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·专家论坛·

口腔微生物与结直肠癌：作用机制及治疗策略

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[摘 要] 结直肠癌(CRC)是全球发病率和病死率均居前列的恶性肿瘤。除肠道微生物失衡外,近年研究证据表明口腔微生物亦在CRC发生发展中发挥关键作用。特定口腔微生物可经“口-肠”轴迁移至肠道及肿瘤组织,通过黏附定植、激活致癌信号通路、增强肿瘤细胞侵袭与迁移能力及重塑肿瘤微环境等机制促进肿瘤进展,并可能影响抗肿瘤治疗应答。这些发现提示口腔微生物在CRC临床治疗中具有潜在的应用价值。本文系统梳理口腔微生物参与CRC疾病进程的分子机制,重点阐述靶向“口-肠”轴的微生物干预策略,剖析现有研究的局限性并展望发展方向,以期为该领域的基础研究与临床转化提供参考。

[关键词] 口腔微生物;结直肠癌;作用机制;治疗策略
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Oral microbiota and colorectal cancer: mechanisms and therapeutic strategies

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[Abstract] Colorectal cancer (CRC), a malignant tumor, is a leading cause of cancer-related morbidity and mortality worldwide. Accumulating evidence suggests that CRC occurrence and development are closely associated not only with intestinal microbiota dysbiosis, but also with oral microbiota. Specific oral microbes can translocate *via* the oral-gut axis to colonize the intestinal tract and distant tumor sites. Through

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mechanisms such as adhesion and colonization, activation of oncogenic signaling pathways, enhancement of tumor cell migration and invasion, and remodeling of the tumor microenvironment, these microbes promote tumor progression and may influence responses to anticancer therapies. These findings highlight the potential of targeting oral microbiota in CRC clinical management. This review systematically summarizes the molecular mechanisms by which oral microbiota contributes to CRC pathogenesis, with a particular focus on microbial intervention strategies that target the oral-gut axis. This review also discusses current research limitations and future directions, aiming to provide a reference for both basic research and clinical translation in this field.

[Key words] oral microbiota; colorectal cancer (CRC); mechanism; therapeutic strategy

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结直肠癌(colorectal cancer, CRC)是全球常见的恶性肿瘤之一[1]。现有研究[2-3]表明,CRC的发生发展是遗传、环境与饮食等多因素共同作用的结果,其中微生物作为关键且可调控的环境因素已成为研究热点。既往研究主要聚焦肠道微生物与CRC的关联,但近期的研究[4]表明,口腔微生物失衡也是导致CRC进展的重要因素。例如,具核梭杆菌(*Fusobacterium nucleatum*, *F. nucleatum*)、微小小单胞菌(*Parvimonas micra*, *P. micra*)等口腔来源细菌可突破口-肠屏障,在肠道乃至肿瘤组织中异位定植甚至异常富集,进而参与CRC的病理进程[5-6]。此外,得益于新一代测序技术的快速发展,口腔真菌与病毒在CRC中的潜在作用亦逐步被揭示[7-8]。随着证据不断积累,基于"口-肠"轴微生物的干预策略有望成为CRC精准治疗的重要组成部分。因此,本文系统梳理口腔关键致病性微生物在CRC演进及治疗中的最新研究进展及作用机制,总结针对"口-肠"轴微生物的多种干预策略,以期为CRC机制探索及防治策略提供新的切入点。

1　关键口腔微生物促进CRC的作用机制

研究[9]表明,CRC患者中"口-肠"轴微生物的跨器官传播显著增强,提示口腔是肠道及瘤内微生物的重要来源,此为口腔微生物参与CRC发生发展提供了新的解释。下文将重点论述具有致癌作用的口腔微生物,概括其参与CRC发生发展的主要机制。

1.1　*F. nucleatum*

*F. nucleatum*是口腔常驻的革兰阴性厌氧菌,在结直肠腺瘤(colorectal adenoma, CRA)和CRC患者的粪便和肿瘤组织中稳定富集[10]。部分CRC患者的唾液与肿瘤组织中可检测到高度同源的*F. nucleatum*菌株[11]。近期针对*F. nucleatum*动物亚种分支2(*F. nucleatum* subsp. animalis clade 2)的研究[12]进一步揭示,该亚种主要来源于口腔,且在CRC中表现出明显的选择性优势和致癌潜能。

