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综 述

NLRP3炎症小体在糖尿病及运动中作用的研究进展

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摘 要：慢性非感染性炎症反应已经被证明是糖尿病发生和发展过程中的重要标志，伴有大量炎症因子的产生，从而加重疾病进程。运动作为诸多无创性抑制炎症反应的重要干预措施，在改善糖尿病症状中有着极为重要的作用。核苷酸结合寡聚化结构域样受体蛋白3 (NOD-like receptor protein 3, NLRP3)炎症小体作为炎症反应的调控因子，通常可以引发多种炎症级联反应和细胞焦亡，与葡萄糖的摄取和血脂异常密切相关。运动可以延缓糖尿病的发病进程，以往的研究聚焦于NLRP3炎症小体对糖尿病的作用，但并未系统阐明运动对该作用的影响。因此，本文综述运动干预通过介导NLRP3炎症小体改善糖尿病症状的研究进展，为运动防治糖尿病提供新的理论基础。

关键词：NLRP3炎症小体；糖尿病；运动

Role of NLRP3 inflammasome in diabetes mellitus and exercise intervention

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Abstract: Chronic inflammatory reaction has been established as an important sign of the occurrence and development of diabetes mellitus (DM), accompanied by the production of a large number of inflammatory factors, thus aggravating the disease progression. As an important non-invasive intervention measure to inhibit inflammation, exercise plays a very important role in the amelioration of DM. NOD-like receptor protein 3 (NLRP3) inflammasome, a regulatory factor of inflammatory response, can induce a variety of inflammatory cascades and cell death, which are closely related to glucose uptake and dyslipidemia regulation. The development of DM can be postponed with exercise. Previous studies have reported the effects of NLRP3 inflammasome on DM, but the crucial role of exercise in this process remains unclear. Therefore, this paper reviews the research progress on the improving effects of exercise intervention on the symptoms of DM by mediating NLRP3 inflammasome, providing a novel theoretical foundation for understanding the prevention and treatment of DM through exercise.

Key words: NLRP3 inflammasome; diabetes mellitus; exercise

据国际糖尿病联盟 (International Diabetes Federation, IDF) 统计，预计到 2045 年，全球糖尿病患者 (≥18 岁) 将会达到 6.93 亿 [1]。糖尿病是由于胰岛素分泌异常或 / 和作用缺陷，导致同化和异化失衡，伴随血糖水平升高的一种慢性代谢性疾病 [2]，常伴有糖尿病心肌病、糖尿病肾病、动脉粥样硬化等疾病的发生 [3]。众多研究显示，机体慢性非感染性炎症是糖尿病发生和发展的重要因素 [4]，其标志特征包括促炎因子的升高，如白细胞介素 -1β (interleukin-1β, IL-1β) 和肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)，抗炎因子水平的降低，如转化生长因子 -β (transforming growth factor β, TGF-β)、IL-22 [5]， 但

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目前炎症反应产生的机制尚不完全清楚。最近证据表明，核苷酸结合寡聚化结构域样受体蛋白3 (NOD-like receptor protein 3, NLRP3) 炎症小体可以调节脂肪组织中内质网应激介导的糖耐量降低、胰岛素抵抗 (insulin resistance, IR)、炎症细胞凋亡和内皮功能障碍 [6]，其大量积累将加速IR的进展 [7]，因此，抑制NLRP3炎症小体的表达就显得极为重要。Vandanmagsar等研究显示，减少热量摄入和运动均可以抑制脂肪组织中NLRP3炎症小体表达，进而缓解肥胖的发展 [8]，自此，关于运动干预NLRP3炎症小体的研究迅速增加。Hu等发现12周太极拳训练能够下调糖尿病前期患者血清中NIMA相关蛋白激酶7 (never in mitosis gene A-related kinase 7, NEK7)、NLRP3炎症小体、活性氧 (reactive oxygen species, ROS)、IL-1β和IL-18水平，进而有效缓解全身炎症，降低血糖、血脂水平，改善IR症状 [9]。本研究组前期研究显示，适宜的有氧运动可以抑制肥胖小鼠的心脏和睾丸组织中炎症的进展，从而改善性腺和心脏功能 [10, 11]。但是目前关于NLRP3炎症小体是否参与运动干预对糖尿病的改善作用未进行系统阐述。因此，本文就NLRP3炎症小体的结构、激活机制、NLRP3炎症小体与糖尿病的关系等方面进行文献综述，并重点阐述不同运动方式干预NLRP3炎症小体，最终延缓糖尿病病程的相关机制，以期为运动治疗糖尿病提供新视角。

1 NLRP3炎症小体概述

1.1 NLRP3炎症小体的结构

NLRP3炎症小体是一种存在于细胞质中的高分子蛋白复合物，由NLRP3蛋白、凋亡相关斑点样蛋白 (apoptosis-associated speck-like protein, ASC) 和“效应器”前半胱天冬氨酸特异性蛋白酶-1 (pro-cysteinyl aspartate specific proteinase-1, pro-caspase-1) 组成 [12]，NLRP3作为NLRP3炎症小体的识别蛋白，主要由C端富含亮氨酸重复结构域 (leucine-rich repeat, LRR)、中央核苷酸结合寡聚化结构域 (nucleotide-binding oligomerization domain, NACHT) 和N端Pyrin结构域 (Pyrin domain, PYD) 三部分构成 [13]，其中的LRR负责识别相应配体，LRR泛素化后，诱导顶端分子机制，调节相应的泛素连接酶，从而调控NLRP3炎症小体的启动，同时介导自身调控和蛋白间的相互作用 [14, 15]；NACHT除了具有促进自身寡聚化的功能外，还具有ATP活性，可促进凋亡蛋白酶活化因子的活化 [16, 17]；而PYD主要负责募集下游效应信号分子。ASC以接头蛋白的形式存在，主要由PYD和半胱天冬氨酸特异性蛋白酶募集结构域 (caspase-activation and recruitment domain, CARD) 构成，分别能与上游NLRP3的PYD和下游pro-caspase-1中的CARD相互结合，产生NLRP3炎症小体 [18]；而由CARD构成的pro-caspase-1作为NLRP3炎症小体的效应蛋白，在静息状态下以pro-caspase-1的形式存在，在接受外界刺激后，自行剪切成caspase-1，进而诱发炎症反应 [19]。

