特约评述

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益生菌辅助防治恶性肿瘤的研究进展

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摘要：癌症作为一个全球性公共卫生难题，其发病率和死亡率不断攀升。益生菌作为一种潜在的辅助防治恶性肿瘤的手段，近年来受到广泛关注。本文系统综述了益生菌在辅助防治恶性肿瘤方面的研究进展。在肿瘤预防方面，益生菌及其代谢产物可通过调控肠道菌群并抑制致癌物生成，调节免疫细胞，减轻炎症反应，降低癌症发生风险。此外，益生菌及其代谢产物短链脂肪酸（SCFA）、吲哚类化合物通过调节肿瘤微环境如调节癌症相关基因表达、PI3K-AKT信号通路及色氨酸-吲哚代谢途径发挥抗肿瘤作用。在辅助治疗恶性肿瘤方面，益生菌对消化系统、生殖系统等多种肿瘤均表现出抑制作用，可通过调节肿瘤微环境中的多种成分和功能，影响肿瘤细胞的增殖和凋亡。益生菌在改善肿瘤治疗副作用方面也发挥积极作用，既可以缓解肿瘤放化疗副作用，如减轻口腔黏膜炎、放射性腹泻等，又有助于肿瘤术后恢复，改善肠道屏障功能，减轻术后的炎症反应。合成生物技术的发展为益生菌的抗肿瘤应用提供了新方向。通过基因工程改造的益生菌，如大肠杆菌 Nissle 1917 和减毒沙门氏菌 VNP20009，已在肿瘤靶向治疗中展现出潜力。结合纳米技术和光动力治疗等新兴手段，益生菌在肿瘤治疗中的应用将更加精准和高效。然而，工程菌的安全性和有效性仍需进一步研究。随着合成生物学的发展，通过深入探索益生菌抗肿瘤的作用机制、优化临床应用方案，并结合新兴技术手段，工程益生菌有望成为肿瘤综合治疗中的重要组成部分，为患者提供更加安全、有效的治疗选择。

关键词：益生菌；肠道菌群；抗肿瘤；肿瘤微环境；合成生物学

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Advancements in the study of probiotics for adjunctive prevention and treatment of malignancies

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Abstract: Cancer continues to pose a significant global public health challenge, as its incidence and mortality rates

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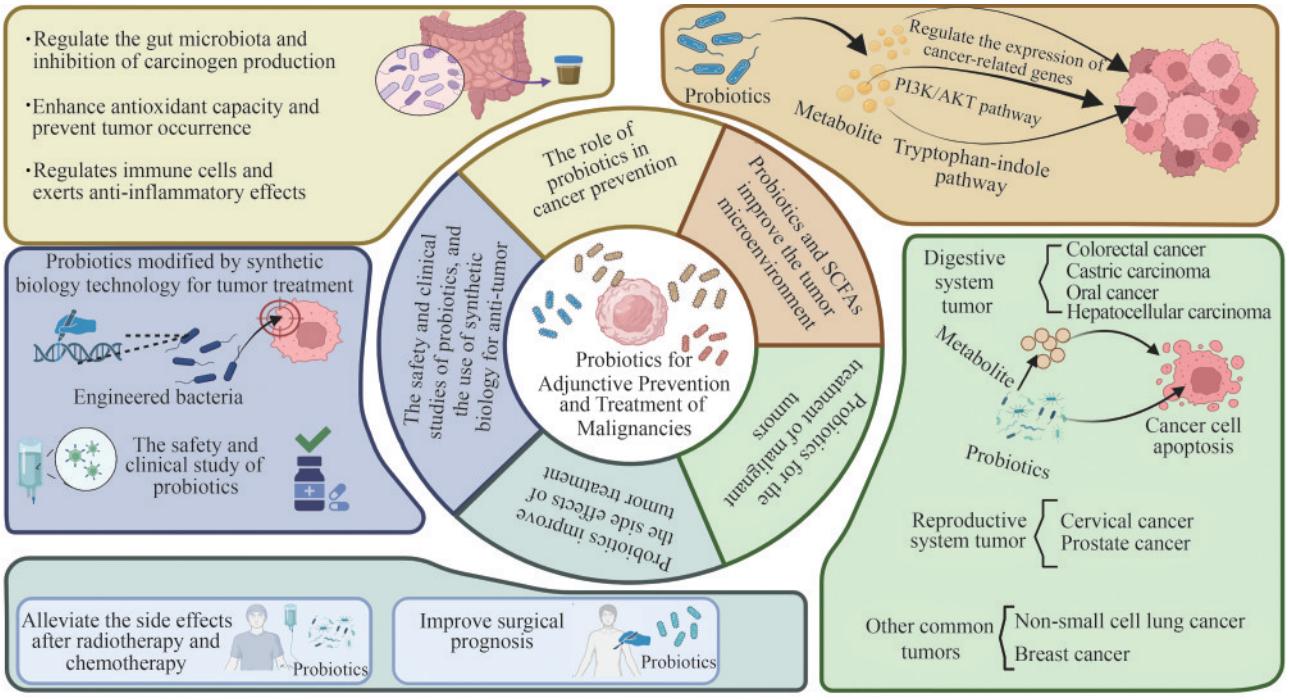
persistently rise. Conventional cancer treatments, which include chemotherapy, radiotherapy, and surgery, often involves severe side effects and potential drug resistance. This comprehensive review examines the pivotal role of probiotics in cancer prevention, treatment, and management, elucidating their underlying mechanisms and clinical applications. Probiotics, defined as beneficial microorganisms that colonize the human gastrointestinal tract and other mucosal surfaces, have emerged as potential adjuncts in the prevention and treatment of cancer . The mechanisms of action include modulating the tumor microenvironment (TME), enhancing immune responses, and inhibiting carcinogenesis. In cancer prevention, probiotics can modulate the gut microbiota to inhibit carcinogen generation. For example, specific strains of Lactobacillus and Bifidobacterium have been shown to decrease the activity of enzymes involved in carcinogen production, such as β -glucuronidase and nitroreductase. Moreover, Probiotics and their metabolites, such as short-chain fatty acids (SCFAs) and indole compounds, play an antitumor role by regulating the tumor microenvironment such as regulating cancer-related gene expression, the PI3K-AKT signaling pathway, and the tryptophan-indole metabolic pathway. In the context of adjuvant therapy for malignant tumors, probiotics have shown inhibitory effects on various cancers in the digestive and reproductive systems. They can modulate the intestinal microenvironment, influence tumor cell proliferation and apoptosis, and ultimately suppress tumor growth. Additionally, probiotics can alleviate the adverse effects of cancer therapies. For example, they can mitigate chemotherapy-induced diarrhea and radiation-induced mucositis, and promote postoperative recovery by enhancing gut barrier function and reducing inflammation. This review offers a comprehensive and systematic synthesis of research on the role of probiotics in the prevention and adjuvant treatment of malignant tumors. It delves into their potential mechanisms of action and explores their clinical applications, aiming to establish a solid theoretical foundation and practical guidance for the integrated management of cancer. Looking ahead, the integration of synthetic biology with probiotics holds significant potential for cancer therapy. Advances in synthetic biology have enabled the enhancement of the anti-tumor efficacy of probiotics through genetic engineering. Engineered strains, such as *Escherichia coli* Nissle 1917 and attenuated *Salmonella typhimurium* VNP20009, have shown potential in tumor-targeted therapy. When combined with emerging technologies such as nanotechnology and photodynamic therapy, the application of probiotics in cancer treatment is expected to become more precise and effective. However, the safety and efficacy of engineered probiotics require further validation, particularly regarding the potential risks associated with long-term use. Future



research should concentrate on personalized probiotic applications, the development of engineered strains, and their synergistic effects with other therapeutic modalities to advance this field. In conclusion, probiotics hold significant promise as adjuncts in cancer prevention and treatment, with the potential to modulate the TME, enhance immune responses, and alleviate treatment-related side effects. Further research is necessary to fully elucidate their mechanisms of action and optimize their clinical application, thereby facilitating their integration into comprehensive cancer care strategies.

