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微生态与胃肠肿瘤的研究现状与进展

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摘 要: 胃肠道肿瘤高发态势严峻, 其防治研究始终是医学领域的重点课题。传统研究认为, 宿主遗传和表观遗传是胃肠肿瘤的主要致病诱因, 但近年来的研究逐渐揭示了胃肠道微生态作为“环境因素”促进胃癌和结直肠癌的发生与发展。本综述系统回顾了我们的团队在该领域的重要突破。在胃癌中, 除了经典的致病菌幽门螺杆菌, 咽峡炎链球菌被鉴定为首个新型促癌菌, 能够直接驱动炎症与胃癌进展。在结直肠癌方面, 厌氧消化链球菌和胃链球菌被确认为新型的肿瘤驱动菌, 而嗜热链球菌和丁酸梭菌等抑癌菌通过分泌特异性代谢产物发挥抗肿瘤效应。同时, 肠道菌群在肿瘤治疗中也发挥着重要作用, 特定菌株能够增强结直肠癌免疫检查点抑制剂的治疗疗效, 噬菌体靶向清除致病菌可有效逆转化疗耐药。深入理解微生态在胃肠肿瘤进展与精准防治中的核心作用, 能为构建基于微生物群的个性化诊疗新范式提供关键支撑。

关键词: 肠道微生态; 胃癌; 结直肠癌; 免疫治疗; 肿瘤微环境

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Gut microbiome in gastrointestinal cancer

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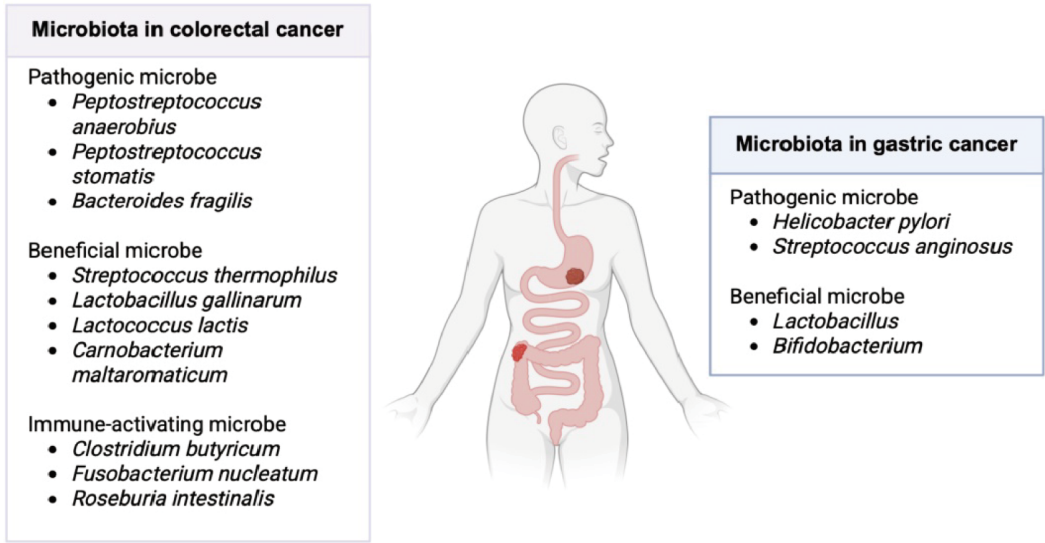
Abstract: The high incidence of gastrointestinal tumors, including gastric and colorectal cancers, poses a significant global health challenge, highlighting the urgent need for developing effective prevention and treatment strategies. In the past decades, research has primarily identified host genetics and epigenetic alterations as the main pathogenic factors driving gastric and colorectal carcinogenesis. However, recent studies have increasingly highlighted the gastrointestinal microbiome as a crucial “environmental factor” that significantly contributes to the occurrence, development, and progression of these malignancies through complex host-microbe interactions. In this review, we systematically explore the important breakthroughs from our work in understanding the role of gut microbiome in gastric and colorectal cancers. In gastric

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cancer, alongside the well-established pathogenic bacterium *Helicobacter pylori*, *Streptococcus anginosus* has emerged as the first novel oncogenic bacterium capable of directly driving gastric inflammation, mucosal atrophy, intestinal metaplasia, and tumorigenesis, representing a new paradigm in gastric carcinogenesis beyond classical pathogens. In colorectal cancer, *Peptostreptococcus anaerobius* and *Peptostreptococcus stomatis* have been confirmed as new tumor-driving pathogens that promote cellular proliferation and create favorable conditions for tumor growth, while beneficial bacteria such as *Streptococcus thermophilus* and *Clostridium butyricum* exert potent anti-tumor effects through producing specific anti-cancer metabolites and modulating host immune responses. Furthermore, certain beneficial strains demonstrate remarkable therapeutic potential by enhancing the efficacy of immune checkpoint blockade therapy in colorectal cancer through immune microenvironment modulation. Conversely, eliminating specific pathogenic bacteria with targeted bacteriophage therapy effectively reverses chemotherapy resistance and restores drug sensitivity. Overall, our current understanding of the gut microbiome in gastrointestinal cancer has established a critical foundation for translating microbiota research into clinical practice, offering novel opportunities for precision medicine and ultimately benefiting patients.



Key words: gut microbiota; gastric cancer; colorectal cancer; immunotherapy; tumor microenvironment

胃癌(gastric cancer,GC)和结直肠癌(colorectal cancer,CRC)是全球发病率和死亡率较高的恶性肿瘤,严重威胁人类健康^[1]。长期以来,胃肠道肿瘤的发生被认为主要与遗传易感性和环境因素有关^[2,3]。然而,随着近年来宏基因组学、代谢组学以及无菌动物模型等技术的快速发展,栖息于消化道内的复杂微生物群逐渐被视为影响肿瘤发生发展的重要“环境”因素^[4-8]。越来越多的证据表明,胃肠道生态失调与炎症转化密切相关,并通过直接诱导DNA损伤、免疫微环境重塑以及代谢物调控等多种机制,在肿瘤的起始^[9]、进展^[10,11]、转移^[12,13]及治疗^[14]反应中发挥着重要作用。本综述系统回顾了近年来在胃癌与结直肠癌微生态研究领域的研究进展,重点讨论了特定致病菌与抑癌微生物的鉴定及其分子作用机制的最新突破,以及微生物群落在诊断标志物和治疗靶点方面的应用潜力,旨在为基于微生态调控的肿瘤精准防治策略提供理论依据与

