

The Role of the NLRP3 in Type 2 Diabetes-Related Inflammation and the Regulatory Impact of Exercise Interventions

Yaodong Guo ¹, Liangchen Li ^{2, *}

¹ Provincial University Key Laboratory of Sport and Health Science, School of Physical Education and Sport Sciences, Fujian Normal University, Fuzhou Fujian, 350007, China

² Guangzhou Sport University, Guangzhou Guangdong, 510500, China

* Corresponding author: Liangchen Li (Email: 2796755635@qq.com)

Abstract: Type 2 diabetes mellitus (T2DM) is a widespread metabolic disorder with a rising global prevalence and is often accompanied by various complications. Chronic inflammation plays a central role in the development and progression of T2DM, with the NLRP3 inflammasome serving as a critical regulator. This inflammasome promotes the release of pro-inflammatory cytokines and induces pyroptotic cell death through caspase-1 activation. In recent years, exercise has emerged as an effective non-pharmacological approach to managing T2DM, partly by inhibiting NLRP3 inflammasome activity and alleviating diabetes-related complications. Various forms of exercise—including aerobic training, resistance training, combined modalities, and high-intensity interval training—can modulate the NLRP3 inflammasome through diverse biological pathways. These interventions help reduce inflammation, enhance metabolic function, and provide systemic protective effects. This review outlines the structure and activation mechanisms of the NLRP3 inflammasome and comprehensively examines how different exercise modalities influence its regulation. The findings offer valuable insights and scientific support for incorporating exercise into the prevention and management strategies for T2DM.

Keywords: NLRP3; T2DM; Inflammation; Exercise.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and progressive β -cell dysfunction. Over recent decades, its prevalence has increased at an alarming rate, making T2DM one of the most pressing global public health challenges. According to projections from the International Diabetes Federation, the number of individuals living with diabetes is expected to exceed 578 million by 2030 and approach 700 million by 2045, underscoring the magnitude of its future burden. Beyond its high prevalence, T2DM is associated with a wide spectrum of long-term complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, which collectively contribute to reduced quality of life and increased mortality. These complications, rather than hyperglycemia per se, account for the majority of diabetes-related healthcare costs and adverse outcomes, highlighting the need to better understand the underlying mechanisms driving disease progression.

Traditionally, T2DM has been viewed primarily as a disorder of glucose metabolism. However, accumulating evidence suggests that this perspective is overly narrow and fails to capture the complex biological processes involved in disease development. In recent years, chronic low-grade inflammation has emerged as a central pathological feature linking obesity, insulin resistance, and vascular dysfunction in T2DM. Inflammation is a fundamental immune response that protects the body against infection and tissue injury, yet when persistently activated at low levels, it may exert deleterious effects on metabolic homeostasis. Unlike acute inflammation, chronic low-grade inflammation is often clinically silent and characterized by sustained elevations in

proinflammatory mediators and continuous activation of innate immune pathways. This inflammatory state is now widely recognized as a key contributor to the initiation and progression of T2DM.

Adipose tissue plays a pivotal role in this process. In the context of obesity, adipose tissue undergoes marked structural and functional remodeling, transitioning from a relatively inert energy storage depot to an active endocrine and immunological organ. Adipocyte hypertrophy, local hypoxia, and lipid overload promote the recruitment and activation of immune cells, particularly proinflammatory macrophages. These cells secrete cytokines such as tumor necrosis factor- α and interleukin-6, which interfere with insulin signaling through multiple mechanisms, including impaired insulin receptor substrate phosphorylation and disrupted downstream signaling cascades. As a result, insulin sensitivity in skeletal muscle, liver, and adipose tissue is progressively reduced, establishing a systemic state of insulin resistance.

