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肠道菌群失调与肝硬化的关系

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摘　要

肝硬化是各种病因导致的慢性肝病的终末阶段，常并发上消化道出血、肝性脑病、感染等多种严重并发症而导致死亡。随着肠道菌群的研究不断增多，我们发现肝硬化患者存在显著的肠道菌群失调，这种变化与肝硬化及其并发症的发生发展相关。本文旨在介绍肝硬化患者肠道菌群的特点，分析肠道菌群失调参与肠屏障受损的机制，指出肠源性病原体移位与宿主免疫应答引发肝脏损伤的原理，简述肠道菌群失调致胆汁酸、丁酸盐代谢紊乱对肝硬化的影响。最后，我们总结了目前以肠道菌群为导向的研究进展和存在的问题，为肝硬化及其并发症的防治提供了新的思路。

关键词

肠道菌群失调，肝硬化，肠－肝轴

The Relationship between Intestinal Dysbacteriosis and Liver Cirrhosis

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Abstract

Liver cirrhosis is the final stage of chronic liver disease of various causes. This disease is often complicated by severe complications such as upper gastrointestinal hemorrhage, hepatic encephalopathy, and secondary infection, leading to death. With the increasing number of studies on the intestinal flora, we found a significant intestinal dysbacteriosis in patients with liver cirrhosis, associated with the emergence and development of liver cirrhosis and its complications. This pa-

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per aims to introduce the characteristics of intestinal flora in patients with liver cirrhosis. We also analyzed the mechanism of intestinal dysbacteriosis involved in intestinal barrier damage. Furthermore, we pointed out the principle of liver injury caused by translocation of intestinal pathogens and host immune response and briefly described the effect of metabolic disorder of bile acid and butyrate caused by the imbalance of intestinal flora on liver cirrhosis. Finally, we reviewed intestinal microbiota-based treatment options and existing problems currently being studied, which can provide new thinking for preventing and treating liver cirrhosis and its complications.

Keywords

Intestinal Dysbacteriosis, Liver Cirrhosis, Intestinal-Liver Axis

1. 引言

肝硬化是由一种或多种病因引起的以肝脏弥漫性纤维化、假小叶形成和肝内外血管增殖为特征的一种病理状态，临床表现为肝功能减退和门静脉高压。肝硬化患者肠道菌群与正常人相比会出现菌群种类和丰度的显著改变，即肠道菌群失调。由于肝脏和肠道之间紧密的解剖关系，使得肝脏易受到肠道细菌及其代谢产物的影响。了解肠道菌群失调对肝硬化发生发展的可能作用机制，有助于以宿主－微生物途径为导向，为肝硬化的治疗提供新的方向。

2. 肝硬化患者肠道菌群的特点

人体肠道中有数以万计的微生物定植，有细菌、真菌及病毒。按生理功能可分为共生菌、病原菌和条件致病菌；按需氧与否可分为需氧菌、兼性厌氧菌、专性厌氧菌。人体定居的肠道微生物 99.9%以上为专性厌氧菌，以厚壁菌门和拟杆菌门为主要优势菌群。肠道微生态平衡时，宿主的营养、免疫、消化等生理功能才能正常运作[1]。

肠道是一个富含微生物的环境，其通过门静脉途径与肝脏建立了紧密的双向关系，即“肠－肝轴”。由于肝脏这种独特的解剖位置和血管系统，门静脉携带营养物质的同时，也可以转移肠道微生物及其代谢产物，包括内毒素、细菌 DNA、内生性乙醇以及活细菌等多种抗原成分。肠道屏障的存在，使肠道菌群与肝脏既相互联系、又相对独立，共同调控机体生理活动[2]。

