Review Article

NLRP3 Inflammasome and Its Central Role in the Cardiovascular Diseases

Yeqing Tong,1,2 Zhihong Wang,3 Li Cai,4,5 Liangqiang Lin,2 Jiafa Liu1, and Jinquan Cheng2,6

1Center for Disease Control and Prevention, 430079 Hubei, China
2Key Laboratory of Molecular Biology of Guangdong Province, Center for Disease Control and Prevention, Shenzhen 518055, China
3Department of Neurology, Shenzhen NO. 2 People’s Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518035, China
4Wuhan Center for Disease Control and Prevention, Wuhan 430015, China
5School of Health Sciences, Wuhan University, Wuhan 430071, China
6School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin Hong Kong, China

Correspondence should be addressed to Jiafa Liu; l_jiafa@163.com and Jinquan Cheng; c_jinquan@163.com

Received 29 July 2019; Revised 26 March 2020; Accepted 31 March 2020; Published 15 April 2020

Guest Editor: Reggiani Vilela Gonçalves

Copyright © 2020 Yeqing Tong et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background/Aims. NLRP3 inflammasome, an inflammasome which consists of nucleotide-binding oligomerization domain-(Nod-) like receptor3 (NLRP3) scaffold, apoptosis-associated speck-like protein (ASC) containing a CARD adaptor, and pro-caspase-1, is assembled after the cytoplasmic leucine-rich repeats (LRRs) of NLRP3 sense pathogens or danger signals. In recent years, the role of inflammasome in cardiovascular diseases has attracted mounting attention, and the in-depth study of its mechanism is gradually clear. Materials. The NLRP3 inflammasome controls the activation of the proteolytic enzyme caspase-1. Caspase-1 in turn regulates the maturation of the proinflammasome cytokines IL-1β and IL-18, which leads to an inflammatory response. We made a mini-review on the association of regulatory mechanisms of NLRP3 inflammasome with the development of cardiovascular diseases systematically based on the recent research studies. Discussion. The inflammasome plays an indispensable role in the development of atherosclerosis, coronary heart diseases (CHD), and heart ischemia-reperfusion (I/R) injury, and NLRP3 inflammasome may become a new target for the prevention and treatment of cardiovascular diseases. Effective regulation of NLRP3 may help prevent or even treat cardiovascular diseases. Conclusion. This mini-review focuses on the association of regulatory mechanisms of NLRP3 inflammasome with the development of cardiovascular diseases, which may supply some important clues for future therapies and novel drug targets for cardiovascular diseases.

1. Introduction

The inflammasome, a multiprotein complex macromolecular intracellular protein which supplies the platform for promoting the maturation of inflammatory cytokines, could promote the maturation of inflammatory cytokines, such as IL-1β and IL-18 [1–5]. These cytokines are extremely powerful molecules with myriad functions that are widely and rapidly induced in the cardiovascular diseases upon infection, trauma, or stress. Therefore, inflammasome is likely to control the inflammation in the development of cardiovascular diseases [6–8]. NLRP3 inflammasome, the most typically inflamma-
However, a number of questions deserve further investigation. How the NLRP3 inflammasome is involved in other cardiovascular diseases, such as hypertension, arrhythmia, and heart failure, remains not very clear. In addition, the exact molecular mechanisms by which NLRP3 inflammasome is activated should also be further examined, too. Whether this complex protein is biochemically and genetically regulated or not may be a new focus in the coming years. Clinical trials have confirmed that IL-1β and its receptor antagonist could be used to treat a variety of cardiovascular diseases [13, 14], and the widely used drug glyburide played a crucial role in the treatment of cardiovascular diseases through the inhibition of the NLRP3 inflammasome [15]. Thus, investigations into NLRP3 inflammasome will shed light on the pathogenesis of cardiovascular diseases and provide critical clues for seeking new targets for clinical cardiovascular diseases drug development.

Despite the potential significance of NLRP3 inflammasome in the pathogenesis of several diseases, emerging evidence suggests that NLRP3 inflammasome events are associated with cardiovascular diseases conditions. Details on the activation mechanism of the NLRP3 inflammasome by a variety of stimulators have yet to be systematic reported [16]. In view of its importance and value in cardiovascular diseases, we systematically reviewed the recent research advances in NLRP3 inflammasome, particularly its specialized role in the cardiovascular diseases. In this review, we summarized the role of NLRP3 in inflammatory response and discussed the relationship between NLRP3 and cardiovascular diseases. We also provided insights into new treatment strategies for targeting NLRP3 inflammasome, as well as the upstream and downstream components of NLRP3 in alleviating cardiovascular diseases.