Importantly, the impact of chronic inflammation extends beyond metabolic tissues and profoundly affects the vascular system. Endothelial dysfunction is a hallmark of diabetic vasculopathy and a critical early event in the development of both macrovascular and microvascular complications. Under physiological conditions, endothelial cells maintain vascular homeostasis by regulating vasodilation, inhibiting thrombosis, and modulating inflammatory responses. In T2DM, prolonged exposure to hyperglycemia and inflammatory mediators increases oxidative stress, reduces nitric oxide bioavailability, and promotes a pro-inflammatory and pro-atherogenic endothelial phenotype. These changes accelerate atherosclerosis and contribute to microvascular injury in organs such as the retina and kidney. Thus, inflammation represents a mechanistic bridge connecting metabolic

dysregulation to vascular damage in T2DM.

At the molecular level, increasing attention has focused on the role of innate immune sensors in mediating inflammation-driven metabolic dysfunction. Among these, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome has emerged as a critical regulatory node. The NLRP3 inflammasome is a multiprotein complex that functions as a cytosolic danger sensor, responding to a wide range of metabolic stress signals, including excess nutrients, reactive oxygen species, and mitochondrial dysfunction. Upon activation, NLRP3 promotes the cleavage of procaspase-1 into its active form, leading to the maturation and release of the potent proinflammatory cytokines interleukin-1 β and interleukin-18, as well as the induction of pyroptotic cell death.

Evidence increasingly suggests that aberrant activation of the NLRP3 inflammasome plays a crucial role in T2DM-related inflammation. Beyond its well-established function in immune cells, NLRP3 is expressed in multiple non-immune cell types relevant to diabetic complications, including endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Activation of NLRP3 in these cells has been linked to endothelial dysfunction, vascular inflammation, and impaired tissue repair, suggesting that it serves as a key mediator translating metabolic stress into inflammatory vascular injury. Consequently, NLRP3 has been proposed as a central molecular hub integrating metabolic disturbances with inflammatory signaling in T2DM.

Given its pivotal role, modulation of NLRP3 activity has attracted growing interest as a potential therapeutic strategy. While pharmacological approaches targeting inflammatory pathways are under active investigation, non-pharmacological interventions have gained increasing attention due to their safety, accessibility, and broad physiological benefits. Among these, physical exercise is widely recognized as a cornerstone of T2DM management. Beyond its well-documented effects on glycemic control, body composition, and cardiovascular fitness, exercise exerts profound anti-inflammatory effects that may directly influence NLRP3 signaling.

Emerging evidence indicates that regular exercise can attenuate chronic low-grade inflammation by reducing adipose tissue mass, improving mitochondrial function, and enhancing antioxidant capacity. Moreover, skeletal muscle contraction induces the release of myokines with immunomodulatory properties, which may counteract proinflammatory signaling at the systemic level. Experimental studies suggest that exercise may suppress NLRP3 inflammasome activation through multiple mechanisms, including the reduction of oxidative stress, improvement of mitochondrial quality control, and modulation of upstream inflammatory signaling pathways. These effects position exercise as a promising, mechanism-based intervention capable of targeting both metabolic and inflammatory components of T2DM.

Despite growing interest, current evidence regarding the interaction between exercise and NLRP3-mediated inflammation remains fragmented. Differences in exercise modality, intensity, duration, and study population have led to heterogeneous findings, making it challenging to draw definitive conclusions. A systematic synthesis of existing evidence is therefore needed to clarify how exercise interventions influence NLRP3 activity and related inflammatory processes in the context of T2DM.

Accordingly, the purpose of this review is to provide an integrated overview of the role of the NLRP3 inflammasome in T2DM-related inflammation and to examine the regulatory effects of exercise interventions on this pathway. Specifically, this review will summarize the structure and activation mechanisms of the NLRP3 inflammasome, evaluate current evidence linking NLRP3 activation to metabolic and vascular dysfunction in T2DM, and discuss how different forms of exercise may modulate NLRP3-mediated inflammatory responses. By integrating findings from basic and clinical research, this review aims to highlight the potential of exercise as a targeted, mechanism-oriented strategy for mitigating inflammation and improving outcomes in individuals with T2DM.