许多研究证据表明，在早期慢性肝病向肝硬化发展过程中，患者肠道菌群发生了改变，不同病因和不同程度肝硬化的肠道菌群改变有所不同，但总体表现为群落结构和组成改变、厌氧菌与需氧菌比例失衡，细菌多样性降低，拟杆菌、双歧杆菌等有益菌减少，肠杆菌和肠球菌等具有潜在致病性细菌及口腔来源的微生物群的丰度增加，而针对肠道致病菌的噬菌体多样性也随肝硬化程度加重而减少[3] [4] [5] [6]。肝硬化相关的肠道微生物改变可能是与促纤维化因子、胆汁流量减少、粘膜及全身免疫反应相关的因素、维生素 D 在肝脏的羟基化受损、利福昔明等抗生素和质子泵抑制剂的使用，以及潜在的疾病病因驱动相关[7] [8] [9] [10]。有趣的是，肠道菌群的组成结构与高住院风险、MELD 评分、肝外器官衰竭、急性－慢性肝衰竭和死亡的风险相关[6] [11] [12]。

由此可见，肝硬化患者存在肠道菌群失调，但需要注意的是，慢性乙型肝炎患者在发生严重肝病之

前，肠道菌群的组成已经发生改变[13]。虽然很难确定两者谁是鸡，谁是蛋，但探索肠道菌群失调对肝硬化发生发展的影响，可能会打破两者之间的恶性循环，为临床针对肝硬化及相关并发症的微生物治疗提供理论支持。

3. 肠道菌群失调对肝硬化发生发展的可能机制

肠屏障的破坏使肝脏暴露于肠道有害物质的环境中，肝脏固有免疫系统被肠道产物激活，引发一系列炎症级联反应和免疫反应而造成肝损伤；肝功能受损又会影响肠道菌群的组成与代谢，形成肠肝恶性循环。以下将介绍肠道菌群失调参与肠屏障破坏、宿主免疫应答以及微生物介导的胆汁酸、丁酸盐代谢紊乱对肝硬化发生发展的影响机制。

3.1. 肠道菌群失调参与肠屏障功能障碍

肠道上皮细胞的紧密连接、血管屏障等结构要素，免疫细胞以及黏膜杯状细胞分泌的黏液、肠道微生物分泌细菌素、抗菌肽等化学要素共同维持着肠道屏障功能。许多研究表明，肠道菌群失调在肠屏障损伤机制中扮演重要角色。Chen 等人[14]观察到肠道菌群紊乱可能诱导肿瘤坏死因子-α 激活肌球蛋白轻链激酶，导致上皮紧密连接蛋白的丢失。同样，Borrero 等人[15]发现肝硬化大鼠的肠黏膜显示出异常的炎症模式，表现为辅助性 T 细胞 1 (helper cell 1, Th1)增多，Th17 减少，这种状态促进了上皮连接蛋白断裂以及肠道菌群移位；而通过肠道净化改善肠道菌群，可降低黏膜免疫细胞的促炎活性与肠菌群移位，这从侧面证实了肠道菌群失调参与了肠道免疫与结构要素的损害。不仅如此，小肠细菌过度生长与肠黏膜杯状细胞及其分泌的黏蛋白减少相关，从而削弱黏液中和有毒物质及隔离肠上皮的作用[16]。另外，肠道菌群失调可能通过对 β-连环蛋白信号通路的干扰，来驱使肠血管屏障的破坏，使得细菌和细菌产物通过肠肝轴到达肝脏[16] [17]。总之，肠道菌群失调能通过多种途径参与了肠屏障的损害，致使肠通透性增加、肠源性病原体及有毒代谢产物移位，可能引发肝脏免疫应答而诱发肝脏损伤。