2. Structure of NLRP3 Inflammasome

NLRP3, the main component of the NLRP3 inflammasome which consists of N-terminal and C-terminal function structural domain, was known as a novel inflammatory gene [13, 17, 18]. The structure of NLRP3 inflammasome is described in Figure 1.

The N-terminal domain includes the hot protein pyrin domain (PYD), the caspase-associated recruitment domain (CARD), and the nucleotide-binding oligomerization domain (NOD/NACHT); the C-terminal domain includes the leucine-rich repeat (LRR) which provides a bracket to identify pathogen-associated patterns and other ligands. When ligands are identified by LRR, the NOD structure domain rearranges and triggers its biological effects [13, 19].

NLRP3 inflammasome, a new inflammasome which oligomerizes upon activation, is constituted by NLRP3, ASC, and pro-caspase-1 [20]. First and foremost, its activation will result in the recruitment of ASC through homotypic PYD-PYD interactions. Secondly, ASC forms large speck-like structures and recruits pro-caspase-1 via CARD-CARD contact, leading to the autocalytic activation of caspase-1 [21]. Finally, activated caspase-1 converts the inactive pro-IL-1β and pro-IL-18 into their activated and secreted forms, mediating the subsequent responses.

3. Mechanisms of NLRP3 Inflammasome Activation

NLRP3 inflammasome is assembled and activated in certain classical types of mechanisms such as the lysosome destabilization, the K⁺ efflux, and Ca²⁺ mobilization as well as the ROS; the mechanisms of NLRP3 Inflammasome activation are described in Figure 2.

3.1. The Lysosome Destabilization Mediating Activation Pathway. The activated pathway mediated by the lysosome destabilization is mainly to activate caspase-1 to process the proinflammatory cytokines interleukin- (IL-) 1β and IL-18. The studies found that urea, cholesterol crystal, and aseptic materials were swallowed into the intracellular to destroy the stability of lysosome membrane and then activate the lysosomal proteases and caspase-1, further activate NLRP3 inflammasome, and promote the process of proinflammatory cytokines interleukin- (IL-) 1β and IL-18 damaging the body [22].

3.2. The K⁺ Efflux- and Ca²⁺ Mobilization-Mediated Activation Pathway. The K⁺ efflux- and Ca²⁺ mobilization-mediated pathway may play a critical role in triggering the NLRP3 inflammasome activation. It can be activated by two pathways: (1) The purinergic 2X7 receptor (P2X7R) is in the upstream of NLRP3 activation. The extracellular ATP is involved in the formation of P2X7R which triggers the K⁺ efflux. K⁺ efflux results in low K⁺ concentrations in

Figure 1: Structure of NLRP3 inflammasome.
the intracellular environment, leading to mitochondrial dysfunction, apoptosis, and the subsequent release of ROS and oxidative mtDNA, which can activate the NLRP3 inflammasome [23, 24]. (2) In response to ATP and other stimuli, Ca2+ released from endoplasmic reticulum storage or the extracellular space can trigger mitochondrial damage, which can also activate NLRP3 inflammasome [25].

3.3. The ROS-Mediated Activation Pathway. Reactive oxygen species (ROS), a powerful oxidant which is mainly produced by the mitochondria, could trigger oxidative stress and activate NLRP3 inflammasome [26]. The complex of thioredoxin and thioredoxin-interacting protein (TXNIP) could dissociate in the high ROS level circumstance. The subsequent binding of TXNIP and NLRP3 leads to the activation of TXNIP-NLRP3 inflammasome and recruitment of ASC and pro-caspase-1 as well as the formation of the active inflammasome complex [27]. Studies have found that reducing the damage of mitochondria by regulating mitochondrial autophagy could inhibit ROS from inducing NLRP3 inflammasome activation. Absence of autophagy will increase the activation of the NLRP3 inflammasome dramatically.