研究思路。
1 微生态在胃癌中的研究进展
1.1 胃癌菌群的失调特征

胃癌是我国发病率第五位,死亡率第三位的常见恶性肿瘤^[15]。其发生通常遵循多阶段的组织学进展过程,即从浅表性胃炎(superficial gastritis, SG)逐步发展为萎缩性胃炎(atrophic gastritis, AG)、肠上皮化生(intestinal metaplasia, IM),最终进展为胃癌^[16]。研究表明,胃癌的发生与宿主自身因素及环境因素密切相关,其中宿主因素包括ABO血型 and 遗传易感性等,环境因素则主要是胃黏膜的微生态失衡^[17]。

大量研究证实,在胃黏膜活检样本中可稳定检测到变形菌门(Proteobacteria)、芽孢杆菌门(Bacillota)、放线菌门(Actinomycetota)和梭杆菌门(Fusobacteriota)等细菌^[18],且胃内微生物群落失衡与胃癌的发生存在显著关联^[19,20]。其中,幽门螺杆菌

菌(*Helicobacter pylori*)感染被广泛认为是胃癌的主要危险因素,它通过引发黏膜炎症和诱导组织学改变,推动胃癌的发生进程^[21]。然而,仅有3%的幽门螺杆菌感染者最终发展为胃癌^[22],这提示除了幽门螺杆菌外,其他微生物也可能促进胃癌的发生和发展。大量研究表明,在胃癌的发生进程中,胃内微生物的多样性和丰度呈逐渐下降的趋势^[17]。除胃组织以外,胃癌患者的口腔和粪便样本中的微生物丰度及多样性也显著低于健康人群^[23,24]。同时,对胃癌患者组织样本的分析显示,胃癌组织中的微生物丰度和多样性显著高于与其配对的癌旁正常组织,这一现象提示胃黏膜微生物可能与胃癌细胞存在潜在的相互作用^[25-27]。

动物实验研究进一步验证了多种微生物对胃癌发生的影响。在感染或未感染幽门螺杆菌的胰岛素-胃泌素(INS-GAS)小鼠模型中,正常肠道菌群可加速胃肿瘤的进展,而抗生素治疗则能延缓肿瘤的发生^[28];此外,定植了正常肠道菌群的无幽门螺杆菌INS-GAS小鼠,其胃癌发生速度显著快于无菌小鼠^[29]。这些研究结果凸显了非幽门螺杆菌微生物在胃癌发生中的潜在作用。进一步地,将胃癌相关失衡的微生物群移植到受体无菌INS-GAS小鼠体内,可促进其胃内癌前病变的发生^[30]。另一项动物研究表明,将肠上皮化生或胃癌患者的胃内微生物群移植到无菌小鼠体内,也能诱导小鼠胃内出现癌前病变^[31]。综上,胃黏膜菌群失调是推动胃癌发展的重要因素之一。

1.2 病原微生物在胃癌发生发展中的作用与机制

澳大利亚病理学家巴里·马歇尔和微生物学家罗宾·沃伦于1982年首次分离了幽门螺杆菌,并证实了其与慢性胃炎和消化性溃疡的关联。这一里程碑式的发现使两位科学家在2005年荣获诺贝尔生理学或医学奖^[32]。在随后的40年里,幽门螺杆菌成为唯一被证实与胃癌相关的细菌。然而,幽门螺杆菌以“一击即走”的方式诱发胃癌,在胃癌的发生发展过程中其丰度显著降低,而非持续存在并发挥作用。当胃黏膜发生肠上皮化生后,根除幽门螺杆菌已无法降低胃癌的发病风险^[33]。在胃癌发生的起始阶段,胃酸及胃内酶分泌功能受损,为多种微生物的定植创造了条件。随着宏基因组学等技术的快速发展,近年来多项研究进一步揭示了胃内微生物群落在胃癌发生和发展中的具体作用^[34,35],发现

链球菌属(*Streptococcus*)、梭杆菌属(*Fusobacterium*)等多个细菌属在胃癌肿瘤组织中显著富集,这为筛选并鉴定具有促胃癌作用的致病性微生物提供了重要线索^[36-38]。

链球菌属广泛存在于人体口腔及胃肠道中,多项研究一致报道,在胃癌患者的胃内癌前病变组织或肿瘤组织中,链球菌属均呈显著富集状态^[39-43]。我们团队于2024年的一项研究首次发现了除幽门螺杆菌以外的首个胃癌致病菌——咽峡炎链球菌^[44]。我们的研究通过系统分析胃癌发生不同阶段的微生物群落变化,发现咽峡炎链球菌与萎缩性胃炎、肠上皮化生及胃癌均存在显著关联。即使在幽门螺杆菌被成功根除后,咽峡炎链球菌仍可诱发胃黏膜的持续性炎症,这表明咽峡炎链球菌参与了胃癌的发生进程^[45]。进一步研究发现,咽峡炎链球菌可在小鼠胃内成功定植。感染咽峡炎链球菌两周后,小鼠胃黏膜会出现急性炎症反应,同时伴随促炎细胞因子的大量分泌;而咽峡炎链球菌长期感染的小鼠,会进一步发生慢性炎症及萎缩、肠化生、低级别上皮内瘤变等癌前病变,其病变进展模式与胃癌患者中经典的科雷亚级联反应高度相似^[46]。将咽峡炎链球菌感染无菌小鼠后,也观察到了一致的结果,这表明该菌无需肿瘤微环境中其他微生物的参与,其自身即可发挥促炎与促肿瘤作用。此外,在短期异体移植瘤模型和长期化学诱导胃癌模型中,咽峡炎链球菌均能显著加速胃癌的发生进程。单细胞RNA测序结果进一步显示,咽峡炎链球菌感染可诱导小鼠胃组织中CD8⁺ T细胞耗竭,同时促进免疫抑制性细胞的浸润。从机制上看,咽峡炎链球菌的表面黏附蛋白TMPC可与胃上皮细胞表面的膜联蛋白A2(ANXA2)受体特异性结合,进而激活丝裂原活化蛋白激酶(MAPK)信号通路。而敲除咽峡炎链球菌中的TMPC基因,或敲除胃癌细胞中的ANXA2基因,均可完全阻断该菌的促肿瘤效应。除了这项研究之外,近期的一项新研究表明,咽峡炎链球菌通过自身代谢产生甲硫氨酸,从而促进胃癌的进展。metE基因是咽峡炎链球菌合成甲硫氨酸的关键基因,敲除metE后,其促进肿瘤的效应显著减弱。此外,从胃癌患者肿瘤组织中分离出的咽峡炎链球菌临床株亦能通过分泌甲硫氨酸诱导胃癌细胞增殖,并加速小鼠体内肿瘤的生长。甲硫氨酸可以激活宿主甲硫氨酸循环的关键酶MAT2A,从而推动肿瘤细胞的增

