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Review 综述

乳杆菌科细菌抑制核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体 3 炎症小体激活的抗炎研究进展

廖成水[1,2*]，贾艳艳[1,2]，余祖华[1,2]，丁轲[1,2]

1 河南科技大学，功能微生物与畜禽健康实验室，河南 洛阳
2 河南科技大学 动物科技学院，洛阳市活载体生物材料与动物疫病防控重点实验室，河南 洛阳

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摘　要：核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体 3 (nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3, NLRP3)炎症小体是固有免疫的重要组分，在机体免疫反应和疾病发生过程中发挥着重要作用。NLRP3 炎症小体异常激活与多种疾病的发生发展密切相关。新近研究发现，乳杆菌科细菌可通过调控 NLRP3 炎症小体活性发挥抗炎作用。因此，本文概述了乳杆菌科细菌直接和间接调控 NLRP3 炎症小体活性的抗炎机制，同时探讨了植物乳植杆菌、干酪乳酪杆菌、鼠李糖乳酪杆菌等在肠道炎症性疾病、肝脏疾病、神经退行性疾病以及代谢与免疫疾病中对 NLRP3 炎症小体的作用，为深入探究乳杆菌科细菌调控 NLRP3 炎症小体的作用机制奠定了基础，并为炎症性疾病治疗提供了新策略。

关键词：乳杆菌科；核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体 3；抑制；激活；炎症

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*Corresponding author. E-mail: liaochengshui33@163.com
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Research advances in the anti-inflammatory effects of the *Lactobacillaceae* through the inhibition of the nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 inflammasome activation

LIAO Chengshui[1,2*], JIA Yanyan[1,2], YU Zuhua[1,2], DING Ke[1,2]

1 Laboratory of Functional Microbiology and Animal Health, Henan University of Science and Technology, Luoyang, Henan, China

2 Luoyang Key Laboratory of Live Carrier Biomaterial and Animal Disease Prevention and Control, College of Animal Science and Technology, Henan University of Science and Technology, Luoyang, Henan, China

Abstract: The nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 (NLRP3) inflammasome, a crucial element of innate immunity, plays a pivotal role in immune responses and disease pathogenesis. Dysregulated activation of the NLRP3 inflammasome is strongly linked to the onset of various diseases. Recent studies have demonstrated that the Lactobacillaceae can exert anti-inflammatory effects by regulating the NLRP3 inflammasome activity. Therefore, this review outlines the anti-inflammatory mechanisms by which the Lactobacillaceae regulate the NLRP3 inflammasome activity both directly and indirectly. Additionally, we discuss the roles of specific strains, such as *Lactiplantibacillus plantarum*, *Lacticaseibacillus casei*, and *Lacticaseibacillus rhamnosus*, in intestinal inflammatory diseases, hepatic disorders, neurodegenerative diseases, and metabolic/immune-related conditions. This review aims to lay a foundation for an in-depth investigation of the precise mechanisms underlying the Lactobacillaceae-mediated regulation of the NLRP3 inflammasome and provides novel therapeutic strategies for inflammatory diseases.

Keywords: *Lactobacillaceae*; nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 (NLRP3); inhibition; activation; inflammation

乳杆菌科(*Lactobacillaceae*)细菌是一类重要的益生菌，广泛存在于人体和动物的肠道中。乳杆菌科细菌的作用主要包括调节肠道菌群、改善消化功能、提高免疫力、抗衰老、抑制病原菌、改善肠道屏障功能、预防心脑血管疾病和抑制肿瘤细胞等[1]。近年研究发现乳杆菌科细菌的益生作用与调控核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3 (nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3, NLRP3)炎症小体的活性密切相关[2]。细胞焦亡是2001年发现的一种由炎症小体激活的程序性细胞死亡方式，其特征表现为质膜孔隙形成、细胞肿胀、胞膜孔道形成及内容物泄漏[3]。细胞焦亡的核心机制涉及胱天蛋白酶(cysteine aspartic acid specific protease, Caspase)家族蛋白(Caspase-1、Caspase-4/5/11)的活化和消皮素(gasdermin, GSDM)蛋白的切割，最终导致细胞膜穿孔和白细胞介素(interleukin, IL)-1β、IL-18的释放[3]。NLRP3炎症小体作为细胞焦亡的关键调控因子，

被认为是炎症性疾病药物研发中的潜在治疗靶点[4]。本文系统总结乳杆菌科细菌调控 NLRP3 炎症小体的抗炎机制研究进展，以及乳杆菌科细菌在疾病防治中的潜在应用，以期为靶向 NLRP3 炎症小体的研究提供参考。

1 细胞焦亡

程序性细胞死亡是机体受到内源性或外源性损伤时维持机体稳态的免疫防御机制，参与清除机体中的受损细胞。细胞焦亡在细胞形态结构、发生发展机制方面与细胞坏死、细胞凋亡等细胞死亡形式具有显著区别[3,5]。GSDM 超家族在细胞焦亡激活中起到关键作用，主要包括人 GSDMA/B/C/D/E 和 DFNB59，以及小鼠 GSDMA1-3、GSDMC1-4、GSDMD、DFNA5 和 DFNB59[6]。消皮素 D (gasdermin D, GSDMD)是首个被确定的细胞焦亡直接执行者，GSDMD 的切割是 Caspase 激活并诱导细胞焦亡的必要且充分条件[3]。GSDMD 的 N 端结构域通过寡聚化在细胞膜上形成孔道，导致细胞渗透压失衡和膜破裂，同时释放促炎因子放大免疫反应[3]。