Mitochondrial dysfunction acts in the upstream of NLRP3 activation by providing ROS to trigger NLRP3 oligomerization or by inducing α-tubulin acetylation to relocate mitochondria to the proximity of NLRP3 [28]. In addition, mitochondria work as a platform for inflammasome assembly. Mitochondrial function may also depend on the downstream of NLRP3 activation. While the molecular mechanisms of mitochondrial dysfunction associated with NLRP3 activation are still unclear, they might be involved in the perturbation of mitochondria by K+ efflux and subsequent intracellular disequilibrium [29]. Thus, mitochondria ROS and NLRP3 machinery appear to be closely interwoven at multiple levels.

4. The Role of NLRP3 Inflammasomes in the Cardiovascular Diseases

Activation of the NLRP3 inflammasome by these mechanisms has been discovered in various disorders, including metabolic syndrome, type 2 diabetes, atherosclerosis, gout, reperfusion injury of the heart, neurodegeneration, such as Alzheimer’s disease, chronic kidney diseases, and more, and more studies suggest that NLRP3 inflammasome is involved in the development of cardiovascular diseases.

4.1. The Association between NLRP3 Inflammasome and Coronary Heart Diseases (CHD). NLRP3 plays a very important role in the early stage of CHD. Low-density lipoprotein (LDL) promotes a cholesterol crystal to deposit in the vessel wall. Then, the macrophages phagocytize the lipoprotein and turn themselves into foam cells. Foam cells are activated by the following mechanisms to initiate inflammatory cycle reaction: (1) The macrophages phagocytize lysosome and then lysosomes are damaged and release ROS and protease to activate NLRP3 [30, 31]. (2) The TLR- (Toll-like receptor-) 12/TLR-4 located in the capsular identifies minimally oxidized LDL and free fatty acids and raises the myeloid differentiation primary response gene 88 and interferon TIR domain-containing adapter-inducing interferon beta (TRIF) to induce nuclear factor-kappa B (NF-κB). NF-κB promotes intracellular NLRP3 gene and IL-1β precursor expression to promote inflammation [32]. (3) The proinflammatory factors induce macrophage, neutrophil, lymphocyte, vascular smooth muscle cell infiltration and activation causing cell death and the accumulation of extracellular cholesterol and cellulose and promoting calcium phosphate crystallization deposition. The deposited crystallization calcium further breaks the lysosome of macrophages [33]. (4) The IL-1β raises mononuclear cells to activate platelets and promotes the release of themselves [34, 35]. (5) The activated macrophages can generate IL-18 causing more vascular smooth
muscle cell necrosis and releasing the organization metalloproteinases to reduce the stability of the plaques [36]. The above mechanisms form the cycle reaction could make plaque size more big and plaque stability more serious. The detailed association between NLRP3 inflammasome and CHD is described in Figure 3.

4.2. The Association between NLRP3 Inflammasome and Myocardial Ischemia/Reperfusion (I/R) Injury. Inflammation plays a key role in the pathophysiology of the I/R injury [37, 38]; however, the mechanism how myocardial I/R induces inflammation remains unclear. Recent evidence indicates that a sterile inflammatory response triggered by tissue damage is mediated through a multiple-protein complex called the NLRP3 inflammasome. Inflammatory response is initiated by the detection of PAMPs and/or DAMPs via extracellular and intracellular pattern recognition receptors [39, 40]. The inflammasome is an initial sensor for danger signals in myocardial I/R injury. Kawaguchi et al. have found that inflammasome activation in cardiac fibroblasts was crucially involved in the initial inflammatory response after myocardial I/R injury [41]. NLRP3 inflammasome was formed by I/R, and its subsequent activation of inflammasomes led to IL-1β production, resulting in inflammatory responses such as inflammatory cell infiltration and cytokine expression in the heart [42]. The activated NLRP3 inflammasome could integrate ASC to activate caspase-1. In mice deficient in apoptosis-associated speck-like adaptor protein and caspase-1, these inflammatory responses and subsequent injuries, including infarct development, myocardial fibrosis, and dysfunction, were markedly diminished [43–45]. Bone marrow transplantation experiments with apoptosis-associated speck-like adaptor protein-deficient mice revealed that NLRP3 inflammasome activation in bone marrow cells and myocardial resident cells such as cardiomyocytes or cardiac fibroblasts plays a crucial role in myocardial I/R injury [41]. The in vitro experiments revealed that hypoxia/reoxygenation stimulated by NLRP3 inflammasome activation in cardiac fibroblasts and hypoxia/reoxygenation-induced activation was mediated through reactive oxygen species.

