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肠道微生物群与结直肠癌：菌群失调特征与关键分子机制的研究进展

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摘　要

结直肠癌是全球高发的消化道恶性肿瘤，其发生发展与肠道微生态失衡存在密切关联。肠道微生物群主要通过其代谢产物调控、免疫炎症激活及直接遗传损伤等机制，改变宿主肠道微环境，影响上皮细胞功能与肠道屏障稳定性，从而参与结直肠癌的发生与发展。本文旨在对肠道微生物群的失调特征及其与结直肠癌相关的关键分子机制进行系统综述，为结直肠癌的早期干预、诊断及治疗提供理论参考。

关键词

肠道微生物群，结直肠癌，菌群失调

Gut Microbiota and Colorectal Cancer: Research Advances in Dysbiosis Characteristics and Key Molecular Mechanisms

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Abstract

Colorectal cancer (CRC) is a highly prevalent malignant tumor of the digestive tract worldwide, and

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its development is closely associated with intestinal microecological imbalance. The gut microbiota primarily influences the host intestinal microenvironment through mechanisms such as metabolite regulation, immune-inflammatory activation, and direct genetic damage, thereby altering epithelial cell function and intestinal barrier stability, and participating in the initiation and progression of colorectal cancer. This article aims to systematically review the characteristics of gut microbiota dysbiosis and its key molecular mechanisms related to colorectal cancer, providing theoretical insights for early intervention, diagnosis, and treatment of colorectal cancer.

Keywords

Gut Microbiota, Colorectal Cancer, Dysbiosis

1. 引言与背景

结直肠癌是全球第四大恶性肿瘤，国家癌症中心 2024 年最新发布的统计数据显示，我国的结直肠癌发病率和死亡率显著上升，且呈逐年增长趋势[1]，严重威胁着人类生命安全。

人体肠道内驻扎着数以万亿计的微生物，包括真菌、细菌、病毒、古菌和原虫等。其不仅影响着人们的消化吸收，还参与了新陈代谢和免疫调节的过程，是体内不可或缺的重要组成成分[2] [3]。近年来，随着高通量测序技术、分子生物学技术和精准医学的快速发展，肠道微生态失调与人类健康疾病的关系，尤其是在结直肠癌中的作用受到密切关注，在生理病理过程中的作用机制也得到了进一步研究。人们发现，肠道微生物群失衡与多种癌症相关，其能够通过影响免疫细胞的聚集、炎症因子的释放等过程影响结直肠癌的发生发展[4]。本文主要就肠道微生物群的失调特征及其与结直肠癌相关的关键分子机制进行综述。

2. 结直肠癌患者菌群失调特征

近年来大量研究表明，结直肠癌患者相较于健康人群呈现特征性肠道微生物群改变，这些改变与结直肠癌的发生发展密切相关。

2.1. 菌群多样性与丰富度降低

一项研究对结直肠癌患者与健康人的粪便微生物群落进行分析，发现结直肠癌患者肠道微生物群呈现特征性 α 多样性改变，其反映物种丰富度的 Chao1 指数显著降低，表明肠道细菌物种总数减少；尽管整体多样性差异有限，但患者菌群 β 多样性(群落组成差异)与健康人群存在显著分离，提示肠道微生态结构发生紊乱。提示菌群整体生态结构失衡[5]。

2.2. 菌群组成的特异性差异

1) 显著富集的促癌相关细菌

与健康人群相比，结直肠癌患者的肠道微生物群在物种组成上呈现阶段性失衡，主要表现为部分促炎或致癌相关菌种的富集，有研究通过对结直肠癌患者粪便样本进行宏基因组和代谢组学分析发现，随着疾病的进程，厚壁菌门、梭杆菌门以及拟杆菌门下的一些细菌丰度不断升高。其中具核梭杆菌

(*Fusobacterium nucleatum*)、微小单胞菌(*Parvimonas micra*)、口腔单胞菌(*Peptostreptococcus stomatis*)、厌氧消化链球菌(*Peptostreptococcus anaerobius*)细菌丰度在疾病早期和晚期都呈现升高，而细小阿托普毕姆菌(*Atopobium parvulum*)、龋齿放线菌(*Actinomyces odontolyticus*)等仅在疾病早期丰度升高[6]。