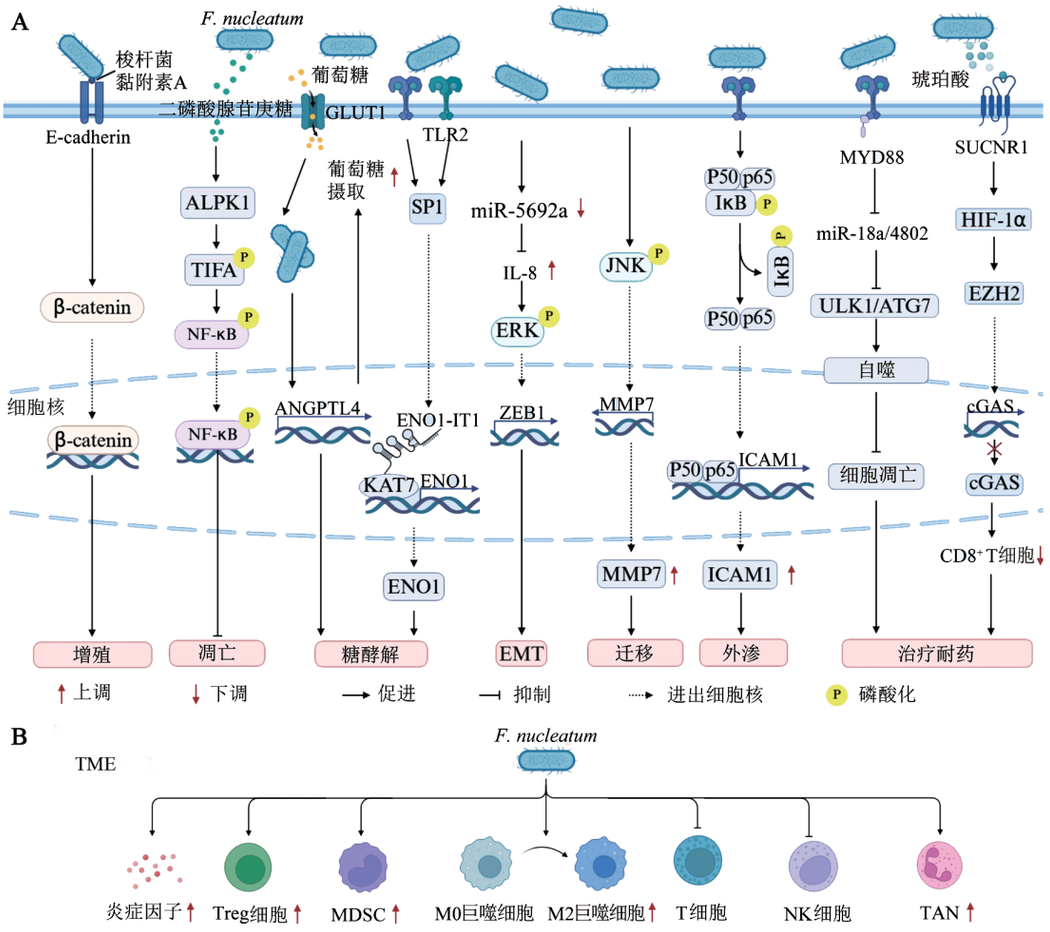
*F. nucleatum*依赖多种毒力因子和代谢产物激活致癌信号通路并促进CRC发生发展[13]。例如,其梭杆菌黏附素A可结合上皮钙黏素(E-cadherin),激活Wnt/β-catenin通路促进CRC细胞增殖[14]。*F. nucleatum*分泌的二磷酸腺苷庚糖可激活ALPK1/TIFA/NF-κB通路,诱导炎症因子表达与抗凋亡反应[15]。此外,*F. nucleatum*还能上调lncRNA烯醇化酶1-内含子转录本1(enolase 1-intronic transcript 1, ENO1-IT1)和血管生成素样蛋白4(angiopoietin-like 4, ANGPTL4),增强糖酵解,以满足肿瘤快速生长的能量需求[16-17]。

在侵袭与转移方面,*F. nucleatum*同样发挥关键作用:(1)调控miR-5692a/IL-8轴诱导上皮间质转化(EMT),增强肿瘤细胞的迁移能力[18];(2)上调MMP7,促进ECM降解,进而增强肿瘤局部浸润[19];(3)通过ALPK1/NF-κB/ICAM1通路增强肿瘤细胞与血管内皮细胞的黏附及外渗,促进远处转移[20]。此外,*F. nucleatum*可诱导M2型巨噬细胞极化,产生IL-6、活性氧(reactive oxygen species, ROS)等促炎因子[21],同时招募髓源性抑制细胞(MDSC)、肿瘤相关巨噬细胞(TAM)等免疫抑制性细胞[22],构建炎症性且免疫抑制性肿瘤微环境(tumor microenvironment, TME),从而为肿瘤的生长提供适宜的土壤。梭杆菌自转运蛋白2(*Fusobacterium* autotransporter protein 2, Fap2)可结合TIGIT受体抑制T细胞及NK细胞的活性,促进免疫逃逸[23]。

*F. nucleatum*亦影响多种抗肿瘤治疗的疗效。例如,*F. nucleatum*会削弱5-氟尿嘧啶(5-FU)和奥沙利铂(oxaliplatin, OXA)诱导的细胞凋亡,导致化疗耐药[24]并降低放疗敏感性、加重放射性肠损伤[25]。在免疫治疗中,*F. nucleatum*衍生的琥珀酸抑制cGAS-IFN-β信号与趋化因子配体(chemokine ligand, CXCL)表达,减少$CD8^+$ T细胞浸润,诱导抗PD-1治疗耐药[26];在部分微卫星稳定性CRC中,*F. nucleatum*富集及其丁酸生成又可缓解T细胞耗竭,增强抗PD-1/PD-L1的治疗效应[27](图1)。

