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Advances in the Role of NLRP3 Inflammasome in Cardiovascular Diseases

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Abstract: The NLRP3 inflammasome is a critical multiprotein signaling platform that activates caspase-1, leading to the maturation of pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18, and triggering inflammatory responses. Inflammation has been implicated as a significant process in cardiovascular diseases. The activation of the NLRP3 inflammasome is associated with the pathogenesis of cardiovascular diseases, including hypertension, atherosclerosis, and heart failure. This article provides an overview of the role, mechanisms, and potential therapeutic interventions related to the activation of the NLRP3 inflammasome in the occurrence and development of cardiovascular-related diseases.

1. Introduction

In recent years, the incidence and mortality rates of cardiovascular diseases (CVD) have been gradually increasing, surpassing those of cancer and posing a significant threat to human health [1]. Inflammasomes were initially reported by Martinon et al. in 2002 and have been shown to mediate the activation of inflammatory mediators, representing a crucial branch of the innate immune system. Inflammation has garnered considerable attention in cardiovascular diseases, and both clinical and experimental data have demonstrated that canakinumab, an anti-inflammatory and anti-thrombotic agent, reduces the risk of cardiovascular events by inhibiting the NLRP3 inflammasome and its associated pathways, as well as the anti-inflammatory effects of colchicine [2]. Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) is a polymeric protein complex and the most extensively studied and characterized inflammasome within the NOD-like receptor (NLR) family. It is characterized by its ability to be activated by a diverse range of stimuli, irrespective of their quantity, origin, structural properties, or chemical composition [3]. Excessive activation of NLRP3 plays a crucial role in cardiovascular diseases such as hypertension, atherosclerosis, myocardial ischemia-reperfusion injury, and heart failure. This article aims to elucidate the relationship between NLRP3 inflammasome activation and the occurrence and development of cardiovascular diseases.

2. The structure of NLRP3 inflammasome

NLRP3 (NOD-like receptor protein 3) is a sensor molecule that plays a central role in the formation of the NLRP3 inflammasome, which is a multiprotein complex involved in the innate immune response against pathogens and self-damage [4]. Among the various types of inflammasomes discovered, NLRP3 within the NOD-like receptor family has been extensively studied. The activation of the NLRP3 inflammasome is primarily triggered by pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), leading to the initiation of immune responses and the secretion of inflammatory factors.

The NLRP3 inflammasome consists of three main components: the sensor molecule NLRP3 protein, the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and the effector caspase-1. The sensor protein has a carboxy (C)-terminal, a central domain, and an amino (N)-terminal domain. The C-terminal and central domains are responsible for ligand recognition and oligomerization, respectively. The N-terminal domain contains a pyrin domain (PYD), which recruits ASC to mediate downstream signaling and initiate a cascade of inflammatory responses [5].

3. Startup and activation of NLRP3

NLRP3 inflammasome activation involves several stages, including the activation of nuclear factor-kappa B (NF-κB) through the interaction of PAMPs, DAMPs, Toll-like receptors (TLRs), or cytokines. This activation leads to the expression and activation of NLRP3, pro-IL-1β, and pro-IL-18, which in turn mediate the deubiquitination of NLRP3 and the phosphorylation of ASC. There are three known modes of NLRP3 inflammasome activation: the classical pathway, the non-classical pathway, and the alternative pathway.

In the non-classical pathway, caspase-11 in mouse macrophages is spontaneously activated and cleaves gasdermin D into its N-terminal and C-terminal domains. The N-terminal domain of gasdermin D forms pores on the lipid membrane, leading to the release of IL-1β and IL-18 and pyroptotic cell death [4]. The alternative pathway refers to the activation of the NLRP3 inflammasome in human monocytes, where lipopolysaccharide (LPS) is recognized by TLR ligands, resulting in the release of endogenous ATP and the activation of the P2X7 receptor, which triggers NLRP3 inflammasome activation.