**Figure 3:** The association between NLRP3 inflammasomes and coronary heart diseases (CHD) in macrophages.
species production and potassium efflux [46, 47]. All of these suggested that NLRP3 inflammasome was one of the most important molecular basis for the initial inflammatory response after I/R. Its activation in cardiac fibroblasts was essential for myocardial I/R injury, so it maybe a potential novel therapeutic target for preventing myocardial I/R injury [48–51]. The detailed association between NLRP3 inflammasome and myocardial I/R injury is described in Figure 4.

4.3. The Association between NLRP3 Inflammasome and Heart Failure. Inflammation is associated with cardiac remodeling and heart failure, but how it is initiated in response to nonischemic interventions in the absence of cell death is still not very clear. Activation of the NLRP3 inflammasome triggers inflammatory gene expression in cardiomyocytes. These responses could provide signals for macrophage recruitment, fibrosis, and myocardial dysfunction in the heart. These studies suggest targeting early inflammatory responses induced by NLRP3 inflammasome-associated signal can prevent the progression to heart failure [52, 53]. The in vivo study also had shown that Tet2 deficiency in hematopoietic cells is associated with greater cardiac dysfunction in murine models of heart failure as a result of elevated IL-1β signaling. Individuals with TET2-mediated clonal hematopoiesis have greater risk of developing heart failure and respond better to IL-1β–NLRP3 inflammasome inhibition [54].

5. Discussion and Conclusion

To sum up, these previous results have a number of therapeutic implications. NLRP3 inflammasome could identify a large number of bacteria, viruses, and some endogenous signals that activate caspase-1 and induce production and secretion of IL-1β and IL-18. Numerous studies have confirmed that the NLRP3 played a vital role in the atherosclerosis and occurrence of cardiovascular diseases [3, 30, 41]. Based on the activation mode of NLRP3, inhibiting NLRP3 inflammasome activation may have beneficial effects in preventing the damage mediated by the sterile inflammatory response in cardiovascular diseases such as CHD and MI. Preventing pathological NLRP3 inflammasome from activation may provide some insight into the future prevention and treatment of cardiovascular diseases [1, 3, 10]. Currently, the most promising treatments for inhibiting NLRP3 are anti-IL-1, inhibition of caspase-1, and P2X7 receptors antagonist [47–49].

Targeting against the assembly and activity of the NLRP3 inflammasome is a potential and novel therapy for inflammasome-associated diseases, especially for cardiovascular diseases [55–60]. Some studies have indicated that blocking S194 phosphorylation can prevent NLRP3 inflammasome activation. Inhibiting NLRP3 phosphorylation could be an effective treatment for NLRP3-related diseases [61]. In addition, other studies have shown that the NLRP3 NACHT domain molecule may be the target for drug development against cardiovascular diseases. Blocking ATP
hydrolysis could inhibit NLRP3 activation and inflamma-
some formation [62, 63].

Further research on the NLRP3 activation mechanisms
and more sophisticated animal experiments as well as clin-
ical trials of molecular targeted agents on NLRP3 are
needed to better shed light on the association between
NLRP3 inflammasome and cardiovascular diseases, as well
as the complicated roles of inflammasome in cardiovas-
cular diseases precisely.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors’ Contributions

Yeqing Tong, Zhihong Wang, and Li Cai contributed equally
to this work.

Acknowledgments

This study was supported by funds (81302497 and 81573237)
from the National Natural Science Foundation of China,
Hubei Natural Science Foundation (No. 2013CFB056,
2016CFB403, and 2017ADC061), Hubei Province’s young
talent program (20171102), Hubei Province’s young top
talent program (20191229), and China Postdoctoral
Scientific Foundation (No. 2014M550394 and 2015T80807).

References

[1] S. Y. Yu, L. Tang, G. J. Zhao, and S. H. Zhou, “Statin protects
the heart against ischemia-reperfusion injury via inhibition
of the NLRP3 inflammasome,” International Journal of Cardi-
ology, vol. 229, pp. 23–24, 2017.

[2] S. Bleda, J. de Haro, C. Varela, A. Ferrueto, and F. Aci, “Ele-
vated levels of triglycerides and vldl-cholesterol provoke activ-
atin of nlrp1 inflammasome in endothelial cells,” Intern-
ation Journal of Cardiology, vol. 220, pp. 52–55, 2016.

