NLRP3炎性小体影响血管衰老的机制及其相关药物的研发

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摘要: NOD (nucleotide binding oligomerization domain) 样受体家族3 (NOD-like receptor protein 3, NLRP3) 炎症小体调控天冬氨酸特异蛋白酶-1 (caspase-1)、白细胞介素-18 (interleukin-18, IL-18) 和IL-1β等细胞因子的分泌并参与衰老过程。研究发现, NLRP3炎性小体在衰老心脏和血管中被异常激活, 抑制NLRP3炎性小体可缓解心脏与血管衰老。本文对NLRP3炎性小体在心脏血管衰老中的研究和相关药物进行综述, 以促进NLRP3炎性小体在心血管衰老中作用机制的发现和相关药物的研发。

关键词: NLRP3炎性小体; 心脏衰老; 血管衰老; 心脑血管疾病; 抗衰老; senolytics

中图分类号: R966　　**文献标识码**: A　　**文章编号**: 0513-4870(2021)03-0696-07

The mechanism of NLRP3 inflammasome affecting vascular aging and the development of related drugs

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Abstract: Nucleotide binding oligomerization domain (NOD)-like receptor protein 3, NLRP3) inflammasomes regulate the secretion of caspase-1, interleukin-18 (IL-18), IL-1β, and other cytokines, and participates in aging. In recent years, it has been found that NLRP3 inflammasomes are abnormally activated in aging heart and vessels, and inhibition of NLRP3 inflammasomes can alleviate heart aging and vascular aging. This review summarizes the research of NLRP3 inflammasome in heart and vascular aging, and the related drugs to promote the discovery of the mechanism of NLRP3 inflammasome in heart and vascular aging and the development of related drugs.

Key words: NLRP3 inflammasome; heart aging; vascular aging; cardiovascular and cerebrovascular disease; anti-aging; senolytics

心脑血管疾病严重危害中老年人生命健康, 衰老是其危险因素, 延缓心脏与血管衰老是防治心脑血管系统老年病的早期有效措施。心脏与血管衰老是随年龄发生的结构改变和功能逐渐衰退的过程, 且2型糖尿病、动脉粥样硬化、高血压和脑血管病等心脑血管疾病会加速这一过程。衰老细胞积累是心脏血管衰老的基础, 衰老细胞分泌大量促细胞炎症因子和金属蛋白酶 (matrix metalloproteinase, MMP) 等衰老分泌相关表型 (senescence-associated secretory phenotype, SASP) 诱导周围细胞衰老, 形成促衰老炎症微环境并扩大衰老[1]。炎症伴随着心血管衰老的发生, 且持续的慢性炎症会加速细胞衰老、降低细胞增殖能力和免疫功能, 进而诱导心脏、血管的结构与功能改变以及加速心脏与血管衰老[2], 而心脑血管疾病更是加剧了炎症加速心脏、血管衰老的过程。因此, 慢性炎症是心血管衰老的重要标志和机制。

炎性小体家族重要成员NOD (nucleotide binding oligomerization domain) 样受体家族3 (NOD-like receptor protein 3, NLRP3) 炎性小体在胸腺、脑、肝和肾等器官衰老过程中发挥重要作用[3], 其可被心脏和

收稿日期: 2020-09-21;　修回日期: 2020-11-10.
基金项目: 国家自然科学基金资助项目 (81773732).
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DOI: 10.16438/j.0513-4870.2020-1513