1.2 NLRP3炎症小体的激活机制

在正常情况下，内源性应激产生的病原体相关分子模式 (pathogen-associated molecular patterns, PAMPs) 或损伤相关分子模式 (damage-associated molecular patterns, DAMPs) 并不足以启动NLRP3炎症小体的激活，此时的pro-caspase-1、pro-IL-1β和pro-IL-18的含量处于较低水平 [20]；当机体受到异常的内外部威胁刺激，打破机体平衡后，NLRP3炎症小体立即组装并激活 [21]；而NLRP3炎症小体激活一般需要两个过程，第一步即启动信号，当PAMPs或DAMPs被Toll样受体 (Toll-like receptors, TLRs) 识别后，将诱导核因子kappa B (nuclear factor-kappa B, NF-κB) 的活化，进而上调pro-caspase-1、pro-IL-1β和pro-IL-18的表达 [22]；第二步主要为NLRP3炎症小体的组装，在启动步骤后，PAMPs或DAMPs诱导机体发生功能上的异常，如K^+外流、溶酶体损伤、ROS与线粒体功能障碍等，进一步诱导NLRP3激活 [23–25]，当受体蛋白在接受刺激后，通常会招募含有PYD结构域的ASC，并与NLRP3中的PYD相互连接，进一步形成NLRP3-ASC复合物 [26]，暴露后的CARD将会与无活性的pro-caspase-1中的CARD相互连接，pro-caspase-1可自行剪切形成有活性的caspase-1，而caspase-1可以将pro-IL-1β和pro-IL-18切割为成熟且具有生物活性的IL-1β和IL-18 [27]；此外，活化的caspase-1还可以剪切消皮素D (gasdermin D, GSDMD) 并释放其N末端结构域，该结构域转移到细胞膜并形成孔，介导炎性细胞因子IL-1β和IL-18的释放，从而引发炎症级联反应 [28] (图1)。

2 NLRP3炎症小体与糖尿病的关系

2.1 NLRP3炎症小体与1型糖尿病(type 1 diabetes mellitus, T1DM)的关系

T1DM主要是由于胰岛β细胞破坏所引起的，身体无法维持胰岛素水平以达到葡萄糖稳态的自身

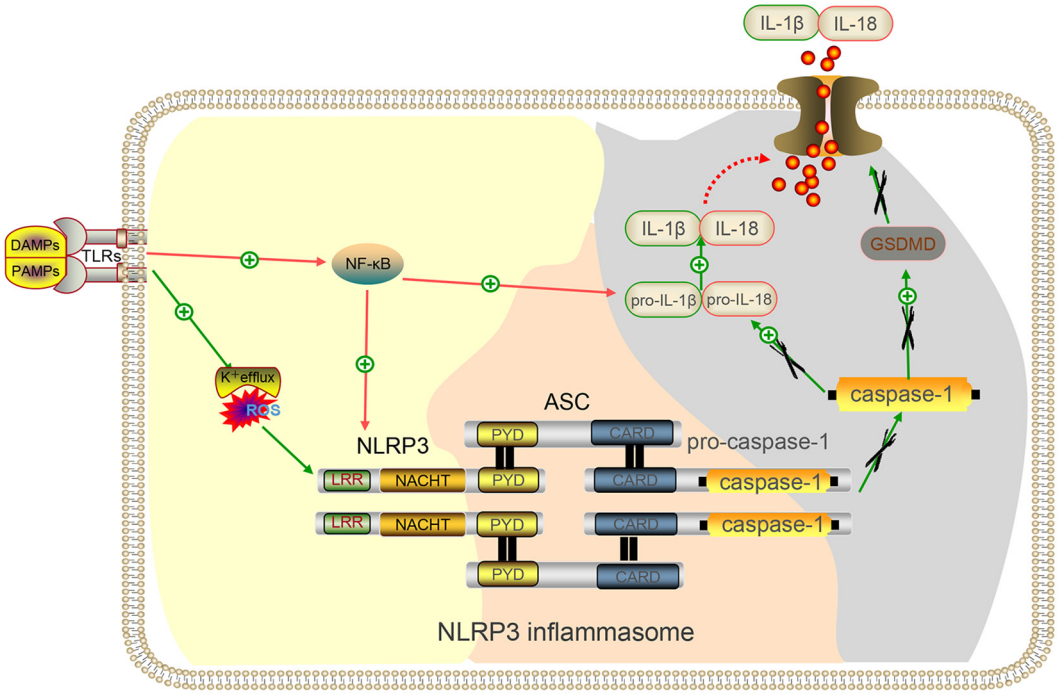

图 1. NLRP3炎症小体的激活机制

Fig. 1. Activation mechanism of NLRP3 inflammasome. Two biological processes must occur for NLRP3 inflammasome activation. The initial step is signal priming. NF-κB is activated when PAMPs or DAMPs activate NLRP3's LRR. Furthermore, there are elevated expression levels pro-IL-1β and pro-IL-18. The NLRP3 inflammasome is put in conjunction during the second stage of the activation signal. Throughout the phase of activation, NLRP3 can be triggered by a variety of stimuli, including K^+ leakage, mitochondrial dysfunction, reactive oxygen species (ROS) generation, lysosomal damage, *etc*. When the receptor protein is stimulated, it usually recruits ASC containing PYD domain and interconnects with PYD in NLRP3, further forming NLRP3-ASC complex. The dormant CARD domain in pro-caspase-1 will be connected to the exposed CARD domain. Pro-caspase-1 is split to generate active caspase-1, and caspase-1 splits pro-IL-1β and pro-IL-18 apart to create mature, physiologically active versions. Additionally, GSDMD may be sheared by activated caspase-1, releasing its N-terminal domain, which then migrates to the cell membrane and creates holes, facilitating the release of pro-inflammatory cytokines, such as IL-1β and IL-18, thus commencing an inflammatory cascade. PAMPs: pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; TLRs: Toll-like receptors; ASC: apoptosis-associated speck-like protein; pro-caspase-1: pro-cysteinyl aspartate specific proteinase-1; LRR: leucine-rich repeat; NACHT: nucleotide-binding oligomerization domain; PYD: Pyrin domain; CARD: caspase-activation and recruitment domain; NF-κB: nuclear factor-kappa B; GSDMD: gasdermin D.

免疫性疾病[29]。有研究显示，T1DM 的病理变化与 NLRP3 炎症小体的表达密切相关[30]，动物研究显示，T1DM 小鼠肾组织和犬的肝脏组织中 NLRP3 炎症小体、ASC、IL-1β 蛋白表达显著高于对照组[31, 32]；Gao 等研究发现，人参皂苷可以下调链脲佐菌素 (streptozotocin, STZ) 诱导的 T1DM 小鼠血清中 NLRP3 炎症小体、谷丙转氨酶 (alanine aminotransferase, ALT) 和谷草转氨酶 (aspartate aminotransferase, AST) 的蛋白表达，还可以降低血糖水平，促进胰岛素的分泌，并通过上调 Nrf2/ARE 途径来减轻 STZ 诱导的 ROS 介导的炎症，并进一步激活抗氧化酶[33]。不过，也有研究结果与上述研究相悖，即 NLRP3 炎症小体可作为病理状态下的保护性因子，Yang 等研究显示，与健康对照组相比，系统性红斑狼疮患者的外周血单核细胞 (peripheral blood mononuclear cells, PBMCs) 中 NLRP3 炎症小体明显降低，与疾病异常情况呈负相关[34]。同样，Liu 等检测了 T1DM 患者的 PBMCs 和粒细胞 (granulocytes, GCs)，发现 NLRP3 炎症小体和 caspase-1 表达水平同样显著降低，此外，*Nlrp3* 基因敲除可下调 caspase-1 和 IL-1β 的蛋白表达水平[35]，验证了 NLRP3 炎症小体的促炎效应。上述结果之间出现相互矛盾可能是 STZ 诱导 TIDM 小鼠时使用的剂量、检测指标、检测组织以及 T1DM 模型的疾病程度不同所致。综上