细胞焦亡的激活机制可分为经典途径与非经典途径[7]。在经典途径中，病原相关分子模式或损伤相关分子模式与对应的模式识别受体结合后，触发 NLRP1、NLRP3、NOD 样受体 C4 (NOD-like receptor C4, NLRC4)、黑色素瘤缺乏因子 2 (absent in melanoma 2, AIM2)、Pyrin 等炎症小体。炎症小体招募并激活 Caspase-1，后者切割 GSDMD 生成 GSDMD 的 N 端结构域(GSDMD N-terminal domain, N-GSDMD)，从而诱导膜孔形成和细胞焦亡[3,5,7]。同时，Caspase-1 促进 IL-1β 和 IL-18 前体的成熟与分泌(图 1)，形成级联炎症反应[7]。在非经典途径中，革兰氏阴性菌的脂多糖(lipopolysaccharide, LPS)直接结合胞内 Caspase-4/5/11 (小鼠为 Caspase-11)，激活后切割 GSDMD 并形成膜孔；此途径无须切割 IL-1β 和 IL-18 的前体，但可直接切割 GSDMD，使 N-GSDMD 转移至细胞膜[7]。此外，活化的 Caspase-4/5/11 会激活 pannexin-1，随后通过释放 K^+激活 NLRP3 炎症小体，最终引发细胞焦亡；在此途径中，NLRP3 炎症小体被激活后进一步活化 Caspase-1 并促进 pro-IL-1β 和 pro-IL-18 的切割[7]。因此，孔道形成蛋白 GSDMD 激活的 Caspase 是细胞焦亡经典和非经典途径的共同特征[7]。另外，GSDMA、GSDMB、GSDMC 和 GSDME 同样可以激活细胞焦亡。A 族链球菌分泌的链球菌致热外毒素 B 可切割 GSDMA 并引发细胞焦亡[8]。细胞毒性淋巴细胞分泌颗粒酶 A 切割 GSDMB 触发细胞焦亡[9]。在肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)存在的情况下，Caspase-8 对 GSDMC 的切割同样可以诱导细胞焦亡[10]。当经典 NLRP3 激活通路被抑制时，Caspase-3 切割 GSDME 诱导巨噬细胞发生细胞焦亡[11]。

2 NLRP3

2002 年，Martinon 等[12]首次将 Caspase 激活复合体描述为“炎症小体”。细胞焦亡的发生依赖于多种炎症小体，其中 NLRP3 炎症小体是目前研究最为深入的炎症小体之一[13]。NLRP3 炎症小体是先天免疫系统中一类高度保守的多蛋白复合物，由 NLRP3 蛋白、凋亡相关斑点样蛋白 (apoptosis-associated speck-like protein containing a CARD, ASC)适配蛋白和 Caspase-1 效应酶构成[13]。NLRP3 炎症小体的核心功能是感知病原体相关分子模式或内源性危险信号，进而触发炎症反应和细胞焦亡[13]。NLRP3 炎症小体中的 NLRP3 蛋白包含 3 个关键结构域：N 端的热蛋白结构域(pyrin domain, PYD)与 ASC 相互作用；中央的核苷酸结合寡聚化结构域具有 ATP 酶活性，可驱动自身寡聚化；C 端的富含亮氨酸重复序列结构域则负责自我抑制及危险信号的识别。ASC 的 N 端 PYD 与 NLRP3 结合，同时 C 端胱天蛋白酶激活募集结构域(caspase activation and recruitment domain, CARD)招募 pro-caspase-1，从而形成完整的炎症

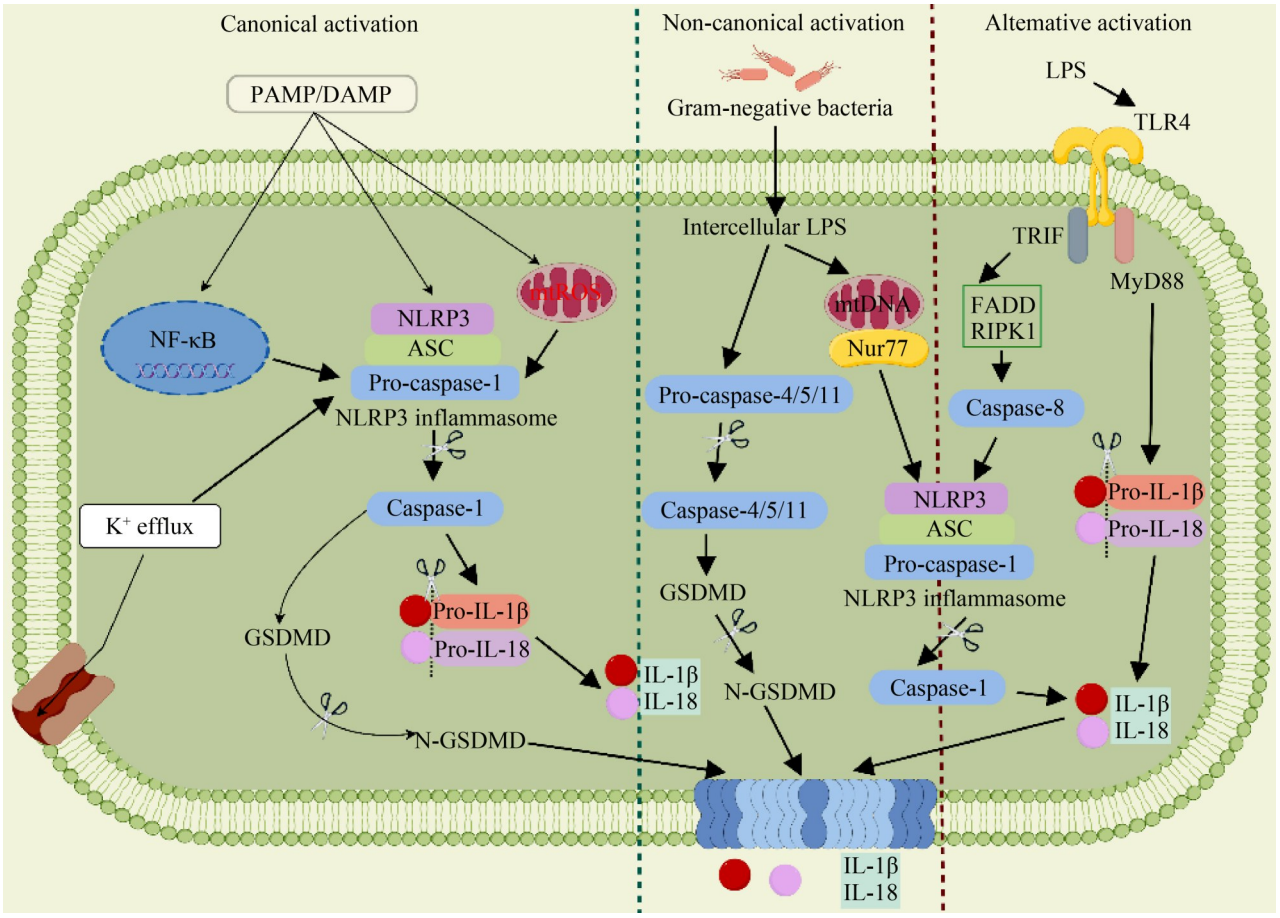

图1 细胞焦亡的激活机制。PAMP：病原相关分子模式；DAMP：损伤相关分子模式；LPS：脂多糖；NLRP3：核苷酸结合结构域富含亮氨酸重复序列和含热蛋白结构域受体3；NLRC4：NOD样受体C4；AIM2：黑色素瘤缺乏因子2；ASC：凋亡相关斑点样蛋白；ROS：活性氧；NF-κB：核因子κB；GSDMA：消皮素A；GSDMB：消皮素B；GSDMC：消皮素C；GSDMD：消皮素D；GSDME：消皮素E；N-GSDMD：GSDMD的N端结构域；TLR4：Toll样受体-4；FADD：Fas相关死亡结构域蛋白质；MyD88：髓系分化初级反应蛋白质88；TRIF：β干扰素TIR结构域衔接蛋白；RIPK1：受体相互作用蛋白激酶1；IL-1β：白细胞介素-1β；IL-18：白细胞介素-18。下同。

