中国科学: 生命科学 2023 年 第 53 卷 第 4 期: 464 ~ 479
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS

评 述

乳酸菌维持动物肠道健康的研究进展

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收稿日期: 2022-06-07; 接受日期: 2022-07-18; 网络版发表日期: 2023-03-07
国家自然科学基金(批准号: 31772642, 81902297)和湖南省自然科学基金(批准号: 2019JJ50220)资助

摘要 肠道微生物群被广泛认为是维持体内平衡最重要的组成部分之一, 与人类及其他哺乳动物的健康和疾病密切相关, 许多疾病的发生都伴随着肠道微生物的紊乱. 一些益生菌常常被用来改善微生物群、调控机体免疫、缓解机体疾病并维持机体健康, 其中乳酸菌是使用最广泛的益生菌. 乳酸菌是革兰氏阳性细菌, 虽然它只是人类肠道微生物群中的一个小成员, 但它调节宿主免疫系统、增强肠道代谢能力和维持肠道微生物群平衡的潜力已得到广泛的证实. 基于此, 本文综述了乳酸菌在维持肠道健康中的作用, 讨论了其通过免疫调节、病原体抑制、屏障功能增强、神经系统信号调节和促进健康物质产生等机制对宿主健康的促进作用, 并探讨了其在炎症性肠病、肠癌、腹泻、肠易激综合征等肠道疾病以及肥胖、Ⅱ型糖尿病、多发性硬化症、抑郁症等其他疾病的预防及治疗中的作用.

关键词 乳酸菌, 益生菌, 肠道微生物, 肠道健康, 免疫调节, 炎症性肠病, 癌症

在人类和其他哺乳动物的胃肠道中寄居着1000多种细菌, 这些细菌在生长过程中不断与宿主相互作用, 形成多种多样的微生物群. 肠道微生物群在肠道稳态、机体发育和抵御病原体等方面发挥着重要作用, 会影响宿主的营养、免疫和生理功能, 从而对宿主的整体健康产生显著的影响[1]. 在机体中补充某些细菌能够促进机体健康, 它们能够以直接或者间接的方式改善微生物群, 这些细菌经常被称为益生菌. 益生菌被视为非致病性活微生物, 当补充足够的量时, 会给宿主带来健康益处[2]. 益生菌现已被广泛应用于临床实践中, 研究最多、使用最广泛的益生菌是乳酸菌(lactic acid bacteria, LAB), 主要包括乳酸杆菌(*Lactobacillus*)和乳球菌(*Lactococcus*)等[3,4].

LAB是革兰氏阳性、非产孢、过氧化氢酶阴性、耐酸、兼性厌氧微生物, 存在于人(*Homo sapiens*)、猪(*Sus taurus*)、仓鼠(*Mesocricetus auratus*)、小鼠(*Mus musculus*)、狗(*Canis lupus familiaris*)等哺乳动物的胃肠道中以及蜜蜂(*Apis mellifera*)等昆虫的肠道中[1]. 在人体从十二指肠到回肠末端的区域、啮齿类动物和鸡(*Gallus gallus*)的上消化道、前胃中, LBA经常作为优势细菌存在, 相比之下, 人体结肠中LBA的比例较低[5].

一些乳酸菌菌株已被证明具有促进健康的功能,

引用格式: 韩雪冰, 元香南, 方俊, 等. 乳酸菌维持动物肠道健康的研究进展. 中国科学: 生命科学, 2023, 53: 464–479
Han X B, Yuan X N, Fang J, et al. Role of lactic acid bacteria in maintaining animal intestinal health (in Chinese). Sci Sin Vitae, 2023, 53: 464–479, doi: 10.1360/SSV-2022-0032

并被广泛应用于预防人类和动物疾病的研究中，这些乳酸菌能够改变肠道微生物群中的微生物数量、控制肠道微生物群生态系统，并且具有免疫调节、改善肠道完整性、病原体抗性、预防乳糖不耐受、抗癌作用、逆转抑郁和焦虑症状、抗肥胖和抗糖尿病活性以及降低血清胆固醇水平等功能.

1　肠道微生物稳态

人体内含有数万亿个微生物个体，大部分在胃肠道(即小肠和结肠)内，包括细菌、病毒、真菌和原生动物，它们共同构成肠道微生态系统. 当婴儿从产道、皮肤、粪便和母乳中获得微生物时，肠道微生物就开始了定植，并受到分娩方式、喂养方式、生活方式、药物和宿主遗传的影响[6]. 肠道微生物群由三个主要门组成: 拟杆菌门(包括卟啉单胞菌属(*Porphyromonas*)、普氏菌属(*Prevotella*)、拟杆菌属(*Bacteroides*)等)、厚壁菌门(包括乳球菌属(*Lactococcus*)、梭菌属(*Clostridium*)和真细菌属(*Eubacteria*)等)和放线菌门(包括双歧杆菌属(*Bifidobacteria*)等)[7]，革兰氏阳性厚壁菌门和革兰氏阴性拟杆菌门已被证明占肠道菌群的90%以上. 在肠道的不同部位, 细菌的数量和组成明显不同, 近端小肠中约有10~10^3 cfu/mL的细菌, 远端小肠中约有10^4~10^7 cfu/mL的细菌，结肠中约有10^4~10^{11} cfu/mL的细菌[8]. 与下消化道相比, 胃和小肠上段的微生物多样性较低. 在健康状况下, 这些微生物与宿主协同存在，为宿主提供营养、免疫发育和宿主防御等方面的益处. 例如，肠道微生物群中的共生细菌能够通过取代有害细菌、与病原体竞争营养物质和产生抗微生物因子的方式来保护宿主. 同时, 这些细菌还能够为宿主提供结构功能，如增强免疫系统、诱导免疫球蛋白A(IgA)、增强黏膜屏障等. 细菌还能通过发酵复合碳水化合物产生短链脂肪酸(short-chain fatty acids, SCFAs)[9]，代谢药物、农药和致癌物等外源物质, 同时合成人体营养所必需的K、B族维生素、叶酸和生物素等物质改善宿主的代谢功能，并参与镁、钙和铁离子的吸收[10]. 此外，肠道微生物群有助于通过产生抗菌化合物来防止病原菌定居，从而保持肠道黏膜屏障的结构完整性[11]. 肠道固有免疫系统的正常运行也依赖于常驻微生物群，肠道微生物群能够调控调节性T细胞(regulatory cells, Tregs)的再生和分布, 从而调节免疫系统中的其他细胞[12].