所述，NLRP3 炎症小体作为先天免疫系统的重要组成部分，广泛分布于免疫器官和免疫细胞 [36, 37]，在 T1DM 中应充当保护机制，但其在 T1DM 中的表达量仍存在一定异议，可能与疾病严重程度相关，且需要进一步研究去完善和验证。

2.2 NLRP3炎症小体与2型糖尿病(type 2 diabetes mellitus, T2DM)的关系

据 2019 年全球疾病负担研究纵向数据统计，从 1990 年至 2019 年，中国男性和女性 T2DM 标准化发病率分别从 0.62% 和 0.16% 增长到 0.99% 和 0.58%，可见 T2DM 已经成为国人不可忽视的健康卫生问题 [38]。T2DM 是由于 IR 伴随胰岛 β 细胞功能缺陷所导致的胰岛素分泌减少 (相对减少) 的一种代谢性疾病 [39]。T2DM 的病理进程通常会伴有 NLRP3 炎症小体的全程参与 [40]；Wu 等研究发现，十二指肠空肠搭桥术可显著降低 T2DM 大鼠糖化血红蛋白和甘油三酯 (triglyceride, TG) 浓度，上调葡萄糖激酶和葡萄糖转运蛋白 2 的表达，并显著下调 NLRP3 炎症小体的 mRNA 和蛋白表达，进而改善 β 细胞功能障碍和葡萄糖耐量；进一步研究显示，敲除 T2DM 大鼠巨噬细胞中 NLRP3 炎症小体可以产生相似的效果 [41]。Niu 等研究显示，在丙型肝炎病毒感染小鼠 β 细胞系 min6 中，过表达 NLRP3 炎症小体逆转丙型肝炎病毒所诱导的 β 细胞焦亡，下调胰岛素分泌 [42]。多种信号通路可直接参与调控 NLRP3 炎症小体进而改善糖尿病，腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK)/ 哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号通路被认为是调节 T2DM 的经典通路，与 NLRP3 炎症小体呈正相关，AMPK 可直接激活 mTOR，下调心肌组织中的 NLRP3 炎症小体和 GSDMD-N 的蛋白表达，并通过缓解糖尿病心肌病引起的细胞焦亡来改善自噬 [43, 44]；Wu 等研究显示，在高糖饮食诱导的糖耐量受损大鼠模型中，维生素 D 可通过 AMPK/mTOR/NLRP3 炎症小体信号通路缓解 β 细胞功能障碍，降低血糖水平 [45]。此外，硫氧还蛋白相互作用蛋白 (thioredoxin interacting protein, TXNIP) 是一种与 IR 相关的蛋白质，沉默 TXNIP 表达可完全阻断肝细胞中果糖诱导的 NLRP3 炎症小体和 ASC 上调以及 caspase-1 的活化，但不能阻断肝细胞中 ROS 产生，进一步研究显示抑制 ROS 产生可以降低 TXNIP 蛋白表达，下调 IL-1β 和 IL-18 水平 [46]；与之相似的是，与未治疗的糖尿病大鼠相比，抑制 ROS/TXNIP/NLRP3 信号通路能显著下调主动脉 IL-1β、iNOS、NLRP3 炎症小体和 TGF-β1 的表达，缓解糖尿病诱导的主动脉中膜纤维组织增生 [47]。上述研究表明，AMPK/mTOR 和 ROS/TXNIP 通路是 NLRP3 的上游通路，并受到自噬和氧化应激的调节，其表达量上调可以促进机体炎症反应和糖代谢异常，进而介导 T2DM 的病理变化。

3 运动通过抑制NLRP3炎症小体缓解糖尿病的发生、发展

3.1 运动对NLRP3炎症小体的调控

目前学术界对运动可以下调炎症因子具有一定的共识，但由于运动调控炎症因子的表达受运动强度、时间、运动类型以及实验对象等相关因素的影响，因此还存在部分争议 [48, 49]。研究显示，与久坐人群相比，急性运动后老年女性血清中 IL-1β 和 TNF-α mRNA 表达明显上调 [50]。此外，急性运动还上调大鼠心肌组织中 NLRP3 炎症小体、自噬相关基因 (*Beclin1*、*Bnip3* 和 *LC3*) 的蛋白表达、线粒体 ROS 生成率和丙二醛 (malondialdehyde, MDA) 含量，且 HE 染色结果显示，心肌组织表现出更多的毛细血管扩张和充血以及炎症细胞浸润 [51]，提示急性运动可以通过诱导线粒体应激激活 NLRP3 炎症小体和自噬水平，进而触发心肌的炎症反应。相比之下，长期运动可作为抑制 NLRP3 炎症小体的最优选择，12 周的有氧运动能显著降下调脉粥样硬化小鼠主动脉中 NLRP3 炎症小体、caspase-1、IL-1β 的 mRNA 和蛋白表达，并显著降低血糖、TG、总胆固醇 (total cholesterol, TC)、低密度脂蛋白胆固醇 (low-density lipoprotein cholesterol, LDL-C)，进而延缓动脉粥样硬化的病程 [52]；Habibi 等发现耐力运动能够下调糖尿病大鼠脊髓组织中 NLTP3 炎症小体、p38-MAPK、TNF-α 和 IL-1β mRNA 表达和血糖水平 [53]，并显著下调糖尿病大鼠血清中的胰岛素、胰岛素抵抗指数 (homeostasis model assessment of insulin resistance, HOMA-IR) 和糖化血清蛋白 (glycated serum proteins, GSP) 水平，极可能增加胰岛素的敏感性，有利于糖尿病防治 [54]。Quiroga 等在人体实验中发现，与肥胖对照组相比，肥胖儿童经历为期 12 周的耐力和力量联合运动后，PBMCs 中葡萄糖水平、NLRP3 炎症小体和 caspase-1 的蛋白表达明显降低 [55]；8 周的耐力运动可显著下调健康老年人群血清中

NLRP3 炎症小体、caspase-1、自噬相关基因 (*Atg12*、*Atg16* 和 *Beclin-1*)、溶酶体相关膜蛋白 2 (lysosome-associated membrane protein-2, LAMP2) 的蛋白表达 [56]，提示运动训练可以通过刺激自噬，抑制 NLRP3 炎症小体，并减少老年受试者 PBMCs 的凋亡；Khakroo Abkenar 等得到的结果却与之相反，19~27 岁的男性受试者在 12 周高强度有氧训练后，血清中的 NLRP3 炎症小体、IL-1β 和 1L-18 的蛋白表达显著上调，而中等强度运动后，NLRP3 炎症小体的蛋白表达明显下调 [57]，出现这样相互矛盾的结果可能与研究中选择的运动强度相关。此外，多种形式的运动对不同组织中 NLRP3 炎症小体的影响及分子机制还需要进一步深入研究。

