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肠道菌群及其代谢产物在结直肠癌中的研究进展

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[摘 要] 结直肠癌(colorectal cancer，CRC)约占全球所有新发癌症的10%。CRC的病因和发病机制尚不完全清楚。由大量肠道微生物组成的肠道菌群位于肠上皮附近，参与机体能量获取、新陈代谢和免疫反应等生理活动。越来越多的证据表明肠道菌群失调可通过直接或间接的方式改变宿主的生理过程来影响CRC的发生、发展和对治疗的反应。此外，肠道菌群影响CRC的机制可以产生新的诊断和治疗方法，但仍有许多未知之处。

[关键词] 肠道菌群失调；代谢产物；结直肠癌；致病途径

Research progress of gut microbiota and its metabolites in colorectal cancer

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Abstract Colorectal cancer (CRC) accounts for about 10% of all new cancer cases globally. However, the etiology and pathogenesis of CRC are not fully understood. The gut microbiota consists of a large number of intestinal microorganisms located near the intestinal epithelium and is involved in host physiological activities such as energy acquisition, metabolism and immune response. Increasing evidence suggests that dysbiosis of gut microbiota can affect the occurrence, development and treatment response of CRC by directly or indirectly altering host physiological processes. Furthermore, the mechanisms by which the gut microbiota affects CRC could lead to new diagnostic and therapeutic approaches, but many remain unknown.

Keywords dysbiosis of gut microbiota; metabolite; colorectal cancer; pathogenic route

据报道，结直肠癌(colorectal cancer，CRC)已成为全球发病率第3、病死率第2的癌症[1-2]，其患者逐渐呈现年轻化趋势[3-4]。CRC病因复杂，遗传和环境因素间的相互作用促进CRC的发生、发展。据估计，遗传因素只占CRC风险的10%~30%，因此环境因素可能在导致散发性CRC方面发挥重要作用[5-6]。在众多环境因素中，肠道菌群近年来被认为是CRC的重要参与者。肠道菌群反映了一个与宿主密切沟通的微生态系统，是一个复杂的、交互式的、多物种的生物

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群落[7-10]。结直肠中寄居着大约3×10^{13}个细菌，在人体消化、代谢、免疫等各方面都有重要作用[11]，因此亦被称为人体的另一大“器官”。然而，肠道炎症、生活饮食习惯及环境差异等因素导致的肠道菌群结构和功能改变(即菌群失调)，可能在疾病中发挥重要作用[12-13]。随着高通量测序及生物信息学的不断进步，人体肠道菌群研究得到了进一步发展，其对健康与疾病的影响也日益被重视。研究[14]发现：CRC患者伴随着肠道菌群失调，其特征是与癌症相关的细菌丰度增加，如表达聚酮合酶基因的大肠杆菌(pks^+ *Escherichia coli*，pks^+ *E. coli*)，产肠毒素脆弱拟杆菌(enterotoxigenic *Bacteroides fragilis*，ETBF)及具核梭杆菌(*Fusobacterium nucleatum*，*F. nucleatum*)等，而保护或有益细菌如罗氏菌属(*Roseburia*)，梭菌属(*Clostridium*)，和双歧杆菌属(*Bifidobacterium*)等丰度减少。因此，探讨肠道菌群与CRC的关系对其预防及诊治至关重要。现对肠道菌群及其代谢产物在CRC发生、发展中的作用以及对预后的影响，包括该过程涉及的分子机制进行综述，同时重点阐述了*F. nucleatum*通过影响癌细胞或调节肿瘤微环境(tumor microenvironment，TME)参与CRC的进展、转移和化疗耐药，并从科学的角度讨论了该领域目前面临的主要挑战和未来的研究方向。

1 肠道菌群概述

肠道菌群是定居于肠道内的庞大微生物群体，据估计，人类肠道中大约有10万亿个细菌，主要有拟杆菌门、厚壁菌门、放线菌门、疣微菌门和变形菌门等[15-16]。这些细菌大致可以分为3类：1)有益菌，如双歧杆菌、乳酸杆菌等；2)有害菌，如*F. nucleatum*、ETBF、幽门螺旋杆菌等；3)中性菌，如大肠杆菌(*Escherichia coli*，*E. coli*)等[17]。肠道与肠道菌群是互利共生的关系，人体正常生理活动与肠道菌群及其代谢产物有着密切联系。肠道菌群与肠道内环境，如消化液、上皮细胞和食源性非生物成分等共同构成肠道微生态，为肠道菌群提供定植生存的环境。同时，肠道菌群间相互制约以达到肠道微生态平衡，并通过肠道对食物的消化吸收、物质代谢和能量转换过程为自身和机体提供营养。研究[8-9,18]表明：肠道菌群失调可造成微生态改变，进而引发炎症性肠病(inflammatory bowel disease，IBD)、CRC等多种疾病。

2 肠道菌群失调影响CRC发生发展的途径

CRC本质上是一种基因突变病，通常由结直肠腺瘤(colorectal adenoma，CRA)发展而来，这一过程被称为腺瘤-癌序列[19]。该序列的特征为染色体不稳定，并发生基因突变。这些因突变或表观遗传变化导致的抑癌基因功能丧失、癌基因功能增强，最终演变为癌[20]。肠道菌群与CRC密切相关，肠道菌群可能通过特定致病菌、影响遗传或表观遗传改变、诱导免疫紊乱及促炎反应状态、改变饮食代谢和产生基因毒素等方式促进CRC的发生、发展。随着菌群研究技术的不断进步，以及菌群研究理念的不断深入，越来越多流行病学证据[21-26]支持CRC患者存在肠道菌群失调。Wang等[21]发现CRC患者肠道优势菌群丰度发生明显改变，厚壁菌门、变形菌门、放线菌门富集，而拟杆菌门、梭杆菌门丰度减少。Liang等[22-23]通过比较CRC患者和健康成人粪便菌群多样性的变化发现，厚壁菌门为CRC患者肠道中的优势菌种，而拟杆菌门丰度则较低。但Ahn等[24]研究结果与以上相反，而与Sinha等[25]一致，即CRC患者粪便中拟杆菌门和梭杆菌门丰度较高，而厚壁菌门、毛螺菌属丰度较低。此外，最近一项研究[26]发现：突变的*p53*基因被回肠和结肠远端的肠道菌群从抑癌基因转变为癌基因。这些数据为阐明肠道菌群在CRC发生、发展中的作用提供了重要证据，肠道菌群失调可通过多种途径直接或间接地影响癌变进程。

2.1 特定致病菌及毒力因子直接损伤致癌途径

CRC患者粪便或组织样本中包含各类肠道微生物及其代谢产物，给癌症精确管理和治疗带来了巨大挑战，而抗生素“一刀切”的干预又将给整个肠道微生态系统带来不可估量的影响，因此，迫切需要确定在肿瘤发生、发展中起关键作用的特定微生物。*F. nucleatum*是一种呈梭形无孢子的革兰氏阴性厌氧菌，主要定植于口腔黏膜。作为一种共生细菌，*F. nucleatum*的长杆状形态对于促进多种生物膜结构的形成及微生物之间的相互作用至关重要[27-28]。最近，*F. nucleatum*对于CRC的影响受到了越来越多学者的关注[29-31]，且多项研究[32-33]表明肿瘤组织中*F. nucleatum*的数量与CRC患者病死率呈正相关。*F. nucleatum*已被报道在影响癌细胞功能和调节TME中发挥重要作用，并参与CRC的进展、转移和化疗耐药[34]。*F. nucleatum*促癌的潜在机制有多种，其最重要的致癌机制是毒力因子、非编码