3.2. 肠源性病原体移位引发肝脏免疫应答

肝脏内的肝星状细胞、Kupffer 细胞表达模式识别受体，如 Toll 样受体(Toll-like receptor, TLR)，能够识别和感应来自微生物区系病原菌或其代谢物上的脂多糖、鞭毛蛋白等，进而介导局部的炎症反应[18]。Xiao 等人[19]发现，移位细菌的鞭毛蛋白通过激活 TLR5 可致白介素-6 (interleukin-6, IL-6)、IL-8、IL-1β 产生增加，使得肝细胞发生氧化应激及炎症反应，进而发生肝细胞的损伤。一些研究也证实了 TLR9 与下游的髓系分化因子 88 在小鼠肝组织中纤维化和胶原沉积密切相关[20]。除此之外，Tedesco 等人[21]发现肝病模型小鼠的肝内 $\gamma\delta$T 细胞可针对肠道来源的病原菌产生 IL-17，从而引发肝胆管周围发生明显的胶原沉积和纤维化。Seo [22]发现敲除 TLR3 的小鼠肝组织中 $\gamma\delta$T 细胞产生的 IL-17 浓度下降以及肝纤维化程度明显降低，表明来自肠道的病原体可能通过 TLR3 途径参与介导了肝纤维化的发生。而最新的文献提出，移位的肠道病原体可以通过肝内 T 细胞受体免疫反应来重塑肝内免疫微环境，导致肝内免疫细胞亚群的激活和异常分布，包括肝内 $\gamma\delta$T 细胞、NK 细胞和 Kupffer 细胞、B 淋巴细胞等，进而调节肝星状细胞促进肝纤维化发展[3]。

由此可见，肠道菌群失调、肠屏障受损、病原菌及代谢产物移位，这一系列改变可被肝细胞 TLR 识别，并通过激活炎症通路，造成了肝脏的“多重打击”，从而诱导了肝炎－肝纤维化－肝硬化的发生发展。

3.3. 肠道菌群代谢紊乱对肝硬化影响

肝脏产生初级胆汁酸(primary bile acid, PBA)并通过胆囊收缩排入肠道，少数 PBA 在肠道微生物作用下转变次级胆汁酸。绝大部分胆汁酸(bile acid, BA)在肠道被重新吸收回肝脏，通过激活法尼醇 X 受体

(farnesoid X receptor, FXR)和 G 蛋白偶联胆汁酸受体来调节胆汁酸合成与代谢，此过程称为 BA 的肠肝循环[23]。BA 不仅可以抑制肠道中有害病原菌生长、促进脂溶性食物的消化和吸收，还可以作为信号分子激活 FXR，诱导内皮细胞的 β 钙连蛋白活化，参与肠屏障的维护和修复[17]。而许多证据表明，肠道菌群紊乱使得BA的合成和代谢失调，导致FXR活性削弱，从而抑制FXR发挥正常的生理功能[24]。Fumitaka 等人[25]发现，肠道微生物代谢产生的脱氧胆酸可通过肝星状细胞衰老相关分泌表型的释放，降低肝脏抗肿瘤免疫的作用，从而加速了肝硬化患者向肝癌的进展。

除了胆汁酸以外，肠道菌群代谢产生的短链脂肪酸，特别是丁酸盐，也参与维持肠道稳态的作用。Sun 等人[26]发现微生物代谢产生的丁酸盐可以抑制炎症信号通路来降低氧化应激和炎症反应。不仅有抗炎作用，丁酸盐在维持肠道屏障的完整性方面起着至关重要的作用[27]。研究表明，肝硬化患者肠菌群产丁酸盐的能力很低，这可能与参与反应的碳水化合物不足和产丁酸盐细菌减少有关[27] [28]。Sheng 等人[29]表明，补充丁酸盐可减轻肝脏炎症，也佐证了丁酸盐产生减少是介导肝纤维化发生的途径之一。总之，肠道菌群紊乱介导的胆汁酸与丁酸盐代谢障碍参与了肝硬化进展，这些结果为进一步探讨肠道菌群紊乱、胆汁酸、丁酸盐和肝硬化发展提供了可能的研究方向。