2) 有益菌群的减少

有研究表明，在结直肠癌患者的肠道微生物群中，部分具有抗炎或维持肠道屏障功能的菌群比例下降，其中一些产短链脂肪酸(SCFA)的菌群丰度下降，如罗氏菌属(*Roseburia*)和普拉梭菌(*Faecalibacterium prausnitzii*)，普拉梭菌具有抗炎特性[7]。部分益生菌类群，如丁酸梭菌(*Clostridium butyricum*)和嗜热链球菌(*Streptococcus thermophilus*)也呈现减少趋势。这些有益菌的减少削弱了肠道屏障保护、抗炎调节及维持微环境稳定的功能[8]。

3) 癌前病变阶段的早期改变

研究发现，某些细菌在腺瘤或早期黏膜内癌阶段特异性升高，例如小阿托波菌(*Atopobium parvulum*)和龋齿放线菌(*Actinomyces odontolyticus*)，提示癌前病变阶段已有细菌出现早期特异性富集，而具核梭杆菌(*Fusobacterium nucleatum*)和穆尔氏(*Solobacterium moorei*)则从早期阶段开始其丰度随病变进展而持续增加[6]。

3. 关键分子机制

结直肠癌的发生发展与肠道微生物群的组成和菌群失调密切相关。肠道微生物可通过代谢、免疫、遗传毒性等多种机制参与结直肠癌发生发展全过程。

3.1. 代谢调控

肠道微生物群进行代谢活动时会通过发酵产生大量代谢产物，如短链脂肪酸(SCFAs)、次级胆汁酸(secondary BAs)、硫化氢(H_2S)等，这些代谢产物通过表观遗传、受体信号及能量代谢等多途径动态调控肠上皮稳态。

SCFAs 是膳食纤维经肠道微生物群发酵产生，包括乙酸(acetate)、丙酸(propionate)、丁酸(butyrate)。它们不仅是肠道上皮细胞的主要能量来源，更是调节宿主肠道稳态的核心信号分子，作用机制复杂且多效[9]。SCFAs (如丁酸)主要经由肠上皮细胞顶膜的单羧酸转运体 1 (MCT1，由 SLC16A1 基因编码)和钠偶联单羧酸转运体 1 (SMCT1，由 SLC5A8 基因编码)主动转运入胞，胞内丁酸一方面作为组蛋白去乙酰化酶(HDAC)抑制剂激活 Wnt/*β*-连环蛋白(*β*-catenin)通路，从而驱动干细胞分化为成熟上皮细胞(如杯状细胞) [9]，另一方面通过 G 蛋白偶联受体(GPR43/GPR109a)信号来激活下游进一步调控免疫与代谢反应，在结肠癌细胞中，GPR109A 激活诱导 caspase 依赖性凋亡[10]，而激活肠上皮细胞 GPR43 后不仅能促进黏蛋白 MUC2 分泌增强肠道屏障[11]，同时还能抑制 Th1 细胞的极化，降低了肠道内的炎症反应水平[12]。同时丁酸作为结肠上皮细胞主要能量来源，通过 *β*-氧化促进增殖[13]。丁酸还通过浓度依赖性机制来进行细胞凋亡的双向调控：低浓度时丁酸通过抑制组蛋白去乙酰化酶(HDAC)活性诱导促凋亡蛋白 Bax 表达，而高浓度则直接触发细胞凋亡，这一机制对维持上皮细胞更新及清除受损细胞具有关键意义[14]。在功能调节方面，短链脂肪酸(SCFAs)能有效加强肠道物理屏障的完整性，其中丁酸盐通过稳定低氧诱导因子(HIF)途径强化屏障功能[15]。系统性 SCFAs 能通过上调紧密连接蛋白 occludin 的表达降低血脑屏障通透性[16]，并通过促进杯状细胞分泌黏蛋白 MUC2 来加固肠道黏液层，从而协同增强屏障防护功能[17]。

次级胆汁酸是初级胆汁酸在肠道中经菌群代谢转化而成的衍生物，主要包括脱氧胆酸(DCA)和石胆酸(LCA) [18]。它们主要通过肠上皮细胞表达的顶端钠依赖性胆汁酸转运体(ASBT)在肠上皮重吸收[19]，或经有机溶质转运体 *α*/*β* (OST*α*/OST*β*)从基底侧排入门脉循环[20]。在细胞内，DCA 可通过激活法尼醇 X

受体(FXR)促进肠道隐窝再生与修复，从而支持上皮屏障的完整性[21]；另外，次级胆汁酸还可通过激活G蛋白偶联胆汁酸受体1 (TGR5)来调控紧密连接蛋白表达，进一步增强肠上皮屏障功能[21]。此外，DCA与LCA能抑制艰难梭菌等病原体生长，起到直接抗菌及增强肠道共生菌产生的抗生素活性的作用来提升结肠的定植抗性[22] [23]。