血管衰老过程中的代谢废物、损伤产物、组织重塑事件和应激因素等激活, 并调控天冬氨酸特异蛋白酶-1 (caspase-1)、白细胞介素-18 (interleukin-18, IL-18) 和IL-1β等炎症因子的活化并引发焦亡, 影响心脏与血管衰老。IL-1β与IL-18是炎症与衰老间的重要信使, 对心脏与血管衰老具有重要作用。Caspase-1、IL-1β和IL-18在正常情况下较少分泌至细胞外, NLRP3炎性小体为caspase-1活化提供平台, 活化的caspase-1切割gasdermin家族成员D (gasdermin D, GSDMD) 在细胞膜上形成孔隙, 进而导致IL-1β和IL-18外漏及细胞焦亡, 引起炎症风暴, 损伤细胞, 并扩大炎症范围[4]。持续的炎性损伤激活细胞DNA损伤反应途径, 经由p53-p21/p16-视网膜母细胞瘤通路导致细胞生长周期停滞和SASP分泌, 进一步加剧炎症与衰老[5,6]。衰老细胞自噬减少, 同时也上调抗凋亡途径信号抑制自身凋亡, 使得衰老细胞长期存在, 衰老细胞的最终结局更倾向于焦亡[7]。NLRP3炎性小体可抑制细胞自噬和凋亡[8], 削弱机体清除功能失调与衰老的细胞, 维持机体稳态的功能。另外, NLRP3炎性小体可引发心肌细胞和神经元焦亡, 更加剧了心血管和神经系统病理结构和功能的改变[9]。

1 NLRP3炎性小体的组成与激活

NLRP3炎性小体由NLRP3、凋亡相关斑点样蛋白 (apoptosis-associated speck-like protein containing CARD, ASC) 和caspase-1共同组装而成[10]。NLRP3炎性小体的活化分为引发和激活[11]: ① 宿主可通过识别病原相关的分子模式和危险相关的分子模式诱导核因子κB (nuclear factor-κB, NF-κB) 活化, 引发NLRP3、caspase-1和pro-IL-1β的转录表达; ② 多种内、外源性刺激物引起细胞应激直接激活NLRP3。常见引起细胞应激的上游信号包括: 细胞外三磷酸腺苷、过量的葡萄糖、神经酰胺、尿酸盐、胆固醇晶体、K^+或Cl^-的流出、Ca^{2+}通量、溶酶体溶解、线粒体功能障碍和高尔基体解体等。NLRP3活化后募集ASC聚合体, 进一步诱导caspase-1的切割活化。Caspase-1活化后介导IL-18和IL-1β等炎症因子的分泌, 与GSDMD在细胞膜上形成孔隙触发焦亡, 释放IL-18和IL-1β等炎症因子进一步扩大炎症反应。此外, 脂多糖 (lipopolysaccharide, LPS) 激活Toll样受体4 (Toll-like receptor 4, TLR4) 可激活NLRP3炎性小体非经典途径, 同样可活化GSDMD并触发焦亡。

2 NLRP3炎性小体对心脏、血管衰老机制的影响

2.1 心脏衰老 心脏衰老主要表现为心肌纤维化、炎性浸润、心室功能失调和心脏节律紊乱[12]。NLRP3炎性小体、IL-18、IL-1β在老年小鼠心脏[13]和衰老心肌[14]中的表达增加, 抑制NLRP3可明显降低胰岛素样生长因子-I信号传导诱导的心肌衰老和磷脂酰肌醇-3-激酶/蛋白激酶B/雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 途径激活引起的SASP, 进而改善心肌自噬、左心室肥厚和年龄依赖性房颤, 最终缓解心脏衰老并延长小鼠寿命。此外, 相比于野生型老年小鼠, *NLRP3*$^{-/-}$老年小鼠心肌细胞的p53、p21蛋白表达水平和端粒缩短比率等衰老指标明显更低, 心脏节律紊乱、心肌纤维化和年龄依赖性PR间期延长等明显改善, 进一步说明NLRP3炎性小体可以通过调节炎症损伤、心肌细胞自噬和心肌代谢, 缓解心肌衰老, 在心脏衰老机制中发挥重要作用[13]。心肌成纤维细胞 (cardiac fibroblasts, CF) 负责心脏细胞外基质 (extracellular matrix, ECM) 产生和迁移, 参与心脏损伤后修复、炎症反应及疤痕形成, CF增殖和胶原蛋白增生可促进CF向成肌纤维细胞的转化, 导致心肌纤维化和心脏收缩舒张功能障碍, 是心脏衰老的标志[13,15,16]。腺苷酸磷酸化蛋白激酶 (adenylate phosphorylated protein kinase, AMPK) 减少、线粒体功能障碍[17]与血浆中棕榈酸酯[18]通过LPS/TLR4通路可激活NLRP3炎性小体, 诱导CF衰老, 促进CF增殖、胶原增生和MMP-2表达, 进而引起ECM改变和心肌纤维化, 最终导致心脏收缩功能下降。NLRP3炎性小体可通过调节心肌代谢和炎症损伤, 诱导心肌和CF衰老, 进而引起ECM、心肌收缩功能改变和心脏衰老, 且抑制NLRP3可缓解心脏衰老, 改善心脏纤维化、心脏节律和心脏收缩功能, 对心脏具有保护作用。

