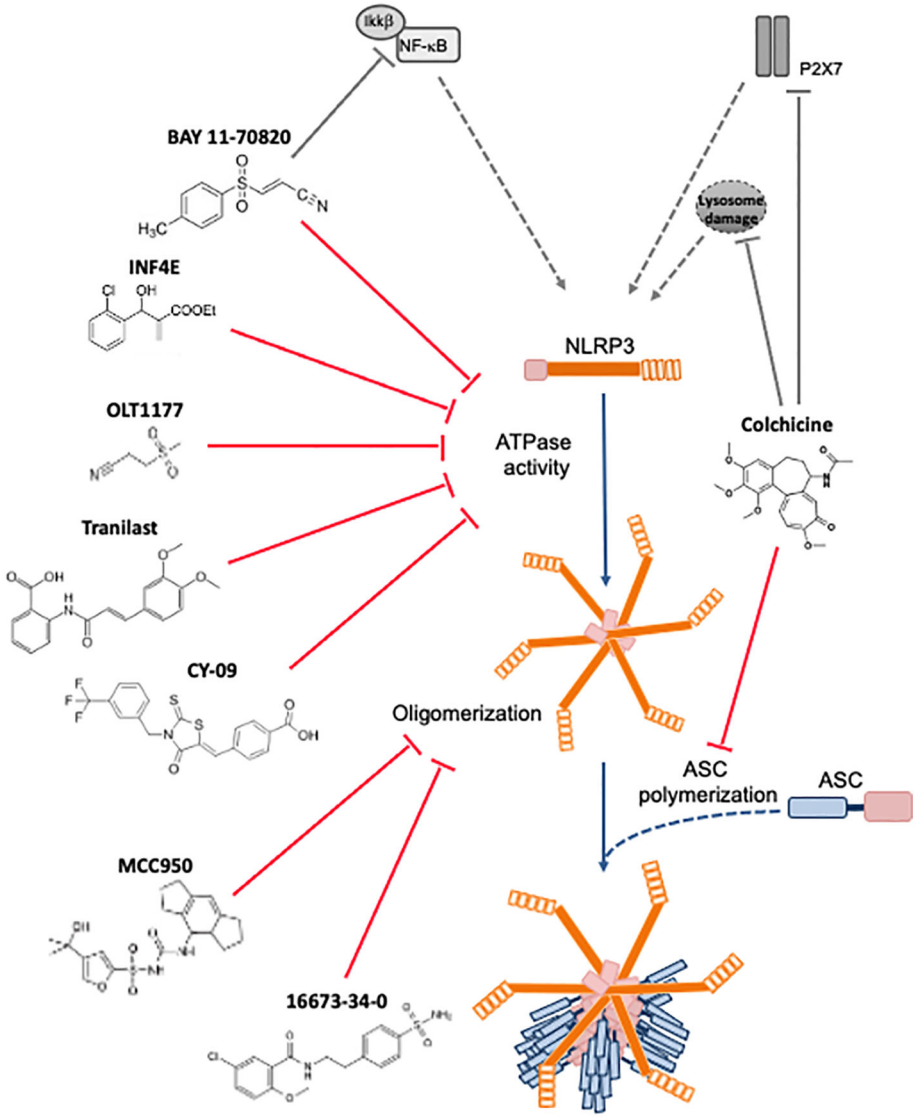

Figure 3.

NLRP3 inhibitors under clinical development in cardiovascular diseases: chemical structure, molecular target and mechanisms of action.

Table 1.

Clinical trials targeting the NLRP3 inflammasome, IL-1 and IL-6 in cardiovascular diseases.