Figure 1 Activation mechanisms of cell pyroptosis. PAMP: Pathogen-associated molecular pattern; DAMP: Damage-associated molecular pattern; LPS: Lipopolysaccharide; NLRP3: Nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3; NLRC4: NOD-like receptor C4; AIM2: Absent in melanoma 2; ASC: Apoptosis-associated speck-like protein containing a CARD; ROS: Reactive oxygen species; NF-κB: Nuclear factor kappa B; GSDMA: Gasdermin A; GSDMB: Gasdermin B; GSDMC: Gasdermin C; GSDMD: Gasdermin D; GSDME: Gasdermin E; N-GSDMD: GSDMD N-terminal domain; TLR4: Toll-like receptor 4; FADD: Fas-associated protein with death domain; MyD88: Myeloid differentiation primary response protein 88; TRIF: TIR domain-containing adapter protein-inducing IFN-β; RIPK1: Receptor-interacting serine/threonine-protein kinase 1; IL-1β: interleukin-1β; IL-18: interleukin-18. The same below.

小体复合物[14]。

NLRP3 炎症小体的激活机制可分为经典、非经典和替代激活 3 条途径[13]。经典途径依赖“两步激活”模型：启动阶段由 Toll 样受体(Toll-like receptor, TLR)或 NOD 样受体识别病原相关分子模式/损伤相关分子模式，激活核因子 κB (nuclear factor kappa B, NF-κB)通路以上调 NLRP3 及 IL-1β 的表达；激活阶段则由离子通量(如 K^+外流)、线粒体损伤或溶酶体破裂等信号触发 NLRP3 寡聚化(图 2)，进而通过 ASC 招募 pro-caspase-1 形成活性复合物[13]。非经典途径主要由胞质内 LPS 激活[15]。人类 Caspase-4/5、小鼠 Caspase-11 直接结合 LPS，切割 GSDMD 诱导细胞焦亡，同时释放的 mtDNA 与 Nur77 蛋白协同激活 NLRP3 炎症小体，形成正反馈环路[15]。替代途径则不依赖于 ASC 和 K^+外流[13]，而是通过 Toll 样受体-4 (Toll-like receptor 4, TLR4)-β 干扰素 TIR 结构域衔接蛋白(TIR domain-containing adapter protein-inducing IFN-β, TRIF)-受体相互作用蛋白激酶 1 (receptor-interacting serine/threonine-protein kinase 1, RIPK1)-Fas 相关死亡结构域蛋白质(fas-associated protein with death domain, FADD)-Caspase-8 信号轴(TLR4-TRIF-RIPK1-FADD-CASP8)直接激活 Caspase-8，从而单步触发 NLRP3 组装。因此，NLRP3 炎症小体既是先天免疫的核心执行者，也是炎症相关疾病的重要治疗靶点，其精准调控对维持免疫稳态至关重要。

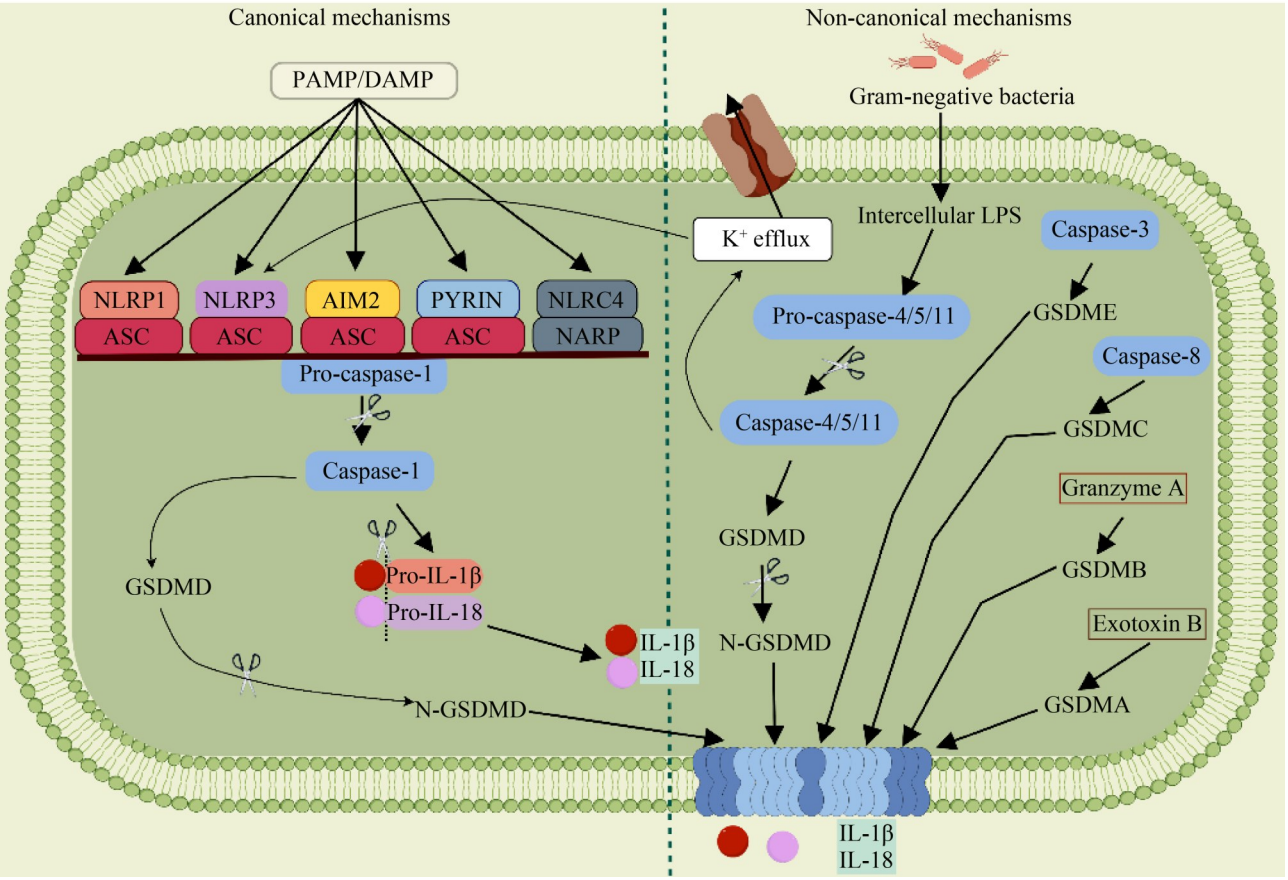

图2　NLRP3炎症小体的激活机制

Figure 2　Activation mechanisms of the NLRP3 inflammasome.

