·综述·

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基于肠道微生态探讨中医药治疗非酒精性脂肪性肝病的作用机制

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摘要：非酒精性脂肪性肝病（NAFLD）是一种与肥胖、胰岛素抵抗和血脂异常相关的多系统疾病，其发病机制较为复杂。肠道菌群失调与NAFLD的发病密切相关，中医药治疗可通过调节肠道菌群及其代谢产物，改善NAFLD患者的实验室指标和临床症状。本文总结了NAFLD与肠道菌群的关系、肠道菌群失调参与NAFLD的发病机制，从肠道菌群角度探讨中医药治疗改善NAFLD的可能等，以期为NAFLD的治疗拓展新的思路。

关键词：非酒精性脂肪性肝病；肠道菌群；中医疗法

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Mechanism of action of traditional Chinese medicine in treatment of nonalcoholic fatty liver disease based on intestinal microecology

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is a multisystem disease associated with obesity, insulin resistance, and dyslipidemia and has a complex pathogenesis. Studies have shown that gut microbiota dysbiosis is closely associated with the onset of NAFLD, and traditional Chinese medicine treatment can improve the laboratory markers and clinical symptoms of NAFLD patients by regulating intestinal microbiota and its metabolites. This article elaborates on the association between NAFLD and gut microbiota, the involvement of gut microbiota dysbiosis in the pathogenesis of NAFLD, and the possible mechanism of traditional Chinese medicine treatment in improving NAFLD from the perspective of gut microbiota, in order to provide new ideas for the treatment of NAFLD.

Key words: Non-alcoholic Fatty Liver Disease; Gut Microbiota; TCM Therapy

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非酒精性脂肪性肝病（NAFLD）是一种与肥胖、胰岛素抵抗和血脂异常有关的多系统疾病，又称代谢相关脂肪性肝病（metabolic associated fatty liver disease，MAFLD），是指排除酒精等明确的肝损害因素，以弥漫性肝细胞大泡性脂肪病变为主要特征的临床病理综合征，其临床疾病谱发展包括单纯性脂肪肝、非酒精性脂肪性肝炎（NASH）、肝硬化和肝细胞癌[1]。NAFLD是全球最常见的慢性肝病，全球患病率为25.24%[2]，中国患病率达29.2%[3]。在患有其他代谢综合征（如肥胖、2型糖尿病）的患者中，NAFLD的患病率大大增加[4]。NAFLD发病机制是复杂和多因素的，目前广受认可的“多重平行打击假说”涉及炎性因子的聚集、自噬、脂肪组织功能异常、

线粒体功能异常、内质网应激、肠道菌群失调、膳食结构改变、遗传基因改变等机制[5]。近年来，NAFLD的发生发展被认为是由肠-肝轴的不平衡和肠道微生物群的代谢物所驱动的[6]，本文将着重探讨NAFLD与肠道菌群的关系、肠道菌群失调参与NAFLD的发病机制、中医药治疗改善NAFLD的可能作用机制。

1 肠道菌群在NAFLD发展过程中的差异

肠道菌群数目庞大、种类繁多，彼此之间以及与宿主细胞相互作用，参与调节机体新陈代谢、免疫反应、维持必需的营养物质供应。肠道菌群失调可能诱发不同类型的疾病，如代谢综合征、心血管疾病、胃肠道疾病等[7-8]。研究发现，健康人群与NAFLD患者的肠道菌群存在显著差异，肠道菌群参与了从单纯性脂肪肝发展到NASH到肝硬化，甚至肝细胞癌的进程，在这一进程的每一阶段，NAFLD患者肠道菌群水平特征也存在差异（表1）。

2 肠道菌群失调参与NAFLD的发病机制

肠道菌群主要通过肠-肝轴对肝脏发挥重要影响。肠道内胆汁酸代谢与肠道通透性改变对肠道菌群的影响与NAFLD的发展密切相关[25]。肠道菌群失衡可能从破坏肠道屏障、影响胆汁酸的代谢、增加机体营养及能量摄入、内源性乙醇的增多、胰岛素抵抗的诱导等方面促进NAFLD的发展[8]。