RNAs(noncoding RNAs，ncRNAs)、免疫调节和细菌代谢[35]。

*F. nucleatum*是一种黏附性细菌，通过表达RadD、FomA、aid1等多种黏附素与宿主细胞相互调控[36-38]。*F. nucleatum*可以附着甚至入侵多种宿主细胞，包括上皮细胞、内皮细胞和成纤维细胞[39]。*F. nucleatum*特有的、最具特征的毒力因子是FadA[40]。一旦FadA与上皮细胞胞外区的上皮型钙黏素(E-cadherin)结合，致使*F. nucleatum*通过黏膜下组织的旁细胞通道侵入到细胞内并直接致癌[20,41-42]。E-cadherin还通过上调β-catenin、Wnt通路，导致*Wnt*基因、炎症基因(如*NF-κB*)和癌基因(如*MYC*和*Cyclin D1*)的表达增加，进而加速肿瘤生长[42]。此外，Guo等[36]还发现FadA/E-cadherin/β-catenin通路导致多功能酶Chk2的过度表达，进而促进了DNA损伤和肿瘤生长。Rubinstein等[43]研究表明：FadA还可通过E-cadherin增加CRC细胞Annexin A1的表达，进而激活β-catenin通路，加速细胞增殖和肿瘤生长。Fap2是*F. nucleatum*最大的外膜蛋白，是一种半乳糖抑制的黏附素[44]，它是调节*F. nucleatum*与CRC细胞表面配体Gal-GalNAc发生黏附的主要效应分子[45]，最终导致CRC组织内*F. nucleatum*的富集。此外，*F. nucleatum*通过Fap2结合TME中的免疫抑制受体TIGIT，抑制杀伤性免疫细胞毒性作用，阻断抗肿瘤免疫反应，进而促进肿瘤细胞增殖和CRC的发生、发展[46]。肝转移是CRC患者死亡的主要原因，然而*F. nucleatum*在CRC转移中的潜在机制仍不十分清楚。Chen等[47]报道了*F. nucleatum*与宿主细胞之间的相互作用会影响宿主N6-甲基腺苷(N6-methyladenosine，m6A)RNA修饰，即通过YAP/FOXD3/METTL3/KIF26B轴减少m6A修饰以促进CRC侵袭。Zhang等[48]研究发现：*F. nucleatum*通过诱导ICAM1的表达增强CRC细胞与内皮细胞的黏附，促进肿瘤细胞外渗和转移，并从机制上证实了一种新的模式识别受体ALPK1，为*F. nucleatum*在参与CRC细胞远处转移中的作用提供了新的见解。肝脏通过门静脉和肠肝循环受到肠道微生态环境的强烈影响[49]，虽然目前已发现*F. nucleatum*促进CRC细胞的增殖与迁移，但肝转移前微环境(pre-metastatic niche，PMN)的变化(如肝脏免疫生态位改变)是否参与*F. nucleatum*这一调控过程尚未得到全面研究，值得进一步探索。

ncRNAs，如microRNAs和lncRNAs，是表观遗传基因表达的转录后调节因子，在多种肿瘤细胞中异常表达[50]。最近基于细菌病原体的研究[51-52]表明ncRNAs是介导细菌和宿主细胞间相互作用的媒介。Yang等[53]研究发现：*F. nucleatum*通过TLR4/MyD88/NF-κB途径促进CRC细胞表达miR-21，进一步通过抑制下游基因*RAS1*激活Mapk通路以促进肿瘤细胞增殖和侵袭。尽管其他细菌如*E. coli*也可以激活肿瘤细胞中的TLR4/MyD88/NF-κB通路，但并不能诱导上调miR-21的表达，这一结果表明miR-21是*F. nucleatum*特异诱导的一种致癌ncRNAs。Hong等[54]研究表明：*F. nucleatum*通过激活CRC细胞lncRNA ENO1-IT1转录，进而促进靶基因*ENO1*表达，提高癌细胞糖酵解水平，导致细胞增殖和肿瘤生长。

*E. coli*属于埃希菌属，是肠道中的次要共生菌群。然而有研究[55]表明：CRC黏膜组织中存在*E. coli*富集现象，并且与肿瘤的分期和预后显著相关。Drewes等[56-58]研究发现：*E. coli*通过激活Wnt通路、促进DNA损伤、干扰DNA修复及失调E-cadherins功能，诱导CRC的发生、发展。此外，pks$^+$ *E. coli*能编码聚酮肽基因毒素，从而导致DNA修复机制受损，诱导DNA双链断裂和染色体畸变，促进肿瘤的发生、发展[59-61]。同样，产细胞致死性肿胀毒素的空肠弯曲菌，因其所产毒素为哺乳动物脱氧核苷酸酶的同源类似物，进而能够增加基因突变频率、累积染色体畸变和诱导肿瘤发生[62]。ETBF的致病性主要取决于所产生的脆弱拟杆菌毒素(*Bacteroides fragilis* toxin，BFT)，这是一种20 kD Zink依赖的金属蛋白酶毒素，通过与结肠细胞上皮受体结合导致E-cadherin裂解，进而破坏肠上皮屏障，引起菌群移位，并通过激活Wnt/β-catenin信号通路，促进炎症性腹泻和肿瘤发生[63-66]。此外，BFT能诱导炎症细胞释放活性氧类物质，促进细胞因子和趋化因子表达，引起DNA损伤，进而致癌[67]。Kim等[68]研究发现：ETBF可单独或与其他致病菌(如*E. coli*)在结肠黏膜中形成细菌生物膜，促进慢性感染和肿瘤形成。

2.2 异常免疫反应及慢性炎症致癌途径

TME主要由肿瘤细胞、免疫细胞和基质细胞等成分构成[69]。最近研究[70]发现：微生物群在各种肿瘤组织中的存在并不是偶然的，而是一种普遍现象，因此瘤内微生物群也被认为是TME的一部分。TME中最丰富的细胞成分是浸润性免疫细胞和间充质支持细胞[69]。尽管肠道菌群与间充质细胞(如肿瘤相关成纤维细胞)之间的相互作用在CRC中研究较少，但肠道菌群对肿瘤免疫微环境的调节被认为是影响CRC发生、发展的重要因素[71-74]。Kostic等[75]研究发现：*F. nucleatum*能够选

