

The NLRP3 Inflammasome as a Novel Therapeutic Target for Cardiac Fibrosis

Jiwen Fan¹, Meng Ren², Binay Kumar Adhikari³, Haodong Wang¹, Yuquan He¹

¹Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, People's Republic of China; ²Department of Medical Oncology, Jilin Provincial Cancer Hospital, Changchun, People's Republic of China; ³Department of Cardiology, Nepal Armed Police Force (APF) Hospital, Kathmandu, Nepal

Correspondence: Yuquan He, Department of Cardiology, China-Japan Union Hospital of Jilin University, No. 126 Xiantai Road, Changchun, People's Republic of China, Tel +86 15604411532, Email heyq@jlu.edu.cn

Abstract: Cardiac fibrosis often has adverse cardiovascular effects, including heart failure, sudden death, and malignant arrhythmias. However, there is no targeted therapy for cardiac fibrosis. Inflammation is known to play a crucial role in the disorder, and the NLR pyrin domain-containing-3 (NLRP3) inflammasome is closely associated with innate immunity. Therefore, further understanding the pathophysiological role of the inflammasome in cardiac fibrosis may provide novel strategies for the prevention and treatment of the disorder. The aim of this review was to summarize the present knowledge of NLRP3 inflammasome-related mechanisms underlying cardiac fibrosis and to suggest potential targeted therapy that could be used to treat the condition.

Keywords: NLRP3 inflammasome, cardiac fibrosis, AIM2, ASC, caspase-1

Introduction

Cardiac fibrosis is a common pathological feature of several cardiovascular diseases, leading to increased stiffness of the ventricular wall and impaired cardiac function.^{1–3} Inflammation is a crucial factor in cardiac fibrosis.⁴ Ischemia, hypoxia, and metabolic changes resulting from multiple causes lead to the infiltration of inflammatory cells and elevated levels of pro-inflammatory cytokines and chemokines.^{4,5} Interactions with damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) can lead to activation and oligomerization of NLRP3 followed by recruitment of the apoptotic speck protein containing a caspase recruitment domain (ASC) and pro-caspase-1.^{6,7} The activated caspase-1 subsequently cleaves pro-IL-1 β and pro-IL-18 to yield mature IL-1 β and IL-18. In addition, caspase-1 triggers pyroptosis by cleaving Gasdermin D (GSDMD), resulting in the binding of the GSDMD N-terminal domain to phospholipids in the cell membrane, forming a GSDMD pore.^{8,9} NLRP3 is an important mediator of both autoimmunity and myocardial fibrosis.^{10–12} Therefore, elucidating the mechanism by which the NLRP3 inflammasome influences cardiac fibrosis and summarizing potential treatments for targeting the inflammasome may suggest promising therapeutic strategies for the prevention and treatment of cardiac fibrosis.

The NLRP3 Inflammasome

The inflammatory response is a normal physiological activity of the body in response to the invasion of external pathogenic microorganisms.¹³ The inflammasome plays a key role in the inflammatory response.^{14,15} Five primary inflammasomes are currently known; these include the NLRP1, NLRP3, NLRC4, IPAF, and AIM2 inflammasomes. Among them, NLRP3 is the best-studied.^{16–18}

The NLRP3 inflammasome is a multiprotein complex formed by the receptor protein NLRP3, the bridging protein ASC, and the pro-caspase-1 effector.¹⁹ The NLRP3 component is made up of three domains: a central nucleotide-binding NACHT domain (NOD domain), a C-terminal leucine-rich repeat (LRR), and an N-terminal pyrin domain (PYD). The NACHT domain contains an ATP-binding site that mediates NLRP3 activation and IL-1 β processing. NLRP3 senses signals from pathogens, such as bacteria, and binds to and cleaves pro-caspase-1 through the bridging protein ASC. On

the one hand, the activated caspase-1 then cleaves GSDMD to form N-GSDMD which, in turn, binds to cell membrane phospholipids to form GSDMD pores, triggering pyroptosis (Figure 1A); on the other hand, activated caspase-1 also cleaves pro-IL-1 β and pro-IL-18 to generate the mature IL-1 β and IL-18, which subsequently induce an inflammatory response (Figure 1B).²⁰