Keywords: probiotics; intestinal flora; antitumor; tumor microenvironment; synthctic biology

癌症（cancer）主要指起源于上皮组织的恶性肿瘤，作为全球公共卫生领域的重大难题，其发病率和死亡率持续攀升，预计2040年死亡人数将增至2940万[1]。在我国，结/直肠癌、胃癌、乳腺癌等高发癌种的防治形势严峻[2]。放/化疗是癌症的主要治疗手段，但常伴随严重副作用和耐药性[3-5]，为了研究恶性肿瘤的发生与发展机制，肿瘤微环境（tumor microenvironment，TME）这一新兴领域弥补了目前在癌症发病机制上研究的不足。Truffi等[6]认为“肿瘤微环境并非只是癌症进展过程中的沉默旁观者，而是积极的推动者”。在肿瘤细胞生长过程中，肿瘤微环境会协调一系列活动，促进血管生成，并排出代谢废物[7]。同样，机体会针对这种异常现象做出反应，肿瘤细胞会被多种免疫细胞浸润，发挥抗肿瘤作用，抑制肿瘤细胞的增殖。因此，有研究者认为，肿瘤微环境中存在一些新的治疗干预靶点[8]。

益生菌是定植在消化道、口腔、生殖系统等部位，当摄入足够剂量后，通过自身及自身分泌的代谢产物来改变宿主某一部位微环境的有益微生物[9]。益生菌的主要特性包括耐酸性、耐胆汁性、免疫刺激作用、对病原体的拮抗活性、抗诱变活性[10-11]。研究表明，益生菌可通过调节肿瘤微环境中的多种成分和功能，预防癌症发生：①抑制有害肠道微生物群的生长[12-13]；②维持肠道屏障[14-15]；③降解潜在致癌物[16-17]；④调节免疫细胞及炎症因子[18-21]。在辅助治疗恶性肿瘤方面，益生菌对消化系统、生殖系统等多种肿瘤均表现出抑制作用，可通过调节肠道微环境，影响肿瘤细胞的增殖和凋亡，进而抑制肿瘤生长[22]。在改善肿瘤副作用方面，有研究发现益生菌在改善手术预后、减轻放/化疗副作用等方面具有积极作用[23]。值得注意的是，合成生物技术的突破为益生菌功能优化提供了新方向，通过基因编辑技术改造的工程菌已展现出肿瘤靶向治疗、免疫调控增强等功能，与纳米技术、光动力治疗等前沿手段的结合展现出精准治疗潜力。本文旨在全面、系统地综述益生菌在辅助防治恶性肿瘤方面的研究进展，深入剖析其潜在的作用机制，并展望合成生物技术改造工程菌的转化应用前景，以期为恶性肿瘤的综合防治提供理论支撑。

1 益生菌在肿瘤预防方面的作用

1.1 调控肠道菌群，抑制致癌物生成

肠道微生物通过与宿主的动态互作，在维持机体健康中发挥关键作用。益生菌通过竞争性排斥机制抑制有害菌过度增殖，抑制致癌物质生成，从而降低肿瘤发生风险[24]。研究表明，肠道中大肠杆菌与产气荚膜杆菌可通过偶氮还原酶（azoreductase）、β-葡萄糖醛酸苷酶（β-glucuronidase）以及硝基还原酶（nitroreductase）利用外来化合物将前致癌物转化为致癌物质，如4-氨基联苯、亚硝胺等[25]。Goldin等[26]发现，受试者在补充嗜酸乳杆菌（*Lactobacillus acidophilus*）后，粪便中的β-葡萄糖醛酸苷酶、硝基还原酶的活性显著降低，提示其具有抑制致癌物生成的潜力。

在食源性病原体相关致癌风险方面，沙门氏菌（*Salmonella*）、幽门螺杆菌（*Helicobacter pylori*，*Hp*）感染已被证实与胃癌发生相关。有研究已经证实沙门氏菌会增加癌症的发病风险[27-29]，

Buddhasiri 等[30] 研究发现罗伊氏乳杆菌（*Limosilactobacillus reuteri*）KUB-AC5可通过抑制沙门氏菌在肠道的定植，显著降低小鼠回肠中促炎基因及炎症因子（如*Kc*、*IL6*、*Nos2*、IFN-γ）表达，减轻了小鼠肠道炎症及全身性扩散，为胃癌预防提供了潜在干预策略。Chen等[31]开展的随机对照试验显示，嗜酸乳杆菌与鼠李糖乳杆菌GG（*Lactobacillus rhamnosus* GG，LGG）的联合使用可显著降低幽门螺杆菌丰度及^{13}C尿素呼气试验峰值浓度，提示了益生菌通过调控病原菌丰度实现肿瘤预防的机制。

1.2 提升抗氧化能力，预防肿瘤发生

机体抗氧化反应的改善与癌症预防密切相关，其核心在于抗氧化系统通过清除活性氧（ROS）、抑制脂质过氧化，提升抗氧化酶活性并增加抗氧化剂含量从而抑制肿瘤的发生[32]。如鼠李糖乳杆菌和嗜酸乳杆菌与益生元组合可通过提升超氧化物歧化酶（superoxide dismutase，SOD）、谷胱甘肽过氧化物酶（glutathioneperoxidase，GPx）活性及谷胱甘肽（glutathione，GSH）水平，显著降低大鼠结肠组织脂质过氧化产物丙二醛（malondialdehyde，MDA）含量，从而减轻DNA氧化损伤，降低肿瘤发生率[33]；发酵黏液乳杆菌GR-3（*Limosilactobacillus fermentum* GR-3）提升了小鼠结肠超氧化物歧化酶活性，增加谷胱甘肽含量，降低了结肠肿瘤的发生率[34]，提示了益生菌通过直接清除氧化产物、激活内源性抗氧化酶与抗氧化剂、提升了机体抗氧化能力，从而预防癌症发生，为癌症预防提供了潜在的干预策略。

1.3 调节免疫细胞，抑制炎症反应

炎症是机体对组织受到外界刺激（如感染或损伤）时产生的一种非特异性反应，在炎症反应过程中，炎性细胞被募集至受损部位，并释放多种免疫因子和细胞因子，以清除病原体、修复受损组织并维持机体稳态[35]，正常情况下，炎症反应是机体维持健康的必要机制，但当炎症持续时间过长或反应过度时，则可能促进癌症的产生[36-38]。在抑制癌症的发生与发展过程中，以T细胞为中心的免疫应答反应起着重要作用。自身免疫性肝炎（autoimmune hepatitis，AIH）是一种慢性炎症性肝病，已有研究证实自身免疫性肝炎患者的肝癌患病率增加[39]，Liu等[40]发现双歧杆菌（*Bifidobacterium*）与乳酸菌复合制剂可通过增加AIH小鼠体内调节性T细胞（regulatory T cells，Treg）数量并抑制炎症因子白细胞介素17A（interleukin 17A，IL-17A）、干扰素γ（interferon γ，IFN-γ）的释放，缓解了AIH小鼠的肝损伤，并抑制肝癌发生。

慢性溃疡性结肠炎与CRC的发生有关[41]，Bertkova等[42]发现用*N*,*N*-二甲基肼（DMH）诱导的结肠炎大鼠在摄入植物乳杆菌（*Lactobacillus plantarum*）6周后，与模型组相比降低了血清胆汁酸浓度、结肠内容物细菌酶活性以及白细胞介素6（interleukin 6，IL-6）的表达，增加肿瘤坏死因子α（tumor necrosis factor alpha，TNF-α）水平，增强了机体免疫能力，对DMH诱导的结肠癌具有预防作用。Li等[43]研究发现植物乳杆菌P8通过减轻炎症因子IL-6、TNF-α水平，上调紧密连接蛋白ZO-1、occludin和黏蛋白MUC-2，减少有害物质渗透，从而阻断结肠炎向肿瘤转化（表1）。

2 益生菌及其代谢产物的抗肿瘤机制

2.1 调控癌症相关基因表达

肿瘤微环境（TME）近年来成为研究癌症发病机制与治疗方法的热点，而益生菌及其代谢产物如短链脂肪酸（short-chain fatty acid，SCFA）可通过调节肿瘤微环境间接或直接发挥抗肿瘤作用[44-46]。人体内SCFA主要生成部位是结肠，且近端结肠浓度最高，SCFA主要来源于肠道中厌氧细菌对肠道内纤维和不可消化糖（不可消化多糖和抗性淀粉）的发酵[47-51]，主要有乙酸（60%）、丙酸（25%）、丁酸及戊酸（15%）[52-54]，其中戊酸主要由蛋白质衍生的支链氨基酸缬氨酸分解代谢产生[55]。