3.2 运动调节NLRP3炎症小体在糖尿病中的作用

3.2.1 不同运动方式通过NLRP3炎症小体对糖尿病表型的影响

美国糖尿病协会建议，患有 T1DM、T2DM 或糖尿病前期的儿童和青少年应保持每天进行至少 60 min 中等或高强度有氧运动，每周至少 3 天进行剧烈的肌肉强化和骨骼强化活动 [58]，定期的体育锻炼对糖尿病有益，很大原因是其可以调节炎症反应 [59]，研究显示，T2DM 大鼠在经过 4 周的低氧运动后，血清中 TC、TG、LDL-C、空腹血糖值 (fasting blood glucose, FBG) 和 IR 水平均下降，HDL-C 水平升高，血脂代谢和炎症反应均得到明显改善 [60]；Bian 等研究显示，12 周的递增跑台训练可下调 IR 小鼠海马内 NLRP3 炎症小体、caspase-1、ASC、NF-κB、GSDMD、NEK7、IL-1β 蛋白表达，缓解炎症反应和细胞焦亡 [61]，但是由于该研究没有测量血糖水平、IR 等糖代谢指标，无法得出运动改善 IR 的确切结论。有研究显示，肥胖合并 T2DM 患者在长达一年的锻炼后，脂肪组织中 IL-1β 和 NLRP3 炎症小体 mRNA 表达与血糖水平显著降低，并伴有 HOMA-IR 的改善 [8]，提示运动可能通过下调 NLRP3 炎症小体改善 T2DM，但是该研究并没有对运动方案严格干预，且未排除饮食及药物对 NLRP3 炎症小体及相关代谢指标的影响；另一项研究则显示出不同的结果，Zaidi 等研究显示，12 个月的有氧和抗阻的组合训练对冠状动脉疾病合并 T2DM 患者的血清中 IL-18、caspase-1 和 NLRP3 炎症小体没有显著影响，但是该研究显示 NLRP3 炎症小体和 caspase-1 在循环白细胞中的基因表达与胰岛素、C 肽、HOMA-IR 呈负相关 [62]，与前人研究相一致 [46]，该研究作为为数不多的人体实验，具有较强的借鉴意义，不过，因其受试人数较多，持续时间较为漫长，存在较多不确定因素，导致研究无法得出明确结果。

抗阻运动普遍定义为肌肉在克服外来阻力时进行的主动运动，这些活动通常涉及多次举起相对较重的物体，以加强各种肌肉群 [63]，对糖尿病人群的糖脂代谢、IR、炎症反应、心肺适能等都有积极的改善作用 [64]。Ji 等研究显示，12 周的抗阻运动显著下调 IR 小鼠海马内 NLRP3 炎症小体、caspase-1、ASC、NF-κB、GSDMD、GSDMD-N、IL-1β 等蛋白表达 [65]，提示抗阻运动可有效改善小鼠炎症反应和细胞焦亡。另外有研究显示，糖尿病前期患者在 6 个月的易筋经和阻力训练后，血清中 NLRP3 炎症小体、IL-1β、HOMA-IR、TG、TC、HDL 和肝损伤标志物 (ALT、AST 等) 的水平显著降低 [66]，提示抗阻运动可通过抑制 NLRP3 炎症小体进而缓解糖尿病前期肝损伤和 IR，但是此实验中无法得出 IR、肝脏病理学改变和 NLRP3 炎症小体之间存在因果关系，仍需在动物实验进行验证。

此外，有氧运动和抗阻运动对糖尿病患者的效果也不尽相同。Fu 等研究显示，与 8 周的有氧运动 (20 m/min，60 min/d，5 d/ 周) 干预相比，抗阻运动 [负重 50%、75%、90% 和 100% 1 次重复大力量 (1 repetition maximum, 1RM)，每个级别 3 次，次间隔 2 min，5 d/ 周，8 周] 更能明显改善 T2DM 小鼠肝脏组织中的血糖浓度和 IR 状态，虽然二者都能使 NLRP3 炎症小体、ASC、caspase-1、IL-1β 等炎症因子水平下降，肝脏形态与结构有所好转，但抗阻运动抑制炎症因子的表达和炎症反应的作用却不及有氧运动 [67]；Li 等研究显示，8 周的抗阻运动 (负重 50%，75%，90% 和 100% 1RM，每个级别 3 次，次间隔 2 min，5 d/ 周，8 周) 可以显著降低糖尿病大鼠的 FBG 和胰岛素指数，升高空腹胰岛素水平，但对于炎症因子的表达并无明显改变，而耐力运动 (60 min/d，5 d/ 周，8 周) 可改善糖尿病大鼠心肌组织中的炎症反应 (NLRP3 炎症小体、ASC、caspase-1 和 IL-1β 表达显著下调)、血脂代谢 (TG、TC、LDL-C 降低)、心肌结构和心功能障碍 [68]。

综上，有氧运动和抗阻运动均能下调 NLRP3 炎症小体，进而改善糖尿病的相关指标，相比之下，有氧运动主要有抑制炎症反应、调节血脂代谢的作用，而抗阻运动主要在调节血糖水平方面有着明显的优势。然而，目前大多数研究集中于长期运动干

预，很少关注急性运动的效果，未来的研究还需要探讨急性运动对糖尿病小鼠血清中 NLRP3 炎症小体及糖脂代谢指标的作用。

3.2.2 运动介导NLRP3炎症小体对糖尿病作用的机制

运动可有效地下调炎症相关基因 (*Nlrp3*、*Adgre1*、*Ccl2* 和 *Nos2*) 的表达水平，显著提升机体的抗炎效应 [69]。机体 NLRP3 炎症小体的激活主要是通过抑制线粒体损伤和 / 或线粒体信号的释放，导致机体 NLRP3 炎症小体出现一种“全有或全无”的状态 [70]。NF-κB 作为影响线粒体功能的重要因子之一，在介导线粒体自噬中发挥一定作用 [71]，因此，建立 NF-κB 信号通路反馈调控机制，可能是运动介导 NLRP3 炎症小体改善糖尿病的关键因素。研究显示，8 周的有氧运动上调糖尿病大鼠主动脉中沉默信息调节因子 1 (sirtuin 1, SIRT1)、烟酰胺磷酸核糖转移酶 (nicotinamide phosphoribosyl transferase, Nampt) 和 IκBα 的蛋白表达，并下调 NF-κB p65 的蛋白表达，进一步降低血清中 TNF-α、IL-1β、单核细胞趋化蛋白 -1 (monocyte chemoattractant protein-1, MCP-1) 和血管细胞黏附分子 -1 (vascular cell adhesion molecule 1, VCAM-1) 含量 [72]，提示有氧运动可能通过 SIRT1/NF-κB 信号通路来缓解糖尿病大鼠血管炎症反应；Ji 等进一步研究显示，在 12 周抗阻运动后，IR 小鼠海马内 AMPK 磷酸化水平、SIRT1 和 NLRP3 炎症小体蛋白表达显著升高，NF-κB 表达降低 [65]，提示抗阻运动通过 AMPK/SIRT1/NF-κB/NLRP3 炎症小体信号通路调控机体的炎症反应；另外，Zhou 等研究显示，每天以 5.6 m/min 的速度运动 60 min，每周 5 天，持续 8 周的有氧运动可以降低小鼠肾脏组织中 MDA、烟酰胺腺嘌呤二核苷酸磷酸氧化酶 4 (NADPH oxidase 4, NOX4)、ROS、线粒体复合物 I 的含量与 TNF-α、IL-18、NF-κB p65、IκBα、NLRP3 炎症小体的蛋白表达，上调超氧化物歧化酶 (superoxide dismutase, SOD) 和谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 表达 [73]，而肾皮质中最丰富的 ROS 来源是 NOX4 [74]，提示运动可通过调控 NOX4/ROS/NF-κB/NLRP3 炎症小体信号通路改善糖尿病的病理变化；Wang 等发现，8 周的跑台运动可抑制糖尿病大鼠脑组织中叉头框转录因子 O 亚族 1 (forkhead box transcription factor O1, FOXO1) 乙酰化，促进 FOXO1 磷酸化，进而抑制 FOXO1 蛋白表达，并下调 NF-κB、TNF-α、NLRP3 炎症小体的蛋白表达，从而抑制炎症反应 [75]，提示运动通过 FOXO1/NF-κB/NLRP3 炎症小体通路抑制炎症反应。上述研究探索运动、NLRP3 炎症小体和糖尿病之间的分子机制 (图 2)，均以 NF-κB 通路为关键节点，但是没有采用细胞实验进行排除其他因素的干扰，后续还需要根据前人研究系统地研究这一信号通路。此外，使用现阶段存在的 NLRP3 炎症小体干预手段 (如特异性敲除、注射相应的激动剂或抑制剂等)[76–78] 探讨运动治疗糖尿病的分子机制，所得结果将具有较强的说服力。