1.2　厌氧消化链球菌(*Peptostreptococcus anaerobius*, *P. anaerobius*)

*P. anaerobius*为口腔常见的革兰阳性厌氧菌。研究[28-29]发现,*P. anaerobius*在CRC患者粪便及黏膜中呈选择性富集,且在CRA及早期腺癌组织中富集尤为显著,提示该菌可能参与腺瘤-癌变序列的启动环节[30]。



A：*F. nucleatum* 驱动CRC恶性表型及诱导治疗耐药的机制；B：*F. nucleatum* 重塑TME。

TIFA：含FHA结构域的TRAF相互作用蛋白（TRAF-interacting protein with FHA domain）；GLUT1：葡萄糖转运蛋白1（glucose transporter 1）；SP1：特异性蛋白1转录因子（specificity protein 1）；IκB：核因子κB抑制蛋白（inhibitor of nuclear factor kappa B）；MyD88：髓样分化因子88（myeloid differentiation primary response 88）；SUCNR1：琥珀酸受体1（succinate receptor 1）；ULK1：unc-51样自噬起始激酶（unc-51 like autophagy activating kinase 1）；ATG7：自噬相关蛋白7（autophagy-related 7）；EZH2：zeste同源物增强子2（enhancer of zeste homolog 2）；cGAS：环状GMP-AMP合成酶（cyclic GMP-AMP synthase）；KAT7：赖氨酸乙酰转移酶7（lysine acetyltransferase 7）；ZEB1：锌指E-盒结合蛋白同源框1（zinc finger E-box-binding homeobox 1）；ICAM1：细胞间黏附分子1（intercellular adhesion molecule 1）。

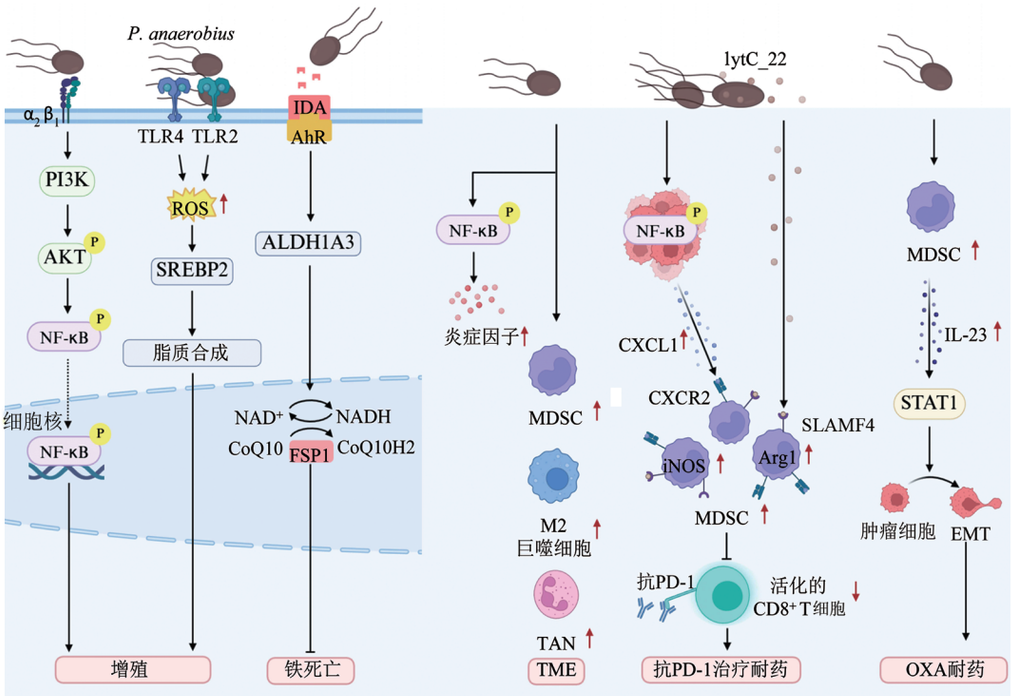
图1　*F. nucleatum* 促进CRC的机制

在上皮细胞中，*P. anaerobius* 经TLR2/4诱导ROS累积并激活甾醇调节元件结合蛋白2（sterol regulatory element-binding protein 2，SREBP2）介导的胆固醇合成，驱动其异常增殖及不典型增殖[31]。其表面蛋白还可与CRC细胞的整合素结合，激活PI3K/Akt/NF-κB通路，促进CRC细胞增殖[28]。此外，*P. anaerobius* 分解色氨酸产生的代谢产物，可抑制肿瘤细胞铁死亡，加速CRC进展[32]。

在小鼠体内，*P. anaerobius* 可显著增加MDSC、TAM浸润并上调IL-10、IFN-γ等因子[28]，同时激活TLR2/4-NF-κB-NLRP3轴诱导巨噬细胞焦亡并释放大量IL-1β，加速“炎-癌”转化[33]。*P. anaerobius* 不仅能诱导CRC细胞分泌CXCL1，募集MDSC，还能分泌lytC_22蛋白增强MDSC的免疫抑制功能，从而削弱抗PD-1治疗疗效[34]。此外，*P. anaerobius* 亦能促进MDSC分泌IL-23，激活STAT3-EMT通路，驱动OXA耐药[29]（图2）。