目前研究已证实，以丁酸盐和戊酸盐为代表的短链脂肪酸主要通过以下3种方式发挥抗肿瘤活性（图1）：

表1 益生菌肿瘤预防方面的作用

Table 1 The role of probiotics in tumor prevention

功能	菌种	剂量	疾病	研究对象	研究结果	参考文献
抑制致癌物质生成	嗜酸乳杆菌	10^{10}个/(mL·d)	—	人	β-葡萄糖醛酸苷酶活性↓、硝基还原酶活性↓	[26]
调节肠道菌群	罗伊氏乳杆菌KUB-AC5	10^9 CFU/d	沙门氏菌感染	C57BL/6小鼠	沙门氏菌数量↓、*Kc*、*IL6*、*Nos2*、IFN-γ↓	[30]
	嗜酸乳杆菌、鼠李糖乳杆菌	6×10^9 CFU/d	*Hp*感染	人	幽门螺杆菌丰度↓	[31]
提升抗氧化能力，预防肿瘤发生	嗜酸乳杆菌、鼠李糖乳杆菌	1×10^9 CFU/(0.1mL·d)	CRC	CRC大鼠感染前服用益生菌	SOD、GPx、GSH↑、MDA↓、肿瘤发生率↓	[33]
	发酵黏液乳杆菌GR-3	1×10^9 CFU/d	CRC	C57BL/6小鼠	SOD、GSH↑、MDA↓，肿瘤发生率↓	[34]
调节免疫细胞，发挥抗炎作用	双歧杆菌与乳酸菌混合	1×10^9 CFU/(kg·d)	AIH	C57BL/6小鼠	Treg↑、ALT↓、AST↓、IL-17A↓、IFN-γ↓、TGF-β↑	[40]
	植物乳杆菌	3×10^9 CFU/mL	结肠炎	Wistar大鼠	TNF-α↑，IL-6↓	[42]

注：Kc、*IL6*、*Nos2*—回肠促炎基因；*Hp*—幽门螺杆菌（*Helicobacter pylori*）；CFU—菌落形成单位；SOD—超氧化物歧化酶；GPx—谷胱甘肽过氧化物酶；GSH—谷胱甘肽；MDA—丙二醛；Treg—调节性T细胞；ALT—谷丙转氨酶；AST—谷草转氨酶；IL-17A—白细胞介素17A；IFN-γ—干扰素-γ；TGF-β—转化生长因子-β；IL-6—白细胞介素6；TNF-α—肿瘤坏死因子α。

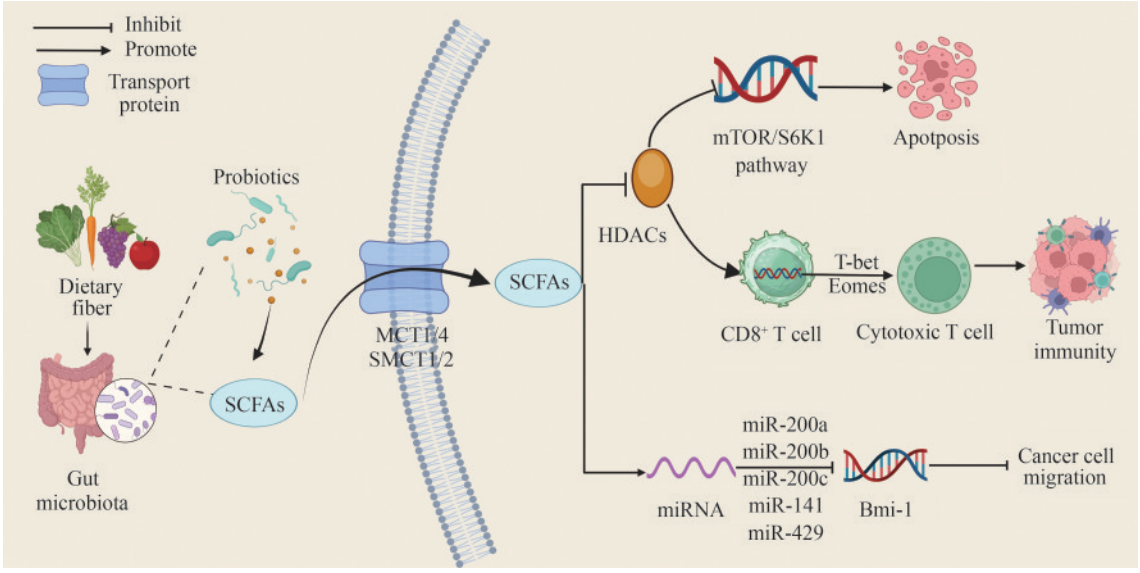


图1 益生菌代谢产生的短链脂肪酸作用于肿瘤微环境的机制

[短链脂肪酸（SCFA）是肠道微生物群通过膳食发酵产生的主要代谢产物，主要通过单羧酸转运蛋白（monocarboxylate transporter，MCT）及Na^+偶联单羧酸转运蛋白（sodium-coupled monocarboxylate transporter，SMCT）进入细胞，直接抑制组蛋白去乙酰酶（HDAC）的活性，可通过mTOR/S6K1信号通路促进肿瘤细胞凋亡。同时，抑制HDAC活性也可促进$CD8^+$ T细胞分化为细胞毒性T淋巴细胞（CTL），增强抗肿瘤免疫能力]

Fig. 1 Mechanism of SCFAs produced by probiotic metabolism acting on the tumor microenvironment

[Short-chain fatty acids (SCFAs) are the main metabolites produced by gut microbiota through dietary fermentation. They enter cells primarily via monocarboxylate transporters (MCTs) and sodium-coupled monocarboxylate transporters (SMCTs), directly inhibiting the activity of histone deacetylases (HDACs) and promoting tumor cell apoptosis through the mTOR/S6K1 signaling pathway. Meanwhile, inhibition of HDAC activity can also promote the differentiation of $CD8^+$ T cells into cytotoxic T lymphocytes (CTLs), thereby enhancing anti-tumor immune capacity.]

（1）抑制HDAC的表达[56] 近期研究表明组蛋白的表达后修饰与肿瘤的发生与发展有关，组蛋白的修饰主要有甲基化、乙酰化、磷酸化等，其中，组蛋白去乙酰化酶（HDAC）和组蛋白乙酰

转移酶（HAT）是关键的表观遗传调节剂[57]，且HDAC在肿瘤细胞中表现出过表达的现象[58]，并与肿瘤免疫相关[59]。SIRT1是HDAC家族蛋白之一，其过表达可导致mTOR/S6K1通路的激活，对肿瘤细胞的增殖有促进作用，而丁酸盐可降低SIRT1的过表达从而抑制mTOR/S6K1通路，促进肿瘤细胞凋亡[60]。

（2）抑制HDAC表达并调节肿瘤微环境中的免疫细胞的转录[61] $CD8^+$ T细胞是抗肿瘤免疫应答的主要执行者，研究发现益生菌代谢产生的戊酸盐可抑制HDAC的活性，从而增加了$CD8^+$ T细胞中细胞毒性T淋巴细胞（cytotoxic T lymphocyte，CTL）转录因子T-bet、Eomes的表达水平，使得CTL细胞比例增加，增强抗肿瘤免疫应答能力[62]。

（3）影响癌症相关基因表达[63] miR-200家族成员可调控癌症相关基因的表达，靶标基因包括*Bmi-1*、*EZH2*、*ZEB2*等[64]，上述基因在肿瘤细胞中都存在异常表达的现象[65-66]，丁酸钠可通过上调miR-200家族的基因表达从而抑制*Bmi-1*基因的表达，使得结肠癌细胞的迁移率降低，体内实验也表明丁酸钠可显著减小肿瘤质量与体积[67]。

2.2 PI3K-AKT信号通路

磷脂酰肌醇3-激酶/蛋白激酶B（PI3K-AKT）信号通路在癌症发生发展中起核心调控作用，其异常调节与肿瘤的发展密切相关，其中，PI3K-AKT的过度活化会导致抗凋亡蛋白（如Bcl-2）的高表达从而抑制肿瘤细胞凋亡，并且还可与下游mTOR信号通路偶联从而促进肿瘤细胞中蛋白质的合成。总的来说，PI3K-AKT的过度激活可促进细胞增殖、抑制凋亡、诱导血管生成及增强侵袭转移能力，推动肿瘤进展[68-69]。

研究表明，益生菌可通过干预PI3K-AKT信号通路发挥抗癌作用，其主要机制包括（图2）：

（1）调控AKT上游蛋白PI3K、PTEN表达水平 PTEN作为抑癌基因，上调其表达水平可使得AKT活性降低；PI3K作为AKT的上游蛋白，下调其表达可抑制第二信使PIP3招募PDK1与AKT蛋白至质膜，避免了AKT的过度活化，进而抑制抗凋亡蛋白Bcl-2的表达，促进肿瘤细胞凋亡[70-74]。

（2）抑制PI3K/AKT/mTOR通路 mTOR作为AKT的下游蛋白，可促进细胞中蛋白质的合成，加剧肿瘤细胞的增殖，而通过抑制PI3K/AKT/mTOR的表达则抑制了这一过程，从而促进肿瘤细胞自噬[75-76]。