In the classical pathway, there are three well-known activation mechanisms. The first is potassium efflux, which is a common triggering factor for upstream signaling of NLRP3 inflammasome activation. When the intracellular potassium concentration is <90 mmol/L, spontaneous formation of the NLRP3 inflammasome occurs, and inhibiting potassium concentration suppresses its activation. Extracellular ATP recruits and activates the purinergic P2X7 receptor and the pannexin-1 hemichannel, leading to potassium efflux, which subsequently activates the NLRP3 inflammasome.

The second mechanism is calcium (Ca^{2+}) signaling. ATP and other stimuli can trigger the release of Ca^{2+} from the endoplasmic reticulum or extracellular space, leading to mitochondrial damage and subsequent activation of the NLRP3 inflammasome. Studies have reported that the Ca^{2+} chelator BAPTA-AM inhibits IL-1β secretion, suggesting the involvement of Ca^{2+} signaling in NLRP3 activation [6]. Lee et al. reported that calcium-sensing receptors (CaSR), a G-protein-coupled receptor (GPCR) acting upstream of phospholipase C (PLC), trigger Ca^{2+} mobilization, resulting in intracellular calcium overload and NLRP3 inflammasome activation. There are also reports suggesting that the increase in Ca^{2+} has a less significant contribution to NLRP3 inflammasome activation compared to the decrease in potassium concentration [7], and the activation mechanism of NLRP3 by the Ca^{2+} signaling pathway requires further investigation.

The third mechanism is the activation of reactive oxygen species (ROS). Mitochondrial dysfunction and the release of reactive oxygen species play crucial upstream events in NLRP3

inflammasome activation. As the concentration of ROS changes, the complex between thioredoxin-interacting protein (TXNIP) and thioredoxin dissociates, and TXNIP binds to NLRP3, inducing NLRP3 inflammasome activation.

The fourth is lysosomal rupture: lysosomal destabilization mediates an activation pathway that primarily activates Caspase-1 to promote the pro-inflammatory cytokines IL-1B and IL-18. It has been found that urea, cholesterol crystals, and sterile material swallowed into cells destabilize lysosomal membranes, which then activate the lysosomal proteases and Caspase-1, further activating the NLRP3asome and promotes the pro-inflammatory cytokines IL-1B and IL-18 to act [8].

4. NLRP3 and Cardiovascular diseases (CVDs)

4.1. NLRP3 and Hypertension

Hypertension is a prevalent chronic non-infectious disease in clinical practice, characterized by sustained elevation of systemic arterial pressure and systolic blood pressure. Salt is one of the important environmental factors in the pathogenesis of hypertension, and hypertension associated with salt intake is referred to as salt-sensitive hypertension. Salt-sensitive hypertension is characterized by chronic inflammation and increased sympathetic nerve activity [9]. NFKB serves as an effective activator of NLRP3, and in the setting of high salt intake, a salt-sensitive hypertension rat model exhibits increased NFKB pathway activity, leading to enhanced NLRP3 and caspase-1 activity, resulting in the generation of pro-inflammatory cytokines and oxidative stress in the paraventricular nucleus, with oxidative stress being a major contributor to hypertension. The activation of the inflammasome is considered a molecular platform for the induction of IL-1β release. The central pro-inflammatory cytokine IL-1β activates the renin-angiotensin system, increases reactive oxygen species (ROS) production in the paraventricular nucleus, and consequently induces hypertension [10]. Activation of the renin-angiotensin-aldosterone system (RAAS) is consistently observed in the fibrotic heart. Angiotensin II (AngII), a bioactive peptide, promotes hypertension by binding to AT1 receptors or exerts negative regulation by binding to AT2 receptors. Studies have shown that continuous infusion of AngII for 7 days in mouse hearts leads to activation of NLRP3 inflammasome and secretion of pro-inflammatory cytokines, and the NLRP3 inflammasome inhibitor EMD638683 can reduce AngII-induced myocardial fibrosis [11]. Yang et al. [12] found that naringin can lower blood pressure in two-kidney, one-clip hypertensive rats by inhibiting the expression of the inflammatory inflammasome NLRP3, reducing the release of inflammatory factors such as TNF-α, IL-1β, and IL-6, and decreasing cardiac and renal tissue fibrosis in hypertensive rats. Recently, a newly discovered selective NLRP3 inhibitor, MCC950, has been shown to attenuate the elevation of blood pressure in hypertensive animal models by inhibiting NLRP3 inflammasome activation [13].