4. 肠道菌群失调与肝硬化并发症的关系

Kang 等[30]发现与肝硬化无菌小鼠相比，肝硬化普通小鼠的血氨水平及系统炎症发生率更高；其中，共生菌数量与血氨及炎症水平呈负相关，而肠杆菌科与血清炎性细胞因子呈正相关。Bajaj 等[31]发现，肝硬化伴轻微肝性脑病(Minimal hepatic encephalopathy, MHE)的粪便和唾液样本中乳杆菌科的相对丰度较高，而没有 MHE 的肝硬化患者，原生的拉克氏菌科的丰度相对较高。由此认为肠道原生菌群的改变可能驱动肝性脑病的发生。由于细菌过度生长、肠屏障损害、肠道细菌移位及机体抗菌免疫能力减弱等综合作用，肝硬化易并发感染，如自发性细菌性腹膜炎，其风险随着肝硬化的进展而增加。而肝硬化失代偿期患者，免疫功能进一步降低，大量肠源性毒素及病原体入血，加剧肝脏损伤与感染，形成恶性循环[32] [33]。

5. 改善肠道菌群失调对肝硬化及其并发症的影响

肠道菌群失调与肝硬化发生发展之间的关系错综复杂，通过抑制肠道病原菌的生长、补充肠道有益菌、粪菌移植、调节 FXR 受体等多种途径，减轻肝硬化患者的肠道菌群失调状态，为延缓肝硬化发展及其并发症的发生开辟了新的治疗途径。

5.1. 口腔与饮食

一项研究表明，肝硬化患者通过治疗牙周炎症后可以改善肝硬化患者的肠道菌群失调，并降低 IL-6 等炎症因子水平。因此，控制口腔炎症可能恢复肠道微生态及控制全身炎症，进而减少对肝脏的损害[34]。富含发酵牛奶、蔬菜、谷物、咖啡和茶的饮食可以增加肝硬化患者肠道微生物多样性，延缓肝硬化进展及并发症的发生[35] [36]。另外，最近一项研究发现，膳食纤维可通过调节肠道菌群组成和增加拟杆菌的丰度来降低血清促炎因子(如 IL-1β 和 IL-6)及 CD3+、CD4+和 CD8+ T 淋巴细胞在肝脏中的浸润，这可能与膳食纤维在肠道发酵产生丰富的短链脂肪酸有关[37]。因此，饮食的选择与搭配对肝硬化患者非常重要。

5.2. 抗生素和噬菌体

肝硬化中肠杆菌科和非肠球菌链球菌是最常见的病原微生物，针对此类病原菌的抗生素能有效抑制肠道细菌移位，可延缓肝硬化进程，治疗肝性脑病、细菌感染等并发症。利福昔明被认为主要在肠道局部起作用，目前已被证明可以修饰肠道微生物群，抑制炎症途径，通过与肠肝轴的相互作用对肝硬化产

生有益作用，目前在肝性脑病中运用广泛[38]。研究发现利福昔明可以通过调节肠道菌群来改善肝性脑病患者的肝脏及神经心理功能，还可以降低感染和静脉曲张破裂出血的发生率[39]。除了利福昔明以外，喹诺酮类的抗生素在肝硬化研究中也日益增多。Moreau 等人[40]发现，连续 6 个月口服诺氟沙星能显著地降低 child-Phgh C 级的肝硬化患者发生任何细菌感染的风险，其中包括艰难梭菌或多重耐药菌。另外，诺氟沙星比利福昔明更有效地预防肝硬化大鼠的细菌易位，这可能与诺氟沙星更能减少肠道微生物中的病原菌有关。这需要更多的临床试验来验证诺氟沙星的有效性及安全性[41]。然而，使用抗生素的长期益处尚不清楚，并且随着肝硬化的进展，大量积聚的病原菌成为了高耐药性病原体的主力军[42]。为此，新兴的噬菌体疗法逐渐浮现。与抗生素相比，噬菌体通过完全正交的模式发挥作用，因此噬菌体可能有效地消除高耐药性细菌。目前，噬菌体在治疗铜绿假单胞菌和鲍曼不动杆菌等多重耐药菌的患者中已取得了成功[43]。然而，由于噬菌体与其靶向细菌的作用机制还未完全被阐明，目前特异性噬菌体疗法还未普及。所以，进一步将噬菌体疗法运用于临床或将有益于控制肝硬化发展及其并发症的发生。

