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述评 EDITORIAL

肠肝轴–肝病防治中的重要目标

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背景资料
近年来, 针对肠-肝轴的研究成为热点, 调节肠道菌群、合理应用抗生素以及促进肠黏膜修复等在延缓慢性肝病进展中具有重要的意义. 肠道在肝病发生发展过程中起着不可忽视的作用, 可能成为肝病及其并发症防治中的新靶点.

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Gut-liver axis: An important target for prevention and treatment of liver diseases

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Abstract

The human intestine harbors a complex and diverse community of microbes that promote metabolism and digestion in their symbiotic relationship with the host. Liver diseases have long been associated with qualitative (dysbiotic) and quantitative (overgrowth) changes in the intestinal microbiota. Extrinsic factors, such as diet and alcohol, contribute to intestinal microbiota dysbiosis. Dysbiosis results in intestinal inflammation, intestinal barrier breakdown, and translocation of microbial products in animal models, further aggravating hepatic injury and inflammation. Microbial metabolites produced in a dysbiotic intestinal environment and host factors are equally important in the pathogenesis of liver diseases. In the current review, we discuss the progress in understanding the role of gut-liver axis dysfunction in the progression of non-alcoholic fatty liver disease, alcoholic liver disease and cirrhosis, and the potential application value of the restoration of intestinal homeostasis in the prevention and treatment of liver diseases.

Key Words: Intestinal microbiome; Gut-liver axis; Chronic liver disease; Prevention and treatment

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摘要

人体肠道内寄居着一个复杂、多样化的微生物群落, 促进与其共生关系的宿主的新陈代谢和消化. 肝病与肠道菌群的定性(失调)

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和定量(过度生长)改变密切相关. 外在因素如饮食、酒精等, 可促进肠道菌群失调. 在动物模型中, 菌群失调可引起肠道炎症、肠屏障破坏以及细菌性产物移位, 进而加剧肝损伤和炎症. 在失调的肠道环境中产生的细菌性产物和宿主因素在肝病发病机制中同样重要. 本文就肠-肝轴失调在非酒精性脂肪性肝病、酒精性肝病以及肝硬化进展中的作用的研究进展和恢复肠道稳态在肝病防治中的潜在应用价值进行简要综述.

关键词: 肠道菌群; 肠-肝轴; 慢性肝病; 预防和治疗

核心提示: 肝病进展过程中, 肠道菌群失调、肠黏膜通透性增加, 细菌及其代谢产物内毒素如脂多糖经门静脉造成肝脏的“二次打击”, 形成肠-肝轴的恶性循环, 加重肝脏和肠道损伤. 故阻断肠-肝轴对于肝病治疗至关重要.

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0 引言

肠道与肝脏具有共同的胚胎学起源即前肠, 二者在结构和功能上有着天然的广泛联系. 肝脏约70%的血供来源于门静脉, 肠源性营养物质和其他信号经门静脉循环传送至肝脏[1], 肝脏作为最大的免疫器官具有招募并激活免疫细胞以响应肠源性代谢物质或病源性信号的显著能力[2]. 1998年Marshall[3]提出了“肠-肝轴”概念: 肠道遭受打击后, 肠屏障功能受损, 肠道内细菌和内毒素经门静脉系统大量进入肝脏, 激活肝脏内Kupffer细胞和肝细胞等, 释放一系列炎性细胞因子[如肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)、白介素-1β(interleukin-1β, IL-1β)、IL-6和干扰素-γ(interferon-γ, IFN-γ)等], 进一步造成肠道黏膜及远隔器官损伤; 另一方面, 肝脏受损后, Kupffer细胞吞噬能力下降、免疫蛋白合成减少以及肝硬化期出现血流动力学改变等, 也会造成肠道功能受损. 肠-肝轴之间通过各种细胞因子和炎症介质相互作用和相互影响, 从而构成了一个复杂的网络结构. 对于肠-肝轴概念的理解和深入的研究有助于我们重新认识疾病的治疗理念, 在临床工作中将肠道和肝脏这两大器官作为整体施治, 将有利于肠道及肝脏疾病治疗水平的提高. 本文就肠-肝轴在各种慢性肝病发病机制及防治中的重要作用展开述评与展望.

研发前沿
肠黏膜屏障功能损伤是多因素联合交互作用的结果, 其发生机制极其复杂, 目前临床上尚缺乏直接针对肝病肠屏障修复的措施, 需要开展更加全面合理的基础及临床实验.