择性的扩增APC^{Min+}小鼠模型肿瘤组织中髓系抑制细胞(myeloid-derived suppressor cells，MDSCs)、肿瘤相关巨噬细胞(tumor-associated macrophages，TAMs)、肿瘤相关中性粒细胞(tumor-associated neutrophils，TANs)和树突状细胞(dendritic cells，DCs)的丰度，进而抑制CRC抗肿瘤免疫和参与肿瘤生物学行为。例如，Arlauckas等[76-77]通过机制实验研究发现M2型TAMs不仅通过表达精氨酸酶-1(arginase-1，Arg-1)抑制T细胞抗肿瘤免疫，而且亦能通过诱导分泌大量生长因子和趋化因子，促进肿瘤增殖、转移和血管生成。此外，Chen等[78]还发现*F. nucleatum*可通过激活TLR4/IL-6/p-STAT3/c-MYC级联反应通路诱导TAMs向M2型极化。另有流行病学研究表明：CRC组织中*F. nucleatum*丰度与CD3$^+$ T细胞水平呈负相关[79]，特别是CD3$^+$CD4$^+$CD45RO$^+$ T细胞[80]，结果显示*F. nucleatum*对CD3$^+$ T细胞存在直接或间接的抑制作用。高丰度的*F. nucleatum*亦可降低NK细胞功能，这种NK细胞活性的降低可能与*F. nucleatum*干预后的促炎细胞因子(如IL-1β和TNF-α)增加有关[81]。此外，与其他革兰氏阴性细菌一样，*F. nucleatum*可以释放细胞外囊泡(extracellular vesicles，EVs)或外膜囊泡(outer membrane vesicles，OMVs)[82-83]，其内含有大量生物活性物质，并参与细菌或细菌宿主细胞间通信[84]。Martin-Gallausiaux等[85]通过分离和纯化*F. nucleatum*衍生的EVs证实，EVs表面蛋白FomA可以与肠上皮细胞的TLR2结合，进而调节宿主先天免疫反应。Engevik等[86]使用从*F. nucleatum*分离的OMVs刺激结肠上皮细胞，发现促炎细胞因子IL-8和TNF的产生明显增加，促进免疫细胞浸润和异常免疫反应。

CRC的发生发展往往伴随着慢性炎症反应[87]。炎性细胞和炎症因子被认为是CRC进展的重要危险因素[77,88-89]。菌群诱发炎症反应多数通过分子模式识别机制与宿主的模式识别受体(pattern recognition receptor，PRRs)相互作用，如Toll样受体(Toll-like receptors，TLRs)。微生物及其代谢产物通过识别肿瘤浸润性髓系细胞的TLRs，促进依赖MyD88介导的炎症因子IL-23的分泌，进而激活炎症因子IL-17a，IL-6和IL-22的产生，促进CRC的发生、发展[73]。除了与上述炎性细胞相互作用外，*F. nucleatum*还可通过刺激CRC细胞诱导产生多种炎症因子，如IL-6、IL-8和TNF-α等，它们与激活NF-κB途径有关[42,75,90]。这些炎症因子可以作用于TME中表达其特定受体的细胞，并以多种方式促进CRC进展。此外，链球菌属(*Streptococcus*)能够增加结肠黏膜IL-8的分泌，并诱导形成高分化CRA，进而促进CRC发生[91]。ETBF能够通过产生BFT，激活STAT3和NF-κB信号传输，进而诱发炎症级联反应致癌[66]。除了炎症因子，肠道菌群刺激的CRC细胞还可以分泌趋化因子。如*F. nucleatum*以依赖Fap2的方式刺激CRC细胞分泌IL-8和CXCL1，进而招募免疫细胞，特别是中性粒细胞，在肿瘤部位富集并促进炎症，同时又以旁分泌方式促进未感染的癌细胞迁移，加速肿瘤进展[92]。此外，*F. nucleatum*还能刺激肿瘤细胞产生CCL20，通过与其配体CCR6结合，招募CCR6$^+$型免疫细胞富集，如Th17、Tregs和DCs细胞等，诱导炎症反应并促进CRC发展[93]。ETBF可通过诱导肠上皮细胞分泌CCL20和PGE2，激活STAT3信号通路，招募Th17细胞并促进IL-17表达，导致炎症性相关结肠癌的发生[66,94]。

2.3 肠道菌群代谢产物间接致癌途径

物质代谢调节是肠道菌群与宿主相互作用的重要方式[95]。肠道细菌参与了多种肠道活性物质的合成及代谢过程，代谢产物及相关酶又与肠道菌群共同参与了肠道微生态平衡的调节[96]。膳食中的营养元素经过肠道细菌的合成与代谢产生多种小分子化合物和酶，如次级胆汁酸、短链脂肪酸、β葡萄糖醛酸酶、B族维生素、维生素K、烟酸及多种氨基酸等，共同参与调节肠道微生态的稳定。然而，当肠道菌群失调引发肠道内致病菌富集时，肠道内产生的氨、酚类、对甲酚等毒性产物亦随之增加，进而通过慢性炎症和DNA损伤参与癌症的发生、发展[9,97]。一些生硫细菌可产生硫化氢(H_2S)，如*F. nucleatum*可以利用自身酶系统将*L*-半胱氨酸代谢为H_2S，进而刺激细胞增殖并增加CRC发生风险[98]。*F. nucleatum*具有巨大的代谢潜力，可利用TME中的氨基酸和多肽作为营养源，产生的各种氨基酸代谢产物(如甲氧基亮氨酸、苯丙氨酸和短链脂肪酸等)，进而作为一种髓系细胞刺激剂促进TME中髓系细胞的扩张[75]。虽然*F. nucleatum*已被证实是丁酸产生菌[99-100]，可利用氨基酸(而非多糖)生成短链脂肪酸家族中的丁酸盐[101]。肠道菌群发酵食物产生丁酸盐被证实具有强大的抗炎和抗肿瘤能力[102]，然而丁酸盐在CRC中的作用尚存争议[103]，仍需进一步研究，并且*F. nucleatum*来源的丁酸盐在CRC中的作用目前仍不清楚。此外，*F. nucleatum*外膜含有脂多糖(lipopolysaccharide，LPS)，通过LPS受体，如TLR4，在肠道炎症或肿瘤中发挥重要

作用[104]。Kong等[105]发现：*F. nucleatum*通过激活TLR4/Keap1/NRF2途径，上调细胞色素P450相关酶CYP2J2的表达，进而促进其代谢产物12，13-EpOME的产生，最终导致CRC侵袭和转移。总之，以上证据表明*F. nucleatum*可间接通过其代谢产物形成局部肿瘤“促癌微环境”加速肿瘤进展。

胆汁酸是宿主与肠道菌群密切联系的另一重要代谢物媒介。高脂饮食条件下，大量胆汁酸进入结肠，此时胆汁酸不仅能够通过扩增特定细菌的丰度(如厌氧菌及类杆菌属)，上调含有胆汁酸去结合酶和胆汁酸7α-脱水酶的表达，进而改变肠道菌群结构[106]，而且被富集的肠道菌群还能够将初级胆汁酸转换为次级胆汁酸[107]。这是一类具有促癌作用的代谢产物，可通过刺激氧化应激反应(如活性氧、活性氮产生)、诱导细胞DNA损伤、激活EGFR及NF-κB等途径促进肿瘤的发生发展[108-110]。宿主-细菌“胆道网络”在宿主免疫反应中也有关键作用，如肠道胆汁酸库是结肠RORγ$^+$亚型Treg细胞的一类重要诱导剂，可通过靶向其胆汁酸核受体影响宿主对炎症性结肠炎的易感性[111]。此外，肠道中的脆弱拟杆菌(*Bacteroides fragilis*，*B. fragilis*)、产气荚膜梭菌等存在高活性糖苷类水解酶(如β葡萄糖醛酸酶)，它可以将外源性致癌物的转化，增加其致癌活性，进而参与肿瘤的发生发展[112]。然而，肠道中的益生菌代谢产物，如乳酸菌和双歧杆菌等，可通过降低β葡萄糖醛酸酶活性起抗癌作用[113]。同时，肠道益生菌亦可通过代谢产生多胺，参与抑制宿主免疫反应、促进癌细胞的增殖、侵袭和转移[114]。

