

NLRP3 炎症小体在矽肺发病机制中的作用研究概况

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摘要:

矽肺是全世界最常见的尘肺病类型之一,从事采矿、建筑和陶瓷等诸多行业的工人有较高的发病风险。职业工人长期反复吸入 $5\text{ }\mu\text{m}$ 以下的游离二氧化硅(SiO_2)粉尘引起炎症反应,进而形成以双肺广泛结节性纤维化为特征的间质性肺疾病。即使工人调离矽尘作业环境,矽肺仍在进行性发展。矽肺的发病机制复杂,Nod 样受体家族蛋白 3(NLRP3)炎症小体在矽肺发病与进展中的作用有待深入研究。NLRP3 炎症小体是一种由 NLRP3、凋亡相关斑点样蛋白和半胱天冬酶-1 组成的多蛋白复合物,参与氧化应激、炎症反应、细胞凋亡和细胞焦亡四个途径,是矽肺的研究热点之一。本文首先概述了 NLRP3 炎症小体的结构、功能和激活机制;进而分析了 NLRP3 炎症小体参与矽肺发生与进展的细胞和分子机制,包括氧化应激、炎症反应、细胞凋亡和细胞焦亡;最后总结了基于不同机制的矽肺治疗药物。本文提出未来应多关注 NLRP3 炎症小体在矽肺发生发展中的作用,以期对矽肺的防治提供新的思路。

关键词: NLRP3 炎症小体;矽肺;肺纤维化;治疗

Review on role of NLRP3 inflammasome in pathogenesis of silicosis FAN Zhenzhen, ZHAO Yehong, LI Bing, LIU Yang, JIANG Junyu, MU Min, TAO Xinrong (School of Medicine/Key Laboratory of Industrial Dust Control and Occupational Health of the Ministry of Education/Anhui Province Engineering Laboratory of Occupational Health and Safety, Anhui University of Science and Technology, Huainan, Anhui 232001, China)

Abstract:

Silicosis is one of the most common forms of pneumoconiosis globally. Workers who engage in mining, construction, ceramics, and many other industries have a high risk of developing silicosis. Chronic and repeated inhalation of free silica (SiO_2) dust ($< 5\text{ }\mu\text{m}$) during working can lead to inflammatory reactions, resulting in interstitial lung disease characterized by extensive nodular fibrosis in both lungs. Once silicosis occurs, it will develop progressively even when the workers are removed from the silica dust environment. The pathogenesis of silicosis is complex, especially the role of nod-like receptor family protein 3 (NLRP3) inflammasome in the pathogenesis and progression of silicosis remains to be further studied. NLRP3 inflammasome, a multi-protein complex composed of NLRP3, apoptosis-associated speck-like protein, and cysteinyl aspartate specific proteinase 1 is involved in oxidative stress, inflammatory response, apoptosis, and pyroptosis, and has become one of the hot spots in silicosis research. This review summarized the structure, function, and activation mechanism of NLRP3 inflammasome. Furthermore, the cellular and molecular mechanisms of NLRP3 in mediating oxidative stress, inflammatory response, apoptosis, and pyroptosis in the progression of silicosis were reviewed. Finally, the potential therapeutic drugs for silicosis based on NLRP3-associated mechanisms were outlined. More attention should be paid to the role of NLRP3 inflammasome in the pathogenesis and progression of silicosis in the future, which will provide new ideas for the prevention and treatment of silicosis.