2.1 *肠道菌群通过肠-肝轴参与NAFLD* 肠-肝轴是指肠道及其微生物群与肝脏之间的双向关系，是由遗传、饮食和环境等多种因素引起和影响的信号复合体[26]。肝脏与肠道双向沟通、相互影响。在生理上，一方面，肝脏通过胆管排泄胆汁及其他生物活性介质与肠道沟通；另一方面，代谢营养物质通过门静脉转运到肝脏。在病理上，肠道细菌及其代谢产物、内源性毒素和炎症因子通过门静脉转运，从而使肝脏易受肠道微环境的影响而发生病理性改变[27]。近年来，越来越多的研究关注肠道菌群如何通过肠-肝轴参与NAFLD的发病机制，并指出肠-肝轴相关研究是防治NAFLD的重要途径。肠道微生物失调往往伴随肠道屏障功能障碍，促进肠道炎症的发生，导致肠道微生物及其代谢产物通过肠道黏膜进入门静脉转运至肝脏中，从而引起肝脏炎性反应及脂肪变性，促进NAFLD的发生发展。

2.2 *肠道菌群破坏肠道屏障引起通透性增加* 肠道黏膜是功能复杂的半透膜屏障，具有选择性渗透功能，一方面吸收营养物质，另一方面可阻挡有害细菌及其代谢产物经门静脉进入肝脏从而进入血液中[28]。而NAFLD患者大多肠黏膜屏障受损，其损害可能是NAFLD进展的诱发或加重条件。

肠道屏障包括机械屏障、化学屏障、微生物屏障和免疫屏障。目前关于NAFLD发病机制研究主要着眼于肠道微生物屏障。肠道菌群主要包括黏膜菌群和肠腔菌群，黏膜菌群主要以双歧杆菌和乳酸菌为主，肠腔菌群多为大肠杆菌和肠球菌，上述菌群黏附在肠道黏膜层上，形成了一个多层次的肠道微生物屏障。该屏障由多种肠道菌群组成，正常情况下这些肠道菌群数量、结构、比例、分布相对稳定，共同参与消化、代谢、免疫等功能[29]。但疾病、免疫、应激等因素可能导致肠道菌群数量、结构以及活性发生改变，发生菌群移位，造成菌群平衡失调紊乱，从而破坏肠道屏障的完整性，肠道通透性增加，促炎因子水平增加[30]。肠黏膜炎症反应增加及肠上皮屏障破坏导致细菌及其代谢产物在肠道内易位[31]，最终导致肝脂肪变性和加速肝纤维化的进展[32-33]。

2.3 *肠道菌群通过肠道微生物-胆汁酸轴影响胆汁酸代谢* 肠道菌群通过影响胆汁酸的正常代谢途径间接影响NAFLD的发生发展。肠道菌群与胆汁酸二者相互影响，一方面，在肠道菌群的作用下，肠道中的初级胆汁酸可转化为次级胆汁酸，肠道菌群的丰度、结构组成等

表1 疾病发展过程中肠道菌群的差异

Table 1 Differences in intestinal flora during disease development

疾病	升高		降低		参考文献
	门水平	科属水平	门水平	科属水平	
单纯性脂肪肝	厚壁菌、变形杆菌、放线菌	脱硫菌	拟杆菌	阿克曼菌、瘤胃球菌科	［9］
NASH	厚壁菌门、变形杆菌	普雷沃菌属、毛螺菌科、另枝菌属、肠杆菌科	拟杆菌门（乳酸菌、瘤胃球菌）	双歧杆菌科、双歧杆菌属、拟杆菌属	［10-14］
肝硬化	变形菌门、梭菌门	肠杆菌科（属）、肠球菌科（属）、韦荣球菌属、链球菌属、梭菌属、普雷沃菌属	拟杆菌门	拟杆菌属、双歧杆菌属、瘤胃球菌属、粪球菌属	［15-19］
肝细胞癌	厚壁菌门	大肠杆菌属、肠球菌属、梭菌属、考拉杆菌属、颤螺菌属、克雷伯杆菌属、嗜血杆菌属、毛螺菌属	拟杆菌门	颤杆菌克属、粪杆菌属、粪球菌属、乳酸杆菌属、双歧杆菌属、经黏液真杆菌属	［20-24］

