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肠–肝轴：肠道菌群调控肝癌发生发展与治疗响应

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摘 要

肝细胞癌(Hepatocellular Carcinoma, HCC)作为全球癌症相关死亡的主要病因之一，其发生发展机制复杂且治疗挑战突出。近年来，连接肠道与肝脏的“肠–肝轴”(Gut-Liver Axis, GLA)在HCC的病理过程中扮演重要角色。本综述系统阐述在HCC发展及治疗响应中，肠道菌群通过GLA发挥的重要作用。肠道菌群失调(Intestinal Dysbacteriosis, ID)是驱动HCC的核心环境因素，其代谢产物破坏肠道屏障、诱发肝脏持续炎症、塑造免疫抑制微环境，驱动肿瘤发生。研究证实，HCC患者具有特征性肠道菌群谱，该“微生物指纹”兼具诊断与预后预测潜力。同时，菌群组成显著影响免疫检查点抑制剂的疗效，使得靶向菌群调控成为增强免疫治疗、改善预后的前沿策略。尽管在机制研究深度与个体化干预方面仍存挑战，但靶向GLA无疑为HCC精准防治开辟全新视角。

关键词

肝细胞癌，肠–肝轴，肠道菌群，菌群失调，免疫治疗

Gut-Liver Axis: The Regulation of Liver Cancer Occurrence and Development as Well as Treatment Response by the Gut Microbiota

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Abstract

Hepatocellular Carcinoma (HCC) is one of the major causes of cancer-related deaths worldwide, and its occurrence and development mechanisms are complex with significant treatment challenges. In recent years, the "Gut-Liver Axis" (GLA), which connects the gut and the liver, plays an important role in the pathological process of HCC. This review systematically elaborates on the significant role of the gut microbiota through the GLA in the development of HCC and the response to treatment. Intestinal Dysbacteriosis (ID) is a core environmental factor driving HCC, and its metabolites damage the intestinal barrier, induce persistent liver inflammation, and shape an immunosuppressive microenvironment, driving tumor occurrence. Studies have confirmed that HCC patients have characteristic gut microbiota profiles, and this "microbial fingerprint" has both diagnostic and prognostic predictive potential. At the same time, the composition of the microbiota significantly affects the efficacy of immune checkpoint inhibitors, making targeting the regulation of the microbiota a promising strategy for enhancing immunotherapy and improving prognosis. Although there are still challenges in the depth of mechanism research and individualized intervention, targeting the GLA undoubtedly opens up a new perspective for the precise prevention and treatment of HCC.

Keywords

Hepatocellular Carcinoma, Gut-Liver Axis, Gut Microbiota, Dysbiosis, Immunotherapy

1. 引言

HCC 在全球恶性肿瘤中发病率位列第六，也是导致癌症相关死亡的第三大原因，每年约造成 80 万人死亡，其高死亡率与晚期诊断、易复发及治疗选择有限密切相关[1]。近年来，尽管靶向治疗和免疫检查点抑制剂的应用取得进展，但耐药性和个体化响应差异仍然是突出难题[2]。因此，探寻影响 HCC 发生发展、治疗响应的关键环境与宿主因素至关重要。GLA 是肠道与肝脏之间通过门静脉循环、胆道、神经内分泌及免疫网络建立的双向调节通路，对维持肝脏稳态具有重要生理意义[3]。肝脏分泌的胆汁酸可影响肠道菌群的组成，而肠道屏障完整性、菌群代谢产物及免疫信号则通过门静脉反馈至肝脏，参与组织修复、炎症调控及营养代谢过程[4]。肠道菌群可调节肝脏局部及全身免疫稳态[5]。因此，GLA 不仅是物理连接，更是动态调控网络，肠道菌群作为“环境传感器”，能将外界刺激转化为生物信号，进而影响肝脏病理生理过程[6]。HCC 的发生通常历经“肝炎–肝硬化–肝癌”的渐进过程。研究证实，ID 不仅是慢性肝病(Chronic Liver Disease, CLD)如非酒精性脂肪性肝病(Non-alcoholic Fatty Liver Disease, NAFLD)、酒精性肝病(Alcoholic Liver Disease, ALD)发展的驱动因素，更是贯穿肝脏恶性转化的“催化剂”和“调节器”[7]。从早期炎症诱导，到肝硬化肠漏内毒素易位，再到肿瘤期免疫微环境塑造，ID 全程参与[8]。本综述旨在系统梳理肠道菌群通过 GLA 调控 HCC 的分子机制、临床证据及靶向菌群的干预策略，为深入理解 HCC 病理生理机制、开发基于 GLA 的新型诊疗技术提供理论参考，推动该领域从相关性研究向因果性干预转变。