2.2 血管衰老 随年龄增长, 血管出现管壁增厚、管腔扩大、张力改变、僵硬、钙化、炎症和新生能力降低等衰老迹象, 内皮功能障碍和ECM改变是血管衰老的主要原因[19]。NLRP3、ASC、caspase-1、IL-1β、肿瘤坏死因子-α和IL-6在小鼠主动脉中的表达随年龄增加而增加, 在老年小鼠主动脉中的表达显著增高, 且IL-1β与血管重塑和内皮衰老密切相关[20]。内皮细胞 (endothelial cells, EC) 和血管平滑肌细胞 (vascular smooth muscle cells, VSMC) 是血管重要的组成细胞, EC和VSMC衰老是血管衰老的基础。EC衰老引起血管内皮通透性和血栓形成增加、血管新生和一氧化氮生成能力降低、收缩舒张功能失调等变化, VSMC衰老调控ECM参与血管重塑和血管张力失调[19,21]。研究发现[20,22], 博来霉素和*D*-半乳糖诱导的EC衰老过程中, NLRP3炎性小体经由活性氧/硫氧还蛋白相互作用蛋白 (thioredoxin interacting protein, TXNIP) 途径激活并调控IL-18、IL-1β等炎症因子成熟与分泌, 激活细胞DNA损伤途径, 通过p53/p21通路诱导EC衰老, 抑制NLRP3炎性

小体可缓解EC衰老、改善EC功能、降低细胞间黏附分子-1及血管−细胞黏附分子-1等黏附因子和炎症因子的表达, 并提高一氧化氮合酶水平。NLRP3炎性小体的激活还可促进内皮祖细胞衰老并引起血管新生和内皮修复能力降低[23]。此外, NLRP3炎性小体与VSMC细胞表型转变、弹性蛋白断裂、胶原增生、钙化等密切相关[24-26], 这与血管张力改变、钙化和血管重塑等血管衰老表现密切相关[19]。因此, NLRP3炎性小体对血管衰老机制具有重要影响, 抑制NLRP3、IL-18、IL-1β在衰老血管中的表达显著增高可缓解EC和内皮祖细胞衰老, 改善EC、内皮祖细胞及VSMC功能。

脑血管衰老与心血管衰老具有相似的机制, 但脑血管衰老又关系到因供血量降低引起的脑萎缩及因血脑屏障完整性下降引起的脑防御功能降低。NLRP3炎性小体引发的炎症损伤和细胞焦亡与老年人血脑屏障损伤[27]和颈内动脉内皮功能障碍[28,29]有关, 但当前关于NLRP3炎性小体对脑血管衰老机制的影响尚待研究。

3 NLRP3炎性小体在心脑血管老年病中的作用

3.1 动脉粥样硬化 动脉粥样硬化是危害老年人生命健康的重要原因, 衰老是动脉粥样硬化的危险因素, 而斑块会加速心血管衰老[30]。血管中衰老细胞随动脉粥样硬化的发展不断增加, 清除衰老细胞可明显缓解斑块形成和发展, 并挽救血管功能与钙化[31,32]。衰老EC通过分泌多种细胞因子导致斑块扩大, 衰老VSMC促进斑块纤维帽的形成并诱导ECM改变, 促进斑块破裂及血管钙化[33], 加快斑块发展和血管损伤。另外, 动脉粥样硬化患者主动脉和冠心病患者外周血中NLRP3、caspase-1和IL-1β水平会异常增加[34]。斑块中的胆固醇晶体、凋亡细胞以及细胞因子激活NLRP3炎性小体加快了EC、VSMC衰老和血管衰老。研究表明[35], 抑制NLRP3炎性小体的表达对小鼠动脉粥样硬化斑块的形成和破裂有保护作用, 可缓解动脉粥样硬化导致的血管衰老。冠心病与脑血管粥样硬化引起的局部组织缺血和坏死可激活损伤部位的NLRP3炎性小体, 加速心脏及脑血管的结构改变与功能衰退[36]。综上, NLRP3炎性小体的激活是衰老和动脉粥样硬化相互调节的重要机制, 也是缓解动脉粥样硬化加速心脏和血管衰老的潜在治疗靶点, 但仍需进一步研究。