也可影响胆汁酸代谢，另一方面，胆汁酸亦可影响肠道菌群的丰度、比例等[34]。肠道菌群通过法尼醇X受体（farnesoid X receptor，FXR）和G蛋白偶联胆汁酸受体5（takeda G- protein-coupled receptor，TGR-5）调节胆汁酸的代谢。作为机体内胆汁酸的重要受体，FXR主要存在于肝脏和回肠之中，TGR-5分布在肠道及肠外多种组织，二者在胆汁酸生成和转运的过程中起着重要的作用。胆汁酸通过激活FXR受体，引起相关系列反应，参与脂质与葡萄糖的代谢，促进脂肪酸氧化，从头抑制脂肪合成，促进甘油三酯清除，抑制炎症反应[35]。TGR-5可促进糖代谢，抑制炎症反应，抑制肝脂肪变性，从而延缓NAFLD的进展。

2.4 肠道菌群失调引起内源性乙醇增多 肠道菌群失调引起代谢产物内源性乙醇增多[36]，从而引起肠道通透性增加、肠道紧密连接被破坏，使得脂多糖（lipopolysaccharide，LPS）和乙醇炎症活化小体触发Toll样受体（Toll-like receptor，TLR）信号，产生多种细胞因子及炎性介质，进一步刺激肝脏发生炎症反应造成肝脏的损伤[36]。

内源性乙醇在肝脏中经过一系列代谢反应被清除。但当乙醛脱氢酶活性过低时，乙醛代谢障碍，导致乙醛在体内蓄积。乙醇和乙醛均可对肝脏造成直接的氧化损伤，通过激活体内相关酶活性，导致体内氧自由基产生增多和脂质过氧化。乙醛可损害肠黏膜，导致肠黏膜通透性增加，内毒素吸收增多，促进NASH发生及持续进展。

2.5 肠道菌群失调诱导胰岛素抵抗 肠道菌群失调可引起胰岛素抵抗，进而引起肝脏内炎症反应增加，从而促进NAFLD的发生发展。换言之，NAFLD是胰岛素抵抗在肝脏的表现形式。LPS可以通过激活TLR-4、TLR-2等通路激活炎症级联反应，促进诱导型NO合成酶的表达，干扰或损伤脂肪细胞中的胰岛素分子信号转导通路，从而诱导胰岛素抵抗[37]，进而导致肝内脂质堆积，改变肝脏内对游离脂肪酸的降解途径，导致NAFLD[38]。

2.6 肠道菌群失调增加机体营养及能量摄入 肠道菌群发酵膳食纤维所产生的短链脂肪酸通过激活G蛋白偶联受体（GPCR）中相关受体的表达，刺激肽酪氨酸分泌增加，肽酪氨酸分泌增加将抑制肠道蠕动、减缓物质运输，进而增加从饮食中获取的营养和能量，最终导致加速肝脂肪生成和堆积[39]；另一方面，短链脂肪酸可促进糖和脂肪合成使产能增加，干扰脂肪酸β氧化使游离脂肪酸在肝脏内累积[40]，还可刺激脂肪细胞中的GPCR41介导的瘦素的产生来调节能量稳态[41]。

3 中医疗法通过调节肠道菌群改善NAFLD的机制

目前，大量临床研究表明，中医疗法中的中药复方[42-43]、针刺[44-45]、穴位贴敷[46-47]、穴位埋线[48-49]、灸法[50]等治疗NAFLD效果显著，各种中医治疗方法可改善NAFLD患者胁肋胀痛、脘腹胀满、食少纳呆、倦怠乏力等临床症状，调控脂肪代谢通路，减轻胰岛素抵抗，增加胰岛素分泌，减轻炎症反应，改善患者的肝功能、血脂指标以及肝脏B超、肥胖情况。