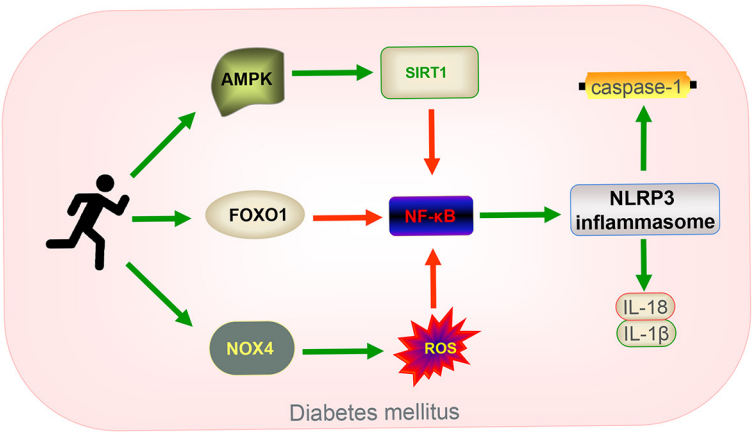

图 2. 运动介导NLRP3炎症小体改善糖尿病症状的分子机制

Fig. 2. Molecular mechanism of exercise-mediated NLRP3 inflammasome improving diabetes mellitus (DM) symptoms. SIRT1: sirtuin 1; AMPK: AMP-activated protein kinase; FOXO1: forkhead box transcription factor O1; NF-κB: nuclear factor-kappa B; NOX4: NADPH oxidase 4; ROS: reactive oxygen species; IL-18: interleukin-18; IL-1β: interleukin-1β.

4 小结与展望

综上所述，NLRP3 炎症小体作为近年来备受关注的一种介导炎症反应发生的明星因子，在糖尿病人群中大量存在。在糖尿病治疗中，运动作为为数不多的无创性干预手段，可通过 NLRP3 炎症小体直接抑制炎症反应，或间接改善血脂异常和降低血糖水平，最终改善糖尿病症状。因此，通过分析不同形式的运动抑制 NLRP3 炎症小体的激活可以为缓解糖尿病及并发症提供新视角 (表 1)。

此外，关于 NLRP3 炎症小体、糖尿病与运动之间的关系研究中仍有诸多问题需要得到有效解决：(1) 需要进一步验证 NLRP3 炎症小体在 T1DM 人群中的表达量及相关作用机制；(2) 需要通过敲除 NLRP3 炎症小体，并结合运动干预，在糖尿病模型中进一步验证其分子机制；(3) 上述研究主要在整体水平 (血液)，而器官分子水平的机制研究相对较少，未来应从组织器官水平，尤其是与代谢密切相关的骨骼肌和脂肪组织中，进一步探讨 NLRP3 炎症小体在不同代谢状态下的变化及其分子机制；此外，对 NLRP3 炎症小体上游信号因子或下游机制的干预作用也是未来研究代谢性疾病中亟待解决的新问题。

参考文献

1 Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271–281.

2 Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol 2020; 16(7): 377–390.

3 Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez

表1. 在糖尿病模型中，运动对NLPR3炎症小体的影响

Table 1. Effect of exercise on the NLPR3 inflammasome in diabetes mellitus (DM) models

Exercise type and time	Species	Detection tissue	NLRP3 inflammasome	Other indicators	References
1 year weight-loss intervention	Obese-T2DM	Adipose tissue	↓	HOMA-IR, IL-1β↓	[8]
12-week Taijiquan exercise	Pre-diabetic patients	Serum	↓	FBG, IR↓	[9]
4-week hypoxic exercise	Rat	Myocardial tissue	↓	TG, TC, LDL-C, FBG↓, HDL-C↑	[60]
12-week incremental treadmill training	Mouse	Hippocampal area	↓	NF-κB, NLRP3, NEK7, ASC, pro-caspase-1, IL-1β↓	[61]
12-month endurance + strength training combination	T2DM patients	Serum	-	IL-18, IR↓	[62]
12-week resistance exercise	Mouse	Hippocampal area	↓	ASC, caspase-1, GSDMD, IL-1β, IL-18↓	[65]
6-month Yijinjing and resistance training	Pre-diabetic patients	Serum	↓	IL-1β, HOMA-IR, TG, TC, HDL, ALT, AST↓	[66]
8-week aerobic exercise	Mouse	Liver tissue	↓	Fat vacuoles in the liver decreased. ASC, IL-1β↓	[67]
8-week resistance exercise	Mouse	Liver tissue	↓	ASC, IL-1β↓	[67]
8-week endurance exercise	Rat	Myocardial tissue	↓	FINS↑, FPG, HOMA-IR, IL-1β↓	[68]
8-week resistance exercise	Rat	Myocardial tissue	-	FPG, TG↓	[68]
8-week aerobic exercise	Mouse	Kidney tissue	↓	NOX4, ROS, MDA↓	[73]
8-week aerobic exercise	Rat	Prefrontal cortex	↓	FOXO1, NF-κB, TNF-α↓	[75]

-: no change; ↑: up-regulation; ↓: down-regulation. HOMA-IR: homeostatic model assessment of insulin resistance; IL-1β: interleukin-1β; FBG: fasting blood glucose; IR: insulin resistance; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NF-κB: nuclear factor-kappa B; NEK7: never in mitosis gene A-related kinase 7; ASC: apoptosis-associated speck-like protein; pro-caspase-1: pro-cysteinyl aspartate specific proteinase-1; IL-18: interleukin-18; GSDMD: gasdermin D; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FINS: fasting insulin; FPG: fasting plasma glucose; NOX4: NADPH oxidase 4; ROS: reactive oxygen species; MDA: malondialdehyde; FOXO1: forkhead box transcription factor O1; NF-κB: nuclear factor-kappa B; TNF-α: tumor necrosis factor-α.

