生 物 工 程 学 报
Chinese Journal of Biotechnology
http://journals.im.ac.cn/cjbcn
DOI: 10.13345/j.cjb.210711

Jun. 25, 2022, 38(6): 2105-2119

·综 述·

肠道菌群在肿瘤发生发展及免疫治疗中作用的研究进展

邓寒丹，范兴丽

杭州医学院 基础医学与法医学院，浙江 杭州 311399

邓寒丹, 范兴丽. 肠道菌群在肿瘤发生发展及免疫治疗中作用的研究进展. 生物工程学报, 2022, 38(6): 2105-2119.
DENG HD, FAN XL. The role of intestinal microbiota in tumor occurrence, development and immunotherapy: a review. Chin J Biotech, 2022, 38(6): 2105-2119.

摘 要：肠道菌群是一个与人体共生的复杂微生物区系，近年来被越来越多的研究者所关注。研究发现，肠道菌群不仅在维持人体正常生理功能中起到重要作用，在肿瘤发生、发展、诊断及治疗中也有不可忽视的作用。本文在对肠道菌群与肿瘤关系进行概述的基础上，重点介绍了肠道菌群促进肿瘤发生、发展的主要机制，以及肠道菌群对抗肿瘤免疫治疗尤其是免疫检查点抑制疗法的影响。此外，文中还总结了目前可行的调节肠道菌群以提高肿瘤治疗疗效的方法，并提出了其中可能存在的困难和挑战。

关键词：肠道菌群；肿瘤；免疫治疗；免疫检查点抑制剂

The role of intestinal microbiota in tumor occurrence, development and immunotherapy: a review

DENG Handan, FAN Xingli

Institute of Basic Medicine and Forensic Medicine, Hangzhou Medical College, Hangzhou 311399, Zhejiang, China

Abstract: The intestinal microbiota is a complex micro-ecological system symbiotic with human body, which has attracted increasing attention in recent years. The intestinal microbiota plays important roles not only in maintaining normal physiological functions of the human body but also in the occurrence, development, diagnosis and treatment of tumors. This review summarized the relationship between the intestinal microbiota and tumor, highlighting the mechanisms by which intestinal microbiota modulates tumor occurrence, development and immunotherapy, particularly the immune checkpoint therapy. This

Received: September 13, 2021; **Accepted:** December 30, 2021; **Published online:** January 5, 2022
Supported by: The Basic Scientific Research Funds of Hangzhou Medical College (KYYB202002)
Corresponding author: FAN Xingli. E-mail: fxl@hmc.edu.cn
基金项目：杭州医学院基本科研业务费基础科研项目计划一般项目 (KYYB202002)

review also summarized the currently available methods for enhancing the efficacy of tumor therapy through regulation of intestinal microbiota. Challenges in the field as well as future perspectives were also discussed.

Keywords: intestinal microbiota; tumor; immunotherapy; immune checkpoint inhibitor

1 肠道菌群的概述

人体 (以重量 70 kg 计) 内的细菌总数大约为 3.8×10^{13} [1],其中肠道菌群数量最为庞大且种类多样。人体内的肠道菌群在分娩、哺乳以及直接接触等过程中获得，随后在不同环境暴露下发生改变[2-3]。肠道菌群与人体共存，达到一种平衡:一方面人体肠道为肠道菌群提供一个温度适宜、富含营养、具有保护性的微环境[4-5];另一方面菌群能帮助人体消化营养物质如复杂的碳水化合物等来提供营养和维生素,拮抗病原微生物。同时，肠道菌群在人体的免疫、代谢和炎症等生理功能中发挥十分重要的作用[6-7]。虽然现阶段已有大量关于肠道菌群的研究，但人体内“健康”菌群的具体组成目前仍未能确定。目前已经明确厚壁菌门 (Firmicutes)、拟杆菌门 (Bacteroidetes)、放线菌门 (Actinobacteria)、变形菌门 (Proteobacteria) 和疣微菌门 (Verrucomicrobia) 等是肠道菌群中的主要门类[8-10]。此外，正常机体的肠道菌群组成也并非永恒不变，其组成受环境、抗生素等药物治疗、饮食习惯、衰老、激素水平、生活习惯等多种因素的影响而发生改变[5,11-13]。

2 肠道菌群与肿瘤发生发展的关系

近年来，有关肠道菌群的研究受到越来越多的关注。研究者发现溃疡性结肠炎和克罗恩病[14]、动脉粥样硬化[15]、多发性硬化症[16]、艰难梭菌感染[17]、阿尔兹海默症[18]等疾病都与菌群失调相关。随着恶性肿瘤发病率的提高，肠道菌群与肿瘤的关系也逐渐成为研究热点[19-21]。然而不同的菌群变化对肿瘤发生发展的影响是不同的，有的改变伴随着对肿瘤生长的抑制，有的改变则促进肿瘤的生长。反之，不同的肿瘤发生也会伴随着不同的菌群改变。有研究发现，腺瘤患者的肠道菌群中厚壁菌门 (Firmicutes)、变形菌门 (Proteobacteria)、拟杆菌门 (Bacteroidetes)、放线菌门 (Actinobacteria)、绿湾菌门 (Chloroflexi)、蓝藻 (Cyanobacteria)、Candidate-division TM7、软壁菌门 (Tenericutes) 的丰度与正常人群相比存在显著性差异，乳球菌 (*Lactococcus*) 和假单胞菌 (*Pseudomonas*) 在癌前组织中富集，而肠球菌 (*Enterococcus*) 和芽孢杆菌 (*Bacillus*) 则丰度降低[22]。此外，有文献报道称，在乳腺癌患者的肠道微生物群中梭菌科 (Clostridiaceae)、粪杆菌属 (*Faecalibacterium*) 和胃瘤菌科 (Ruminococcaceae) 的相对丰度增高，而多尔氏菌属 (*Dorea*) 和毛螺菌科 (Lachnospiraceae) 的相对丰度降低[23]。

2.1 肠道菌群与肿瘤发生

2.1.1 肠道菌群自身及代谢产物的直接促癌作用

有些肠道细菌本身就是致癌物[24]。目前已知的肠道致癌细菌包括胆管癌相关的伤寒沙门氏菌 (*Salmonella typhi*)[25]以及与原发性肝癌、胃癌相关的幽门螺杆菌 (*Helicobacter* spp.)[26-27]等。其中，幽门螺杆菌已经被世界卫生组织确定为Ⅰ类致癌物[28]。有研究发现，一些肠道菌群的代谢物本身为癌转化剂或致癌物，如部分肠道微生物能通过门静脉系统将肝脏产生的初级胆汁酸转化成脱氧胆酸等次级胆汁酸，从而引起

DNA 损伤、肝毒性和癌性病变[29]。此外，肠道菌群中的梭菌科和瘤胃菌科 (Ruminococcaceae) 等能够通过产生 β-葡萄糖醛酸酶加快肠道内雌激素的早期解离，使得游离雌激素水平增高，从而诱导乳腺肿瘤发生[30-31]。