2. 菌群驱动 HCC 发展机制

2.1. 代谢调控失衡

肠道菌群通过代谢活动产生的多种生物活性物质，经 GLA 入肝后，直接调控肝细胞命运，其代谢失衡

是 HCC 发生的重要驱动因素。首先，相关菌群可将膳食中的卵磷脂、胆碱转化为氧化三甲胺(Trimetlylamine oxide, TMAO)，TMAO 与肝脏炎症及纤维化相关，是 CLD 向 HCC 进展的独立危险因素，并能通过激活 MARK 通路，促进 HCC 细胞增殖与转移[9]。此外，胆汁酸(Bile Acids, BAs)和短链脂肪酸(Short Chain Fatty Acids, SCFAs)代谢在 HCC 发生中呈现出显著的“双刃剑”效应。人体正常状态下，初级胆汁酸(Primary Bile Acids, PBAs)在肠道菌群作用下转化为次级胆汁酸(Secondary Bile Acids, SBAs)，参与脂质消化及维持肝脏代谢稳态。在肝纤维化及肝硬化阶段，肝脏合成功能和肠肝循环受损，BAs 池扩大，SBAs 比例明显增加，由于 SBAs 具有细胞毒性，能够诱导线粒体功能障碍，其遗传毒性产生的活性氧会造成 DNA 损伤，加速肝细胞恶性转化[10]。当进入 HCC 阶段后，SBAs 被证实能够激活 STAT3 等致癌通路，同时抑制抗肿瘤免疫，促进肿瘤生长和免疫逃逸[11]。经门静脉入肝脏的丁酸等 SCFAs，在正常生理状态下能够保护肠道屏障及抗炎，有助于预防癌症及肝损伤。当进展至晚期肝硬化及 HCC 阶段，肿瘤代谢重编程导致丁酸等 SCFAs 代谢途径改变，反而会抑制肝细胞生长，诱发胆汁淤积，驱动肝细胞癌变[12] [13]。

2.2. 肠道屏障破坏与系统性炎症

肠道屏障的健康可阻止肠内细菌进入血液循环。ID 引发的“肠漏”是连接肠道与肝脏炎症的核心病理环节，也是 HCC 发展的重要前提[14]。肝功能减退会诱发 ID 与肠道屏障损伤，引发持续性炎症反应。肝硬化阶段，由于肠道通透性增加，导致内毒素/脂多糖(Lipopolysaccharide, LPS)等易位入门静脉，引发“门静脉毒血症”[15]。LPS 通过激活肝脏 Kupffer 细胞表面 TLR4 受体，启动下游 NF-κB 信号通路，促进 IL-6、TNF-α 等促炎因子释放，触发级联炎症反应[16]。长期炎症刺激可激活肝星状细胞，使其转化为肌成纤维细胞，促进细胞外基质沉积与肝纤维化，为 HCC 发展奠定基础[17]。

2.3. 免疫监视逃逸

肠道菌群通过调控肝脏免疫微环境，助长肿瘤免疫逃逸。ID 可进一步促进肝内调节性 T 细胞(Regulatory Cells, Tregs)和髓源性抑制细胞(Myeloid-derived Suppressor Cells, MDSCs)的活化与扩增，其分泌的 TGF-β、IL-10 等因子抑制细胞毒性 T 细胞(Cytotoxic T Lymphocyte, CTL)和自然杀伤细胞(Natural Killer Cell, NKL)的肿瘤杀伤功能[18]。同时，菌群失调产生的 LPS 等代谢物，通过 TLR4 信号诱导肿瘤相关巨噬细胞(Tumor-Associated Macrophages, TAMs)的向 M2 型极化，后者分泌促进血管生成与免疫抑制因子，促进肿瘤进展与转移[19]。

2.4. 表观遗传与信号通路调控

菌群代谢产物通过表观遗传修饰与信号通路调控，干预肝细胞基因表达程序，驱动恶性转化。丁酸作为菌群代谢产物，同时也是组蛋白去乙酰化酶(Histone Deacetylases, HDACs)抑制剂，在正常肝细胞中具有保护作用，通过影响宿主细胞组蛋白乙酰化状态，调控原癌基因与抑癌基因的表达[20]。肠道菌群产生的 SBAs 可激活表皮生长因子受体(Epidermal Growth Factor Receptor, EGFR)等促癌信号，促进 AKT 磷酸化与 mTORC 通路活化，加速细胞增殖与蛋白合成[21]。