肠道微生物的活性和组成与宿主健康和疾病都密切相关，会影响包括心血管、神经、免疫和代谢系统在内的许多器官系统，一个平衡良好的肠道微生物种群(内环境稳定)对于宿主和微生物群以互利关系共存至关重要. 当疾病发生的时候, 肠道微生物群组成往往会发生改变，如心血管疾病、癌症、恶性肿瘤、Ⅱ型糖尿病、肥胖、结肠炎、哮喘、精神疾病、炎症性肠病(inflammatory bowel disease, IBD)和许多免疫疾病[13~15]. Toll样受体(Toll-like receptors, TLRs)能够维持肠道稳态, 控制免疫反应, 并调控微生物群, 在肠道免疫中起着至关重要的作用，肠道微生物群可以通过TLRs控制炎症反应的进程. 益生菌能够调节肠道微生物群, 从而缓解疾病, 促进机体健康. 研究显示, 饲喂益生菌饲料后，高脂肪饮食喂养的小鼠显示出肠道微生物群组成的变化，小鼠体内革兰氏阳性细菌和放线菌(*Actinomycetes*)数量减少[16]. 而在高血脂小鼠模型中, 饲喂乳酸杆菌也导致微生物群组成发生了显著变化, 拟杆菌(*Bacteroides*)和疣状菌(*Verrucomicrobia*)丰度增加、厚壁菌(*Firmicutes*)丰度降低[17]. 由此可见，益生菌，特别是乳酸菌，在维持人类和动物的肠道微生物生态系统中发挥着重要作用.

2　肠道中的乳酸菌

乳酸菌是一类能利用可发酵碳水化合物产生大量乳酸的细菌的统称. 这类细菌在自然界分布极为广泛, 具有丰富的物种多样性，广泛存在于人体的肠道中且具有重要的生理功能，主要包括乳杆菌属(*Lactobacillus*)、链球菌属(*Streptococcus*)、明串珠菌属(*Leuconostoc*)和片球菌属(*Pediococcusacidilactici*)，这些属在形态、酸碱度和耐盐性、最适温度、生境和致病潜力方面有所不同. 目前研究和使用最广泛的益生菌是乳杆菌和双歧杆菌[18,19]. 这两个属的物种(包括短双歧杆菌(*Bifidobacterium breve*)、长双歧杆菌(*Bifidobacterium longum*)、发酵乳杆菌(*Lactobacillus fermentum*)、植物乳杆菌(*Lactobacillus plantarum*)、干酪乳杆菌(*Lactobacillus casei*)或鼠李糖乳杆菌(*Lactobacillus rhamnosus*))天然存在于人类胃肠道中，在维护人类健康方面发挥着关键作用[20].

到目前为止，研究人员已经从人类的胃肠道、皮

肤及阴道中分离出乳酸菌[21,22]. 据估计, 乳酸菌占人类十二指肠细菌总数的6%, 约占结肠细菌总数的0.3%[23]. 在猪的体内也检测到了相似水平的乳酸菌, 其在近端[24]和远端[25]肠道中分别占总菌数的5%和0.1%. 与人体和猪中不同, 乳酸菌在恒河猴(*Macaca mulatta*)小肠和大肠中含量均较高(分别占所有细菌的30%和10%)[26]. 在啮齿类动物中, 乳酸菌在回肠中的比例为30%~60%, 在结肠中约为25%[27]. 在已知的超过200种乳酸菌中, 只有少数几种一直和人类胃肠道有联系, 其中最丰富的包括*Lactobacillus casei*, *L. delbruckeii*, *L. murinus*, *L. plantarum*, *L. rhamnosus*和*L. ruminus*. 进一步的研究表明, 肠道中检测到的乳酸菌中很大一部分可能是外来的, 不形成稳定的种群, 而其他一些很少从肠道以外的环境中分离出来, 被认为是肠内微生物[28]. Walter[28]报道了17种在肠道中常见的乳酸菌, 分别是*L. acidophilus*, *L. brevis*, *L. casei*, *L. crispatus*, *L. curvatus*, *L. delbrueckii*, *L. fermentum*, *L. gasseri*, *L. johnsonii*, *L. paracasei*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. ruminis*, *L. sakei*, *L. salivarius*和*L. vaginalis*, 其中大部分被鉴定为外来微生物. 而*L. ruminis*和*L. salivarius*被发现在多个受试者中存在持续超过18个月[29]. 还有一些研究人员探究了乳酸菌在肠道内的定植能力, 结果表明, 与*L. acidophilus*相比, *L. mucosae*和*L. reuteri*在肠道中的丰度更高, 且更容易从粪便样本中获取到[30]. 还有一些研究显示了肠道中乳酸菌比例的变化与疾病的相关性, 发现肠道乳酸菌的减少经常伴随着一些疾病的发生, 在Ⅰ型糖尿病[31]、IBS[32]、多发性硬化[33]和人类免疫缺陷病毒感染[34]等疾病患者的肠道中, 乳酸菌常常被耗尽.

3 乳酸菌对于宿主的有益作用

目前普遍认为, 乳酸菌对于宿主健康的有益作用是通过多种机制产生的, 包括诱导免疫调节、防止生理应激、抑制病原体、微生物调节和改善肠道上皮的屏障功能等(图1). 表1给出了一些乳酸菌菌株对各种疾病模型中细胞因子及微生物的调控.

3.1 免疫调节

约70%的免疫系统以肠道相关淋巴组织(gut-associated lymphatic tissue, GALT)的形式定位于胃肠道, 乳酸菌与免疫系统之间存在一种相互作用的关系, 免疫系统选择性地接受乳酸菌的定植, 乳酸菌又可以反过来调节免疫功能[35]. 许多研究表明, 乳酸菌对免疫相关基因表达、炎症途径活性和免疫标记物水平有影响, 通过多种机制调节肠上皮细胞NF-κB、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、磷脂酰肌醇3激酶(phosphatidylinositol 3 ki-

表 1 调控疾病模型中细胞因子及微生物的乳酸菌

Table 1 Lactic acid bacteria regulating cytokines and microorganisms in disease models