2.1.2 肠道菌群通过诱导炎症或免疫抑制途径的间接促癌作用

肠道菌群可以通过诱导炎症或发挥免疫抑制作用而间接发挥促肿瘤作用[32]。有研究报道肠毒素性脆弱拟杆菌 (enterotoxigenic *Bacteroides fragilis*, *ETBF*) 可以通过产生促炎性脆弱杆菌毒素参与结肠上皮细胞的多种信号转导，如上调丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号，刺激炎症状态，促进肿瘤形成[33-35]。Thiele 等还发现，*ETBF* 可以促进髓系干细胞分化为髓系抑制细胞，进而通过病原性炎症途径诱导结直肠癌 (colorectal cancer, CRC) 的发生发展[36]。此外，有研究表明具核梭杆菌 (*Fusobacterium nucleatum*, *FN*) 能够通过减少 $CD4^+$ T 细胞数量和下调 Tox 蛋白表达抑制机体抗肿瘤免疫功能，从而加快 CRC 的发展进程[37]。在人类肿瘤和小鼠肿瘤模型研究中，研究者还发现 *FN* 的 Fap2 蛋白与人体抑制性受体 IG 和 ITIM 域蛋白 T 细胞免疫受体 (TIGIT) 结合可以抑制机体的抗肿瘤免疫功能[38-39]。Rubinstein 等还发现 *FN* 能分泌 FadA 黏附素，结合上皮细胞钙黏蛋白的胞外区域，刺激连环蛋白通路，激活炎症反应和癌变[40]。

2.1.3 肠道菌群组成改变影响肿瘤的发生发展

研究表明，肥胖症患者的肠道中厚壁菌门丰度增高，其产生的细菌脂多糖 (lipopolysaccharide, LPS) 被血液吸收运输至肝脏后与肝细胞 toll 样受体 4 (toll-like receptor 4, TLR4) 结合激活免疫炎症反应，持续高水平 LPS 诱导的免疫炎症反应促进了肝癌的发生[41-42]。

然而不同细菌丰度的改变会对肿瘤的发生发展产生不同的影响。部分肠道菌群具有抗肿瘤作用[43-46]，如高丰度约氏乳酸杆菌能增加白介素-10 (interleukin-10, IL-10) 和转化生长因子-β (transforming growth factor-β, TGF-β) 的分泌，降低促炎因子浓度，减少 T 细胞浸润，进而降低小鼠淋巴瘤的发生率[47]，该类菌群的清除或丰度降低会间接导致肿瘤的发生。Blaser 和 Falkow 提出了一种假设，他们认为某些疾病的出现是由于肠道中重要的微生物清除或丰度降低，而不是机体暴露于有害微生物的机会增多[48-50]。有文献报道，反复使用抗生素造成的肠道菌群失调与消化道肿瘤的发生发展之间存在联系[51-52]。Anderson 等报道，由于抗生素的使用，幽门螺杆菌得以逐步根除，但是随之而来的是食管腺癌、胃食管反流病和巴瑞特氏食道症的发病率迅速上升[53]。动物实验表明，无菌 (germ-free, GF) 小鼠、使用广谱抗生素的小鼠以及无特异性免疫增强细菌小鼠的抗肿瘤治疗效果明显低于正常小鼠[54-56]。在一项针对转移性肺癌、肾癌和膀胱癌患者进行的独立回顾性分析中表明，抗生素的使用降低了程序性细胞死亡蛋白 1/程序性细胞死亡配体 1 (programmed cell death protein 1/programmed cell death 1 ligand 1, PD-1/PD-L1) 的单克隆抗体治疗效果[54]。此外，肠道菌群可调节恶性血液肿瘤异基因造血干细胞移植后出现感染和移植物抗宿主病 (graft versus host disease, GVHD) 的风险，而早期应用全身广谱抗生素可能降低肠道中保护性梭状菌 (protective *Clostridiales*) 的丰度，增加 GVHD 风险和移植相关的死亡率[57]。

2.2 肠道菌群对抗肿瘤免疫治疗的影响

基于肿瘤的免疫逃逸功能以及机体免疫功能下降等原因，目前很多肿瘤的治疗仍是医学界的难题[58]。抗肿瘤免疫疗法的出现给许多

患者带来了新希望,尤其是通过免疫检查点调节抗肿瘤免疫反应的研究,为肿瘤治疗带来了突破。然而,由免疫检查点抑制剂 (immune checkpoint inhibitor, ICI) 疗法引起的自身免疫和免疫耐受之间的失衡会导致常见并发症,即免疫相关不良事件 (immune-related adverse events, IRAEs),也称抗肿瘤免疫治疗毒性[59]。近年来,随着研究不断深入,研究者发现肠道微生物群不仅能调节机体的免疫功能,还能增强抗肿瘤免疫治疗效果。不仅如此,部分肠道菌群还可以减少 IRAEs 的发生[60]。

2.2.1 肠道菌群对宿主免疫系统的影响

肠道菌群与宿主免疫系统之间相互作用,调节机体免疫功能[61]。表达于固有免疫细胞表面的模式识别受体能够识别影响肠道微生物定植的病原相关分子模式和损伤相关分子模式,其中 TLRs 和 NOD 样受体在识别和监控病原微生物的过程中起到关键性作用,能有效降低肠道部位的感染几率[62]。肠道菌群表达的微生物相关分子模式 (microbial-related molecular pattern, MAMP) 可以激活固有免疫细胞的 TLRs,促进免疫耐受,而一旦菌群紊乱,MAMPs 将刺激树突状细胞 (dendritic cell, DC)、巨噬细胞产生促炎因子导致免疫失衡。研究表明,肠道中部分细菌的缺失会影响 TLRs 抑制信号通路中的多个分子,如核因子 κB、MYD88 等,为肿瘤细胞创造了免疫逃逸的机会,同时也导致肠道中促肿瘤炎症的产生[63]。也有研究发现,GF 小鼠肠道内相关淋巴组织存在发育缺陷[64],以及在黏膜免疫中起到关键作用的免疫球蛋白 A 在其肠道内分泌下降等问题[65]。

肠道菌群也会影响机体的适应性免疫。研究表明,肠道中的脆弱拟杆菌能够通过其荚膜多糖活化并诱导调节性 T 细胞 (regulatory cell T reg, Tregs) 产生 IL-10,从而抑制结肠炎[66]。此外,相关研究发现肠道内的乳酸杆菌、双歧杆菌等能诱导 Tregs 的生成,生成的 Tregs 细胞能维持机体对肠道内抗原的耐受[67]。将梭状芽孢杆菌定植于小鼠体内,能够提高其体内 TGF-β 水平,表达 Foxp3 转录因子,发挥 Tregs 样诱导作用;同时,幼鼠口服摄入梭状芽孢杆菌,成年后将表现出对结肠炎和全身免疫球蛋白 E 反应的耐受性[68]。

2.2.2 肠道菌群可增强抗肿瘤免疫治疗效果

近年来,研究表明肠道菌群能通过提高机体抗肿瘤免疫功能增强抗肿瘤免疫治疗效果(表 1)。肠道菌群菌体通过 TLR4 启动肿瘤浸润髓系细胞,其产生的肿瘤坏死因子迅速诱导出血性坏死,最终通过 $CD8^+$ T 细胞发挥抗肿瘤作用,从而延缓肿瘤生长并延长生存期[69-71]。肠道菌群还能通过代谢产物的局部和远距离效应影响机体抗肿瘤免疫功能[72]。Paulos 等发现,辐射损伤肠道中释放出的 LPS 可激活 TLR4 途径刺激的天然免疫应答,促进 $CD8^+$ T 细胞增殖,使抗肿瘤 $CD8^+$ T 细胞过继转移的疗效显著提高[73]。在结直肠肿瘤、宫颈癌和非转移性 MCA205 肉瘤等小鼠模型中也证实了肠道菌群能影响抗肿瘤 T 细胞的过继性转移,进而提高肿瘤治疗效果[74-76]。而抗生素治疗和 LPS 中和会使抗肿瘤疗效降低[71,73],这也从侧面证实了肠道菌群及 LPS 一定程度上能提高机体抗肿瘤功能。