4.2. NLRP3 and Heart failure

Heart failure (HF) refers to impaired ventricular pumping or filling, often caused by structural or functional abnormalities of the heart, and is characterized by irreversibility. It is the ultimate outcome of various cardiovascular diseases. Cardiac remodeling and fibrosis are the major mechanisms underlying the development of HF. Cellular apoptosis is a key step in the remodeling process. The roles of reactive oxygen species (ROS) and oxidized low-density lipoprotein cholesterol (oxLDL-C) in HF have been well established. In recent years, scholars have discovered a new research direction, highlighting the opposing roles of ROS-generating NO synthases and inducible nitric oxide synthase (iNOS). Excessive iNOS leads to excessive production of NO, resulting in cell apoptosis and remodeling. Caspase-3 in the NLRP1 inflammasome activates IL-1B/IL-18. IL-1B induces aberrantly high levels of NO production through iNOS, leading to myocardial damage, while IL-18 promotes

overexpression of iNOS. Under hypoxia, cardiac fibroblasts trigger NLRP3 inflammasome activation, leading to inflammatory injury following enhanced ischemic injury, and hypoxia also induces further fibrosis by increasing collagen production in fibroblasts, ultimately resulting in ventricular remodeling [14]. Guo et al. [15] found that XinKang Injection inhibits the expression of NLRP3, Caspase-1, and GSDMD-N proteins in the apoptotic pathway, thereby alleviating myocardial inflammation and protecting cardiomyocytes. Lu et al. [16] reported that Danshensu, a component of traditional Chinese medicine Salvia miltiorrhiza, inhibits the elevated levels of reactive oxygen species in the myocardium caused by acute HF, suppresses NLRP3 inflammasome activation, reduces Caspase-1 protein cleavage activity, and inhibits the release of downstream inflammatory signaling factors, thereby suppressing immune responses and alleviating myocardial cell damage. Stasis paralysis capsule can inhibit NLRP3 activation during the development of HF and reduce the release of IL-1β to inhibit calcium ion efflux from myocardial sarcoplasmic reticulum, improve myocardial excitatory-contractile coupling and intra- and extracellular calcium ion environment, and attenuate inflammatory response of cardiomyocytes, so as to improve the ventricular remodeling and protect the contractile function of cardiomyocytes [17].