氧化三甲胺(trimethylamine N-oxide，TMAO)是由肠道菌群代谢产生的，是几种炎症相关疾病发病的决定因素，如慢性肾功能不全和冠心病[115-117]。最近一份研究[118]发现：布劳特氏菌属(*Blautia*)、瘤胃球菌属(*Ruminococcus*)、柔嫩梭菌属(*Faecalibacterium*)等梭菌目(*Clostridiales*)衍生的代谢产物TMAO通过细胞焦亡作用，增强了CD8$^+$ T细胞介导的抗肿瘤免疫，进而改善了乳腺癌患者免疫治疗效果。此外，Xu等[119]通过全基因组分析发现：TMAO与CRC在免疫系统、细胞周期、癌症途径中存在共同的基因通路，TMAO可能是CRC风险的一个重要的标志物，值得进一步研究。肠道菌群可以将饮食中的色氨酸代谢成吲哚、吲哚乙酸酯、色胺、吲哚醛、吲哚乳酸和吲哚丙烯酸酯等，进而激活芳香烃受体(aryl hydrocarbon receptor，AhR)，从而减轻黏膜炎症反应，维持肠道内环境稳态[120-123]。例如，乳酸杆菌属(*Lactobacilli*)代谢色氨酸产生AHR配体吲哚-3-醛，刺激第3组固有淋巴样细胞，进而诱导IL-22的产生，上调抗菌肽(anti-microbial peptide，AMP)的表达，增加对白色念珠菌(*Candida albicans*)等病原体的定植抗性[123]。同样，Lin等[124]研究发现：与健康人群相比，CRC患者粪便代谢物中乙酸、丁酸、丙酸、葡萄糖、谷氨酰胺水平明显降低，而琥珀酸、脯氨酸、丙氨酸、二甲基甘氨酸、缬氨酸、谷氨酸、亮氨酸、异亮氨酸和乳酸水平明显升高，这些代谢产物的变化可能与肠道菌群失调有关，并通过影响上皮细胞脱落、炎症和先天免疫反应参与CRC的发生、发展。

3 肠道菌群在 CRC 中的临床价值

3.1 CRC 新的早期生物标志物

生物标志物可间接提示疾病发生、严重程度以及预后。目前临床上最常用来早期大规模筛查CRC的方法是粪便隐血试验，然而该试验对CRC的诊断缺乏一定的特异性[125]。如前所述，CRC患者肠道菌群与健康人群存在明显差异，基于这一特异性，肠道菌群有可能成为新的CRC风险早期生物标志物。*F. nucleatum*作为一种CRC特异菌，对CRC的发生、发展及预后都有显著影响，并且已被证实是预测CRC风险的一个重要生物标志物[126-127]。此外，粪便免疫化学检测联合*F. nucleatum*与单独应用粪便免疫化学检测相比，诊断CRC的敏感度和特异度更高[22,127-128]。Zeller等[128]基于宏基因组测序技术，对来自不同国家和地区独立队列的粪便样品进行丰度数据检测，建立基于6种细菌的诊断模型，发现联合粪便隐血试验的曲线下面积明显优于单一筛查策略。检测数据表明：微生物标志物作为一种快速且非侵入性筛查，联合现有的筛查方法不失为一种互补策略，为进一步提高CRC诊断的阳性率和准确性、早期预防疾病提供可能。随着研究的不断深入，肠道菌群与CRC预后的关系也不断被揭示。Flanagan等[32-33]发现：肿瘤组织中*F. nucleatum*的相对丰度与CRC患者的总体生存率(overall survival，OS)呈负相关。这意味着肠道菌群不仅能够用于CRC的早筛，而且作为CRC预后的生物标志物同样具有临床应用价值，这是肠道菌群研究在CRC领域向临床转化又一重要实例。

3.2 CRC 新的治疗干预靶点

CRC患者根治性术后通常需要接受系统药物化疗，如奥沙利铂、5-氟尿嘧啶(5-fluorouracil，

5-FU)等[129]。然而临床上部分患者因为耐药最终导致肿瘤复发，且晚期CRC患者的5年生存率低于10%[130]。因此阐明CRC患者化疗耐药的机制、寻找CRC新的治疗干预靶点对于改善CRC患者预后具有重要意义。肠道菌群不仅对于CRC的发生、发展有重要的影响，且对于CRC的化疗及免疫治疗的效果亦存在不可忽视的作用[131-132]。例如，环磷酰胺、奥沙利铂化疗和CpG^-寡核苷酸免疫治疗对无菌或抗生素处理的荷瘤鼠反应敏感度明显下降，提示其发挥抗肿瘤作用依赖于完整的肠道菌群[133-135]。肠道菌群影响化疗药物抗癌作用机制主要包括菌群易位、免疫调节、代谢和酶降解等途径[136]。Geller等[137]研究发现：肠道中某些菌群依赖胞苷脱氨酶可将CRC小鼠模型中化疗药物吉西他滨代谢成为一种无活性的产物，进而促进吉西他滨耐药，而应用抗生素环丙沙星处理后，以上耐药现象被消除。除了细菌本身，肠道菌群亦可能通过其代谢产物间接影响抗肿瘤治疗效果。He等[138]研究发现：肠道菌群代谢物丁酸可通过依赖ID2的方式增强细胞毒性$CD8^+$ T细胞功能，进而促进奥沙利铂抗肿瘤疗效。最近研究多集中在*F. nucleatum*对CRC化疗耐药的影响。Zhang等[139]研究发现：*F. nucleatum*通过激活TLR4/NF-κB途径上调CRC细胞中BIRC3的表达，进而直接抑制caspase级联反应和减少细胞凋亡蛋白的表达，促进癌细胞对5-FU的耐药性。Yu等[132]证明*F. nucleatum*通过选择性丢失miR-18a*和miR-4802，激活自噬通路进而抑制细胞凋亡，降低CRC细胞对奥沙利铂和5-FU药物敏感度，导致肿瘤复发。虽然已发现*F. nucleatum*通过诱导癌细胞自噬或凋亡途径导致CRC化疗耐药，但*F. nucleatum*参与这一过程的确切毒力因子或代谢产物尚未可知，其分子机制亦值得进一步研究。