多项研究表明,肠道内拟杆菌能提高细胞毒性 T 淋巴细胞抗原 4 (cytotoxic T-lymphocyte antigen-4, CTLA-4) 阻断的抗肿瘤免疫治疗效果[55,77]。GF 小鼠口服拟杆菌 (*Bacteroides* spp.),能促进肿瘤内 DC 细胞成熟,肿瘤引流区淋巴结 Th1 反应升高,从而使抗 CTLA-4 肿瘤免疫治疗效果提高[77]。Vétizou 等研究发现,服用了万古霉素的小鼠肠道内拟杆菌 (*Bacteroides*)

和伯克氏杆菌 (*Burkholderiales*) 明显增加，而革兰氏阳性梭菌 (*Clostridiales*) 显著减少，CTLA-4 阻断的抗肿瘤治疗作用增强[55]。Sivan 等发现双歧杆菌能改变 DC 细胞活性，进而改善肿瘤特异性 $CD8^+$ T 细胞功能，从而提高抗 PD-L1 的抗肿瘤免疫治疗效果[56,78-79]。Vétizou 等发现，脆弱拟杆菌、多形拟杆菌、伯克氏杆菌等能影响 CTLA-4 抑制剂的有效性，抗 CTLA-4 治疗后拟杆菌和伯克氏杆菌的相对丰度快速降低，而梭菌的相对丰度升高[55]。当然，随着人们对肠道菌群与抗肿瘤免疫治疗之间的研究不断深入，肠道菌群与抗肿瘤免疫治疗效果之间的关系有待进一步研究[80]。

2.2.3 肠道菌群对抗肿瘤免疫治疗毒性作用的影响

抗肿瘤免疫治疗疗法的出现，为晚期恶性肿瘤，特别是非小细胞肺癌、黑色素瘤和肾细胞癌等的治疗带来了新突破[81-83]。然而抗肿瘤免疫治疗往往会伴随一些并发症，即 IRAEs[84]。有文献报道肠道菌群与 IRAEs 相关[85-86]，而结肠炎是常见的 IRAE[87]。

Dubin 等发现，在接受抗 CTLA-4 抗体治疗的转移性黑色素瘤患者中，未出现结肠炎并发症患者的粪便中有较高丰度的拟杆菌门 (Bacteroidetes)，包括拟杆菌科 (Bacteroidaceae)、理研菌科 (Rikenellaceae)、巴恩斯氏菌科

表 1 影响抗肿瘤免疫治疗的细菌及其代谢产物

Table 1 Bacteria and their metabolites affecting anti-tumor immunotherapy

Tumor	Bacteria/bacterial metabolites	Mechanism	Immunotherapy	References
MC38 colon carcinoma	*Alistipes* and *Ruminococcus* (+), *Lactobacillus* (–)	TLR4 activation→tumor-associated myeloid cells product TNF→$CD8^+$ T cell response	Anti-IL-10R/CpG-ODN	[71]
B16F10 melanoma	Metabolites: LPS↑ (+)	TBI→intestinal microbiota→LPS↑→$CD8^+$ T cell activation	ACT	[73]
Colorectal tumors	Bacteria↓ (–)	CTX+ACT ($CD4^+$ T cell)→durable complete remission→Antibiotics→lose efficacy	CTX+ACT	[74]
Cervical cancer	*Bacteroidetes* and *Clostridiales* (+)	Vancomycin→dysbacteriosis→$CD8\alpha^+$ DCs↑→IL-12p70↑→ACT efficacy↑	ACT	[75]
MCA205 sarcomas	*Lactobacilli* and *Enterococci* (+)	Vancomycin blunts CTX-induced pT_H17 differentiation, which is mandatory for the tumoricidal activity of chemotherapy	CTX+ACT	[76]
Melanoma	*Bifidobacterium* (+)	*Bifidobacterium*→DC→function of $CD8^+$ T cell↑→anti-PD-L1↑	Anti-PD-L1	[56]
Metastatic melanoma	*Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium* (+)	Reconstitution of germ-free mice with fecal material→T cell responses↑→anti-PD-L1↑	Anti-PD-L1	[79]
Melanoma	*Bacteroidetes fragilis*, *Bacteroides thetaiotaomicron*, *Burkholderiales* (+)	*Bacteroides* spp.→DC→Th1 immune responses↑→anti-CTLA-4	Anti-CTLA-4	[55]

Note: "↑": increase, "↓": decrease, (+): positive correlation, (–): negative correlation, TNF: tumor necrosis factor, TBI: lymphodepletion with total body irradiation, LPS: lipopolysaccharide, DC: dendritic cell, pT_H17: "pathogenic" T helper 17 cells.

(Barnesiellaceae)，表明抗 CTLA-4 相关结肠炎的发生可能与肠道内特定的菌群组成有关[88]。用脆弱拟杆菌和伯克氏菌对抗生素处理后的小鼠进行肠道重建，能够减少抗 CTLA-4 治疗后发生结肠炎的概率[89]。也有研究表明，虽然高丰度的拟杆菌门能降低 ICI 免疫治疗患结肠炎的风险，但是此类患者往往伴随 ICI 治疗后的不良预后；而厚壁菌门 (Firmicutes)、粪杆菌属 (*Faecalibacterium*) 丰度较高而拟杆菌门丰度较低的患者虽然患结肠炎的风险较高，但无进展生存期 (progression-free survival) 和总生存期 (overall survival) 更长[85-90]。由此能够看出特定的菌群丰度提高 ICI 疗效的同时增加了结肠炎易感性[91]。

目前，人们对 IRAEs 的发病机制知之甚少。Chaput 等称抗 CTLA-4 治疗产生的结肠炎可能与厚壁菌门诱导的 $ICOS^+$Treg 细胞与 $ICOS^+CD4^+$ T 细胞比例的增加有关[85]，但并未完全解释 IRAEs 的发病机制，这也是未来抗肿瘤研究需要解决的问题。

3 肠道菌群在抗肿瘤治疗中的应用

现已证实肠道菌群在肿瘤的发生、发展、治疗、诊断及预后诊断中起到重要的作用，可以为抗肿瘤治疗提供新的方法，减少抗肿瘤免疫治疗的副作用，这让肠道菌群在肿瘤治疗领域具有了一定的应用前景。目前，可以通过合理使用抗生素、粪菌移植 (fecal microbiota transplantation, FMT)、益生菌干预以及益生元使用、饮食调节等方法来调节肠道菌群组成，从而来提高抗肿瘤治疗效果。

3.1 肠道菌群可作为肿瘤诊断的标志物

近年来已有相关临床研究表明，肠道菌群可作为潜在指标被应用于肿瘤的早期诊断[92]或预后诊断[93] (表 2)。对中国、奥地利、美国、德国、法国等地共 526 位 CRC 患者的粪便亚基因组样本进行了分析，发现了 CRC 患者肠道中的 7 种富集菌，包括脆弱拟杆菌、*FN*、溶孢卟啉单胞菌 (*Porphyromonas asaccharolytica*)、微单胞菌 (*Parvimonas micra*)、中间普氏菌 (*Prevotella intermedia*)、芬氏别样杆菌 (*Alistipes finegoldii*) 和嗜热微生物弧菌 (*Thermanaerovibrio acidaminovorans*)，并确定了它们在人群中的稳定性，表明了可以应用细菌标志物作为 CRC 无创性诊断的诊断指标[94-95]。也有研究表明，肠道菌群组成种类的变化可能成为肺癌更方便且高效的生物诊断标志物，可为肺癌的预测、早期诊断提供特定的肠道微生物监测指标[96]。Zhuang 等发现，肺癌患者的肠道菌群组成和正常对照组有显著的差异，其粪便中肠球菌丰度明显增高，而放线菌和双歧杆菌丰度降低。同时，正常对照组的肠道菌群功能谱明显高于肺癌组，且肺癌患者通过多种途径表现出各种代谢物水平的降低和肿瘤易感性的增强[97]。肝癌早期症状不明显，缺乏特异性早期诊断标志物，这使得较多肝癌患者确诊时为时已晚，肝脏与肠道菌群之间的相互作用使得肠道菌群作为诊断肝脏肿瘤的生物标志物成为可能[98]。研究发现肝硬化患者艾克曼菌 (*Akkermansia*) 丰度低，而链球菌 (*Streptococcus*) 和肠杆菌 (Enterobacteriaceae) 丰度相对较高[99]。肝细胞癌患者体内拟杆菌[99-100]和瘤胃菌科增多，而双歧杆菌减少[99]。上述研究表明，以肠道菌群为标志物有望成为肝癌诊断的一种重要方法。