5.3. 益生菌、益生元

益生菌及益生菌衍生的成分，如细菌素、脂磷壁酸、表层蛋白和分泌蛋白，对肠屏障功能具有保护作用。新的研究发现鼠李糖乳杆菌不仅能够增强肠粘蛋白的表达，降低革兰氏阴性菌脂多糖或肿瘤坏死因子 α 诱导的肠屏障损伤，还可通过肠道 FXR 信号通路来调节肝脏胆汁酸的合成和排泄，减少肝硬化阶段肝内胆汁淤积造成的肝脏损伤和纤维化[44] [45]。Santo 表示增加小肠乳酸杆菌不仅可以通过增加 FXR 来调节胆汁酸稳态，还可激活肠道免疫效应，特别是巨噬细胞的抗炎反应，来减轻肝纤维化程度[46]。另外，经基因工程改造的大肠杆菌能降低小鼠的高氨血症和提高其存活率，有益于肝性脑病的治疗[45]。同样，益生元低聚木糖可以降低肠通透性、提高局部和全身的抗炎能力，起到对抗肝硬化发展的作用[47]。除了单用一种益生菌方案，多菌群益生菌可增加代偿性肝硬化患者的微生物组丰富度及多样性，有利于改变肠道微生物组功能和肠道屏障功能[48]。然而，在一项抗生素诱导的微生物失调的试验组中，加用益生菌导致了自体微生物群的恢复延迟，其原因可能是多种益生菌通过表达抗菌肽，阻碍了微生物区系的重新生长，因此需要开发个性化的益生菌方法来维持肠道微生态的稳态，包括益生菌的组合方式及用药持续时间[49]。

5.4. 粪菌移植

粪菌移植(fecal microbial transplant, FMT)是一种借用健康肠道微生物成分来恢复生理状态肠菌的方法。在一项动物试验中，粪菌移植通过改变肝硬化小鼠的肠道菌群，重建了肝内免疫微环境，进而调节肝星状细胞的激活来延缓肝纤维化的进展[3]。Bajaj 等人[50]证实，FMT 可调节 BA 谱的代谢能力，重建肠道微生物多样性和功能。另外，在肝硬化和复发性肝性脑病患者中，经抗生素预处理后的粪便微生物口服胶囊具有良好的耐受性、长期安全性及有效性[51] [52]。在此类研究中，粪菌移植可改善晚期肝硬化患者认知功能参数，并减少了肝性脑病的复发。这可能与健康人的粪菌改善了肝硬化患者神经炎症和减少小胶质细胞激活有关[53]。此外，另一项证据表明，粪菌移植可以逆转高脂高果糖饮食大鼠的早期门静脉高压症，这可能是减轻肝硬化门静脉高压的一种新型治疗方式[54]。尽管粪菌移植在上述研究中取得了成功，但大部分研究着重于研究粪菌移植后肠道微生物区系的变化及对肝硬化的短期临床结局，目前长期的临床随访结果尚还缺乏，并且目前有报道粪菌移植可以引起严重的肠道感染。所以，粪菌移植的安全性和有效性还有待进一步验证。

6. 小结与展望

肠道菌群紊乱与肝硬化及其并发症具有密切关系，主要通过肠－肝轴影响其发生发展，如参与肠屏

障损害、致使肠道细菌及其有毒的代谢产物移位、介导了胆汁酸、丁酸盐代谢功能紊乱，促进肝脏炎症的级联反应及肝细胞的损伤。但需要注意的是，大多数研究多为粪便物分析，可能与肠道微生物存在差异。除此之外，目前仍有许多问题亟待解决，如肝硬化患者肠道菌群紊乱的原因，以便于临床医生早期干预。另外，对于肝硬化肠道菌群紊乱的患者，益生菌、抗生素选用的时机、种类与疗程，粪菌移植的有效性与安全性，这些都需大量前瞻性随机对照临床试验验证。总之，更好地理解肠道菌群失调通过肠肝轴发挥致病机制，研究最佳的肠道菌群靶向治疗组合以改善肝硬化的预后，将会对延缓肝硬化发生发展及预防相关并发症起到一定的治疗决策作用。

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