3.2 2型糖尿病 2型糖尿病是一种与年龄相关的代谢性疾病, 高血糖与晚期糖基化终产物 (advanced glycation end products, AGEs) 可诱导心脏血管结构功能障碍和衰老[37-39]。NLRP3炎性小体的激活促进了胰岛β细胞的凋亡及功能异常[40], 抑制其可改善胰岛素抵抗和糖尿病并发症, 缓解机体衰老[41]。*NLRP3*基因多态性与2型糖尿病患者大血管并发症相关, NLRP3炎性小体与IL-1β在2型糖尿病患者外周血、心脏和血管中异常增高, 可直接促进糖尿病性心肌病 (diabetic cardiomyopathy, DCM) 和动脉粥样硬化的发生发展, IL-1β也被认为是对2型糖尿病诱导心血管衰老的重要炎症因子[39,42]。在2型糖尿病动物模型研究中, 抑制NLRP3炎性小体在糖尿病小鼠血管和DCM鼠心脏中的异常激活可改善肌凋亡、心室重塑、左心室功能衰退和心脏炎症等心脏衰老表现[43-45], 并显著降低动脉粥样硬化的发病率并改善血管衰老症状[46]。在体外研究中, 抑制NLRP3炎性小体在高糖高脂和AGEs模拟的2型糖尿病细胞外环境诱导EC和心肌细胞衰老过程中的异常激活, 可缓解EC衰老和心肌凋亡、纤维化和炎症[18,22,47]。因此, NLRP3炎性小体在2型糖尿病诱导EC、心肌细胞衰老中具有重要作用, 抑制NLRP3炎性小体是缓解2型糖尿病诱导心血管衰老和防治2型糖尿病并发症的潜在手段。

3.3 高血压 高血压的发展也是血管衰老的过程, *NLRP3*基因多态性与高血压发病相关[48], 抑制NLRP3炎性小体及其下游细胞因子在高血压患者心血管系统中的异常激活可降低小鼠高血压发病率[49]。内皮功能障碍和血管硬化是高血压发生的关键, 高血压导致血管内皮炎症、氧化应激加剧, 以及血管紧张素II (angiotensin II, Ang II)、前列腺素和超氧阴离子等水平增高, 进一步加重内皮功能障碍和血管硬化的恶性循环。NLRP3炎性小体被发现与原发性高血压诱导小鼠主动脉重塑和老年小鼠对Ang II升压反应增高有关, 抑制NLRP3炎性小体的降低不仅可缓解肾素−血管紧张素系统引起的血管炎症和氧化应激损伤, 还可降低VSMC表型转化、增殖和钙感应受体的表达, 进而缓解血管纤维化、胶原增生并稳定血压[47,50,51]。高血压引起的心室肌纤维化、心肌肥大和心脏功能受损与NLRP3炎性小体的激活相关, 抑制NLRP3炎性小体具有缓解心脏高压力负荷下心肌细胞的焦亡和心脏炎症、改善心脏重塑和心脏功能的作用[20,52]。因此, NLRP3炎性小体对高血压和心血管衰老有重要影响。

3.4 脑血管疾病 脑血管衰老加剧了脑血管疾病和神经系统退行性疾病的风险。缺血性和出血性脑血管疾病是中老年人常见的脑血管疾病, 调节NLRP3炎性小体具有保护老年人脑血管和预防神经系统退行性疾病的作用[27]。血脑屏障受损是出血性脑血管病和血管性痴呆的早期事件, NLRP3炎性小体、caspase-1、IL-1β对血脑屏障损伤、渗透性增加和细胞间紧密性降低有促进作用, 致使脑血管出血风险升高[53]。调控NLRP3炎性小体的表达不仅可降低脑出血风险, 还可预防脑