4.3. NLRP3 and Atherosclerosis

Atherosclerosis is a chronic inflammatory disease, and smoking is one of the important causes of atherosclerosis. Nicotine present in tobacco can increase the activation of NLRP3 and ASC, promoting the activation of the NLRP3 inflammasome. The NLRP3 inflammasome serves as a bridge between lipid metabolism and inflammation. When endothelial cells are damaged due to abnormal uptake of low-density lipoprotein and cholesterol, the NLRP3 inflammasome is activated [18]. Low-density lipoprotein inhibits the expression of tet methylcytosine dioxygenase 2 (TET2) in vascular endothelium in a dose-dependent manner, leading to endothelial dysfunction and atherosclerosis by improving mitochondrial function, activating the NF-κB pathway, upregulating the protein levels of NLRP3, caspase-1, and IL-1β in endothelial cells, and inducing cellular apoptosis [19]. After endothelial dysfunction, monocytes adhere to the lesion site, differentiate into macrophages, and engulf oxidized LDL and cholesterol crystals (Ch Cs), promoting lipid accumulation and foam cell formation. Deposition of Ch Cs induces lysosomal damage in macrophages and activates the NLRP3 inflammasome, further contributing to the instability of atherosclerotic plaques. Research has reported that NLRP3 activation promotes neutrophil recruitment and the formation of neutrophil extracellular traps in plaques. With the secondary necrosis of apoptotic vascular smooth muscle cells within the plaque, the release of IL-1α and IL-1β is promoted, triggering chronic inflammatory responses associated with atherosclerosis [20]. Zeng Xiangfa [21] et al. found that resolving phlegm and activating blood circulation could reduce blood lipid levels, down-regulate the expression of inflammatory factors by inhibiting the TLR4/NFKB/NLRP3 inflammatory signaling pathway, and reduce vascular damage and lipid accumulation, thus alleviating AS. Ge Fan [22] et al. found that astragaloside significantly down-regulated the expression of NLRP3, ASC, and Caspase-1 proteins in diabetic rats, and thus alleviated the inflammation of diabetic artery in early stage atherosclerosis rats. Inflammatory state of diabetic rats in the early stage of atherosclerosis was reduced by astragaloside.

4.4. NLRP3 and diabetic cardiomyopathy

Diabetic cardiovascular complications are the leading cause of death in diabetes mellitus, and the lesion sites include both large vessels and microvessels. Diabetic cardiomyopathy (DCM) caused by diffuse damage to microvessels is one of the hot spots in current research. It has been confirmed that chronic inflammation is one of the important causes of DCM, and chronic inflammation can trigger

the activation of inflammatory vesicles, such as NLRP3, which leads to cell death. The activation mechanism of NLRP3 inflammatory vesicles in DCM mainly relies on the production of large amounts of reactive oxygen species (ROS) in a hyperglycemic environment, and the large amount of ROS promotes the development of the thioredoxin interacting protein (THIP). A large amount of ROS induces thioredoxin-intelacting protein (TXNIP) to bind to NLRP3, thereby inducing the activation of NLRP3 inflammatory vesicles and inducing cellular pyroptosis [23]. Now, it was shown that Yunzhi extract could attenuate NLRP3 inflammasome activation by inhibiting the NF-KB pathway, which led to a reduction in the levels of caspase-1, IL-1β, IL-18, and NLRP3 inflammasome in DM rats, thus reducing cardiac inflammation and improving cardiac function [24]. Li Xuelian et al. found that diabetic rat models treated with quercetin significantly inhibited inflammatory vesicle protein expression and improved interstitial fibrotic lesions and myocardial apoptosis, and that quercetin attenuated high glucose-induced impaired cardiac function in diabetic rats by mediating NLRP3 inflammatory vesicles [25]. Yang Zhangliang et al. found that the establishment of a small type 2 diabetes model by high-fat feeding combined with streptozotocin (STZ) revealed that mice in the model group showed disturbed myocardial fiber arrangement, inflammatory cell infiltration of myocardial tissues, cardiomyocyte hypertrophy and necrosis. After 8 weeks of ursolic acid intervention, cardiomyopathy was significantly improved in diabetic mice, and the mechanism was related to the inhibition of NLRP3 inflammatory vesicle activation and reduction of IL-1B expression [26].

