

· 综述 ·

DOI: 10.12449/JCH250930

肠道菌群稳态在肝细胞癌发生发展中的作用及相关靶向干预策略

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摘要: 肝细胞癌(HCC)作为全球第六大常见恶性肿瘤,其隐匿性发病特征和高死亡率对人类健康构成严重威胁。本文综述肠道菌群(GM)稳态在HCC发生发展中的分子机制与干预策略,旨在为HCC的干预和治疗提供新思路。GM失调、肠渗漏、微生物相关分子模式、细菌易位及代谢产物等在HCC进展中发挥关键作用。GM失衡可能导致免疫逃逸,进而促进肿瘤细胞增殖和转移。本文详细论述GM与HCC的关系,深入分析GM在HCC发生发展中的作用机制,研究胆汁酸相关代谢产物、短链脂肪酸相关代谢产物及其他代谢产物在HCC中的作用,并探讨靶向GM治疗HCC的策略,包括益生菌、益生元、抗生素和Toll样受体4拮抗剂的使用及粪便微生物群移植等方法。本文强调,维护肠道屏障完整和GM稳态在HCC防治中具有重要意义,为开发新的诊疗策略提供方向。

关键词: 癌, 肝细胞; 胃肠道微生物组; 治疗学

基金项目: 国家自然科学基金(82174330, 82374418); 陕西省科技厅科研基金(2024JC-YBMS-650, 2024SF-YBXM-528); 陕西省科技厅创新团队(2022TD-55); 陕西省中医药管理局(SZY-KJCYC-2023-049, SYZ-KJCYC-2023-087); 陕西省中医药管理局“双链融合”创新团队(2022-SLRH-LJ-002)

The role of gut microbiota homeostasis in the occurrence and development of hepatocellular carcinoma and targeted intervention strategies

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Abstract: Hepatocellular carcinoma (HCC), as the sixth most common malignant tumor worldwide, poses a serious threat to human health due to its insidious onset and high mortality rate. This article reviews the molecular mechanisms and intervention strategies of gut microbiota (GM) homeostasis in the development and progression of HCC, in order to provide new ideas for the intervention and treatment of HCC. Studies have shown that GM dysbiosis, intestinal leakage, microbial-associated molecular pattern, bacterial translocation, and metabolic products play key roles in the progression of HCC. GM imbalance may lead to immune escape, thereby promoting tumor cell proliferation and metastasis. This article elaborates on the association between GM and HCC, deeply analyzes the mechanism of action of GM in the development and progression of HCC, investigates the role of bile acid-related metabolites, short-chain fatty acid-related metabolites, and other metabolites in HCC, and explores the strategies for targeting GM in the treatment of HCC, including probiotics, prebiotics, antibiotics, Toll-like receptor 4 antagonists, and fecal microbiota transplantation. This article emphasizes that maintaining the integrity of the intestinal barrier and GM homeostasis is of great significance in the prevention and treatment of HCC, which provides a direction for developing new diagnosis and treatment strategies.

Key words: Carcinoma, Hepatocellular; Gastrointestinal Microbiome; Therapeutics

Research funding: National Natural Science Foundation of China (82174330, 82374418); Shaanxi Province Science and Technology Department Research Fund (2024JC-YBMS-650, 2024SF-YBXM-528); Shaanxi Province Science and Technology Department Innovation Team (2022TD-55); Shaanxi Province Traditional Chinese Medicine Administration (SZY-KJCYC-2023-049, SZY-KJCYC-2023-087); Shaanxi Province Traditional Chinese Medicine Administration “Dual Chain Integration” Innovation Team (2022-SLRH-LJ-002)

肝细胞癌(hepatocellular carcinoma, HCC)作为全球范围内常见的肝脏恶性肿瘤,其发病率在各类癌症中排名第六,死亡率则高居第三^[1]。HCC的发生因素主要包括慢性乙型或丙型肝炎病毒感染、代谢相关脂肪性肝病、肝硬化、长期酗酒、黄曲霉素暴露等^[2],其发展是一个多阶段的病理过程,涉及遗传和表观遗传改变,慢性炎症和纤维化病理因素,以及肝脏微环境的重构^[3]。肿瘤的异质性和肿瘤微环境的免疫抑制特性为HCC的治疗带来巨大挑战。