殖^[47]。综上,咽峡炎链球菌是一种新型的胃癌促癌菌,能够在胃癌发生的不同阶段发挥诱癌与促癌的双重作用。

除咽峡炎链球菌外,大量研究及Meta分析通过大样本的胃组织活检数据证实了多种特定胃微生物在胃癌患者体内的富集现象。然而,不同研究结果之间存在高度差异。一项涵盖825份胃组织活检样本的研究指出,普雷沃菌属(*Prevotella*)、韦荣球菌属(*Veillonella*)、小单胞菌属(*Parvimonas*)及消化链球菌属(*Peptostreptococcus*)在胃癌患者的胃组织中呈现出富集状态^[24]。另一项包含1 270份胃活检样本的Meta分析则进一步发现,放线杆菌属(*Actinobacillus*)、放线菌属(*Actinomyces*)、小单胞菌属(*Parvimonas*)以及罗思菌属(*Rothia*)也同样富集于胃癌患者体内^[48]。此外,涵盖2 198名研究对象的一项研究进一步证实梭杆菌属(*Fusobacterium*)、纤毛菌属(*Leptotrichia*)和咽峡炎链球菌在胃癌患者胃组织中的丰度显著升高^[49]。综合来看,这些研究结果呈现出高度异质性,反映了不同人群内部及人群间胃微生物群的重大差异,且与研究对象特征(如年龄、族群、饮食习惯等)、胃部病理状态以及测序技术的选择等因素密切相关。

1.3 胃癌相关抑癌微生物的作用与机制

乳杆菌属(*Lactobacillus*)、双歧杆菌属(*Bifidobacterium*)等乳酸菌类有益菌在胃癌研究中被证实具有抑制癌症的潜力。多项研究表明,部分菌株能够耐受胃内的强酸环境、消化酶及胆盐的影响,从而在胃内成功生存^[50,51]。在肠上皮化生(IM)及胃上皮内瘤变(early gastric neoplasm, EGN)患者体内,乳酸菌类有益菌的丰度均显著降低。乳杆菌属作为多个益生菌制剂的重要核心成分,在胃部的定植与胃内2型固有淋巴细胞(ILC2)丰度的增加密切相关,促进ILC2分泌免疫球蛋白A(IgA),从而增强胃黏膜的免疫保护作用^[52]。然而,乳杆菌在胃癌中的丰度变化趋势目前尚存争议,这与其作为益生菌的固有认知相悖。一小部分研究报道指出胃癌组织中乳酸菌丰度降低^[53],但绝大多数研究发现,乳杆菌在不同人群胃癌患者的胃部^[26,27,48,54-57]和粪便样本^[23,58]中呈富集状态。但植物乳杆菌(*L. plantarum*)、鼠李糖乳杆菌(*L. rhamnosus*)、干酪乳杆菌(*L. casei*)、罗伊氏乳杆菌(*L. reuteri*)等多种乳杆菌属均被证实具有抑制胃

癌的潜力^[59-62],其代谢产物能够增强免疫反应,并通过调节PTEN、Bax、TLR4和AKT等信号通路和分子的表达,抑制细胞增殖并诱导胃癌细胞凋亡,从而发挥抗胃癌的作用。因此,未来需要开展更多针对性的研究,以厘清乳杆菌属在胃癌中的具体作用机制,并将临床前研究成果有效转化为临床应用。

与乳杆菌属相比,双歧杆菌属在胃癌防治中的作用更为明确。研究发现,与慢性胃炎患者相比,胃癌患者胃内的双歧杆菌丰度显著降低^[24,63,64]。与对照组相比,早期胃肿瘤及低风险肠上皮化生患者胃黏膜中双歧杆菌属丰度下降了约98.4%^[53]。此外,胃癌患者的粪便样本中双歧杆菌丰度也显著降低,与幽门螺旋杆菌相关的胃病发展密切相关,表明双歧杆菌的减少可能间接与胃癌的发生存在关联^[65]。多项机制研究证实,双歧杆菌属在胃癌中具有显著的抗肿瘤作用。热灭活的双歧杆菌能够诱导肿瘤细胞凋亡并抑制肿瘤生长^[66]。此外,研究表明双歧杆菌通过下调COX2的表达,显著抑制胃癌细胞的增殖和血管生成,提示其具有作为新型安全治疗手段的潜力^[67](图1)。

2 微生态在肠癌中的研究进展

2.1 结直肠癌微生态的失调特征

人体肠道微生物群是一个由细菌、真菌、病毒和古菌组成的复杂生态系统,肠道细菌作为胃肠道中丰度最高的微生物类群,其总量与人体宿主自身细胞数量大致相当^[68,69]。在机体内,肠道微生物群呈现动态变化但整体相对稳定的状态,这种稳态对维持健康至关重要^[70]。当这种生态平衡被打破时,即形成所谓的菌群失调,这一状态指的是与疾病发生、发展相关的微生物群组成及功能的各种异常改变^[71-74]。研究表明,结直肠癌的发生与肠道菌群失调,尤其是肠道细菌失调密切相关^[75]。研究通过将结直肠癌患者或健康人的粪便进行粪菌移植(fecal microbiota transplantation, FMT)至多种小鼠模型后发现,接受结直肠癌患者粪菌移植的AOM(偶氮甲烷)诱导常规小鼠,其结肠息肉发生率、高级别异型增生比例及黏膜炎症评分均显著高于健康人粪菌移植组和对照组。在无菌小鼠中,结直肠癌患者粪菌移植组的结肠上皮细胞增殖活性(Ki-67和PCNA阳性细胞比例)显著升高,同时活性 β -连环蛋白表达也上调。通过粪菌移植模型,研究人员发现结直肠癌