B, Mora-Fernández C, Marchant V, Donate-Correa J, Navarro-González JF, Ortiz A, Ruiz-Ortega M. Targeting inflammation to treat diabetic kidney disease: the road to 2030. Kidney Int 2023; 103(2): 282–296.

4 Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity 2022; 55(1): 31–55.

5 Yao Y, Song Q, Hu C, Da X, Yu Y, He Z, Xu C, Chen Q, Wang QK. Endothelial cell metabolic memory causes cardiovascular dysfunction in diabetes. Cardiovasc Res 2022; 118(1): 196–211.

6 Romero A, Dongil P, Valencia I, Vallejo S, Hipólito-Luengo Á S, Díaz-Araya G, Bartha JL, González-Arlanzón MM, Rivilla F, de la Cuesta F, Sánchez-Ferrer CF, Peiró C. Pharmacological blockade of NLRP3 inflammasome/IL-1β-positive loop mitigates endothelial cell senescence and dysfunction. Aging Dis 2022; 13(1): 284–297.

7 Wu M, Yang Z, Zhang C, Shi Y, Han W, Song S, Mu L, Du C, Shi Y. Inhibition of NLRP3 inflammasome ameliorates podocyte damage by suppressing lipid accumulation in diabetic nephropathy. Metabolism 2021; 118: 154748.

8 Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 2011; 17(2): 179–188.

9 Hu S, Hu Y, Long P, Li P, Chen P, Wang X. The effect of tai chi intervention on NLRP3 and its related antiviral inflammatory factors in the serum of patients with pre-diabetes. Front Immunol 2022; 13: 1026509.

10 Wang X, Yi X, Tang D. Regular aerobic exercise activates PDGF-BB/PDGFR-β signaling and modulates the inflammatory-anti-inflammatory balance in diet-induced obese mice. Obes Res Clin Pract 2021; 15(4): 387–394.

11 Chang B, Song C, Gao H, Ma T, Li T, Ma Q, Yao T, Wang M, Li J, Yi X, Tang D, Cao S. Leptin and inflammatory factors play a synergistic role in the regulation of reproduction in male mice through hypothalamic kisspeptin-mediated energy balance. Reprod Biol Endocrinol 2021; 19(1): 12.

12 Xu J, Núñez G. The NLRP3 inflammasome: activation and regulation. Trends Biochem Sci 2023; 48(4): 331–344.

13 Akther M, Haque ME, Park J, Kang TB, Lee KH. NLRP3 ubiquitination-A new approach to target NLRP3 inflammasome activation. Int J Mol Sci 2021; 22(16): 8780.

14 Song H, Zhao C, Yu Z, Li Q, Yan R, Qin Y, Jia M, Zhao W. UAF1 deubiquitinase complexes facilitate NLRP3 inflammasome activation by promoting NLRP3 expression. Nat Commun 2020; 11(1): 6042.

15 Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cell Mol Immunol 2021; 18(5): 1141–1160.

16 Hochheiser IV, Pilsl M, Hagelueken G, Moecking J, Marleaux M, Brinkschulte R, Latz E, Engel C, Geyer M. Structure of the NLRP3 decamer bound to the cytokine release inhibitor CRID3. Nature 2022; 604(7904): 184–189.

17 Xu H, Chen J, Chen P, Li W, Shao J, Hong S, Wang Y, Chen L, Luo W, Liang G. Costunolide covalently targets NACHT domain of NLRP3 to inhibit inflammasome activation and alleviate NLRP3-driven inflammatory diseases. Acta Pharm Sin B 2023; 13(2): 678–693.

18 Hochheiser IV, Behrmann H, Hagelueken G, Rodríguez-Alcázar JF, Kopp A, Latz E, Behrmann E, Geyer M. Directionality of PYD filament growth determined by the transition of NLRP3 nucleation seeds to ASC elongation. Sci Adv 2022; 8(19): eabn7583.

19 Moretti J, Jia B, Hutchins Z, Roy S, Yip H, Wu J, Shan M, Jaffrey SR, Coers J, Blander JM. Caspase-11 interaction with NLRP3 potentiates the noncanonical activation of the NLRP3 inflammasome. Nat Immunol 2022; 23(5): 705–717.

20 Faria SS, Costantini S, de Lima VCC, de Andrade VP, Rialland M, Cedric R, Budillon A, Magalhães KG. NLRP3 inflammasome-mediated cytokine production and pyroptosis cell death in breast cancer. J Biomed Sci 2021; 28(1): 26.

21 Gao L, Dong X, Gong W, Huang W, Xue J, Zhu Q, Ma N, Chen W, Fu X, Gao X, Lin Z, Ding Y, Shi J, Tong Z, Liu T, Mukherjee R, Sutton R, Lu G, Li W. Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis. Br J Pharmacol 2021; 178(17): 3533–3552.

22 Urwanisch L, Luciano M, Horejs-Hoeck J. The NLRP3 inflammasome and its role in the pathogenicity of leukemia. Int J Mol Sci 2021; 22(3): 1271.

23 Mayes-Hopfinger L, Enache A, Xie J, Huang CL, Köchl R, Tybulewicz VLJ, Fernandes-Alnemri T, Alnemri ES. Chloride sensing by WNK1 regulates NLRP3 inflammasome activation and pyroptosis. Nat Commun 2021; 12(1): 4546.

24 Cai B, Zhao J, Zhang Y, Liu Y, Ma C, Yi F, Zheng Y, Zhang L, Chen T, Liu H, Liu B, Gao C. USP5 attenuates NLRP3 inflammasome activation by promoting autophagic degradation of NLRP3. Autophagy 2022; 18(5): 990–1004.

25 Zhang Y, Yin K, Wang D, Wang Y, Lu H, Zhao H, Xing M. Polystyrene microplastics-induced cardiotoxicity in chickens via the ROS-driven NF-κB-NLRP3-GSDMD and AMPK-PGC-1α axes. Sci Total Environ 2022; 840: 156727.

26 Li S, Wang L, Xu Z, Huang Y, Xue R, Yue T, Xu L, Gong F, Bai S, Wu Q, Liu J, Lin B, Zhang H, Xue Y, Xu P, Hou J, Yang X, Jin T, Zhou R, Lou J, Xu T, Bai L. ASC deglutathionylation is a checkpoint for NLRP3 inflammasome activa-