2.3 色氨酸的代谢通路——吲哚途径

色氨酸是人体内的必需氨基酸，可经过肠道微生物的作用代谢成吲哚。具体而言，是指在肠道微生物菌群的作用下，膳食色氨酸可在益生菌的作用下经脱氨、脱羧等反应生成吲哚及其衍生物，如吲哚、吲哚乙酸等，此类代谢产物可参与肿瘤免疫[77]。益生菌代谢色氨酸产生的吲哚-3-乙酸（indole-3-acetic acid，3-IAA）可增强癌症化疗效果，具体而言，3-IAA被中性粒细胞来源的髓过氧化物酶（myeloperoxidase，MPO）氧化，并结合化疗诱导活性氧降解酶谷胱甘肽过氧化物酶3（glutathione peroxidase 3，GPX3）和谷胱甘肽过氧化物酶7（glutathione peroxidase 7，GPX7）的表达下调，导致癌细胞中ROS的积累和自噬的下调，从而损害了癌细胞的代谢适应性，最终抑制癌细胞的增殖[78]。此外，益生菌代谢产生的吲哚-3-醛（indole-3-carboxaldehyde，I3A）可通过作用于肿瘤微环境中的$CD8^+$ T细胞，激活芳香烃受体（AhR），促进产生IFN-γ的$CD8^+$ T细胞分化和效应功能，增强免疫检查点抑制剂（immune checkpoint inhibitor，ICI）疗效，为癌症治疗提供新策略和潜在生物标志物[79]。总的来说，益生菌通过代谢色氨酸产生的吲哚类化合物为癌症治疗提供新了方向（图3）。

3 益生菌对恶性肿瘤辅助治疗的功效

目前，益生菌对恶性肿瘤的治疗功效的研究分为基础研究和临床治疗两方面，在基础研究层面，动物实验设计通常采用益生菌单药干预方案或与益生元协同作用以系统评估其抗肿瘤活性及作用机制；而临床治疗中，益生菌多作为辅助治疗手段与常规抗肿瘤药物形成联合治疗方案，益生菌对不同种类的恶性肿瘤的治疗功效如下：

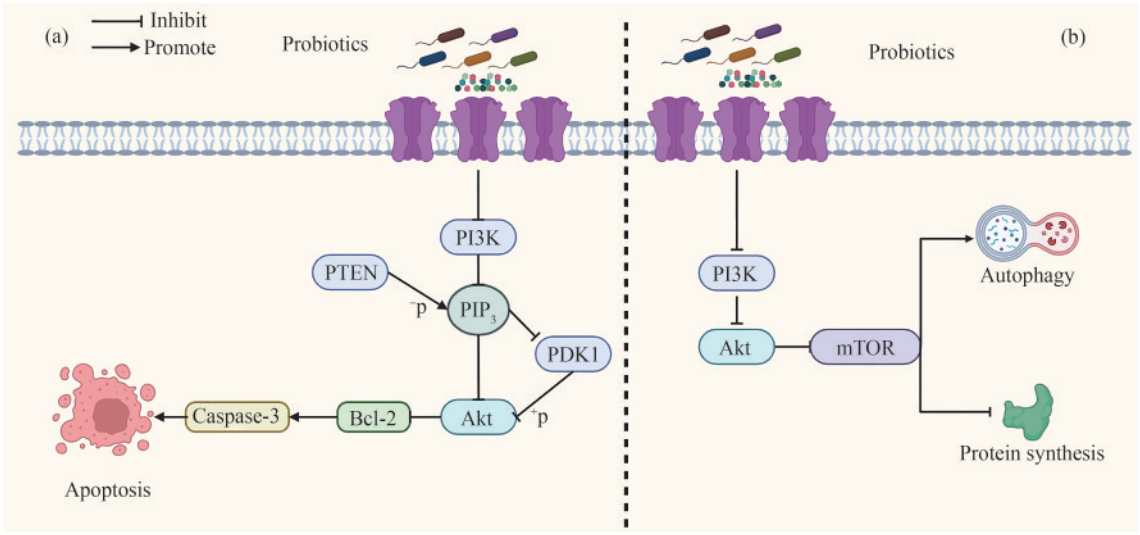


图 2　益生菌及其代谢产物通过 PI3K-AKT 信号通路发挥抗肿瘤活性机制

[（a）益生菌通过调控 PI3K、PTEN、PDK1 表达，进而下调 AKT 表达，抑制 Bcl-2 产生，从而促进在细胞凋亡中起核心作用的蛋白酶 Caspase-3 表达上升，促进肿瘤细胞凋亡。（b）益生菌通过 PI3K/AKT/mTOR 信号通路，促进肿瘤细胞自噬及抑制肿瘤细胞合成蛋白质，从而发挥抗肿瘤作用]

Fig. 2　The mechanism of anti-tumor activity of probiotics and their metabolites through the PI3K-AKT signaling pathway

[(a) Probiotics regulate the expression of PI3K, PTEN, and PDK1, thereby downregulating AKT expression and inhibiting the production of Bcl-2. This promotes an increase in the expression of Caspase-3, a protease that plays a central role in cell apoptosis, and thus induces apoptosis of tumor cells. (b) Probiotics exert anti-tumor effects by promoting autophagy of tumor cells and inhibiting protein synthesis in tumor cells through the PI3K/AKT/mTOR signaling pathway.]

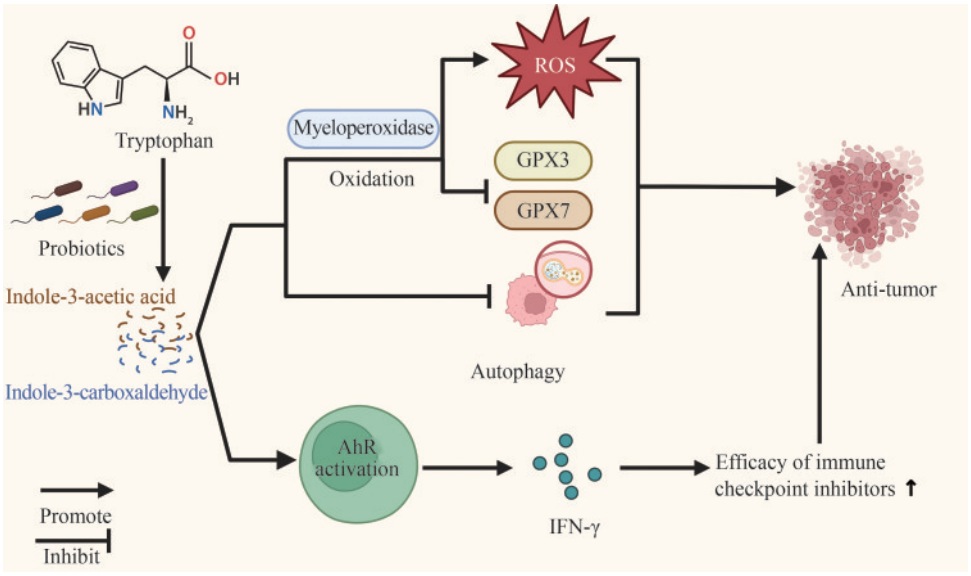


图 3　益生菌通过代谢色氨酸产生吲哚类化合物发挥抗肿瘤活性机制

Fig. 3　Mechanism diagram of how probiotics exert antitumor activity by metabolizing tryptophan to produce indole compounds

3.1　消化系统肿瘤

3.1.1　结直肠癌

近年来，结直肠癌（colorectal cancer，CRC）已成为消化系统疾病中较为突出的肿瘤病症，是美国的第三大常见癌症[1]。研究证实益生菌通过多种途径干预 CRC 进程，例如，副干酪乳杆菌（*Lacticaseibacillus paracasei*）的活性成分展现出显著抗肿瘤特性[80]，其分泌的细胞外囊泡（*Lp*EV）通过抑制 PDK1/AKT/Bcl-2 信号通路，有