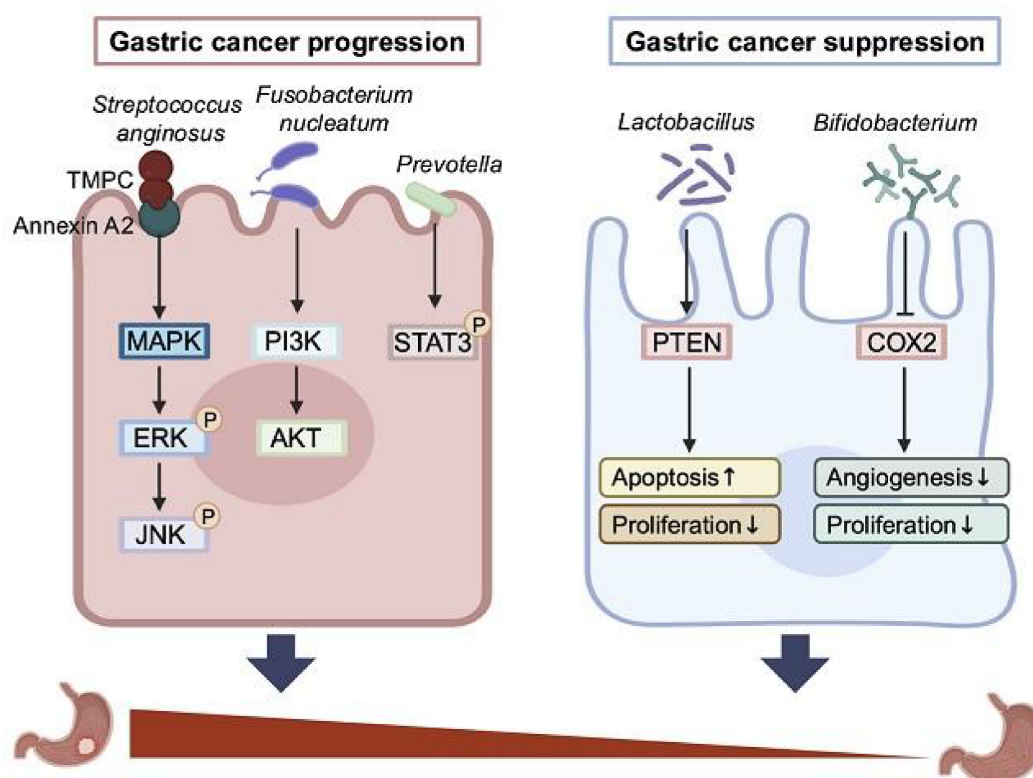


图1 微生态在胃癌中的作用与机制

在胃癌微环境中,咽峡炎链球菌通过TMPC-Annexin A2轴激活MAPK信号通路,促进胃癌的发生与发展。同时,核梭杆菌和普雷沃菌属分别激活胃癌宿主细胞的PI3K/AKT和STAT3信号通路,进一步促进胃癌的进展。乳杆菌属则能促进肿瘤细胞的凋亡,抑制其增殖,从而对胃癌产生抑制作用;而双歧杆菌属通过抑制血管生成和细胞增殖来抑制胃癌的发生。

Figure 1 Mucosal microbiota in gastric cancer

In the gastric cancer microenvironment, *Streptococcus anginosus* activates the MAPK signaling pathway via the TMPC-Annexin A2 axis, promoting the occurrence and development of gastric cancer. Meanwhile, *Fusobacterium nucleatum* and *Prevotella* activate the PI3K/AKT and STAT3 signaling pathways in gastric cancer cells, further promoting cancer progression. The *Lactobacillus* can induce apoptosis in tumor cells and inhibit proliferation, thereby exerting a suppressive effect on gastric cancer. In addition, *Bifidobacterium* inhibits the occurrence of gastric cancer by suppressing angiogenesis and cell proliferation.

患者的粪便微生物群具有直接的促肿瘤作用,这为肠道菌群失衡与结直肠癌(CRC)之间的“因果关系”提供了直接的实验证据^[12]。

针对肠道微生物群存在显著的地域和种族异质性,多项荟萃分析已明确了特定细菌的存在与不同人群的结直肠癌发生发展均存在共性关联^[76-78]。研究分别纳入了来自不同地区的969份和768份结直肠癌患者的粪便样本,并进行宏基因组测序分析,鉴定出多种在结直肠癌患者体内富集的核心致病菌。这些菌株包括具核梭杆菌(*F. nucleatum*)、微小单胞菌(*Parvimonas micra*)、胃链球菌(*Peptostreptococcus stomatis*)、厌氧消化链球菌(*P. anaerobius*)、不解糖卟啉单胞菌(*Porphyromonas asaccharolytica*)、摩尔链球菌(*Solobacterium moorei*)及中间普雷沃菌(*Prevotella intermedia*)等多种口腔致

病菌^[77,79]。此外,多项研究在结直肠癌患者的肠道微生物群中也检测到口腔致病菌丰度的显著升高,如具核梭杆菌、摩尔链球菌及毛螺菌属菌株(*Lachnospirillum* spp.),提示肠道菌群失调可能是结直肠癌发生的诱发因素^[80,81]。除了口腔致病菌外,产肠毒素脆弱拟杆菌(*enterotoxigenic Bacteroides fragilis*)、产pks毒素大肠杆菌(*pks⁺ Escherichia coli*)、解链食子酸链球菌(*Streptococcus gallolyticus*)以及摩氏摩根菌(*Morganella morganii*)等结肠固有细菌在结直肠癌患者中也显著富集^[82-85]。近年来,越来越多的研究开始关注结直肠癌患者体内有益肠道细菌的耗竭,这些细菌具有抑癌作用,包括嗜热链球菌(*S. thermophilus*)^[86]、唾液链球菌(*S. salivarius*)^[87]、鸡乳杆菌(*Lactobacillus gallinarum*)^[6]、丁酸梭菌(*Clostridium butyricum*)^[88]、乳酸乳球菌(*Lactococcus*

lactis)^[89]和麦芽芳香肉杆菌(*Carnobacterium maltaromaticum*)^[90]。这些有益菌与致病菌之间可能形成竞争或拮抗关系。因此,肠道菌群失调会打破结直肠癌患者体内促癌致病菌与抑癌菌的平衡状态,这一失衡不仅与结直肠癌的发病机制密切相关,也为疾病的主动干预及生物标志物的研发提供了潜在思路与方向。

由于结直肠癌患者样本中真菌的丰度通常较低,并且个体间存在高度异质性,因此关于结直肠癌患者真菌组的研究较为有限。然而,多项研究表明,结直肠癌患者具有特征性的真菌组谱,其核心特征是担子菌门(Basidiomycota)与子囊菌门(Ascomycota)的比值显著升高^[91,92]。在物种水平上,多种曲霉属真菌(*Aspergillus*)在结直肠癌患者体内呈现高度富集状态^[93]。另一项涉及多个队列的大样本研究发现,结直肠癌患者的粪便样本中存在多种持续富集的真菌物种,包括兰贝尔曲霉(*Aspergillus rambellii*)、虫草属菌株(*Cordyceps* sp. RAO-2017)、美丽白粉菌(*Erysiphe pulchra*)、恶疫霉(*Moniliophthora perniciosa*)、杨生球腔菌(*Sphaerulina musiva*)和辣椒疫霉(*Phytophthora capsici*),而川地曲霉(*Aspergillus kawachii*)则在结直肠癌患者体内呈现持续性耗竭的特征^[91,93]。同时,结直肠息肉和腺瘤患者体内也检测到真菌组失衡,但程度相较于结直肠癌患者较轻,这提示真菌也可能参与了结直肠癌的早期发生过程^[94-96]。