Hakim 等对急性淋巴细胞白血病 (acute lymphoblastic leukemia, ALL) 患者体内的肠道菌群进行研究，发现 ALL 患者体内变形菌门、厚壁菌门的丰度变化能够预测放疗后副作用程度，当患者体内的变形菌门丰度较高时，发热性中性粒细胞减少的发生率增加；厚壁菌门中

的链球菌科丰度较高时，伴发腹泻的风险显著增加；而厚壁菌门中的肠球菌科为优势菌时，发热性中性粒细胞减少和腹泻的发生率均显著增加[101]。*FN* 是一种具有促癌作用的肠道细菌，Mima 等对 1 069 例直肠癌和结肠癌患者进行了随访研究，并检测其癌组织中 *FN* 的 DNA 含量，结果显示 CRC 组织中 *FN* 的 DNA 含量与生存期负相关[102]。Yu 等通过生物信息学和功能研究揭示了 *FN* 能通过激活自噬提高 CRC 患者对化疗的耐药性，导致治疗失败、病情复发[103]。这些研究证实了肠道菌群可作为预后诊断的生物标志物。

表 2　可作为癌症早期诊断或预后诊断指标的细菌富集/变化情况

Table 2　Bacterial enrichment/changes that can be used as an indicator for early diagnosis or prognostic diagnosis of cancer

Cancer	Bacterial enrichment/change	Diagnosis/prognosis	References
CRC	*Eubacterium hallii*, *Parvimonas micra*, *Peptostreptococcusstomatis*, *Eubacterium eligens*, *Parabacteroides merdae*, *Oscillospira*, *Streptococcus salivarius*, *Clostridium symbiosum*, *Clostridium hathewayi*	Diagnosis	[92]
CRC	*Bacteroidetes fragilis*, *FN*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *Prevotella intermedia*, *Alistipes finegoldii*, *Thermanaerovibrio acidaminovorans*	Diagnosis	[94]
Lung cancer	*Enterococcus*↑, *Bifidobacterium* and Actinobacteria↓	Diagnosis	[97]
Liver cancer	*Bacteroides* and Ruminococcaceae↑, *Bifidobacterium*↓	Diagnosis	[99]
Liver cancer	*Streptococcus parasanguis*, *Streptococcus salivarius*, *streptococcus mutans*, *Streptococcus thermophilus*, *Haemophilus parainfluenzae*, *Veillonella*, *Veillonella dispar*↑, *Akkermansia muciniphila*, *Prevotella*, *Alistipes*↓	Diagnosis	[100]
ALL	Proteobacteria	Prognosis: febrile neutropenia	[101]
ALL	Streptococcaceae	Prognosis: diarrheal illness	[101]
ALL	Enterococcaceae	Prognosis: febrile neutropenia and diarrheal illness	[101]
CRC	*FN*↑	Prognosis: shorter survival	[102]
CRC	*FN*↑	Prognosis: chemoresistance	[103]
Pancreatic cancer (qi-stagnancy and blood stasis)	*Bacteroides*, *Prevotella*, *Faecalibacterium*, *Bifidobacterium*, *Roseburia*	Prognosis: median survival time-12 months	[93]
Pancreatic cancer (syndrome of dampness-heat due to spleen deficiency)	*Bacteroides*, *Streptococcus*, *Escherichia*/*Shigella*, *Klebsiella*, *Prevotella*	Prognosis: median survival time-8 months	[93]
Pancreatic cancer (endoretention of damp heat)	*Bacteroides*, *Escherichia*/*Shigella*, *Klebsiella*, *Faecalibacterium*, *ClostridiumXIVa*	Prognosis: median survival time-18 months	[93]

Note: CRC: colorectal cancer, ALL: acute lymphoblastic leukemia, "↑": increase, "↓": decrease.

3.2 通过抗生素的合理使用调节肠道菌群提高抗肿瘤疗效

抗生素的合理使用可以去除肠道内的多种细菌，其中部分菌群的去除可以减少抗肿瘤治疗后的并发症和副作用。吻合口瘘 (anastomotic leak, AL) 是结肠癌患者结直肠切除术后常见的并发症之一[104]，有研究表明术前联合口服抗生素能将结直肠手术的 AL 发生率从 5.7%降低到 2.8%[105]。然而，抗生素使用中一个突出的问题就是缺乏特异性，非靶向性杀菌会导致菌群失调，从而降低抗肿瘤治疗的效果[77]。Ahmed 等发现，在 PD-L1 表达没有统计学差异的情况下，在治疗前和/或后 2 周接受抗生素治疗的肺癌、肾癌、肝癌、黑色素瘤、头颈部癌患者抗 PD-L1 应答率较未接受抗生素治疗的患者低，使用广谱抗生素的肿瘤患者抗 PD-L1 治疗效果低于使用革兰氏阳性菌敏感的窄谱抗生素的肿瘤患者[106]。然而，Hakozaki 等发现治疗前接受抗生素治疗的非小细胞肺癌患者抗 PD-1 治疗效果低于非抗生素治疗的患者，在多因素分析中肿瘤患者生存率与治疗前是否使用抗生素之间无显著相关性[107]。目前有学者认为，免疫治疗前后使用抗生素与免疫治疗效果无直接关系，这可能是由于微生物组成成分会在抗生素停用后快速发生改变[108]。为了解决抗生素使用缺乏特异性的问题，未来可以采用联合益生菌用药、利用小分子靶向致癌细菌毒素、具有高度特异性的吞噬治疗等策略来提高治疗的有效性[109]。

3.3 通过粪菌移植调节肠道菌群提高抗肿瘤疗效

菌群移植作为一种恢复肠道菌群的新型治疗方法，在临床和研究中的重要地位日益凸显。菌群移植最明确的适应症为复发性艰难梭菌感染，有效性高达 92%[110]。目前正在使用粪菌移植治疗各种疾病，包括肝性脑病、肠易激综合征、代谢综合征、GVHD 和自闭症等[111-115]。动物实验中，Routy 等发现移植了对 PD-1 抑制剂敏感小鼠粪菌的小鼠表现出肿瘤生长延迟，肿瘤微环境中的 $CXCR3^+CD4^+$ T 细胞积累，脾 T 细胞的 PD-L1 上调等现象[54]。Matson 等发现，将对 PD-1 抑制剂敏感和不敏感的黑色素瘤患者的粪菌分别移植到 GF 小鼠，然后植入黑色素瘤细胞，其中移植 PD-1 抑制剂不敏感患者粪菌的 3 只小鼠中有 2 只表现出肿瘤生长快的特征，而移植 PD-1 抑制剂敏感患者粪菌的 3 只小鼠中有 2 只表现出肿瘤生长慢的特征[79]。