2. The NLRP3 Inflammasome: Structural Components and Activation Process

2.1. Structure of the NLRP3 Inflammasome

The NLRP3 inflammasome is a cytoplasmic innate immune signaling complex whose classical composition comprises the receptor NLRP3, the adaptor protein ASC, and the effector protein procaspase-1. These three components complete the “recognition-assembly-effect” cascade through homodimerization mediated by the death domain family. At the domain level, NLRP3 exhibits a typical three-domain configuration: N-terminal PYD, central NACHT, and C-terminal LRR. During assembly, NLRP3's PYD recruits ASC via PYD–PYD interactions, while ASC further connects procaspase-1 through CARD - CARD interactions, thereby providing a scaffold for the close-proximity aggregation and activation of caspase-1(1, 2). Unlike static ternary complexes, the core structural significance of ASC within inflammasomes lies in its capacity for higher-order aggregation, forming signal-amplifying aggregates. Cai et al. (2014) demonstrated at the cellular and biochemical levels that ASC undergoes prion-like aggregation, thereby translating upstream receptor-triggered events into observable higher-order assemblies(3). Dick et al. (2016) further provided structural and mechanistic evidence demonstrating that ASC speck formation involves filamentous oligomerization of ASC ^ PYD and cross-linking of filamentous structures by ASC ^ CARD, thereby elucidating the structural basis for “threshold amplification” during inflammasome assembly(4).

The ATP-binding / hydrolysis capacity and oligomerization propensity of the NACHT domain constitute the key conformational drivers for NLRP3's transition from a resting state to assembly. However, NLRP3 is often not activated by direct recognition of a single common ligand, but is more commonly regarded as responding to common intracellular homeostasis disturbances triggered by multiple types of stimuli. This is also one of the sources of its structural regulatory complexity(2). Regarding the “licensing” step, Shi et al. (2016) identified NEK7 as a cytokine essential for NLRP3 activation and assembly, positioning it as a critical node occurring after ion homeostasis alterations but before ASC recruitment(5). Sharif et al. (2019) further resolved the cryo-EM structure of the NLRP3–NEK7 complex, providing a structural explanation for how NEK7 stabilizes NLRP3 conformation and “opens the floodgates” for subsequent assembly(6). At a level closer to the full-length conformation, Ohto et al. (2022) reported the oligomeric structure of full-

length NLRP3. Combined with the inhibitor MCC950, they elucidated the structural basis for its regulation of NLRP3 conformation stability and oligomerization, providing direct evidence for “structure-drugs” docking(7).

At the effector end, procaspase-1 recruitment is not merely passive insertion; its CARD-mediated aggregation also exhibits self-organizing characteristics. Li et al. (2018) revealed through cryo-EM evidence of CARD filamentous structures that ASC / NLRC4 can promote caspase-1 CARD nucleation and assembly via CARD aggregation, structurally elucidating the spatial organization of caspase-1 activation(8). Moreover, inflammasome effects are not infinitely amplified: Boucher et al. (2018) proposed that caspase-1 self-cleavage serves as an intrinsic mechanism to terminate inflammasome activity, establishing a molecular basis for a closed-loop “assembly-activation-termination” cycle(9). Thus, the evidence chain spanning structural composition, assembly morphology, and critical licensing/termination steps collectively indicates that NLRP3 inflammasome is not a simple “tripartite assembly”, but rather a dynamic structural system driven by NLRP3 conformational transitions, ASC higher-order aggregation, and caspase-1 aggregation-activated activation.