2.2 结直肠癌病原微生物的作用与机制

多项研究表明,结直肠癌的病原微生物可通过诱导宿主细胞促癌通路、调控肿瘤免疫微环境以及诱导炎症等多种机制促进结直肠癌的发生发展^[97-103]。厌氧消化链球菌(*P. anaerobius*)是一种革兰氏阳性厌氧球菌,是人体口腔及肠道的共生菌之一,已证实其与心内膜炎、泌尿生殖道感染和胃肠道感染等多种疾病相关^[104-108]。研究发现,厌氧消化链球菌在结直肠癌患者的粪便和肿瘤组织中显著富集,并在中国与西方多类人群中得到了验证^[76,109]。在小鼠模型中,厌氧消化链球菌通过与肠上皮细胞表面的TLR2和TLR4结合,诱导细胞内活性氧(ROS)产生,进而激活固醇调节元件结合蛋白2(SREBP2)介导的胆固醇生物合成通路,促进肠细胞的增殖及不典型增生,加速小鼠肠癌的发生发展。使用ROS清除剂、TLR2/4抑制剂或SREBP2抑制剂可以阻断该菌的促癌作用。这一研究明确了厌氧消化链球菌作

为结直肠癌驱动菌的作用及其介导的“TLR2/4-ROS-SREBP2-胆固醇合成”的核心机制。

进一步研究发现,厌氧消化链球菌可通过其表面蛋白PCWBR2与结直肠癌细胞中过表达的整合素 α_2/β_1 特异性结合,激活黏着斑激酶(FAK)介导的PI3K-Akt-NF- κ B信号通路,促进结直肠癌细胞的增殖并抑制凋亡。同时,厌氧消化链球菌可诱导结直肠癌细胞中白细胞介素-10、干扰素- γ 等促炎细胞因子的表达,导致髓系来源抑制细胞(MDSCs)、肿瘤相关巨噬细胞和粒细胞样肿瘤相关中性粒细胞等免疫抑制性细胞的显著富集,从而重塑肿瘤免疫微环境,并在Apc^{Min/+}小鼠模型中加速肠癌的进展。该研究发现RGDS肽、小干扰RNA或抗体阻断整合素 α_2/β_1 ,能够显著削弱该菌的黏附及促癌效应,明确了厌氧消化链球菌介导的PCWBR2-整合素 α_2/β_1 轴作为结直肠癌治疗的潜在靶点^[110]。

除厌氧消化链球菌外,结直肠癌患者的粪便和黏膜中富集的另一革兰氏阳性厌氧菌——胃链球菌(*P. stomatis*)^[111],可通过其表面黏附蛋白FBA与结直肠癌细胞中过表达的整合素 α_6/β_4 特异性结合,激活ERBB2-MEK-ERK-p90RSK信号通路,促进肿瘤细胞增殖、抑制凋亡并破坏肠道屏障功能,在Apc^{Min/+}小鼠和AOM/DSS(葡聚糖硫酸钠)诱导的结直肠癌模型中促进肿瘤发生发展。同时,胃链球菌介导的Erb-b2受体酪氨酸激酶2(Erb-b2 receptor tyrosine kinase 2, ERBB2)激活能够绕过表皮生长因子受体(EGFR)抑制剂(如西妥昔单抗和厄洛替尼)以及BRAFV600E抑制剂(如维莫非尼)的抑癌作用,通过持续激活MAPK信号通路导致结直肠癌对多种受体酪氨酸激酶(RTK)抑制剂产生耐药性。阻断FBA-整合素 α_6/β_4 间的相互作用或靶向ERBB2,可以有效逆转胃链球菌的促癌效应及治疗耐药^[112]。

2.3 结直肠癌相关抑癌微生物的作用与机制

结直肠癌患者体内缺失的某些细菌已被证实具有抑癌作用,这些细菌通过其表面蛋白与肿瘤细胞直接相互作用,或分泌抑癌代谢物^[113-115]、外泌体^[116,117]及蛋白质^[8],从而抑制结直肠癌的发生发展。粪菌移植是一项通过将健康供体的粪便微生物群整体移植至受体肠道,以重建肠道微生态平衡的创新性生物技术,其临床应用已从复发性艰难梭菌感染(rCDI)的成功治疗拓展至多种消化系统疾病的干预^[118],包括炎症性肠病(溃疡性结肠炎与克罗

恩病)^[119,120]、肠易激综合征^[121]、肝性脑病^[122]及抗生素相关性腹泻^[123]等,展现出显著的疗效与良好的安全性。鉴于肠道菌群失调与结直肠癌发生发展之间的密切关联,FMT作为一种能够系统性调控肠道微生物组成的干预手段,在结直肠癌的防治领域也展现出广阔的应用前景与转化潜力。一项探索粪菌移植联合替雷利珠单抗及呋喹替尼治疗难治性微卫星稳定型转移性结直肠癌的II期临床试验结果显示,该三联方案作为三线及以上治疗可获得9.6个月的中位无进展生存期和13.7个月的中位总生存期,客观缓解率达20%,疾病控制率高达95%,且安全性可控,为这一免疫治疗耐药人群提供了具有临床应用前景的新型治疗策略^[124]。

针对具体的抑癌菌株,研究发现,在结直肠癌患者的粪便中,益生菌嗜热链球菌(*Streptococcus thermophilus*)的丰度显著降低。该细菌可通过分泌 β -半乳糖苷酶将乳糖分解为半乳糖从而发挥抑癌作用。在小鼠肠癌模型中,嗜热链球菌灌胃处理可调节小鼠肠道菌群的组成,促进双歧杆菌和乳杆菌等有益菌的富集,同时还干扰了肿瘤细胞的能量稳态,抑制葡萄糖摄取并下调己糖激酶2的表达,激活AMPK,诱导YAP Ser127的磷酸化,使其滞留在细胞质中,从而抑制Hippo信号通路。此外,嗜热链球菌促进氧化磷酸化并抑制糖酵解(Warburg效应),在Apc^{Min/+}小鼠和AOM诱导的小鼠肠癌模型中显著抑制肿瘤生长,并在体外抑制结直肠癌细胞的增殖,诱导细胞周期的G₀/G₁期阻滞及凋亡。敲除嗜热链球菌的 β -半乳糖苷酶可逆转其抑癌效应,而补充半乳糖则可恢复其对结直肠癌的预防作用^[86]。

鸡乳杆菌(*Lactobacillus gallinarum*)通过调节肠道菌群组成,富集乳杆菌属和双歧杆菌属等有益菌,减少潜在致病菌丰度从而抑制结直肠癌发生发展。同时,鸡乳杆菌分泌的小于3 kDa的非蛋白质类代谢产物吲哚-3-乳酸可与结直肠癌细胞表面的芳香烃受体(AhR)结合,特异性地诱导结直肠癌细胞的凋亡并抑制增殖,而对正常结肠上皮细胞无抑制作用。在多种小鼠肠癌模型中,鸡乳杆菌及吲哚-3-乳酸都能显著减少肿瘤数量与缩小肿瘤体积,阻断AhR则会消除其抑癌效应,从而明确了鸡乳杆菌及其代谢产物吲哚-3-乳酸(indole-3-lactic acid, ILA)在结直肠癌预防中的作用机制^[125]。