菌种	疾病模型	疾病	调控
B. breve	人类结肠	结肠炎	上调IL-8, IL-10和IL-12
L. acidophilus, *L. rhamnosus*, *B. bifidum*	C57BL/6小鼠	Ⅱ型糖尿病	上调厚壁菌和放线菌, 下调拟杆菌
L. acidophilus	SPE雄性SD小鼠	非酒精性脂肪肝	上调大肠杆菌(*Escherichia coli*)、肠球菌(*Enterococcus*), 下调双歧杆菌和拟杆菌
L. acidophilus	BALB/c小鼠	溃疡性结肠炎	上调乳酸杆菌和双歧杆菌, 下调葡萄球菌(*Staphylococcus*)
L. acidophilus	雌性BALB/c小鼠	克罗恩病	下调IL-23
L. acidophilus	TS4Cre×APC^{lox468}小鼠后代	结直肠癌	上调IL-10和IL-12, 下调Treg
L. acidophilus	C57BL/6小鼠	炎症性肠病	上调IL-10, 下调IL-6, IL-1β和IL-17
L. casei	C57BL/6小鼠	结直肠癌	上调Th_{17}, Th_{22}, IL-10和IL-22, 下调Treg
L. plantarum	BALB/c小鼠	氧化应激	上调拟杆菌和厚壁菌
L. johnsonii	C57BL/6小鼠	急性肝损伤	上调IL-22、乳酸杆菌
L. fermentum	BALB/c小鼠	高胆固醇血症	上调乳酸杆菌

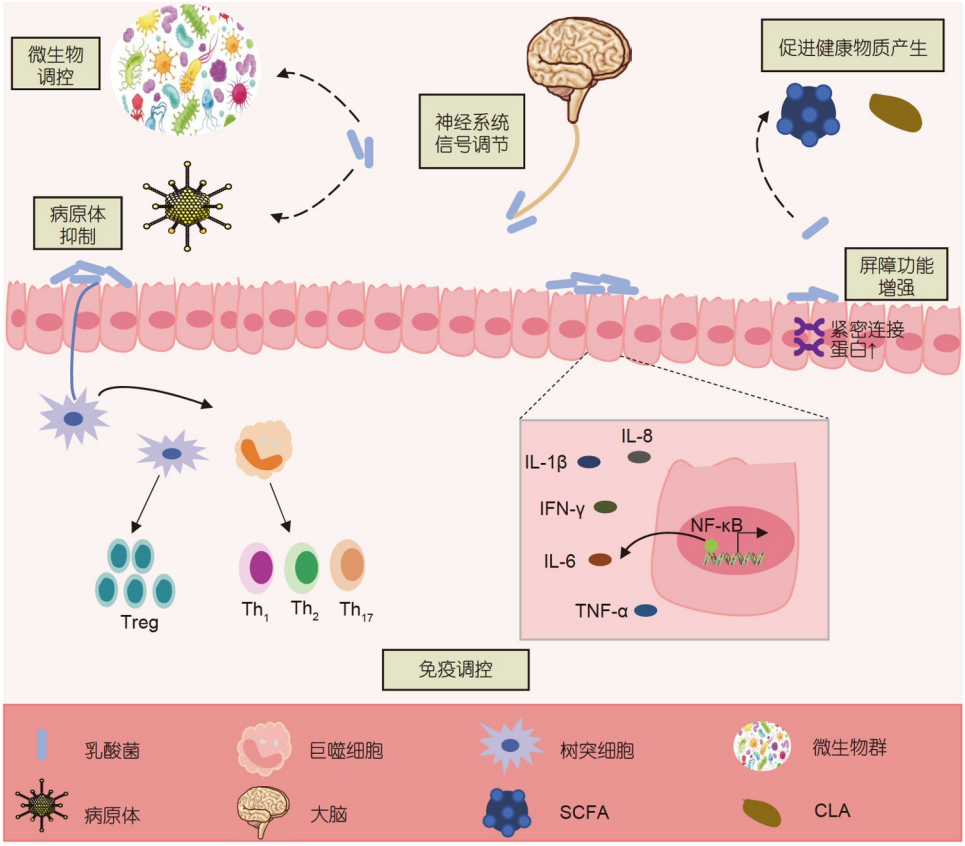

图 1　乳酸菌的主要作用机制. 乳酸菌可能对宿主有多种影响, 包括促进健康物质的产生(如SCFA, CLA)、直接和间接抑制病原体、改善屏障功能、调控微生物群、调节神经系统信号、免疫调节. Treg: 调节性T细胞; Th: 辅助性T细胞; SCFA: 短链脂肪酸; CLA: 共轭亚油酸; IL: 白细胞介素; TNF-α: 肿瘤坏死因子-α; INF-γ: 干扰素-γ

Figure 1　Main mechanisms of action of lactic acid bacteria. Note: *Lactobacillus* has a variety of effects on the host, including promoting the production of healthy substances (such as SCFA, CLA), inhibiting pathogens, improving barrier function, regulating microbiota, regulating nervous system signals and immune system. Treg: regulatory T cells; Th: helper T cells; SCFA: short chain fatty acids; CLA: conjugated linoleic acid; IL: interleukin; TNF-α: Tumor necrosis factor-α; INF-γ: Interferon-γ

nase, PI3K)、过氧化物酶体增殖物激活受体-γ、C反应蛋白(C-reactive protein, CRP)、白细胞介素(interleukin, IL)-6、IL-8、肿瘤坏死因子(tumor necrosis factor, TNF)-α、IL-1β和γ干扰素(IFN-γ)的表达[36], 还能够以菌株特异性和剂量依赖性的方式调节免疫细胞, 如巨噬细胞、自然杀伤(naturalkiller, NK)细胞、抗原特异性细胞毒性T淋巴细胞介导的非特异性细胞免疫反应以及细胞因子的释放[37]. 大多数乳酸菌能够刺激抗原呈递细胞(antigen-presenting cells, APCs)产生IL-12, 随后激活宿主NK细胞并促进1型辅助性T(Th_1)细胞应答[38]. 有些乳酸菌还能够通过不同的机制增强获得性免疫并诱导肠道中IgA的分泌, 进而激活B淋巴细胞和T细胞[39]. 此外, 包括磷壁酸、脂磷壁酸(lipoteichoic acid, LTA)、脂蛋白和胞外多糖(exopoly saccharides, SEP)在内的乳酸菌组分还被证明是免疫反应的诱导剂[40]. 乳酸杆菌介导的TLR2通过LTA刺激TNF-α的分泌[41], *Lactobacillus rhamnosus* GG (LGG)中的免疫刺激细胞表面附属物(SpaCBA)在体外介导与人肠黏液的结合以及TNF-α, IL-6, IL-10和IL-12的TLR2依赖性调节[42].