Inflammasome activation is dependent on a stringent regulatory mechanism that includes priming and activation.²⁰ The priming stage is the first step.¹² Recognition of microbial ligands by Toll-like receptors (TLRs) and the stimulation of cytokines such as TNF α trigger nuclear factor kappa (NF- κ B) to upregulate NLRP3, pro-caspase-1, and pro-IL-1 transcription (Figure 1C).^{21,22} A study by Toldo et al found that the priming stage is required for NLRP3 inflammasome activation and that even overexpression of NLRP3 (constitutively active) cannot activate caspase-1 when pro-caspase-1 is insufficient.²³ The second step is the activation of the inflammasome complex by the oligomerization of NLRP3 and the recruitment of ASC and pro-caspase-1.²⁴ Different endogenous and exogenous signals can induce the assembly of different inflammasomes. For example, AIM2 is a class of DNA receptors with a C-terminal HIN200 structural domain that recognizes and binds autologous or heterologous DNA.¹⁶ NLRP3 inflammasome activation pathways are more complex and are classified according to the source of the activation signal: 1) the induction of K⁺ efflux through P2X7 receptors by extracellular ATP;^{25,26} 2) the generation of reactive oxygen species (ROS) through PAMP and DAMP activation;²⁷ 3) the formation of intracellular crystalline or granular structures leading to lysosomal rupture and the release of enzymes such as tissue protease B;²⁸ 4) endoplasmic reticulum (ER) stress; 5) autophagy dysfunction;²⁹ 6) Ca²⁺ overload. The most common activation mechanism is K⁺ efflux resulting from bacterial toxins and particulate matter.³⁰ Several recent studies have found that NEK7 plays a key role in this process^{31,32} and that NEK7 knockout in mice inhibits both NLRP3 inflammasome activation and IL-1 β production.³³