1 肠-肝轴与非酒精性脂肪性肝病

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是遗传-环境-代谢应激相关性肝病, 与肥胖、胰岛素抵抗(insulin resistance, IR)及血脂异常密切相关[4], 其疾病谱包括非酒精性脂肪肝(nonalcoholic fatty liver, NAFL)及由其进展而来的非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)、肝纤维化、肝硬化和肝细胞癌[5]. 目前, NAFLD是欧美等西方发达国家肝功能酶学异常和慢性肝病最常见的原因. 在我国, 由于生活习惯和饮食结构的改变, 发病率亦逐年增加. NAFLD的发病机制尚不完全清楚, 目前几乎都处于假说阶段, 占主导地位的是1998年Day等[6]提出的“二次打击”学说. 该假说认为: IR引起肝脏中脂质堆积, 形成NAFLD的第一次打击; 在此基础上, 线粒体功能障碍、氧化应激和脂质过氧化损伤则可能是NAFLD进一步发生发展的重要“二次打击”因素.

最近, 越来越多的证据表明肠道菌群在IR、肥胖和相关代谢紊乱中的作用, 针对肠道菌群与NAFLD发病机制关系的研究成为热点[7]. 肠道菌群参与NAFLD发病的机制是复杂的、多因素的, 主要包括: 调节能量平衡; 增加碳水化合物发酵成短链脂肪酸(short chain fatty acids, SCFAs); 刺激肝脏合成甘油三酯; 调节内源性大麻素系统和胆碱代谢, 后者是极低密度脂蛋白合成和肝脏脂质转运所必需的; 调节胆汁酸平衡; 产生内源性乙醇; 产生细菌源性毒素, 如脂多糖(lipopolysaccharide, LPS), 激活肝脏巨噬细胞释放促炎性细胞因子, 引起肝细胞的炎症反应[4,8]. 肠道菌群失调导致小肠中SCFAs产生增加, SCFAs是肝脏脂肪合成和糖异生的底物, 与G蛋白偶联受体(G protein-coupled receptors, GPRs)相互作用释放肽YY(peptide YY, PYY), 调节肠道蠕动和营养吸收. SCFAs刺激肝脏碳水化合物反应元件结合蛋白(carbohydrate response element binding protein,

创新盘点

本文较清楚地阐述了肠-肝轴概念, 系统地分析了肠-肝轴在非酒精性脂肪性肝病、酒精性肝病、肝硬化及其并发症如肝性脑病中的重要作用.

chREBP), 增加脂肪合成[9]. 采用无菌动物模型的研究[10]发现, 缺乏肠道菌群的小鼠可抵抗高脂饮食诱导的肥胖、脂肪肝和IR. Bäckhed等[11]研究证实无菌小鼠定植正常小鼠盲肠菌群后, 体脂含量增加60%, IR发生并且肝脏甘油三酯含量增加2倍. 将瘦素缺陷型ob/ob肥胖小鼠的盲肠菌群移植到无菌野生型小鼠, 引起这些小鼠脂肪增加和从食物中获取热量增多[12]. 从ob/ob肥胖小鼠的菌群移植可降低肝脏磷酸化腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)及其下游参与脂肪酸合成的靶点, 选择性抑制循环脂蛋白脂酶抑制剂饥饿诱导性脂肪细胞因子(fasting-induced adipocyte factor, FIAF), 促进肝脏脂肪合成及脂肪细胞内和肝脏甘油三酯沉积[9].

肠道菌群可能促进NAFLD的进展. 喂养蛋氨酸-胆碱缺乏饮食的小鼠发生NASH与肠道菌群组成的变化有关, 尤其是炎症小体缺乏引起的紫单胞菌科数目增加[13]. 炎症小体是外源性病原相关分子模式(pathogen-associated molecular patterns, PAMPs)和内源性损伤相关分子模式(damage-associated molecular patterns, DAMPs)的传感器, 调节前体细胞裂解为炎性细胞因子如前IL-1β和前IL-18[14]. 与炎症小体核苷酸结合寡聚化结构域NOD样受体蛋白3和9(nucleotide-binding domain and leucine-rich repeat containing protein 3/9, NLRP 3/9)缺失有关的菌群失调导致增加的LPS和细菌性DNA通过门静脉循环入肝, 分别激活Toll样受体4和9(toll-like receptor 4/9, TLR-4/9), 增加TNF-α表达, 诱导肝脏的炎症反应, 从而促进NASH进展为NAFLD. 将野生型小鼠和炎症小体缺失小鼠共饲养可加剧脂肪肝和肥胖[13], 为证实肠道菌群可能是这些疾病发生的关键机制提供了直接证据.