肠道微生物以细菌为主导,是人体微生态系统的重要组成部分,因此相关研究主要集中于肠道细菌^[4]。微生物群落的组成会随着个体的成长不断变化,并在一定时期内保持生理稳态。肠道微生物群落利用脂多糖(lipopolysaccharide, LPS)、脂蛋白及代谢产物等特定组分形成生物屏障并调控免疫反应,其多样性和稳定性对维持人体健康至关重要。

近期研究揭示肠道菌群(gut microbiota, GM)在HCC的发生和发展中发挥关键作用,包括促进炎症反应、肝损伤、纤维化、肝再生等^[5]。此外,GM失衡可能导致免疫逃逸,从而促进肿瘤细胞增殖和转移^[6]。这些发现为解析HCC的发病机制提供了新视角,也为疾病预防和治疗提供了潜在的新策略。本文回顾GM稳态在HCC发生发展中的分子机制和干预策略,以期对HCC的干预和治疗提供新的思路。

1 GM与HCC的关系

肠道微生物的生态失调,即GM的病理性改变,对肝病发展至HCC具有显著影响,其通过肠-肝轴影响肝脏炎症微环境。肠-肝轴作为GM和肝胆系统交流的桥梁,通过门静脉循环实现双向调控^[7]。肠道屏障的完整性对抵御内毒素、LPS等有害物质的侵袭至关重要,而酗酒、不良饮食习惯、抗生素滥用、心理压力等因素会破坏此屏障,导致肠道通透性增加并形成肠漏,使得病原体和有害物质进入血液循环。临床数据显示,患有酒精性肝炎、肝硬化、HCC等慢性肝病的患者,其肠道上皮屏障的通透性增加,血清中LPS的含量也相应升高^[8]。这种状态不仅会加剧肝脏的炎症反应和纤维化过程,还可能

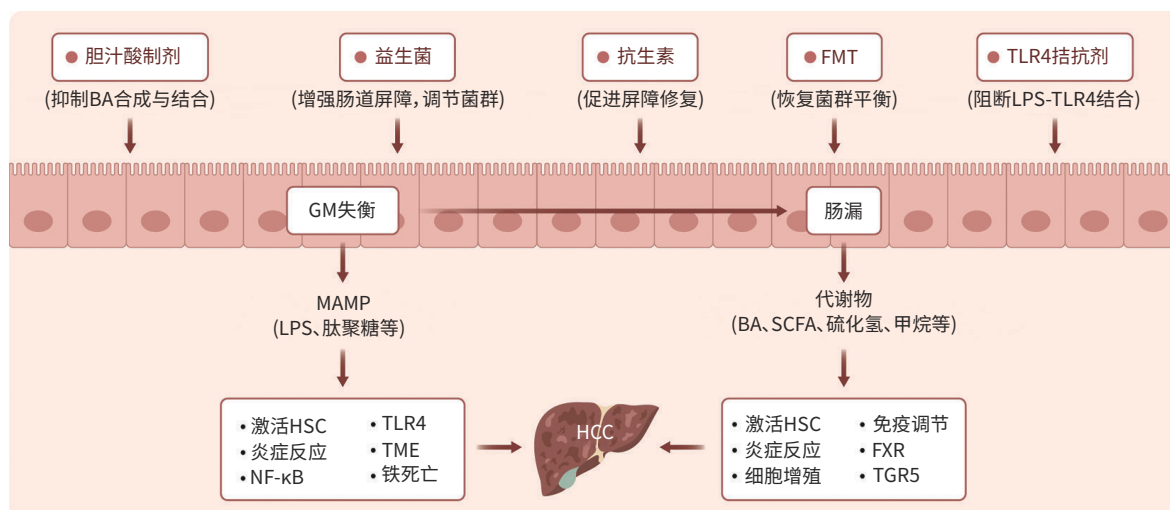
通过激活Toll样受体(toll-like receptor, TLR)4/NF- κ B等炎症信号通路,促进肝星状细胞(hepatic stellate cell, HSC)的活化,从而加速肝纤维化和HCC的发展^[9]。同时,短链脂肪酸(short-chain fatty acid, SCFA)等具有抗炎和抑制肿瘤细胞增殖作用的有益代谢产物,可能因肠道屏障损伤而减少。研究表明,利用印苦楝内酯等干预措施调节肠-肝轴,可改善肠道屏障功能,减轻炎症反应,防止细菌移位,为HCC的防治提供新的策略^[10]。