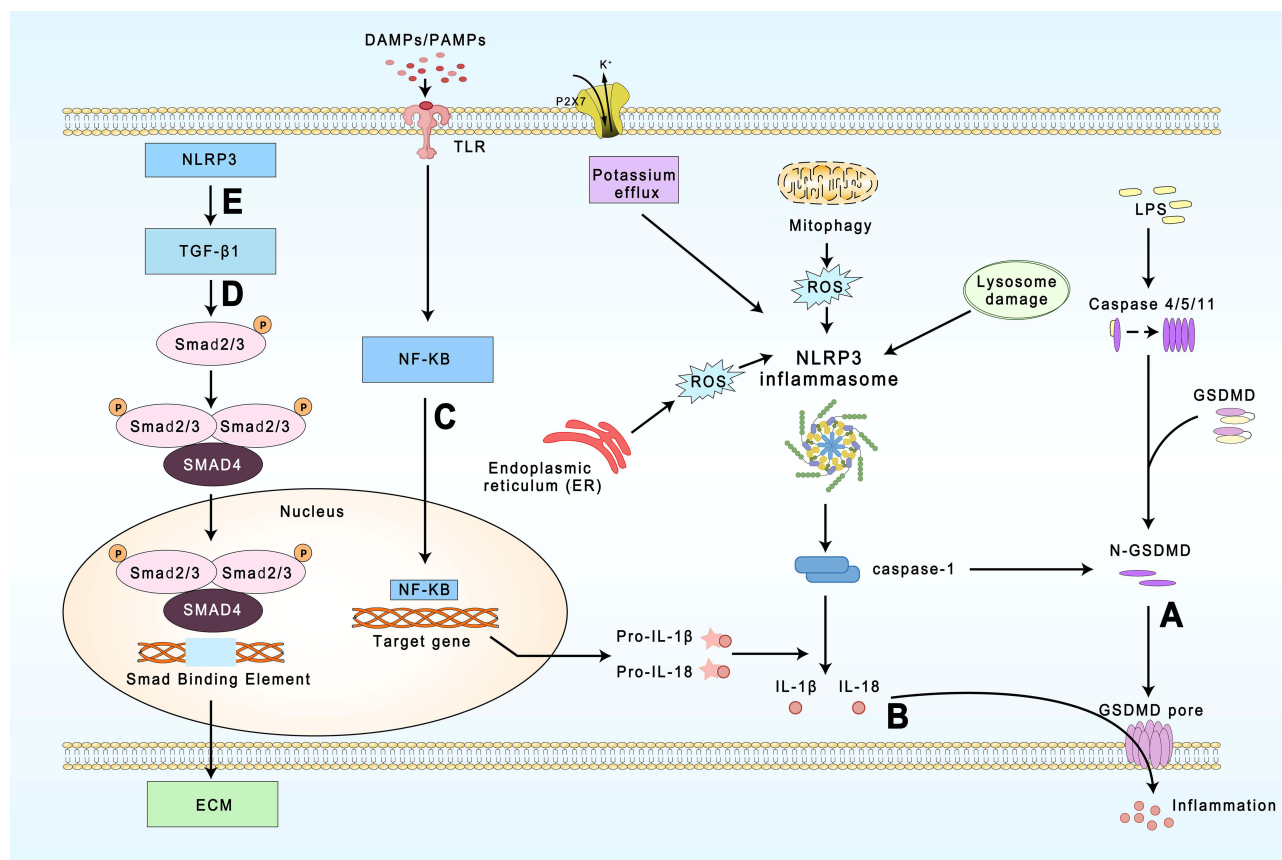


Figure 1 Regulation and function of NLRP3 inflammasome during cardiac fibrosis. (A) Caspase-1 activated by NLRP3 as well as caspase-4,5 and caspase-11 in the non-classical pathway are able to trigger pyroptosis. (B) Caspase-1 cleaves and activates pro-IL-1 β and pro-IL-18, and is released extracellularly through the GSDMD pore. (C) The priming stage of NLRP3 inflammasome. (D) and (E) TGF- β /Smad is an important pathway leading to cardiac fibrosis and NLRP3 is capable of regulating it.

The Golgi apparatus plays an important role in the transportation of newly synthesized proteins from the ER and is also closely involved in innate immunity.³⁴ Interruption of ER-Golgi transport has been found to block both NLRP3 inflammasome assembly and caspase-1 activation.^{35,36} After activation, NLRP3 interacts with the ER sterol regulatory element-binding protein 2 (SREBP2) and the SREBP cleavage-activating protein (SCAP) to form the NLRP3-SCAP-SREBP2 triplex. After entry of NLRP3-SCAP-SREBP2 into the cis-Golgi network (CGN), NLRP3 dynamically traverses the Golgi to the trans-Golgi network (TGN), where it is phosphorylated by protein kinase D (PKD).³⁷ In addition, a variety of NLRP3 activators can cause the breakdown of the TGN, and phosphatidylinositol-4-phosphate (PtdIns4P) on the dispersed TGN (dTGN) becomes the “site” of NLRP3 inflammasome aggregation and assembly. In addition to phosphorylating NLRP3, PKD can activate NLRP3 through phosphatidylinositol-4 kinase 3 β .³⁸

Pathogenesis of Cardiac Fibrosis

Cardiac fibrosis is an alteration of myocardial cells and the myocardial interstitium caused by a variety of pathological factors. It leads to abnormalities in cardiac function and metabolism and is commonly seen at the end-stage of several cardiovascular diseases.^{2,3,39} Cardiac fibrosis results from both the differentiation of cardiac fibroblasts and excessive accumulation of extracellular matrix (ECM), leading to myocardial stiffness and reduced compliance of the ventricular wall.^{40,41} Cardiac fibroblasts are major matrix-producing cells, and represent one of the largest cell populations in normal mammalian hearts and are closely involved in the maintenance of normal cardiac function as well as cardiac remodeling in pathological states.^{42,43} The presence of fibroblasts in the healthy heart suggests that they may play a role in homeostasis in vivo. The fibroblasts are activated after cardiac injury, leading to their differentiation into myofibroblasts, which are the cells principally responsible for pathological cardiac remodeling.⁴⁴ Fibrogenic signaling cascades are triggered by fibrogenic growth factors (including TGF- β and PDGFs), cytokines (including TNF α , IL-1, IL-6, and IL-10), and neurohumoral pathway components binding to surface receptors and the subsequent activation of downstream signaling cascades.⁴⁵ Current research has revealed a close connection between the well-studied TGF- β /Smad signaling pathway and cardiac fibrosis, affecting both the secretion and degradation of ECM components and myofibroblast differentiation (Figure 1D).⁴⁶ In addition, the involvement of the innate immune system in the regulation of heart functioning and remodeling is well-documented.⁴⁷

The NLRP3 Inflammasome in the Development of Cardiac Fibrosis

Cardiac fibrosis is a pathological condition common to a variety of cardiovascular diseases and is characterized by excessive ECM deposition resulting in tissue damage and organ dysfunction. The NLRP3 inflammasome has been associated with the development of cardiac fibrosis.³⁶ Increasing experimental evidence indicates that NLRP3 inflammasome expression is elevated in fibrotic cardiac tissue and, conversely, that cardiac fibrosis is mitigated by inflammasome inhibition.^{48,49} Louwe et al reported that transplantation of *Nlrp3*^{-/-} bone marrow in mice after myocardial infarction attenuated cardiac remodeling compared with wild-type bone marrow, suggesting that the absence of the NLRP3 inflammasome in hematopoietic cells reduces adverse remodeling.⁵⁰ Previous studies have demonstrated that TGF- β stimulation regulates NLRP3 inflammasome activation.^{28,51} However, recent research has found that TGF- β signaling pathways are regulated by NLRP3, rather than the reverse situation of TGF- β regulating NLRP3 (Figure 1E). Cáceres et al reported that serelaxin, which targets the expression of both TLR-4 and the NLRP3 inflammasome, reduced the levels of TGF- β 1 and IL-1 β in cardiac myofibroblasts.⁵² Research in this area is still in a preliminary stage, and further information is needed to clarify these interactions in cardiac fibrosis. The selective NLRP3 inhibitor MCC950 has been shown to be effective in treating a variety of inflammatory diseases in which NLRP3 is involved.⁵³ A study by Gao et al found that in mice with induced myocardial infarction, MCC950 was able to reduce cardiac fibrosis and improve cardiac function by inhibiting NLRP3 inflammasome expression in cardiac fibroblasts.⁵⁴ Animal studies have shown that angiotensin II activates the NLRP3 inflammasome, leading to cardiac fibrosis and the inflammatory response, and that these pathological changes can be reversed by MCC950.⁵⁵

