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Review 综　述

高抗菌活性乳酸菌拮抗食源性致病菌的研究进展

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Li Haixin, Kou Xiuying, Xie Xinqiang, Zhang Jumei, Wu Qingping. High antibacterial activity of lactic acid bacteria against food-borne pathogens. *Acta Microbiologica Sinica*, 2022, 62(10): 3732–3740.

摘　要：食源性致病菌严重威胁人类的生命健康。服用抗生素是目前最有效的治疗手段。但不规范使用抗生素，导致耐药性细菌日趋普遍。乳酸菌是公认的食品级安全微生物，因其具有拮抗致病菌、增强免疫功能、加强肠道屏障、平衡肠道菌群等功能而具有良好的应用前景，有望成为下一代安全、稳定、经济的生物抗菌剂，以减少甚至替代抗生素的使用。本文通过阐述乳酸菌抗菌物质、抗菌机制及抗菌功能特性等，以促进乳酸菌的研究和应用。

关键词：乳酸菌；食源性致病菌；抗菌机制；抗菌物质

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High antibacterial activity of lactic acid bacteria against food-borne pathogens

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Abstract: Food-borne pathogens threaten human life and health and antibiotics are the most effective choice at the moment. However, the irregular use of antibiotics has led to the rising prevalence of drug-resistant bacteria. Lactic acid bacteria are recognized as safe food-grade microorganisms. They boast good application prospects attributing to the functions of antagonizing pathogenic bacteria, improving immune regulation, strengthening intestinal barrier, and balancing intestinal microbiota. They are expected to become the next generation of safe, stable, and economical biological antibacterials to reduce or even replace antibiotics. This article describes the antibacterial substances, antibacterial mechanisms, and antibacterial functional properties of lactic acid bacteria to promote the research on and application of them.

Keywords: lactic acid bacteria; food-borne pathogens; antibacterial mechanism; antibacterial substance

全世界每年暴发多起食源性致病菌感染的案例，严重危害人类健康，造成了巨额疾病负担[1]。常见的食源性致病菌有肠出血性大肠杆菌 O157:H7、鼠伤寒沙门氏菌、单增李斯特氏菌及金黄色葡萄球菌等[2]。目前，使用抗生素是治疗致病菌感染的主流方案。但是，耐药菌已呈现新常态，对人类的健康带来严重的威胁。因此，迫切寻求一种安全、稳定、高效、无毒、无残留、经济的生物抗菌剂，以减少甚至可以替代抗生素的使用。

乳酸菌是一类可代谢碳水化合物产生乳酸的细菌的统称，部分菌株已被联合国粮食及农业组织和世界卫生组织列为益生菌。这类细菌具有分布广、应用广、丰度高和功能强等特点。研究表明，乳酸菌由于能够产生多种抗菌物质，从而具有良好拮抗食源性致病菌的能力[3–6]。此外，乳酸菌还能维持胃肠道菌群稳态、增强肠道屏障功能、改善免疫力等[7]。因此，近年来食品领域掀起研究乳酸菌的热潮。目前乳酸菌的研究主要包括发挥抗菌功能的物质基础以及这些物质的分子作用机制的解析。本文对乳酸菌产生的抗菌物质及其作用机制进行综述，为乳酸菌的应用和研究提供参考。

1 乳酸菌的抗菌物质

乳酸菌可代谢产生如细菌素、有机酸、过氧化氢、胞外多糖、铁载体和生物表面活性剂等抗菌物质，因而具有良好的抗菌活性[7–8]。细菌素是细菌代谢过程中合成并分泌到周围环境中的一类杀菌蛋白或多肽物质。根据 Klaenhammer 的建议将细菌素分为 4 类[9]。Ⅰ类细菌素在翻译后进行一定的修饰且含羊毛硫氨基酸，称为