3. 从临床前到临床的相关证据

3.1. HCC 相关的肠道菌群

大量研究证实，HCC 患者肠道菌群，在 HCC 发展中起到关键作用，呈现出与健康人群及肝硬化患者截然不同的失调模式[22]。HCC 患者肠道菌群结构失调，主要表现为肠道菌群 α 多样性降低，提示肠道微生态稳定性下降。在菌群组成上，普雷沃菌、韦荣球菌等革兰阴性菌富集，其可能是内毒素主要来源，而产有益代谢物的瘤胃球菌丰度则显著降低[23]。研究证实，HCC 患者肠道中大肠杆菌过度增殖，

是疾病进展的重要因素[24]。此外，脆弱拟杆菌产生的毒素可破坏免疫反应、损伤肠道屏障，促进炎症与肿瘤进展，其丰度与患者预后不良相关[25]。相反，阿克曼氏菌有益菌的减少往往提示保护作用缺失，预后较差[23]。

3.2. 菌群作为HCC诊断及预后标志物

近年来，基于肠道菌群特征构建的诊断模型，在早期HCC检测中保持较高准确性，弥补传统血清标志物甲胎蛋白(Alpha-Fetoprotein, AFP)敏感性不足的缺点[26] [27]。研究发现，菌群特征可预示肝硬化向HCC转化的风险，菌群比值较高的肝硬化患者，发展为HCC的概率显著增加[28]。在治疗预测与预后评估方面，肠道菌群具有重要价值。一方面，基于菌群特征构建的风险评估系统，能够有效分层患者预后，与传统临床分期系统形成互补，提升预后预测准确性[29]。另一方面，菌群特征还能预测HCC患者对免疫检查点抑制剂的治疗响应，为个体化免疫治疗方案提供依据[30]。研究显示，特定菌种的丰度与HCC患者总体生存期、术后复发风险等预后因素密切相关，使其成为疾病预后评估的重要指标[29]。

3.3. 临床前模型的因果验证

动物实验中的粪菌移植(Fecal Microbiota Transplantation, FMT)研究，为肠道菌群驱动HCC发生提供直接因果证据。实验中，将HCC患者的粪便菌群移植给无菌或经抗生素处理的小鼠体内，可导致受体小鼠出现肿瘤负荷增加现象，模拟HCC病理发展过程[31]。这一结果不仅证实了HCC患者菌群特征的人源化传递，更明确了ID在HCC发生中的驱动作用。在动物模型中，补充特定益生菌可显示出抑制肿瘤的效果[32]；然而使用广谱抗生素清除肠道菌群后，肿瘤发生率显著降低，证实肠道菌群是HCC发生的必要条件[33]。此外，有研究表明，饮食干预，比如高纤维饮食及限制特定氨基酸摄入，可通过改变菌群组成有效抑制HCC进展[34]。

4. 靶向肠道菌群的防治策略

4.1. 调节免疫治疗应答

在HCC免疫治疗方面，肠道菌群提供了预测工具与干预方向[35]。研究证实，肠道菌群是影响免疫检查点抑制剂疗效的关键因素。治疗前菌群特征能预测其应答，应答良好者肠内富含阿克曼氏菌、普拉梭菌等菌群；而应答不佳的患者肠内以韦荣球菌、肠球菌等菌群为主[36] [37]。这些有益菌属的存在与肿瘤微环境中CD8$^+$ T细胞浸润程度相关[38]。除免疫治疗外，菌群的特征也与靶向治疗效果及肝切除术后复发风险相关。例如，具核梭杆菌高丰度的HCC患者，术后生存期较短，对索拉菲尼的应答效果不佳[39] [40]。

4.2. 靶向肠道菌群干预策略

基于肠道菌群对HCC治疗响应的影响，靶向菌群的干预方式已成为提升治疗效果的新兴方向。目前干预主要包括直接补充、整体重塑和间接调控三类途径。直接补充策略以益生菌、益生元及合生元为代表。益生菌可增加肠内有益菌丰度，进而优化菌群构成。益生元能够提供菌群生长所需营养底物，间接促进有益菌增殖。合生元促进菌群调节，直接补充方式安全易实施，能够增强免疫治疗效果[41]。FMT是实现菌群整体重塑的直接手段[42]。研究证实，将免疫治疗有效的患者粪便菌群移植至无效的患者体内，可改善后者治疗反应，逆转免疫耐药。间接调控方式主要包括饮食调整和合理使用抗生素。高纤维饮食和地中海饮食模式被证实可促进有益菌生长，产生具有免疫调节作用的代谢产物[43]；临床谨慎广谱抗生素使用，以免破坏菌群平衡，削弱免疫疗效。