[3] S. Toldo, C. Marchetti, A. G. Mauro et al., “Inhibition of the
NLRP3 inflammasome limits the inflammatory injury follow-
ing myocardial ischemia–reperfusion in the mouse,” Intern-
ation Journal of Cardiology, vol. 209, pp. 215–220, 2016.

[4] X. Liu, Z. Zhang, J. Ruan et al., “Inflammasome-activated gas-
dermin D causes pyroptosis by forming membrane pores,” Na-
ture, vol. 535, no. 7610, pp. 153–158, 2016.

[5] L. Vande Walle, D. Jiménez Fernández, D. Demon et al., “Does
caspase-12 suppress inflammasome activation?,” Nature,
vol. 534, no. 7605, pp. E1–E4, 2016.

[6] D. S. El-Agamy, H., H. Almaramh, N. Ahmed, B. Bojan,
W. D. Alrohily, and M. . A. Elkablawy, “Anti-inflammatory
effects of vardenafil Against cholestatic liver damage in mice: a
mechanistic study,” Cellular Physiology and Biochemistry,
vol. 47, no. 2, pp. 523–534, 2018.

[7] K. B. Shah, A. G. Mauro, M. Flattery, S. Toldo, and A. Abbate,
“Formation of the inflammasome during cardiac allograft
rejection,” International Journal of Cardiology, vol. 201,
pp. 328–330, 2015.

[8] Q. Hu, B. Wei, L. Wei et al., “Sodium tanshinone IIA sulfonate
ameliarates ischemia-induced myocardial inflammation and
lipid accumulation in Beagle dogs through NLRP3 inflamma-
some,” International Journal of Cardiology, vol. 196, pp. 183–
192, 2015.

[9] M. H. Liu, “FGF-21 alleviates diabetes-associated vascular
complications: Inhibiting NF- kB/NLRP3 inflammasome-
mediated inflammation?,” International Journal of Cardiology,
vol. 185, pp. 320–321, 2015.

[10] B. Tang, G. X. Chen, M. Y. Liang, J. P. Yao, and Z. K. Wu,
“Ellagic acid prevents monocrotaline-induced pulmonary
artery hypertension via inhibiting NLRP3 inflammasome
activation in rats,” International Journal of Cardiology,
vol. 180, pp. 134–141, 2015.

[11] H. Zhang, S. Chen, M. Zeng et al., “Apelin-13 administration
protects against LPS-induced acute lung injury by inhibiting
NF-κB pathway and NLRP3 inflammasome activation,” Cellu-
lar Physiology and Biochemistry, vol. 49, no. 5, pp. 1918–1932,
2018.

[12] Q. Su, L. Li, Y. Sun, H. Yang, Z. Ye, and J. Zhao, “Effects of the
TLR4/Myd88/NF-κB signaling pathway on NLRP3 inflamma-
some in coronary microembolization-induced myocardial
injury,” Cellular Physiology and Biochemistry, vol. 47, no. 4,
p. 1497–1508, 2018.

[13] V. Compan, F. Martín-Sánchez, A. Baroja-Mazo et al., “Apo-
tosis-associated speck-like protein containing a CARD forms
specks but does not activate caspase-1 in the absence of NLRP3
during macrophage swelling,” Journal of Immunology,
vol. 194, no. 3, p. 1261–1273, 2015.

[14] W. Q. Huang, P. Wei, R. Q. Lin, and F. Huang, “Protective
effects of microrna-22 against endothelial cell injury by target-
ing NLRP3 through suppression of the inflammasome signal-
ing pathway in a rat model of coronary heart disease,” Cellular
Physiology and Biochemistry, vol. 43, no. 4, pp. 1346–1358,
2017.

[15] P. Tang, R. Zhu, W. P. Ji et al., “The NLRP3/Caspase-1/Inter-
leukin-1β axis is active in human lumbar cartilaginous end-
plate degeneration,” Clinical Orthopaedics and Related
Research, vol. 474, no. 8, pp. 1818–1826, 2016.

[16] Z. Fan, M. Lu, C. Qiao, Y. Zhou, J. H. Ding, and G. Hu, “Micro-
RNA-7 enhances subventricular zone neurogenesis by inhibiting
NLRP3/caspase-1 axis in adult neural stem cells,” Molecular
Neurobiology, vol. 53, no. 10, pp. 7057–7069, 2016.