免疫治疗近年来不断被发展和完善，已成为癌症治疗的主要手段之一。肠道菌群可通过重塑机体免疫调节而发挥抗肿瘤疗效。Routy等[74]研究发现：使用抗生素干预的癌症患者对抗PD-1免疫疗法的反应性较低，且用抗PD-1应答患者的肠道菌群移植(fecal microbiota transplantation，FMT)重建无菌小鼠肠道菌群组成可以改善抗肿瘤免疫反应。Vétizou等[140]发现：给无菌荷瘤小鼠FMT *B. fragilis*后，其CTLA-4诱导$CD4^+$ T淋巴细胞发挥抗肿瘤免疫效应得以恢复。此外，Drewes等[56]研究发现：CRC患者肠道中的双歧杆菌和类杆菌能通过增强DCs功能，诱导$CD8^+$ T活化并促进在TME中富集，进而发挥抗癌功效。以上数据提示我们未来可能通过调节肠道菌群及其代谢产物改善CRC治疗效果，为发展个性化癌症治疗策略提供新的靶点。

4 展望

目前的研究已经深入探讨了肠道菌群及其代谢产物与CRC发生、发展、治疗以及预后之间的关系，为肠道菌群在CRC领域的临床应用提供了理论基础。然而当前研究仍存在许多亟待解决的问题。首先，肿瘤相关致病菌是正常组织共生体的局部主动增殖，还是伴随肿瘤进展从其他部位被动募集目前仍不清楚；其次，肠道菌群与CRC各种临床问题之间的相关性并不代表二者之间的因果关系，是肠道菌群的改变影响了疾病的变化，还是疾病的发生引起了肠道菌群失调，以及因果关系发生背后的机制，这些问题均需要大规模前瞻性队列研究进一步阐明。再次，虽然在研究肠道菌群衍生的关键代谢物方面取得了积极进展，然而，目前大部分的研究只停留在了代谢产物与宿主疾病相关性这一水平上，其相互作用背后的分子机制仍知之甚少。FadA、Fap2和LPS是目前已被广泛接受的*F. nucleatumis*致癌分子，然而*F. nucleatumis*代谢产物是否参与这一过程及其背后发挥的具体作用机制目前仍不十分清楚。最后，除了发现新的分子外，对肠道菌群代谢物的研究还需要关注：明确产生代谢小分子化合物的特定肠菌、代谢过程涉及的关键基因和酶以及代谢产物对宿主的生物学影响等方面。未来应用新技术研究和操纵肠道菌群，以精确地干预特定致病菌或益生菌及其代谢产物，如组学联合分析、单菌/细胞测序技术等方法或许有助于解决这些问题。此外，聚焦饮食干预对肠道菌群及其代谢产物的潜在作用亦是未来调控CRC风险的研究方向，并以此为基础开发一种可负担、无创便捷的筛查试验对于CRC的诊断、治疗和预后都具有重要的临床价值。

参考文献

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2018, 68(6): 394-424.
2. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020[J]. CA Cancer J Clin, 2020, 70(3): 145-164.

3. Akimoto N, Ugai T, Zhong R, et al. Rising incidence of early-onset colorectal cancer - a call to action[J]. Nat Rev Clin Oncol, 2021, 18(4): 230-243.
4. Hofseth LJ, Hebert JR, Chanda A, et al. Early-onset colorectal cancer: initial clues and current views[J]. Nat Rev Gastroenterol Hepatol, 2020, 17(6): 352-364.
5. Graff RE, Möller S, Passarelli MN, et al. Familial risk and heritability of colorectal cancer in the nordic twin study of cancer[J]. Clin Gastroenterol Hepatol, 2017, 15(8): 1256-1264.
6. Jiao S, Peters U, Berndt S, et al. Estimating the heritability of colorectal cancer[J]. Hum Mol Genet, 2014, 23(14): 3898-3905.
7. Charbonneau MR, Blanton LV, DiGiulio DB, et al. A microbial perspective of human developmental biology[J]. Nature, 2016, 535(7610): 48-55.
8. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease[J]. N Engl J Med, 2016, 375(24): 2369-2379.
9. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier[J]. Gut, 2016, 65(2): 330-339.
10. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism[J]. Nature, 2016, 535(7610): 56-64.
11. Valdes AM, Walter J, Segal E, et al. Role of the gut microbiota in nutrition and health[J]. BMJ, 2018, 361: k2179.
12. Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease[J]. J Allergy Clin Immunol, 2020, 145(1): 16-27.
13. Illiano P, Brambilla R, Parolini C. The mutual interplay of gut microbiota, diet and human disease[J]. FEBS J, 2020, 287(5): 833-855.
14. Janney A, Powrie F, Mann EH. Host-microbiota maladaptation in colorectal cancer[J]. Nature, 2020, 585(7826): 509-517.
15. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome[J]. Nature, 2012, 486(7402): 207-214.
16. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body[J]. PLoS Biol, 2016, 14(8): e1002533.
17. Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota[J]. World J Gastroenterol, 2015, 21(29): 8787-8803.
18. Cross AJ, Moore SC, Boca S, et al. A prospective study of serum metabolites and colorectal cancer risk[J]. Cancer, 2014, 120(19): 3049-3057.
19. Waller A, Findeis S, Lee MJ. Familial adenomatous polyposis[J]. J Pediatr Genet, 2016, 5(2): 78-83.
20. Raskov H, Burcharth J, Pommergaard HC. Linking gut microbiota to colorectal cancer[J]. J Cancer, 2017, 8(17): 3378-3395.
21. Wang T, Cai G, Qiu Y, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers[J]. ISME J, 2012, 6(2): 320-329.
22. Liang Q, Chiu J, Chen Y, et al. Fecal bacteria act as novel biomarkers for noninvasive diagnosis of colorectal cancer[J]. Clin Cancer Res, 2017, 23(8): 2061-2070.
23. Zackular JP, Rogers MA, Ruffin MT 4th, et al. The human gut microbiome as a screening tool for colorectal cancer[J]. Cancer Prev Res (Phila), 2014, 7(11): 1112-1121.
24. Ahn J, Sinha R, Pei Z, et al. Human gut microbiome and risk for colorectal cancer[J]. J Natl Cancer Inst, 2013, 105(24): 1907-1911.
25. Sinha R, Ahn J, Sampson JN, et al. Fecal microbiota, fecal metabolome, and colorectal cancer interrelations[J]. PLoS One, 2016, 11(3): e0152126.
26. Kadosh E, Snir-Alkalay I, Venkatachalam A, et al. The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic[J]. Nature, 2020, 586(7827): 133-138.
27. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions[J]. Nat Rev Microbiol, 2018, 16(12): 745-759.
28. Zhang Y, Wang X, Li H, et al. Human oral microbiota and its modulation for oral health[J]. Biomed Pharmacother, 2018, 99: 883-893.
29. Bashir A, Miskeen AY, Hazari YM, et al. *Fusobacterium nucleatum*, inflammation, and immunity: the fire within human gut[J]. Tumour Biol, 2016, 37(3): 2805-2810.
30. Castellarin M, Warren RL, Freeman JD, et al. *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma[J]. Genome Res, 2012, 22(2): 299-306.
31. Kostic AD, Gevers D, Pedamallu CS, et al. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma[J]. Genome Res, 2012, 22(2): 292-298.
32. Flanagan L, Schmid J, Ebert M, et al. *Fusobacterium nucleatum* associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome[J]. Eur J Clin Microbiol Infect Dis, 2014, 33(8): 1381-1390.
33. Mima K, Nishihara R, Qian ZR, et al. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis[J]. Gut, 2016, 65(12): 1973-1980.
34. Wang S, Liu Y, Li J, et al. *Fusobacterium nucleatum* acts as a pro-carcinogenic bacterium in colorectal cancer: from association to causality[J]. Front Cell Dev Biol, 2021, 9: 710165.
35. Hashemi Goradel N, Heidarzadeh S, Jahangiri S, et al. *Fusobacterium nucleatum* and colorectal cancer: a mechanistic overview[J]. J Cell Physiol, 2019, 234(3): 2337-2344.
36. Guo L, Shokeen B, He X, et al. Streptococcus mutans SpaP binds to RadD of *Fusobacterium nucleatum* ssp. polymorphum[J]. Mol Oral Microbiol, 2017, 32(5): 355-364.
37. Kaplan A, Kaplan CW, He X, et al. Characterization of aid1, a novel