此外,肝动脉化疗栓塞等临床治疗手段可通过干预GM和改善肠屏障功能有效治疗HCC,减少肿瘤引起的菌群失调和LPS水平升高现象^[11]。这些研究进展充分凸显维护肠道屏障完整性和GM稳态在HCC防治中的重要性,并为开发新的诊疗策略提供依据。GM与HCC的关系见图1。

2 GM在HCC发生发展中的作用机制

2.1 微生物相关分子模式(microbe-associated molecular pattern, MAMP) MAMP是肠道微生物释放的一类分子,可经肠壁进入血液循环,影响肝脏和其他器官功能^[12]。在健康状态下,肠道屏障功能的有效性可将进入肝脏的MAMP水平维持在较低状态,避免过度的免疫激活。当MAMP水平升高(尤其在肝脏中)时,可能触发一系列炎症反应,激活HSC并促进纤维化,这些过程均与HCC的发展密切相关^[13]。

LPS不仅是常用的标志物,也是研究的焦点。LPS可与肝细胞、Kupffer细胞及HSC上表达的TLR4受体结合,引发炎症因子过度产生,导致肝脏炎症反应和氧化应激^[14],而阻断TLR4-LPS信号轴可有效降低小鼠HCC的发生率。LPS还可促进HCC细胞株HepG2的增殖,并上调HepG2细胞中IL-6和IL-8等炎症因子的表达,这一过程可能通过激活NF- κ B和STAT-3等相关信号通路促进HCC的发展^[15]。最近的一项研究发现,LPS可通过TLR4/NF- κ B/NLRP3信号通路抑制人类HCC细胞系Bel-7402和SMMC-7721的增殖,将细胞周期阻滞于G1期,且不影响细胞凋亡^[16]。此外,表皮调节蛋白作为HCC进展的关键介质,在LPS影响下的癌症微环境中发挥重要作用,不仅能促进肿瘤细胞生长和表皮生长因子阳性



注:BA,胆汁酸;FMT,粪便微生物群移植;TLR4,Toll样受体4;GM,肠道菌群;MAMP,微生物相关分子模式;LPS,脂多糖;HSC,肝星状细胞;TME,肿瘤微环境;NF- κ B,核因子 κ B;HCC,肝细胞癌;SCFA,短链脂肪酸;FXR,法尼醇X受体;TGR5,武田G蛋白偶联受体5。

图1 GM与HCC的关系

Figure 1 The relationship between GM and HCC

HCC细胞的迁移与侵袭,还可通过IL-8信号传导促进肿瘤新生血管形成^[17]。上述研究结果均表明血清LPS水平在HCC发病机制和疾病进展中具有重要影响,为通过调节肠道微生物群和肠道屏障功能预防与治疗HCC提供潜在策略。

除了LPS,肽聚糖也得到广泛研究。作为革兰阳性细菌细胞壁的主要成分,肽聚糖可通过与NLR(NOD样受体)、TLR等模式识别受体相互作用激活宿主的免疫反应,促进炎症体活化并提升IL-12和IL-8等促炎细胞因子水平,从而影响肿瘤微环境和HCC的发展^[18]。