3 乳杆菌科细菌抑制 NLRP3 炎症小体的主要机制

乳杆菌科细菌是最常见的乳酸菌，参与将碳水化合物转化为乳酸的代谢过程。乳杆菌科细菌作为益生菌，其主要作用包括促进消化和代谢、控制炎症和过敏反应、抗氧化、降低胰岛素抵抗、辅助减肥，以及激活固有免疫反应和获得性免疫反应[16]，还能抑制异常细胞增殖以发挥抗肿瘤活性[17]。此外，乳杆菌科细菌可抑制 NLRP3 炎症小体表达，从而降低炎症反应[2]。

3.1 抑制 NLRP3 炎症小体的关键分子

NLRP3 炎症小体经典激活通路的关键分子为 NLRP3、ASC、Caspase-1 和 GSDMD。研究表明植物乳植杆菌(*Lactiplantibacillus plantarum*) NC8 及其代谢产物乙酸通过抑制 NLRP3 的表达显著降低胰腺和巨噬细胞中 IL-1β 的释放水平，进而缓解 1 型糖尿病小鼠的炎症反应[18]。类似机制在干酪乳酪杆菌(*Lacticaseibacillus casei*) SYF-08 中也得到验证，该菌株下调 FXR-NLRP3 信号通路有效减轻铅中毒小鼠的神经炎症和肠道损伤[19]。类干酪乳酪杆菌(*Lacticaseibacillus paracasei*) KW3110 可阻断 NLRP3 炎症小体活化抑制 Caspase-1/IL-1β 分泌，而鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*) GG (ATCC53103)却表现出促炎特性，显著增加 IL-1β 和 TNF-α 分泌[20]。然而在奶牛乳腺上皮细胞模型中，鼠李糖乳酪杆菌 GR-1 不仅抑制 NLRP3、ASC 和 Caspase-1 的表达，还能有效减轻大肠杆菌诱导的炎症损伤[21]。后续研究进一步证实，鼠李糖乳酪杆菌 GR-1 可抑制蜡样芽孢杆菌激活的 NLRP3、ASC、Caspase-1 p20、GSDMD p30 等，同时降低 IL-1β 和 IL-18 水平[22]。因此，植物乳植杆菌、干酪乳酪杆菌、类干酪乳酪杆菌和鼠李糖乳酪杆菌可直接干预 NLRP3 炎症小体的关键分子，调控促炎因子的释放，但精确的作用靶点与分子机制仍需深入解析。

3.2 调节活性氧(reactive oxygen species, ROS)和线粒体功能对 NLRP3 炎症小体的调控作用

ROS 通过氧化应激、线粒体损伤和离子通道调控等多途径激活 NLRP3 炎症小体，进而引发细胞焦亡和炎症因子释放。乳杆菌可通过干预 ROS 代谢网络间接调控 NLRP3 的激活，其作用机制主要涉及 2 条关键路径。首先，乳杆菌激活抗氧化系统减少 ROS 生成。植物乳植杆菌 DP189 在帕金森病模型中通过激活核转录因子红系 2 相关因子 2 (nuclear factor erythroid-2 related factor 2, Nrf2)/抗氧化响应元件(antioxidant response element, ARE)和过氧化物酶体增殖物激活受体 γ 辅激活因子 1α (peroxisome proliferator-activated receptor γ coactivator 1α, PGC-1α)通路显著增强抗氧化能力，从而阻断 ROS 介导的 NLRP3 活化[23]。另一株植物乳植杆菌 45 通过抑制 LPS 诱导巨噬细胞 RAW264.7 产生 ROS，显著下调 NLRP3 表达[24]。其次，乳杆菌通过修复线粒体功能清除 ROS。约翰逊氏乳杆菌(*Lactobacillus johnsonii*) L531 促进线粒体自噬清除受损线粒体，从而抑制沙门菌感染引发的 ROS 积累及 NLRP3 炎症小体激活[25]。鼠李糖乳酪杆菌 GR-1 不仅诱导 PINK1/Parkin 介导的线粒体自噬清除受损线粒体，还能同时减少 ROS 生成和 NLRP3 活化，最终降低 IL-1β 和 TNF-α 释放以缓解大肠杆菌诱导的奶牛乳房炎[26]。因此，植物乳植杆菌、约翰逊氏乳杆菌和鼠李糖乳酪杆菌可调节 ROS 和线粒体功能实现对 NLRP3 炎症小体的调控作用。

3.3 调节信号通路对 NLRP3 炎症小体的调控作用

乳杆菌科细菌通过多靶点调控 NLRP3 炎症

小体的上游信号通路。首先，在 NF-κB 通路调控方面，嗜酸乳杆菌(*Lactobacillus acidophilus*) KBL409 抑制 NF-κB 核转位显著降低慢性肾病模型中的 NLRP3 和 IL-1β 表达[27]。类似地，植物乳植杆菌 45 抑制 LPS 诱导巨噬细胞 RAW264.7 的 NF-κB 活化，进而下调 NLRP3 表达[24]。此外，鼠李糖乳酪杆菌 GG 可阻断 TLR4/NF-κB/NLRP3 级联反应，降低 TNF-α、IL-1β、IL-6 和 IL-2 分泌，从而缓解硫酸葡聚糖钠(dextran sulfate sodium, DSS)诱导的小鼠结肠炎[28]；而约翰逊氏乳杆菌 L531 也可抑制 TLR4/NF-κB/NLRP3 通路，进而有效改善沙门菌诱导的肠道损伤[29]。另一株鼠李糖乳酪杆菌 GCC-3 在草鱼模型中通过抑制 NLRP3/GSDME 通路减轻肠道炎症，同时平衡 TOR/NF-κB 信号抑制细胞焦亡[30]。其次，在 AMP 活化蛋白激酶(AMP-activated protein kinase, AMPK)信号轴调控中，鼠李糖乳酪杆菌 217-1 发酵桔梗根激活 AMPK 抑制 NF-κB/NLRP3 通路，从而减轻 DSS 诱导的小鼠结肠炎[31]。最新研究进一步揭示，罗伊特氏黏液乳杆菌(*Limosilactobacillus reuteri*) CICC 6126 及其代谢物 γ-氨基丁酸(γ-aminobutyric acid, GABA)通过 AMPK 通路直接抑制巨噬细胞 NLRP3 活化[32]。乳杆菌科细菌对 Nrf2 通路的协同调控作用尤为突出。在 D-半乳糖/脂多糖诱导的小鼠急性肝损伤模型中，植物乳植杆菌 KSFY06 通过平衡 Keap1-Nrf2/ARE 和 NLRP3/NF-κB 信号通路增强抗氧化与抗炎效应[33]。更有代表性的是植物乳植杆菌 DP189 在激活 Nrf2/ARE 和 PGC-1α 双通路的同时抑制氧化应激和 NLRP3 炎症小体，改善帕金森病神经炎症[23]。约翰逊氏乳杆菌 L531 可清除受损线粒体并调控 NF-κB-SQSTM1 线粒体自噬信号，不仅抑制 NLRC4/NLRP3 炎症小体激活，还能阻断仔猪腹泻模型中婴儿沙门菌的扩散[25]。因此，嗜酸乳杆菌、植物乳植杆菌、鼠李糖乳酪杆菌、约翰逊氏乳杆菌和罗伊特氏黏液乳杆菌等可从线粒体质量控制到炎症信号抑制的动态干预 NF-κB、TLR4、AMPK、Nrf2 等关键信号节点，从而调控 NLRP3 炎症小体，为 NLRP3 相关疾病的靶向治疗提供了理论依据。