3.2　病原体抑制

乳酸菌能够通过竞争性排除肠道中的病原微生物发挥有益作用, 主要机制为创造不利于病原微生物生存的微环境、消除细菌受体位点、产生抗微生物物质、耗尽病原体生存所需的可用营养物质等[43]. 乳酸杆菌和双歧杆菌已被证明能抑制多种病原体, 包括*E. coli*, *Salmonella*, *Helicobacter pylori*, *Listeria monocy-*

*togenes*和轮状病毒[44]. 一些乳酸菌还可以通过产生抗微生物物质, 如乳酸、乙酸、乙醇、细菌素和其他抗菌化合物来改变它们的局部环境, 为病原体创造一个有害的微环境[45]. 一些双歧杆菌在体内产生醋酸盐, 通过创造酸性环境抑制产生志贺毒素的*E. coli* O157:H7[46]. *L. salivarius* UCC118产生Abp118细菌素可保护小鼠免受*L. monocytogenes*感染[47]. 乳酸菌抑制病原微生物的另一种方式是通过肠细胞病原体受体的空间位阻, 限制病原菌的附着[48]. 例如, *L. acidophilus* A4可以通过上调黏蛋白-2(MUC2), IL-8, IL-1β和TNF-α来拮抗*E. coli* O157:H7与肠上皮细胞的黏附[49].

3.3 屏障功能增强

肠屏障包括黏液层、抗菌肽、分泌性IgA和上皮连接黏附复合物, 能够保持上皮完整性并保护生物体免受环境的影响, 如果肠道上皮屏障的完整性受损, 各种抗原可能会进入黏膜下层, 引发炎症反应[50]. 乳酸菌稳定肠道屏障功能的几种潜在机制包括上调紧密连接(tight junction, TJ)蛋白(claudin-1, occludin和ZO-1)、改善跨上皮电阻、促进黏液分泌(通过结肠上皮细胞中MUC2, MUC3和MUC1的上调)、升高丁酸水平以及调节微生物[51], 这些作用可能由局部分泌的代谢物介导, 如乳酸杆菌在T84细胞屏障模型中调节许多编码黏附连接蛋白如E-钙黏蛋白、B-连环蛋白的基因的表达[52], *L. plantarum*产生的羟基顺式-12-十八碳烯酸(HYA)能够通过G-蛋白偶联受体(G protein-coupled receptor, GPR)-40-丝裂原活化蛋白激酶(MEK)-细胞外信号调节激酶(ERK)途径调节TNF受体2的表达, 从而抑制TJ通透性和IFN-γ, TNF-α诱导的occludin, ZO-1和claudin-1的下调[53]. 一些乳酸菌菌株还可以增加黏液屏障, 通过刺激杯状细胞释放黏蛋白颗粒来阻止病原体进入上皮细胞, 维持肠道通透性、增加顶端紧密连接的细胞间完整性[54], 如乳酸杆菌菌株在HT29细胞中诱导MUC3的表达[55], *L. casei* GG在Caco-2细胞中诱导MUC2的表达[56].

3.4 神经系统信号调节

有实验证明, 乳酸菌能够影响肠道和中枢神经系统的信号传导, 并对宿主产生抗焦虑及抗抑郁的作用. 一些乳杆菌和乳球菌能够通过谷氨酸脱羧作用产生γ-氨基丁酸[57,58], γ-氨基丁酸是脊椎动物中枢神经系统中分布最广泛的神经递质, 也在肠道水平起调节作用, 虽然γ-氨基丁酸不能绕过血脑屏障, 但它可以作为肠道平滑肌上的松弛分子, 降低轻度高血压患者的血压[59]. 喂食*L. rhamnosus* JB-1的小鼠大脑中γ-氨基丁酸(gamma-aminobutyric acid, GABA)-A和GABA-B受体的mRNA表达出现特定区域性变化, 与皮质酮对应激和焦虑相关行为的反应减弱有关, 而这种情况在迷走神经切断的动物中未观察到[60]. 用*L. reuteri* ATCC PTA 6475治疗可恢复因母体HFD而降低的脑室旁核的催产素水平, 并改善社会行为[61]. *Lactococcus lactis* subsp. *cremoris* FT4也可以通过从乳蛋白中产生血管紧张素1转换酶抑制肽(ACE抑制剂)来调节血压[35]. 虽然不是所有的乳酸菌都是人类肠道中稳定的寄生菌, 但是可以从食物中获取并在合适的条件下持续定植.

3.5 促进健康物质的产生

许多由肠道微生物群产生和代谢的有益化合物已被证明在维持体内平衡和抑制癌症等方面发挥着重要作用. 由肠道微生物群的特定群体产生的SCFA, 如乙酸盐、丙酸盐和丁酸盐, 除了作为能量来源外, 还被证明是影响免疫系统、细胞死亡和增殖、肠激素产生和脂肪生成的信号分子[62]. 虽然乳酸菌不直接参与SCFA的生产, 但某些双歧杆菌和乳酸杆菌的益生菌菌株可以调节肠道微生物群组成, 从而影响SCFA的产生[63]. 还有些双歧杆菌和乳酸杆菌能产生促进健康的共轭亚油酸(conjugated linoleic acid, CLA), 这是一种已知的抗癌剂, 还具有显著的抗肥胖作用[64]. 硒是一种对抗细菌和病毒感染[65]、限制氧化低密度脂蛋白相关动脉粥样硬化形成[66]以及控制氧化状态、免疫缺陷、全身炎症[67]的关键营养素. 许多证据表明, 补充硒具有防癌作用, 且血液中的硒水平与癌症死亡率呈负相关. 一些乳酸菌菌株能够将无机亚硒酸盐固定到含硒氨基酸中, 从而促进硒的生物合成[35].

4 乳酸菌在肠道疾病中的作用

4.1 炎症性肠病

IBD是一种以胃肠道炎症为特征的慢性疾病, 受环境、遗传、免疫和微生物因素的影响. 克罗恩病(crohn disease, CD)和溃疡性结肠炎(ulcerative colitis, UC)是IBD的两种主要表现形式, 它们有共同的特征,

但也会表现出生理病理上的差异[68]. 近些年来的研究表明乳酸菌有助于IBD的治疗, 其中*L. plantarum*是治疗IBD最常用的乳酸菌之一, 它在预防和治疗IBD病方面的作用机制是多种多样的, 其中包括细菌素的产生. 在Yin等人[69]构建的小鼠模型中, 接受了缺乏植物乳杆菌素细菌素的*L. plantarum* LM0419处理的小鼠与不接受细菌处理的对照组具有相似的TNF-α和IL-6水平, 而接受了野生型*L. plantarum* NCIMB8826处理的小鼠具有较低的炎症细胞因子水平. 同时, *L. plantarum* NCIMB8826还缓解了IBD小鼠的肠道微生物失调, IBD诱导的小鼠中拟杆菌属显著增加, 而在给予*L. plantarum* NCIMB8826治疗后该属的菌种减少.