1.3　牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P. gingivalis*）

P. gingivalis 是牙周炎的关键致病菌，主要定植于龈下菌斑[35]。研究[36]表明，*P. gingivalis* 可经“口-肠”轴迁移至肠道，在CRC患者的肿瘤组织和粪便中显著富集，与不良预后相关。



α2/β1：整合素α2/β1（integrin alpha 2/beta 1）；IDA：吲哚-3-丙烯酸（indole-3-acrylic acid）；AhR：芳烃受体（aryl hydrocarbon receptor）；ALDH1A3：乙醛脱氢酶1家族成员A3（aldehyde dehydrogenase 1 family member A3）；NAD^+：烟酰胺腺嘌呤二核苷酸（氧化型）（nicotinamide adenine dinucleotide, oxidized）；NADH：烟酰胺腺嘌呤二核苷酸（还原型）（nicotinamide adenine dinucleotide，reduced）；CoQ10：辅酶Q10（coenzyme Q10）；CoQ10H2：还原型辅酶Q10（reduced coenzyme Q10）；FSP1：铁死亡抑制蛋白1（ferroptosis suppressor protein 1）；iNOS：诱导型一氧化氮合酶（inducible nitric oxide synthase）；Arg1：精氨酸酶1（arginase 1）；SLAMF4：信号淋巴细胞激活分子家族成员4（signaling lymphocytic activation molecule family member 4）。

图2　*P. anaerobius*促进CRC的作用机制

*P. gingivalis*可通过破坏肠道屏障及激活致癌信号促进CRC发生发展。一方面，*P. gingivalis*可下调紧密连接蛋白1及闭锁蛋白等的表达，并分泌牙龈蛋白酶切割肠道黏蛋白2，破坏肠道屏障[37-38]。另一方面，*P. gingivalis*能黏附并侵入CRC细胞，激活MAPK/ERK及NF-κB等促癌信号通路，促进细胞增殖、迁移与侵袭[39-40]。此外，*P. gingivalis*激活NOD样受体热蛋白结构域相关蛋白3（NOD-like receptor family pyrin domain containing 3, NLRP3）炎症小体，促进IL-1β等炎症因子的释放，并募集MDSC、TAM等髓系细胞浸润TME，从而促进肿瘤进展[36]。研究[41]发现，*P. gingivalis*可诱导恒定自然杀伤T细胞高表达几丁质酶3样蛋白1，显著削弱其抗肿瘤活性。其细胞壁成分肽聚糖还能上调CRC细胞PD-L1的表达，进一步促进免疫逃逸[42]。

1.4　胃消化链球菌（*Peptostreptococcus stomatis*, *P. stomatis*）

*P. stomatis*是源于口腔的革兰阳性球菌，常定植于龈下菌斑并与牙周炎相关[43]。多个队列研究[44-45]表明，其在CRC患者粪便及肿瘤组织中均稳定富集。

在小鼠体内，*P. stomatis*通过果糖-1, 6-二磷酸醛缩酶（fructose-1, 6-bisphosphate aldolase, FBA）与CRC细胞整合素结合，激活ERBB2-MEK-ERK-p90轴，导致上皮细胞增殖、抑制凋亡并破坏肠道屏障，从而促进CRC发生[44]。在肥胖相关CRC中，*P. stomatis*与益生菌普氏栖粪杆菌（*Faecalibacterium prausnitzii*）存在“代谢互养”，提示两者可能协同促癌[45]。值得注意的是，在KRAS野生型CRC中，*P. stomatis*介导的ERBB2持续激活可绕过对表皮生长因子受体的依赖，削弱表皮生长因子受体抑制剂（如西妥昔单抗）的疗效；在BRAF V600E突变型CRC中亦降低BRAF抑制剂（如维莫非尼）的作用[44]，提示其可能是影响靶向药物疗效的重要微生物因素。

1.5　*P. micra*

*P. micra*为口腔黏膜与龈下菌斑中常见的机会致病菌，可以自龈下迁移至肠道甚至肿瘤组织[6]。BERGSTEN等[46]根据系统发育将*P. micra*分为A型、B型，其中A型具有更强的黏附和溶血能力。在结肠上皮细胞和CRC患者肿瘤黏膜中，A型*P. micra*可诱导

多种抑癌基因、原癌基因及EMT相关基因启动子的异常DNA甲基化,从而驱动CRC发生发展[46]。ZHAO等[47]发现,*P. micra*可通过激活Wnt/β-catenin通路促进结肠上皮细胞增殖,并诱导结肠Th17细胞浸润与相关促炎因子分泌,进而促进肿瘤发生。此外,*P. micra*还能上调miR-218-5p激活RAS/ERK/c-Fos通路,促进CRC进展[48];诱导M2巨噬细胞极化并促进其分泌IL-8,增强CRC细胞的恶性表型并导致顺铂耐药[49]。

1.6 中间普雷沃菌(*Prevotella intermedia*, *P. intermedia*)