出血后损伤[54]与血管性痴呆[55]的发生。同时, NLRP3炎性小体激活及IL-1β对由颈动脉闭塞和脑静脉血栓形成引起的缺血性脑卒中[56]具有促进作用, 抑制其可降低缺血性中风的发病率及神经血管的损伤[36]。NLRP3炎性小体对阿尔茨海默症、帕金森病与脑血管病等老年病的发生发展具有重要影响, 但目前针对NLRP3炎性小体对脑血管衰老机制的影响尚待研究。

4 NLRP3炎性小体相关的缓解心脏、血管衰老的药物

4.1 天然产物 当前国际研究药物抗衰老作用大多以衰老细胞为靶标, 研究药物抗机体衰老作用较少。多种天然产物具有缓解心脏、血管衰老, 且可调控NLRP3炎性小体的表达 (表1)。白藜芦醇[20]、紫甘薯色素[22,57]和厚朴酚[14]可通过阻断NLRP3炎性小体抑制EC衰老与心肌衰老, 可能通过调节NLRP3炎性小体缓解心血管衰老。阿魏酸、人参皂苷、红景天苷、槲皮素、姜黄素、黄芪多糖和当归多糖等都是具有抗衰老活性和心血管系统保护作用的天然产物。人参皂苷[58]可缓解血管内皮衰老, 阿魏酸[59]具有治疗老年大鼠血管功能衰退和高血压引起的血管结构功能改变作用。姜黄素[51]可通过阻断NLRP3炎性小体抑制高血压引起的VSMC表型转化和异常增殖。红景天苷具有缓解动脉粥样硬化引起的内皮衰老, 红景天苷与槲皮素可通过抑制NLRP3炎性小体, 缓解IL-1β引起的血管炎症[60]。抗炎、抗氧化和清除自由基是大多数天然产物发挥抗衰老活性的机制[61], 天然产物是潜在的以NLRP3炎性小体为靶点发挥抗衰老活性的药物。

4.2 合成化合物 MCC950是一种通过修饰NLRP3活化构象而抑制NLRP3炎性小体寡聚激活的抑制剂, 具有潜在治疗痛风、动脉粥样硬化和阿尔茨海默症等NLRP3相关综合征的作用。MCC950可通过增强自噬和激活过氧化物酶体增殖剂激活受体-α改善老年小鼠年龄依赖性的代谢疾病发生和健康状况[62], 降低老年小鼠弹性血管对Ang II的高反应性, 改善血管张力、降低炎症和血管氧化应激反应[63]。MCC950还可改善糖尿病脑病和脑缺血后血管神经元重塑, 降低高血压心肌病心肌细胞焦亡和心脏炎症, 进而挽救心肌纤维化和心脏衰老[52]。二甲双胍是常用降糖药, 具有抗炎、抗氧化和调节糖脂代谢作用, 长期给药具有改善老年小鼠身体机能、延长小鼠寿命的作用[64]。二甲双胍抑制AMPK/mTOR和AMPK/TXNIP途径降低NLRP3炎性小体水平, 减少动脉粥样硬化和2型糖尿病心血管并发症的发生, 缓解心血管重塑[45,46]。雷帕霉素是大环内酯类抗真菌药物, 通过抑制mTOR通路调节细胞自噬、葡萄糖代谢和蛋白质核酸合成稳态, 具有缓解衰老和延长寿命的作用[65]。雷帕霉素还可抑制血管氧化应激与AMPK激活, 逆转衰老血管的内皮功能障碍和血管僵硬, 并降低血管细胞周期蛋白的表达[66]。此外, 雷帕霉素还具有抑制NLRP3炎性小体和促进细胞自噬的作用, 是潜在通过调节NLRP3炎性小体缓解心血管衰老的药物。

Table 1 Anti-aging interventions and effects in nucleotide binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome inhibition. IL-1β: Interleukin-1β; VSMC: Vascular smooth muscle cells; NO: Nitric oxide; AMPK: Adenosine 5'-monophosphate-activated protein kinase; NF-κB: Nuclear factor-κB; mTOR: Mammalian target of rapamycin; SASP: Senescence-associated secretory phenotype