肽聚糖识别蛋白2通过与CCL5启动子结合,促进HCC中CCL5的产生,增强抗肿瘤免疫反应^[19]。其中NK细胞和CD8⁺T细胞在该过程中发挥关键作用,可能通过增强肿瘤浸润淋巴细胞的活性来促进抗肿瘤免疫反应^[19]。这些研究为解析MAMP在肝脏疾病中的作用机制提供了新的视角,也为HCC的早期诊断和治疗提供了潜在的新策略。

2.2 胆汁酸(bile acid, BA)相关代谢产物 BA作为内源性信号分子,在肝脏和肠道稳态中发挥核心作用^[20]。肝脏分泌的大部分BA经肠道循环再吸收,通过门静脉返回肝脏,形成BA的肝肠循环^[21]。人体内的初级BA主要包括胆酸和鹅去氧胆酸,次级BA则包括脱氧胆酸、石胆酸和熊去氧胆酸。BA还可与甘氨酸或牛磺胆酸结合形成结合型BA,进一步参与肝肠轴的调节。微生物可通过影响宿主的代谢信号通路间接调节BA的合成,部分微生物还可直接参与初级BA的合成过程。最新研究发现,肠道共生菌小克里斯滕森氏菌能将宿主衍生的BA

修饰为具有3-O-酰化取代结构的新型次级BA,这类酰化BA作为天然的法尼醇X受体(farnesoid X receptor, FXR)拮抗剂,可调节宿主代谢^[22]。GM产生的吲哚-3-丙酸可持续调动T细胞杀伤肿瘤,增强抗程序性死亡受体1单抗在实体肿瘤中的疗效^[23]。

已有研究证实,鹅去氧胆酸可通过激活炎性小体促进HCC的发展^[24];脱氧胆酸能通过促进HSC分泌衰老相关分泌表型及多种炎症和致癌因子,加速HCC的进程^[25];牛磺胆酸可能通过激活HSC推动肝硬化的进程。在HCC的发生过程中,包括牛磺胆酸在内的BA异常积累,可诱导肝细胞中巨噬细胞极化,形成免疫抑制性肿瘤微环境,有利于HCC的发展^[26]。上述结果表明,BA代谢异常可能在HCC发病机制中发挥重要作用。

BA通过激活FXR和武田G蛋白偶联受体5(takeda G-protein coupled receptor 5, TGR5)发挥生理作用^[27]。FXR通路调节对HCC的发展产生抑制或促进的双重作用。在生态失调状态下,BA信号传导受损,导致FXR和TGR5活化受到抑制,其中FXR活化不足可能增加肝脂肪积累,从而促进肿瘤的发生^[28];TGR5活化不足则可能导致调节性T细胞活化,改变HSC的衰老相关分泌表型,增加促炎和促癌因子的产生,影响M2样巨噬细胞的极化,并损害抗肿瘤免疫应答和免疫细胞的招募^[29]。TGR5主要通过改善代谢综合征间接预防HCC的发展,还可通过负调节NF- κ B因子的转录活性预防慢性肝炎^[30]。BA代谢异常可能通过改变TGR5甲基化水平来调节肿瘤免疫微环境,从而促进肿瘤免疫逃逸和HCC的发展^[31]。

初级BA和次级BA对CXC亚族趋化因子配体16

(CXC chemokine ligand 16, CXCL16)的表达具有相反的调节作用,而万古霉素类抗生素可通过清除特定细菌影响肝自然杀伤细胞的聚集和肝肿瘤的生长。石胆酸水平升高可通过抑制CXCL16表达,减少CXCR6⁺自然杀伤细胞的积累和干扰素- γ 的产生,最终促进HCC的发展^[32]。在人体肿瘤和非肿瘤组织中,CXCL16的表达与初级BA呈正相关,与次级BA呈负相关,这表明GM介导的BA代谢可能通过调节免疫反应参与HCC的发展过程。