*P. intermedia*是龈沟生物膜的早期定植者[50]。研究[51]发现,*P. intermedia*在CRC患者肿瘤组织中的丰度升高,且常与*F. nucleatum*共聚集,这种共聚集现象与患者淋巴结转移及远处转移相关。体外实验结果[51]表明,*P. intermedia*能显著增强CRC细胞的迁移和侵袭能力,且部分效应不依赖菌体与细胞直接接触,提示其可能通过旁分泌促进肿瘤进展。

1.7 小韦荣球菌(*Veillonella parvula*, *V. parvula*)

*V. parvula*为口腔常驻厌氧菌,肠道炎症产生的高浓度硝酸盐有利于其在肠道异位定植并扩张[52]。研究表明,*V. parvula*是右半结肠癌的特征菌之一[53],且其丰度升高与较晚分期、更高淋巴结转移率及较差预后相关[54]。机制上,*V. parvula*可激活肠道黏膜免疫,上调B淋巴细胞刺激因子及其受体表达,增加肿瘤黏膜B细胞浸润,从而加速腺瘤-癌变进程[54]。

1.8 其他口腔微生物

口腔真菌虽在总体微生物群中丰度较低,但多项队列研究与泛癌分析提示其与CRC相关[7,55]。C型凝集素受体Dectin-3主要表达于髓系免疫细胞,能识别白念珠菌(*Candida albicans*, *C. albicans*)并启动固有免疫应答。研究[56]发现,Dectin-3缺失的小鼠表现出更高真菌及肿瘤负荷,其机制与*C. albicans*诱导巨噬细胞糖酵解和IL-7分泌,驱动3型固有淋巴样细胞产生IL-22并促进上皮增殖有关。部分研究[57]提示,*C. albicans*可激活Wnt/β-catenin通路增强上皮细胞增殖。热带念珠菌(*Candida tropicalis*, *C. tropicalis*)与CRC免疫抑制和化疗耐药相关。该菌在MDSC中激活NLRP3炎性小体,促进IL-1β分泌[58],并通过Dectin-3/Syk-PKM2-HIF-1α轴诱导糖酵解重编程,显著增强MDSC的免疫抑制功能,从而促进CRC发生发展[59]。此外,*C. tropicalis*可增强肿瘤细胞糖酵解和乳酸生成,并经GPR81-cAMP-PKA-CREB轴下调错配修复蛋白MLH1的表达,诱导OXA耐药[60]。

病毒亦被认为是潜在促癌因素。流行病学数据[61]提示,人乳头状瘤病毒(HPV)感染与CRC风险升高相关。BODAGHI等[62]在约51%的CRC组织中检出HPV DNA。AMBROSIO等[63]进一步发现,HPV阳性CRC中p53和RB常表达缺失并伴随肿瘤免疫监视降低及肿瘤相关微生物群组成的显著改变,提示其可能通过促进免疫逃逸及扰乱肠道微生态参与CRC发生。此外,CRC中EB病毒(EBV)合并感染率约18%[64],并与炎症性肠病风险增加相关[65],提示EBV可能参与"炎-癌"转化,但目前其在CRC中的作用尚缺乏直接证据。

综上,口腔作为肠道及肿瘤内微生物的重要储库,特定菌群可经"口-肠"轴易位至肠道及肿瘤组织中,通过多种机制促进CRC演进:(1)破坏肠道黏膜屏障并诱发持续的炎症反应;(2)依赖毒力因子及代谢产物激活Wnt/β-catenin、NF-κB、MAPK/ERK、PI3K/Akt等促癌信号通路并促进代谢重编程,进而增强肿瘤细胞增殖、抗凋亡及EMT等恶性表型;(3)通过重塑TME,促进MDSC、TAM等免疫抑制性细胞募集与功能增强,抑制T/NK细胞抗肿瘤效应或上调免疫检查点分子表达,实现免疫逃逸。此外,部分口腔微生物可通过影响免疫浸润与激活旁路信号等方式影响抗肿瘤治疗的疗效,提示其不仅参与疾病进程,也可能是影响治疗反应与预后的重要因素。

2 针对"口-肠"轴微生物的治疗策略

鉴于口腔微生物在CRC发生、进展及治疗耐药中的关键作用,靶向调控"口-肠"轴微生物,在延缓肿瘤进展并提升现有治疗疗效方面具有巨大潜力。目前已经提出了多种策略,包括抗生素、抗菌肽、噬菌体、益生菌/益生元、纳米药物、药物再利用、中医药干预及饮食调节等(图3)。

2.1 局部治疗策略

2.1.1 抗生素

抗生素可以直接清除"口-肠"轴致病菌。研究[66]表明,牙周炎患者联合抗生素治疗,可显著改善牙周状况,减少*P. gingivalis*等口腔病原体。在CRC小鼠中,甲硝唑等抗生素可抑制肠道及瘤内致癌菌,提高免疫治疗及放疗敏感性[25-26]。研究[67]证实,多西环素还具有良好的细胞穿透性,可清除CRC细胞中*F. nucleatum*,从而抑制其介导的免疫抑制和促癌作用。然而,流行病学研究[68]提示,长期或反复抗生素暴露可能增加CRC风险。因此,在应用抗生素时,应遵循人群分层、短期使用的原则,以实现治疗效益最大化并降低远期风险。