Keywords: NLRP3 inflammasome; silicosis; pulmonary fibrosis; therapy

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矽肺是一种因职业工人长期暴露于可吸入性游离二氧化硅(silicon dioxide, SiO_2)粉尘环境中,最终引起职业性肺纤维化的疾病^[1]。新近研究证实,矽肺进展与 Nod 样受体家族蛋白 3(nod-like receptor family protein 3, NLRP3)炎症小体

有关^[2]。本文综述了 NLRP3 炎症小体活化机制及其在矽肺发病机制中作用的研究进展, 以期对矽肺的预防和诊疗探索提供新的思路。

1 NLRP3 炎症小体的结构与功能

“炎症小体”最初是由 Martinon 等^[3]在 2002 年报告。目前已证实 NOD 样受体(nod-like receptor, NLR)家族和 PYHIN (pyrin and HIN domain) 家族都可形成炎症小体。其中 NLR 家族中的 NLRP3 有别于其他炎症小体, 具有表达面广、活化方式多和影响范围大等特点, 可被多种刺激因子激活。NLRP3 炎症小体是以传感器 NLRP3 为支架, 适配器凋亡相关斑点样蛋白(apoptosis-associated speck-like protein, ASC)通过结合效应体半胱天冬酶-1(cysteiny aspartate specific proteinase 1, Caspases-1)进而形成的胞质多蛋白促炎复合物^[4]。

NLRP3 分别由三部分结构域组成: ①NLRP3 的中间区域, 被称为核苷酸结合域(nucleotide-binding domain, NBD), NBD 结构域的 TPase 活性对 NLRP3 的自我关联和功能至关重要; ②C 端的一个典型 NLR 蛋白家族的亮氨酸重复序列受体(leucine rich repeat, LRR)结构域, LRR 结构域负责 NLRP3 与其他蛋白的相互作用, 是炎症小体和 ASC 斑点形成的必要条件; ③N 端含有的热蛋白结构域(pyrin domain, PYD)。PYD 结构域允许 NLRP3 与其他炎症小体蛋白相互作用, 这些相互作用受磷酸化调节^[5]。ASC 作为一个双适配器蛋白分子, 包含两个转导结构域, 一个是连接上游 NLRP3 的 PYD, 另一个是连接下游 Caspase-1 的募集结构域(caspase recruitment domain, CARD), 最终形成 NLRP3-ASC-Caspase-1 紧密复合物。Caspase-1 被激活后, 可产生成熟活化形式的白细胞介素 1 β (interleukin-1 β , IL-1 β)和白细胞介素 18(interleukin-18, IL-18)。NLRP3 炎症小体结构见图 1。

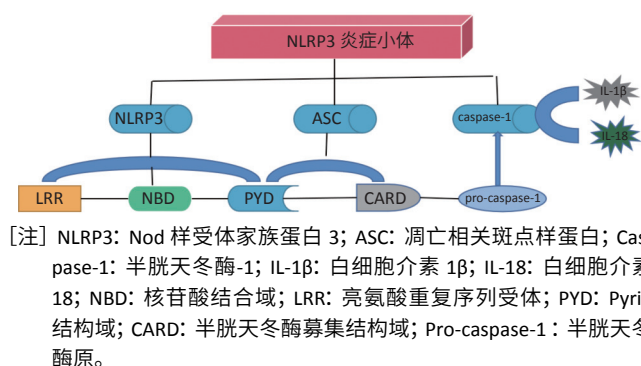


图 1 NLRP3 炎症小体的结构

Figure 1 Structure of NLRP3 inflammasome

2 NLRP3 炎症小体的激活机制

信号 1(启动途径)和信号 2(激活途径)是 NLRP3 炎症小体活化的关键步骤。微生物成分或内源性分子等配体在细胞膜上与 Toll 样受体 4(toll like receptors 4, TLR4)相结合, 从而诱导核因子 κ B(nuclear factor kappa-B, NF- κ B)信号通路激活, 导致 NLRP3、Pro-IL-1 β 、Pro-caspase-1 和 Pro-IL-18 的表达被触发, 这种预先处理的途径被定义为启动步骤。而激活步骤涉及一系列细胞和分子相关信号事件, 包括①离子通道; ②细胞器损伤; ③补体系统和蛋白质激酶 R(protein kinases R, PKR)通路; ④嘌呤受体信号、坏死信号和 Z-DNA 结合蛋白 1(z-dna binding protein 1, ZBP1)途径。这些信号事件进一步可导致 NLRP3 炎症小体复合物的合成(图 2)。