[17] X. S. Ren, Y. Tong, L. Ling et al., “NLRP3 gene deletion attenu-
ates angiotensin II-induced phenotypic transformation of
vascular smooth muscle cells and vascular remodeling,” Cellu-
lar Physiology and Biochemistry, vol. 44, no. 6, pp. 2269–2280,
2018.

[18] J. Qi, X. J. Yu, X. L. Shi et al., “NF-κB blockade in hypothalamic
paraventricular nucleus inhibits high-salt-induced hyperten-
sion through NLRP3 and caspase-1,” Cardiovascular Toxicol-
ology, vol. 16, no. 4, pp. 345–354, 2016.

[19] Q. Zhang, W. Yu, S. Lee, Q. Xu, A. Naji, and A. D. le, “Bisphos-
phonate induces osteonecrosis of the jaw in diabetic mice via
NLRP3/caspase-1-dependent IL-1β mechanism,” Journal of
Bone and Mineral Research, vol. 30, no. 12, pp. 2300–2312,
2015.

[20] M. Muroi and K. Tanamoto, “Zinc- and oxidative property-
dependent degradation of pro-caspase-1 and NLRP3 by ziram
in mouse macrophages,” Toxicology Letters, vol. 235, no. 3,
p. 199–205, 2015.

[21] F. Madouri, N. Guillou, L. Faucqennier et al., “Caspase-1 activa-
tion by NLRP3 inflammasome dampens IL-33-dependent
house dust mite-induced allergic lung inflammation,” Journal of
Molecular Cell Biology, vol. 7, no. 4, pp. 351–365, 2015.
[22] M. A. Katsnelson, K. M. Lozada-Soto, H. M. Russo, B. A. Miller, and G. R. Dubyak, "NLRP3 inflammasome signaling is activated by low-level lysosome disruption but inhibited by extensive lysosome disruption: roles for K\textsuperscript{+} efflux and Ca\textsuperscript{2+} influx," *American Journal of Physiology-Cell Physiology*, vol. 311, no. 1, pp. C83–C100, 2016.

[23] C. J. Groß, R. Mishra, K. S. Schneider et al., "K\textsuperscript{+} Efflux-independent NLRP3 inflammasome activation by small molecules targeting mitochondria," *Immunity*, vol. 45, no. 4, pp. 761–773, 2016.

[24] R. Muñoz-Planillo, P. Kuffa, G. Martínez-Colón, B. L. Smith, T. M. Rajendiran, and G. Núñez, "K\textsuperscript{+} efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter," *Immunity*, vol. 38, no. 6, pp. 1142–1153, 2013.

[25] S. Lacroix-Lamandé, M. Fanton d’Andon, E. Michel et al., "Downregulation of the Na/K-ATPase pump by leptospirot glycolipoprotein activates the NLRP3 inflammasome," *Journal of Immunology*, vol. 188, no. 6, pp. 2805–2814, 2012.

[26] J. Wu, X. Li, G. Zhu, Y. Zhang, M. He, and J. Zhang, "The role of resveratrol-induced mitophagy/autophagy in peritoneal mesothelial cells inflammatory injury via NLRP3 inflammasome activation triggered by mitochondrial ROS," *Experimental Cell Research*, vol. 341, no. 1, pp. 42–53, 2016.

[27] H. Shi, Z. Zhang, X. Wang et al., "Inhibition of autophagy induces IL-1β release from ARPE-19 cells via ROS mediated NLRP3 inflammasome activation under high glucose stress," *Biochemical and Biophysical Research Communications*, vol. 463, no. 4, pp. 1071–1076, 2015.

[28] S. Yang, C. Xia, S. Li, L. du, L. Zhang, and R. Zhou, "Defective mitophagy driven by dysregulation of rheb and KIF5B contribute to mitochondrial reactive oxygen species (ROS)-induced nod-like receptor 3 (NLRP3) dependent proinflammatory response and aggravates lipotoxicity," *Redox Biology*, vol. 3, pp. 63–71, 2014.

[29] J. Tschopp and K. Schroder, "NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production?*," *Nature Reviews. Immunology*, vol. 10, no. 3, pp. 210–215, 2010.

[30] J. He, Y. Yang, and D.-Q. Peng, "Monosodium urate (MSU) crystals increase gout associated coronary heart disease (CHD) risk through the activation of NLRP3 inflammasome," *International Journal of Cardiology*, vol. 160, no. 1, pp. 72-73, 2012.