3.1 中医疗法调节肠道菌群丰度

3.1.1 中药治疗 一项研究[43]表明，中药复方降脂方可通过调节肠道菌群丰度，增加NAFLD患者胰岛素分泌、调控代谢通路，减少脂肪堆积，降低血脂水平，减少肝细胞损伤，减轻炎症反应。降脂方显著下调NAFLD患者肠道菌群中厚壁门相对丰度，上调拟杆菌门、栖粪杆菌属、罕见小球菌属、布劳特菌属相对丰度。栖粪杆菌属和布劳特菌属均可产生短链脂肪酸，可缓解肥胖、减轻炎症反应和改善菌群失调。布劳特菌属可减少肥胖症的发病率，其菌属相对丰度与内脏脂肪面积呈显著负相关关系[51]，亦可调控具有重要生物学功能的菌群（双歧杆菌属、拟杆菌属、霍尔德曼菌属等），影响益生菌（阿克曼黏菌属、产丁酸菌属、乳杆菌属等）。维生素可保护肝细胞，参与肝脂质代谢，而相关研究[52]表明，罕见小球菌属与维生素的吸收和利用相关。综合分析，降脂方通过调控肠道菌群丰度来增加短链脂肪酸的生成、减轻炎症反应、改善脂质代谢、促进维生素吸收及利用来达到治疗NAFLD的目的。运用化脂复肝颗粒[53]、健肝降脂丸[54]治疗NAFLD，通过改变肠道菌群群落结构，降低了厚壁菌与拟杆菌的比例，增加了肠道菌群的多样性及优势菌的丰度，减轻炎症反应，降低血脂，改善肝功能，缓解肝脏中脂肪细胞堆积，从而达到治疗NAFLD目的。

3.1.2 针刺治疗 一项研究[55]表明，针灸可以通过调节肠道菌群组成显著改善高脂饮食诱导的NAFLD大鼠的脂质代谢、肝功能指标和全身炎症反应。针刺可降低厚壁菌与拟杆菌（F/B）的比例，增加拟杆菌门S24-7菌科、普雷沃菌科、拟杆菌科、布劳特菌属、未分类拟杆菌、拟杆菌属和普雷沃菌属的丰度，降低瘤胃球菌科的丰度。该研究通过对肠道菌群相关性分析表明，脂质代谢、炎症因素、肝脂肪变性与肠道菌群改变密切相关。针刺可能通过调节肠道菌群的组成显著改善高脂饮食诱导的NAFLD大鼠的脂质代谢及全身炎症反应。

3.2 中医疗法修复肠道屏障 研究[56]显示，肠道黏膜屏障损伤的NASH大鼠经参葛方干预后，紧密连接蛋白Occludin的分布和表达显著升高。Occludin蛋白是维持肠道上皮细胞连接最主要的紧密连接蛋白，完整的上皮细胞屏障是肠黏膜屏障发挥正常功能的关键。该研究结果提示，参葛方可改善NASH大鼠肠上皮细胞紧密连接的破坏，修复肠道黏膜屏障，降低肠道通透性，从而减少内毒素、病原体等有害物质进入血液。另有研究[57]显示，五味子乙素干预NAFLD小鼠后可显著增加紧密连接蛋白ZO-1、Occludin等肠道黏膜屏障相关基因的表达，改善肠道黏膜屏障，降低肠道通透性，减少LPS进入肝脏，减少炎症因子释放，延缓NAFLD的发展。

3.3 中医疗法调节胆汁酸代谢 研究[58]显示，NAFLD大鼠经柴胡人参药干预后，可激活FXR信号的6种胆汁酸（鼠胆酸、猪去氧胆酸、石胆酸、6-酮基石胆酸、别胆酸、牛磺石胆酸）水平显著升高，肠道中FXR基因和蛋白的表达水平显著升高。柴胡人参药对通过激活FXR信号通路，从而调节胆固醇的代谢，减少肝脂肪的积累，减轻肝脏炎症反应，减轻肝损伤，发挥治疗NAFLD的作用。

4 小结

综上所述，NAFLD的发病与肠道菌群丰度、结构数量及多样性的改变密切相关，肠道菌群从肠-肝轴，破坏肠道屏障，调节胆汁酸代谢、引发内源性乙醇增多、诱导胰岛素抵抗、增加机体营养与能量摄入等方面参与NAFLD的发生发展。中医药疗法中的中药复方、穴位埋线、穴位贴敷、针灸治疗等对于NAFLD的疗效显著，可以通过调节肠道菌群的丰度、比例等调节代谢通路，减少脂质堆积和炎症反应，延缓肝脂肪变性，达到治疗NAFLD的目的。目前，从肠道菌群角度探讨中医疗法治疗NAFLD作用机制的相关研究较少，尤其针刺相关临床研究更少，因此本文仅从调节肠道菌群丰度、修复肠道屏障和调节胆汁酸代谢3个方面论述中医疗法通过调节肠道菌群治疗NAFLD的作用机制。笔者认为，针刺是一种安全、无副作用、疗效确切的中医外治方法，且针刺治疗NAFLD在多项研究中已显现良好效果，因此未来仍需深入研究，以期拓展NAFLD治疗方案。

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