在HCC的预后中,BA亦发挥着重要作用。淋巴结转移作为HCC转移的重要途径,显著降低患者的生存率和预后。研究表明,在转移性淋巴结中BA高度积聚,而正常淋巴结或原发性肿瘤中无此现象,且BA组分可显著增强HCC细胞的侵袭能力^[31]。

综上所述,恢复BA稳态被认为是一种潜在的HCC治疗策略,尤其是BA与肠道微生物群的复杂相互作用为HCC的治疗提供新的视角。多项研究表明,靶向BA和微生物群可预防HCC的发展,抑制肿瘤的进展,并改善患者的预后。

2.3 SCFA 相关代谢产物 SCFA包括乙酸盐、丁酸盐和丙酸盐,是厚壁菌门和拟杆菌门的厌氧细菌经发酵膳食纤维产生的最终代谢产物^[33]。在结肠中,乙酸是含量最丰富的SCFA类型。SCFA在调节细胞生长与分化、预防炎症、抑制细胞增殖和促进癌细胞凋亡方面发挥着重要作用。研究显示,SCFA的摄入可减少小鼠的肝病发展和HCC结节形成^[34];此外,HCC小鼠的SCFA水平下降,其中乙酸盐下降尤为明显,而乙酸盐能够抑制HCC患者中3型先天淋巴样细胞产生IL-17A^[35],这表明SCFA可能对慢性肝病和HCC的进展具有延缓作用。

最新研究发现,紫锥菊多糖诱导HCC细胞凋亡的过程中,产生丙酸和丁酸的肠道微生物群(如粪球菌、梭菌和罗斯拜瑞氏菌)数量显著增加,这与肠紧密连接蛋白表达增强和肠屏障功能修复相关^[36],暗示肠道中丙酸和丁酸水平与HCC进展存在潜在联系。

在临床治疗方面,肠道微生物的研究为解决索拉非尼耐药问题提供了新的策略。索拉非尼作为多靶点酪氨酸激酶抑制剂,能够抑制晚期HCC的血管生成和肿瘤细胞增殖,但耐药性使其疗效受到限制。研究发现,HCC患者血浆中的丁酸水平较低,而补充丁酸盐可提高索拉非尼的疗效。基于此发现,研究人员开发了一种新型纳米颗粒,通过共包封丁酸盐和索拉非尼,并采用抗磷脂酰肌醇蛋白聚糖3抗体修饰,以延长药物的保留时间,提高靶向性,从而增强抗癌效果,显著延缓HCC的进展^[37]。此外,这种纳米颗粒在HCC靶向性和安全性方面表现出色^[37]。

另有研究构建了一种新型纳米颗粒平台,通过丁酸盐和索拉非尼的联合修饰,实现口服给药后药物在癌细胞中的释放。索拉非尼通过耗尽谷胱甘肽过氧化物酶4和谷胱甘肽引发铁凋亡,盐霉素则通过增强细胞内铁和脂质过氧化水平加速铁凋亡进程。这种组合策略不仅可诱导铁死亡损伤,还能激发强烈的全身免疫应答,有效消除肿瘤并建立免疫记忆,表明口服给药的铁死亡诱导剂可能成为治疗HCC的有效策略^[38]。

SCFA在调节免疫和抗炎方面具有多种功能,是当前临床和试验研究的潜在重要靶点,其相关机制的深入探索可能为HCC治疗提供新的靶点。

2.4 其他代谢产物 除了SCFA,肠道微生物产生的精氨酸、亚精胺和多胺等多种代谢产物在HCC中的潜在作用和治疗价值成为当前研究的热点,但其具体作用机制尚需进一步阐明(表1)。随着肠道微生物与肝脏疾病关联研究的深入,未来可能会发现更多此类代谢产物在HCC中的作用机制和治疗潜力的新见解,这对发展新的HCC治疗策略具有重要意义。

3 靶向GM治疗HCC

在制订针对GM的HCC治疗策略时,需重视益生菌、益生元、粪便微生物群移植(fecal microbiota transplantation, FMT)、抗生素及TLR4拮抗剂等方法对调节肠道微生物平衡及影响HCC发展的作用。这些策略的深入研究和合理应用,有望为HCC治疗带来新的突破。