除了动物模型研究，目前也有临床试验将 FMT 与肿瘤治疗相结合。相关临床试验表明，将对抗 PD-1 治疗敏感的转移性黑色素瘤患者粪便微生物群移植给对抗 PD-1 耐药的转移性黑色素瘤患者，再配合抗 PD-1 治疗，其有效率可达 30%。通过肿瘤活检发现，肿瘤内浸润 $CD8^+$ T 细胞、Th1 细胞、抗原提呈细胞增加[116-117]。另有临床试验表明，通过 FMT 对慢性放射性肠炎 (chronic radiation enteritis, CRE) 患者进行治疗后，60%的患者腹泻、直肠出血、腹/直肠疼痛和大便失禁等 CRE 常见症状得到改善，且无与 FMT 治疗相关的死亡及感染性并发症发生[118]。最新的一项临床试验发现，给 20 例转移性肾细胞癌患者进行为期 4 周的 FMT 治疗，4 周后转移性肾细胞癌患者酪氨酸激酶抑制剂引起的腹泻得到有效缓解[119]。尽管动物实验和临床试验表明 FMT 可作为抗肿瘤治疗的辅助治疗，但 FMT 的应用依然具有局限性，如何选择更加有效的供体，提高供体与患者之间的匹配程度以及明确 FMT 的机制等仍是 FMT 辅助抗肿瘤治疗需要解决的问题。

3.4 通过益生菌和益生元调节肠道菌群提高抗肿瘤疗效

“益生菌” (probiotics) 是细菌或活菌的组

合。机体摄入足量的益生菌有益于健康[120-121]。在成人和儿童肿瘤患者中安全性和有效性的评估分析显示，益生菌可能具有抗肿瘤作用，但机制尚不清楚[122]。在临床试验中发现，给 CRC 患者注射益生菌后肠道黏膜和粪便中微生物组成发生改变，产丁酸的细菌数量有所增加，对维持正常结肠的稳态起重要的作用[123]。此外，Xia 等通过给 77 例晚期鼻咽癌患者使用益生菌治疗后发现，益生菌通过改善肠道菌群结构，增强鼻咽癌患者的免疫应答，显著降低了患者化疗引起的口腔黏膜炎的严重程度[124]。最新临床研究还证明了癌症患者使用植物乳杆菌 299v 可减轻肠内营养相关胃肠道症状，如恶心、呕吐、腹泻等[125]。另有研究表明，浅表性膀胱癌患者经过尿道电切联合表阿霉素膀胱灌注治疗后口服干酪乳杆菌 (*Lactobacillus casei*) 一年，虽然总生存率没有明显变化，但复发率明显降低[126]。然而也有研究显示，使用益生菌会增加肿瘤外显率和多样性，这可能是由于给药时间不同造成的[127]。

益生元 (prebiotics) 即是被宿主不可消化或吸收的膳食纤维，它是益生菌的养料，能促进益生菌的生长，有益于人体健康[128]。目前已有研究发现联合应用菊粉、低聚果糖等益生元能使结肠中的双歧杆菌数目增加，菊粉和低聚果糖被肠道菌群迅速完全发酵并产生短链脂肪酸，同时抑制了外周血单个核细胞分泌 IL-2 的增加，并增加了癌症患者体内 IFN-γ 的产生。这些发现使菊粉、低聚果糖等益生元成为预防 CRC 的重要手段[129]。晚期黑色素瘤患者对免疫治疗的不良反应与患者肠道菌群的低多样性有关，益生菌和益生元的应用可以在一定程度上改善此类问题[130]。因此，益生菌和益生元在协助抗肿瘤治疗领域具有很好的应用前景。

3.5 通过饮食调节肠道菌群提高抗肿瘤疗效

饮食的改变影响着肠道微生物群，不同食物的摄入不仅在塑造肠道菌群组成方面起着重要的作用，还能引起菌群代谢产物如包括丁酸在内的短链脂肪酸 (short chain fatty acids, SCFAs) 的相对变化[28,131]。丁酸既是一种 SCFAs 又是一种组蛋白去乙酰化酶抑制剂，能上调 CRC 细胞的肿瘤抑制基因表达以及免疫细胞中的抗炎基因表达[132-135]，当机体内摄入水果和蔬菜时能引起拟杆菌门、厚壁菌门的丰度增高，膳食纤维被代谢成大量丁酸，而摄入精致谷物和添加糖则会引起其代谢浓度降低[136]。此外，富含全谷物和纤维的饮食能降低与结肠癌相关的 *FN* 感染的风险[137]。相反，氨基酸的发酵会产生如氨、酚、硫化氢等有害代谢产物，从而促进癌症等疾病的发生[138]。有研究表明，小鼠高脂饮食会导致细菌易位进入血液、激活炎症[139]，表现出高水平的胰岛素抵抗和脂肪组织炎症[140]，而高纤维和益生元的摄入增加了其体内的菌群多样性，并降低了 IL-6、胰岛素抵抗和餐后血糖峰值[141]。因此，通过合理的饮食调节改变肠道菌群结构，能够增强抗肿瘤免疫反应，减少炎症反应，可在一定程度上有益于癌症治疗。

4 总结与展望

肠道菌群与肿瘤之间的关系是近几年的研究热点。大量临床前/临床研究已经证实了肠道菌群与抗肿瘤免疫之间的关系以及其对抗肿瘤免疫治疗的影响，但是肠道菌群对肿瘤发生、发展以及抗肿瘤免疫治疗影响的具体机制尚不十分明确，需要上升到分子水平进行研究。同时，我们也需要进行大量的研究去探索肠道菌群中有益于抗肿瘤免疫治疗的优势菌群，确定每种临床状况相应的最有利的菌群组成，但这也需要我们解决长期以来肠道菌群中厌氧菌难培养、多种细菌难分离等问题，制定干预策略实现个性化的疗法。通过应用 FMT、益生菌等

方法调节菌群能在一定程度上提高抗肿瘤治疗效果，但动物模型与人体肠道菌群的差异性(如人类和小鼠肠道中虽然存在许多共同菌属，但其中细菌基因的同源性很低)、临床试验受限、风险难以控制等问题都使肠道菌群应用于治疗具有局限性，这也是我们需要继续努力的方向。尽管运用肠道菌群作为诊断工具、靶向治疗癌症和其他疾病仍处在较为初级的阶段，但不少研究已经证明了其可能性，未来有可能成为精准医疗的前沿方向。

REFERENCES

[1] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol, 2016, 14(8): 1-14.

[2] Li W, Deng Y, Chu Q, et al. Gut microbiome and cancer immunotherapy. Cancer letters, 2019, 447: 41-47.

[3] Biasucci G, Rubini M, Riboni S, et al. Mode of delivery affects the bacterial community in the newborn gut. Early Hum Dev, 2010, 86(1): 13-15.

[4] Zitvogel L, Galluzzi L, Viaud S, et al. Cancer and the gut microbiota: an unexpected link. Sci Transl Med, 2015, 7(271): 1-24.

[5] Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer, 2013, 13(11): 800-812.

[6] Dzutsev A, Goldszmid RS, Viaud S, et al. The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. Eur J Immunol, 2015, 45(1): 17-31.

[7] Jia W, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat Rev Gastroenterol Hepatol, 2018, 15(2): 111-128.

[8] Kamada N, Chen GY, Inohara N, et al. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol, 2013, 14(7): 685-690.

[9] Derrien M, Vaughan EE, Plugge CM, et al. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. Int J Syst Evol Microbiol, 2004, 54(5): 1469-1476.