羊毛硫氨酸；其他 3 类细菌素一般不进行翻译后的修饰，且不含羊毛硫氨酸，称为非羊毛硫抗生素[10]。细菌素是一类天然物质，具有抗菌能力强、易降解、不残留、绿色安全等优点，在食品添加剂领域具有良好的运用前景。目前，广泛用于食品行业的代表性细菌素是乳酸链球菌素(nisin)。nisin 最早发现于 1928 年，1953 年首次在英国上市，并于 1988 年被美国食品和药物管理局(FDA)批准用于食品添加剂[6,11]。乳酸菌还可通过糖发酵产生多种有机酸，主要包括乳酸、乙酸、柠檬酸、苹果酸、丙酸以及苯乳酸等，均具有一定的抗菌作用[12–15]。何艳霞等利用 HPLC 分析发现，*Lactiplantibacillus plantarum* DT2-4 发酵上清液中主要的抗菌物质是苯基乳酸、乳酸、乙酸、柠檬酸、苹果酸[16]。此外，乳酸菌还可以产生其他抗菌物质，例如二氧化碳、二乙酰、脂肪酸等[17]。

2 乳酸菌抗菌机制

2.1 分泌抗菌物质

乳酸菌可以通过产生有机酸降低肠道的 pH 值抵抗致病菌的入侵。研究表明，有机酸产生的 H^+能够作用于食源性致病菌细胞膜表面电位和膜蛋白活性，破坏细胞膜的稳定性[5]。部分有机酸具有亲脂性，可以靶向结合到菌体细胞膜并促进细胞质子和离子的泄露，进而发挥拮抗致病菌的功能[18]。乳酸菌细菌素抗菌机制大致可以分为两个方面：作用于食源性致病菌细胞壁(膜)和作用于细胞内相关物质[19]。细菌素通过靶向细胞膜上特定的受体分子进行特异性结合[20–22]或者通过自身的疏水性和阳离子特性进行非特异性结合,作用于致病菌细胞壁(膜)表面形成穿孔，破坏其完整性和膜渗透性，导致膜内物质泄漏或者失衡而致死。在所有细菌素中研究最多的就是 nisin，nisin 通过靶向脂质Ⅱ组成复合体与细胞膜特异性结合形成孔，此外通过干扰细胞壁的合成抑制菌的生长[19]。细菌素还可以通过干扰 DNA、RNA 和蛋白质代谢来抑制基因表达和蛋白质合成，从而起到杀灭靶细胞的作用[19]。综合现有细菌素的抗菌机制研究可知，两种作用方式并不是相互独立，而是相辅相成，共同发挥抗菌的过程。过程往往需要一种或者多种不同作用机制协同发挥作用。细菌素首先作用于靶细胞的细胞壁(膜)，待靶细胞的细胞壁和细胞膜完整性受到破坏后，细菌素便可以驱动小分子物质被动外流，例如钾和磷酸根离子、氨基酸、ATP 等。细胞内小分子物质的外流会引起质子动力或者至少一个分量(Δψ、ΔpH)的减少或者耗散。质子动力的消耗造成了细胞内 ATP 水平低，缺乏相关的离子和辅因子，这将导致大分子如 DNA、RNA、蛋白质和多糖的合成受到抑制，进而导致微生物生长受阻和随后的细胞死亡[23]。

2.2 竞争黏附部位

乳酸菌的竞争性排斥建立在细菌间相互作用的基础上，这种相互作用通过竞争可利用的营养物质和细菌黏附位点来介导[24]。某些乳酸菌菌株具有良好的疏水性、自聚性和黏附特性，可以通过表面蛋白和黏蛋白之间的相互作用在肠道形成物理屏障进而阻断食源性致病菌的黏附以及生长繁殖。乳酸菌也可以和致病菌竞争胃肠道上皮连接位置和结合宿主细胞的受体位点，阻断致病菌例如大肠杆菌、单增李斯特氏菌、艰难梭菌、金黄色葡萄球菌在肠道中定殖[25]。菌株排斥竞争的程度取决于其特异性，并可能由菌株细胞表面的黏附素的分布以及对竞争的特异性受体的亲和力所决定[26]。乳酸菌还可以和致病菌进行营养和能源的竞争，阻止其获得在肠道生长和增殖所需的能量。除了如上所述的竞争排斥外，乳酸菌还可以通过分泌生物表面

