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乳酸菌在肠道健康中的功能及应用现状

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摘　要

乳酸菌(Lactic Acid Bacteria, LAB)作为肠道益生菌，可以产生有机酸和细菌素等具有抗菌活性的代谢产物。近年来，研究者们将LAB的应用逐渐从食品领域扩大到对人类健康的功能上，发现其可以通过调节肠道菌群和肠道免疫从而维持肠道微生态的稳定，同时对结肠癌也具有预防作用。本文总结了LAB维持肠道健康的作用机制，为通过LAB干预，从而预防及治疗肠道疾病提供新的思路。

关键词

乳酸菌，肠道菌群，肠道免疫，肠道微生态

Function and Application Status of Lactic Acid Bacteria in Intestinal Health

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Abstract

Lactic Acid Bacteria (LAB), as intestinal probiotics, can produce metabolites with antibacterial activity, such as organic acids and bacteriocins. In recent years, researchers have gradually expanded the application of LAB from the field of food to the function of human health. It has been found that it can maintain the stability of intestinal microecology by regulating intestinal microbiota and intestinal immunity and has a preventive effect on colon cancer. This paper summarized the mechanism of action of LAB to maintain intestinal health and provided a new idea for the prevention and treatment of

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intestinal diseases.

Keywords

Lactic Acid Bacteria, Gut Microbiota, Gut Immunity, Intestinal Microecology

1. 引言

在健康人体内，结肠和直肠上皮的结构和功能以及免疫系统需要有益的微生物群来维持。肠道菌群结构和多样性受到宿主年龄、饮食结构、胰腺酶、肠道微环境、生活压力、药物和生活方式等因素的影响；同时，这些微生物群的失调也会导致宿主发生肥胖、哮喘、炎症性肠病(IBD)、精神障碍，甚至是结肠癌等疾病的风险[1]-[4]。此外，肠道中的有益微生物群不仅可以维护肠道屏障的完整性，同时还具有促进营养物质的吸收等功能[5]-[8]。由此可知，肠道有益菌可以为宿主的健康保驾护航。

乳酸菌(Lactic Acid Bacteria, LAB)作为肠道益生菌，在提高食物的吸收、增强宿主对感染的抵抗力、增强肠道的免疫系统、调节宿主的新陈代谢等方面起着重要的作用[8]。世界卫生组织和联合国粮食及农业组织建议适量补充 LAB 对人体健康是有益的[2]。本文将对 LAB 在维持肠道健康中的作用及调控机制进行阐述，这将为 LAB 对肠道疾病的预防及治疗提供新的思路。

2. 乳酸菌与肠道微生态及肠屏障的关系

LAB 作为肠道益生菌对肠道健康的促进作用包括对肠道菌群的调节、降低肠道病原菌的丰度、调节免疫系统，从而减少结肠炎症，预防结肠癌的发生[9]-[13]。

2.1. 调节肠道菌群，降低肠道有害菌的丰度及酶活

动物体肠道中的共生活菌数大约是 10^4~10^{11} CFU/ml。胃、小肠、结肠的共生菌主要为肠杆菌科、梭菌科，以及 LAB 等。然而，肠道内某些有害菌群的增加可能会产生对宿主有害的代谢物，如 NAD(P)H 脱氢酶(偶氮还原酶)、硝基还原酶、β-葡萄糖醛酸酶、β-葡萄糖苷酶和 7-α-脱羟基酶，这些物质可能会诱导结直肠癌(Colorectal Cancer, CRC)的发生[14] [15]。Stringer 等人报道，伊立替康引起的大鼠模型腹泻与 β-葡萄糖醛酸酶水平升高，以及 LAB 和双歧杆菌等有益菌株的减少有关，同时共生细菌如大肠杆菌和脆弱拟杆菌在结肠癌患者中也大量存在，并显示出致癌酶活性的增加[16]。这些酶被认为可作为诊断 CRC 的生物标志物。肠道 LAB 可通过正向调控肠道菌群来预防 CRC。它们可能通过产生结肠发酵产物、短链脂肪酸(Short Chain Fatty Acid, SCFA)和抗菌肽对 CRC 促进菌发挥抗菌活性。LAB 将原致癌物和致癌物转化为毒性较低的代谢物，帮助它们解毒，从而预防 CRC，这主要是通过 I 期和 II 期酶完成的，这两种酶协助调节致癌物的毒性、诱变和肿瘤效应[17]。

LAB 可以产生细菌素、有机酸等具有抗菌性能的代谢产物。近年来，LAB 细菌素因具有抑制多种 G^+ 和 G^-细菌的功能，常常被建议用作抗生素的替代品。其抗菌机制主要是使其他细菌细胞膜受损，使得细胞质内的物质外溢，最终导致细菌细胞死亡，而产生细菌素的 LAB 自身对细菌素具有免疫功能[18] [19]。