在结直肠癌患者的粪便中,益生菌乳酸乳球菌

(*Lactococcus lactis*)新菌株HkyuLL 10也通过双重机制发挥抑癌作用。一方面,HkyuLL 10可富集约氏乳杆菌和肠乳杆菌等有益菌,改善菌群失衡。另一方面,其分泌的分子量大于100 kDa的功能性蛋白 α -甘露糖苷酶能够特异性抑制结直肠癌细胞的增殖,并促进凋亡,对正常结肠上皮细胞无影响。在Apc^{Min/+}小鼠、AOM/DSS诱导的结直肠癌模型及无菌小鼠肠癌模型中,HkyuLL 10均能显著减少肿瘤数量与缩小肿瘤体积。通过构建结直肠癌异种移植模型,验证发现 α -甘露糖苷酶能有效抑制肿瘤生长,热灭活或蛋白酶K处理则使其抑癌作用失效。这一研究明确了HkyuLL 10及其分泌蛋白 α -甘露糖苷酶在结直肠癌预防中的重要作用^[89]。

研究还发现,在结直肠癌患者中,肠道菌群存在性别差异^[126,127]。女性结直肠癌患者粪便中特异性耗竭的益生菌麦芽香肉杆菌(*Carnobacterium maltaromaticum*)可以通过雌激素依赖的机制发挥女性特异性抑癌作用。研究表明,雌激素通过激活ESR1信号通路上调结肠上皮细胞表面SLC3A2的表达,与麦芽香肉杆菌表面的DD-羧肽酶结合,促进麦芽香肉杆菌在肠道中的定植。同时,麦芽香肉杆菌与肠道中的普拉梭菌(*Faecalibacterium prausnitzii*)等微生物发生代谢互作,将自身产生的7脱氢胆固醇(7-DHC)转化为活性维生素D(VD),激活宿主维生素D受体(VDR)信号通路,进而抑制结直肠癌细胞增殖,促进细胞凋亡,并改善肠道屏障功能、减轻炎症反应。在雌性Apc^{Min/+}小鼠和AOM诱导的结直肠癌模型中,麦芽香肉杆菌能够显著延缓雌性小鼠的肿瘤进展,而雌激素剥夺会消除其抑癌效应,VDR抑制剂或VDR敲除也会阻断该作用。研究明确了“雌激素-SLC3A2-麦芽香肉杆菌-维生素D-VDR”轴在女性结直肠癌预防中的核心机制,为女性结直肠癌的益生菌精准防治提供了新的策略^[90]。

2.4 肠道微生态在结直肠癌治疗中的作用

2.4.1 研究进展

近年来,免疫检查点抑制剂在黑色素瘤、淋巴瘤等多种肿瘤的治疗中取得了显著疗效^[128,129]。然而,约85%的结直肠癌患者属于微卫星稳定型(MSS),这类肿瘤被称为免疫“冷肿瘤”,其特征是肿瘤突变负荷低,并且对免疫检查点抑制疗法无反应^[130]。在结直肠癌肿瘤微环境中,厌氧消化链球菌通过两重机制分别诱导MDSCs的募集与活化,从

而削弱抗PD-1治疗效果。一方面,厌氧消化链球菌的表面蛋白与结直肠癌细胞中的整合素 α_2/β_1 结合,激活NF- κ B信号通路,诱导CXCL1的分泌,进而通过CXCL1-CXCR2轴招募CXCR2⁺ MDSCs浸润肿瘤组织。另一方面,厌氧消化链球菌分泌的50~100 kDa蛋白IyC_22直接与MDSCs表面的Slamf4受体结合,促进ARG1和iNOS的表达,提高MDSCs的免疫抑制能力,最终抑制细胞毒性CD8⁺ T细胞的活性,导致抗PD-1治疗失效。通过RGDS肽阻断整合素 α_2/β_1 或使用抗体阻断Slamf4受体,可以有效逆转厌氧消化链球菌介导的免疫抑制及治疗耐药^[131]。因此,迫切需要新的策略来增强结直肠癌中免疫检查点抑制剂治疗的疗效。

我们进一步开展了针对免疫治疗增敏策略的研究,发现丁酸梭菌(*Clostridium butyricum*)在结直肠癌患者以及多种癌症免疫治疗无效的患者粪便中的丰度显著降低。丁酸梭菌表面蛋白secD与结直肠癌细胞膜上过表达的GRP78受体相结合,抑制PI3K-AKT-NF- κ B信号通路,减少免疫抑制性细胞因子IL-6的分泌。同时,丁酸梭菌可分泌有益代谢物丁酸,联合激活细胞毒性CD8⁺ T淋巴细胞,抑制M2型肿瘤相关巨噬细胞的极化,重塑促癌的肿瘤免疫微环境。在MSI-H和MSS型的多种小鼠肠癌模型中,丁酸梭菌单独或与抗PD-1联合使用均能显著抑制肿瘤生长,且在无菌小鼠中同样有效,证实了其单独定植即可发挥作用。该效应在huCD34⁺人源化小鼠及结直肠癌患者来源的类器官与自身肿瘤浸润淋巴细胞共培养体系中得到验证,明确了secD-GRP78-IL-6信号通路是丁酸梭菌增强免疫治疗效果的核心机制^[88]。

此外,针对免疫激活细菌产生的有益代谢物如何促进结直肠癌免疫治疗也取得了进展。鸡乳杆菌通过其分泌的代谢产物吡啶-3-羧酸(ICA)增强抗PD-1治疗效果,该效应在MSI-H(MC38)和MSI-L(CT26)同种异体小鼠模型以及AOM/DSS诱导的肠癌模型中得到了验证。机制上,吡啶-3-羧酸一方面抑制肿瘤组织中吡啶胺2,3-双加氧酶1(IDO1)的表达,减少免疫抑制性代谢产物犬尿氨酸(Kyn)的产生;另一方面,吡啶-3-羧酸与犬尿氨酸竞争结合CD4⁺ T细胞表面的芳香烃受体,以竞争性抑制的方式阻断Kyn介导的芳香烃受体激活及其后续调节性T细胞(Treg)分化,同时增强CD8⁺ T细胞的效应功能,重塑肿瘤免疫微环境。在无菌小鼠中,鸡乳杆