3.1 益生菌 益生菌作为一类对宿主健康有益的活微生物,主要包括乳酸菌和双歧杆菌^[50],研究已证实其在治疗或预防HCC方面的潜在作用。特定的益生菌如假长双歧杆菌可通过产生乙酸盐激活G蛋白偶联受体43受体,进而抑制IL-6/JAK1/STAT3信号通路,阻断非酒精性脂肪性肝病-HCC的进展^[51];同时,益生菌治疗能够减少肝脏中的炎症反应和细胞死亡,对非酒精性脂肪性肝病相关的HCC具有治疗作用^[52];嗜酸乳杆菌可通过分泌戊酸在小鼠中展现出抗肿瘤效果^[53]。

益生菌在预防术后感染和改善肝移植术后移植肝功能方面也展现出优良效果。例如,长双歧杆菌能够促进小鼠肝功能的恢复^[54],表明调节肠道微生物群可改善HCC患者的术后效果;通过减少细菌移位和改善内毒素血症,益生菌可在肝硬化和HCC的调节中发挥作用^[55];益生菌的抗病毒活性使其在辅助治疗中可降低乙型肝炎病毒感染进展为HCC的风险^[56]。Ni等^[57]借助新指数Ddys评估HCC患者GM的紊乱程度,发现该指数与HCC患者分期呈正相关,为GM分析在HCC中的应用提供新视角。

表1 不同代谢产物在HCC中的机制及作用
Table 1 The mechanism and role of different metabolites in HCC

代谢产物	机制	作用	参考文献
吡啶-3-乙酸	通过诱导血红素加氧酶1的表达以及直接清除自由基发挥作用	减轻RAW264.7巨噬细胞中的炎症反应和自由基产生	[39]
	在非酒精性脂肪性肝病的研究中,IAA通过缓解肝脏脂肪生成、氧化应激和炎症反应发挥作用	减轻小鼠的肝损伤	[40]
吡啶丙酸	在非酒精性脂肪性肝病的研究中,增强线粒体氧化磷酸化作用	改善线粒体呼吸缺陷	[41]
多氨	与mTOR和RAS等致癌信号通路存在交叉作用	可能成为癌症治疗的潜在靶点	[42]
精氨酸	精氨酸耗竭	诱导HCC细胞死亡	[43]
	通过RNA结合基序蛋白39控制代谢基因的表达	促进肿瘤形成	[44]
	L-精氨酸和5-FU联合应用可通过iNOS/NO/AKT途径抑制有氧糖酵解酶,从而抑制糖代谢	抑制HCC细胞的糖代谢	[45]
亚精胺	激活微管相关蛋白1S介导的自噬,缓解自噬中的癌细胞缺陷	预防肝纤维化和HCC	[46]
	通过在mRNA和蛋白水平上减少细胞外基质蛋白水平以及增加HSC中脂滴数量发挥作用	抑制HSC的活化	[47]
甲烷	通过激活PI3K/AKT/GSK-3 β 信号通路上调IL-10的表达	抑制NF- κ B和MAPK信号通路	[48]
硫化氢	调节3-巯基丙酮酸硫转移酶的表达	双向调节HCC进展	[49]

尽管益生菌在动物模型和患者中的治疗效果已得到证实,但不同益生菌的作用差异仍需进一步研究。多数益生菌无法在肠道中永久定植,因此需通过前瞻性实验评估其长期干预HCC的有效性和安全性。