4.5. NLRP3 and myocardial ischemia-reperfusion

The inflammatory response after myocardial infarction can encapsulate necrotic tissue and form a scar. However, too strong or too weak an inflammatory response can affect scar formation and increase the risk of cardiac rupture. The inflammatory response that occurs during reperfusion to salvage the border region of infarcted myocardium can damage this portion of the myocardium, i. e. ischemia-reperfusion injury, and the sterile inflammatory response triggered by tissue damage is mediated by multiple protein complexes via NLRP3 inflammasomes. The NLRP3 inflammasomes are formed by the I/R, and their subsequent activation of inflammasomes results in the production of IL-1β, which leads to an inflammatory response, for example, in the cardiac inflammatory cell infiltration and cytokine expression. It has been shown that cinnamic acid reduces the protein expression of NLRP3, pro-Caspase-1, Caspas3-1, ASC, IL-18, and IL-1β, decreases the area of myocardial infarction, reduces myocardial damage enzymes, and improves cardiac function, suggesting that cinnamic acid effectively protects cardiomyocytes through inhibition of the NLRP3/Caspase-1/GSDMD pathway from MIRI, attenuating inflammatory responses and oxidative stress, and also inhibiting the activation of NLRP3 inflammatory vesicles and cellular focal death-related signaling pathways in myocardial tissues, thereby attenuating the extent of MIRI [27]. Xiao Min et al. [28] found that jinxiangdan could attenuate the inflammatory response of MIRI, improve myocardial injury, and inhibit cardiomyocyte apoptosis in rats with MIRI, and its mechanism of action may be the inhibition of the activity of the NLRP3/Caspase-1/IL-1β signaling pathway. Wang et al. [29] found that Sihmiao yong'an Tang Plus could, through the inhibition of the activity of the NLRP3 inflammatory vesicle signaling pathway Reducing the release of inflammatory factors such as IL-18 and IL-1β, decreasing the content of MDA in myocardial tissues, and increasing the level of SOD, thus improving myocardial tissue lesions and ultrastructural changes in MIRI rats. Wang Danshu et al. [30] confirmed that puerarin regulates NLRP3 inflammatory vesicle activation by inhibiting the TLR4/MyD88/NF-κB signaling pathway, inhibits NF-κB protein phosphorylation, and reduces the release of inflammatory factors, such as IL-18 and IL-1β, thus reducing the inflammatory response and effectively preventing and controlling MIRI.

4.6. NLRP3 and other cardiovascular diseases

Pathological cardiac remodeling due to aortic stenosis is associated with poor clinical prognosis after transcatheter aortic valve replacement (TAVR). Sacubitril/sartan (Sac/Val) administration of angiotensin receptor blockers and neutral lysosomal enzyme inhibitors was found to attenuate cardiac fibrosis and inflammation with a decrease in cardiac weight and cardiomyocyte size observed in the mouse heart. Sac/Val treatment alleviated HF after pressure overload and significantly inhibited nuclear factor (NF)-KB conduction abnormalities and NLRP3 activation in mice. activation of inflammatory vesicles. This suggests that Sac/al ameliorates myocardial fibrosis and functional abnormalities in mice by inhibiting NLRP3 inflammasome [31]. Myocardial infarction (MI) is the result of severe and prolonged ischemia leading to myocardial cell death. The NLRP3 inflammasome recognizes various danger signals and induces sterile inflammation, and sustained sterile inflammation in myocardial tissue is an important triggering factor for the development of acute myocardial infarction (AMI). Tan et al. [32] reported that Lingbao Huxin Dan inhibits the expression of NLRP3 and Caspase-1 proteins, thereby suppressing the activation of inflammatory factors IL-1β and IL-18, reducing the infarct area, and alleviating acute ischemia in myocardial tissue. Atrial fibrillation (AF) is a type of arrhythmia, and recent studies have found a link between AF and the activation of the NLRP3 inflammasome. Zhao et al. [33] found that a traditional Chinese medicine formula for promoting blood circulation and removing blood stasis inhibits the activation of the NLRP3 inflammasome, counteracts myocardial fibrosis, improves myocardial remodeling, and delays the onset and progression of atrial fibrillation. Viral myocarditis (VM) is an inflammatory change in the myocardium caused by viral invasion, with coxsackievirus being a common culprit. The apoptotic pathway plays a role in VM induced by coxsackievirus B3, and the NLRP3 inflammasome is an important pathway in cellular apoptosis, being activated to initiate cellular apoptosis by inhibiting the action of AMP-activated protein kinase. Zhang et al. [34] demonstrated that muscone significantly alleviates myocardial cell swelling, myocardial fiber disruption, inflammatory cell infiltration, and myocardial cell necrosis in mice with CVB3-induced VM. Muscone may exert myocardial protection through the AMPK/NLRP3 pathway.