活性剂、建立与受体相似的生物膜、代谢产生相关酶降解碳水化合物受体的方式抑制食源性致病菌的黏附[27]。

2.3 增强肠道屏障功能

肠上皮屏障对正常生理功能非常重要。上皮屏障受损可导致肠道疾病，如肠道病原体感染、炎症性肠道疾病、肥胖和肠易激综合征[25]。乳酸菌可以通过增强肠道黏膜的物理屏障和化学屏障，起到保护宿主肠道的作用。肠道屏障的功能很大程度上取决于黏液层和紧密连接蛋白[28–29]。黏液层主要由黏蛋白和肠道杯状细胞组成。肠道杯状细胞可以分泌主要由 MUC-2 形成的黏蛋白[30]。黏蛋白通过提供物理化学屏障来限制病原体进入，为上皮细胞提供相当大的保护以抵御病原体的侵袭并确保黏液层的完整性[2,30]。紧密连接蛋白由跨膜蛋白组成，位于肠上皮细胞的顶部[31]。Claudin、occludin、ZO-1 是肠上皮细胞中重要的紧密连接蛋白[32]。紧密连接蛋白形成半透性屏障，可以限制有害物质的进入，在维持肠上皮屏障通透性方面发挥重要作用[33]。本研究团队发现 *Pediococcus pentosaceus* IM96 可以缓解肠出血性大肠杆菌 O157:H7 诱导的上皮屏障破坏并增加感染小鼠空肠中 MUC-2、occludin、ZO-1 的浓度[34]。相关研究也表明，VSL#3 益生菌配方能够诱导结肠上皮细胞黏蛋白基因表达和分泌[35]。*Bifidobacterium infantis* 可以增加 T84 细胞中 ZO-1 和 occludin 的表达[36]。此外，*Limosilactobacillus frumenti* 可以通过上调早期断奶仔猪的紧密连接蛋白(包括 ZO-1、occludin 和 claudin-1)，从而显著改善肠黏膜完整性[37]。

2.4 免疫调节

众所周知，乳酸菌可以调节宿主的先天性和获得性免疫反应[38]，取代肠道中的病原体，从而预防肠道疾病[7]。这些细菌能够调节肠道上皮细胞、树突状细胞、单核/巨噬细胞以及 T、B 淋巴细胞的功能。摄入致病菌可以引起系统性或者肠道炎症，进而损失肠道屏障。树突状细胞是一种具有特征性突起的免疫细胞，可将抗原呈递给免疫 B 和 T 细胞。接着 $CD4^+$ T 细胞受到信号刺激后可在细胞因子的作用下分化为不同的亚群：Th1、Th2 和调节性 T 细胞(regulatory cells，Treg)[39]。益生菌通过诱导产生不同的细胞因子调节胃肠道免疫反应，且具有菌株特异性。乳酸菌通过干扰 NF-κB 和 MAPK 炎症信号通路，下调免疫细胞促炎细胞因子例如 IL-1β、IL-6、IL-8、TNF-α 的分泌[40–41]。同时乳酸菌还可以通过促进 IL-10 和 TGF-β 等抗炎细胞因子的分泌来调节黏膜免疫反应[42–44]。本研究团队发现 *Limosilactobacillus fermentum* GDMCC 61827 可显著下调经 UVB 损伤的皮肤细胞的促炎因子表达水平，例如 IL-1β、IL-6、IL-8；在体内可有效缓解紫外辐照豚鼠皮肤光老化症状和皮肤炎症。此外，经团队采样分离得到的 *Lactiplantibacillus plantarum* 1-Z 在体外能缓解胃癌细胞 AGS 和正常胃上皮细胞 GES 的促炎因子 IL-8 的水平上调；在体内也能够降低幽门螺杆菌感染小鼠的促炎因子 TNF-α、IL-8 和 IL-1β 的上调水平。和本团队研究结果一样，相关研究表明 *Lactiplantibacillus plantarum* CCFM1143 可显著降低产肠毒素大肠杆菌感染小鼠的促炎因子 TNF-α 和 IL-6 的表达，上调抗炎因子 IL-10 的表达水平[45]。此外，在感染时乳酸菌还可以刺激肠道产生分泌型 IgA (secretory IgA，SIgA)。SIgA 可以结合并干扰病原体细胞膜上的黏附细胞受体来抑制病原体与肠道上皮细胞的黏附，从而保护肠上皮免受侵袭。