硫化氢(H_2S)主要由肠道内的硫酸盐还原菌(如脱硫弧菌属 Desulfovibrio)通过代谢含硫氨基酸产生[24] [25]。H_2S的生物学效应具有显著的浓度依赖性，研究表明，生理浓度或低浓度的H_2S对肠上皮细胞具有明确的保护作用，其核心机制之一是激活线粒体生物合成。研究显示，在Caco-2细胞模型中，较低浓度的外源性H_2S (1×10^{-7}~1.5×10^{-3} M)可激活PGC-1α，进而上调其下游靶点TFAM和COX-4的表达，并增加线粒体DNA拷贝数，从而增强线粒体功能与细胞能量代谢，支持肠上皮细胞增殖[26]。当浓度升高时，H_2S则会上调促炎症因子表达，影响细胞免疫应答，诱导氧化应激，并通过ROS爆发与COX-2介导的炎症信号激活细胞凋亡[27]。此外，过量H_2S还能通过抑制细胞色素c氧化酶活性阻断ATP生成，最终引发细胞凋亡[28]。这种浓度依赖的双重作用使H_2S在肠道微环境稳态中发挥关键且复杂的调控功能。在大鼠肠缺血/再灌注损伤模型中，外源性H_2S能够通过抑制氧化应激(如降低MDA水平并提升GSH和SOD活性)以及调节促凋亡因子(如Bax/Bcl-2比例)来减少细胞凋亡，从而保护肠黏膜上皮细胞[29]。在屏障功能方面，H_2S可通过CBS-H_2S轴维持肠上皮紧密连接结构完整。研究表明，外源性H_2S供体能减轻结肠炎小鼠的肠上皮损伤，该作用与通过S-巯基化修饰RNA结合蛋白HuR、抑制其与COX-2 mRNA结合进而降低局部炎症反应有关[30]。

3.2. 炎症与免疫调控

肠道微生物群作为肿瘤免疫微环境的关键调控因素，通过调节免疫细胞功能和激活特定炎症通路促使局部及全身形成慢性促瘤炎症环境[31]。

1) 调节免疫细胞功能：肠道微生物群及其代谢产物调节关键免疫细胞的功能与分化来改变肿瘤微环境。菌群失调激活Toll样受体(TLR)信号，驱动髓源性抑制细胞(MDSCs)扩增、诱导肿瘤相关巨噬细胞(TAMs) M2型极化及调节性T细胞(Treg)分化[32]；此类细胞分泌IL-10和TGF-β等抑制因子，直接抑制$CD8^+$T细胞功能并破坏抗肿瘤免疫监视。同时菌群信号诱导调节性T细胞(Treg)分化[33]，进而分泌IL-10和TGF-β等抑制因子来阻断$CD8^+$T细胞功能以破坏抗肿瘤免疫监视[34]。

2) 激活炎症通路：菌群持续激活关键炎症通路是连接失调菌群与促瘤免疫环境的核心环节。

在结直肠癌微环境中，TLR/NF-κB通路的激活非常关键：革兰氏阴性菌(如具核梭杆菌、大肠杆菌)细胞壁中的脂多糖(LPS)属于病原体相关分子模式(PAMP) [35]，能够特异性识别并结合宿主细胞(如肠上皮细胞及免疫细胞)表面的TLR4及其共受体MD-2蛋白[36] [37]。此结合过程通过髓样分化因子88 (MyD88)依赖性信号通路激活下游级联反应[38] [39]，促使核因子-κB (NF-κB)发生核易位[40]，进而上调白细胞介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α)等促炎细胞因子的基因转录水平[39]，直接促进肿瘤细胞增殖与存活[41] [42]；该通路同时上调程序性死亡配体-1 (PD-L1)等免疫检查点分子表达，有效抑制效应T细胞功能并介导免疫逃逸过程[43]。其中有一突破性研究发现共生菌来源的四酰单磷酸脂质A (4A-MPLA)通过TRIF/IFN-β轴诱导抗炎性$ROR\gamma t^+$Treg分化进而抑制Th17介导的炎症[44]，这一发现首次阐述了肠道微生物群通过TLR4通路来调控免疫平衡的具体机制。

NLRP3炎症小体是另一条核心通路，NLRP3炎症小体被菌群代谢产物(如胞外ATP)激活后释放IL-1β和IL-18 [45]，这些因子在肿瘤微环境中发挥双重效应：IL-1β通过STAT3信号通路驱动上皮-间质转化(EMT)，增强肿瘤侵袭转移能力[46]；同时二者协同招募并激活MDSC等抑制性细胞，形成免疫抑制恶性循环[47]。