Hypertension is also one of the major diseases that endanger human health. Persistent hypertension can lead to left ventricular hypertrophy and myocardial fibrosis, which is a determinant of heart failure and a risk to human health. NLRP3 plays an important role in the pathogenesis of hypertensive cardiac fibrosis (Figure 2). A study by Lv et al found

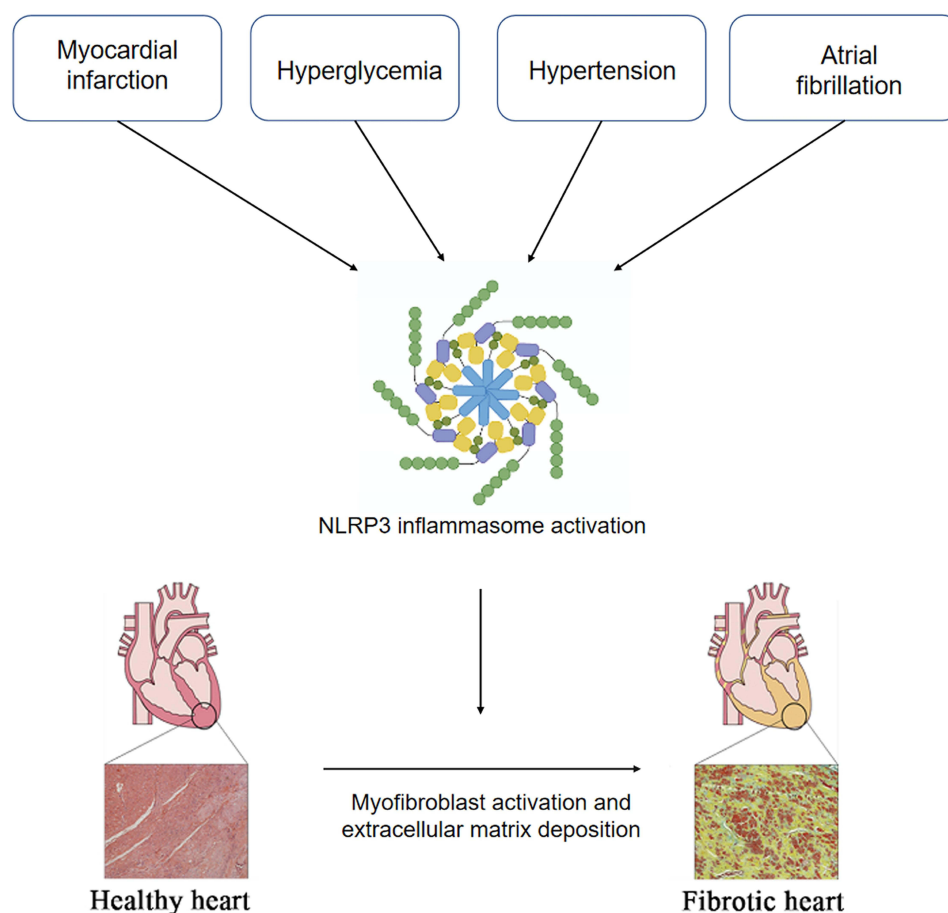


Figure 2 NLRP3 inflammasome activation in cardiovascular diseases to promote cardiac fibrosis. Under pathological conditions, such as myocardial infarction, hypertension, and hyperglycemia, atrial fibrillation, NLRP3 inflammasome in cardiomyocytes and fibroblasts are activated, collaboratively promoting the inflammatory cascade and pyroptosis. The resultant cardiac inflammation triggers myofibroblast activation and cardiac fibrosis.