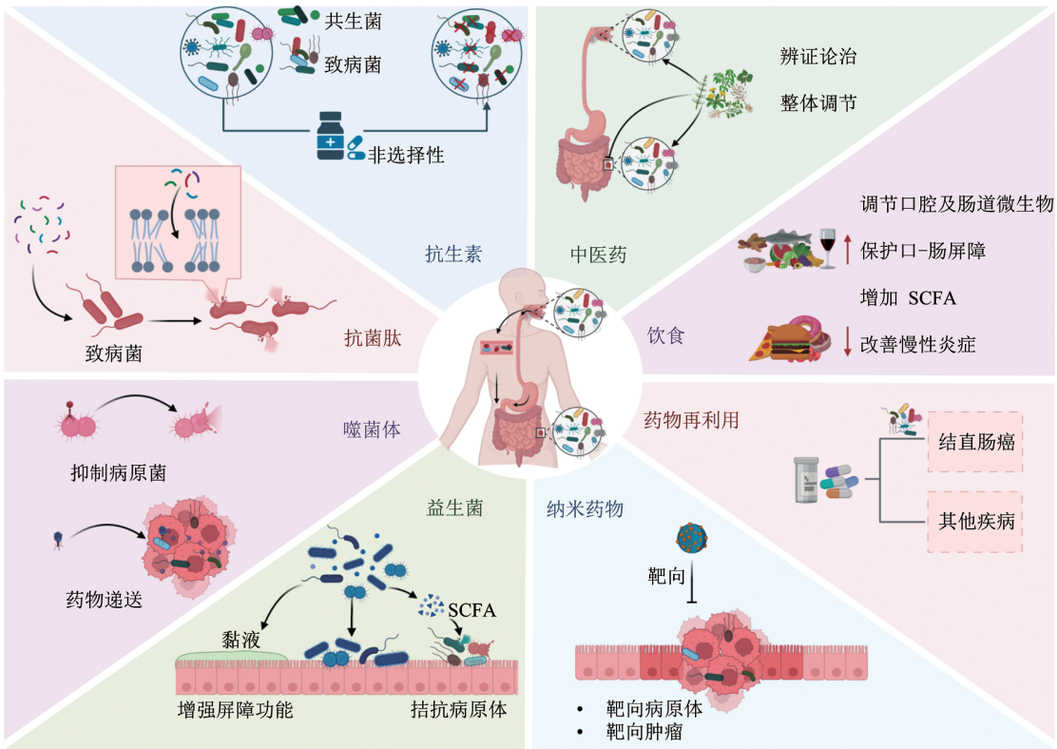


图3　针对“口-肠”轴微生物的CRC干预策略

2.1.2　抗菌肽

抗菌肽是固有免疫的重要效应分子，能直接破坏细菌细胞膜而发挥杀菌作用[69]。因天然抗菌肽普遍存在稳定性差、半衰期短等问题，从而限制了其临床应用[70]。JIA等[71]在Jelleine-Ⅰ基础上优化获得的Br-J-Ⅰ，可以靶向梭杆菌黏附素A并破坏*F. nucleatum*细胞膜，从而抑制*F. nucleatum*活性及其诱导的CRC进展。而LIU等[72]设计的工程化抗菌肽，可以选择性清除*F. nucleatum*并降低对常驻菌群的非特异性扰动。总体而言，抗菌肽具备与标准治疗联用以改善微生态失衡并提升治疗反应的潜力。

2.1.3　噬菌体

噬菌体是特异性感染并裂解细菌的病毒，其高度宿主特异性有助于在靶向清除病原菌的同时保护共生菌群[73]。在口腔中，噬菌体FNU1能特异性裂解*F. nucleatum*并破坏其生物膜[74]；而针对难以获得直接裂解性噬菌体的细菌（如*P. gingivalis*），可通过间接裂解其互养细菌以降低其毒力与丰度[75]。在肠道中，噬菌体TCUFN3可抑制*F. nucleatum*诱导的CRC细胞增殖与EMT[76]。此外，噬菌体本身可作为药物递送载体。例如，ZHENG等[77]将特异性识别*F. nucleatum*的P2噬菌体与负载化疗药物的纳米颗粒偶联，实现了药物精准递送及化疗增敏。

值得注意的是，噬菌体具有一定免疫原性，重复给药可能产生中和抗体并加速其清除，从而削弱治疗及递送效能；同时，裂解革兰氏阴性菌可能导致脂多糖短期升高并诱发炎症反应[78]。