4. 临床转化挑战与干预策略展望

随着对肠道微生物群在结直肠癌中作用机制的深入解析，针对其临床应用的研究已进入快速发展阶段。当前，基于微生物调控的创新疗法在临床试验中展现出多样化潜力：一方面，粪菌移植(FMT)技术联合免疫治疗药物在晚期患者中观察到肿瘤显著消退现象，部分病例甚至达到病理学定义的完全缓解，提示其对免疫微环境的调节价值[48]；另一方面，特定功能益生菌的分子机制研究取得突破，例如丁酸梭菌(*Clostridium butyricum*)通过表面蛋白 SecD 与癌细胞 GRP78 受体结合，可阻断 PI3K-AKT-NF-κB 信号通路传导，降低 IL-6 等免疫抑制因子水平，从而提高免疫检查点抑制剂对微卫星稳定型肿瘤的治疗应答。此类发现已在人源化动物模型及患者类器官平台中获得验证，相关菌株目前正处于 I/II 期临床试验阶段，预计 2026~2028 年完成 III 期试验并获批用于结直肠癌治疗[49]。

在辅助治疗方面，包含双歧杆菌与乳酸杆菌的复合制剂表现突出。一项涉及 96 例转移性结直肠癌患者的研究表明，益生菌干预组化疗相关性腹泻发生率较对照组下降 75%，同时肠道屏障功能指标(如血清 D-乳酸及二胺氧化酶浓度)显著改善，证实其减轻治疗毒性的临床价值[50]。

然而，微生物疗法仍面临显著个体化差异的挑战，主要限制因素包括：(1) 不同患者的肠道菌群基线构成差异导致标准化方案响应率波动，需结合宏基因组特征筛选功能标志菌群；(2) 肠道微生物生态系统的高度稳定性使外源益生菌定植效率受限，需通过基因工程技术优化菌株适应性[51]；(3) 宿主遗传多态性、免疫状态波动及外部环境干扰等因素形成的复杂调控网络，增加了微生物干预的不可预测性。这些瓶颈问题的突破将依赖于跨组学分析技术与合成生物学工具的协同创新。

因此，未来微生物干预需向系统化与精准化方向演进。膳食调控作为基础性微生态干预措施，其潜在价值日益凸显：高纤维膳食可选择性促进产丁酸菌增殖，提升短链脂肪酸(SCFAs)浓度，进而增强肠道屏障功能并抑制炎症反应[52] [53]；而高脂饮食则易促使胆汁酸转化菌(如拟杆菌属)过度增殖，导致脱氧胆酸(DCA)等具有遗传毒性的次级胆汁酸累积[54]-[56]。这些发现提示，结合个体菌群特征制定的精准营养方案，有望成为结直肠癌预防领域的新型公共卫生干预策略。

5. 展望

目前，肠道微生物群在结直肠癌发生发展过程中的相关作用研究已取得实质性进展，但癌变全过程的调控机制仍有待进一步探索。结直肠癌患者存在特征性的肠道微生物群紊乱，这类紊乱可通过释放代谢产物、调控机体免疫、造成基因损伤等途径推动肿瘤发展，且该过程会与宿主遗传背景、表观遗传修饰、肠屏障功能状态及环境因素相互作用，共同构建肿瘤微环境。后续相关研究需整合多组学与系统生物学研究策略，打破仅对微生物组成进行单一分析的局限，全面解析微生物-宿主的相互作用网络。

后续研究可以筛选结直肠癌特异性的微生物与代谢物(如短链脂肪酸、次级胆汁酸)，以此开发疾病诊断与预后评估的标志物；同时，还针对促癌菌群与保护性菌群，设计菌群移植、益生元补充、代谢物补充等精准干预方案；在免疫治疗方面，可以研究肠道微生物通过 TLR/NF-κB、NLRP3 等信号通路调控肿瘤免疫微环境的内在机制，为肿瘤联合免疫治疗挖掘新的作用靶点。

此外，根除某些细菌所带来短期疗效的同时会引发肠道微生物群失衡，从而导致疾病进展。因此，未来研究还需重点关注菌群干预策略的伦理相关问题，避免破坏肠道微生物群落的生态平衡。各类靶向干预手段均需评估其对肠道微生态稳态的长期影响，确保在恢复菌群－宿主共生关系的基础上，实现结直肠癌防治的预期目标。

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