在 CRC 患者中，肠道中的胆固醇和胆汁酸迅速转化为细菌产物，导致正常菌群酶功能受损，产生有

害物质。因此，食用 LAB 减少这些酶的活性。例如，LAB 抑制细菌酶的能力减少初级胆汁酸的脱羟基以及口服鼠李糖乳杆菌(*Lactobacillus rhamnosus*, *L. rhamnosus*) GG 通过减少 β 葡萄糖醛酸酶的活性。口服嗜酸乳杆菌(*Lactobacillus acidophilus*, *L. acidophilus*)和两歧双歧杆菌(*Bifidobacterium bifidum*, *B. bifidum*) 3 周可以降低粪便中硝基还原酶的活性；此外，SCFA 是由益生 LAB 产生的，其中最常见的有 *L. rhamnosus*、罗伊氏乳杆菌(*Lactobacillus reuteri*, *L. reuteri*)、*Bifidobacterium*、*L. acidophilus* 等[20]-[22]。

2.2. 调节免疫系统

肠道微生物及其代谢组已被证明，在粘膜和全身水平上对先天免疫和适应性免疫的差异调节中发挥了显著的作用。CRC 发生时肠道组织炎症具有损伤肠道屏障的特点，促进了细菌的易位和促炎细胞因子对肿瘤微环境的诱导[23]。Uronis 等人研究了肠道微生物群与大肠菌相关癌症的发生之间的关系，并将其归因于 TLR/MyD88 通路的活化，他们将慢性结肠炎的严重程度和结直肠肿瘤的发展，以及细菌引起的炎症驱动的腺瘤进展，为细菌与侵袭性癌的发展进行了关联[24]。Vannucci 等人研究发现，无菌大鼠比常规大鼠表现出更强的抗癌免疫反应，肿瘤体积更小、数量更少，这是由于所遇到的抗原性挑战更低，并且没有细菌来源的生理炎症[25]。此外，研究者们也报道了免疫能力强和免疫受损的小鼠体内微生物组成的差异，以及适应性免疫在调节肠道菌群中的重要性。益生菌还通过产生抗炎细胞因子来延长免疫刺激功能，通过分泌抗氧化和抗癌化合物来增强肠道屏障功能[26]。

此外，研究还发现，服用短双歧杆菌(*Bifidobacterium breve*, *B. breve*)和长双歧杆菌(*Bifidobacterium longum*, *B. longum*)，与抗 PD-L1 治疗在控制肿瘤上表现出了相同的治疗程度；并且，联合治疗几乎消除了肿瘤的生长，提高了 PD-L1 敲除抗体对肿瘤的效率[27]。树突状细胞(Dendritic Cells, DCs)、T 细胞和自然杀伤(Natural Killer, NK)细胞是重要的免疫细胞，它们能够防御肿瘤的发生[28] [29]。针对特定的模式识别受体(Pattern Recognition Receptors, PRRs)和通路可以刺激直流调节功能，包括 Toll 样受体在内的模式识别受体被益生菌或其成分识别并启动信号级联，介导不同的基因表达谱。研究表明，益生菌与 DC 诱导 IL-10 有很强的相关性[30]。

3. 肠道益生菌对肿瘤的形成及发展的预防与干预研究

3.1. 诱导 CRC 细胞的抗增殖和凋亡反应

细胞凋亡是 CRC 中肿瘤细胞死亡的基本途径之一。然而，癌细胞作用的重要途径之一是对细胞凋亡过程的负调控或抵抗[31]。在肿瘤中，大多数凋亡控制和生存途径都发生了不受欢迎的变化。这些变化主要发生在凋亡的主要调控因子中，包括 p53 [32]。大多数癌症中，p53 的突变转录因子控制细胞增殖的正常状态和保护基因组结构和基因毒性以及 NF-κB 和酪氨酸激酶受体，如表皮生长因子受体(EGFR)、血小板衍生生长因子受体和血管内皮生长因子受体[33]。此外，Bcl-2 家族抗凋亡蛋白的突变会抑制 BAD 等促凋亡蛋白，并抑制肿瘤细胞在肠道环境中生长和侵袭所诱导的 p53 上调凋亡调节剂 PUMA。在 CRC 小鼠模型中检测了含乳双歧杆菌(*Bifidobacterium lactis*, *B. lactis*)的耐药菌株的使用，在这些小鼠中，在有致癌物存在的情况下，在短时间内启动了凋亡过程。部分研究结果表明，Caco-2 细胞系在与 *L. rhamnosus*、双歧杆菌、大肠杆菌 K12 和米囊异养菌共培养期间发生凋亡[34]。丙酸杆菌(*Propionibacterium freudenreichii*)在结肠癌和胃癌细胞系中产生 SCFA，通过诱导细胞死亡来抑制细胞生长[35] [36]。在细胞死亡过程中，观察到 Caspase 3 的激活、氧自由基的产生和线粒体膜的通透性的改变。由于 LAB 的存在，饮用乳制品对预防和治疗 CRC 是有益的。乳酸菌对癌细胞的几种凋亡机制主要包括：1) 诱导癌细胞的细胞毒性作用；2) 分泌具有癌细胞毒性作用的特定代谢物；3) 调控凋亡基因，诱导癌细胞凋亡。