综上所述，乳酸菌可能通过分泌抗菌物质、与致病菌竞争黏附部位、增强肠道屏障功能及免疫调节等途径发挥抗菌活性(图 1)。

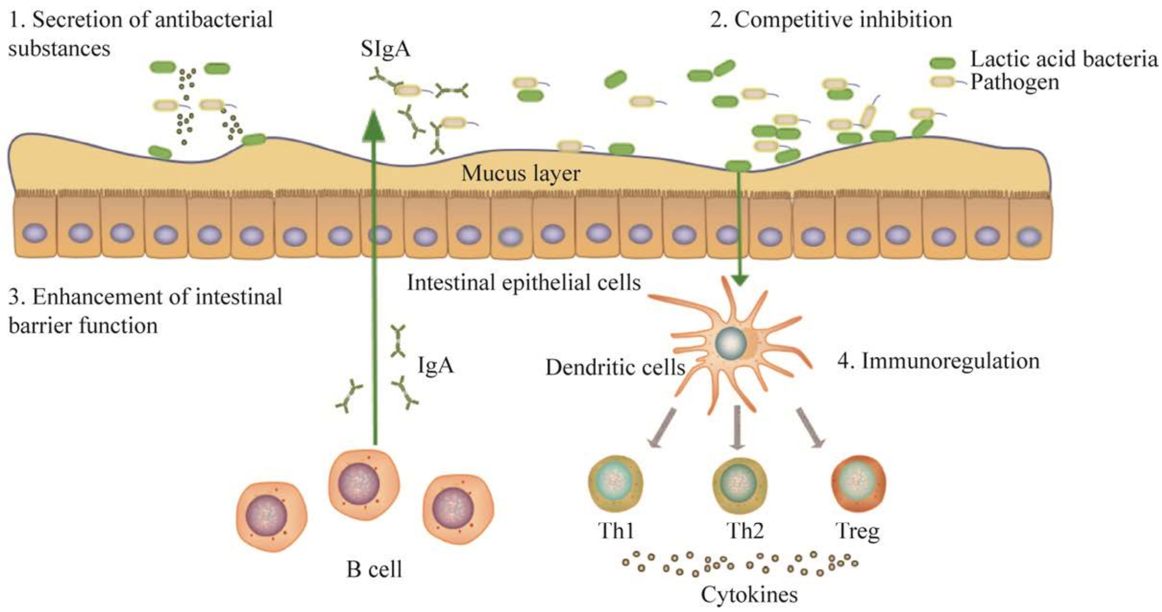

图 1　乳酸菌抗菌机制作用图

Figure 1　Antibacterial mechanism of lactic acid bacteria.

3　乳酸菌抗菌物质的应用前景

3.1　乳酸菌抗菌物质在医药领域的应用前景

由于近年来抗生素的不规范使用和滥用，导致出现了很多具有多重耐药性的致病菌。而在农业和食品生产环境中使用抗生素更是加剧了超级耐药菌出现的频率和数量。人类也会因长期食用抗生素而出现肠道菌群紊乱的现象，菌群结构失衡进而造成肠道功能失调，还会导致抗生素伴联性症状，如腹泻、超感染等。同时抗生素的大量使用势必会通过自然选择和进化作用使得耐药基因扩散、传播与集聚，最终给人类的生命健康带来严重的威胁。因此急需寻求其他抗菌剂以缓解抗生素的使用频率，而乳酸菌及其代谢产物是一项很好的选择。