3.4 乳杆菌科细菌代谢产物对 NLRP3 炎症小体的调控作用

乳杆菌科细菌的代谢产物如短链脂肪酸(short-chain fatty acid, SCFA)、胞外囊泡(extracellular vesicles, EVs)、GABA、多糖、脂肪酸等也参与调控细胞焦亡，发挥抗炎效应。干酪乳酪杆菌 ATCC 393 的代谢产物抑制 NLRP3-Caspase-1 通路，显著降低 IL-1β 和 IL-18 的释放，有效缓解 DSS 诱导的小鼠结肠炎[34]。鼠李糖乳酪杆菌 GG 的 EVs 阻断 TLR4-NF-κB-NLRP3 信号轴，减轻 DSS 诱导的小鼠结肠炎[28]。约翰逊氏乳杆菌的 EVs 通过关闭细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)通路，激活 M2 型巨噬细胞，抑制肠上皮细胞 NLRP3 活化，从而减轻 ETEC K88 引起的不良影响[35]。相比之下，罗伊特氏黏液乳杆菌 CICC 6126 产生的 GABA 可抑制巨噬细胞 NLRP3 炎症小体激活，显著减轻心肌缺血再灌注损伤[32]。卷曲乳杆菌(*Lactobacillus crispatus*) 7-4 分泌的胞外多糖(EPS 7-4)通过阻断 ASC 寡聚化直接抑制炎症小体组装，有效限制鼠伤寒沙门菌(*Salmonella enterica* serovar Typhimurium)诱导的肠道细胞焦亡[36]。因此，干酪乳酪杆菌、鼠李糖乳酪杆菌、约翰逊氏乳杆菌、罗伊特氏黏液乳杆菌和卷曲乳杆菌等通过分泌代谢产物实现对 NLRP3 炎症小体的调控作用。

诱导癌细胞焦亡是一种潜在的肿瘤治疗策略。罗伊特氏黏液乳杆菌的代谢产物 reuterin 在肝癌模型中通过三重协同机制发挥抗肿瘤效应。

首先，reuterin 破坏线粒体自噬导致 mtDNA 泄漏，随后激活 STING 信号通路促进 Caspase-1/GSDMD 表达，同时抑制受体相互作用蛋白激酶 3 (receptor-interacting serine/threonine-protein kinase 3, RIPK3)切割，阻断坏死性凋亡通路，将细胞死亡模式特异性导向细胞焦亡途径；该过程的抗肿瘤效应具有分子依赖性，STING 或 Caspase-8 基因敲除会完全逆转 reuterin 的抗肿瘤效果[37]。植物乳植杆菌 ZS2058 产生的共轭亚麻酸 1 (conjugated linolenic acid 1, CLNA1) 和 CLNA2 以不同途径诱导结肠癌细胞焦亡。CLNA1 激活 Caspase-1/GSDMD 通路发挥作用，而 CLNA2 则激活非经典 Caspase-4/5 途径触发焦亡，两者均不依赖凋亡机制[38]。

3.5 乳杆菌科细菌影响肠道菌群间接调控 NLRP3 炎症小体

乳杆菌科细菌发挥益生作用的主要方式是重塑肠道稳态，而乳杆菌科细菌抗炎作用也与菌群-宿主互作过程紧密相关。瑞士乳杆菌(*Lactobacillus helveticus*) LZ-R-5 抑制拟杆菌属(*Bacteroides*)和丹毒丝菌属(*Erysipelothrix*)的繁殖，恢复肠道菌群多样性，显著降低 DSS 诱导的小鼠结肠炎中 NLRP3 相关炎症因子[39]。类似地，植物乳植杆菌 MA2 可增加 SCFAs 的产量调节肠道菌群结构，从而抑制 TLR4/NF-κB/NLRP3 通路[40]。嗜酸乳杆菌则影响核苷酸结合寡聚结构域 1 (nucleotide-binding oligomerization domain 1, NOD1)/NLRP3 信号通路，抑制 IL-1β 和 IL-18 释放，显著增强断奶仔猪的肠道物理屏障[41]。肠道紧密连接蛋白是肠道屏障的重要成分，乳杆菌通过增强闭锁小带-1 (zonula occludens-1, ZO-1)、Occludin 和 Claudin-1 的表达修复肠道屏障[22,29,34]。沙门菌(*Salmonella*)及其分泌效应蛋白可激活 NLRP3 炎症小体[42-43]。研究表明约翰逊氏乳杆菌 L531 可阻断 TLR4/NF-κB/NLRP3 炎症小体信号通路，缓解鼠伤寒沙门菌诱导的紧密连接蛋白表达下调造成的肠道损伤[29]。干酪乳酪杆菌 ATCC 393 及其代谢产物增加肠道紧密连接蛋白的表达，经 NLRP3-(Caspase-1)/IL-1β 信号通路缓解 DSS 诱导的小鼠结肠炎[34]；而鼠李糖乳酪杆菌 GR-1 则通过保护细胞间紧密连接 ZO-1 和 Occludin 完整性，直接抑制蜡样芽孢杆菌诱导的牛乳腺上皮细胞 NLRP3 活化[22]。

