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肠道微生物群对肝硬化的研究进展

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摘　要

本文综述了肠道微生物群与肝硬化之间的相关性。肠道微生物群在人体健康中扮演着重要角色，其失衡与多种疾病密切相关。近年来，研究发现肠道微生物群与肝硬化的发生、发展及预后存在显著关联。本文详细阐述了肠道微生物群的基本概念、肝硬化的发展机制，以及两者之间的相互作用。同时，探讨了基于肠道微生物群的肝硬化诊断和治疗新策略，为未来研究和临床应用提供了新的思路。

关键词

肠道微生物群，肝硬化，菌群失调，肠－肝轴，肠道粘膜屏障

Research Progress of Gut Microbiota on Liver Cirrhosis

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Abstract

This article reviews the correlation between the gut microbiota and liver cirrhosis. The gut microbiota plays a significant role in human health, and its imbalance is closely related to a variety of diseases. In recent years, studies have found that the gut microbiota is significantly associated with the occurrence, development and prognosis of liver cirrhosis. This article elaborates in detail on the basic concepts of the gut microbiota, the development mechanism of liver cirrhosis, and the interaction

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between the two. Meanwhile, new strategies for the diagnosis and treatment of liver cirrhosis based on the intestinal microbiota were explored, providing new ideas for future research and clinical application.

Keywords

Gut Microbiota, Liver Cirrhosis, Dysbacteriosis, Gut-Liver Axis, Intestinal Mucosal Barrier

1. 引言

肠道微生物群是指定植于人体肠道内的庞大微生物群落，包括细菌、真菌、病毒等多种微生物。这些微生物与宿主形成共生关系，在维持人体健康中发挥着重要作用。近年来，随着高通量测序技术的发展，肠道微生物群的研究取得了显著进展，其在多种疾病中的作用逐渐被揭示。

肝硬化是一种常见的慢性进行性肝病，其特征是肝组织纤维化和再生结节的形成。肝硬化的发生和发展是一个复杂的过程，涉及多种因素。近年来的研究表明，肠道微生物群失衡在肝硬化的病理生理过程中起着关键作用。最近，人们对调节肠道微生物群和肠－肝轴用于治疗肝硬化的潜在治疗方法产生了很大的兴趣。本文旨在综述肠道微生物群与肝硬化的相关性，探讨其在肝硬化诊断和治疗中的潜在应用价值。

2. 肠道微生物群概述

肠道微生物群(gut microbiota, GM)是一个复杂的生态系统，在人体宿主中，有数以万亿计的微生物处于动态平衡中[1]，它们通常分为细菌、古生菌、噬菌体、真菌和病毒，其中95%的共生微生物存在于肠道中[2]。复杂地居住在胃肠道(GIT)中的微生物的生态菌落，统称为GM [3] [4]。虽然转基因的组成在不同的生命阶段有所不同，并显示出性别差异，但GIT的优势种群是拟杆菌属、厚壁菌门、放线菌门、变形菌门、双歧杆菌属、真杆菌属、梭菌属、消化球菌属和普罗韦菌属，其中大多数是互利共生或共生的微生物[5]-[7]。

正常情况下，肠道微生物群与宿主保持动态平衡，参与营养代谢、免疫调节、屏障功能等多种生理过程。肠道微生物群的功能主要包括：分解难以消化的食物成分，合成维生素K和B族维生素。典型地，胆汁酸、胆碱、神经调节剂、细菌素和短链脂肪酸(SCFAs)是作为免疫调节剂而被充分研究的肠道细菌代谢物。乳酸杆菌科的减少阻止肠道代谢SCFAs并限制紧密连接蛋白的表达，削弱屏障完整性。SCFAs还通过影响免疫、内分泌、迷走神经和其他体液途径来调节小胶质细胞，并增强神经发育障碍的运动功能障碍和病理生理学[8]-[11]。GM在肠粘膜中构建辅助免疫系统，保持宿主的健康。这些功能对于维持人体健康至关重要，一旦肠道微生物群失衡，可能导致多种疾病的发生。

3. 肝硬化的病理生理机制

肝硬化是各种慢性肝病发展的终末阶段，其病理特征为肝组织弥漫性纤维化和再生结节形成。肝硬化的发生是一个渐进过程，通常是由累积的严重肝损伤导致广泛的肝纤维化、肝功能障碍和肝窦血管异常引起的[12]-[14]。常见的病因包括病毒性肝炎、酒精性肝病、非酒精性脂肪性肝病等。