[10] Belcheva A, Irrazabal T, Martin A. Gut microbial metabolism and colon cancer: can manipulations of the microbiota be useful in the management of gastrointestinal health? Bioessays, 2015, 37(4): 403-412.

[11] Tomasello G, Mazzola M, Leone A, et al. Nutrition, oxidative stress and intestinal dysbiosis: influence of diet on gut microbiota in inflammatory bowel diseases. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub, 2016, 160(4): 461-466.

[12] Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. Cell Mol Life Sci, 2017, 74(16): 2959-2977.

[13] Savin Z, Kivity S, Yonath H, et al. Smoking and the intestinal microbiome. Arch Microbiol, 2018, 200(5): 677-684.

[14] Franzosa EA, Sirota-Madi A, Avila-Pacheco J, et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. Nat Microbiol, 2019, 4(2): 293-305.

[15] Chen ML, Yi L, Zhang Y, et al. Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. mBio, 2016, 7(2): e02210-02215.

[16] Cignarella F, Cantoni C, Ghezzi L, et al. Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metab, 2018, 27(6): 1222-1235.e6.

[17] Rodríguez C, Romero E, Garrido-Sanchez L, et al. Microbiota insights in *Clostridium difficile* infection and inflammatory bowel disease. Gut Microbes, 2020, 12(1): 1-25.

[18] Kim MS, Kim Y, Choi H, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut, 2020, 69(2): 283-294.

[19] Heshiki Y, Vazquez-Uribe R, Li J, et al. Predictable modulation of cancer treatment outcomes by the gut microbiota. Microbiome, 2020, 8(28): 1-14.

[20] Uribe-Herranz M, Rafail S, Beghi S, et al. Gut microbiota modulate dendritic cell antigen presentation and radiotherapy-induced antitumor immune response. J Clin Invest, 2020, 130(1): 466-479.

[21] Li R, Zhou R, Wang H, et al. Gut microbiota-stimulated cathepsin K secretion mediates TLR4-dependent M2 macrophage polarization and promotes tumor metastasis in colorectal cancer. Cell Death Differ, 2019, 26(11): 2447-2463.

[22] Lu Y, Chen J, Zheng J, et al. Mucosal adherent bacterial dysbiosis in patients with colorectal adenomas. Sci Rep, 2016, 6: 1-10.

[23] Fernández M, Reina-Pérez I, Astorga J, et al. Breast

cancer and its relationship with the microbiota. Int J Environ Res Public Heal, 2018, 15(8): 1747-1767.

[24] 高志光. 肠道菌群结构异常与大肠癌发病风险及预后的相关性研究[D]. 上海: 上海交通大学, 2015.
Gao ZG. The correlative research of the effect of intestinal microbiota dysbiosis on the risk and prognosis of colorectal cancer[D]. Shanghai: Shanghai Jiao Tong University, 2015 (in Chinese).

[25] Di Domenico EG, Cavallo I, Pontone M, et al. Biofilm producing *Salmonella typhi*: chronic colonization and development of gallbladder cancer. Int J Mol Sci, 2017, 18(9): e1887-e1901.

[26] Huang Y, Fan XG, Wang ZM, et al. Identification of *Helicobacter* species in human liver samples from patients with primary hepatocellular carcinoma. J Clin Pathol, 2004, 57(12): 1273-1277.

[27] Elzouki ANY, Buhjab SI, Alkialani A, et al. Gastric cancer and *Helicobacter pylori* infection in the eastern Libya: a descriptive epidemiological study. Arab J Gastroenterol, 2012, 13(2): 85-88.

[28] Schistosomes, liver flukes and *Helicobacter pylori*. IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 7-14 June 1994. IARC monographs on the evaluation of carcinogenic risks to humans, 1994, 61: 1-241.

[29] Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature, 2013, 499(7456): 97-101.

[30] Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. CA Cancer J Clin, 2017, 67(4): 326-344.

[31] Plottel CS, Blaser MJ. Microbiome and malignancy. Cell Host Microbe, 2011, 10(4): 324-335.

[32] Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol, 2017, 14(9): 527-539.

[33] Dejea CM, Fathi P, Craig JM, et al. Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science, 2018, 359(6375): 592-597.

[34] Boleij A, Hechenbleikner EM, Goodwin AC, et al. The *Bacteroides fragilis* toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clin Infect Dis, 2015, 60(2): 208-215.

[35] Grivennikov S, Karin E, Terzic J, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell, 2009, 15(2): 103-113.

[36] Thiele Orberg E, Fan H, Tam AJ, et al. The myeloid immune signature of enterotoxigenic *Bacteroides fragilis*-induced murine colon tumorigenesis. Mucosal Immunol, 2017, 10(2): 421-433.

[37] Chen T, Li Q, Zhang X, et al. TOX expression decreases with progression of colorectal cancers and is associated with CD4 T-cell density and *Fusobacterium nucleatum* infection. Hum Pathol, 2018, 79: 93-101.

[38] Kostic AD, Chun E, Robertson L, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe, 2013, 14(2): 207-215.

[39] Gur C, Ibrahim Y, Isaacson B, et al. Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack. Immunity, 2015, 42(2): 344-355.

[40] Rubinstein MR, Wang X, Liu W, et al. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe, 2013, 14(2): 195-206.

[41] Carpino G, Del Ben M, Pastori D, et al. Increased liver localization of lipopolysaccharides in human and experimental NAFLD. Hepatology, 2020, 72(2): 470-485.

[42] Barczyńska R, Litwin M, Sliżewska K, et al. Bacterial microbiota and fatty acids in the faeces of overweight and obese children. Pol J Microbiol, 2018, 67(3): 339-345.

[43] Zitvogel L, Daillère R, Roberti MP, et al. Anticancer effects of the microbiome and its products. Nat Rev Microbiol, 2017, 15(8): 465-478.

[44] Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell Host Microbe, 2014, 15(3): 317-328.

[45] Brennan CA, Garrett WS. Gut microbiota, inflammation, and colorectal cancer. Annu Rev Microbiol, 2016, 70: 395-411.

[46] Hold GL. Gastrointestinal microbiota and colon cancer. Dig Dis, 2016, 34(3): 244-250.

[47] Yamamoto ML, Maier I, Dang AT, et al. Intestinal bacteria modify lymphoma incidence and latency by affecting systemic inflammatory state, oxidative stress, and leukocyte genotoxicity. Cancer Res, 2013, 73(14): 4222-4232.

[48] Blaser MJ, Falkow S. What are the consequences of the disappearing human microbiota? Nat Rev Microbiol, 2009, 7(12): 887-894.

[49] Blaser MJ. Disappearing microbiota: *Helicobacter*

pylori protection against esophageal adenocarcinoma. Cancer Prev Res (Phila), 2008, 1(5): 308-311.

[50] Strachan DP. Hay fever, hygiene, and household size. BMJ, 1989, 299(6710): 1259-1260.

[51] Zhu Z, Huang J, Li X, et al. Gut microbiota regulate tumor metastasis via circRNA/miRNA networks. Gut Microbes, 2020, 12(1): 1-16.

[52] Boursi B, Mamtani R, Haynes K, et al. Recurrent antibiotic exposure may promote cancer formation—another step in understanding the role of the human microbiota? Eur J Cancer, 2015, 51(17): 2655-2664.

[53] Anderson LA, Murphy SJ, Johnston BT, et al. Relationship between *Helicobacter pylori* infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut, 2008, 57(6): 734-739.

[54] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science, 2018, 359(6371): 91-97.

[55] Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science, 2015, 350(6264): 1079-1084.

[56] Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science, 2015, 350(6264): 1084-1089.