Study (year)	Pharmacological target	Disease (Total No. of patients enrolled)	Study design	Main findings	Ref.
OLATEC-HF (2021)	NLRP3	Stable HFrEF (NYHA Class II-III) (30)	Randomization: Dapansutrile (OLT1177) or placebo 4:1 (500, 1000, or 2000 mg/day)	Treatment with dapansutrile for 14 days was safe and well tolerated in patients with stable HFrEF. Improvements in left ventricular EF and in exercise time were observed in cohort of patients receiving dapansutrile at a dose of 2000 mg/day	202
COLchicine Cardiovascular Outcomes Trial (COLCOT) (2019)	NLRP3 (non selective)	AMI < 30 days (4745)	Randomization: colchicine or placebo 1:1 (0.5 mg/day)	Colchicine led to a significantly lower risk of ischemic cardiovascular events as compared to placebo	207
Low Dose Colchicine Trial (LoDoCo) (2013)	NLRP3 (non selective)	Stable CAD (532)	Randomization: colchicine or no colchicine 1:1 (0.5 mg/day)	Colchicine on top of standard therapy was effective in preventing cardiovascular events in patients with established stable CAD	208
Colchicine in Patients with Chronic Coronary Disease (LoDoCo2) (2020)	NLRP3 (non selective)	Chronic CAD (5522)	Randomization: colchicine or placebo 1:1 (0.5 mg/day)	Colchicine significantly reduced the risk of cardiovascular events in patients with chronic CAD	210
COlchicine in Patients with ACS (COPS) (2020)	NLRP3 (non selective)	ACS (795)	Randomization: colchicine or placebo 1:1 (0.5 mg twice a day for 1 month, 0.5 mg/day for 11 months)	Colchicine in addition to standard care did not significantly affect cardiovascular outcomes at 12 months in patients with ACS and it was associated with a higher rate of mortality	213
Colchicine Therapy and Plaque Stabilization in Patients With ACS (2018)	NLRP3 (non selective)	ACS < 30 days (80)	Non-randomized: Colchicine or no colchicine (0.5 mg/day)	Low-dose colchicine therapy improved plaque morphology and reduced hsCRP	214
Colchicine in acute ST-segment elevation myocardial infarction (2015)	NLRP3 (non selective)	ACS <12 hours (151)	Randomization: Colchicine or placebo 1:1 (loading dose 2 mg followed by 1 mg/day for 5 days)	Reduction in infarct size measured by area-under-the-curve for CK-MB	211
Colchicine in acute ST-segment elevation myocardial infarction (2021)	NLRP3 (non selective)	ACS <12 hours (192)	Randomization: Colchicine or placebo 1:1 (loading dose 2 mg followed by 1 mg/day for 5 days)	No effect on infarct size, trend toward reduction in CRP at 48 hours, trend toward lower heart failure events at 3 months	212
COlchicine for Recurrent Pericarditis (CORP) (2011)	NLRP3 (non selective)	First recurrence of pericarditis (120)	Randomization: colchicine or placebo 1:1 (0.5 to 1.0 mg/day)	Colchicine reduced the risk of recurrence and at 18 months	216
Efficacy and Safety of Colchicine for Treatment of Multiple Recurrences	NLRP3 (non selective)	Recurrent pericarditis (240)	Randomization: colchicine or placebo 1:1 (0.5 to 1.0 mg/day)	Colchicine in combination with conventional anti-inflammatory therapy significantly reduced the	217

Study (year)	Pharmacological target	Disease (Total No. of patients enrolled)	Study design	Main findings	Ref.
of Pericarditis: a Multicentre, Double-Blind, Placebo-Controlled Randomised Trial (CORP-2) (2014)				rate of subsequent recurrences of pericarditis	
Effects of Interleukin-1β Inhibition with Canakinumab on Hemoglobin A1c, lipid, C-reactive protein, Interleukin-6, and Fibrinogen: a Phase IIb randomized, placebo-controlled trial (CANTOS pilot trial) (2012)	IL-1β	Subjects with well-controlled diabetes mellitus at high cardiovascular risk (556)	Randomization: Canakinum ab or placebo 1:1:1:1:1 (5, 15, 50, 150 mg monthly)	Canakinum ab significantly reduced inflammation without major effects on low-density lipoprotein cholesterol or high-density lipoprotein cholesterol	240
Canakinumab ANti-inflammatory Thrombosis Outcomes Study (CANTOS) (2017)	IL-1β	AMI > 30 days (10061)	Randomization: Canakinum ab or placebo 1:1:1:1.5 (50,150 or 300 mg monthly)	Canakinum ab significantly reduced hsCRP, the incidence of recurrent AMI and the rate of atherothrom botic events in patients with established atherosclerotic disease	241
Virginia Commonwealth University Anakinra Remodeling Trial (VCUART/VCU ART2) (2010, 2015)	IL-1β	Acute STEMI <12 hrs (40)	Randomization: Anakinra or placebo 1:1 (100 mg/day)	Anakinra reduced hsCRP and the incidence of death or new onset HF	253,254,256
Virginia Commonwealth University Anakinra Remodeling Trial 3 (VCUART3) (2020)	IL-1β	Acute STEMI < 12 hrs (99)	Randomization: Anakinra or placebo 1:1:1 (100 or 200 mg/day)	Anakinra significantly reduced the area under the curve for hsCRP at 14 days, and reduced the incidence of death or new onset HF and of death or HF hospitalization	255,256
Effects of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes (MRC-ILA Heart Study) (2015)	IL-1β	NSTEMI < 48 hrs (182)	Randomization: Anakinra or placebo 1:1 (100 mg/day)	Anakinra significantly reduced systemic inflammator y markers without improving clinical outcomes	257
Safety and Efficacy of Anakinra in Heart Failure (AIR-HF) (2012)	IL-1β	Stable HFrEF (NYHA Class II-III) (7)	Non-randomized: anakinra (100 mg/day)	Anakinra significantly reduced systemic inflammatory markers and improved peak aerobic exercise capacity and ventilatory efficiency	260
Interleukin-1 Blockade with Canakinumab to Improve Exercise Capacity in Patients with Chronic Systolic Heart Failure and hsCRP (CANTOS sub-study) (2018)	IL-1β	AMI > 30 days, Stable HFrEF (NYHA Class II-III) (15)	Randomization: Canakinum ab or placebo 1:1:1:1.5 (50,150 or 300 mg)	Canakinum ab improved peak aerobic exercise capacity and reduced the rate of hospitalizations for HF	261
REcently Decompensate d Heart failure Anakinra	IL-1β	HFrEF < 14 days post-discharge (60)	Randomization: anakinra or placebo 1:1:1 (100 mg/day for 2 or 12 weeks)	Anakinra reduced hsCRP, and improved peak aerobic exercise capacity and quality of life	262