2.2. Activation and Regulatory Mechanisms of the NLRP3 Inflammasome

The activation of the NLRP3 inflammasome involves the integrated actions of multiple intracellular and extracellular signals. In general, NLRP3 activation is described as a two-signal process: the priming signal is triggered by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), leading to activation of the NF- κ B pathway and upregulation of NLRP3 as well as pro-inflammatory cytokine precursors; the second signal is elicited by various stressors that promote NLRP3 oligomerization and inflammasome assembly (activation and regulation of the inflammasome)(10). Under mitochondrial stress, the generation of mitochondrial ROS and calcium overload are considered key triggers. In addition, potassium efflux is regarded as an important step in NLRP3 activation, and this process is accompanied by direct binding of NEK7 to NLRP3, thereby facilitating inflammasome assembly (mitochondrial stress: mechanistic insights into NLRP3 inflammasome activation) (recent advances in mechanisms of NLRP3 inflammasome activation and its inhibitors)(10). Changes in lysosomal membrane permeability also play an important role in NLRP3 activation; upon lysosomal rupture, released cysteine cathepsins such as cathepsin B can further promote NLRP3 activation(11). These proteases may modulate inflammasome activity and autophagic degradation through interactions with autophagy-related proteins. Moreover, chloride and sodium fluxes have been proposed as potential regulatory factors, although the underlying mechanisms remain incompletely understood. Collectively, these mechanisms position the NLRP3 inflammasome as a critical regulator of diverse inflammatory responses, ultimately inducing the maturation and release of IL-1 β and IL-18 and promoting pyroptosis and other forms of inflammatory cell death, thereby exerting important immunomodulatory effects(12).

3. Pathological Association Between the NLRP3 Inflammasome and Type 2 Diabetes Mellitus

The NLRP3 inflammasome plays a pivotal role in the pathogenesis of T2DM and its associated complications, with its activation closely linked to vascular inflammation, atherosclerosis, and pyroptosis. Under hyperglycemic conditions, NLRP3 is activated in peripheral blood mononuclear cells, leading to the release of the pro-inflammatory cytokine IL-1 β . This, in turn, triggers endothelial inflammation and contributes to the development of atherosclerotic lesions(13). In murine models, knockdown of NLRP3 has been shown to reduce the expression of vascular adhesion molecules and attenuate atherosclerosis, suggesting that NLRP3 may serve as a promising therapeutic target for diabetic vascular complications(14). Furthermore, NLRP3-mediated pyroptosis contributes to pancreatic β -cell dysfunction and insulin resistance by promoting the release of pro-inflammatory cytokines, including IL-1 β and IL-18, thereby exacerbating the inflammatory milieu in T2DM. Pharmacological inhibition of NLRP3, such as with the small molecule inhibitor MCC950, has demonstrated potential in alleviating inflammation and delaying the progression of diabetic complications. Recent reviews further emphasize that NLRP3 activation, triggered by diverse inflammatory signals, amplifies downstream inflammatory responses, aggravates insulin resistance, and disrupts glucose homeostasis, thereby accelerating metabolic deterioration in T2DM. Additionally, NLRP3 is implicated in lipid metabolism regulation and gut microbiota homeostasis. Its excessive activation may aggravate systemic inflammation and metabolic dysregulation, thus playing a critical role in the progression of T2DM and the development of its complications(13).

4. Regulation of the NLRP3 Inflammasome by Different Types of Exercise

4.1. Regulation of the NLRP3 Inflammasome by Aerobic Exercise

Firstly, aerobic exercise can suppress oxidative stress by upregulating antioxidant pathways such as Nrf2, thereby reducing NLRP3 inflammasome activation and alleviating cerebral ischemia-reperfusion injury(15). In addition, aerobic exercise modulates fibroblast growth factor 21 (FGF21) to reduce pyroptosis mediated by the NLRP3 inflammasome, thereby mitigating atherosclerosis(16). Sustained moderate-intensity aerobic exercise also alleviates chronic inflammatory burden by improving mitochondrial function and reducing NLRP3 activity(17). Aerobic exercise influences NLRP3 inflammasome activation through the regulation of metabolic signaling pathways, such as reducing pro-inflammatory responses via cholesterol metabolism and oxidative stress pathways(18). It also modulates neuroinflammation associated with post-stroke depression via the NF- κ B/NLRP3/5-HT pathway, effectively relieving depressive symptoms(19). Under hyperglycemic conditions, CD38-mediated Ca²⁺ signaling exacerbates NLRP3 activation, suggesting that aerobic exercise may attenuate diabetes-related vascular inflammation by inhibiting CD38 activity or calcium release(20).