肠道微生物群的组成与IBD发病率之间有很强的联系, 与健康人相比, IBD患者粪便和肠道微生物群的生物多样性和组成会发生一定程度的改变, 紊乱的肠道菌群会进一步加重已存在的炎症状态, 从而加重IBD[11]. 色氨酸(Tryptophan, Trp)是人体必需氨基酸, 研究发现, 在结肠炎小鼠模型中补充色氨酸会降低苏氨酸、蛋氨酸和脯氨酸的水平, 进而改变结肠中IL-22的浓度, 并调控肠道微生物群[70]. 有趣的是, 肠道内Trp浓度可能与乳酸杆菌介导的肠道免疫调节有关. 实验证明, *L. reuteri*通过将Trp代谢为吲哚-3-乳酸, 促进T细胞分化为双阳性T淋巴细胞(double-positive intraepithelial T lymphocytes, DPIELs), 进而激活$CD4^+$ T细胞上的芳香烃受体(aryl hydrocarbon receptor, AhR), 下调转录因子Thpok, 最终诱导其分化为DPIELs[71](图2). DPIELs是免疫耐受细胞, 可以进行主动免疫反应减少IBD患者的肠道炎症. 为了进一步研究*L. reuteri*和Trp在DPIELs产生中的关系, 研究人员用高、中、低剂量Trp喂养正常小鼠和无菌小鼠4周, 结果发现, 即使是高剂量的Trp也不能诱导无菌小鼠产生DPEILs, 但它以剂量依赖的方式显著增加了正常小鼠中的DPIELs. 以上研究表明, 健康肠道中的有益菌可以依靠Trp来发挥其免疫调节功能.

其他乳酸菌也被证明在调节生物失调和减少炎症方面有效. *L. fermentum* KBL374和*L. fermentum* KBL375改变了葡聚糖硫酸钠(Dextran Sulfate Sodium Salt, DSS)诱导的结肠炎小鼠的肠道微生物群, 改善了

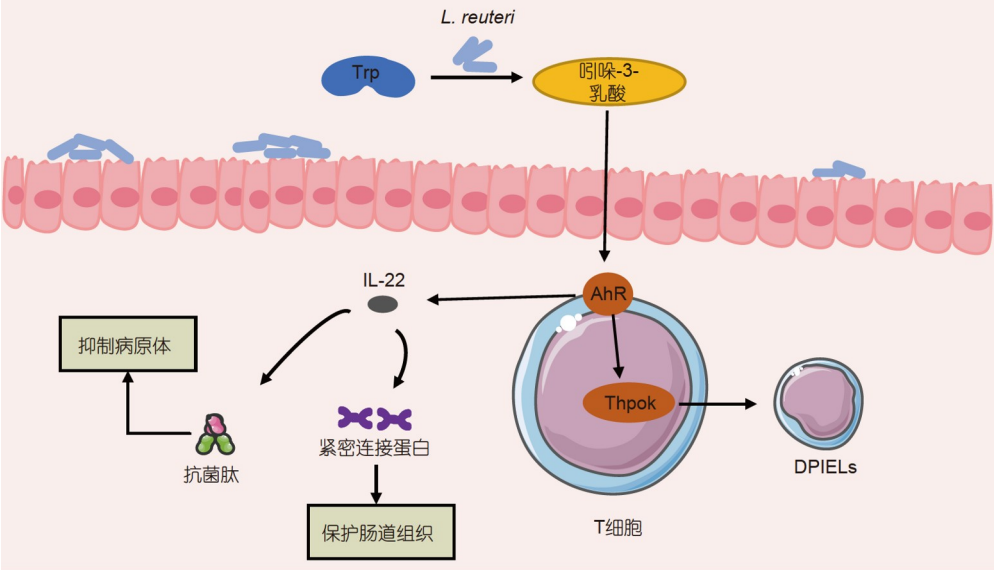

图 2　乳酸菌对IBD的免疫调节作用. 乳酸菌通过将Trp代谢为吲哚-3-乳酸, 激活T细胞上的AhR, 下调转录因子Thpok, 最终诱导其分化为DPIELs. 同时, AhR的激活促进IL-22的产生, IL-22通过诱导产生抗菌肽来抑制肠道病原体, 并通过增加紧密连接蛋白的表达来保护肠道组织免受炎症损伤, 从而增强先天免疫反应. Trp: 色氨酸; AhR: 芳香烃受体; DPIELs: 双阳性T淋巴细胞; IL-22: 白细胞介素-22

Figure 2　Immunomodulatory effects of lactic acid bacteria on IBD. By metabolizing Trp to indole-3-lactic acid, *Lactobacillus* activates AhR on T cells, downregulates the transcription factor Thpok, and eventually induces its differentiation into DPIELs. Meanwhile, the activation of AhR promotes the production of IL-22, which suppresses intestinal pathogens by inducing the production of antimicrobial peptides, and protects intestinal tissues from inflammatory damage by increasing the expression of tight junction proteins, thereby enhancing the innate immune response. Trp: tryptophan; AhR: aromatic hydrocarbon receptor; DPIELs: double positive T lymphocytes; IL-22: interleukin-22

肠道生物失调, 降低了*Bacteroides*和*Mucisprillium*的比例, 并增加了乳酸杆菌的比例. 与此同时, 还降低了促炎细胞因子水平(IFN-γ, IL-4, IL-13, IL-6, TNF, IL-17A, IL-1β, CCL2和CXCL1), 并增加了抗炎细胞因子IL-10的水平[72]. 在口服*L. rhamnosu* 2周后, 从CD患者分离的外周$CD4^+$ T细胞产生更少的IFN-γ和IL-2[73]. 在益生菌组合中, 口服VSL#3(一种由三种双歧杆菌、四种乳杆菌和嗜热链球菌组成的益生菌组合)可降低溃疡性结肠炎患者中TLR-2的表达, 增加IL-10产生, 并下调IL-12p40水平, 有效诱导轻中度溃疡性结肠炎患者病情的缓解[74].