4 乳杆菌科细菌在不同疾病模型中的应用

4.1 肠道炎症性疾病

NLRP3 泛素化修饰异常会导致其过度活化，进而促进 IL-1β 等促炎因子释放，加重肠道炎症[44]。乳杆菌科细菌通过直接抑制 NLRP3 炎症小体激活在溃疡性结肠炎和感染性肠炎中展现出抗炎特性。嗜酸乳杆菌 ATCC 4356 可通过 SCFAs/线粒体自噬/NLRP3 信号轴减少肠道溃疡性结肠炎上皮细胞焦亡[45]。约翰逊氏乳杆菌 L531 靶向抑制 TLR4/NF-κB/NLRP3 信号级联反应，有效缓解沙门菌感染引起的肠上皮屏障损伤[29]。此外，乳杆菌可协同抗氧化策略间接抑制 NLRP3 炎症小体活化。短发酵剂乳杆菌(*Levilactobacillus brevis*) 23017 联合鞣花酸激活 Nrf2/血红素加氧酶-1 (heme oxygenase-1, HO-1)通路，抑制 NLRP3 炎症小体，从而减轻肠道损伤[46]。嗜酸乳杆菌 HSCC LA042 联合中药复方通过三重协同机制改善 DSS 诱导的小鼠结肠炎：抑制 NLRP3 炎症小体活化，阻断 Caspase-1 和 GSDMD 剪切；恢复肠道屏障完整性；重塑菌群结构，减少致病菌(如埃希氏菌属-志贺氏菌属)并增加有益菌(如阿克曼氏菌属)的丰度[47]。因此，嗜酸乳杆菌、约翰逊氏乳杆菌和短发酵剂乳杆菌可通过多靶点调控 NLRP3 炎症小体及其上游信号来干预肠道炎症。

4.2 肝脏疾病

NLRP3 炎症小体的异常激活在各种类型的肝损伤中起着重要作用。NLRP3 通过线粒体损伤诱导 ROS 生成，促进 IL-1β 和 IL-18 等促炎因子释放，加剧炎症反应和肝细胞焦亡[48]。嗜酸乳杆菌 KLDS 1.0738 发酵的枣汁和植物乳植杆菌 KSFY06 可直接阻断 NLRP3 炎症级联反应，从而缓解肝损伤[33,49]。嗜酸乳杆菌 KLDS 1.0738 发酵的枣汁可直接阻断抑制 NLRP3/Caspase-1/IL-1β 信号轴，显著改善 CCl_4 诱导的慢性肝损伤[49]。在 D-半乳糖/脂多糖诱导的小鼠急性肝损伤中，植物乳植杆菌 KSFY06 可下调 Keap1、NLRP3、ASC、Caspase-1、NF-κB、IL-18 以及 MAPK14 p38 等关键分子表达，从多条通路减少炎症[33]。鼠李糖乳酪杆菌 GG 通过胆汁酸-FXR 轴抑制 NLRP3 炎症小体，缓解雷公藤甲素诱导的肝毒性[50]。“肠-肝对话”在慢性肝病的治疗中具有重要意义。南极磷虾肽可调节肠道菌群(乳杆菌)-胆汁酸-NLRP3 轴，不仅减少肝星状细胞活化，还能抑制 NLRP3 信号通路，减轻肝纤维化[51]，为慢性肝病的治疗提供新的思路和方法。因此，嗜酸乳杆菌、植物乳植杆菌和鼠李糖乳酪杆菌可靶向 NLRP3 炎症小体及相关通路，在急/慢性肝损伤模型中展现出显著保护作用。

4.3 神经退行性疾病

NLRP3 炎症小体失调介导的神经炎症对一些神经退行性疾病的发生发展具有关键作用，如阿尔茨海默病、帕金森病、亨廷顿病、多发性硬化症、肌萎缩侧索硬化症和朊病毒病等[52]。植物乳植杆菌 DP189 可抑制 NLRP3 炎症小体和氧化应激，减少帕金森病模型中 α-突触核蛋白聚集，从而改善 1-甲基-4-苯基-1,2,3,6-四氢吡啶诱导的神经退行性病变[23]。植物乳植杆菌 MA2 可调节糖代谢和 NLRP3 通路，减少阿尔茨海默病脑内 β-淀粉样蛋白沉积[40]。热灭活鼠宿主关联乳杆菌(*Ligilactobacillus murinus*) CICC23140 可抑制小胶质细胞 NLRP3 激活，保护多巴胺能神经元[53]。这 3 个菌株均直接以 NLRP3 炎症小体为核心靶点。干酪乳酪杆菌 SYF-08 调节胆汁酸代谢和 FXR-NLRP3 信号，减少铅中毒诱导的神经炎症[19]，为环境毒素相关脑损伤提供了干预思路。戊糖乳植杆菌(*Lactiplantibacillus pentosus*) S-PT84 表现出非 NLRP3 依赖的独特机制，通过上调凋亡抑制蛋白 BIRC3，减少 LPS 诱导的神经元焦亡，该过程与抑制 NLRC4 炎症小体的激活有关，同时不影响 NLRP1 和 NLRP4[54]。因此，植物乳植杆菌、鼠宿主关联乳杆菌、干酪乳酪杆菌和戊糖乳植杆菌可靶向神经炎症和代谢紊乱相关通路，在帕金森病、阿尔茨海默病等神经退行性疾病中展现出潜在治疗价值。

4.4 代谢与免疫疾病

NLRP3 炎症小体过度和不当激活会促进 IL-1β、IL-18 等细胞因子的成熟与释放，这些细胞因子以自分泌或旁分泌方式作用于局部微环境。这些炎症因子的异常积累可诱导胰岛素抵抗、脂质代谢失衡等，参与多种炎症相关疾病的病理进程，如糖尿病、肥胖、痛风、动脉粥样硬化、高血压以及过敏性疾病[55]。乳杆菌科细菌可以抑制细胞焦亡与炎症因子释放，如植物乳植杆菌 ATCC 8014 抑制 NLRP3/Caspase-1/GSDMD 通路，减少高级糖基化终末产物诱导的糖尿病足溃疡内皮细胞焦亡，同时降低 IL-1β 和 IL-18 的分泌，从而有效阻断炎症级联反应并加速伤口愈合[56]。类似地，加氏乳杆菌(*Lactobacillus gasseri*) BCRC14619 通过稳定 GAPDH 蛋白抑制角质细胞凋亡和 NLRP3 炎症小体，从而有效缓解特应性皮炎[57]。同时，乳杆菌可以调控氧化应激与代谢平衡发挥作用，如植物乳植杆菌 45 激活含 SH2 结构域蛋白酪氨酸磷酸酶 2 通路抑制氧化应激，进而影响骨代谢中的 NLRP3 表

