·综述·

NLRP3炎症小体在特应性皮炎中的调控机制及治疗应用

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摘要 特应性皮炎是一种由遗传、免疫及环境因素共同导致的慢性炎症性皮肤病，具有持续性和复发性特征。核苷酸结合寡聚化结构域样受体蛋白3（NLRP3）炎症小体通过多种刺激物激活后促进炎性细胞因子白细胞介素（IL）-1β和IL-18成熟，进而调节辅助性T淋巴细胞（Th）2/Th1免疫偏移，在特应性皮炎急性期和慢性期的发病过程中发挥关键作用，抑制其活化可显著减轻特应性皮炎的症状。本综述系统总结了NLRP3炎症小体在特应性皮炎中的致病机制及治疗应用的研究进展，为靶向NLRP3炎症小体的抑制剂应用于特应性皮炎治疗提供了理论基础。

关键词 特应性皮炎；炎症小体；核苷酸结合寡聚化结构域样受体蛋白3；抑制剂
中图分类号 R758.2 **文献标志码** A **文章编号** 0258-4646（2026）04-0372-05
网络出版地址 https://link.cnki.net/urlid/21.1227.R.20260414.1623.012
DOI：10.12007/j.issn.0258-4646.2026.04.014

Regulatory mechanism and therapeutic application of NLRP3 inflammasome in atopic dermatitis

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Abstract Atopic dermatitis（AD）is a chronic inflammatory skin disease caused by genetic，immunological and environmental factors，with persistent and recurrent characteristics. Nucleotide-binding oligomerization domain-like receptor protein 3（NLRP3）inflammasome promotes the maturation of inflammatory factors interleukin（IL）-1β and IL-18 through the activation of various stimuli，and then regulate the helper-T lymphocytes（Th）2/Th1 immune shift，which plays a key role in the pathogenesis of atopic dermatitis in acute and chronic phases. Inhibition of its activation can significantly alleviate symptoms of AD. This review systematically summarizes the research progress in the pathogenesis and therapeutic applications of the NLRP3 inflammasome in AD，which provides a theoretical basis for the application of inhibitors targeting this inflammasome for the treatment of atopic dermatitis.

Keywords atopic dermatitis；inflammasome；nucleotide-binding oligomerization domain-like receptor protein 3；inhibitor

特应性皮炎是一种复杂的慢性炎症性皮肤病，具有显著的临床异质性和治疗抵抗性[1]。虽然近年来其治疗方法不断改进，但由于疾病的高度异质性和复杂的发病机制，约30%的患者对现有治疗反应不佳[2]。因此，进一步阐明疾病的发病机制并开发个体化治疗策略有重要意义。炎症小体是一类细胞内多蛋白复合物，在先天性免疫系统中作为模式识别受体发挥核心作用[3]。其中，核苷酸结合寡聚化结构域样受体蛋白3（nucleotide-binding oligomerization domain-like receptor protein 3，NLRP3）炎症小体与特应性皮炎的发展密切相关[4]。近年来，多种NLRP3炎症小体抑制剂在特应性皮炎动物模型中疗效显著，但其临床应用仍面临挑战[5-6]。本文总结了NLRP3炎症小体的结构及其激活机制，并概述了其在特应性皮炎病理机制中作用的研究进展，同时探讨了NLRP3炎症小体抑制剂在该疾病中潜在的治疗应用，旨在为特应性皮炎治疗策略的开发提供理论基础。

1 NLRP3炎症小体的结构特征和激活机制

1.1 NLRP3炎症小体的结构特征

NLRP3炎症小体是一种细胞内多蛋白复合物，由NLRP3蛋白、含CARD结构域的凋亡相关斑点样蛋白（aoptosis-associated speck-like protein containing card，ASC）以及pro-caspase-1组成[7]。NLRP3属于

基金项目：国家自然科学基金（82060573）
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收稿日期：2025-07-28
网络出版时间：2026-04-15 11:40:28

NOD样受体蛋白家族(NOD like receptor,NLR),包含3个主要功能域,分别为N端的PYD结构域、中央的NACHT结构域和C端的富含亮氨酸的重复结构域。其中,PYD结构域介导蛋白质相互作用,NACHT结构域负责寡聚化,而LRR结构域则参与配体识别及自我抑制调节[8]。ASC作为支架蛋白,通过其PYD结构域与NLRP3的PYD结构域结合,并通过CARD结构域连接pro-caspase-1,从而完成炎症小体的组装[9]。pro-caspase-1是caspase-1的无活性前体,在炎症小体形成后通过自身切割产生酶活性的caspase-1 p20/p10异源二聚体[10]。活化的caspase-1作为NLRP3炎症小体的核心效应蛋白,负责切割pro-IL-1β和pro-IL-18,并生成成熟炎性细胞因子IL-1β和IL-18[11]。