2.1 离子通道

近年来, Na⁺^[6]、K⁺^[7]、Ca²⁺^[8]和 Cl⁻^[9-10]四种离子通道参与 NLRP3 炎症小体的激活相继被报道。Na⁺内流在 NLRP3 炎症小体激活中发挥作用。被相关物质运送到溶酶体的尿酸单钠晶体可导致细胞内 Na⁺超载、水内流和细胞肿胀, 从而造成细胞内 K⁺浓度下降^[11], 促进 NLRP3 炎症小体的活化。此外, 细胞内储存钙转移到胞质已经被证明是 NLRP3 炎症小体被众多激活因子(如: 尼日利亚霉素、ATP 和颗粒物等)活化的关键^[8]。在 Ca²⁺的作用下, 钙敏受体信号加速 NLRP3 炎症小体复合物组装^[8]。另外, Cl⁻的体积调节阴离子通道和细胞内 Cl⁻通道, 可调节 NLRP3 炎症小体的激活^[9-10]。

2.2 细胞器损伤

受损的线粒体、溶酶体以及高尔基体均与 NLRP3 炎症小体活化有关。Zhou 等^[12]首次发现受损线粒体在 NLRP3 激活中的作用。线粒体功能障碍为 NLRP3 炎症小体复合物的激活提供了关键机制, 通过过度生成线粒体活性氧(mitochondrion reactive oxygen species, mtROS), 诱导线粒体 DNA 的胞质易位以及乙酰化微管蛋白 α 的生成, 使线粒体在 NLRP3 附近重新定位^[13]。溶血磷脂酰胆碱作为质膜主要脂质成分, 当溶酶体受损和 K⁺排出时, 可导致泡沫细胞形成, 并触发人内皮细胞和单核细胞中 NLRP3 炎症小体活化^[14]。除以上线粒体及溶酶体细胞器与 NLRP3 活化密切相关外, 研究人员还发现 NLRP3 的活化与高尔基体受损有关, NLRP3 活化可促进反式高尔基网络分解为分散反式高尔基网络的囊泡, 进而将一个内部的多碱基区域与脂质磷脂酰肌醇 4-磷酸结合而发生 NLRP3 的募集。NLRP3 一旦被招募到分散反式高尔基网络中, 可以募集 ASC 形