that the expression of NLRP3 and IL-1 β was significantly elevated in cardiac tissues in mouse model of angiotensin 2 (Ang II) infusion-induced hypertension, with a facilitative effect on the conversion of fibroblasts to myofibroblasts.⁵⁶ Triptolide, an immunomodulator, exerts dose-dependent anti-cardiac fibrosis effects by inhibiting both the activation of the inflammasome and the release of IL-1 β in AngII-stimulated cardiac fibrosis.⁵⁷

The rupture of unstable coronary atherosclerotic plaques is the main cause of acute myocardial infarction, and the ischemic necrotic myocardium can release large amounts of ATP and oxidative stress products (reactive oxygen species) to activate the NLRP3 inflammasome. Kawaguchi et al examined myocardial tissue from patients with myocardial infarction and found that the main inflammatory cell infiltrates at infarction site were macrophages and neutrophils and that the ASC expression levels were significantly elevated in these cells.⁵⁸ As ASC is a component of the NLRP3 inflammasome, this increased expression suggests that NLRP3 inflammasomes in immune cell infiltrates are involved in pathological processes in the myocardial tissue after myocardial infarction.⁵⁹ Kawaguchi et al treated isolated cultured cardiomyocytes and cardiac fibroblasts from neonatal mice with LPS and found that LPS significantly induced IL-1 β production in cardiac fibroblasts from wild-type mice while reducing its production in the cardiac fibroblasts of ASC-/- mice. In contrast, LPS did not affect IL-1 β production in cardiomyocytes.⁵⁸ Sandanger et al observed the expression of NLRP3, IL-1 β , and IL-18 mRNA in the ventricular myocardia of mice after the induction of myocardial infarction by ligation of the coronary arteries, and found that the expression levels of NLRP3, IL-1 β , and IL-18 mRNA were significantly higher in the myocardial infarction group compared with the sham group and that this elevation was mainly associated with cardiac fibroblasts. In addition, they also created an ischemia-reperfusion model using NLRP3-knockout mice, observing significantly improved cardiac function and reduced ischemic damage in the knockout mice compared

with their wild-type counterparts.⁶⁰ These *in vivo* experimental studies suggest that NLRP3 inflammasomes play an important role in myocardial infarction and ischemia-reperfusion injury, and that intervention in the processes of NLRP3 inflammasome activation may provide useful clinical applications for improving myocardial fibrosis and cardiac remodeling after myocardial ischemia-reperfusion injury (Figure 2).

The inflammasome has also been found to be activated by hyperglycemia and to contribute significantly to the cardiac fibrosis typical of diabetic cardiomyopathy (DCM)(Figure 2).^{61–63} Hyperglycemia leads to a dramatic elevation in mitochondrial ROS generation and reduces the body's antioxidant capacity.^{64,65} Under normal conditions, the oxidoreductase thioredoxin (TRX) binds to the thioredoxin-binding protein (TXNIP), inhibiting its activity. Overproduction of ROS leads to the dissociation of the TXNIP-TRX complex, and the subsequent binding of TXNIP to NLRP3 to induce inflammasome assembly.^{66,67} A study by Che et al suggested that inhibition of the NLRP3 inflammasome significantly ameliorated cardiac function and collagen production in diabetic mice.⁶⁸ Knockdown of dual oxidase 1 (DUOX1) has been observed to inhibit the ROS-dependent pyroptosis pathway and reverse activin A-induced cardiac fibrosis.⁶⁹ Zhang et al showed that hyperglycemia-induced overproduction of ROS and activation of P2X7R increased NLRP3 inflammasome expression and that this activation of the NLRP3 inflammasome activation was essential for collagen synthesis.⁷⁰ In contrast, H3 relaxin effectively inhibited both ROS production and P2X7R activation and attenuated myocardial fibrosis. In addition, a study by Yao et al found that combined treatment with syringin and tilianin in diabetic rats prevented mitochondrial membrane depolarization and ROS production, while decreasing NLRP3 expression and improving cardiac function.⁷¹

Atrial fibrillation(AF) is the most common cardiac arrhythmia, and its prevalence in the population increase annually.⁷² Although the mechanisms responsible for AF have not been fully elucidated. Recent studies have found an association between AF, NLRP3 inflammasome and cardiac fibrosis and AF (Figure 2).^{73–75} Expression of the NLRP3 inflammasome has been found to be elevated in the atrial cardiomyocytes of individuals with paroxysmal and chronic AF. Yao et al established a cardiomyocyte-specific knock-in mouse model expressing constitutively active NLRP3 (CM-KI) and found that CM-KI mice developed spontaneous premature atrial beats and induced atrial fibrillation that were able to be reversed by the NLRP3 inhibitor MCC950.⁷⁶ In addition, obesity is a known risk factor for atrial fibrillation and is associated with an enhanced inflammatory response.^{77–79} Recent studies have shown that obesity-induced atrial arrhythmias are driven by atrial NLRP3 inflammasomes, providing a molecular link between obesity-induced atrial fibrillation and NLRP3 inflammasome activation.⁸⁰ Qiu et al reported that salvianolate may attenuates atrial fibrillation and interstitial fibrosis by suppressing the TXNIP/NLRP3 inflammasome signaling pathway in post-MI rats.⁷⁵