gene involved in *Fusobacterium nucleatum* interspecies interactions[J]. Microb Ecol, 2014, 68(2): 379-387.

38. Liu PF, Shi W, Zhu W, et al. Vaccination targeting surface FomA of *Fusobacterium nucleatum* against bacterial co-aggregation: implication for treatment of periodontal infection and halitosis[J]. Vaccine, 2010, 28(19): 3496-3505.
39. Han YW. *Fusobacterium nucleatum*: a commensal-turned pathogen[J]. Curr Opin Microbiol, 2015, 23: 141-147.
40. Xu M, Yamada M, Li M, et al. FadA from *Fusobacterium nucleatum* utilizes both secreted and nonsecreted forms for functional oligomerization for attachment and invasion of host cells[J]. J Biol Chem, 2007, 282(34): 25000-25009.
41. Fardini Y, Wang X, Témoin S, et al. *Fusobacterium nucleatum* adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity[J]. Mol Microbiol, 2011, 82(6): 1468-1480.
42. Rubinstein MR, Wang X, Liu W, et al. *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin[J]. Cell Host Microbe, 2013, 14(2): 195-206.
43. Rubinstein MR, Baik JE, Lagana SM, et al. *Fusobacterium nucleatum* promotes colorectal cancer by inducing Wnt/β-catenin modulator Annexin A1[J]. EMBO Rep, 2019, 20(4): e47638.
44. Coppenhagen-Glazer S, Sol A, Abed J, et al. Fap2 of *Fusobacterium nucleatum* is a galactose-inhibitable adhesin involved in coaggregation, cell adhesion, and preterm birth[J]. Infect Immun, 2015, 83(3): 1104-1113.
45. Abed J, Emgård JE, Zamir G, et al. Fap2 mediates *Fusobacterium nucleatum* colorectal adenocarcinoma enrichment by binding to tumor-expressed Gal-GalNAc[J]. Cell Host Microbe, 2016, 20(2): 215-225.
46. 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[J]. Immunity, 2015, 42(2): 344-355.
47. Chen S, Zhang L, Li M, et al. *Fusobacterium nucleatum* reduces METTL3-mediated m6A modification and contributes to colorectal cancer metastasis[J]. Nat Commun, 2022, 13(1): 1248.
48. Zhang Y, Zhang L, Zheng S, et al. *Fusobacterium nucleatum* promotes colorectal cancer cells adhesion to endothelial cells and facilitates extravasation and metastasis by inducing ALPK1/NF-κB/ICAM1 axis[J]. Gut Microbes, 2022, 14(1): 2038852.
49. Sethi V, Kurtom S, Tarique M, et al. Gut microbiota promotes tumor growth in mice by modulating immune response[J]. Gastroenterology, 2018, 155(1): 33-37.e6.
50. Dragomir MP, Kopetz S, Ajani JA, et al. Non-coding RNAs in GI cancers: from cancer hallmarks to clinical utility[J]. Gut, 2020, 69(4): 748-763.
51. Aguilar C, Mano M, Eulalio A. MicroRNAs at the host-bacteria interface: host defense or bacterial offense[J]. Trends Microbiol, 2019, 27(3): 206-218.
52. Dong J, Tai JW, Lu LF. MiRNA-microbiota interaction in gut homeostasis and colorectal cancer[J]. Trends Cancer, 2019, 5(11): 666-669.
53. Yang Y, Weng W, Peng J, et al. *Fusobacterium nucleatum* increases proliferation of colorectal cancer cells and tumor development in mice by activating toll-like receptor 4 signaling to nuclear factor-κB, and up-regulating expression of microRNA-21[J]. Gastroenterology, 2017, 152(4): 851-866.e24.
54. Hong J, Guo F, Lu SY, et al. F. nucleatum targets lncRNA ENO1-IT1 to promote glycolysis and oncogenesis in colorectal cancer[J]. Gut, 2021, 70(11): 2123-2137.
55. Bonnet M, Buc E, Sauvanet P, et al. Colonization of the human gut by *E. coli* and colorectal cancer risk[J]. Clin Cancer Res, 2014, 20(4): 859-867.
56. Drewes JL, Housseau F, Sears CL. Sporadic colorectal cancer: microbial contributors to disease prevention, development and therapy[J]. Br J Cancer, 2016, 115(3): 273-280.
57. Gagnière J, Raisch J, Veziant J, et al. Gut microbiota imbalance and colorectal cancer[J]. World J Gastroenterol, 2016, 22(2): 501-518.
58. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer[J]. Cell Host Microbe, 2014, 15(3): 317-328.
59. Cougnoux A, Dalmasso G, Martinez R, et al. Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype[J]. Gut, 2014, 63(12): 1932-1942.
60. Cuevas-Ramos G, Petit CR, Marcq I, et al. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells[J]. Proc Natl Acad Sci U S A, 2010, 107(25): 11537-11542.
61. Nougayrède JP, Homburg S, Taieb F, et al. *Escherichia coli* induces DNA double-strand breaks in eukaryotic cells[J]. Science, 2006, 313(5788): 848-851.
62. He Z, Gharaibeh RZ, Newsome RC, et al. *Campylobacter jejuni* promotes colorectal tumorigenesis through the action of cytolethal distending toxin[J]. Gut, 2019, 68(2): 289-300.
63. Sears CL, Geis AL, Housseau F. *Bacteroides fragilis* subverts mucosal biology: from symbiont to colon carcinogenesis[J]. J Clin Invest, 2014, 124(10): 4166-4172.
64. Silva-García O, Valdez-Alarcón JJ, Baizabal-Aguirre VM. Wnt/β-catenin signaling as a molecular target by pathogenic bacteria[J]. Front Immunol, 2019, 10: 2135.
65. Sun J, Kato I. Gut microbiota, inflammation and colorectal cancer[J]. Genes Dis, 2016, 3(2): 130-143.
66. Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal

promotes colon tumorigenesis via activation of T helper type 17 T cell responses[J]. Nat Med, 2009, 15(9): 1016-1022.