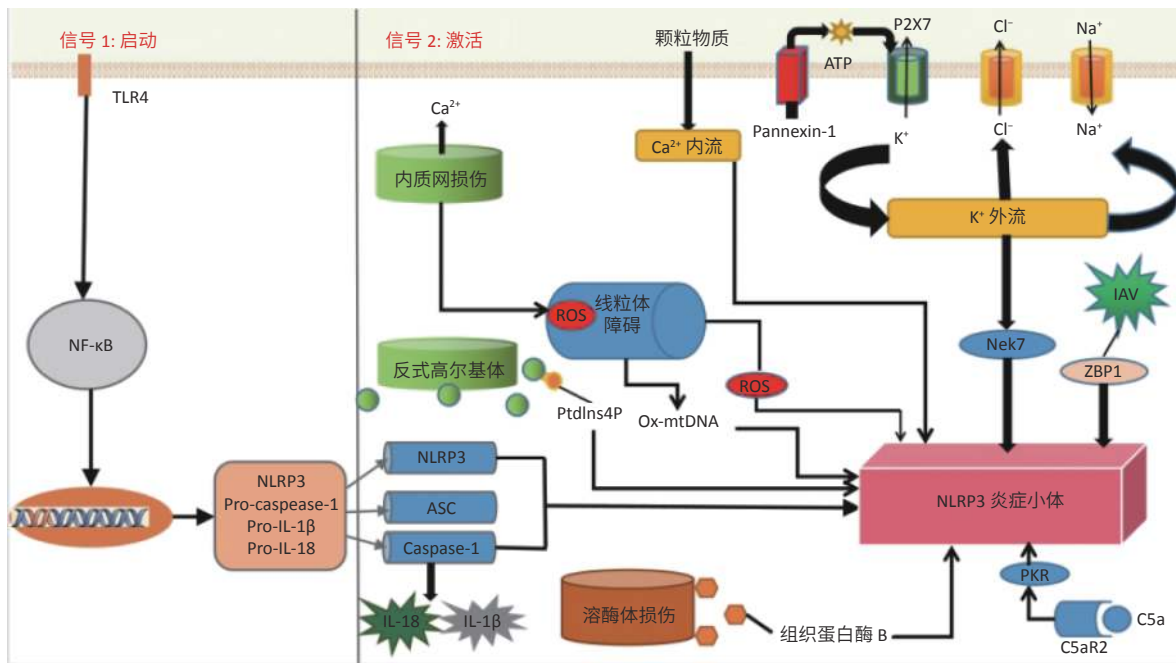
成 NLRP3 炎症小体^[15]。

2.3 补体系统和 PKR 通路

补体系统的膜攻击复合物可致使 NLRP3 炎症小体激活,进而促进炎症因子的释放,诱发炎症反应^[16]。 γ 干扰素介导的人内皮细胞中膜攻击复合物的内化导致 NLRP3 易位到核内,并导致核内 NF- κ B 诱导激酶依赖的 NLRP3 炎症小体组装,导致相关疾病的发生^[17]。补体 C5a/补体 C5a(C5aR)受体通路通过放大巨噬细胞中 PKR 的表达来加速 NLRP3 炎症小体的活化进程,提示 PKR 是 NLRP3 的重要激活因子^[18]。

2.4 嘌呤受体信号、坏死信号和 ZBP1 途径

腺苷和 ATP 受体激活 NLRP3 炎症小体后,参与各类代谢和退行性疾病过程。P2X7R 是独特的配离子门调控通道,被认为是 NLRP3 炎症小体组织和 IL-1 β 分泌的强激活信号。NLRP3 炎症小体和受体相互作用蛋白激酶(receptor-interacting protein kinase, RIPK)1 和 3 参与的坏死信号途径密切相关。而 ZBP1 不仅激活 NLRP3 炎症小体介导的细胞焦亡^[19],还可直接感知甲型流感病毒(influenza A virus, IAV)感染并促进 RIPK3 和 Caspase-8 激活,进而导致 NLRP3 炎症小体的组装^[7]。



[注] TLR4: Toll 样受体 4; NF- κ B: 核因子 κ B; NLRP3: Nod 样受体家族蛋白 3; Pro-caspase-1: 前半胱天冬酶-1; Pro-IL-1 β : 白细胞介素 1 β 前体; Pro-IL-18: 白细胞介素 18 前体; ASC: 凋亡相关斑点样蛋白; Caspase-1: 半胱天冬酶-1; IL-1 β : 白细胞介素 1 β ; IL-18: 白细胞介素 18; PKR: 蛋白质激酶 R; ZBP1: Z-DNA 结合蛋白 1; ROS: 活性氧; IAV: 甲型流感病毒; PtdIns4P: 磷脂酰肌醇 4-磷酸; NEK7: 有丝分裂基因 A 相关激酶 7; Ox-mtDNA: 氧化的线粒体 DNA; C5aR2: 补体 C5a 受体 2; Pannexin1: 血清连接蛋白 1; ATP: 腺嘌呤核苷三磷酸。

图 2 NLRP3 炎症小体的激活机制

Figure 2 Activation mechanism of NLRP3 inflammasome

3 NLRP3 炎症小体与矽肺进展关键细胞

肺泡巨噬细胞(alveolar macrophage, AM)、人支气管上皮细胞、成纤维细胞和肺泡上皮细胞在 SiO₂ 的作用下,不同程度地激活 NLRP3 炎症小体,影响矽肺的发展进程。AM 内的 NLRP3 炎症小体活化后参与矽肺进展^[20]。AM 通过细胞表面受体和膜胆固醇识别硅颗粒,吞噬后的晶体 SiO₂ 较难降解,从而引起溶酶体损伤,最后导致 NLRP3 炎症小体被激活。此外, NLRP3 炎症小体在人支气管上皮细胞中广泛存在^[21]。SiO₂ 作用于人支气管上皮细胞导致 NLRP3 炎症小体组装和 Caspase-1 激活的经典和非经典途径的信号输出,有助于矽肺结节和纤维化的发展^[22]。