Furthermore, the use of the MCC950 inhibitor confirms the role of NLRP3 activation in worsening cerebral ischemic injury, indicating that aerobic exercise may alleviate brain damage through similar mechanisms(20). In kidney disease and inflammatory bowel disease, NLRP3 activation is closely associated with tissue fibrosis and chronic inflammation; aerobic exercise may help attenuate these pathological changes by downregulating NLRP3 activity(21, 22).

In summary, these studies demonstrate that aerobic exercise regulates the NLRP3 inflammasome through multiple mechanisms and offers potential anti-inflammatory benefits across a range of disease conditions.

4.2. High-intensity Interval Training Regulates the NLRP3 Inflammasome

High-intensity interval training (HIIT) has attracted growing attention as a time-efficient exercise modality capable of eliciting pronounced metabolic and inflammatory adaptations. Emerging evidence suggests that HIIT may suppress NLRP3 inflammasome activity through multiple, interrelated mechanisms. In intervention studies, HIIT has been shown to downregulate NLRP3 gene expression, accompanied by reduced secretion of the pro-inflammatory cytokines IL-1 β and IL-18, thereby attenuating chronic low-grade inflammation(23). Beyond direct effects on inflammasome components, HIIT appears to influence upstream and downstream regulatory pathways relevant to NLRP3 signaling. Reduced expression of ACE2 in adipose tissue and skeletal muscle following HIIT has been associated with attenuation of NLRP3-related pyroptotic signaling, suggesting a potential role in limiting inflammatory cell death(23). In parallel, HIIT upregulates FNDC5, a myokine-related factor that activates the AMPK pathway, enhances antioxidant enzyme activity, and suppresses NF- κ B signaling. Through these mechanisms, HIIT may simultaneously dampen inflammasome priming and reduce oxidative stress-driven activation, creating an unfavorable environment for sustained NLRP3 signaling.

Compared with moderate-intensity continuous exercise, HIIT may exert unique regulatory effects on the inflammasome by rapidly altering cellular energy balance and redox status. These acute but potent metabolic perturbations could partially explain its influence on inflammatory signaling pathways. Nevertheless, current evidence is primarily derived from specific populations, such as individuals with obesity, and the mechanistic links between HIIT, ACE2 modulation, FNDC5 signaling, and NLRP3 activation remain incompletely defined.

Overall, available findings support the notion that HIIT can modulate NLRP3 inflammasome activity through coordinated effects on inflammatory priming, oxidative stress, and pyroptosis-related pathways. Further studies, particularly in individuals with type 2 diabetes, are needed to clarify the tissue-specific responses and long-term implications of HIIT-based interventions for inflammasome regulation.

4.3. The Regulation of the NLRP3 Inflammasome by Resistance Exercise

Emerging evidence from both experimental models and human intervention studies suggests that resistance exercise may attenuate metabolic inflammation, at least in part, through inhibition of NLRP3 inflammasome activation. In animal models of high-fat diet-induced metabolic dysfunction, both resistance and endurance training improve

overall metabolic profiles. However, resistance training appears to exert a more pronounced suppressive effect on NLRP3-related gene expression in adipose tissue, implying that different exercise modalities may engage distinct inflammatory regulatory pathways.

Human studies provide further support for this observation. In a randomized intervention involving older adults with prediabetes, long-term exercise programs incorporating resistance training were associated with improved insulin sensitivity and reduced liver injury, alongside decreased NLRP3 inflammasome activity in peripheral blood mononuclear cells (PBMCs) (24). Notably, NLRP3 activation showed positive correlations with markers of insulin resistance and hepatic dysfunction, reinforcing its relevance to metabolic impairment. Similarly, resistance training in healthy older adults has been linked to reduced NLRP3 inflammasome activation in PBMCs, accompanied by enhanced autophagic activity and reduced cellular damage(25). These findings suggest that resistance exercise may influence inflammasome regulation through mechanisms related to cellular quality control and inflammatory stress buffering.