另外, 有一些研究表明, 很大比例的IBD患者存在营养缺乏, 主要是维生素和矿物质(铁、维生素B12、维生素D、维生素K、叶酸、硒、锌、维生素B6和维生素B1)[75]. 因此, 接受治疗的IBD病患者经常需要接受营养补充以及额外的热量和蛋白质, 从而促进黏膜愈合[76]. 乳酸菌能产生不同的维生素, 一些维生素的补充已被证明能有效对抗肠道炎症[77]. 例如, Levit等人[78,79]研究表明, 由于核黄素的产生, *L. plantarum* CRL2130减轻了小鼠化学诱导的肠道炎症, 不仅如此, 口服这种核黄素高产菌株还有效减轻了5-氟尿嘧啶诱导的炎症损伤[80].

4.2 癌症

大肠癌, 也称为肠癌或结肠癌, 是一种可能会发生在大肠任何部位的癌症. 该病的症状包括血便和体重减轻, 它主要是由年龄和生活方式引起的, 患有IBD的人患结直肠癌的风险增加. 最近的研究探索了乳酸菌通过改变肠道微生物群及其可能的免疫调节机制在预防结直肠癌中的作用. 乳酸杆菌可以刺激宿主的免疫细胞, 包括树突状细胞、NK细胞或Th_1反应[81]. 口服从传统自制酸奶和新生儿粪便中分离的*L. acidophilus*可通过免疫反应调节或改变细胞因子环境来减少肿瘤生长, 降低肿瘤生长速度, 增加淋巴细胞增殖, 在活体乳腺癌小鼠模型中保护Th细胞并激活抗肿瘤细胞[82]. 对由7种不同乳酸杆菌、双歧杆菌和链球菌组成的益生菌混合物治疗的偶氮甲烷诱导的结肠癌小鼠模型的研究表明, 由于黏膜$CD4^+$ T极化的调节和基因表达的变化, 结肠癌的发生受到抑制[83].

粪便中胆汁酸过量会引起pH降低, 进而影响肠屏障的完整性, 导致结肠癌的发生[84]. 而乳酸菌如嗜酸乳杆菌和双歧杆菌已被证明在调节酸碱度和胆汁酸方面具有重要作用, 可有效预防癌症[84,85]. 另一种癌症预防机制认为, 乳酸杆菌和双歧杆菌菌株能够结合和降解潜在致癌物. 与结肠癌风险增加相关的诱变化合物常见于不健康的食物, 尤其是油炸类食品, 志愿者摄入乳酸杆菌菌株减轻了富含熟肉饮食的致突变作用, 在尿和粪便中杂环芳香胺(HAAs)的含量也减少[85]. 此外, 补充膳食乳酸菌也已证明可下调小鼠对3-氨基-1-甲基-5H-吡啶(4,3-β)吲哚(TrpP-2)及其代谢物的摄取[86]. 许多微生物衍生的分子, 包括SCFA(例如, 丁酸和丙酸)和组蛋白脱乙酰酶, 也与结直肠癌和淋巴瘤的抗癌特性有关.

饮食、生活方式和肠道微生物群组成都与大肠癌的发病密切相关, 饮食或环境的变化会导致的肠道内的微生物失调, 产生毒性因子以及一些有害的代谢物导致大肠癌, 细菌性癌症可以通过抑制群体感应和生物膜的微生物群来预防和治疗[87]. 补充足够量的乳酸菌可以通过平衡肠道微生物区系预防结直肠癌的发生[88]. 乳酸菌还能够产生多种代谢物用于预防和治疗癌症(表2), 细菌脂多糖(lipopolysaccharide, LPS)是革兰氏阴性细菌外膜的关键成分, 可激活TLR4, 从而激活免疫T细胞介导的抗肿瘤反应[89]. 由乳酸杆菌提取物产生的SCFA、CLA和其他抗癌产品可诱导癌细胞凋亡[90]. 来源于*L. plantarum* ZS2058的CLA1能够激活caspase-1并诱导Caco-2细胞焦亡, 而CLA2则能够通过caspase-4/5介导的途径诱导Caco-2细胞焦亡[91]. 一些乳酸菌产生的蛋白质和包括核酸在内的其他代谢物能够抑制肿瘤生长及增殖[90]. 铁色素是一种抗肿瘤候选药物, 其抑癌性能优于一些常规抗癌药物, 且对肠内非癌细胞的影响小于常规药物[92]. 实验证明, 来源于铁色素的*L. casei* ATCC 334对大肠癌具有高度的抑制作用. 近些年来, 使用乳球菌开发的癌症疫苗也得到了发展. 研究显示, 一种针对人乳头瘤的疫苗可为免疫小鼠提供全面的预防性保护, 并且还能够诱导肿瘤诱发小鼠中肿瘤的消退[93].

乳酸菌还能够延缓肿瘤的形成、抑制癌细胞的增殖、预防与癌症治疗相关的危及生命的副作用. Kumar等人[94]研究发现, 从发酵食品中分离的*L. plantarum* AS1通过抗氧化依赖机制调节1,2-二甲基肼自由基诱导的大鼠结肠癌发生发展. *L. lactis* NK34通过抑制癌细胞的增殖, 如人肺癌细胞系(SK-MES-1)、人结肠

表 2　用于预防和治疗癌症的益生菌代谢物

Table 2　Metabolites of lactic acid bacteria for the prevention and treatment of cancer

代谢物	功能	来源
脂多糖、胞外多糖	激活TLR4, 从而激活免疫T细胞介导的抗肿瘤细胞反应	*L. acidophilus*, *B. brevis*, *L. plantarum*
共轭亚油酸、SCFA	诱导癌细胞凋亡	*L. reuteri*, *L. salivarius*
蛋白质、核酸	抗增殖、抗氧化、促凋亡、预防癌细胞转移	*Bifidobacterium*, LGG
铁载体	抑制癌细胞生长及增殖	*L. casei*

癌细胞系(DLD-1, HT-29, LoVo)、人胃腺癌细胞系(AGS)和人乳腺癌细胞系(MCF-7细胞), 显示出强烈的抗癌和抗炎作用[90]. *L. plantarum* YYC-3代谢物能够抑制MMP2, MMP9, VEGFA基因和蛋白表达及蛋白分泌, 通过下调VEGF/MMPs信号通路有效抑制结直肠癌细胞生长、侵袭和迁移[95]. 此外, 表达过氧化氢酶的乳酸乳球菌的应用也已被证明能减少H_2O_2的产生, 减少结肠损伤和炎症, 从而抑制肿瘤的侵袭和增殖[96].