另外, Cassel 等^[23]在 NLRP3 炎症小体和肺纤维化的研究中发现 SiO₂ 可诱导巨噬细胞产生活性氧,促进 Caspase-1 的激活以及随后的 IL-1 β 释放并且加速成纤维细胞分泌胶原。还有相关研究已经证明肺泡 II 型上皮细胞的衰老参与了矽肺的形成,并且肺泡 II 型上皮细胞的肥大和增生是矽肺的重要特征之一^[24]。

4 NLRP3 炎症小体参与矽尘对肺组织的损伤机制及治疗

NLRP3 炎症小体可调控促炎细胞因子分泌,并通过氧化应激、炎症反应、细胞凋亡和细胞焦亡促进矽肺的早期发展,其参与矽尘对肺组织的损伤机制并基

于不同机制的矽肺治疗药物总结如下。

4.1 氧化应激

活性氧(reactive oxygen species, ROS)和氧化应激的增加是 SiO₂ 暴露早期发生的常见细胞反应^[25]。当吸入 SiO₂ 颗粒时,它们被 AM 吞噬,从而促使 ROS 的释放。ROS 可作为 SiO₂ 暴露后 NLRP3 炎症体激活的初始信号^[26],激活 NLRP3 炎症小体进而诱导氧化应激^[27]。氧化应激使上皮细胞的形态和功能异常,包括细胞因子合成与分泌,加速了上皮间充质转化和凋亡,导致成纤维细胞和细胞外基质的增加,最终导致矽尘所致的肺部损伤^[28]。此外,Caspase-1 是 NLRP3 炎症小体的效应蛋白,促进成熟的 IL-1 β 分泌,进而诱导促进转化生长因子 β (transforming growth factor- β , TGF- β) 生成。氧化应激通过增加过氧化氢水平、脂质过氧化、DNA 降解和蛋白质损伤加速 TGF- β 1 介导的纤维形成。有研究证实 TGF- β 1/Smad(drosophila mothers against decapentaplegic)和核因子 E2 相关因子 2(nuclear factor E2 related factor 2, Nrf2) 信号通路之间有联系^[29],该通路介导了肌成纤维细胞的增殖并加速了肺纤维化进程^[30]。Nrf2 具有抑制氧化应激反应,负调控 TGF- β 1 介导的促纤维化作用^[31]。有研究表明,丹参酮 IIA 作为天然产物之一,其潜在机制为强化抗氧化防御系统,通过调节在 NLRP3 炎症小体活化后诱发的上皮间充质转化和 TGF- β 1/Smad 信号级联反应,激活 Nrf2 相关抗氧化信号,最终降低 SiO₂ 暴露诱导的氧化应激,从而减轻 SiO₂ 诱导的肺纤维化^[29]。

4.2 炎症反应

激活 NLRP3 炎症小体能激发高迁移率族蛋白 B1(high mobility group box-1, HMGB1)分泌(在细胞焦亡期间 HMGB1 以可溶性分子从细胞中释放)。HMGB1 作为一种损伤相关模式分子,在被靶细胞识别之后与 TLR-4 结合,TLR4/髓样分化因子(myeloid differentiation factor 88, MyD88)/NF- κ B 信号轴在 MyD88 和 NF- κ B 激活之后被触发,从而导致细胞发生炎症反应^[32]。此外,NF- κ B 信号通路可介导胶原蛋白的合成,促进肿瘤坏死因子(tumor necrosis factor- α , TNF- α)、IL-1 β 、TGF- β 等细胞因子的转录,导致肺部炎症损伤^[33]。Liu 等^[34]发现牛蒡子苷和牛蒡子苷元通过 TLR-4/MyD88/NF- κ B 途径抑制 SiO₂ 诱导的 NLRP3 炎症小体激活及 IL-1 β 等炎症因子和 α -平滑肌肌动蛋白的分泌,从而改善炎症反应。