达[24]，而类干酪乳酪杆菌 KW3110 则抑制 NLRP3 炎症小体，延缓高脂饮食诱导的代谢异常[20]。罗伊特氏黏液乳杆菌 CICC 6126 能够抑制巨噬细胞 NLRP3 活化，减轻心肌缺血再灌注损伤，展现出心血管保护潜力[32]。嗜酸乳杆菌 NX2-6 虽然能改善高脂饮食诱导的糖代谢紊乱，但其作用机制独立于胰腺的细胞焦亡[58]。因此，植物乳植杆菌、加氏乳杆菌、类干酪乳酪杆菌、罗伊特氏黏液乳杆菌和嗜酸乳杆菌可干预 NLRP3 炎症小体信号通路，在糖尿病、心血管疾病、骨代谢异常等炎症相关疾病中发挥治疗作用。

5 乳杆菌科细菌激活 NLRP3 炎症小体

乳杆菌科细菌对 NLRP3 炎症小体具有抗炎保护作用，但也有研究显示乳杆菌科细菌可激活 NLRP3 炎症小体，进而促进炎症反应。在斑马鱼中，TLR4ba 可识别鼠李糖乳酪杆菌 GG 的 SpaC 菌毛，激活 Caspase-3/GSDMEa 通路，诱导肠道上皮细胞焦亡，最终导致菌群失调[59]。然而，干酪乳酪杆菌的细胞壁提取物(*Lactobacillus casei* cell wall extract, LCWE)是特异性结合 TLR2 而非 TLR4 来启动炎症信号[60]。嗜酸乳杆菌 NCFM 的脂磷壁酸和 S 层蛋白可激活巨噬细胞 TLR2 和 NOD2 受体，进而调控 NLRP3/NLRC4 炎症小体活性[61]。TLR2 的激活可触发 MyD88 依赖的 NF-κB 通路，使 NLRP3、pro-IL-1β 等炎症因子的转录水平显著上调[61]。在猪肠道相关淋巴组织中，德氏乳杆菌(*Lactobacillus delbrueckii*)和加氏乳杆菌通过 TLR2/NLR 配体作用诱导 NLRP3 表达增强，进而调控局部免疫应答[62]。在启动信号的基础上，LCWE 进一步通过溶酶体途径触发 NLRP3 的“激活信号”。LCWE 可被宿主细胞吞噬并转运至溶酶体，其成分(如肽聚糖)会引起溶酶体膜通透性增加，释放组织蛋白酶 B 至胞质[63]。组织蛋白酶 B 作为一种溶酶体蛋白酶，直接作用于 NLRP3 蛋白后可促进其寡聚化，并与 ASC、Caspase-1 形成功能性炎症小体复合体[63]。此外，溶酶体损伤还可能通过钾离子外流或 ROS 产生等机制间接激活 NLRP3。NLRP3 的激活最终会导致 Caspase-1 的自我剪切活化，进而将 pro-IL-1β 和 pro-IL-18 切割为成熟形式。在 LCWE 诱导的急性肺损伤模型中，NLRP3 基因敲除小鼠的肺部 IL-1β 水平下降[60]。在川崎病模型中，利用 LCWE 诱导的冠状动脉炎来研究 IL-1β 的成熟，发现其依赖于 NLRP3 炎症小体的激活[64]。miR-223 缺陷小鼠因失去对 NLRP3 的负调控能力，在 LCWE 刺激后表现出更严重的血管炎，且 IL-1β 水平升高[65]。

6 总结与展望

筛选具有特定功能的益生菌是当前微生物学和食品科学领域的研究热点。作者所在团队近年来主要开展功能益生菌的筛选和鉴定研究，重点探究了这些乳杆菌科细菌的生物学特性及其功能[66-70]。细胞焦亡在病原体感染中发挥双重作用[4,42-43,71]，而 NLRP3 炎症小体是炎症性疾病药物研发的潜在靶点[4]。本文系统综述了乳杆菌科细菌对 NLRP3 炎症小体的调控作用及其机制研究进展(表 1)。乳杆菌科细菌作为一类重要的益生菌，可通过抑制 NLRP3 炎症小体的关键分子、调节 ROS 和线粒体功能、调控信号通路(如 NF-κB、AMPK、Nrf2 等)以及通过代谢产物(如 GABA、多糖)与肠道菌群间接调控 NLRP3 等途径发挥抗炎作用。目前研究已在肠道炎症、肝损伤、神经退行性疾病等多种炎症性疾病模型中验证了乳杆菌科细菌的潜在保护作用，为开发基于益生菌的精准抗炎疗法提供了理论依据。

表1 乳杆菌科细菌对NLRP3炎症小体的调控作用的研究进展概况

Table 1 Outline of study on the regulatory effects of the *Lactobacillaceae* on NLRP3 inflammasome during recent years

Strains	Model	Events	References
Lactobacillus acidophilus			
ATCC 4356	DSS-induced UC in rats	Increase SCFAs; inhibit NLRP3; promote autophagy	[45]
HSCC LA042	DSS-induced UC in mice	Inhibit NLRP3 activation; block Caspase-1 and GSDMD cleavage; restore intestinal barrier integrity; reconstruct the microbiota structure	[47]
KLDS 1.0738	CCl_4-induced chronic liver injury in mice	Block the NLRP3/Caspase-1/IL-1β signaling axis	[49]
KBL409	Chronic kidney disease in mice	Inhibit NF-κB nuclear translocation; reduce NLRP3 and IL-1β expression	[27]
NX2-6	High-fat diet in mice	Improve hepatic energy metabolism *via* the FGF21/AMPKα/PGC-1α/NRF1 pathway	[58]
–	Weaned piglets	Increase occluding; decrease NLRP3, caspase-1, IL-1β, and IL-18	[41]
Levilactobacillus brevis			
23017	Eimeria infection in chickens	Activate Nrf2/HO-1; inhibit ChTLR15/NLRP3/IL-1β	[46]
SYF-08	Pb-induced injury in young mice	Inhibit FXR-NLRP3	[19]
ATCC 393	DSS-induced UC in mice	Increase occludin, ZO-1, and claudin-1; reduce NLRP3, Caspase-1, IL-1, and IL-18	[34]
Lactobacillus crispatus 7-4	*Salmonella enterica* serovar Typhimurium infection in mice	Block ASC oligomerization; directly inhibit the assembly of the inflammasome; inhibit pyroptosis	[36]
Lactobacillus gasseri BCRC14619	Ovalbumin and *Dermatophagoides pteronyssinus*-induced atopic dermatitis in mice and THP1 cells	Block Caspase-3 cascade; inhibit NLRP3	[57]
Lactobacillus helveticus LZ-R-5	DSS-induced UC in mice	Increase TGF-β1; downregulate NLRP3	[39]
Lactobacillus johnsonii			
L531	*Salmonella enterica* serovar Infantis model of piglet diarrhea	Regulate NLRC4/NLRP3/NF-κB signaling pathways; inhibit mitochondrial damage	[25]
L531	*Salmonella enterica* serovar Typhimurium infection in IPEC-J2 cells	Inhibit TLR4, MyD88, p-IκBα, p-p65, IL-6, IL-1β, IL-18, TNF-α, and NLRP3 inflammasome activation; increase ZO-1, Occludin, and Claudin-1	[29]
–	ETEC K88 infection in mice and bone marrow-derived macrophages from BALB/c mice	Reduce intestinal inflammation; activate M2 macrophages; inhibit NLRP3 activation	[35]
Ligilactobacillus murinus CICC23140	6-OHDA-induced dopamin neuronal damage in rats	Inhibit NLRP3 activation; release pro-inflammatory cytokine	[53]
Lactobacillus paracasei KW3110	Inflammatory disorder in bone marrow-derived macrophages from BALB/c mice	Inhibit NLRP3, AIM2, NLRC4, and Caspase-1 activation and IL-1β secretion	[20]