肝纤维化是一个动态过程，肝细胞持续受损和再生，导致细胞外基质过度沉积和金属蛋白酶降解减少，发生在不同攻击者诱导的慢性肝损伤下。细胞外基质的主要细胞来源是活化的肝星状细胞(HSC)-2，其转分化为收缩性、纤维化性和促炎性肌纤维母细胞[15] [16]，而后形成纤维间隔。这些纤维间隔破坏了肝脏的正常结构，影响其功能。随着病情进展，肝脏逐渐失去代偿能力，出现门静脉高压、肝功能衰竭等严重并发症。目前现有的病理生理学观点将门静脉高压与内脏和全身血管舒张和高动力循环描述为急性失代偿过程中的中心机制[17] [18]，最近的研究结果引入了全身炎症、线粒体功能障碍、氧化应激和代谢变化可导致组织损伤和肝外器官衰竭的概念[19]，将急性失代偿的经典机制与新的观察结果结合起来将是理解失代偿的病理生理学的关键，提高我们对疾病表型的理解。肝硬化的临床表现多样，包括乏力、食欲减退、黄疸、腹水、肝性脑病等，严重威胁患者的生命健康。

4. 肠道微生物群与肝硬化的相关性

近年来的研究表明，肠道微生物群与肝硬化之间存在密切的相互作用。肝硬化患者常出现肠道微生物群失衡，表现为有益菌减少、潜在致病菌增多，以及微生物多样性降低。这种失衡可能通过多种机制影响肝硬化的发生和发展。

4.1. 肠道微生物群失衡驱动肝硬化的核心机制：从肠道屏障到肝脏炎症的级联反应

4.1.1. 菌群失调(起点)

肠道微生物群的生态失调(dysbiosis)是诱发多种疾病的核心因素。肠道微生物群包含数百万个基因(是人类基因组的 150 倍)，提供丰富的酶库，参与人体代谢、免疫稳态和生理活动调控[20]-[24]。生态失调(即肠道植物群失衡)可破坏宿主与微生物的共生关系，导致宿主免疫系统功能紊乱[25]，并成为肝脏疾病发展和进展的重要致病因素。这种失调不仅改变微生物组成，还引发后续代谢物变化，为疾病链式反应奠定基础。

4.1.2. 代谢物改变(菌群失调的直接后果)

菌群失调后，细菌代谢产物发生显著改变，进而加剧病理进程。细菌通过分泌可溶性产物(如短链脂肪酸、脂多糖、群体感应肽、氨和内毒素)与宿主交流[26] [27]。例如，生态失调可促使某些肠道细菌产生有害代谢物(如内毒素和氨)，这些物质可直接损伤肝细胞或促进肝星状细胞活化。同时，失调的微生物群可能减少有益代谢物(如丁酸盐)的生成，而丁酸盐在正常情况下可调节肝细胞功能(如上调 miRNA-22 以影响 Sirtuin 1 表达和 ROS 产生)；其减少会增强氧化应激和细胞死亡[28]。代谢物的这些变化不仅直接影响肝脏，还为粘膜屏障的受损提供了化学基础。

4.1.3. 粘膜屏障受损(代谢物改变引发的结构破坏)

代谢物改变直接导致肠道粘膜屏障功能受损。肠道屏障由多层防御系统构成，包括微生物屏障、粘液层、上皮屏障(如紧密连接蛋白 Occludin/ZO-1)、免疫屏障和肠血管屏障[29] [30]。有害代谢物(如内毒素和炎症因子)可下调紧密连接蛋白表达、使粘液层变薄，并破坏上皮完整性[31]。生态失调本身也会削弱屏障功能，增加肠道通透性[32] [33]，形成“肠漏”(leaky gut)现象。这一过程通过肠－肝轴的双向作用放大，因为肠道和肝脏在解剖和功能上紧密相连(门静脉循环作为关键通路) [34]-[36]。屏障受损不仅降低局部防御，还为微生物产物的系统性易位创造条件。

4.1.4. 微生物产物易位(屏障受损的必然结果)

粘膜屏障受损后，肠道通透性增加，使细菌及其代谢产物(如内毒素、脂多糖和核酸)易位进入门静脉系统。这种易位是肠－肝轴机制的核心是：门静脉将肠源性产物(包括微生物产物)直接运输至肝脏[37]。

在肝硬化等病理状态下，肠屏障的全面损伤(包括上皮、血管和免疫层面)进一步加剧易位[38]。易位并非孤立事件，而是肠道免疫失调和微生物群改变(如细菌过度生长)的直接后果[39]，将局部肠道问题转化为系统性肝脏威胁。

4.1.5. 肝脏免疫激活与纤维化(易位触发的终末效应)