Autophagy is associated with NLRP3 inflammasome-mediated cardiac fibrosis. Autophagy is a cellular self-digestion mechanism for the cell's own metabolic needs and the recycling of organelles and other cellular material.⁸¹ Autophagy negatively regulates inflammasome activation by suppressing intracellular ROS production.⁸² Autophagy was found to be impaired in a mouse model of cardiac injury with isoproterenol injection and ligation of the left anterior descending artery, leading to reduced cardiac fibrosis; antifibrotic treatment with aspirin significantly ameliorated cardiac fibrosis, while rapamycin, an autophagy promoter, was able to counteract cardiac fibroblast promotion, suggesting that autophagy plays an important role in the development of cardiac fibrosis.⁸³

Pyroptosis is a form of programmed cell death, characterized by persistent cell distension resulting in rupture of the cell membrane and the discharge of cellular contents, triggering an inflammatory reaction.^{84,85} The classical pyroptotic pathway is activated by the presence of pathogens, bacteria, and other signals, and leads to the interaction of NLRP3 with the ASC N-terminal PYD domain and the recruitment and cleavage of pro-caspase-1.⁸⁴ The cleaved caspase-1 product then promotes the secretion of IL-1 β and IL-18 into the extracellular space, leading to inflammatory necrosis of the cell. The nonclassical pyroptotic pathway is triggered by other members of the caspase family, namely, caspases-4 and -5 in humans and caspase-11 in mice.^{86,87} Pyroptosis is also capable of leading to cardiac fibrosis.^{88,89} Clinical studies have shown that both structural changes in the heart and the presence of fibrosis after myocardial infarction severely interfere with the treatment of heart failure.^{90,91} Nie et al found that hydrogen gas inhalation by rats with myocardial infarction blocked NLRP3-mediated pyroptosis and ameliorated myocardial infarction-induced cardiac remodeling and fibrosis.⁶⁴ Luo et al reported that silencing the NLRP3 gene in a rat model of type 2 diabetes reduced cardiomyocyte pyroptosis and cardiac fibrosis, together with slowing the progression of DCM.⁹² Furthermore, NLRP3 derived from the mitochondria in

cardiac fibroblasts was able to promote fibrotic signaling, regulate mitochondrial ROS production, and modulate fibroblast differentiation by a novel mechanism independent from the inflammasome.²⁸ To summarize, pyroptosis has the potential to be a therapeutic target for the treatment of cardiac fibrosis in the future.

The NLRP3 Inflammasome as a Target for Pharmacological Inhibition

In the previous sections of this review, we have discussed the mediation of inflammatory responses by the NLRP3 inflammasome and its role in the development of cardiac fibrosis. This evidence suggests that targeting the NLRP3 inflammasome and its associated factors may be effective for treating cardiac fibrosis (Table 1).

NLRP3 Inhibitors

Research over the past few decades has identified various agents that block NLRP3 activation. These include MCC950, INF4E, Tranilast, OLT1177, Cy-09, JC-124, allopurinol, colchicine, vincristine, and hydrogen gas.⁹³ MCC950 is a selective inhibitor of the NLRP3 inflammasome and does not affect NLRP1 and AIM2 inflammasomes.⁵³ It inhibits