5. NLRP3 and drugs

Cardiac glycosides such as digoxin are Na+/K+-ATPase inhibitors and are widely used to treat CHF and arrhythmias. Epidemiology has shown an association between digoxin treatment and an elevated rate of death broadly. It was found that wowbaine induced an inflammatory response in the heart when mice were perfused with lipopolysaccharide. In vitro experiments showed that wowbaine induced NLRP3 inflammatory vesicle activation, which was mediated by K+ efflux. This suggests that cardiac inflammation and dysfunction are promoted by cardiac glycosides via NLRP3 inflammatory vesicles and provides new insights into the underlying mechanisms of cardiac glycosides' adverse effects [35]. MCC950, a diaryl sulfonylurea-containing compound, is the most intensively investigated inhibitor of NLRP3, and works by directly binding to the WalkerB motif in the NLRP3NACHT structural domain, preventing ASC oligomerization and subsequent IL-1β release to inhibit NLRP3 inflammatory vesicle activity [36]. Colchicine (colchicine) is a choroidal phenolic ketone alkaloid that has been in clinical use for more than 200 years, with good efficacy in pain relief and treatment of gouty inflammation, and the effectiveness of the treatment of acute pericarditis, recurrent polychondritis, and cutaneous vasculitis has also been confirmed to varying degrees. Colchicine blocks NLRP3 inflammatory vesicle formation at two levels: preventing P2X7-mediated pore formation and inhibiting intracellular transport and the spatial arrangement of NLRP3 and ASC resulting in the inability to oligomerize [37]. It was found that low-dose treatment was found to be beneficial in improving coronary plaques and stabilizing morphology in patients with acute coronary

syndromes. CY-09, with molecular formula C19H12F3NO3S2, is a selective and direct inhibitor of NLRP3 by binding to the ATP motif of the NACHT structural domain, thereby inhibiting NLRP3 assembly and ATPase activity. Its use in myocardial remodeling mice has been found to exhibit improved cardiac function and reduced myocardial fibrosis in the clinic. Glibenclamide (Glyburide) is the first second-generation sulfonylurea oral hypoglycemic agent used in the clinic [38] and is widely used in the treatment of type II diabetes. It was found that in LPS/ATP-induced macrophages, glibenclamide was able to inhibit NLRP3 inflammatory vesicles in macrophages with specificity. Whereas the high dose required for the anti-inflammatory properties of glibenclamide leads to severe hypoglycemia, the newly developed 1667334-0 lacks the cyclohexylurea portion of the compound, which is able to specifically inhibit NLRP3 inflammatory vesicles without affecting glucose metabolism, and the study demonstrated that improved cardiac function and reduced interstitial fibrosis were detected in a mouse model of myocardial ischemia/reperfusion.

6. Summary

An increasing number of studies indicate that the activation of NLRP3 inflammasome plays a significant role in the pathogenesis and progression of diverse cardiovascular disorders. Consequently, targeting the NLRP3 inflammasome and its associated pathways has emerged as a promising therapeutic strategy for numerous cardiovascular conditions. Activation of the NLRP3 inflammasome triggers the release of pro-inflammatory cytokines, including IL-1β and IL-18, thereby instigating inflammatory responses. Conversely, inhibitory interventions have demonstrated a potential to mitigate cardiovascular pathology. Further investigations are warranted to unravel the intricate mechanisms governing the activation and regulation of the NLRP3 inflammasome, with a particular emphasis on elucidating the molecular processes underlying its assembly and activation. Such endeavors hold promise for identifying novel therapeutic targets to prevent, diagnose, and develop safe treatment modalities for cardiovascular diseases.

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