Compared with aerobic exercise, resistance training may exert unique anti-inflammatory effects by promoting skeletal muscle remodeling and increasing muscle mass, thereby altering systemic metabolic demand and inflammatory signaling. Improvements in autophagy and mitochondrial quality control observed after resistance training are consistent with regulatory pathways known to constrain NLRP3 activation, as outlined earlier. Although existing studies vary in design and population characteristics, the converging evidence supports a potential role for resistance exercise in modulating NLRP3-driven metabolic inflammation.

Nevertheless, current data remain limited, particularly in individuals with established type 2 diabetes. Further well-controlled studies are needed to clarify the dose-response relationship, tissue-specific effects, and long-term impact of resistance training on NLRP3 inflammasome activity in clinical populations. Such work will be essential for defining the therapeutic value of resistance exercise as a targeted component of lifestyle interventions for T2DM.

4.4. The Regulation of the NLRP3 Inflammasome by Combined Aerobic and Resistance Exercise

NLRP3 inflammasome through mechanisms that extend beyond those observed with single-modality training. A 12-week intervention integrating aerobic and resistance exercise has been shown to remodel the gut microbiota of children with obesity toward a healthier composition, accompanied by reduced intestinal permeability and attenuation of lipopolysaccharide (LPS)-driven TLR4 signaling(26). Given the role of TLR4-NF- κ B signaling in inflammasome priming, these changes may lower the basal inflammatory tone required for NLRP3 activation.

In parallel, combined exercise increases the production of anti-inflammatory short-chain fatty acids while reducing pro-inflammatory metabolites, further weakening inflammasome-related signaling. These microbiota-derived metabolites are known to influence systemic immune responses and may indirectly modulate NLRP3 activation thresholds. In addition, reductions in osteopontin (OPN) levels following exercise have been associated with restrained release of inflammatory

mediators, contributing to the alleviation of chronic low-grade inflammation at the systemic level (26).

Although current evidence is largely derived from specific populations, such as children with obesity, these findings highlight the potential advantage of combined exercise modalities in targeting multiple upstream drivers of NLRP3 activation simultaneously. By improving metabolic status, reinforcing gut barrier integrity, and dampening inflammatory priming signals, combined aerobic and resistance exercise may influence both the initiation and amplification phases of inflammasome activation. Collectively, these observations support a multi-pathway, multi-level regulatory role of combined exercise interventions on the NLRP3 inflammasome, providing a mechanistic rationale for their application in the non-pharmacological management of T2DM and related metabolic inflammatory disorders.

5. Summary and Future Prospects

An increasing number of studies now suggest that type 2 diabetes mellitus cannot be adequately described as a disorder of glucose metabolism alone. Rather, it reflects a broader, systemic disturbance in which metabolic stress and chronic low-grade inflammation remain intertwined over time. Within this framework, the NLRP3 inflammasome has drawn particular attention, as it appears to sit at the crossroads of nutrient overload, oxidative stress, and innate immune activation. Evidence discussed in this review points to a role for dysregulated NLRP3 activity in both metabolic dysfunction and diabetes-related vascular injury. Notably, its influence is not confined to immune cells; endothelial cells, vascular smooth muscle cells, and cardiomyocytes also seem to be involved. Against this backdrop, exercise emerges as more than a general lifestyle recommendation, showing potential to influence this inflammatory pathway and offering a mechanistically plausible, non-pharmacological option for T2DM management.