Classification	Drug	Anti-aging intervention	Mechanism
Natural compound	Resveratrol	↑ Longevity, healthspan; relieved senescence of endothelial cells and cardiomyocytes	↓ NLRP3, IL-1β
	Purple sweet potato pigment	↑ Longevity, healthspan; relieved senescence of endothelial cells and cardiomyocytes	↓ NLRP3, IL-1β
	Honokiol	Relieved cardiomyocytes senescence	↓ NLRP3, IL-1β
	Curcumin	Inhibit VSMC phenotypic transformation and proliferation in hypertension	↓ NLRP3, IL-1β
	Ferulic acid	Improved vasorelaxation in aging rats and hypertensive rats	Scavenge the free radical; anti-inflammatory
	Ginsenoside Rb1	Relieved endothelial senescence and dysfunction	↑ Sirt1, NO
	Salidroside	Relieved endothelial senescence in atherosclerosis	↓ AMPK/NF-κB/NLRP3; regulate the cell cycle
Synthetic compound	Metformin	↑ Longevity, healthspan	↓ NLRP3, IL-1β, AMPK
	MCC950	↑ Healthspan; improved blood pressure in aged mice	↓ NLRP3, IL-1β
	Rapamycin	↑ Longevity, healthspan; relieved vascular aging	↓ mTOR, NLRP3; ↑ autophagy
Senolytics	Dasatinib plus quercetin	↑ Longevity, healthspan	Induce apoptosis of senescent cells; inhibition of the SASP
	Fisetin	↑ Longevity, healthspan	Induce apoptosis of senescent cells; inhibition of the SASP
	Digoxin	↑ Longevity, healthspan	Induce apoptosis of senescent cells; inhibition of the SASP

4.3 Senolytics Senolytics是一类能特异性诱导衰老细胞凋亡、减弱SASP分泌的药物。达沙替尼 (dasatinib, D) 与槲皮素 (quercetin, Q) 联合鸡尾酒疗法 (简称DQ)[67]是目前较为认可的senolytics, DQ可减少小鼠体内衰老细胞数量和SASP, 改善小鼠机能、缓解衰老和延长小鼠寿命。在DQ治疗糖尿病肾病与肺纤维化患者的临床试验中[68], DQ表现出清除衰老细胞和改善患者身体机能的作用。DQ还可逆转老年小鼠和动脉粥样硬化小鼠的血管功能、钙化和血管重塑。Fisetin[69]是一种从黄栌中提取的安全指数高的黄酮类天然产物, 具有比槲皮素更强的抗衰老活性, 有望替代毒副作用较大的senolytics, 但fisetin具有多种活性, 抗衰老的作用机制尚需研究。强心苷类[70]抗心衰药物同样具有诱导衰老细胞死亡和抑制SASP分泌的作用, 但抗衰老活性和用药剂量仍需进一步研究。Senolytics类药物不断被发现, 但如何提高其对衰老细胞的靶向性和药物治疗仍处于研究阶段。

5 结语

NLRP3炎性小体及其下游IL-18和IL-1β在心脏血管衰老和动脉粥样硬化、2型糖尿病、高血压、脑血管病等老年病过程中可异常激活, 抑制NLRP3炎性小体可缓解心血管系统中重要组成细胞的衰老, 改善心血管系统与衰老相关的结构组织功能变化, 进而缓解心血管衰老。当前, 以NLRP3炎性小体为抗衰老靶点的药物不断被发现, 如白藜芦醇、紫甘薯色素、厚朴酚、姜黄素等天然产物和MCC950、二甲双胍等合成化合物可通过抑制NLRP3炎性小体明显改善心血管系统的细胞衰老, 缓解心脏和血管衰老, 并调节身体机能、延长寿命。因此, NLRP3炎性小体是一个缓解心脏和血管衰老并可早期防治心脑血管老年病的新型靶点。

作者贡献: 吉晓漫负责整体写作, 徐明负责文章修改。
利益冲突: 所有作者均声明不存在利益冲突。

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