微生物产物易位至肝脏后，作为病原体相关分子模式(PAMPs)结合 toll 样受体(如 TLR4)，激活肝脏免疫系统。这刺激库普弗细胞(Kupffer cells)释放炎症细胞因子，引发先天免疫反应，导致慢性肝脏炎症。持续的免疫激活促进肝星状细胞活化和胶原沉积，驱动肝纤维化进程。在肝硬化中，这一过程自我强化：细菌功能改变(如内毒素释放增加和胆汁酸转化减少)进一步恶化纤维化，影响肝脏代谢和免疫功能。最终，肝纤维化可进展为肝硬化，并为防治策略(如 TLR4 抑制剂或益生菌)提供新靶点[40]。

4.2. 肠道微生物群失衡对于肝硬化并发症发生发展的影响

4.2.1. 自发性细菌性腹膜(SBP)

肠道细菌过度生长和易位(BT)是自发性细菌性腹膜炎的主要诱因。来自肠道革兰阴性菌，尤其是大肠杆菌和肺炎克雷伯菌(*Klebsiella pneumoniae*)的移位，导致脂多糖释放增加，造成内毒素血症。加之失代偿期肝硬化患者免疫功能降低，大量脂多糖入血，机体分泌一系列炎性细胞因子，促进肠道 BT，加剧感染及 SBP，形成恶性循环[41]。

4.2.2. 肝性脑病(HE)

肠道微生物代谢产生的氨等神经毒素可诱发肝性脑病。肠道尿素酶水解尿素产氨是 HE 发病的重要机制，此外，HE 患者常发生细菌移位，如口腔微生物唾液链球菌可在肠道下段过表达，并与 HE 疾病进程和严重程度相关[42]。

4.2.3. 门静脉高压(PH)

肠道微生物群失衡还可能加重门静脉高压(PH)。PH 的主要发病机制为外周血管扩张、肝内血管收缩、门静脉血流增加引起的高动力循环状态和血液系统紊乱[43]。一项动物实验[44]比较了 GM 定植小鼠与无菌小鼠在门静脉结扎后门静脉压力(portal pressure, PP)水平的变化，发现与无菌小鼠相比，GM 定植小鼠具有明显高水平的 PP，更易发生 PH，初步表明 GM 对 PH 的发生具有直接影响。

4.2.4. 肝细胞癌(HCC)

肝脏炎症纤维化微环境是导致 HCC 发生的重要机制之一。肠道中革兰阴性菌产生大量 LPS，通过 Toll 样受体(TLR) 4 介导的胞内信号转导途径激活核因子 NF-κB，增加促炎因子(TNFα、IL-6)释放，刺激肿瘤生长因子活化，表明 GM-LPS-TLR4 轴引起的肝细胞损伤和炎症反应能够促进 HCC 发生[45]。

因此，调节肠道微生物群可能成为预防和治疗肝硬化并发症的新策略。

5. 基于肠道微生物群的肝硬化诊断和治疗

随着对肠道微生物群与肝硬化关系的深入研究，基于肠道微生物群的诊断方法逐渐受到关注。通过分析粪便或血液中的微生物标志物，可以辅助肝硬化的早期诊断和分期。例如，某些特定菌群的比例变化与肝硬化的严重程度相关，可作为无创诊断指标。此外，基于肠道微生物群的代谢组学分析也有助于评估肝硬化患者的预后。在治疗方面，调节肠道微生物群已成为肝硬化管理的新策略。

5.1. 益生菌、益生元和合生元制剂

益生菌被定义为活的微生物，如人类来源的细菌或酵母菌，食用时可提供健康益处[46]。许多研究在

不同环境下使用不同类型的益生菌对非酒精性脂肪肝和肠易激综合征患者进行[47] [48]的研究表明，益生菌通过促进肠道中有益细菌的生长和减少有害细菌来调节肠道微生物群[49] [50]。

1995 年，Roberfroid 和吉布森首次将益生元确定并定义为一种难消化的食物成分，其通过选择性地刺激细菌的生长或活性而对改善宿主健康具有有益作用[51]。食物成分可以喂养肠道微生物菌群，其分解产物如短链脂肪酸被释放到血液循环中，不仅影响胃肠道，还影响其他远端器官[52]。即，益生元是诱导肠道中有益微生物的生长或活性的食物成分。

益生菌和益生元的协同组合被定义为合生元[53]。合生元是为了克服益生菌可能存在的生存困难而开发的。除了促进益生菌和细菌的生长外，合生元还有助于更有效地维持肠道内的稳态和维持健康的身体[54]。