That said, the current picture is far from complete. One unresolved issue concerns timing. It is still difficult to determine when NLRP3 activation becomes most relevant during the course of T2DM. Does it contribute early on, helping to trigger insulin resistance, or does it mainly reflect prolonged metabolic stress? Alternatively, it may act as a reinforcing mechanism, once activated, further accelerating disease progression. Adding to this uncertainty, much of what we know about these processes comes from experimental models. How well these findings translate to human T2DM—especially given the wide variability in clinical presentation—remains an open question.

There are also clear gaps in our understanding of tissue- and cell-specific regulation. While adipose tissue inflammation has understandably received much attention, recent work suggests that NLRP3 activation in non-immune cells, particularly within the vascular endothelium, may be especially relevant for diabetic vascular complications. Whether similar regulatory mechanisms operate across different tissues, or whether each cell type responds to metabolic stress in a distinct manner, is still poorly defined. Addressing this issue will likely require more targeted, cell-specific approaches than those commonly used to date.

The same complexity applies to exercise-based interventions. Although exercise is consistently associated with anti-inflammatory effects, findings related specifically to NLRP3 regulation are not always consistent. Differences in exercise mode, intensity, duration, and participant

characteristics make it difficult to compare studies directly or to draw firm conclusions. Aerobic training, resistance exercise, and high-intensity interval training may all affect NLRP3 signaling, but possibly through different mechanisms involving mitochondrial function, redox balance, or inflammatory signaling pathways. At present, the lack of methodological consistency limits our ability to define clear mechanistic patterns.

Looking ahead, future research would benefit from longitudinal, mechanism-driven designs that track NLRP3-related responses across different stages of T2DM. Greater integration between inflammasome biology and exercise prescription research may help clarify how metabolic stress and physical activity interact at the tissue level. Ultimately, viewing exercise through an immunometabolic lens may improve its translational relevance and support the development of more targeted, individualized strategies for preventing and managing T2DM and its complications.

References

- [1] Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell*. 2002;10(2):417-26.
- [2] Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol*. 2019;19(8):477-89.
- [3] Cai X, Chen J, Xu H, Liu S, Jiang QX, Halfmann R, Chen ZJ. Prion-like polymerization underlies signal transduction in antiviral immune defense and inflammasome activation. *Cell*. 2014;156(6):1207-22.
- [4] Dick MS, Sborgi L, Rühl S, Hiller S, Broz P. ASC filament formation serves as a signal amplification mechanism for inflammasomes. *Nat Commun*. 2016;7:11929.
- [5] Shi H, Wang Y, Li X, Zhan X, Tang M, Fina M, et al. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. *Nat Immunol*. 2016;17(3):250-8.
- [6] Sharif H, Wang L, Wang WL, Magupalli VG, Andreeva L, Qiao Q, et al. Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. *Nature*. 2019;570 (7761): 338-43.
- [7] Ohto U, Kamitsukasa Y, Ishida H, Zhang Z, Murakami K, Hirama C, et al. Structural basis for the oligomerization-mediated regulation of NLRP3 inflammasome activation. *Proc Natl Acad Sci U S A*. 2022;119(11):e2121353119.
- [8] Li Y, Fu TM, Lu A, Witt K, Ruan J, Shen C, Wu H. Cryo-EM structures of ASC and NLRC4 CARD filaments reveal a unified mechanism of nucleation and activation of caspase-1. *Proc Natl Acad Sci U S A*. 2018;115(43):10845-52.
- [9] Boucher D, Monteleone M, Coll RC, Chen KW, Ross CM, Teo JL, et al. Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. *J Exp Med*. 2018;215 (3): 827-40.
- [10] Campden RI, Zhang Y. The role of lysosomal cysteine cathepsins in NLRP3 inflammasome activation. *Arch Biochem Biophys*. 2019;670:32-42.
- [11] Latz E, Xiao TS, Stutz A. Activation and regulation of the inflammasomes. *Nat Rev Immunol*. 2013;13(6):397-411.
- [12] Yabal M, Calleja DJ, Simpson DS, Lawlor KE. Stressing out the mitochondria: Mechanistic insights into NLRP3 inflammasome activation. *J Leukoc Biol*. 2019;105(2):377-99.