效阻断结肠癌细胞增殖与迁移[72]。肠道罗斯拜瑞氏菌（*Roseburia intestinalis*）与结直肠癌细胞HCT116、LoVo、SW480共培养可显著抑制肿瘤细胞的活力[81]，并且肠道罗斯拜瑞氏菌代谢产生的丁酸盐可抑制结直肠癌的发生，降低了结直肠癌小鼠的肿瘤发生率，同时结肠组织中紧密连接蛋白ZO-1和Claudin-3的蛋白表达显著增加，改善了肠道的屏障功能[82]。T细胞在肿瘤免疫过程中发挥重要作用，而肠道微生物可激活肿瘤微环境中的免疫细胞[83]，从而提升肿瘤免疫能力。例如Engevik等[84]从健康受试者粪便中分理出11种稀有菌株，分别是：*Parabacteroides distasonis*、*Parabacteroides gordonii*、*Alistipes senegalensis*、*Parabacteroides johnsonii*、*Paraprevotella xylaniphila*、*Bacteroides dorei*、*Bacteroides uniformis* JCM 5828、*Eubacterium limosum*、*Ruminococcus bacterium* cv2、*Phascolarctobacterium faecium*、*Fusobacterium ulcerans*。这些菌株能够增强树突状细胞（dendritic cell，DC）中MHC-Ⅰ类的表达，激活IFN-γ+ $CD8^+$ T细胞，增加IFN-γ+ $CD8^+$ T细胞的数量，以抑制CRC的生长。临床研究进一步验证了益生菌辅助治疗结直肠癌的功效，例如在化疗期间服用双歧杆菌的结肠癌患者，免疫功能指标（$CD3^+$、$CD4^+$、$CD4^+/CD8^+$）提升，且两年生存率更高[85]。此外，副干酪乳杆菌SD1与LGG SD11联合使用后，与安慰剂组相比，结直肠癌患者的促炎细胞因子（IL-1β、TNF-α、IL-6、IL-8、IL-17A）水平显著降低，抗炎细胞因子（IL-10、IL-12）水平显著升高，肠液中的乙酸、丙酸、丁酸较治疗前有显著增加[86]。上述研究表明，益生菌通过调控肠道菌群、免疫调节、促进细胞凋亡等方面发挥抑制结肠癌发展的作用。

3.1.2 胃癌

胃癌（gastric carcinoma，GC）作为全球第五大常见恶性肿瘤及第四大致死性癌症[87]，其发病机制与胃肠道微生物的失衡密切相关，其中幽门螺杆菌被明确为关键致癌因子[88]，该菌通过诱发慢性炎症反应和改变胃肠道环境，促进胃黏膜病变[40]。近年来，益生菌的拮抗作用为胃癌防治提供了新视角，尤其是其在降低幽门螺杆菌在胃肠道内定植方面有着研究潜力，Abedi等[89]发现布氏乳杆菌（*Lactobacillus buchneri*）通过分泌含细菌素的无细胞上清液可选择性抑制*Hp*定植并可上调促凋亡基因*Bax*、*Caspase-3*和*Caspase-9*的表达，诱导胃癌细胞启动凋亡程序。Yu等[90]发现健康个体肠道菌群代谢产物如丁酸盐和乙酸盐可增加人胃癌细胞系SNU-216、MGC-803、HGC-27凋亡率，并抑制了人胃黏膜上皮细胞GES-1中与凋亡相关蛋白BAX、Bcl-2、Caspase-3的表达，显著增强了抗凋亡蛋白Bcl-2的表达，在保护胃黏膜的同时促进了胃癌细胞的凋亡。Han等[91]对人胃癌患者的粪便样本进行菌群分析，发现乳酸菌属（*Lactobacillus*）高丰度患者在接受PD-1/PD-L1［抗程序性死亡受体1（programmed death 1，PD-1）/程序性死亡配体1（programmed death-ligand 1，PD-L1）］抑制剂治疗时无进展生存期（progression-free-survival，PFS）显著延长，机制上可能与增强氨基酸代谢通路及重塑肠道菌群多样性相关，这为益生菌辅助肿瘤免疫治疗提供了分子层面的证据支持。上述研究共同揭示了益生菌通过拮抗病原菌、调控细胞凋亡和改善免疫微环境等机制干预胃癌进程的潜力。

3.1.3 口腔癌

口腔癌（oral cancer）是南亚、东南亚、西太平洋大部分地区男性癌症死亡的常见原因[92]。研究显示，益生菌与植物活性成分的协同作用可提升抗肿瘤效果，例如，近期对口腔癌细胞HSC-3的一项研究表明栀子苷和LGG联合用药可上调肿瘤细胞相关凋亡基因的表达并增加HSC-3的凋亡率，效果尤其高于单独使用栀子苷处理HSC-3组[93]。*MAPK*基因和*PTEN*基因分别促进和抑制癌症的发展进程，另一项研究报道了植物乳杆菌对人口腔表皮样癌细胞KB的抑制作用，植物乳杆菌通过上调*PTEN*基因和下调*MAPK*基因在口腔癌细胞的信号转导过程中发挥作用[94]。植物乳杆菌ATCC 8014抑制了口腔癌大鼠中Bcl-2的表达，并逆转了癌症导致的体重减轻[95]。目前，益生菌在口腔癌的研究多局限于体外和动物实验，缺乏临床研究验证其实际效果，但益生菌仍具有辅助治疗口腔癌的应用潜力。

3.1.4 肝细胞癌

肝细胞癌（hepatocellular carcinoma，HCC）是最常见的原发性肝癌类型，预计在未来10年内HCC的发病率将持续上升[96]。研究表明，益生菌及其代谢产物在HCC的发病机制及其治疗中发挥着重

要作用。乙酸盐是益生菌代谢产物中常见物质之一，Hu等[97]研究发现HCC小鼠血清中的乙酸盐水平较野生型小鼠更低，因此将经罗伊氏乳杆菌灌胃的无菌小鼠的粪便样本制备成混悬液后，对HCC小鼠进行口服灌胃治疗，发现HCC小鼠肝脏肿瘤的数量和相对大小均减少，谷丙转氨酶（ALT）与谷草转氨酶（AST）的水平均显著降低，且血清中的乙酸盐水平有显著增加，这表明罗伊氏乳杆菌衍生的乙酸可在HCC小鼠中发挥抗癌作用。Srikham等[98]从母乳中分理出了唾液链球菌（*Streptococcus saliva*）BP8、BP156、BP160，发现这些菌株对HepG2细胞增殖有显著抑制作用，能诱导癌细胞DNA片段化，使得细胞凋亡。IL-17作为Th17细胞的标志性细胞因子，已被证明与HCC患者肿瘤血管生成的发展有关，Th17极化是肿瘤发生过程中的一个关键因素[99-100]。研究发现，摄入益生菌可以减少Th17极化[14]，Khedr等[101]发现嗜酸乳杆菌ATCC 4356通过抑制炎症相关的TLR2/STAT-3/P38-MAPK通路，减少IL-17生成，从而减轻HCC的发展进程。临床研究中，鼠李糖乳杆菌Probio-M9能延长PD-1抑制剂在治疗不可切除肝癌患者的总生存期、客观缓解率、疾病控制率、手术转化率及无进展生存期[102]。

表2中列举了一些益生菌对常见消化系统肿瘤的抑制作用。

3.2 生殖系统肿瘤

3.2.1 宫颈癌

宫颈癌（cervical cancer）是全球女性第二大癌症死亡原因，多由高危型HPV感染引起[103-104]，诸多研究已证明益生菌在预防宫颈癌方面的有效性[105-106]，Liu等[107]发现卷曲乳杆菌Chen-01（*Lactobacillus crispatus* Chen-01）可显著降低感染高危型HPV病毒载量，重构阴道菌群使其接近于健康人群，并改善了阴道炎症，从而防治宫颈癌的发生。Riaz Rajoka等[108]发现干酪乳杆菌和副干酪乳杆菌能降低宫颈癌细胞中的Bcl-2，增加*Bax*基因的表达，并且宫颈癌细胞具有细胞毒性。在另一

表2 益生菌对常见消化系统肿瘤的抑制作用

Table 2 Inhibitory effect of probiotics on common digestive system tumors

肿瘤类型	菌种/代谢产物	研究结果	参考文献
结直肠癌	副干酪乳杆菌PC-H1	PDK1和AKT↓，Bcl-2↓，细胞凋亡率↑	[72]
	肠道罗斯拜瑞氏菌	肿瘤发生率↓，ZO-1↑，Claudin-3↑，CDK6↓	[82]
	11种从粪便中分离的细菌	MHC-Ⅰ↑，IFN-γ+ $CD8^+$ T细胞↑	[84]
	双歧杆菌	$CD3^+$、$CD4^+$、$CD4^+/CD8^+$↑，D-乳酸、二胺氧化酶↓	[85]
	副干酪乳杆菌SD1与鼠李糖乳杆菌SD11	IL-1β、TNF-α、IL-6、IL-8、IL-17A↓，IL-10、IL-12↑，SCFA↑	[86]
胃癌	布氏乳杆菌/无细胞上清液	BAX、Caspase-3、Caspase-9↑，细胞凋亡率↑	[89]
	健康人群的粪便菌群/乙酸盐、丁酸盐	SNU-216、MGC-803、HGC-27凋亡率↑，GES-1细胞中BAX、caspase-3、Bcl-2↑	[90]
口腔癌	鼠李糖乳杆菌	Caspase-3、Caspase-8、Caspase-9、BAX、p53、p21、Fas↑，Bcl-2、Bcl-xL↓，HSC-3抑制率↑	[93]
	植物乳杆菌	PTEN↑，MAPK↓	[94]
	植物乳杆菌ATCC 8014	Bcl-2、TLR4、NFκB↓	[95]
肝细胞癌	罗伊氏乳杆菌	ALT、AST↓，IL-17A↓，乙酸盐↑	[97]
	嗜酸乳杆菌ATCC 4356	ALT↓，TLR2、STAT-3、P38-MAPK↓，IL-17↓	[101]
	鼠李糖乳杆菌Probio-M9	客观缓解率、疾病控制率、无进展生存期、总生存期、手术转化率↑	[102]