研究表明，通过使用益生菌、益生元和合生元制剂调节肠道微生物群，可以有效治疗严重肝病的几种并发症，如肝性脑病[55]。这些在肝纤维化诱导的动物和患者中的改善的发现突出了调节肠道微生物组的重要性，改善肝硬化患者的临床症状和实验室指标。

5.2. 粪菌移植

粪菌移植是指将健康捐赠者的粪便悬浮液经过处理后移植到患者的肠道，以恢复患者肠道微生物群落的平衡，促进疾病恢复。在肝硬化的发展中，肠道微生物的多样性逐渐减少，失代偿时更为明显[56]。肠道微生物的改变在粪便和肠黏膜中最显著，主要表现为毛螺菌科、瘤胃球菌科等有益菌减少，以及肠球菌科、葡萄球菌科和肠杆菌科等致病菌增多，并且此种改变与肝硬化的并发症相关，特别是 HE [57]。

Sydor 等[58]的研究表明，与非肝硬化患者相比，肝硬化患者血清中初级胆汁酸及次级胆汁酸水平降低。肝硬化患者产生次级胆汁酸能力减弱的原因可能是梭状芽孢杆菌种类的相对减少，经过粪菌移植治疗后次级胆汁酸会有所增加[59]。因此，粪菌移植可能通过影响胆汁酸代谢，进而发挥其部分治疗作用。

作为一种新兴的治疗方法，在肝硬化尤其是肝性脑病的治疗中显示出良好前景。可促进“良好”微生物群的生长，可以改善患者的生态失调并改善肝性脑病症状。

5.3. 饮食干预

针对肠道微生物群的饮食干预也是肝硬化管理的重要组成部分。高纤维饮食以及多种生物的补充剂可促进有益菌生长，改善患者的生态失调并改善其预后[60]；限制蛋白质摄入可减少氨的产生，有助于预防肝性脑病。未来，基于肠道微生物群的个性化治疗策略有望进一步提高肝硬化治疗的效果。

6. 总结和展望

肠道微生物群失衡通过“菌群失调→代谢物改变→屏障损伤→微生物易位→肝脏炎症/纤维化”的级联反应驱动肝硬化进展，这一机制虽在多维度研究中得到验证，但当前转化医学仍面临显著局限：机制研究过度依赖动物模型(如门静脉结扎大鼠)，难以模拟人类肝硬化复杂表型，且临床观察(如唾液链球菌与肝性脑病关联)未能明确因果时序；治疗试验存在严重异质性(见表 1)，突出表现为终点指标偏差(肝性脑病症状 vs 胆汁酸代谢)、安慰剂效应未控(仅 23%采用活性安慰剂)及菌株特异性忽视(广谱制剂掩盖拮抗效应)。

Table 1. Comparison of key clinical trials on the treatment of complications of liver cirrhosis with probiotics
表 1. 益生菌治疗肝硬化并发症的关键临床实验对比

关键研究	设计及样本量	干预措施	主要终点	阳性结果
Campion, D. 等人[55]	RCT, n = 120	合生元(乳杆菌 + 果寡糖) 6 个月	肝性脑病(HE)分级、血氨水平	HE 改善率 38% vs 对照组 18% ($p < 0.05$)

续表

Andresen, V. 等人[48]	RCT, n = 200	热灭活双歧杆菌 MIMBb75	IBS 症状评分	腹痛缓解率提高 30% ($p = 0.01$)
Egresi, A. 等人[47]	n = 45	传统酸奶(含保加利亚乳杆菌)	NAFLD 肝脂肪变程度(超声)	肝酶 ALT 下降 15% ($p < 0.05$)
Bajaj J. S. 等人[59]	n = 20	粪菌移植(FMT)	微生物功能或临床失代偿事件	次级胆汁酸升高；感染率下降 40%

因此，未来突破需聚焦三大方向。第一，机制升级：采用患者源性类器官–微生物共培养解析菌株特异性代谢物(如丁酸盐)对肝星状细胞的直接作用，结合纵向多组学区分驱动性菌群与继发标志物。第二，精准干预：开发靶向并发症的益生菌(如尿素酶阴性菌防治肝性脑病)依据受体生态位缺失(如梭菌空缺)个体化匹配 FMT 供体，并联合屏障修复剂突破定植抵抗。第三，风险控制：前瞻性队列追踪菌群–肝硬化因果时序，建立 FMT 供体耐药基因/促癌菌株(如具核梭杆菌)筛查体系。唯有破解菌株特异性机制并标准化临床设计，方能实现肠道微生物靶向治疗的精准转化。

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