1.2　NLRP3炎症小体的激活机制

1.2.1　经典途径:NLRP3炎症小体的经典激活途径包括启动和激活2个阶段。启动过程涉及细胞在初始信号刺激下,通过模式识别受体激活转录因子NF-κB,从而诱导NLRP3和pro-IL-1β的表达上调[12]。激活过程则指已启动的细胞在离子流、线粒体活性氧、乙酰化修饰和干扰素基因刺激因子等第二信号刺激下,NLRP3、ASC和pro-caspase-1等蛋白组装成炎症小体复合物,进而激活caspase-1,最终诱导细胞焦亡并释放成熟的IL-1β和IL-18[12]。

1.2.2　非经典途径:NLRP3炎症小体的非经典激活途径涉及小鼠caspase-11直接识别胞质中的脂多糖以促进NLRP3炎症小体活化。研究[13]表明,在*caspase-11*基因敲除小鼠中,革兰氏阴性菌感染后*caspase-11*缺失导致其底物蛋白GSDMD的切割被抑制,从而阻断细胞焦亡过程并减少IL-1β分泌。胞质内革兰氏阴性菌释放的脂多糖可直接结合并激活caspase-11,活化的caspase-11通过切割GSDMD形成跨膜孔道,诱发焦亡性细胞死亡,但caspase-11自身无法直接切割pro-IL-1β或pro-IL-18[14-15]。GSDMD形成的孔道通过促进NLRP3炎症小体活化,进而诱导caspase-1的激活及IL-1β、IL-18的成熟和分泌[12]。

1.2.3　替代途径:除经典和非经典途径外,NLRP3炎症小体还存在替代性激活途径。研究[16]表明,脂多糖可通过其受体TLR4信号通路激活单核细胞中的炎症小体。脂多糖刺激导致ATP释放至胞外,通过与P2X7受体结合并诱导钾离子外流,从而激活NLRP3炎症小体[16]。此外,脂多糖还可通过TLR4/β-干扰素TIR受体结构域衔接蛋白/丝氨酸-苏氨酸激酶-1/Fas相关死亡结构域蛋白/caspase 8信号通路激活NLRP3炎症小体,从而促进caspase-1活化及IL-1β和IL-18的成熟和分泌[17-18]。然而,该替代途径具有细胞类型和物种特异性,目前仅在人与猪的单核细胞以及小鼠树突状细胞中得到验证[19-20]。

2　NLRP3炎症小体与特应性皮炎发生

NLRP3炎症小体激活促进活性IL-1β和IL-18的成熟与释放。在特应性皮炎中,表皮屏障破坏使环境刺激物和微生物易于侵入,而微生物定植提供直接激活信号,二者通过调控NF-κB信号通路诱导NLRP3炎症小体激活,导致IL-1β释放并加剧局部炎症反应[21]。在特应性皮炎发展过程中,IL-1β、IL-33及IL-18协同作用,共同驱动皮肤免疫失调[22-23]。其中,IL-18作为NLRP3炎症小体的下游产物,在特应性皮炎患者血清和病变组织中表达上调[24],并通过促进辅助性T细胞(helper T cell,Th)2型免疫应答参与炎症放大和屏障功能障碍[25]。此外,IL-18与IL-37协同作用,调节Th1/Th2/Th17炎症反应,从而构成特应性皮炎的炎症调控网络[26]。

除了IL-1β和IL-18外,GSDMD作为NLRP3炎症小体的下游关键效应分子,在特应性皮炎的发病机制中发挥重要作用。基于基因表达综合数据集的分析表明,特应性皮炎患者皮肤组织中*GSDMD* mRNA表达显著上调[27]。NLRP3炎症小体激活后可通过活化caspase-1,裂解GSDMD并介导细胞焦亡,从而促进IL-1β和IL-18等促炎细胞因子的释放。多项研究[27-28]表明,抑制NLRP3炎症小体及GSDMD介导的细胞焦亡可显著减轻特应性皮炎的炎症反应和病理症状。然而,GSDMD在特应性皮炎中的具体激活机制及其与疾病进展的关系仍需进一步阐明。

IL-33通过其特异性受体生长刺激表达基因2激活肥大细胞、Th2细胞和嗜酸性粒细胞,在特应性皮炎的发生和发展中发挥核心作用[29]。研究[30]发现,NLRP3蛋白可作为IL-33的转录因子促进其表达,且NLRP3与IL-33在特应性皮炎小鼠模型中表达水平呈显著正相关。NLRP3通过与上皮细胞转录因子干扰素调节因子4相互作用直接调节IL-33的表达。然而,在NLRP3缺陷的特应性皮炎小鼠模型中IL-33的表达下调,而NLRP3炎症小体抑制剂MCC950和

VX-765对HaCaT细胞中IL-33的表达无抑制作用。这一现象提示NLRP3对IL-33转录的调控可能独立于NLRP3炎症小体途径，同时也可能源于HaCaT细胞在准确模拟人特应性皮炎复杂免疫环境方面的局限性。