注：PDK1—丙酮酸脱氢酶激酶同工酶1；AKT—蛋白激酶B；Bcl-2—B淋巴细胞瘤-2基因；MHC-Ⅰ—主要组织相容性复合体Ⅰ；$CD3^+$—$CD3^+$ T淋巴细胞；$CD4^+$—$CD4^+$ T淋巴细胞；$CD8^+$—$CD8^+$ T淋巴细胞；IL-1β—白介素1β；IL-8—白介素8；IL-10—白介素10；IL-12—白介素12；SCFA—短链脂肪酸；ZO-1、Claudin-3—结肠组织紧密连接蛋白；CDK6—细胞周期蛋白依赖性蛋白激酶6；BAX、Caspase-3、Caspase-8、Caspase-9—凋亡相关蛋白；Bcl-xL—Bcl-2家族蛋白；PTEN—肿瘤抑制因子；MAPK—丝裂原活化蛋白激酶；TLR4—Toll样受体4；NF κB—核转录因子κB；ALT—谷丙转氨酶；IL-17—白介素17；IL-17A—白介素17A；TLR2—Toll样受体2；STAT-3—信号转导和转录激活因子3；p38-MAPK—丝裂原活化蛋白激酶。

项研究中，研究人员从健康女性阴道菌群中分离出的加氏乳杆菌G10（*Lactobacillus rhamnosus* G10）、加氏乳杆菌H15（*Lactobacillus rhamnosus* H15）产生的胞外多糖（EPS）能够抑制HeLa细胞的增殖[109]。益生菌可通过调节免疫反应抑制宫颈癌的发展，如干酪乳杆菌（*Lactobacillus casei*）、植物乳杆菌、LGG和嗜酸乳杆菌联合使用可激活NK细胞和树突状细胞成熟[110]来发挥抗宫颈癌作用。Abdolalipour等[111]发现干酪乳杆菌TD-2可增强免疫调节剂的抗肿瘤活性，增强了肿瘤内肿瘤坏死因子相关凋亡诱导配体（TNF-related apoptosis-inducing ligand，TRAIL）介导的凋亡，并减少了免疫和炎症反应抑制因子IL-10的产生。总的来说，益生菌可通过重塑阴道菌群、宫颈癌细胞凋亡、增强免疫因子的抗癌活性辅助治疗宫颈癌。

3.2.2 前列腺癌

在全球范围内，前列腺癌（prostate cancer）是男性发病率第二高的恶性肿瘤，且在全球新发病癌症中位列第五[112]。Rosa等[113]发现添加了嗜酸乳杆菌La-03对前列腺癌细胞系（PC-3和DU-145），有抑制作用，增加了前列腺癌细胞系的凋亡率，活细胞数减少，激活癌细胞的凋亡程序，促使癌细胞凋亡。Celebioglu[114]发现，LGG与水杨酸联合作用可使癌细胞周围的微环境酸化，显著降低了人前列腺癌细胞PC-13的细胞活性，这表明益生菌具有抑制前列腺癌的潜力。

3.3 其他常见恶性肿瘤

肺癌在恶性肿瘤中所占比例较高，非小细胞型肺癌（non-small cell lung cancer，NSCLC）作为最常见的肺癌类型，具有高发病率和死亡率的特点[115]。既往研究发现，益生菌可作为癌症治疗的辅助手段来提高疗效，Gui等[116]在肺癌小鼠模型中，嗜酸乳杆菌与抗癌药物顺铂联合使用，增强了顺铂对癌症相关基因，如*VEGFA*、*Bax*等基因的调控效果，促进$CD8^+$ T细胞中相关免疫基因表达，减小了肿瘤体积并提高了生存率。这表明顺铂的抗肿瘤特性，如促凋亡和抗增殖活性，有望通过引入益生菌得到增强。益生菌与癌症常见疗法联合使用已在临床上有研究，Daillère等[117]研究发现接受海氏肠球菌（*Enterococcus hirae*）和肠巴氏杆菌（*Barnesiella intestinihominis*）联合铂类化疗药物治疗的晚期肺癌患者有更长的无进展生存时间。Tomita等[118]发现118名NSCLC晚期患者在接受免疫检查点阻断（immune checkpoint blockade，ICB）联合酪酸梭菌（*Clostridium butyricum*）治疗后，患者的无进展生存时间和5年总体生存率显著延长。

乳腺癌（breast cancer，BC）是全球女性最常见的肿瘤之一，尽管在诊断和治疗方面取得了重大进展，但每年仍有4万多人死亡[119]。诸多研究表明，益生菌干预可诱导癌细胞凋亡并抑制其增殖。益生菌代谢产物的生物活性受到越来越多的关注，Ayyash等[120]从骆驼奶中分离了一种新型植物乳杆菌C70，以其产生的胞外多糖（EPS）为研究对象，发现EPS-C70有较强的抗氧化活性，并且在浓度为10 mg/mL时，对乳腺癌细胞系的细胞毒性高达73.1%，其机制可能是EPS与癌症生长因子在癌症细胞膜受体上的竞争、诱导细胞凋亡或坏死、抑制基因转录或细胞增殖的能力有关。Hassan等[121]从健康女性母乳中分离出了粪肠球菌1053（*Enterococcus faecalis* UPM 1053）可影响人乳腺癌细胞系MCF-7的G0/G1期，抑制细胞增殖，诱导乳腺癌细胞凋亡。临床研究中，益生菌常与放化疗结合用于治疗乳腺癌，提升肿瘤免疫能力和减轻机体炎症反应，如凝结芽孢杆菌（*Bacillus coagulans*）可提升乳腺癌患者肿瘤免疫效果，$CD4^+/CD8^+$细胞比例显著提升[122]。双歧杆菌可增加患者体内中$CD3^+$、$CD4^+$、$CD4^+/CD8^+$细胞比例，炎症因子IL-6、IL-8、TNF-α的水平显著降低[123]。总的来说，益生菌可诱导癌细胞凋亡并抑制其增殖，减轻炎症反应，并提升机体肿瘤免疫能力，从而治疗乳腺癌。

4 益生菌对肿瘤治疗副作用改善效果的影响

4.1 益生菌对肿瘤放/化疗副作用的缓解效果

迄今为止，放/化疗仍然是治疗癌症的最常见的方式，但副作用较大，同时肿瘤复发率、转移率较高。目前体内外研究已证实益生菌具有抗炎、

抗增殖和抗病原体等性质。因此，一些学者对接受放/化疗的癌症患者展开观察研究，结果表明，放疗会损伤患者原有的微生物群[124]，导致多种并发症的发生[125-127]，益生菌减轻放/化疗副作用主要包括：

（1）口腔黏膜炎　如植物乳杆菌MH-301、鼠李糖乳杆菌LGG-18可降低鼻咽癌患者口腔黏膜炎的严重程度[128]；长双歧杆菌（*Bifidobacterium longum*）、乳杆菌（*Lactobacillus*）和粪肠球菌可显著降低头颈部肿瘤患者放化疗后口腔黏膜炎的发生率[129]。

（2）放射源性腹泻（RID）　嗜酸乳杆菌LA-5与动物双歧杆菌乳亚种BB-12（*Bifidobacterium animalis* subsp. *lactis* BB-12）可减轻盆腔外放疗患者的腹泻发生[130]；植物乳杆菌YS4、罗伊氏乳杆菌LR06、罗伊氏乳杆菌LR08、加氏乳杆菌LG019、嗜酸乳杆菌LA16、动物双歧杆菌BLa019、短双歧杆菌（*Bifidobacterium breve* strain）、长双歧杆菌、鼠李糖乳杆菌、瑞士乳杆菌LZ-R-5（*Lactobacillus helveticus* LZ-R-5）组成的混合菌剂可显著降低放化疗后癌症患者腹泻发生率，并显著降低厌氧菌的丰度；短双歧杆菌Yakult、干酪乳杆菌代田株（*Lactobacillus casei* strain Shirota）可降低放疗后癌症患者腹泻发生率，且粪便中的双歧杆菌属、总乳杆菌属和干酪乳杆菌亚群的菌属的丰度有所提升[131]。