[31] M. E. Heid, P. A. Keyel, C. Kamga, S. Shiva, S. C. Watkins, and R. D. Salter, "Mitochondrial reactive oxygen species induces NLRP3-dependent lysosomal damage and inflammasome activation," *Journal of Immunology*, vol. 191, no. 10, pp. 5230–5238, 2013.

[32] S. Y. Chuang, C. H. Yang, C. C. Chou, Y. P. Chiang, T. H. Chuang, and L. C. Hsu, "TLR-induced PAI-2 expression suppresses IL-1β processing via increasing autophagy and NLRP3 degradation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 40, pp. 16079–16084, 2013.

[33] H. Ahn, J. Kim, E. B. Jeung, and G. S. Lee, "Dimethyl sulfoxide inhibits NLRP3 inflammasome activation," *Immunobiology*, vol. 219, no. 4, pp. 315–322, 2014.

[34] M. Aloi, L. Tromba, G. di Nardo et al., "Premature subclinical atherosclerosis in pediatric inflammatory bowel disease," *The Journal of Pediatrics*, vol. 161, no. 4, pp. 589–594.e1, 2012.

[35] R. Alten, J. Gomez-Reino, P. Durez et al., "Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, Phase II, dose-finding study," *BMC Musculoskeletal Disorders*, vol. 12, no. 1, p. 153, 2011.

[36] F. Zheng, S. Xing, Z. Gong, W. Mu, and Q. Xing, "Silence of NLRP3 suppresses atherosclerosis and stabilizes plaques in apolipoprotein E-deficient mice," *Mediators of Inflammation*, vol. 2014, Article ID 507208, 8 pages, 2014.

[37] H.-Y. Kim, S.-J. Kim, and S.-M. Lee, "Activation of NLRP3 and AIM2 inflammasomes in Kupffer cells in hepatic ischemia/reperfusion," *The FEBS Journal*, vol. 282, no. 2, pp. 259–270, 2015.

[38] Y. Qi, M. Zhao, Y. Bai et al., "Retinal ischemia/reperfusion injury is mediated by Toll-like receptor 4 activation of NLRP3 inflammasomes," *Investigative Ophthalmology & Visual Science*, vol. 55, no. 9, pp. 5466–5475, 2014.

[39] Y. Liu, K. Lian, L. Zhang et al., "TNXIP mediates NLRP3 inflammasome activation in cardiac microvascular endothelial cells as a novel mechanism in myocardial ischemia/reperfusion injury," *Basic Research in Cardiology*, vol. 109, no. 5, p. 415, 2014.

[40] P. J. Bakker, L. M. Butter, N. Claessen et al., "A tissue-specific role for Nlrp3 in tubular epithelial repair after renal ischemia/reperfusion," *The American Journal of Pathology*, vol. 184, no. 7, pp. 2013–2022, 2014.

[41] M. Kawaguchi, M. Takahashi, T. Hata et al., "Inflammasome activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury," *Circulation*, vol. 123, no. 6, pp. 594–604, 2011.

[42] M. Moriyama, I. Y. Chen, A. Kawaguchi et al., "The RNA- and TRIM25-binding domains of influenza virus NS1 protein are essential for suppression of NLRP3 inflammasome-mediated Interleukin-1β secretion," *Journal of Virology*, vol. 90, no. 8, pp. 4105–4114, 2016.

[43] F. T. Cero, V. Hillestad, I. Sjaastad et al., "Absence of the inflammasome adaptor ASC reduces hypoxia-induced pulmonary hypertension in mice," *American Journal of Physiology-Lung Cellular and Molecular Physiology*, vol. 309, no. 4, pp. L378–L387, 2015.

[44] K. M. Boini, T. Hussain, P. L. Li, and S. S. Koka, "Trimethylamine-N-oxide instigates NLRP3 inflammasome activation and endothelial dysfunction," *Cellular Physiology and Biochemistry*, vol. 44, no. 1, pp. 152–162, 2018.

[45] H. Li, S. Zhang, F. Li, and L. Qin, "NLRX1 attenuates apoptosis and inflammatory responses in myocardial ischemia by inhibiting MAVS-dependent NLRP3 inflammasome activation," *Molecular Immunology*, vol. 76, pp. 90–97, 2016.