菌单独定植即可发挥该效应,而吡啶-3-羧酸可模拟鸡乳杆菌的抑癌作用,补充犬尿氨酸或使用芳香烃受体拮抗剂则会逆转该效应^[6]。肠道罗斯氏菌(*Roseburia intestinalis*)分泌的丁酸作为其代谢产物促进结直肠癌免疫治疗疗效。在MC38和CT26小鼠原位移植瘤模型中,肠道罗斯氏菌或丁酸能够诱导颗粒酶B⁺、IFN- γ ⁺及TNF- α ⁺的细胞毒性CD8⁺ T细胞产生,进而抑制肿瘤生长,并显著提升抗PD-1治疗对小鼠MSS型肠癌的疗效。机制上,丁酸直接与CD8⁺ T细胞表面的TLR5受体结合,激活NF- κ B信号通路以增强CD8⁺ T细胞的活性^[132]。

尽管具核梭杆菌(*Fusobacterium nucleatum*)通常会促进肿瘤发生,但其也能增强微卫星稳定型结直肠癌免疫治疗的疗效,且结直肠癌患者肿瘤内具核梭杆菌的高丰度与免疫治疗的响应率存在正相关^[133]。机制研究发现,具核梭杆菌分泌的丁酸作为关键代谢产物,通过进入CD8⁺ T细胞核抑制组蛋白去乙酰化酶3/8(HDAC3/8)的活性,促进Tbx21基因启动子区域H3K27的乙酰化,上调转录因子TBX21(T-bet)的表达,进而抑制PD-1分子的转录,缓解CD8⁺ T细胞的耗竭并增强其效应功能。敲除具核梭杆菌的丁酸合成基因或敲低CD8⁺ T细胞中的TBX21会使其免疫激活作用失效,而HDAC3/8抑制剂则可以模拟具核梭杆菌的免疫激活作用,明确了具核梭杆菌产生的代谢物通过宿主细胞表观遗传修饰增强MSS型结直肠癌免疫治疗效果的分子机制^[134]。

除了免疫治疗,肠道菌群还影响结直肠癌的化疗疗效。研究显示,化疗无响应的结直肠癌患者的粪便及黏膜中,脆弱拟杆菌(*Bacteroides fragilis*)的丰度显著升高,且其高丰度与患者的不良预后相关。脆弱拟杆菌可以在多种小鼠肠癌模型中削弱5-氟尿嘧啶(5-FU)和奥沙利铂(OXA)的化疗效果。研究表明,该菌通过其表面蛋白SusD/RagB与结直肠癌细胞表面的Notch1受体直接结合,激活Notch1信号通路,诱导上皮间质转化及肿瘤干细胞特性,从而抑制化疗诱导的细胞凋亡,介导化疗耐药。该效应不依赖于其产生的毒素BFT,非产毒型脆弱拟杆菌(NTBF)同样可以通过此机制促进耐药,而敲除SusD/RagB或使用Notch1抑制剂(DAPT)可以阻断该耐药效应。此外,靶向脆弱拟杆菌的噬菌体VA7能够特异性清除该菌,同时无明显毒副作用,能够有效逆转其介导的化疗耐药,恢复结直肠癌在体内和

体外对5-FU和OXA的敏感性,明确了脆弱拟杆菌是结直肠癌化疗耐药相关的核心致病细菌,靶向清除其噬菌体VA7可为结直肠癌化疗增敏提供新的治疗策略^[135](图2)。

3.4.2 研究方向

未来,针对免疫激活菌促进结直肠癌免疫治疗或化疗疗效的临床试验需综合考虑多个关键因素。首先,人群的分层与入组标准至关重要,研究应明确区分微卫星稳定型与微卫星不稳定型肿瘤患者的微生物组特征差异,并探讨将抗生素和质子泵抑制剂(PPI)的使用历史作为重要的分层因素。这些药物可能通过降低菌群多样性来显著影响免疫检查点抑制剂的疗效,因此在入组前设定合理的洗脱期和排除标准是必要的。其次,干预方式和给药参数的设计同样重要。研究应比较不同活菌制剂、关键代谢物(如短链脂肪酸、色氨酸代谢产物)及噬菌体的给药途径,并明确剂量梯度(如CFU或mg/kg)、疗程周期(诱导期与维持期),同时阐述与免疫检查点抑制剂或化疗的时序关系,例如菌群干预是否应在治疗

前进行,以重塑免疫微环境。此外,定植与疗效监测指标的建立也是评估的重要环节。应建立多维度的评估体系,不仅要通过宏基因组测序或特异性qPCR追踪供体菌的定植情况和受体菌群的扰动,还需进行代谢组学检测,关注粪便或血清中丁酸、异戊酸等关键代谢物的浓度变化。同时,动态监测外周血和肿瘤浸润淋巴细胞中CD8⁺/FoxP3⁺比例、PD-1表达水平及系统性炎症等指标。最后,在安全性和质量控制方面,应严格把控活菌制剂的生产过程,防止杂菌污染并确保批次稳定性和维持细菌活性。此外,噬菌体疗法需要评估宿主范围的变化、基因水平转移的风险以及抗药性菌株的选择压力。参照FDA及EMA对于活体生物治疗药物(LBPs)的监管框架,讨论不良事件的分级标准与长期的安全性跟踪策略,对确保临床试验的安全性和有效性至关重要。

4 总结与展望

综上所述,胃肠微生态研究已取得显著进展。研究从早期对菌群失调特征的描述,发展到如今识

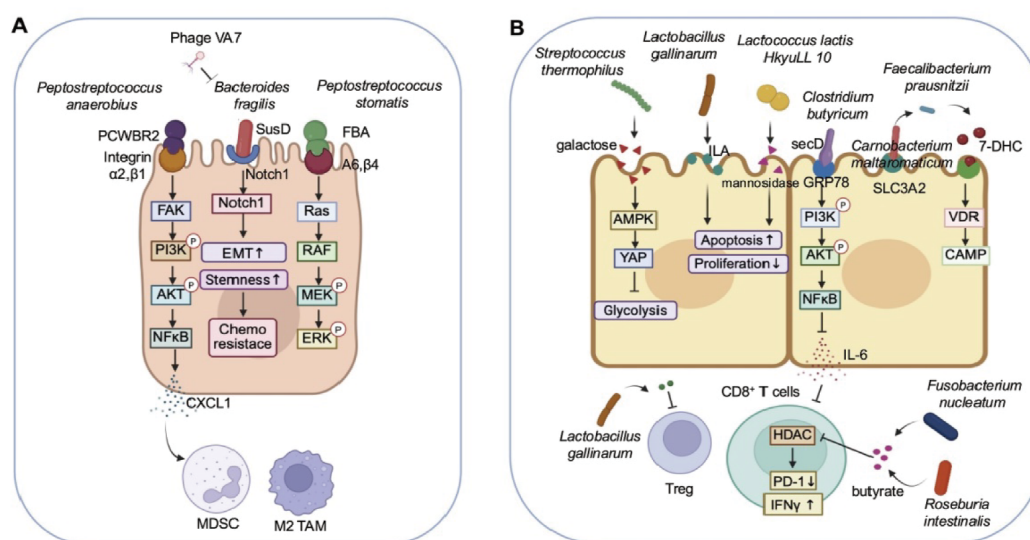


图2 微生态在结直肠癌中的作用与机制

(A)厌氧消化链球菌、脆弱拟杆菌和胃链球菌能够激活结直肠癌细胞的促癌通路,促进肿瘤免疫微环境中MDSCs和M2型巨噬细胞的浸润,从而推动结直肠癌的进展。(B)嗜热链球菌、鸡乳杆菌、乳酸乳球菌HkyuLL 10、丁酸梭菌和麦芽香肉杆菌等细菌可以抑制结直肠癌细胞的生长,分泌丁酸等代谢物,激活肿瘤免疫微环境中的CD8⁺ T细胞,并抑制Treg细胞,从而发挥抗肿瘤效应并增强结直肠癌的免疫治疗效果。