4.3. 与现有疗法协同潜力

肠道菌群调节不仅可作为独立辅助治疗手段，更能展现出与局部治疗、靶向治疗、系统化疗等标准疗法协同作用。菌群调节的核心，主要在于利用菌群干预，发挥“治疗增效器”与“毒性缓冲器”双重功能，从多维度提高综合治疗效益。首先，在局部治疗中，例如肝动脉化疗栓塞术(Transcatheter Arterial Chemoembolization, TACE)中，良好的菌群可减轻术后炎性反应，促进肝组织修复并增强局部抗肿瘤免疫，进而改善疗效[44] [45]。其次，在靶向及系统性化疗中，肠道菌群可通过影响药物代谢、调节肿瘤微环境、增强免疫应答等途径，提升靶向药物疗效与化疗药物的耐受性[46] [47]。

5. 挑战与未来展望

5.1. 临床应用中的风险与教训

虽然靶向肠道菌群为HCC开辟了新的治疗途径，但在其临床应用过程中，往往伴随不可忽视的潜在风险，既往临床试验的失败为未来转化提供了至关重要的教训。临床应用中的核心风险是多维度的。首先，生物安全性风险突出，活菌制剂能够导致抗生素耐药基因在肠道菌群间水平转移，而成分复杂的FMT存在条件致病菌及传播耐药的隐患，对免疫功能低下的HCC患者构成直接威胁。其次，疗效与生态风险并存，外源性干预可能不可逆的破坏宿主原有的肠道微生态平衡，使其长期健康影响难以预测。此外，“有益菌”群体结论存在个体化差异，甚至因其独特的病理生理背景而产生有害作用。最后，伦理与监管框架尚不完善，相关疗法在长期安全监测、标准化等方面仍缺乏统一国际规范。肠道菌群调节除了上述临床中尚存的风险之外，其既往临床试验的失败案例，为我们揭示了几大原则性错误。首先，忽视特定病理生理背景是致命因素，其中最为深刻的警示是PROPATRIA研究，其揭示了在重症炎症状态下使用益生菌，反而会增加患者病死率，因此在晚期HCC患者中使用必须谨慎。其次，使用成分和机制不明确的“黑箱”制剂，是导致早期研究结果不可重复、损害领域信誉的主要原因。最后，临床设计缺乏患者分层，未能基于基线菌群等生物标志物筛选潜在获益人群，最终导致疗效信号被稀释。

5.2. 当前面临的挑战

尽管靶向肠道菌群为HCC防治提供了极具前景的新模式，但该领域从基础研究到临床应用，仍面临诸多挑战。首先，因果关系的复杂性与机制的研究深度不足。现阶段，大多数研究停留在揭示菌群组成与HCC临床结局的相关性层面。肠道菌群是一个复杂的生态系统，对于宿主的影响是多因素、多层面的，明确特定菌种或代谢产物是HCC的“驱动者”还是“伴随者”，并阐明其精确的分子机制，是当前研究的核心任务。其次，个体菌群组成差异显著。单一普适性干预策略效果有限，如何实现精准菌群干预成为重大挑战。最后，干预的安全性与标准化缺失。FMT作为侵入性治疗，其供体筛选、制剂制备、给药途径及长期安全性等方面缺乏国际统一标准与伦理规范，益生菌、合生元等制剂的单一性及不同菌种之间的差异性，使其在免疫缺陷患者中的安全性亟待关注。

5.3. 未来发展方向

未来研究应朝着精准化与功能化迈进。首先，利用多组学技术解析具有明确生物学功能的微生物模块，并结合无菌动物、基因编辑等技术开展因果验证，深化机制研究。其次，发展新一代微生物疗法。包括设计能够靶向抗肿瘤药物、降解促癌代谢物、增强免疫应答工程菌及开发特定菌群代谢物作为新型治疗药物。再者，推动严谨的临床转化至关重要，应开展多中心、大规模、随机双盲对照的前瞻性临床试验(Randomized Controlled Trial, RCT)，系统评估FMT、益生菌及合生元干预、饮食治疗等在HCC预防与治疗中的安全性与有效性。最后，借助人工智能整合多维数据，构建个性化风险预测与治疗反应评估模

型，最终实现基于宿主菌群特征的动态营养与微生物治疗，迈向真正的精准医疗。

6. 挑战与未来展望

肠道菌群通过 GLA 在 HCC 的发生、发展及治疗响应中发挥着核心调控作用。其代谢产物可破坏肠道屏障，诱发慢性炎症，直接驱动恶性转化并塑造免疫抑制微环境。越来越多的临床证据支持肠道的“微生物指纹”作为新型诊断与预后生物标志物的潜力，同时揭示了菌群构成是影响免疫检查点抑制剂疗效的关键因素，这使得靶向菌群成为增强治疗效果、改善预后的前沿策略。目前，此领域在科学认知向临床实践转化的过程中，仍面临挑战，但通过聚焦菌株功能机制解析、创新微生物疗法、开展高质量临床研究及融合智能技术，靶向 GLA 必将为 HCC 精准防治体系带来革命性突破。

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