[46] M. Takahashi, "NLRP3 inflammasome as a novel player in myocardial infarction," *International Heart Journal*, vol. 55, no. 2, pp. 101–105, 2014.

[47] W. M. C. Jong and C. J. Zuurbier, "A role for NLRP3 inflammasome in acute myocardial ischaemia-reperfusion injury?*," *Cardiovascular Research*, vol. 99, no. 1, p. 226, 2013.

[48] G. Lordén, I. Sanjuán-García, N. de Pablo et al., "Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation," *Journal of Experimental Medicine*, vol. 214, no. 2, pp. 511–528, 2017.

[49] M. Karmakar, M. A. Katsnelson, G. R. Dubyak, and E. Pearlman, "Neutrophil P2X\textsubscript{7} receptors mediate NLRP3 inflammasome-dependent IL-1β secretion in response to ATP," *Nature Communications*, vol. 7, no. 1, article 10555, 2016.
[50] M. Takahashi, “Role of NLRP3 Inflammasome in cardiac inflammation and remodeling after myocardial infarction,” *Biological & Pharmaceutical Bulletin*, vol. 42, no. 4, pp. 518–523, 2019.

[51] S. Toldo and A. Abbate, “The NLRP3 inflammasome in acute myocardial infarction,” *Nature Reviews Cardiology*, vol. 15, no. 4, pp. 203–214, 2018.

[52] N. J. Byrne, N. Matsumura, Z. H. Maayah et al., “Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure,” *Circulation: Heart Failure*, vol. 13, no. 1, article e006277, 2020.

[53] T. Suetomi, A. Willeford, C. S. Brand et al., “Inflammation and NLRP3 inflammasome activation initiated in response to pressure overload by Ca\(^{2+}\)/calmodulin-dependent protein kinase II δ signaling in cardiomyocytes are essential for adverse cardiac remodeling,” *Circulation*, vol. 138, no. 22, pp. 2530–2544, 2018.

[54] S. Sano, K. Oshima, Y. Wang et al., “Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome,” *Journal of the American College of Cardiology*, vol. 71, no. 8, pp. 875–886, 2018.

[55] P. Hong, R. N. Gu, F. X. Li et al., “NLRP3 inflammasome as a potential treatment in ischemic stroke concomitant with diabetes,” *Journal of Neuroinflammation*, vol. 16, no. 1, p. 121, 2019.

[56] A. G. Mauro, A. Bonaventura, and A. Abbate, “Drugs to inhibit the NLRP3 inflammasome: not always on target,” *Journal of Cardiovascular Pharmacology*, vol. 74, no. 3, pp. 225–227, 2019.

[57] C. J. Zuurbier, “NLRP3 inflammasome in cardioprotective signaling,” *Journal of Cardiovascular Pharmacology*, vol. 74, no. 4, pp. 271–275, 2019.

[58] W. Zhou, C. Chen, Z. Chen et al., “NLRP3: a novel mediator in cardiovascular disease,” *Journal of Immunology Research*, vol. 2018, Article ID 5702103, 8 pages, 2018.

[59] L. E. Pavillard, F. Marín-Aguilar, P. Bullon, and M. D. Cordero, “Cardiovascular diseases, NLRP3 inflammasome, and western dietary patterns,” *Pharmacological Research*, vol. 131, pp. 44–50, 2018.

[60] R. Mastrocola, M. Aragno, G. Alloatti, M. Collino, C. Penna, and P. Fagliaro, “Metaflammation: tissue-specific alterations of the NLRP3 inflammasome platform in metabolic syndrome,” *Current Medicinal Chemistry*, vol. 25, no. 11, pp. 1294–1310, 2018.

[61] N. Song, Z. S. Liu, W. Xue et al., “NLRP3 phosphorylation is an essential priming event for inflammasome activation,” *Molecular Cell*, vol. 68, no. 1, pp. 185–197.e6, 2017.

[62] X. Huang, Z. Feng, Y. Jiang et al., “VSIG4 mediates transcriptional inhibition of Nlrp3and Nlrl1β in macrophages,” *Science Advances*, vol. 5, no. 1, article eaau7426, 2019.

[63] R. C. Coll, J. R. Hill, C. J. Day et al., “MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition,” *Nature Chemical Biology*, vol. 15, no. 6, pp. 556–559, 2019.