4.3 细胞凋亡

发生在矽肺进展初期的 AM 凋亡可以缓解炎症反应以及清理肺部损伤细胞,从而促进肺部功能的重建。

而在矽肺的晚期,过量的 AM 细胞凋亡会损害身体。NLRP3 炎症小体在细胞凋亡中发挥作用^[35]。凋亡细胞通过 NLRP3 炎症小体介导释放的炎症相关细胞因子,进一步招募炎性细胞到特定位置,加重炎症反应,加快肺纤维化进程。SiO₂ 诱导细胞凋亡的复杂调控网络如下:当 SiO₂ 侵入肺泡时,产生 mtROS 诱导 NLRP3 炎症小体的活化,释放凋亡蛋白酶激活因子-1,进而启动 Caspase 级联反应,激活 Caspase-3,破坏聚腺苷二磷酸核糖聚合酶,进一步导致 DNA 断裂(细胞凋亡的特征)^[36]。此外,TNF- α 被认为是矽肺早期诊断的生物标志^[37],TNF- α 的激活加重了 AM 凋亡。然而,TNF- α 也刺激 NF- κ B 信号通路下调 NLRP3 的表达,以削弱 SiO₂ 毒性作用引起的细胞凋亡。TNF- α 通过膜受体蛋白介导 NLRP3-Caspase-1-ASC 复合物的形成,促进 Pro-IL-1 β 形成 IL-1 β ^[38]。IL-1 β 不仅可诱导炎症反应,还可调节 AM 凋亡。有研究表明,柚皮素能够通过激活 NLRP3 信号通路上调超氧化物歧化酶 2(superoxide dismutase 2, SOD2) 基因的表达,从而促进脂肪组织间充质干细胞的增殖^[39]。脂肪组织间充质干细胞可降低线粒体凋亡过程中有关蛋白的表达水平,减少过度凋亡^[40],进而起到保护肺的作用。

4.4 细胞焦亡

NLRP3 炎症小体的激活会诱导 Caspase-1 依赖的高度炎症性的焦亡。而膜穿孔蛋白(Gasdermin-D, GSDMD) 是 Caspase-1 的通用底物^[41]。GSDMD 蛋白含有的氨基端 Gasdermin-N 和羧基端 Gasdermin-C 结构域被 Caspase-1 切割分开,进而释放具有内源性诱导细胞凋亡活性的氨基端片段。GSDMD-NT 寡聚并与选定的质膜磷酸肌苷或心磷脂结合,诱导质膜上形成孔,最终使得胞膜裂解,释放促炎细胞因子和胞质内容物^[42]。有研究证实,在吸入 SiO₂ 后诱导的 AM 病变,导致溶酶体内部破坏,促进 Caspase-1 将 Pro-IL-1 β 切割成成熟的 IL-1 β ,从而诱导细胞焦亡的发生^[43]。宋占帅等^[44]研究发现 NLRP3 炎症小体抑制剂 MCC950 通过降低 NLRP3 蛋白的表达,减少 Caspase-1 的自身激活,抑制炎症介质 IL-1 β 和 IL-18 表达,最终降低 TGF- β 1 的合成,从而起到抗细胞焦亡的作用。

5 小结与展望

迄今,矽肺依旧是全球亟待解决的公共卫生问题。近年来,NLRP3 炎症小体对矽肺发展进程的影响备受关注,并拟通过严格控制 NLRP3 炎症小体的激活,阻断相关的信号通路,从而预防过度的氧化应激、炎症

反应、细胞凋亡以及细胞焦亡过程的发生,探讨矽肺防治的新途径。

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