2.1.4　益生菌/益生元

除了清除促癌微生物外，摄入益生菌/益生元已成为CRC重要的辅助干预策略。益生菌可通过竞争黏附位点、分泌抗菌物质、调控宿主代谢与免疫等途径发挥保护作用[79-80]。例如，在*F. nucleatum*阳性CRC小鼠中，动物双歧杆菌（*Bifidobacterium animalis*）能减轻肿瘤负荷和局部炎症，部分逆转其诱导的上皮屏障损伤[81]。此外，益生菌的代谢产物，如短链脂肪酸（short-chain fatty acid, SCFA），还可通过抑制组蛋白去乙酰化酶、激活G蛋白偶联受体及调节能量代谢等途径，诱导肿瘤细胞凋亡、抑制增殖并维持肠道稳态[82]。为提高益生菌在消化道内的存活与定植，近年来开发了多种递送系统。例如，透明质酸-菊粉包裹的粪肠球菌（*Enterococcus faecium*）制剂可实现结肠靶向富集，显著增强其针对*F. nucleatum*的抑菌活性并减轻相关肿瘤负荷[83]。

益生元是指能被宿主菌群选择性利用并赋予健康获益的底物[84]。经典的益生元如低聚果糖、菊粉等，能促进双歧杆菌（*Bifidobacterium*）和乳酸杆菌（*Lactobacillus*）等有益菌增殖，增加SCFA生成，强化肠道屏障并降低病原体易位风险[84]。合生元（益

生菌联合益生元)在调节肠道微环境、增强抗癌效应方面展现出协同效应,是未来调节微生态的重要发展方向。

2.1.5 纳米药物

纳米药物凭借其精准靶向性和多功能集成等优势,为精准靶向"口-肠"轴致病性微生物提供了可及性路径。在口腔中,纳米药物可降低牙周病原菌的口腔负荷,并显示出良好的抗生物膜活性。例如,银纳米颗粒对来自牙周炎患者及健康受试者的口腔生物膜均具有显著抑制作用[85],提示其有望作为口腔微生态干预的候选工具,用于控制*P. gingivalis*等形成的致病性生物膜。在肠道及TME中,双重靶向病原菌和肿瘤的纳米递药系统,可实现杀菌和抗肿瘤的一体化治疗。例如,仿生纳米颗粒Mel-SiO_2@CCM通过CRC细胞膜包裹,在同源黏附及Fap2与肿瘤细胞Gal-GalNAc相互作用的共同驱动下富集于肿瘤局部,实现对瘤内*F. nucleatum*的精准攻击和协同裂解肿瘤细胞[86]。

此外,基于灭活菌体或其关键抗原构建的纳米疫苗,为增强细菌阳性CRC的抗肿瘤免疫提供了临床前证据。例如,负载*F. nucleatum*外膜抗原与CpG佐剂的纳米颗粒,可选择性清除瘤中*F. nucleatum*、提高化疗敏感性并减少远处转移[87]。以灭活*P. anaerobius*构建的仿生纳米疫苗,可利用其对CRC的天然亲和性实现主动靶向递送,在重塑瘤内微生物组的同时激活树突状细胞与T细胞应答,以抑制肿瘤的生长和转移[88]。

总体而言,纳米药物有望实现从口腔到肠道乃至肿瘤局部的空间精准递送,且兼具抑菌、抗肿瘤等多重功能,为精准干预微生物-肿瘤相互作用提供了可能。

2.1.6 药物再利用

已有多种上市药物显示出通过调控"口-肠"轴微生物辅助防治CRC的潜力,其中阿司匹林可有效调节口腔及肠道菌群结构[89]。体外研究[90]进一步表明,阿司匹林及其主要代谢产物水杨酸可抑制*F. nucleatum*生长,下调梭杆菌黏附素A、Fap2等多种毒力因子的表达,从而抑制其促炎和促肿瘤能力。一线降糖药物二甲双胍可抑制牙周病原菌[91]、改善肠道菌群失调并抑制CRC进展[92-93],通过调控MYC/miR-361-5p/SHH轴逆转*F. nucleatum*介导的肿瘤干细胞特性与5-FU耐药[94]。阿卡波糖作为α-葡萄糖苷酶抑制剂,可通过调节肠道微生物和色氨酸代谢,提高瘤内CXCL10水平并促进$CD8^+$ T细胞浸润,从而增强抗PD-1治疗疗效[95]。研究发现,他汀类药物抑制*P. gingivalis*等口腔致病菌生长[96],并通过重塑肠道菌群,增加罗伊氏乳杆菌(*Lactobacillus reuteri*)及其色氨酸代谢产物,抑制Th17细胞分化,进而预防CRC[97]。流行病学研究[98]提示,他汀类药物的使用与CRC较好预后相关。总之,这些药物展现了通过调节微生物干预CRC的潜力,但仍需明确获益人群特征、优化用药时机与剂量并系统评估其长期安全性与不良反应。

2.2 中医药

2.2.1 中药单体

中药单体是指从中药中提取的具有明确化学结构和特定生物活性的化合物。近年来多种中药单体被证实可通过调节"口-肠"轴微生物发挥抗CRC作用。例如,厚朴酚、和厚朴酚对*P. gingivalis*、*P. intermedia*等牙周致病菌具有显著抑菌和抗生物膜作用,且对牙龈细胞毒性低于氯己定[99-100]。多中心随机对照试验结果显示,小檗碱显著降低CRA复发风险[101],并可通过调节肠道菌群、改善炎症并增强黏膜屏障以发挥化学预防和治疗CRC的作用[54]。灵芝多糖则通过调节肠道菌群组成和SCFA生成、增强黏液层和紧密连接蛋白表达,下调TLR4/MyD88/NF-κB信号,从而降低肿瘤负荷[102]。