(待续)

(续表1)

Strains	Model	Events	References
Lactiplantibacillus plantarum			
NC8	Type 1 diabetes in mice	Inhibit NLRP3	[18]
DP189	MPTP-induced Parkinson's disease in mice	Activate Nrf2/ARE and PGC-1α signaling; inhibit NLRP3	[23]
45	LPS stimulation in MC3T3-E1 and RAW264.7 cells	Inhibit NOX4, P22, P47, IL-1β, NLRP3, IRF3, RANK, β-catenin, and INF-β	[24]
KSFY06	D-galactose/LPS-induced acute liver injury in mice	Downregulate Keap1, NLRP3, ASC, Caspase-1, NF-κB, IL-18, and MAPK1/p38; upregulate Nrf2, HO-1, NQO1, IκB-α, and Trx	[33]
ZS2058	CLNA-stimulated Caco-2 cells	CLNA1 activates Caspase-1 to induce cell pyroptosis; CLNA2 activates Caspase-4/5 to induce cell pyroptosis	[38]
MA2	D-galactose/$AlCl_3$-induced Alzheimer's disease in rats	Alleviate intestinal mucosal damage; regulate TLR4/MYD88/NLRP3 signaling pathway to block the activation microglia and neuroinflammation	[40]
ATCC 8014	Advanced glycation end products-stimulated human umbilical vein endothelial cells	Downregulate NLRP3 and Caspase-1 p20	[56]
Lactiplantibacillus pentosus S-PT84	LPS-stimulated SH-SY5Y cells	Inhibit IL-1β, IL-18, cleaved Caspase-1, and GSDMD-N	[54]
Limosilactobacillus reuteri CICC 6126	Ischemia/reperfusion-induced acute ischemic cardiac injury/LPS-stimulated bone marrow-derived macrophages	Inhibit lysosomal leakage and NLRP3 activation; inhibit macrophage polarization to the pro-inflammatory M1 phenotype	[32]
Lacticaseibacillus rhamnosus			
GR-1	*E. coli* infection in primary bovine mammary epithelial cells	Reduce NLRP3, Caspase-1 and ASC, IL-1β/6/8/18, and TNF-α; upregulate IL-10	[21]
GR-1	*Bacillus cereus* infection in MAC-T cells	Increase ZO-1 and occluding; decrease NLRP3, ASC, Caspase-1 p20, GSDMD p30, IL-1β, and IL-18	[22]
GR-1	*E. coli* infection in MAC-T cells	Inhibit ROS to relieve NLRP3 activation and apoptosis; enhance PINK1/Parkin-mediated mitochondrial activation	[26]
GG	DSS-induced UC in mice	Inhibit TLR4-NF-κB-NLRP3 signaling axis to relieve intestinal inflammation	[28]
GG	Triptolide-induced liver injury in mice	Increase bile salt hydrolase activity; reduce conjugated bile acids; upregulate hepatic FXR expression; inhibit NLRP activation	[50]
217-1	DSS-induced UC in mice	Activate AMPK; reduce the release of pro-inflammatory cytokines; inhibit NF-κB signaling pathway and NLRP3 expression	[31]
GCC-3	DSS-induced intestinal inflammation in juvenile grass carp	Decrease the expression of TLR4, NOD receptors, NF-κB, NLRP3, and GSDME; increase the expression of TOR; inhibit cell pyroptosis	[30]

−: No found.

尽管当前研究揭示了乳杆菌科细菌通过多种途径抑制 NLRP3 炎症小体的激活，但仍需进一步详细解析乳杆菌科细菌调控 NLRP3 炎症小体的具体作用靶点和信号传导通路。更重要的是应关注乳杆菌科细菌菌株特性对其抗炎效果的影响。不同种类的乳杆菌科细菌在代谢特性、基因表达和功能活性上存在差异，这些差异可能导致乳杆菌科细菌在调控 NLRP3 炎症小体时表现出不同的效果。功能型益生菌通常具有特异性物质发挥具体作用[70-71]，因此需要明确乳杆菌科细菌中激活 NLRP3 炎症小体的具体物质。未来研究可结合多组学技术、基因编辑工具及类器官模型，揭示乳杆菌科细菌调控 NLRP3 炎症小体的时空特异性机制。多项研究报道了乳杆菌科细菌的细胞壁组分可激活 NLRP3 炎症小体，在临床转化前需从体内外进一步验证乳杆菌科细菌的安全性和有效性。随着人们对肠道微生物组与宿主健康关系认识的深入，未来研究还应关注乳杆菌科细菌与宿主互作的动态网络(如肠道菌群-免疫-代谢轴)。此外，乳杆菌科细菌与其他微生物或药物的联合应用也是一个值得探索的方向，如 reuterin 与索拉非尼联用可能增强肝癌疗效。同时，优化乳杆菌科细菌菌株、制定个体化治疗方案以及探索乳杆菌科细菌与其他治疗手段的联合应用，有望进一步提高乳杆菌科细菌在炎症性疾病治疗中的疗效和安全性。

作者贡献声明

廖成水：提出概念，数据收集与监管，数据分析，执行调研，项目管理，提供资源，监督管理，完成呈现，撰写文章；贾艳艳：方法论；余祖华：编辑修改；丁轲：获取基金，审阅。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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