4.3　腹泻

抗生素相关性腹泻(antibiotic associated diarrhea, AAD)是抗生素治疗的一种常见不良反应, 主要通过三种机制产生: 肠道致病菌的过度生长、通过抑制内源性肠道菌群改变胆汁酸和非吸收碳水化合物的代谢以及抗生素的直接药理作用[97]. García等人[98]分析了乳酸杆菌和双歧杆菌菌株的特定益生菌组合(Pearls IC©)对阿莫西林-克拉维酸治疗抗生素相关性腹泻的效果、安全性和耐受性, 结果表明Pearls IC©能够延迟腹泻的发病时间, 证明了其对抗生素相关性腹泻的有益作用. 艰难梭菌是造成AAD的原因之一, 由于对抗生素的耐药性降低, 可导致大肠感染[99], 而乳酸菌可有效预防成人和儿童艰难梭菌相关性腹泻[100,101].

病原体引起的急性腹泻可引起胃肠炎、血便或严重的腹腔感染, 这些感染可导致疾病并增加经济负担, 乳酸菌如LGG和*L. reuteri*在治疗急性腹泻方面具有卓越的效果[102,103]. 欧洲儿科胃肠病、肝病和营养学会的一项研究让患者随机接受口服补液加安慰剂或口服补液加LGG, 结果显示, 服用LGG的患者与服用安慰剂的患者相比, 腹泻的平均持续时间更短、住院时间更短[104]. 此外, 服用LGG的患者不太可能出现持续性腹泻. Lai等人[105]探讨了*L. casei*对腹泻期间儿童的临床症状、肠道微生物群和炎症标志物的影响, 结果表明, 使用*L. casei*治疗的急性腹泻儿童粪便IgA升高、乳铁蛋白和钙卫蛋白表达下调. 与对照组相比, 服用乳酸菌的儿童肠道双歧杆菌和乳酸杆菌的数量增加, 且食欲与体重增加, 腹痛、腹胀以及腹泻情况有较大程度的改善.

4.4　肠易激综合征

肠易激综合征(irritable bowel syndrome, IBS)是一种常见的临床变异性疾病, 特征是腹痛、腹胀、肠胃胀气和排便习惯改变, 这些症状可能是由于小肠中的细菌过度生长, 导致发酵活动增加和气体产生[106]. 乳酸菌能够对IBS的几种致病途径产生有益影响, 包括通过增加有益菌(双歧杆菌和乳酸杆菌等)和减少病原体来恢复改变的肠道微生物群, 从而减少与病原菌增殖相关的炎症[107]、胆盐代谢的变化[108]、恢复正常的结肠环境[109]. 此外, 在IBS患者中观察到低度炎症、结肠黏膜中炎症细胞增加、促炎细胞因子和TLRs的增加[110], 这些都给乳酸菌治疗IBS提供了病理生理学支持. 治疗IBS最常用的乳酸菌包括乳酸杆菌和双歧杆菌, VSL#3也可以减少腹胀和肠胃气胀[103]. Skrzydło-Radomańska等人[111]评估了含有乳酸杆菌和双歧杆菌益生菌菌株以及短链低聚果糖的合生元制剂在腹泻显性IBS(IBS-D)成年患者中的作用, 结果表明多菌株合生元制剂与IBS-D患者症状的显著改善相关, 且耐受性良好.

5　乳酸菌在其他疾病中的作用

肥胖现在被认为是一种全球性的流行病, 与肠道中厚壁菌门和拟杆菌门的比率(F/B)相关, 肥胖个体的厚壁菌门比例较高, 拟杆菌门比例较低[112]. 拟杆菌拥有产生参与脂质和碳水化合物代谢的酶的基因, 厚壁菌拥有更多导致发酵终产物增加的基因, 包括SCFA合成酶[113]. LGG和*L. sakei* NR28降低了肥胖小鼠的F/B

比，不仅如此，这两种菌株还减少了附睾脂肪量、CoA羧化酶、脂肪酸合酶和肝脏硬脂酰CoA去饱和酶-1[114]. 在喂食高脂肪食物的小鼠中施用*L. plantarum* Ln4可以减少体重增加和附睾脂肪量，并降低血浆甘油三酯[115]. 在用*L. plantarum* Ln4处理的小鼠的白色脂肪组织中，CRP、胰岛素样生长因子结合蛋白-3(Insulin-like growth factor binding protein 3, IGFBP-3)和单核细胞趋化蛋白-1(Monocyte chemotactic protein-1, MCP-1)等脂肪因子的蛋白水平也降低. 此外，这种菌株还能够调控参与调节葡萄糖和脂代谢的几个肝脏基因的表达，促进IRS2，Akt2，AMPK和LPL的表达并抑制CD36的表达, 从而改善糖耐受和胰岛素反应.

Ⅱ型糖尿病(diabetes mellitus type 2, T2DM)是一种长期代谢紊乱疾病, 以高血糖为特征. T2DM最常见的症状包括口渴加剧、尿频和原因不明的体重减轻, 同时还与多种并发症相关，如冠心病、动脉粥样硬化、肾病、视网膜病变和足部病变[116]. T2DM的病因复杂，涉及环境和遗传因素之间的相互作用[117]，主要原因是在胰岛素抵抗(IR)的背景下，β细胞产生的胰岛素不足，肝脏不适当地将葡萄糖释放到血液中[118]. 乳酸菌可以通过改善肠道完整性、降低全身LPS水平、增加肠粘连蛋白、降低内质网(endoplasmic reticulum, ER)应激以及改善外周胰岛素敏感性干预T2DM的进程[119~121]. 乳酸菌还可通过改善糖耐受、调节脂质代谢、改善抗氧化状态以及调节肠道菌群和SCFA组成发挥抗糖尿病作用[122,123]. *B. longum*能够使血浆LPS, IL-1β, 肠道过氧化物酶水平和肠道炎症活动指数正常化，并显著上调广泛参与IBD和糖尿病的RegI蛋白表达[124]. *L. reuteri* GMNL-263通过上调过氧化物酶体增殖物激活受体α(PPAR-α)和GLUT4的表达，下调脂质体基因如Srebp-1c，FAS和Elvol6的表达，从而延缓T2DM的发展[125].