2.2.2 中药复方

中药复方是中医辨证论治思想的集中体现,其临床疗效与微生物密切相关。研究[103]证明,半夏泻心汤可以干预FadA与E-cadherin的结合,阻断Wnt/β-catenin通路,延缓"炎-癌"转化;体外实验[104]亦显示,半夏泻心汤可抑制*F. nucleatum*诱导的CRC细胞增殖、迁移和侵袭。葛根芩连汤在CRC患者中可通过调节肠道菌群,降低致病菌、增加双歧杆菌、乳酸杆菌等有益菌比例,从而增强肠道免疫功能、修复上皮屏障[105]。消癌解毒方可降低肠道中拟杆菌门与普雷沃菌科等促癌菌,富集厚壁菌门及产丁酸菌等有益菌,并重塑胆汁酸、脂肪酸等代谢通路,阻延CRC进展[106]。

综上所述,中医药通过整体调节"口-肠"轴微生物、增强上皮屏障功能、阻断口腔微生物异位定植及抑制相关致癌信号通路等途径,在CRC防治中展现出独特优势。

2.3 饮食调节

饮食调节是重塑"口-肠"轴微生态、预防CRC的重要策略。研究[107]表明,以高脂、高糖、红肉和超加工食品等为特征的西方饮食模式与CRC发生风险升高密切相关,尤其是远端结肠和直肠肿瘤。其中,高脂饮食可导致肠道菌群失调,促使溶血磷脂酸等促炎代谢物累积并损害肠道屏障,从而驱动CRC发生[108]。高糖饮食可促进牙周病原体增殖、加剧黏膜

免疫反应并破坏口-肠屏障[109]。红肉和加工肉摄入增多与罹患CRC风险增加相关,其机制可能与*F. nucleatum*等致病菌扩增及硫化氢等促癌产物蓄积有关[110-111]。此外,超加工食品可直接扰乱口腔与肠道微生物稳态,诱发代谢紊乱和轻度炎症[112],并增加CRA和CRC风险[113]。

健康的膳食模式更有利于维持微生物稳态并降低CRC风险。研究[3]显示,以全谷物、蔬果、坚果及植物油等为基础的地中海饮食、健康植物性饮食及"审慎饮食"等与CRC风险下降相关。上述饮食模式的共同特点是富含可发酵膳食纤维和多酚类化合物等,这些成分可为产丁酸菌等有益菌提供充足的底物,促进SCFA生成,从而有助于增强肠道屏障并缓解慢性炎症[114]。值得注意的是,特定膳食纤维如聚葡萄糖和抗性糊精Fibersol-2在体外可诱导*F. nucleatum*产生更多丁酸,提示其可能部分逆转该菌的促癌特性[115]。此外,多不饱和脂肪酸(如Omega-3)在体外可抑制*P. gingivalis*等口腔致病菌的生长与生物膜形成,在体内研究中亦显示出改善牙周炎炎症反应的潜力[116]。

这些研究凸显了饮食调节在CRC预防与管理中的重要性。通过建立并长期坚持健康的饮食习惯,有望维护机体整体健康,从而降低CRC相关风险。

3 结　语

本文基于口腔微生物与CRC关联性的现有证据,重点阐述关键口腔致病菌驱动CRC发生发展及治疗耐药的作用机制,系统梳理靶向"口-肠"轴微生物的干预策略,以期为从"口-肠"轴跨器官视角开展CRC的机制研究、开发微生物靶向干预手段及联合治疗增敏的临床转化策略提供参考。尽管口腔微生物与CRC的研究日益增多,但现有证据仍存在一些局限:(1)口腔微生物与CRC的因果关系尚不明确,多数证据仍停留在相关性层面。未来应依托多中心前瞻性队列,整合宏基因组/宏转录组等多组学数据,并结合干预性研究,以系统验证其因果关联。(2)对口腔微生物异位定植过程中发生的适应性变化认识不足。以*F. nucleatum* subsp. *animalis* clade 2为例,其在CRC肿瘤生态位中富集;相较非癌口腔分离株呈现差异性的遗传特征,提示肿瘤生态位对口腔相关菌株存在选择作用,并可能伴随适应性重塑[12],亟须加强菌株溯源与功能验证研究。(3)部分细菌(如*P. micra*)分离、培养难度较大,真菌与病毒因丰度偏低、检测手段灵敏度不足,制约了相关研究的作用机制阐明与可重复验证。未来需进一步优化取样与检测流程,结合无菌动物模型、类器官共培养与体外培养组学等体系,以深化机制研究;(4)目前多数干预性研究仍处于临床前阶段,且个体间微生物组具有高度异质性,增加了临床转化的复杂性。未来应重视整合口腔及肠道微生物特征、宿主临床病理信息等,构建可推广的风险预测与人群分层模型,通过多中心前瞻性队列及随机对照临床试验验证其临床效益与安全性。

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