Wang 等研究发现 *Lacticaseibacillus casei* LC2W 可抑制大肠杆菌 O157:H7 在体内定殖，降低结肠炎的严重程度[46]。Ren 等研究发现混合植物乳杆菌菌剂可以抑制金黄色葡萄球菌引起的炎症并改善小鼠肠道菌群[47]。Liu 等研究发现 *Lactiplantibacillus plantarum* ST-III 在控制食源性致病菌流行方面具有巨大潜力，可以通过抑制沙门氏菌的生长、增强肠道屏障功能和免疫调节降低沙门氏菌对小鼠的致死作用[48]。在体内除了乳酸菌本身具有良好的抗菌活性外，乳酸菌的代谢产物也具有一定的抗菌能力。研究表明细菌素可抑制多种食源性致病菌，具有防治致病菌感染的功效[49–50]。乳酸菌细菌素 pediocin PA-1 可有效地特异性治疗被单增李斯特氏菌感染的小鼠[19]。Kim 等发现细菌素 lacticin NK34 在体外可抑制金黄色葡萄球菌，在体内对其感染具有预防和治疗作用[51]。此外，乳酸菌产生的有机酸会改变胃肠道环境的 pH 值，降低致病菌肠道感染的风险[7]。Wang 等的研究也表明有机酸和中链脂肪酸混合物可以改善肠出血性大肠杆菌 O157:H7 感染小鼠的炎症反应和肠屏障功能障碍[52]。综上所述，乳酸菌及其代谢产物能够很好地缓解和抑制肠道内部

致病菌的感染，将来可以和抗生素协调使用从而降低抗生素的使用频率，为细菌耐药性防控做出贡献。

3.2 乳酸菌抗菌物质在食品领域的应用前景

乳酸菌细菌素可加入奶制品、肉制品、蔬菜等食品中有效抑制甚至杀灭食源性致病菌从而延长保质期，具有很好作为生物抗菌剂与防腐剂的潜力。目前食品领域中应用最为广泛的是 nisin 和 pediocin PA-1，nisin 能够抑制包括同属乳酸菌、单增李斯特氏菌、金黄色葡萄糖菌和肉毒梭状芽孢杆菌在内的多种革兰氏阳性菌[53]；pediocin PA-1 在靶细胞质膜上形成孔来改变其细胞通透性，能明显够抑制单增李斯特氏菌的生长繁殖[54]。*Enterococcus faecium* 产生的 enterocin A 和 enterocin B 可运用于防治肉制品如火腿、猪肉及发酵香肠的英诺克李斯特氏菌[55]。此外，研究表明乳酸菌在果蔬发酵过程中能够产生有机酸和细菌素拮抗食源性致病菌生长[56]。细菌素 enterocin AS-48 能够明显抑制蔬菜中的蜡样芽胞杆菌和果汁中的蜡样芽胞杆菌、单增李斯特氏菌和金黄色葡萄球菌[57]。近年来，该领域的较大进展是开发出含有抗菌剂的可食用薄膜和涂层。它们由生物聚合物层组成，可以保护食品免受环境影响，通过在食品的加工，运输和储存过程中抑制食品中的病原体来提高食品安全性[58]。

4 展望

目前，乳酸菌在抗菌领域的应用仍然存在很多问题有待解决。例如，乳酸菌菌种资源有待进一步挖掘；筛选功能菌种体系方法缺乏创新高效；抗菌物质存在抗菌谱窄和不稳定现象；活性菌株特异性抗菌机制不明确等。针对上述问题，本团队加强了全球重要样本采集和菌种资源勘探，定向捕获并选择性分离了样本中宝贵的健康功能微生物资源。目前本团队已经构建了含有 2 万余株乳酸菌的菌种资源库，并对菌株的全基因组和代谢特征谱进行分析，构建了国内重要的健康功能微生物科学数据库，准确高效地定向选育无毒力基因和耐药基因的安全菌株；利用机器学习构建预测模型，进行拮抗食源性致病菌的高通量筛选，靶向挖掘高效拮抗食源性致病菌的抗菌谱广、活性高、抗逆性强的健康功能乳酸菌。未来研究还应该利用基因组学、转录组学、蛋白组学、代谢组学等多组学联合方式全方位探索功能菌株的作用机制。此外，乳酸菌的抗菌功能领域仍需不断创新和发现，为保障人类健康提供物质基础。

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