Table 1 Cardiac Fibrosis Therapies Targeting the NLRP3 Inflammasome Pathway

Drugs	Disease Model	Mechanism	References
MCC950	Coronary artery ligation	Binds noncovalently to NLRP3 and prevent ASC oligomerization	[54]
INF4E	Hearts isolated and perfused following myocardial I/R	Inhibits the NLRP3 ATPase activity	[93]
Tranilast	Coronary artery ligation	Suppresses NLRP3 inflammasome and reduce collagen synthesis	[97]
OLT1177	Hearts isolated and perfused following myocardial I/R	Block ATPase activity of NLRP3 and inhibits NLRP3 oligomerization	[95]
Cy-09	Coronary artery ligation	Binds directly to the ATP-binding motif of the NACHT domain, inhibiting NLRP3 assembly and ATPase activity.	[94]
Hydrogen gas	Coronary artery ligation	Reduces the expression of NLRP3-mediated pyroptosis-related protein and alleviates collagen synthesis	[64]
Vincristine	ISO-induced cardiac fibrosis	Downregulated the colocalization of NLRP3 and ASC, and directly inhibited NLRP3 inflammasome activation	[107]
VX-765	Hearts isolated and perfused following myocardial I/R	Inhibits caspase-1 activation.	[112]
VX-740	Type II collagen-induced arthritis	Inhibits caspase-1 activation.	[111]
AC-YVAD-CMK	SHR	Inhibits caspase-1 activation.	[115]
Canakinumab	Patients with previous myocardial infarction	Specifically inhibits IL-1 β	[118]
Anakinra	Patients with COVID-19	Antagonise human IL-1 receptor	[121]
Allopurinol	Fructose-induced metabolic syndrome	Suppresses NLRP3 inflammasome and alleviates cardiac fibrosis	[102]
Colchicine	Coronary artery ligation	Prevents P2X7-related pyroptosis and inhibits NLRP3 inflammasome assembly	[105]
Metformin	STZ-induced diabetes	Inhibits NLRP3 inflammasome and promotes autophagy.	[123]
Empagliflozin	TAC-induced HF	Inhibits NLRP3 inflammasome, and reduces pro-inflammatory cytokines.	[126]
Emodin	LPS-induced myocardial injury	Inhibits NLRP3 inflammasome-mediated pyroptosis and alleviates cardiac inflammation.	[131]
HQQR	SHR	Inhibits pyroptosis and alleviates cardiac fibrosis.	[115]
Triptolide	ISO-induced cardiac fibrosis	Inhibits NLRP3 inflammasome assembly and NLRP3-TGF- β 1-Smad signaling pathway activation	[57]
Salvianolate	Coronary artery ligation	Inhibits TGF- β 1/Smad2/3 and TXNIP/NLRP3 inflammasome signaling pathways	[75]

Abbreviations: ASC, adaptor protein apoptosis-associated speck-like protein; NLRP3, nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing protein 3; SHR, spontaneously hypertensive rats; HF, heart failure; I/R, ischemic/reperfusion; COVID-19, Corona Virus Disease 2019; STZ, Streptozotocin; LPS, Lipopolysaccharide; TAC, transverse aortic constriction; ISO, isoproterenol; HQQR, Huoxue Qianyang Qutan recipe.

ATPase activity and prevents the formation of the NLRP3 oligomer and has been shown to effectively ameliorate cardiac fibrosis in mice with myocardial infarction.⁵⁴ CY-09 and OLT1177 prevent ASC polymerization and inflammasome assembly.^{94,95} Tranilast binds directly to the NACHT domain of NLRP3, preventing the interaction between NLRP3 and ASC.^{96–98} Tranilast also reduces collagen synthesis, but the mechanism is unclear.⁹⁹ Hydrogen gas reduces inflammasome levels and has anti-inflammatory effects.¹⁰⁰ A study by Nie et al observed that hydrogen inhalation reduced the levels of pyroptosis-related proteins after NLRP3 activation and also reduced collagen synthesis in rats with myocardial infarction.¹⁰¹ Allopurinol is a xanthine oxidase inhibitor used primarily for treating gout. Kang et al reported that allopurinol alleviated cardiac fibrosis and inflammation induced by fructose by counteracting CD36-mediated TLR4/6-IRAK4/1 signaling to prevent NLRP3 inflammasome activation.¹⁰² Colchicine is an alkaloid that is also used for treating gout and familial Mediterranean fever due to its potent anti-inflammatory effects.^{103,104} Colchicine can prevent P2X7-mediated pyroptosis and inhibit NLRP3 inflammasome activation.^{105,106} Vincristine reduced the colocalization of NLRP3 and ASC, and directly inhibited NLRP3 inflammasome activation and cardiac fibrosis in LPS-ATP-stimulated cardiac fibroblasts.¹⁰⁷ Further research is required to verify the clinical applicability of these NLRP3 inflammasome-targeting compounds.