[57] Jenq RR, Taur Y, Devlin SM, et al. Intestinal blautia is associated with reduced death from graft-versus-host disease. Biology of blood and marrow transplantation: Journal of the American Society for Blood and Marrow Transplantation, 2015, 21(8): 1373-1383.

[58] Ge Z, Wu S, Zhang Z, et al. Mechanism of tumor cells escaping from immune surveillance of NK cells. Immunopharmacol Immunotoxicol, 2020, 42(3): 187-198.

[59] Wang Q, Xu R. Immunotherapy-related adverse events (irAEs): extraction from FDA drug labels and comparative analysis. JAMIA Open, 2019, 2(1): 173-178.

[60] Fessler J, Matson V, Gajewski TF. Exploring the emerging role of the microbiome in cancer immunotherapy. J Immunother Cancer, 2019, 7(1): 108-123.

[61] D'Alessandro G, Antonangeli F, Marrocco F, et al. Gut microbiota alterations affect glioma growth and innate immune cells involved in tumor immunosurveillance in mice. Eur J Immunol, 2020, 50(5): 705-711.

[62] O'Neill LA, Golenbock D, Bowie AG. The history of toll-like receptors-redefining innate immunity. Nat Rev Immunol, 2013, 13(6): 453-460.

[63] Tanoue T, Umesaki Y, Honda K. Immune responses to gut microbiota-commensals and pathogens. Gut Microbes, 2010, 1(4): 224-233.

[64] Bouskra D, Brézillon C, Bérard M, et al. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature, 2008, 456(7221): 507-510.

[65] Moreau MC, Ducluzeau R, Guy-Grand D, et al. Increase in the population of duodenal immunoglobulin A plasmocytes in axenic mice associated with different living or dead bacterial strains of intestinal origin. Infect Immun, 1978, 21(2): 532-539.

[66] Round JL, Mazmanian SK. Inducible $Foxp3^+$ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. PNAS, 2010, 107(27): 12204-12209.

[67] Cebula A, Seweryn M, Rempala GA, et al. Thymus-derived regulatory T cells contribute to tolerance to commensal microbiota. Nature, 2013, 497(7448): 258-262.

[68] Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. Science, 2011, 331(6015): 337-341.

[69] Scheiermann J, Klinman DM. Clinical evaluation of CpG oligonucleotides as adjuvants for vaccines targeting infectious diseases and cancer. Vaccine, 2014, 32(48): 6377-6389.

[70] Guiducci C, Vicari AP, Sangaletti S, et al. Redirecting *in vivo* elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection. Cancer Res, 2005, 65(8): 3437-3446.

[71] Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science, 2013, 342(6161): 967-970.

[72] Chen D, Jin D, Huang S, et al. *Clostridium butyricum*, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. Cancer Lett, 2020, 469: 456-467.

[73] Paulos CM, Wrzesinski C, Kaiser A, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific $CD8^+$ T cells via TLR4 signaling. J Clin Invest, 2007, 117(8): 2197-2204.

[74] Kuczma MP, Ding ZC, Li T, et al. The impact of

antibiotic usage on the efficacy of chemoimmunotherapy is contingent on the source of tumor-reactive T cells. Oncotarget, 2017, 8(67): 111931-111942.

[75] Uribe-Herranz M, Bittinger K, Rafail S, et al. Gut microbiota modulates adoptive cell therapy via CD8α dendritic cells and IL-12. JCI Insight, 2018, 3(4): e94952(1-18).

[76] Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science, 2013, 342(6161): 971-976.

[77] Villéger R, Lopès A, Carrier G, et al. Intestinal microbiota: a novel target to improve anti-tumor treatment? Int J Mol Sci, 2019, 20(18): e4584-e4609.

[78] Snyder A, Pamer E, Wolchok J. Could microbial therapy boost cancer immunotherapy? Science, 2015, 350(6264): 1031-1032.

[79] Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science, 2018, 359(6371): 104-108.

[80] Derosa L, Routy B, Kroemer G, et al. The intestinal microbiota determines the clinical efficacy of immune checkpoint blockers targeting PD-1/PD-L1. Oncoimmunology, 2018, 7(6): e1434468(1-3).

[81] Brueckl WM, Ficker JH, Zeitler G. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). BMC Cancer, 2020, 20(1): 1185-1201.

[82] Jerby-Arnon L, Shah P, Cuoco MS, et al. A cancer cell program promotes T cell exclusion and resistance to checkpoint blockade. Cell, 2018, 175(4): 984-997.e24.

[83] Derosa L, Routy B, Fidelle M, et al. Gut bacteria composition drives primary resistance to cancer immunotherapy in renal cell carcinoma patients. Eur Urol, 2020, 78(2): 195-206.

[84] Naidoo J, Cottrell TR, Lipson EJ, et al. Chronic immune checkpoint inhibitor pneumonitis. J Immunother Cancer, 2020, 8(1): e000840(1-7).

[85] Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol, 2017, 28(6): 1368-1379.

[86] Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat Med, 2018, 24(12): 1804-1808.

[87] Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol, 2018, 4(12): 1721-1728.

[88] Dubin K, Callahan MK, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun, 2016, 7: 10391-10399.

[89] Gori S, Inno A, Belluomini L, et al. Gut microbiota and cancer: how gut microbiota modulates activity, efficacy and toxicity of antitumoral therapy. Crit Rev Oncol Hematol, 2019, 143: 139-147.

[90] Frankel AE, Coughlin LA, Kim J, et al. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia, 2017, 19(10): 848-855.

[91] Luo B, Zhang Y, Zhang C, et al. Intestinal microbiota: a potential target for enhancing the antitumor efficacy and reducing the toxicity of immune checkpoint inhibitors. Cancer Lett, 2021, 509: 53-62.

[92] 张昕雨, 张璟, 朱小强, 等. 基于宏基因组学分析构建诊断大肠癌的肠道菌群标签. 上海交通大学学报(医学版), 2018, 38(9): 1019-1026.
Zhang XY, Zhang J, Zhu XQ, et al. Bacterial signatures for diagnosis of colorectal cancer by fecal metagenomics analysis. J Shanghai Jiao Tong Univ (Med Sci Ed), 2018, 38(9): 1019-1026 (in Chinese).

[93] 陈卓, 钱祥, 张爱琴, 等. 基于肠道菌群结构特征研究胰腺癌不同中医证型与预后的相关性. 浙江中西医结合杂志, 2019, 29(12): 965-969.
Chen Z, Qian X, Zhang AQ, et al. Correlation between different TCM syndrome types of pancreatic cancer and their prognosis based on structural characteristics of intestinal flora. Zhejiang JITCWM, 2019, 29(12): 965-969 (in Chinese).

[94] Dai Z, Coker OO, Nakatsu G, et al. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. Microbiome, 2018, 6(1): 70-82.

[95] Wirbel J, Pyl PT, Kartal E, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nat Med, 2019, 25(4): 679-689.

[96] Zheng Y, Fang Z, Xue Y, et al. Specific gut microbiome signature predicts the early-stage lung cancer. Gut Microbes, 2020, 11(4): 1030-1042.