67. Liu QQ, Li CM, Fu LN, et al. Enterotoxigenic *Bacteroides fragilis* induces the stemness in colorectal cancer via upregulating histone demethylase JMJD2B[J]. Gut Microbes, 2020, 12(1): 1788900.
68. Kim HR, Rhee KJ, Eom YB. Anti-biofilm and antimicrobial effects of zerumbone against Bacteroides fragilis[J]. Anaerobe, 2019, 57: 99-106.
69. Maman S, Witz IP. A history of exploring cancer in context[J]. Nat Rev Cancer, 2018, 18(6): 359-376.
70. Nejman D, Livyatan I, Fuks G, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria[J]. Science, 2020, 368(6494): 973-980.
71. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system[J]. Science, 2012, 336(6086): 1268-1273.
72. Greer JB, O'Keefe SJ. Microbial induction of immunity, inflammation, and cancer[J]. Front Physiol, 2011, 1: 168.
73. Grivennikov SI, Wang K, Mucida D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth[J]. Nature, 2012, 491(7423): 254-258.
74. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors[J]. Science, 2018, 359(6371): 91-97.
75. Kostic AD, Chun E, Robertson L, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment[J]. Cell Host Microbe, 2013, 14(2): 207-215.
76. Arlauckas SP, Garren SB, Garris CS, et al. Arg1 expression defines immunosuppressive subsets of tumor-associated macrophages[J]. Theranostics, 2018, 8(21): 5842-5854.
77. Galdiero MR, Marone G, Mantovani A. Cancer inflammation and cytokines[J]. Cold Spring Harb Perspect Biol, 2018, 10(8): a028662.
78. Chen T, Li Q, Wu J, et al. *Fusobacterium nucleatum* promotes M2 polarization of macrophages in the microenvironment of colorectal tumours via a TLR4-dependent mechanism[J]. Cancer Immunol Immunother, 2018, 67(10): 1635-1646.
79. Mima K, Sukawa Y, Nishihara R, et al. *Fusobacterium nucleatum* and T cells in colorectal carcinoma[J]. JAMA Oncol, 2015, 1(5): 653-661.
80. Borowsky J, Haruki K, Lau MC, et al. Association of *Fusobacterium nucleatum* with specific T-cell subsets in the colorectal carcinoma microenvironment[J]. Clin Cancer Res, 2021, 27(10): 2816-2826.
81. Kim YJ, Kim BK, Park SJ, et al. Impact of *Fusobacterium nucleatum* in the gastrointestinal tract on natural killer cells[J]. World J Gastroenterol, 2021, 27(29): 4879-4889.
82. Liu J, Hsieh CL, Gelincik O, et al. Proteomic characterization of outer membrane vesicles from gut mucosa-derived fusobacterium nucleatum[J]. J Proteomics, 2019, 195: 125-137.
83. Liu L, Liang L, Yang C, et al. Extracellular vesicles of *Fusobacterium nucleatum* compromise intestinal barrier through targeting RIPK1-mediated cell death pathway[J]. Gut Microbes, 2021, 13(1): 1-20.
84. Macia L, Nanan R, Hosseini-Beheshti E, et al. Host- and microbiota-derived extracellular vesicles, immune function, and disease development[J]. Int J Mol Sci, 2019, 21(1): 107.
85. Martin-Gallausiaux C, Malabirade A, Habier J, et al. Fusobacterium nucleatum extracellular vesicles modulate gut epithelial cell innate immunity via FomA and TLR2[J]. Front Immunol, 2020, 11: 583644.
86. Engevik MA, Danhof HA, Ruan W, et al. *Fusobacterium nucleatum* secretes outer membrane vesicles and promotes intestinal inflammation[J]. mBio, 2021, 12(2): 02706-20.
87. Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer[J]. Nat Rev Immunol, 2021, 21(10): 653-667.
88. West NR, McCuaig S, Franchini F, et al. Emerging cytokine networks in colorectal cancer[J]. Nat Rev Immunol, 2015, 15(10): 615-629.
89. Wong SH, Zhao L, Zhang X, et al. Gavage of fecal samples from patients with colorectal cancer promotes intestinal carcinogenesis in germ-free and conventional mice[J]. Gastroenterology, 2017, 153(6): 1621-1633.e6.
90. Koi M, Okita Y, Carethers JM. *Fusobacterium nucleatum* infection in colorectal cancer: linking inflammation, DNA mismatch repair and genetic and epigenetic alterations[J]. J Anus Rectum Colon, 2018, 2(2): 37-46.
91. Ellmerich S, Schöller M, Duranton B, et al. Promotion of intestinal carcinogenesis by *Streptococcus bovis*[J]. Carcinogenesis, 2000, 21(4): 753-756.
92. Casasanta MA, Yoo CC, Udayasuryan B, et al. *Fusobacterium nucleatum* host-cell binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration[J]. Sci Signal, 2020, 13(641): aba9157.
93. Ye X, Wang R, Bhattacharya R, et al. *Fusobacterium nucleatum* subspecies animalis influences proinflammatory cytokine expression and monocyte activation in human colorectal tumors[J]. Cancer Prev Res (Phila), 2017, 10(7): 398-409.
94. Housseau F, Wu S, Wick EC, et al. Redundant innate and adaptive sources of IL17 production drive colon tumorigenesis[J]. Cancer Res, 2016, 76(8): 2115-2124.
95. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions[J]. Science, 2012, 336(6086): 1262-1267.
96. 徐婷, 刘璐, 张军东. 肠道菌群与人体代谢[J]. 中国微生态学杂志, 2014, 26(7): 858-862.
XU Ting, LIU Lu, ZHANG Jundong. Host-gut microbiota metabolic interactions[J]. Chinese Journal of Microecology, 2014, 26(7): 858-862.
97. Le Gall G, Guttula K, Kellingray L, et al. Correction: Metabolite

quantification of faecal extracts from colorectal cancer patients and healthy controls[J]. Oncotarget, 2019, 10(17): 1660.