4.2　益生菌对肿瘤术后恢复效果的影响

对于肿瘤手术患者，术后应激会引起肠通透性增加、肠道生态失调、细菌易位等，是增加术后感染的重要致病因素，益生菌可通过减轻炎症反应、恢复肠道通透性的方式减轻肿瘤术后副作用[132-133]。临床研究中，胃癌患者在术前服用由婴儿双歧杆菌（*Bifidobacterium infantis*）、嗜酸乳杆菌、粪肠球菌、蜡样芽孢杆菌（*Bacillus cereus*）组成的复合益生菌制剂，结果显示与未补充益生菌组相比，术前补充益生菌显著降低了胃切除术后的白细胞水平、空腹血糖水平、空腹胰岛素水平，从而减轻胃癌术后的炎症反应[134]；术前服用酪酸梭菌（*Clostridium butyricum*）可显著增加肠黏膜屏障功能指标（MUC2、SIgA）的表达水平，修复了肠黏膜屏障功能，降低结直肠癌患者黏膜通透性[135]。腹腔镜肝癌术后胃肠功能障碍患者在治疗过程中服用双歧杆菌活菌胶囊后肠黏膜屏障（D-乳酸、降钙素原、二胺氧化镁）指标显著升高，且胃肠道并发症发生率降低[136]。

5　益生菌的临床疗效及安全性评价研究进展

益生菌作为活的微生物制剂，其安全性与临床研究进展已成为当前医学与营养学领域的研究热点。益生菌的安全性评价与临床研究进展已形成较为系统的科学认知体系，其安全风险主要集中在潜在致病性、代谢产物毒性、耐药基因转移及特殊人群应用风险等方面。国际上主要采用欧洲安全资格认证（QPS）和美国公认安全（GRAS）体系进行微生物安全性评估，我国通过《可用于食品的菌种名单》《可用于婴幼儿食品的菌种名单》等法规逐步完善菌种管理，并建立了包含菌株鉴定、毒力试验、耐药性评估在内的安全性评价程序[137]，目前国家批准的可用于食品的益生菌菌种名单见表3，可用于保健食品的菌种名单见表4。

临床研究显示，益生菌通过调节肠道菌群平衡、增强免疫应答及改善代谢功能，在癌症相关疾病中展现出协同治疗潜力。目前国内对于益生菌的临床研究报道较多，见表5。临床研究进展表明，益生菌在多种恶性肿瘤治疗中具有调节肠道菌群、增强免疫功能及减轻治疗相关不良反应的作用。在乳腺癌、胃癌、结直肠癌等实体瘤的化疗或靶向治疗中，益生菌可通过抑制促炎信号通路、促进抗肿瘤免疫细胞活化或修复肠道屏障功能等途径，提升化疗或免疫治疗效果。然而，当前临床应用仍面临挑战。一方面，多数研究集中于短期干预效果，长期安全性数据匮乏；另一方面，市场产品存在菌株标识模糊、功效夸大等问题，亟需建立标准化的质量控制体系。未来研究应聚焦于菌株作用机制的深度解析、个体化治疗方案的临床验证，以推动益生菌临床医学转化。

表3 国家批准的可用于食品的益生菌菌种名单

Table 3 List of probiotic strains approved by countries for use in food

菌属	菌种
双歧杆菌属（*Bifidobacterium*）	青春双歧杆菌（*B. adolescentis*）、动物双歧杆菌动物亚种（*B. animalis* subsp. *animalis*）、动物双歧杆菌乳亚种（*B. animalis* subsp. *lactis*）、两歧双歧杆菌（*B. bifidum*）、长双歧杆菌长亚种（*B. longum* subsp. *longum*）、长双歧杆菌婴儿亚种（*B. longum* subsp. *infantis*）、短双歧杆菌（*B. breve*）
乳杆菌属（*Lactobacillus*）	嗜酸乳杆菌（*L. acidophilus*）、卷曲乳杆菌（*L. crispatus*）、德氏乳杆菌保加利亚亚种（*L. delbrueckii* subsp. *bulgaricus*）、德氏乳杆菌乳亚种（*L. delbrueckii* subsp. *lactis*）、格氏乳杆菌（*L. gasseri*）、瑞士乳杆菌（*L. helveticus*）、约氏乳杆菌（*L. johnsonii*）、马乳酒样乳杆菌马乳酒样亚种（*L. kefiranofaciens* subsp. *kefiranofaciens*）
乳酪杆菌属（*Lacticaseibacillus*）	干酪乳酪杆菌（*L. casei*）、副干酪乳酪杆菌（*L. paracasei*）、鼠李糖乳酪杆菌（*L. rhamnosus*）
黏液乳杆菌属（*Limosilactobacillus*）	发酵黏液乳杆菌（*L. fermentum*）、罗伊氏黏液乳杆菌（*L. reuteri*）
乳植杆菌属（*Lactiplantibacillus*）	植物乳植杆菌（*L. plantarum*）
联合乳杆菌属（*Ligilactobacillus*）	唾液联合乳杆菌（*L. salivarius*）
广布乳杆菌属（*Latilactobacillus*）	弯曲广布乳杆菌（*L. curvatus*）、清酒广布乳杆菌（*L. sakei*）
链球菌属（*Streptococcus*）	唾液链球菌嗜热亚种（*S. salivarius* subsp. *thermophilus*）
乳球菌属（*Lactococcus*）	乳酸乳球菌乳亚种（*L. lactis* subsp. *lactis*）、乳酸乳球菌乳亚种（双乙酰型）（*L. lactis* subsp. *lactis biovar diacetylactis*）、乳脂乳球菌（*L. cremori*）
丙酸杆菌属（*Propionibacterium*）	费氏丙酸杆菌谢氏亚种（*P. freudenreichii* subsp. *shermanii*）
丙酸菌属（*Acidipropionibacterium*）	产丙酸丙酸菌（*A. acidipropionici*）
明串珠菌属（*Leuconostoc*）	肠膜明串珠菌肠膜亚种（*L. mesenteroides* subsp. *mesenteroides*）
片球菌属（*Pediococcus*）	乳酸片球菌（*P. acidilactici*）、戊糖片球菌（*P. pentosaceus*）
魏茨曼氏菌属（*Weizmannia*）	凝结魏茨曼氏菌（*W. coagulans*）
动物球菌属（*Mammaliicoccus*）	小牛动物球菌（*M. vitulinus*）
葡萄球菌属（*Staphylococcus*）	木糖葡萄球菌（*S. xylosus*）、肉葡萄球菌（*S. carnosus*）
克鲁维酵母属（*Kluyveromyces*）	马克斯克鲁维酵母（*K. marxianus*）

表4 国家批准的可用于保健食品的益生菌菌种名单

Table 4 List of probiotic strains approved by countries for use in health foods

菌种	拉丁名
双歧双歧杆菌	*B. bifidum*
婴儿双歧杆菌	*B. infantis*
长双歧杆菌	*B. longum*
短双歧杆菌	*B. breve*
青春双歧杆菌	*B. adolescentis*
德氏乳杆菌保加利亚种	*Lactobacillus delbrueckii* subsp. *bulgaricus*
嗜酸乳杆菌	*L. acidophilus*
干酪乳杆菌干酪亚种	*L. casei* subsp. *casei*
嗜热链球菌	*Streptococcus thermophilus*
罗伊氏乳杆菌	*Lactobacillus reuteri*

6 合成生物技术在提升益生菌抗肿瘤效果方面的应用展望

合成生物学技术的发展为抗肿瘤治疗提供了创新性策略（图4），通过基因工程改造益生菌以增强其抗肿瘤效果已成为研究热点[143-145]。以大肠杆菌菌株Nissle 1917（*Escherichia coli* strain Nissle 1917，EcN）为例，其安全性及瘤内定植能力使其成为理想底盘菌[146-147]，美国Synlogic公司开发的SYNB1891通过合成生物学改造使EcN特异性表达STING激动剂环二磷酸腺苷，激活抗原呈递细胞并增强免疫反应[148]。临床研究显示，SYNB1891

表5 临床研究中益生菌辅助治疗恶性肿瘤的研究进展

Table 5 Research progress on probiotics as an adjunctive treatment for malignant tumors in clinical studies