tion. J Exp Med 2021; 218(9): e20202637.
27 Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. Cell Mol Immunol 2021; 18(9): 2114–2127.
28 Wang L, Hauenstein AV. The NLRP3 inflammasome: Mechanism of action, role in disease and therapies. Mol Aspects Med 2020; 76: 100889.
29 Syed FZ. Type 1 diabetes mellitus. Ann Intern Med 2022; 175(3): ITC33–ITC48.
30 Li Z, Guo J, Bi L. Role of the NLRP3 inflammasome in autoimmune diseases. Biomed Pharmacother 2020; 130: 110542.
31 Birnbaum Y, Bajaj M, Qian J, Ye Y. Dipeptidyl peptidase-4 inhibition by Saxagliptin prevents inflammation and renal injury by targeting the Nlrp3/ASC inflammasome. BMJ Open Diabetes Res Care 2016; 4(1): e000227.
32 Huo H, Wu H, Ma F, Li X, Liao J, Hu L, Han Q, Li Y, Pan J, Zhang H, Tang Z, Guo J. *N*-acetyl-*L*-cysteine ameliorates hepatocyte pyroptosis of dog type 1 diabetes mellitus via suppression of NLRP3/NF-κB pathway. Life Sci 2022; 306: 120802.
33 Gao Y, Li J, Chu S, Zhang Z, Chen N, Li L, Zhang L. Ginsenoside Rg1 protects mice against streptozotocin-induced type 1 diabetic by modulating the NLRP3 and Keap1/Nrf2/HO-1 pathways. Eur J Pharmacol 2020; 866: 172801.
34 Yang Q, Yu C, Yang Z, Wei Q, Mu K, Zhang Y, Zhao W, Wang X, Huai W, Han L. Deregulated NLRP3 and NLRP1 inflammasomes and their correlations with disease activity in systemic lupus erythematosus. J Rheumatol 2014; 41(3): 444–452.
35 Liu H, Xu R, Kong Q, Liu J, Yu Z, Zhao C. Downregulated NLRP3 and NLRP1 inflammasomes signaling pathways in the development and progression of type 1 diabetes mellitus. Biomed Pharmacother 2017; 94: 619–626.
36 Zhang XN, Yu ZL, Chen JY, Li XY, Wang ZP, Wu M, Liu LT. The crosstalk between NLRP3 inflammasome and gut microbiome in atherosclerosis. Pharmacol Res 2022; 181: 106289.
37 Dixon KO, Tabaka M, Schramm MA, Xiao S, Tang R, Dionne D, Anderson AC, Rozenblatt-Rosen O, Regev A, Kuchroo VK. TIM-3 restrains anti-tumour immunity by regulating inflammasome activation. Nature 2021; 595(7865): 101–106.
38 Li Y, Guo C, Cao Y. Secular incidence trends and effect of population aging on mortality due to type 1 and type 2 diabetes mellitus in China from 1990 to 2019: findings from the Global Burden of Disease Study 2019. BMJ Open Diabetes Res Care 2021; 9(2): e002529.
39 Ying W, Fu W, Lee YS, Olefsky JM. The role of macrophages in obesity-associated islet inflammation and β-cell abnormalities. Nat Rev Endocrinol 2020; 16(2): 81–90.
40 Bhansali S, Bhansali A, Dutta P, Walia R, Dhawan V. Metformin upregulates mitophagy in patients with T2DM: A randomized placebo-controlled study. J Cell Mol Med 2020; 24(5): 2832–2846.
41 Wu D, Yan ZB, Cheng YG, Zhong MW, Liu SZ, Zhang GY, Hu SY. Deactivation of the NLRP3 inflammasome in infiltrating macrophages by duodenal-jejunal bypass surgery mediates improvement of beta cell function in type 2 diabetes. Metabolism 2018; 81: 1–12.
42 Niu B, Yao L, Zhang Y, Xia X, Su H. LncRNA KCNQ1OT1 promoted hepatitis C virus-induced pyroptosis of β-cell through mediating the miR-223-3p/NLRP3 axis. Ann Transl Med 2021; 9(17): 1387.
43 Chen H, Tran D, Yang HC, Nylander S, Birnbaum Y, Ye Y. Dapagliflozin and ticagrelor have additive effects on the attenuation of the activation of the NLRP3 inflammasome and the progression of diabetic cardiomyopathy: an AMPK-mTOR interplay. Cardiovasc Drugs Ther 2020; 34(4): 443–461.
44 Yang F, Qin Y, Wang Y, Meng S, Xian H, Che H, Lv J, Li Y, Yu Y, Bai Y, Wang L. Metformin inhibits the NLRP3 inflammasome via AMPK/mTOR-dependent effects in diabetic cardiomyopathy. Int J Biol Sci 2019; 15(5): 1010–1019.
45 Wu M, Lu L, Guo K, Lu J, Chen H. Vitamin D protects against high glucose-induced pancreatic β-cell dysfunction via AMPK-NLRP3 inflammasome pathway. Mol Cell Endocrinol 2022; 547: 111596.
46 Zhang X, Zhang JH, Chen XY, Hu QH, Wang MX, Jin R, Zhang QY, Wang W, Wang R, Kang LL, Li JS, Li M, Pan Y, Huang JJ, Kong LD. Reactive oxygen species-induced TXNIP drives fructose-mediated hepatic inflammation and lipid accumulation through NLRP3 inflammasome activation. Antioxid Redox Signal 2015; 22(10): 848–870.
47 Amin FM, Abdelaziz RR, Hamed MF, Nader MA, Shehatou GSG. Dimethyl fumarate ameliorates diabetes-associated vascular complications through ROS-TXNIP-NLRP3 inflammasome pathway. Life Sci 2020; 256: 117887.
48 Knudsen NH, Stanya KJ, Hyde AL, Chalom MM, Alexander RK, Liou YH, Starost KA, Gangl MR, Jacobi D, Liu S, Sopariwala DH, Fonseca-Pereira D, Li J, Hu FB, Garrett WS, Narkar VA, Ortlund EA, Kim JH, Paton CM, Cooper JA, Lee CH. Interleukin-13 drives metabolic conditioning of muscle to endurance exercise. Science 2020; 368(6490): eaat3987.
49 Pallikadavath S, Walters GM, Kite TA, Graham-Brown M, Ladwiniec A, Papadakis M, McCann GP, Singh A. Exercise, inflammation and acute cardiovascular events. Exerc Immunol Rev 2022; 28: 93–103.