3　NLRP3炎症小体抑制剂与特应性皮炎治疗

3.1　NLRP3炎症小体抑制剂

磺酰脲类化合物MCC950是一种常用的NLRP3抑制剂，通过结合NLRP3的NACHT结构域抑制NLRP3炎症小体的激活[31]。然而，类风湿性关节炎Ⅱ期临床试验中发现其可以增加血清肝转氨酶水平，从而导致肝脏毒性，这一不良反应限制了其临床应用[31]。MCC950的结构优化衍生物ZYIL1已在临床试验中被证实具有更好的安全性[32]。曲尼司特作为一种色氨酸代谢物类似物，可与NLRP3的NACHT结构域相互作用，并抑制NLRP3炎症小体的激活，其通过与NLRP3的亲核表面残基形成共价结合发挥作用[33-34]，临床上已批准用于治疗哮喘、瘢痕疙瘩和肥厚性瘢痕[35]。Dapansutrile（OLT1177）是一种口服活性β–磺腈分子，可以抑制NLRP3-ATP酶活性和下游炎症反应，并作为腈衍生物形成共价加合物靶向NACHT结构域[34,36]。早期临床试验[34]表明，其在健康志愿者中安全且耐受性良好。DFV890是一种外周限制性NLRP3抑制剂，可改善早期SARS-CoV-2清除、临床状态和住院结局[37]。MM01是一种小分子ASC特异性抑制剂，通过与ASC的CARD结构域表面结合，在空间上阻断ASC斑点组装及前天冬氨酸蛋白酶–1招募所需的CARD结构域同型相互作用[38]。此外，靶向ASC的单克隆抗体IC-100及单链抗体VHHASC也正在开发中[39-40]。

3.2　NLRP3炎症小体抑制剂在特应性皮炎治疗中应用的限制

特应性皮炎作为一种慢性、复发性炎症性皮肤疾病，其病理特征表现为表皮屏障功能障碍和免疫应答异常。目前缺乏关于NLRP3炎症小体抑制剂治疗特应性皮炎的临床研究证据。临床前实验发现腹腔注射Drp1抑制剂mdivi-1通过抑制线粒体分裂相关蛋白Drp1间接阻断NLRP3炎症小体激活，从而减轻实验性特应性皮炎模型的症状[41]。然而，在长期药物治疗过程中，药物的透皮递送效率受限于皮肤屏障特性、药物理化性质及制剂类型等多种因素。现有NLRP3炎症小体抑制剂大多呈现较低的亲脂性，预示其皮透性不佳，这直接制约了其局部给药治疗特应性皮炎的应用前景。

优化药物剂型是提高经皮给药效率的关键策略。乳膏、凝胶或泡沫等剂型可有效增强药物的皮肤渗透性[42]。透皮促渗剂（二甲基亚砜、氮酮和丙二醇等）通过改变皮肤屏障结构提高药物渗透性，尤其适用于类固醇激素、镇痛药和亲脂性药物的递送，但可能引起皮肤红斑和水肿等不良反应[43-45]。相比之下，精油及其活性成分作为天然促渗剂，可暂时可逆地降低角质层屏障功能而不损伤活细胞，促进药物透皮吸收[46]，对亲水性和亲脂性药物均展现出良好的临床适用性和安全性。调控药物释放动力学是增强抑制剂疗效的核心策略。通过制剂技术（水凝胶、脂质纳米载体和微针技术等）精确控制药物释放速率可在皮肤内维持长效稳定的药物治疗浓度，减少给药频率并提高患者依从性，从而显著提升总体治疗效果[47-50]。这些策略通过协同增效机制提高经皮给药效率、减少不良反应并增加治疗获益，为改善特应性皮炎患者生活质量提供了重要技术支撑。

4　展望

特应性皮炎是由免疫失调驱动的慢性炎症性皮肤疾病，核心治疗理念为免疫稳态的恢复。该疾病的炎症级联反应可影响从表皮角质层到真皮的全层组织，其中上皮损伤引发的IL-33过度释放驱动了Th2免疫应答的过度活化，这是特应性皮炎慢性化和难治性的关键因素。因此，抑制IL-33活性及其下游信号传导可能成为特应性皮炎的有效治疗策略。近年来，NLRP3炎症小体作为炎症性疾病治疗靶点的研究取得了显著进展，已开发出多种用于疾病治疗的NLRP3炎症小体抑制剂。鉴于当前特应性皮炎治疗药物常伴有显著的不良反应，靶向NLRP3炎症小体的抑制剂可以特异性调控炎症通路，可能成为特应性皮炎潜在的理想治疗方法。NLRP3炎症小体通过促进炎性细胞因子释放加剧特应性皮炎发展，其抑制可有效减轻特应性皮炎的症状。在动物模型中，NLRP3抑制剂通过下调IL-1β等炎性细胞因子改善皮肤炎症及临床指标。此外，NLRP3在巨噬

细胞中可直接作为IL-33的上游调控因子，通过上调IL-33表达调节Th2免疫应答。

综上所述，目前亟需通过动物模型和临床试验进一步评估NLRP3抑制剂在特应性皮炎治疗中的应用价值。然而，多数抑制剂的真皮递送效率仍未得到证实，需探索其在皮肤组织的有效递送或开发新型递送系统以增强治疗潜力。

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