Study (year)	Pharmacological target	Disease (Total No. of patients enrolled)	Study design	Main findings	Ref.
Response Trial (REDHART) (2017)					
REcently Decompensated Heart failure Anakinra Response Trial II (REDHART2)	IL-1β	HFrEF < 14 days post-discharge (estimated enrollment 102)	Randomization: anakinra or placebo 1:1 (100 mg/day 24 weeks)	Ongoing study	263
Diastolic Heart failure Anakinra Response Trial (D-HART) (2014)	IL-1β	Stable HFpEF (12)	Randomization: anakinra or placebo 1:1 (100 mg/day 14 days)	Anakinra reduced hsCRP, and improved peak exercise capacity and quality of life score	264
Diastolic Heart failure Anakinra Response Trial 2 (D-HART2) (2018)	IL-1β	Stable HFpEF (31)	Randomization: anakinra or placebo 1:1 (100 mg/day 12 weeks)	Anakinra treatment reduced hsCRP, increased treadmill exercise time and improved quality of life, albeit in absence of a significant change in peak oxygen consumption	265
Effects of Interleukin-1 Inhibition on Vascular and Left Ventricular Function in Rheumatoid Arthritis Patients (2008)	IL-1β	RA (23)	Randomization: anakinra or placebo 1:1 (150 mg/day)	Acute and chronic anakinra treatment reduced nitrooxidative stress and improves vascular and Left ventricular function in RA patients	270
Effects of Interleukin-1 Inhibition on Vascular and Left Ventricular Function in Rheumatoid Arthritis Patients with CAD (262)	IL-1β	RA and chronic stable CAD (80)	Randomization: anakinra or placebo 1:1 (100 mg)	Anakinra treatment improved endothelial and coronary aortic function, ameliorated left ventricular myocardial deformation and twisting	271
Effect of Anakinra on Recurrent Pericarditis among Patients with Colchicine Resistance and Corticosteroid Dependence (AIRTRIP) (2016)	IL-1β	Recurrent pericarditis (21)	Open-label anakinra followed by a double-blind withdrawal step with anakinra or placebo until pericarditis occurred (2 mg/kg per day, up to 100 mg)	Anakinra compared to placebo reduced the risk of recurrence	126
Efficacy and Safety of Rilonacept for Recurrent Pericarditis: Results from a Phase II Clinical Trial (2020)	IL-1α/IL-1β	Recurrent pericarditis (25)	Rilonacept 320 mg loading dose, followed by 160 mg weekly maintenance dose for at least 6 weeks	Rilonacept was safe, reduced background corticosteroid therapy, and led to a rapid and sustained improvement in pain, inflammation and health-related quality of life	124
Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis (RHAPSODY) (2021)	IL-1α/IL-1β	Recurrent pericarditis (86)	Randomization after a 12-week run-in period with Rilonacept: Rilonacept or placebo 1:1 (320 mg loading dose, followed by 160 mg weekly maintenance dose)	Rilonacept was associated with rapid resolution of recurrent pericarditis episodes and to a significantly lower risk of pericarditis recurrence compared to placebo	125
ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) (2021)	IL-6	STEMI < 6 hours from symptoms (199)	Randomization: tocilizumab or placebo 1:1 (280 mg)	Tocilizumab treatment reduced systemic inflammation and increases myocardial savage index	291

Study (year)	Pharmacological target	Disease (Total No. of patients enrolled)	Study design	Main findings	Ref.
Trial to Evaluate Reduction in Inflammation in Patients with Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE) (2021)	IL-6	Chronic Kidney Disease and hsCRP >2 mg/L (264)	Randomization: ziltivekimab or placebo 1:1:1:1 (7.5, 15 or 30 mg)	Ziltivekimab treatment reduced biomarkes of inflammation and thrombosis	292
Effects of Ziltivekimab Versus Placebo on Cardiovascular Outcomes in Participants with Established Atherosclerotic Cardiovascular Disease, Chronic Kidney Disease and Systemic Inflammation (ZEUS)	IL-6	Atherosclerotic Cardiovascular Disease, Chronic Kidney Disease and Systemic Inflammation (estimated enrollment 6200)	Randomization: ziltivekimab or placebo 1:1 (15 mg/month)	Ongoing study	290

Abbreviations: HF = Heart Failure, HFrEF = Heart Failure with reduced Ejection Fraction, NYHA = New York Heart Association, AMI = Acute Myocardial Infarction, CAD = Coronary Artery Disease, hsCRP = high-sensitive C-Reactive Protein, ACS = Acute Coronary Syndrome, STEMI = ST-segment elevation myocardial infarction, NSTEMI = non ST-segment elevation myocardial infarction, HFpEF = Heart Failure with Preserved Ejection Fraction, RA = rheumatoid arthritis.