菌种	肿瘤类型	研究结果	参考文献
副干酪乳杆菌SD1、LGG SD11	结直肠癌	IL-1β、TNF-α、IL-6、IL-8、IL-17A↓，IL-10、IL-12↑，乙酸、丙酸、丁酸↑	[86]
鼠李糖乳杆菌Probio-M9	肝癌	总生存期、客观缓解率、疾病控制率、手术转化率及无进展生存期↑	[102]
海氏肠球菌、肠巴氏杆菌	肺癌	无进展生存时间、总生存时间↑	[118]
双歧杆菌	肝癌	D-乳酸、降钙素原、二胺氧化镁↑	[136]
	结直肠癌	CA19-9、CA72-4↓，卡氏功能状态评分↑，胃肠道不良反应发生率↓	[138]
	胃癌	Hp根除率↑，IL-6、hs-CRP、TNF-α↓，DL、MIVP、IMSP↑	[139]
	食管癌	$CD4^+$、$CD4^+/CD8^+$↑，NKG2A↓，NKG2D↑，D-乳酸↓，二胺氧化酶↑	[140]
	乳腺癌	$CD4^+$、$CD4^+/CD8^+$↑，$CD8^+$↓，CRP、IL-6、TNF-α↓	[141]
	宫颈癌	$CD4^+$、$CD3^+$、$CD4^+/CD8^+$↑，$CD8^+$↓，IL-6、IL-1β、TNF-α↓	[142]

注：CA19-9—糖类抗原19-9；CA72-4—糖类抗原72-4；$CD3^+$—$CD3^+$ T淋巴细胞；$CD4^+$—$CD4^+$ T淋巴细胞；$CD8^+$—$CD8^+$ T淋巴细胞；$CD4^+/CD8^+$—$CD4^+$ T淋巴细胞与$CD8^+$ T淋巴细胞比值；NKG2A—T淋巴细胞表面抑制性受体A；NKG2D—T淋巴细胞表面活化性受体；DL—胃癌黏膜情况参数，病灶边界线；MIVP—胃癌黏膜情况参数，不规则微血管；IMSP—胃癌黏膜情况参数，不规则微结构；hs-CRP—超敏C反应蛋白。

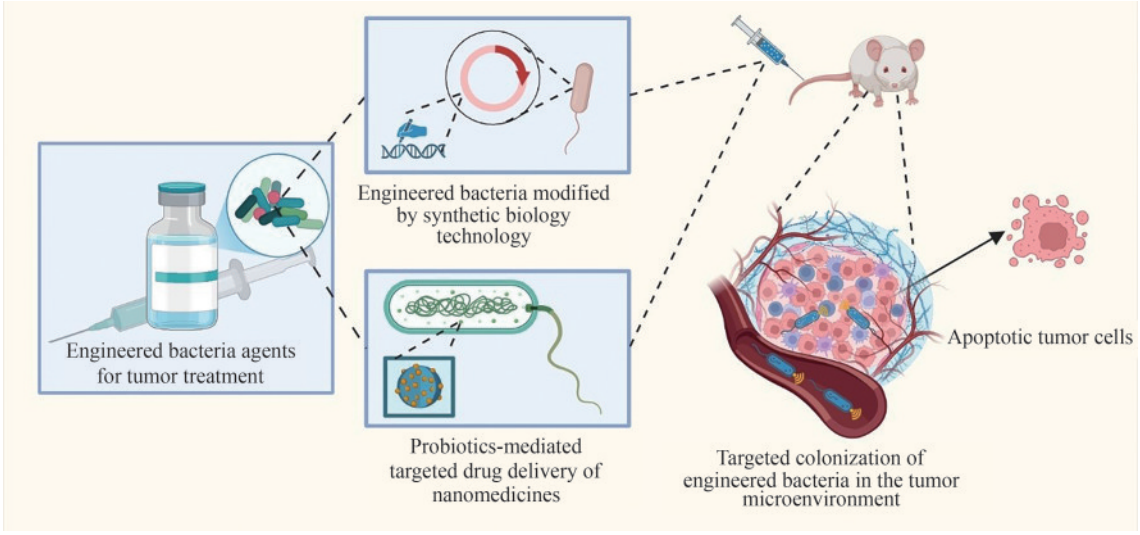


图4 合成生物学技术改造的工程益生菌用于肿瘤治疗

Fig. 4 Engineered probiotics modified by synthetic biology technology for tumor treatment

与免疫检查点抑制剂联合使用时，可显著提高疾病稳定率并减轻肿瘤微环境中的炎症反应[149]。此外，鼠伤寒沙门氏菌衍生的减毒菌株VNP20009通过敲除毒性基因，展现出良好的肿瘤靶向性和抗肿瘤活性[150]，VNP20009不仅能直接抑制肿瘤生长，还能通过与PD-1/PD-L1阻断疗法联合，显著降低肿瘤细胞增殖标志物Ki67的表达，进一步增强抗肿瘤效果[151]。

近期研究发现入侵肿瘤细胞的细菌表面存在的抗菌肽可以被肿瘤细胞识别，这表明合成生物学与纳米技术在抗肿瘤治疗中的协同潜力，纳米颗粒的物化特性使其成为药物递送的理想载体，而光响应模块的应用则为精准肿瘤治疗提供了新思路。例如，基于蓝光响应模块EL222和上转换纳米颗粒（UCNs@FA）的近红外光响应细菌（EcN@EL222-TNFα）通过局部光激活实现TNF-α的精准表达，实现肿瘤的精准消融[152]。此外，小韦荣球菌与载药纳米颗粒结合的生物杂交系统通过调节肿瘤微环境中M2型巨噬细胞的比例，显著抑制了肿瘤生长并增强了免疫反应[153]。光敏剂二氢卟吩e6与抗肿瘤药物偶联的双歧杆菌药物递送系统则通过光动力和声动力协同治疗，实现了高

效肿瘤靶向清除[154]。

肿瘤的免疫逃逸是指肿瘤通过抑制免疫细胞活性、激活免疫抑制信号或改变微环境代谢等方式，逃避免疫系统识别和清除的能力[155-156]。近期研究发现入侵肿瘤细胞的细菌表面组分可被肿瘤细胞识别，这使工程菌携带药物进入肿瘤微环境成为可能[157-158]。通过合成生物技术对细菌表面组分进行改造，提升工程菌在肿瘤微环境中的定植与靶向治疗效率，例如有研究对工程菌表面荚膜多糖的表达进行调控，保护工程菌不被免疫系统清除，使细菌向远端肿瘤转运并显著抑制肿瘤生长[159]。Cao等[160]设计了细胞膜包裹细菌的方法，使其具有低炎症反应、高血液保留率、低正常器官积累和高肿瘤定植能力的优势。总的来说，合成生物学的发展，可有效避免经工程改造的益生菌逃逸至外环境，并且削弱肿瘤的免疫逃逸能力。

7 总 结

益生菌作为一类有益微生物，近年来在辅助防治恶性肿瘤方面的研究取得了显著进展。本文综述了益生菌在肿瘤预防、辅助治疗及改善治疗副作用等方面的作用机制及其临床应用潜力。研究表明，益生菌通过调控肠道菌群、释放代谢产物、调节免疫细胞等多种途径，能够有效抑制肿瘤的发生与发展。具体而言，益生菌能够抑制有害菌的生长，维持肠道屏障功能，降解潜在致癌物，并通过调节肿瘤微环境中的免疫细胞和炎症因子，发挥抗肿瘤作用。此外，益生菌及其产生的代谢产物在抑制癌细胞增殖、促进癌细胞凋亡方面表现出显著的生物活性，通过多种途径发挥抗肿瘤活性。在辅助治疗恶性肿瘤方面，益生菌对消化系统、生殖系统等多种肿瘤均表现出抑制作用。例如，益生菌能够通过调节肠道菌群，影响肿瘤细胞的增殖和凋亡，进而抑制肿瘤生长。在改善肿瘤治疗副作用方面，益生菌在增强免疫功能、减轻放化疗副作用等方面具有积极作用。研究表明，益生菌能够显著降低放化疗引起的口腔黏膜炎、放射性腹泻等副作用，并改善术后患者的肠道屏障功能和免疫功能。

合成生物技术改造的益生菌用于肿瘤治疗虽展现出潜力，但仍面临诸多挑战。首先是安全性，早期使用活细菌治疗癌症，因感染风险大而发展受限。如今对细菌进行基因工程改造虽可降低毒性，但在提升疗效的同时保持安全性仍是难题。其次是治疗的有效性，目前工程菌与药物联合治疗恶性肿瘤是常见手段，但系统递送联合化疗和免疫疗法会显著增加毒性。工程菌虽能选择性在肿瘤定植，但如何更高效地递送治疗药物、增强对肿瘤细胞的杀伤作用，以及避免肿瘤细胞产生耐药性，都是提升治疗效果需要攻克的关键问题。这些挑战限制了工程菌在癌症治疗中的广泛应用和疗效提升，合成生物学的发展将克服这些问题，在未来利用合成生物技术改造的工程菌将成为一种极其具有潜力的防治恶性肿瘤的手段。

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