研究发现，多发性硬化症(multiple sclerosis, MS)患者肠道中乳酸杆菌的相对丰度低于健康成人[33]，在啮齿动物的MS模型中也观察到类似的肠道乳酸杆菌的消耗[126]. 同样, 一项对MS患者的随机对照试验发现乳酸菌降低了患者的抑郁、焦虑和压力以及血清CRP[127]. MS患者体内AhR配体的循环水平低于健康成人，而乳酸菌对这些化合物的维持或补充起到了积极作用[128].

母亲的产前压力可能会影响婴儿的微生物群，潜在地损害认知发展. 在人体中，产前皮质醇浓度与婴儿肠道乳酸杆菌和乳酸球菌水平呈负相关，与变形杆菌呈正相关[129]. 在产前应激的啮齿类动物模型中，观察到乳酸菌减少，后代的微生物群被破坏[130]. 产前低剂量青霉素注射或高脂肪饮食可诱发小鼠长期生态失调和行为缺陷，这些缺陷可以通过给母鼠补充含有乳酸菌的益生菌或通过给后代补充*L. reuter*来预防[61,131]. 在微生物-肠-脑轴缺失的成年小鼠模型中研究发现, 给药含有乳酸菌的益生菌对认知和结肠功能都有有益影响, 同时能够恢复肠道失调[132,133]. 一项临床试验研究了含有*L. acidophilus*, *L. casei*和*Bifidobacterium bifidum*的益生菌胶囊对重度抑郁症患者的疗效，结果表明，与安慰剂相比，接受益生菌干预的患者的抑郁量表得分显著降低[134]. 值得注意的是, 研究人员还发现, 与安慰剂相比，益生菌干预组的炎症标志物如血清胰岛素、胰岛素抵抗稳态模型评估(HOMA-IR)和血清hs-CRP显著降低.

婴儿肠绞痛是一种常见的婴儿病症，表现为婴儿易怒、烦躁或哭闹，没有明显的原因，没有婴儿发育不良、发烧或健康不良的证据，长时间反复发作[135]. 患有婴儿肠绞痛的婴儿存在肠道微生物群失调、屏障改变和轻度慢性胃肠炎症. 肠绞痛婴儿的肠道生物失调表现为双歧杆菌、乳酸杆菌和产丁酸杆菌的水平降低, 导致更易引发炎症的肠道环境, 肠黏膜的不成熟也有可能使有毒化合物从肠腔进入到血液中[136]. 一项针对46名3~16周龄婴儿肠绞痛的初步研究中发现，与乳糖酶膳食补充剂相比，木葡聚糖加*L. reuteri* SGL01和*B. breve* SGB01能够显著减少婴儿哭泣的平均持续时间[137].

此外，各种基于乳球菌的动物疾病疫苗也已开发出来，且大多效果良好. 在家禽疾病中，针对H5N1病毒进行了广泛的研究，乳球菌疫苗能够诱导高血凝素A(haemagglutinin A，HA)特异性血清IgG和粪便IgA, 分泌形式比细胞内表达疫苗更有效[93]. 除此之外，其他基于乳球菌的疫苗包括针对H1N1[138]、H5N2[139]、禽传染性支气管炎病毒[140]和空肠弯曲杆菌感染[141]的疫苗也正在积极开发研究中.

6 总结与展望

对细菌的全基因组测序和宏基因组分析使我们

能够在复杂的生态系统即机体内拼凑出宿主和微生物之间的共生关系. 在这些微生物中, 乳酸菌占据着重要的位置, 能够影响其他微生物、调控机体免疫、对机体健康具有深远的影响. 正如本文中所综述的, 乳酸菌能够通过调节免疫相关基因表达、炎症途径活性和免疫标记物对宿主进行免疫调节; 通过竞争性以及空间阻位抑制病原体的生长; 通过上调紧TJ、改善跨上皮电阻、促进黏液分泌、调节微生物等机制增强肠道屏障; 调节肠道和中枢神经系统的信号传导; 促进SCFA、CLA、维生素等健康物质的产生. 从而在IBD、癌症、腹泻和IBS等肠道疾病的预防和治疗中发挥着重要的作用, 同时还能够促进肥胖、T2DM、MS、抑郁症、婴儿肠绞痛等其他疾病的缓解和康复.

但是乳酸菌和地球上的每一个有机体一样, 都不是完美的, 它们有产生生物活性不良胺(如组胺和酪胺)的风险[35]. 细菌的突变、基因重组和进化频率可以在几年内改变情况. 就在几十年前, 大肠杆菌还被认为是安全的, 梭状芽胞杆菌是高致病性的. 如今, 一些大肠杆菌菌株已被证明会导致死亡, 梭状芽孢杆菌甚至被提议作为益生菌[142]. 因此, 还需进行长期的持续性的研究, 并借助各种组学方法, 评估乳酸菌的长期疗效、安全性以及如何受到环境的影响. 然而, 考虑到乳酸菌缺乏主要的细菌致病特性(毒素、入侵潜力)和在肠道生态系统中提供的所有有益特性, 目前可以得出结论, 乳酸菌不仅很好地适应了与宿主共生的生活, 而且还可以帮助宿主保持健康状态, 并可能提高其性能和寿命.

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Role of lactic acid bacteria in maintaining animal intestinal health

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The gut microbiota is one of the most important components in maintaining the homeostasis of the host and is closely associated with health and disease in humans and other mammals, as many diseases are accompanied by intestinal microbiota disorders. Probiotics are often used to modulate the microbiota and immunity, alleviate disease, and maintain body health, and lactic acid bacteria (LAB) are the most widely used probiotic. LAB are Gram-positive bacteria, which only account for a small part of the human intestinal microbiota, but their potential to regulate the host immune system, enhance intestinal metabolism, and maintain the balance of the intestinal microbiota has been widely confirmed. Therefore, we summarized the role of LAB in maintaining intestinal health and discussed their contribution to host health through immunoregulation, inhibition of pathogens, enhanced barrier function, regulation of nervous system signaling, and the production of healthy substances. We also explored the role of LAB in the prevention and treatment of intestinal diseases, such as inflammatory bowel disease, cancer, diarrhea, and irritable bowel syndrome, as well as obesity, type 2 diabetes, multiple sclerosis, depression, and other diseases.

lactic acid bacteria, probiotics, intestinal microorganisms, intestinal health, immune regulation, inflammatory bowel disease, cancer

doi: 10.1360/SSV-2022-0032