3.2 抗生素 抗生素对GM的影响及在HCC治疗中的作用成为新兴的研究热点,其中利福昔明作为一种广谱抗生素,因具有耐药性低、安全高效等特点,在临床上广泛应用。已有研究表明,利福昔明- α 可能会减缓酒精相关肝病患者的肝纤维化进展,还可增强对入侵致病菌的抗菌反应,促进肠道屏障修复,减少肠道的口腔化并减轻全身炎症,进而抑制肝性脑病的发生发展^[58]。最近的一项研究发现,利福昔明通过激动肠道孕烷X受体并介导NF- κ B途径,在腹泻患者中促进肠道微生物群的生态失调,且在炎症、氧化应激和铁调亡多种机制中均可发挥调控作用^[59]。尽管利福昔明在肝纤维化、肝硬化、肝性脑病中的治疗效果显著,但其对HCC发展的影响尚未明确。因此,迫切需要研究确定长期抗生素治疗对HCC发展的影响。

3.3 BA制剂 以奥贝胆酸为代表的BA制剂在治疗肝病方面已取得一定成果。作为鹅去氧胆酸的半合成衍生物和FXR激动剂,奥贝胆酸通过抑制胆酸合成、促进胆汁分泌、降低门静脉高压等机制来改善原发性胆汁性肝硬化、非酒精性脂肪性肝病等疾病的肝功能^[60-61];其衍生物C7在动物模型中可显著改善肝损伤和纤维化,且无瘙痒等副作用。熊去氧胆酸通过缓解内质网应激、改善T细胞反应,展现出肝癌治疗的潜力^[62],与索拉非尼联合应用可延长晚期HCC患者的中位生存期,并降低肝功能恶化风险;鹅去氧胆酸联合索拉非尼也能通过调

节肿瘤微环境增强疗效。此外,FXR和TGR5受体可通过改变BA代谢产物调控肿瘤干细胞特性,影响HCC的复发和耐药性,其拮抗剂可显著抑制肿瘤干细胞活性^[63]。未来可能需要研发更多的BA制剂,为HCC治疗提供更多选择。

3.4 FMT和TLR4拮抗剂 FMT通过将健康人体粪便中的GM移植到患者体内,用以恢复菌群平衡,尽管在动物模型中显现出治疗潜力,但目前尚缺乏针对HCC患者的临床研究。2021年,Baruch等^[64]开展的首个FMT治疗HCC的人体临床试验结果显示,FMT能引起肿瘤微环境中基因表达和免疫细胞浸润的积极变化,但健康肠道微生物群能否长期稳定存在于人体中仍需进一步研究。TLR4是一种在人体免疫系统中发挥重要作用的受体,其拮抗剂可通过抑制TLR4信号传导减轻肝肾损伤、肝功能衰竭和全身炎症^[65]。但目前TLR4拮抗剂用于治疗癌症尚未获得监管机构的批准,其在HCC治疗中的具体作用和效果仍需更多临床研究确定。

4 小结与展望

近年来,肠道微生物组在健康和疾病中的作用得到深入研究,尤其在HCC的预防、诊断和治疗方面,但对其调节机制的认知仍存在局限性。现有研究虽揭示肠道微生物群在HCC中的变化特征,但受样本量小、单中心研究等限制,结果的普遍适用性不足。此外,饮食习惯、抗生素使用和饮酒等多种因素均可能影响肠道微生物群的组成,进而影响HCC的发展。因此,未来研究需考虑这些复杂因素并开展多中心、大规模的研究,以深入探讨此类问题。

利益冲突声明: 本文不存在任何利益冲突。

作者贡献声明: 崔艳负责设计课题,分析资料,撰写论文;焦俊喆、闫瑞娟、闫曙光、魏海梁参与收集数据,修改论文;常占杰、张海博、李京涛负责拟定写作思路,指导撰写文章并最后定稿。

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收稿日期: 2025-01-17; 录用日期: 2025-03-14

本文编辑: 林姣

引证本文: CUI Y, JIAO JZ, YAN RJ, et al. The role of gut microbiota homeostasis in the occurrence and development of hepatocellular carcinoma and targeted intervention strategies[J]. *J Clin Hepatol*, 2025, 41(9): 1913-1919.

崔艳, 焦俊喆, 闫瑞娟, 等. 肠道菌群稳态在肝细胞癌发生发展中的作用及相关靶向干预策略[J]. *临床肝胆病杂志*, 2025, 41(9): 1913-1919.