Inhibition of Caspase-1, IL-1 β , and IL-18

Considering that the NLRP3 inflammasome is a multiprotein complex, targeting other components of the complex or the products of the inflammasome may also be a useful treatment for cardiac fibrosis. VX-765 (belnacasan) and VX-740 (pralnacasan) are selective caspase-1 inhibitors.¹⁰⁸ VX-765 and VX-740 are structurally similar and are both precursor drugs that are converted in the presence of plasma esterase to the active metabolites VRT-043198 and VRT-18858, which selectively inhibit caspase-1.^{109–112} However, clinical trials of VX-740 and VX-765 were discontinued due to hepatotoxicity observed in animal toxicity studies.^{109,113} AC-AC-YVAD-CMK is also an irreversible caspase-1 inhibitor that increases cell permeability.¹¹⁴ A study by Lu et al showed that AC-YVAD-CMK has an antifibrotic role through its inhibition of NLRP3 inflammasome signaling in obese hypertensive rats.¹¹⁵ In addition, it was also found that AC-YVAD-CMK was able to downregulate pressure overload-induced cardiomyocyte pyroptosis and improve cardiac function at both in vivo and in vitro levels.¹⁰⁸

IL-1 β is a key factor in the innate immune system.²⁶ IL-1 β expression is significantly elevated in cardiovascular disease and cardiac fibrosis.^{107,116} The human monoclonal antibody canakinumab binds and inhibits IL-1 β .¹¹⁷ In a study involving 10061 patients with preexisting myocardial infarction, canakinumab was found to significantly reduce the inflammatory response.¹¹⁸ In addition to monoclonal antibodies, IL-1 receptor antagonists can also block IL-1 signaling. Anakinra, a human IL-1 receptor antagonist produced by genetic recombination technology, is the only FDA-approved drug used in neonatal-onset multisystem inflammatory disease (NOMID).^{119,120} A retrospective analysis found that anakinra treatment reduced the levels of high-sensitivity C-reactive protein and increased potassium and calcium fluxes in 29 COVID-induced ARDS patients, leading to a significant increase in 21-day overall survival (90% vs 56%).¹²¹ However, due to the small patient base and single-center nature of the study, the results need to be verified by a multicenter prospective study design.

Other Anti-Fibrotic Drugs

Metformin is used for treating type 2 diabetes either alone or in combination with other hypoglycemic agents.¹²² Yang et al reported that metformin blocks the NLRP3 inflammasome through inhibition of the AMPK/mTOR pathway, and improves cardiac fibrosis in mice with diabetic cardiomyopathy.¹²³ Empagliflozin (EMPA) selectively inhibits the sodium-glucose co-transporter 2. Recent clinical trials have shown that EMPA can reduce the risk of hospitalization for heart failure and cardiovascular death in patients with type 2 diabetes.^{124,125} Moreover, EMPA has also been shown to be effective in reducing cardiac fibrosis and inflammation by preventing NLRP3 inflammasome activation in two rodent models of heart failure.¹²⁶

Various Chinese medicinal herbs have also been shown to block both NLRP3 inflammasome activation and the development of cardiac fibrosis. Triptolide, a compound isolated from a Chinese medicinal herb, has demonstrated anticancer activities against a variety of tumor types, including leukemia, breast cancer, and lung cancer.^{127,128} Pan et al

reported that triptolide prevented NLRP3 inflammasome assembly and activation of the NLRP3-TGF- β 1-Smad signaling pathway, reducing myocardial hypertrophy and fibrosis caused by pressure overload.⁵⁷ Huoxue Qianyang Qutan recipe (HQQR) is a widely used Chinese herbal compound that can reduce blood pressure and improve lipid metabolism in obese hypertensive patients.^{115,129} Recent findings have reported that HQQR could reduce cardiac fibrosis by inhibiting the NLRP3 inflammasome signaling pathway in obese hypertensive rats.¹¹⁵ Emodin is a natural medicine that is effective for treating several chronic diseases; it has various pharmacological properties, including antioxidant, antimicrobial, antidiabetic, and immunosuppressive effects.¹³⁰ A study by Xiao et al found that Emodin has anti-fibrotic action through the suppression of NLRP3 inflammasome activation induced by LPS.¹³¹ Overall, these findings suggest potential treatments for cardiac fibrosis by targeting the NLRP3 inflammasome.

Conclusion

The NLRP3 inflammasome is a signaling protein complex with wide spread expression in cardiovascular tissues and cells. As it is able to be activated by a wide variety of pathogens and danger signals, the NLRP3 inflammasome plays an important role in cardiac fibrosis associated with atherosclerosis, myocardial infarction, diabetic cardiomyopathy, atrial fibrillation, and many other cardiovascular diseases. Targeting NLRP3 inflammasome signaling may thus be a promising treatment for cardiac fibrosis, as inhibition of the NLRP3 inflammasome and its associated signaling may both improve cardiac function and reduce cardiac fibrosis. Furthermore, Chinese herbal extracts have recently attracted attention for their ability to alleviate cardiac fibrosis, although their underlying mechanisms of action have yet to be verified. Currently, most of the evidence is provided by animal and in vitro cell experiments, and the clinical efficacy of these potential treatments is still unclear. Thus, further investigations are required in the future.

Disclosure

The authors report no conflicts of interest in this work.

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