50 Gomarasca M, Micielska K, Faraldi M, Flis M, Perego S, Banfi G, Ziemann E, Lombardi G. Impact of 12-week moderate-intensity aerobic training on inflammasome complex activation in elderly women. Front Physiol 2022; 13: 792859.
51 Li H, Miao W, Ma J, Xv Z, Bo H, Li J, Zhang Y, Ji LL. Acute exercise-induced mitochondrial stress triggers an inflammatory response in the myocardium via NLRP3 inflammasome activation with mitophagy. Oxid Med Cell Longev 2016; 2016: 1987149.
52 Li XH, Liu LZ, Chen L, Pan QN, Ouyang ZY, Fan DJ, Pan X, Lu SY, Luo QH, Tao PY, Huang HQ. Aerobic exercise regulates FGF21 and NLRP3 inflammasome-mediated pyroptosis and inhibits atherosclerosis in mice. PLoS One 2022; 17(8): e0273527.
53 Habibi A, Taheri A, Habibi S. Attenuation of some inflammatory markers by endurance training in the spinal cord of rats with diabetic neuropathic pain. Contrast Media Mol Imaging 2022; 2022: 6551358.
54 Hansen D, De Strijcker D, Calders P. Impact of endurance exercise training in the fasted state on muscle biochemistry and metabolism in healthy subjects: can these effects be of particular clinical benefit to type 2 diabetes mellitus and insulin-resistant patients? Sports Med 2017; 47(3): 415–428.
55 Quiroga R, Nistal E, Estébanez B, Porras D, Juárez-Fernández M, Martínez-Flórez S, García-Mediavilla MV, de Paz JA, González-Gallego J, Sánchez-Campos S, Cuevas MJ. Exercise training modulates the gut microbiota profile and impairs inflammatory signaling pathways in obese children. Exp Mol Med 2020; 52(7): 1048–1061.
56 Mejías-Peña Y, Estébanez B, Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, de Paz JA, González-Gallego J, Cuevas MJ. Impact of resistance training on the autophagy-inflammation-apoptosis crosstalk in elderly subjects. Aging (Albany NY) 2017; 9(2): 408–418.
57 Khakroo Abkenar I, Rahmani-Nia F, Lombardi G. The effects of acute and chronic aerobic activity on the signaling pathway of the inflammasome NLRP3 complex in young men. Medicina (Kaunas) 2019; 55(4): 105.
58 American Diabetes Association. 4. Lifestyle management: Standards of medical care in diabetes-2018. Diabetes Care 2018; 41(Suppl 1): S38–S50.
59 Yarizadeh H, Eftekhar R, Anjom-Shoae J, Speakman JR, Djafarian K. The effect of aerobic and resistance training and combined exercise modalities on subcutaneous abdominal fat: A systematic review and meta-analysis of randomized clinical trials. Adv Nutr 2021; 12(1): 179–196.
60 Tang M (唐觅), Yan QY, Li RY. Hypoxic exercise could improve lipid metabolism, antioxidant capacity and inhibit NLRP3 inflammasome signaling pathway in myocardium of type 2 diabetic rats. Genom Appl Biol (基因组学与应用生物学) 2020; 39(7): 3249–3255 (in Chinese).
61 Bian XP (卞学鹏), Ji RF, Liu BB, Hu JY, Li MM, Xue XL, Lou SJ. Aerobic exercise reduces the expression of pyroptosis-related proteins and inflammatory factors in hippocampus of mice with insulin resistance. Acta Physiol Sin (生理学报) 2020; 72(4): 455–462 (in Chinese).
62 Zaidi H, Byrkjeland R, Njerve IU, Åkra S, Solheim S, Arnesen H, Seljeflot I, Opstad TB. Effects of exercise training on inflammasome-related mediators and their associations to glucometabolic variables in patients with combined coronary artery disease and type 2 diabetes mellitus: Sub-study of a randomized control trial. Diab Vasc Dis Res 2019; 16(4): 360–368.
63 Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The Physical Activity Guidelines for Americans. JAMA 2018; 320(19): 2020–2028.
64 Engin B, Willis SA, Malaikah S, Sargeant JA, Yates T, Gray LJ, Aithal GP, Stensel DJ, King JA. The effect of exercise training on adipose tissue insulin sensitivity: A systematic review and meta-analysis. Obes Rev 2022; 23(7): e13445.
65 Ji RF (姬瑞方), Bian XP, Liu BB, Hu JY, Xue XL, Lou SJ. Effects of resistance exercise on pyroptosis-related proteins in hippocampus of insulin resistant mice. Chin J Appl Physiol (中国应用生理学杂志) 2020; 36(5): 456–461 (in Chinese).
66 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.
67 Fu Y (付玉), Shang HY, Li SC. Aerobic and resistance exercises can alleviate liver inflammation in type 2 diabetic rats. Chin J Tissue Eng Res (中国组织工程研究) 2022; 26(29): 4666–4671 (in Chinese).
68 Li N (黎妮). Effects of different exercise on NLRP3 inflammasome and IL-1β in myocardium of type 2 diabetic rats [D/OL]. Chengdu Sport University (成都体育学院), 2018 (in Chinese). https://kns.cnki.net/kcms2/article/ abstract?v=quEz3ePNgzbeCy9UFg8mvbff8LmhRoS46qRw0NoX-0gCn_e8FCNRGKFNc5oeEwBnpGiS8eg-jyt6sB-gnI44OH43KzKLEUChRiRdt_fXz0DYcacS1bR_8wb-g==&uniplatform=NZKPT&language=gb
69 Zhu JY, Chen M, Mu WJ, Luo HY, Guo L. Higd1a facilitates exercise-mediated alleviation of fatty liver in diet-induced obese mice. Metabolism 2022; 134: 155241.
70 Afonina IS, Zhong Z, Karin M, Beyaert R. Limiting inflammation-the negative regulation of NF-κB and the NLRP3 inflammasome. Nat Immunol 2017; 18(8): 861–869.

71 Dhingra R, Rabinovich-Nikitin I, Rothman S, Guberman M, Gang H, Margulets V, Jassal DS, Alagarsamy KN, Dhingra S, Valenzuela Ripoll C, Billia F, Diwan A, Javaheri A, Kirshenbaum LA. Proteasomal degradation of TRAF2 mediates mitochondrial dysfunction in doxorubicin-cardiomyopathy. Circulation 2022; 146(12): 934–954.

72 Li J (李俊). Effects of aerobic exercise on vascular inflammation and SIRT1/NF-κB signaling pathway in type 2 diabetic rats. J Beijing Sport Univ (北京体育大学学报) 2018; 41(5): 57–63 (in Chinese).

73 Zhou Z, Ying C, Zhou X, Shi Y, Xu J, Zhu Y, Wang M, Li Y, Li X, Xiang J. Aerobic exercise training alleviates renal injury in db/db mice through inhibiting Nox4-mediated NLRP3 inflammasome activation. Exp Gerontol 2022; 168: 111934.

74 Muñoz M, López-Oliva ME, Rodríguez C, Martínez MP, Sáenz-Medina J, Sánchez A, Climent B, Benedito S, García-Sacristán A, Rivera L, Hernández M, Prieto D. Differential contribution of Nox1, Nox2 and Nox4 to kidney vascular oxidative stress and endothelial dysfunction in obesity. Redox Biol 2020; 28: 101330.

75 Wang Q, Hu J, Liu Y, Li J, Liu B, Li M, Lou S. Aerobic exercise improves synaptic-related proteins of diabetic rats by inhibiting FOXO1/NF-κB/NLRP3 inflammatory signaling pathway and ameliorating PI3K/Akt insulin signaling pathway. J Mol Neurosci 2019; 69(1): 28–38.

76 Li Z, Huang Z, Zhang H, Lu J, Tian Y, Wei Y, Yang Y, Bai L. P2X7 receptor induces pyroptotic inflammation and cartilage degradation in osteoarthritis via NF-κB/NLRP3 crosstalk. Oxid Med Cell Longev 2021; 2021: 8868361.

77 Wang Q, Zhou H, Bu Q, Wei S, Li L, Zhou J, Zhou S, Su W, Liu M, Liu Z, Wang M, Lu L. Role of XBP1 in regulating the progression of non-alcoholic steatohepatitis. J Hepatol 2022; 77(2): 312–325.

78 Lin HC, Chen YJ, Wei YH, Lin HA, Chen CC, Liu TF, Hsieh YL, Huang KY, Lin KH, Wang HH, Chen LC. Lactic acid fermentation is required for NLRP3 inflammasome activation. Front Immunol 2021; 12: 630380.