3.2. 修复肠道粘膜屏障

在健康的情况下，肠上皮与正常菌群相互协作，阻止致病菌、外来抗原和其他有害物质从肠腔进入体内[37]。粘膜通透性的破坏和改变是导致消化系统疾病的主要原因，同时也将导致微生物和病原体的入侵，这一屏障的一个重要组成部分是覆盖在上皮细胞的黏液层，包括黏液糖蛋白和三叶因子。黏液中含有多种黏液素，其中上皮黏液素 2 (MUC2)是由 MUC2 基因编码的，在健康炎症性肠病中起重要作用。研究表明，通过补充 LAB 抑制组蛋白去乙酰化酶(Histone Deacetylase, HDAC)可增加肠上皮细胞中 MUC2 的表达，而 LAB 代谢物丁酸盐暴露于结肠组织可导致粘液合成增加。注射乳酸菌代谢产物 SCFA 不仅可以增加 MUC2 的表达，还可以增加 MUC1、MUC3、MUC4 等其他黏液蛋白的表达[38]。

3.3. 乳酸菌对结肠癌的预防作用

LAB 作为肠道益生菌，常常与发酵的食品及饮品联系在一起[39]。LAB 的菌体可以附着在肠道上皮细胞上，通过产生有机酸和细菌素等抗菌物质来阻止有害微生物的生长，因此在肠道内可以帮助机体抵抗致病菌的侵袭从而发挥益生特性[40] [41]。此外，它们还可以通过活化巨噬细胞、NK 细胞以及释放多种细胞因子，从而增强非特异性细胞免疫反应。同时，它们还可以通过增加 IgA (+)细胞的数量来改善肠道黏膜免疫系统[42]。鉴于 LAB 的益生特性，同时又具有对人体无害等特点已被应用于食品、药品等多种领域；例如“复合乳酸菌胶囊”用于治疗腹泻。近年来，随着对 LAB 的深入研究，人们发现，其不仅具有抗菌特性，同时还具有抗癌的潜力。研究发现，将约氏乳杆菌*(Lactobacillus johnsonii*, *L. johnsonii*) BCRC17010 与结肠癌细胞 HT-29 进行共培养时，*L. johnsonii* BCRC17010 可以促进 HT-29 的凋亡途径中关键基因在转录水平和蛋白水平的表达，从而诱导了 HT-29 细胞的凋亡[43]。此外，干酪乳杆菌(*Lactobacillus casei*, *L. casei*)、鼠李糖乳杆菌(*Lactobacillus rhamnosus*, *L. rhamnosus*)、副干酪乳杆菌(*Lactobacillus paracasei*, *L. paracasei*)以及植物乳杆菌(*Lactobacillus plantarum*, *L. plantarum*)也分别被证实在细胞水平上可以对结肠癌细胞 HT-29 和 Caco-2 展示出抑制作用[44]-[46]。目前，Chikindas 等人甚至提议可以将乳酸链球菌所产生的细菌素 nisin 作为一种抗癌肽，因为它可以靶向作用于癌细胞上，其机制可能是由于在癌细胞的细胞膜上有其特异性的结合位点[45]。除此之外，还有诸多文献表明，LAB 可以通过不同的凋亡途径从而诱导黑色素瘤细胞和头颈部鳞状癌细胞的凋亡，进而达到抑制癌症的效果[47]-[49]。化学诱导动物模型的体内研究(1,2-二甲基肼，DMH；2,4,6-三硝基苯磺酸；TNBS；AOM；DSS；MNNG)并且基因敲除的动物模型提供的证据表明，给药 LAB 对 CRC 有显著的保护作用：1) 抗肿瘤和抗增殖活性；2) 减少异常隐窝病灶；3) 产生 SCFA；4) 下调促炎性细胞因子；5) 抑制病原体和致癌微生物；6) 调节免疫系统；7) 降低致癌酶的活性[18]-[22]。随着技术的进步和肠道微生物组研究的深入，为探索具有益生菌特性和抗 CRC 活性的新菌株提供了机会。

在过去的研究中，LAB 抗癌症的潜力主要是由于其具有抗癌细胞增殖、诱导癌细胞凋亡以及抗氧化性[50]；例如，LAB 可以与调控细胞周期的蛋白质相互作用，从而抑制癌细胞的增殖。虽然癌细胞往往对凋亡具有固有的抵抗力，但是 LAB 可以通过激活癌细胞的 Caspases 途径以及下调抗凋亡 Bcl-2 蛋白和上调促凋亡 Bax 蛋白来打破这种耐药性。这些细菌的抗癌作用也与它们在微生物群中的多途径作用有关[51]。然而，其抗癌作用的确切机制尚不清楚，仍需要进一步研究。

4. 总结

LAB 作为肠道菌群的成员之一，在肠道内达到一定的剂量时即可对宿主的健康起到益生作用。近年来，随着对 LAB 的深入研究，人们发现其功能不仅局限于抵抗致病菌和腐败菌，以及维持肠道微环境的稳态，从而减少疾病的发生，同时对结肠癌细胞的生长和转移也具有抑制作用。虽然已有大量文献支持

LAB 对 CRC 具有防控的潜力，但是对于 LAB 对 CRC 的治疗机制仍有待进一步的探讨。

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