98. Szabo C, Coletta C, Chao C, et al. Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer[J]. Proc Natl Acad Sci U S A, 2013, 110(30): 12474-12479.
99. Dahlstrand Rudin A, Khamzeh A, Venkatakrishnan V, et al. Short chain fatty acids released by *Fusobacterium nucleatum* are neutrophil chemoattractants acting via free fatty acid receptor 2 (FFAR2)[J]. Cell Microbiol, 2021, 23(8): e13348.
100. Llama-Palacios A, Potupa O, Sánchez MC, et al. Proteomic analysis of *Fusobacterium nucleatum* growth in biofilm versus planktonic state[J]. Mol Oral Microbiol, 2020, 35(4): 168-180.
101. Vital M, Howe AC, Tiedje JM. Revealing the bacterial butyrate synthesis pathways by analyzing (meta)genomic data[J]. mBio, 2014, 5(2): e00889.
102. 陈慧敏. 大肠肿瘤的发生及膳食纤维之代谢组学研究[D]. 上海: 上海交通大学, 2011.
CHEN Huimin. The occurrence of colorectal cancer and the metabolomic study of dietary fiber[D]. Shanghai: Shanghai Jiaotong University, 2011.
103. Guan X, Li W, Meng H. A double-edged sword: role of butyrate in the oral cavity and the gut[J]. Mol Oral Microbiol, 2021, 36(2): 121-131.
104. Chen Y, Peng Y, Yu J, et al. Invasive *Fusobacterium nucleatum* activates beta-catenin signaling in colorectal cancer via a TLR4/P-PAK1 cascade[J]. Oncotarget, 2017, 8(19): 31802-31814.
105. Kong C, Yan X, Zhu Y, et al. *Fusobacterium nucleatum* promotes the development of colorectal cancer by activating a cytochrome P450/epoxyoctadecenoic acid axis via TLR4/Keap1/NRF2 signaling[J]. Cancer Res, 2021, 81(17): 4485-4498.
106. Wells JE, Hylemon PB. Identification and characterization of a bile acid 7alpha-dehydroxylation operon in *Clostridium sp.* strain TO-931, a highly active 7alpha-dehydroxylating strain isolated from human feces[J]. Appl Environ Microbiol, 2000, 66(3): 1107-1113.
107. de Aguiar Vallim TQ, Tarling EJ, Edwards PA. Pleiotropic roles of bile acids in metabolism[J]. Cell Metab, 2013, 17(5): 657-669.
108. Azcárate-Peril MA, Sikes M, Bruno-Bárcena JM. The intestinal microbiota, gastrointestinal environment and colorectal cancer: a putative role for probiotics in prevention of colorectal cancer?[J]. Am J Physiol Gastrointest Liver Physiol, 2011, 301(3): G401-G424.
109. Goodwin AC, Destefano Shields CE, Wu S, et al. Polyamine catabolism contributes to enterotoxigenic *Bacteroides fragilis*-induced colon tumorigenesis[J]. Proc Natl Acad Sci U S A, 2011, 108(37): 15354-15359.
110. Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome[J]. Nature, 2013, 499(7456): 97-101.
111. Song X, Sun X, Oh SF, et al. Microbial bile acid metabolites modulate gut RORγ+ regulatory T cell homeostasis[J]. Nature, 2020, 577(7790): 410-415.
112. Li Y, Zhang X, Wang L, et al. Distribution and gene mutation of enteric flora carrying β-glucuronidase among patients with colorectal cancer[J]. Int J Clin Exp Med, 2015, 8(4): 5310-5316.
113. Goldin BR, Gorbach SL. Alterations of the intestinal microflora by diet, oral antibiotics, and *Lactobacillus*: decreased production of free amines from aromatic nitro compounds, azo dyes, and glucuronides[J]. J Natl Cancer Inst, 1984, 73(3): 689-695.
114. Soda K. The mechanisms by which polyamines accelerate tumor spread[J]. J Exp Clin Cancer Res, 2011, 30(1): 95.
115. Tang WH, Wang Z, Kennedy DJ, et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease[J]. Circ Res, 2015, 116(3): 448-455.
116. Wang Z, Roberts AB, Buffa JA, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis[J]. Cell, 2015, 163(7): 1585-1595.
117. Wu K, Yuan Y, Yu H, et al. The gut microbial metabolite trimethylamine N-oxide aggravates GVHD by inducing M1 macrophage polarization in mice[J]. Blood, 2020, 136(4): 501-515.
118. Wang H, Rong X, Zhao G, et al. The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer[J]. Cell Metab, 2022, 34(4): 581-594.e8.
119. Xu R, Wang Q, Li L. A genome-wide systems analysis reveals strong link between colorectal cancer and trimethylamine N-oxide (TMAO), a gut microbial metabolite of dietary meat and fat[J]. BMC Genomics, 2015, 16(Suppl 7): S4.
120. Cervantes-Barragan L, Chai JN, Tianero MD, et al. *Lactobacillus reuteri* induces gut intraepithelial CD4+CD8αα+ T cells[J]. Science, 2017, 357(6353): 806-810.
121. Natividad JM, Agus A, Planchais J, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome[J]. Cell Metab, 2018, 28(5): 737-749. e4.
122. Wlodarska M, Luo C, Kolde R, et al. Indoleacrylic acid produced by commensal peptostreptococcus species suppresses inflammation[J]. Cell Host Microbe, 2017, 22(1): 25-37. e6.
123. Zelante T, Iannitti RG, Cunha C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22[J]. Immunity, 2013, 39(2): 372-385.
124. Lin Y, Ma C, Liu C, et al. NMR-based fecal metabolomics fingerprinting as predictors of earlier diagnosis in patients with colorectal cancer[J]. Oncotarget, 2016, 7(20): 29454-29464.
125. Zarkavelis G, Boussios S, Papadaki A, et al. Current and future biomarkers in colorectal cancer[J]. Ann Gastroenterol, 2017, 30(6):

613-621.

126. Baxter NT, Ruffin MT 4th, Rogers MA, et al. Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions[J]. Genome Med, 2016, 8(1): 37.
127. Wong SH, Kwong TNY, Chow TC, et al. Quantitation of faecal *Fusobacterium* improves faecal immunochemical test in detecting advanced colorectal neoplasia[J]. Gut, 2017, 66(8): 1441-1448.
128. Zeller G, Tap J, Voigt AY, et al. Potential of fecal microbiota for early-stage detection of colorectal cancer[J]. Mol Syst Biol, 2014, 10(11): 766.
129. Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of patients with late-stage colorectal cancer: ASCO resource-stratified guideline[J]. JCO Glob Oncol, 2020, 6: 414-438.
130. Dahan L, Sadok A, Formento JL, et al. Modulation of cellular redox state underlies antagonism between oxaliplatin and cetuximab in human colorectal cancer cell lines[J]. Br J Pharmacol, 2009, 158(2): 610-620.
131. Gopalakrishnan V, Helmink BA, Spencer CN, et al. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy[J]. Cancer Cell, 2018, 33(4): 570-580.
132. Yu T, Guo F, Yu Y, et al. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy[J]. Cell, 2017, 170(3): 548-563. e16.
133. Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment[J]. Science, 2013, 342(6161): 967-970.
134. Laurent A, Nicco C, Chéreau C, et al. Controlling tumor growth by modulating endogenous production of reactive oxygen species[J]. Cancer Res, 2005, 65(3): 948-956.
135. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide[J]. Science, 2013, 342(6161): 971-976.
136. Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity[J]. Nat Rev Gastroenterol Hepatol, 2017, 14(6): 356-365.
137. Geller LT, Barzily-Rokni M, Danino T, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine[J]. Science, 2017, 357(6356): 1156-1160.
138. He Y, Fu L, Li Y, et al. Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic $CD8^+$ T cell immunity[J]. Cell Metab, 2021, 33(5): 988-1000. e7.
139. Zhang S, Yang Y, Weng W, et al. *Fusobacterium nucleatum* promotes chemoresistance to 5-fluorouracil by upregulation of BIRC3 expression in colorectal cancer[J]. J Exp Clin Cancer Res, 2019, 38(1): 14.
140. Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota[J]. Science, 2015, 350(6264): 1079-1084.

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