- [13] Wan Z, Fan Y, Liu X, Xue J, Han Z, Zhu C, Wang X. NLRP3 inflammasome promotes diabetes-induced endothelial inflammation and atherosclerosis. *Diabetes Metab Syndr Obes.* 2019; 12:1931-42.
- [14] Ding S, Xu S, Ma Y, Liu G, Jang H, Fang J. Modulatory Mechanisms of the NLRP3 Inflammasomes in Diabetes. *Biomolecules.* 2019;9(12).
- [15] Hou Y, Wang Y, He Q, Li L, Xie H, Zhao Y, Zhao J. Nrf2 inhibits NLRP3 inflammasome activation through regulating Trx1/TXNIP complex in cerebral ischemia reperfusion injury. *Behav Brain Res.* 2018;336:32-9.
- [16] Li XH, Liu LZ, Chen L, Pan QN, Ouyang ZY, Fan DJ, et al. Aerobic exercise regulates FGF21 and NLRP3 inflammasome-mediated pyroptosis and inhibits atherosclerosis in mice. *PLoS One.* 2022;17(8):e0273527.
- [17] Zhang T, Ding S, Wang R. Research Progress of Mitochondrial Mechanism in NLRP3 Inflammasome Activation and Exercise Regulation of NLRP3 Inflammasome. *Int J Mol Sci.* 2021;22(19).
- [18] Ortega MA, De Leon-Oliva D, García-Montero C, Fraile-Martínez O, Boaru DL, de Castro AV, et al. Reframing the link between metabolism and NLRP3 inflammasome: therapeutic opportunities. *Front Immunol.* 2023;14:1232629.
- [19] Guo C, Chi Z, Jiang D, Xu T, Yu W, Wang Z, et al. Cholesterol Homeostatic Regulator SCAP-SREBP2 Integrates NLRP3 Inflammasome Activation and Cholesterol Biosynthetic Signaling in Macrophages. *Immunity.* 2018;49(5):842-56.e7.
- [20] Li JP, Wei W, Li XX, Xu M. Regulation of NLRP3 inflammasome by CD38 through cADPR-mediated Ca²⁺ release in vascular smooth muscle cells in diabetic mice. *Life Sci.* 2020;255:117758.
- [21] Wang H, Zhong D, Chen H, Jin J, Liu Q, Li G. NLRP3 inflammasome activates interleukin-23/interleukin-17 axis during ischaemia-reperfusion injury in cerebral ischaemia in mice. *Life Sci.* 2019;227:101-13.
- [22] Mulay SR. Multifactorial functions of the inflammasome component NLRP3 in pathogenesis of chronic kidney diseases. *Kidney Int.* 2019;96(1):58-66.
- [23] Armannia F, Ghazalian F, Shadnouch M, Keyvani H, Gholami M. Effects of High-Intensity Interval Vs. Moderate-Intensity Continuous Training on Body Composition and Gene Expression of ACE2, NLRP3, and FNDC5 in Obese Adults: A Randomized Controlled Trial. *Med J Islam Repub Iran.* 2022;36:161.
- [24] Zhang T, Tian J, Fan J, Liu X, Wang R. Exercise training-attenuated insulin resistance and liver injury in elderly pre-diabetic patients correlates with NLRP3 inflammasome. *Front Immunol.* 2023;14:1082050.
- [25] Mejías-Peña Y, Estébanez B, Rodríguez-Miguel P, Fernández-Gonzalo R, Almar M, de Paz JA, et al. Impact of resistance training on the autophagy-inflammation-apoptosis crosstalk in elderly subjects. *Aging (Albany NY).* 2017;9(2): 408-18.
- [26] Quiroga R, Nistal E, Estébanez B, Porras D, Juárez-Fernández M, Martínez-Flórez S, et al. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. *Exp Mol Med.* 2020;52(7):1048-61.