Figure 2 Gut microbiota in colorectal cancer

(A) *Peptostreptococcus anaerobius*, *Bacteroides fragilis*, and *Peptostreptococcus stomatis* can activate oncogenic pathways in colorectal cancer cells, promoting the infiltration of MDSCs and M2 macrophages in the tumor immune microenvironment, thereby driving the progression of colorectal cancer. (B) Bacteria such as *Streptococcus thermophilus*, *Lactobacillus gallinarum*, *Lactococcus lactis HkyuLL 10*, *Clostridium butyricum*, and *Carnobacterium maltaromaticum* can inhibit the growth of colorectal cancer cells by secreting metabolites like butyrate, activating CD8⁺ T cells in the tumor immune microenvironment, and suppressing Treg cells, thus exerting anti-tumor effects and enhancing the efficacy of colorectal cancer immunotherapy.

表1 微生态在胃肠肿瘤中的作用
Table 1 Roles of microbiota in gastric and colorectal cancer

菌株	肿瘤类型	效应方向	关键机制	参考文献
咽峡炎链球菌	胃癌	促进肿瘤进展	通过TMPC-Annexin A2-MAPK促进胃癌进展	[44]
厌氧消化链球菌	结直肠癌	促进肿瘤进展	诱导TLR2/4-ROS-SREBP2-胆固醇合成	[109]
厌氧消化链球菌	结直肠癌	促进肿瘤进展	通过PCWBR2-整合素α2/β1定植肠道	[110]
胃链球菌	结直肠癌	促进肿瘤进展	通过FBA-整合素α6/β4定植肠道	[112]
嗜热链球菌	结直肠癌	抑制肿瘤进展	代谢产生β-半乳糖苷酶	[86]
鸡乳杆菌	结直肠癌	抑制肿瘤进展	代谢产生吡啶-3-乳酸	[125]
乳酸乳球菌HkyluLL 10	结直肠癌	抑制肿瘤进展	代谢产生α-甘露糖苷酶	[89]
麦芽香肉杆菌	结直肠癌	抑制肿瘤进展	通过“雌激素-SLC3A2-麦芽香肉杆菌-维生素 D-VDR”轴抑癌	[90]
厌氧消化链球菌	结直肠癌	诱导免疫治疗耐药	通过CXCL1-CXCR2激活MDSC;分泌LytC_22激活MDSC	[131]
丁酸梭菌	结直肠癌	促进免疫治疗疗效	通过“secD-GRP78-IL-6”轴激活CD8 ⁺ T细胞	[88]
鸡乳杆菌	结直肠癌	促进免疫治疗疗效	分泌吡啶-3-羧酸抑制Treg细胞	[6]
肠道罗斯氏菌	结直肠癌	促进免疫治疗疗效	分泌丁酸激活CD8 ⁺ T细胞	[132]
具核梭杆菌	结直肠癌	促进免疫治疗疗效	分泌丁酸激活CD8 ⁺ T细胞	[134]

别出明确的肿瘤驱动菌,包括咽峡炎链球菌和厌氧消化链球菌等,同时揭示了乳杆菌、双歧杆菌和丁酸梭菌等有益菌的抑癌机制,阐明了微生物通过表面黏附蛋白与宿主受体的直接互作、分泌毒性因子或抑癌代谢物,以及调控胆固醇合成和免疫检查点等具体分子通路,介导其促癌或抑癌效应,为建立胃肠道微生态与消化系统肿瘤的因果关系提供了重要证据。此外,微生物在克服免疫治疗耐药和提升化疗敏感性方面的潜力日渐显现,展现了其作为下一代肿瘤治疗策略的光明前景(表1)。

尽管如此,胃肠肿瘤微生态领域仍面临诸多挑战。现有研究存在显著的人群异质性、样本来源差异和技术平台偏差,导致部分结果的可重复性不足^[136]。大多数促癌菌的分子机制尚未被完全阐明,且缺乏跨队列验证。针对有益菌及其与肿瘤治疗药物疗效相关的临床转化研究仍处于初步阶段,需要进一步评估其在复杂肿瘤微环境中的稳定性、安全性和有效性^[137,138]。

对于未来微生态在胃肠肿瘤中的研究,我们应从大规模的前瞻性人群队列入手,系统整合多组学技术,包括宏基因组学、代谢组学、蛋白质组学和宿主转录组学,深入挖掘并筛选出具有诊断、预后预测和治疗响应评估价值的微生物标志物,并进一步在多国、多民族及多地域的独立队列中进行验证,采用标准化的样本处理流程和生物信息学分析方法,以最大限度地消除地域差异、饮食习惯和遗传背景带来的偏倚。与此同时,我们应充分利用多种胃肠肿瘤动物模型体系,包括基因工程小鼠模型(如Apc^{Min/+}和

Kras突变模型)、致癌物诱导模型(如AOM/DSS诱导的肠癌模型)、患者来源异种移植模型(PDX),以及无菌(germ-free)与悉生(gnotobiotic)小鼠模型,在可控条件下精准验证特定菌株的促癌或抑癌因果效应。在此基础上,结合培养组学与代谢组学,深入解析关键功能代谢产物和细菌效应蛋白的分子作用机制,阐明它们通过调控宿主免疫应答、DNA损伤修复、炎症信号通路以及肿瘤免疫微环境等方式影响胃肠肿瘤的发生发展。进一步地,我们应推动高质量临床研究的开展,在标准治疗(包括化疗、放疗、靶向治疗和免疫治疗)的基础上,系统评估微生态干预对胃肠肿瘤患者临床结局的改善效果,明确最佳干预时机、给药方案及受益人群特征,探索个体化微生态疗法。通过调控胃肠道微生态的平衡,恢复宿主与微生物的共生关系,有望为胃肠肿瘤的精准预防与个性化治疗开辟全新路径。

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