[97] Zhuang H, Cheng L, Wang Y, et al. Dysbiosis of the gut microbiome in lung cancer. Front Cell Infect Microbiol, 2019, 9: 112-121.
[98] Gupta H, Youn GS, Shin MJ, et al. Role of gut microbiota in hepatocarcinogenesis. Microorganisms, 2019, 7(5): 121-137.
[99] Ponziani FR, Bhoori S, Castelli C, et al. Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology, 2019, 69(1): 107-120.
[100] 郑微, 赵鹏, 张永宏, 等. 宏基因组测序技术分析原发性肝癌患者肠道菌群特征. 中华实验和临床感染病杂志, 2021, 15(3): 149-157.
Zheng W, Zhao P, Zhang YH, et al. Metagenomic analysis on characteristics of intestinal flora of patients with primary liver cancer. Chin J Exp Clin Infect Dis, 2021, 15(3): 149-157 (in Chinese).
[101] Hakim H, Dallas R, Wolf J, et al. Gut microbiome composition predicts infection risk during chemotherapy in children with acute lymphoblastic leukemia. Clin Infect Dis, 2018, 67(4): 541-548.
[102] Mima K, Nishihara R, Qian ZR, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. Gut, 2016, 65(12): 1973-1980.
[103] Yu T, Guo F, Yu Y, et al. *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy. Cell, 2017, 170(3): 548-563.e16.
[104] Qvist, Niels and 2015 European Society of Coloproctology collaborating group. The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit. Colorectal disease: the official journal of the Association of Coloproctology of Great Britain and Ireland, 2017, 19(8): 296-311.
[105] Scarborough JE, Mantyh CR, Sun Z, et al. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: an analysis of colectomy-targeted ACS NSQIP. Ann Surg, 2015, 262(2): 331-337.
[106] Ahmed J, Kumar A, Parikh K, et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. Oncoimmunology, 2018, 7(11): e1507670(1-6).
[107] Hakozaki T, Okuma Y, Omori M, et al. Impact of prior antibiotic use on the efficacy of nivolumab for non-small cell lung cancer. Oncol Lett, 2019, 17(3): 2946-2952.
[108] Ng KM, Aranda-Díaz A, Tropini C, et al. Recovery of the Gut Microbiota after Antibiotics Depends on Host Diet, Community Context, and Environmental Reservoirs. Cell host & microbe, 2019, 26(5):650-665.
[109] Cougnoux A, Delmas J, Gibold L, et al. Small-molecule inhibitors prevent the genotoxic and protumoural effects induced by colibactin-producing bacteria. Gut, 2016, 65(2): 278-285.
[110] Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. Aliment Pharmacol Ther, 2017, 46(5): 479-493.
[111] Bajaj JS, Salzman NH, Acharya C, et al. Fecal microbial transplant capsules are safe in hepatic encephalopathy: a phase 1, randomized, placebo-controlled trial. Hepatology, 2019, 70(5): 1690-1703.
[112] El-Salhy M, Hatlebakk JG, Gilja OH, et al. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut, 2020, 69(5): 859-867.
[113] Hartstra AV, Schüppel V, Imangaliyev S, et al. Infusion of donor feces affects the gut-brain axis in humans with metabolic syndrome. Mol Metab, 2020, 42: 101076-101093.
[114] Van Lier YF, Davids M, Haverkate NJE, et al. Donor fecal microbiota transplantation ameliorates intestinal graft-versus-host disease in allogeneic hematopoietic cell transplant recipients. Sci Transl Med, 2020, 12(556): 8926-8937.
[115] Kang DW, Adams JB, Gregory AC, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome, 2017, 5(1): 10-26.
[116] Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science, 2021, 371(6529): 602-609.
[117] Davar D, Dzutsev AK, McCulloch JA, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science, 2021, 371(6529): 595-602.
[118] Ding X, Li QQ, Li P, et al. Fecal microbiota transplantation: a promising treatment for radiation enteritis? Radiother Oncol, 2020, 143: 12-18.
[119] Ianiro G, Rossi E, Thomas AM, et al. Faecal microbiota

transplantation for the treatment of diarrhoea induced by tyrosine-kinase inhibitors in patients with metastatic renal cell carcinoma. Nat Commun, 2020, 11(1): 4333-4339.

[120] Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol, 2014, 11(8): 506-514.

[121] Guarner F. Probiotics. Int J Food Microbiol, 1998, 39(3): 237-238.

[122] Hassan H, Rompola M, Glaser AW, et al. Systematic review and meta-analysis investigating the efficacy and safety of probiotics in people with cancer. Support Care Cancer, 2018, 26(8): 2503-2509.

[123] Hibberd AA, Lyra A, Ouwehand AC, et al. Intestinal microbiota is altered in patients with colon cancer and modified by probiotic intervention. BMJ Open Gastroenterol, 2017, 4(1): e000145(1-12).

[124] Xia C, Jiang C, Li W, et al. A phase Ⅱ randomized clinical trial and mechanistic studies using improved probiotics to prevent oral mucositis induced by concurrent radiotherapy and chemotherapy in nasopharyngeal carcinoma. Front Immunol, 2021, 12: 618150(1-14).

[125] Kaźmierczak-Siedlecka K, Folwarski M, Ruszkowski J, et al. Effects of 4 weeks of *Lactobacillus plantarum* 299v supplementation on nutritional status, enteral nutrition tolerance, and quality of life in cancer patients receiving home enteral nutrition-a double-blind, randomized, and placebo-controlled trial. Eur Rev Med Pharmacol Sci, 2020, 24(18): 9684-9694.

[126] Naito S, Koga H, Yamaguchi A, et al. Prevention of recurrence with epirubicin and *Lactobacillus casei* after transurethral resection of bladder cancer. J Urol, 2008, 179(2): 485-490.

[127] Arthur JC, Gharaibeh RZ, Uronis JM, et al. VSL#3 probiotic modifies mucosal microbial composition but does not reduce colitis-associated colorectal cancer. Sci Rep, 2013, 3: 2868-2877.

[128] Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol, 2017, 14(8): 491-502.

[129] Rafter J, Bennett M, Caderni G, et al. Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. Am J Clin Nutr, 2007, 85(2): 488-496.

[130] Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science, 2018, 359(6371): 97-103.

[131] 周青青, 蒋丰岭, 王家妮, 等. 不同饮食摄入对小鼠糖脂代谢、肠道菌群的影响. 食品研究与开发, 2021, 42(10): 16-23.
Zhou QQ, Jiang FL, Wang JN, et al. Effects of different dietary ingestions on glucose and lipid metabolism, intestinal microbiota in mice. Food Res Dev, 2021, 42(10): 16-23 (in Chinese).

[132] Donohoe DR, Holley D, Collins LB, et al. A gnotobiotic mouse model demonstrates that dietary fiber protects against colorectal tumorigenesis in a microbiota-and butyrate-dependent manner. Cancer Discov, 2014, 4(12): 1387-1397.

[133] Donohoe DR, Collins LB, Wali A, et al. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell, 2012, 48(4): 612-626.

[134] Davie JR. Inhibition of histone deacetylase activity by butyrate. J Nutr, 2003, 133(7 suppl): 2485S-2493S.

[135] Chang PV, Hao L, Offermanns S, et al. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. PNAS, 2014, 111(6): 2247-2252.

[136] Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med, 2017, 15(1): 73-90.

[137] Mehta RS, Nishihara R, Cao Y, et al. Association of dietary patterns with risk of colorectal cancer subtypes classified by *Fusobacterium nucleatum* in tumor tissue. JAMA Oncol, 2017, 3(7): 921-927.

[138] Hills R, Pontefract B, Mishcon H, et al. Gut microbiome: profound implications for diet and disease. Nutrients, 2019, 11(7): 1613-1653.

[139] Soldati L, Di Renzo L, Jirillo E, et al. The influence of diet on anti-cancer immune responsiveness. J Transl Med, 2018, 16(1): 75-93.

[140] Gentile CL, Weir TL. The gut microbiota at the intersection of diet and human health. Science, 2018, 362(6416): 776-780.

[141] Bultman SJ. Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. Mol Nutr Food Res, 2017, 61(1): 1500902(1-21).

(本文责编　陈宏宇)