肥胖和NAFLD的治疗是具有挑战性的. 靶向肠-肝轴的益生菌、益生元和合生元有效治疗NAFLD的确切机制尚未完全阐明, 可能是通过调节肠道菌群的组成和抗菌因子的产生, 改善肠上皮通透性和功能, 调节局部和全身的免疫系统, 以及调节脂质代谢和能量平衡[15-17]. 饮食习惯通过增加产内毒素革兰阴性菌的比例, 可能加速肝纤维化进程, 这种菌群失调作为一种辅助因子促进NAFLD慢性肝损伤[18]. 故通过调整饮食调节肠道微生态系统可作为肥胖及NAFLD治疗进一步研究的问题.

2 肠-肝轴与酒精性肝病

酒精性肝病(alcoholic liver disease, ALD)是由于长期大量饮酒所致的慢性肝病. 初期通常表现为脂肪肝, 进而可发展为酒精性肝炎、酒精性肝纤维化和酒精性肝硬化. ALD在欧美国家多见, 近年我国的发病率也有上升, 据一些地区流行病学调查发现, 我国成人的ALD患病率约为4%-6%, 故ALD在我国已成为一个不可忽视的问题. 多种致病因素参与ALD的发生发展, 酒精及其代谢产物通过线粒体损伤和内质网应激诱导活性氧(reactive oxygen species, ROS)和肝细胞损伤[19,20]; 早期活化的趋化因子, 尤其是单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)和IL-18, 分别促进肝脏巨噬细胞聚集和招募肝脏中性粒细胞[21]. 研究[22]表明, 与健康对照组相比较, 无肝病证据酗酒者及酒精性肝炎或酒精相关肝硬化患者血浆内毒素(如LPS)水平较高, LPS通过TLR-4激活肝脏Kupffer细胞和聚集的巨噬细胞, Kupffer细胞的激活是ALD发病机制中的一个核心要素, 这表明肠源性毒素在ALD中的重要作用.

肠黏膜的完整性取决于肠上皮细胞肠腔面防御素保护层、肠上皮细胞间紧密连接(tight junctions, TJs)蛋白及肠壁上的肠道免疫细胞的功能. 酒精对肠道内这些功能具有直接作用或通过酒精及其代谢产物乙醛的血流分布发挥间接作用. 高浓度酒精急性摄入可引起肠上皮细胞的损伤和死亡, 血中酒精含量增加与TJ蛋白occludin、ZO-1 mRNA表达水平降低有关[22]. 在Caco-2肠上皮细胞, 酒精通过上调ROS诱导的细胞色素P4502E1增加昼夜节律蛋白、昼夜节律运动输出周期故障(circadian locomotor output cycles kaput, CLOCK)和周期生物钟2(period circadian clock 2, PER2)的表达, 从而引起肠道通透性增加[23]. 在体内, 肠黏蛋白-2缺陷改善了小鼠ALD, 这与共生菌杀伤和细菌过度生长预防的增加相关[24]. 此外, ALD本身可通过增加血循环中TNF-α、IL-1β水平破坏TJs, 促进肠黏膜炎症反应, 降低肠屏障功能.

肠道细菌过度生长和菌群失调是ALD患者“肠漏”发生机制中的重要因素[25,26]. 体外研究[27]表明, 酒精直接并选择性作用于细菌的

生长, 肠道细菌过度生长产生乙醇反过来会影响肠道通透性. 酒精诱导肠道菌群改变的宏基因组分析表明, 酒精喂养小鼠可使其肠道细菌多样性减少, 并且随着时间推移出现菌门转化, 正常喂养小鼠肠道菌群中拟杆菌门和厚壁菌门占大多数, 酒精喂养可明显增加放线菌门的数目, 且厚壁菌门增加的比例高于拟杆菌门[28]. ALD小鼠模型的另一项研究[29]表明, 细菌移位出现在菌群改变之前, 并与小肠中杀菌的C型凝集素Reg3b和Reg3g的表达降低有关. 慢性酒精喂养也会改变胃肠道内容物的代谢成分, 从而改变胃肠道微生物的营养来源[30]. 例如, 酒精喂养导致肠道中所有氨基酸和支链氨基酸的减少[30], 这表明慢性酒精喂养可以直接和间接地改变肠道微生物的组成.

大多数研究已经表明, 探索能够防止酒精诱导的“肠漏”和/或肠源性炎症信号进入肝脏的干预措施对于阻止或延缓ALD的发展具有重要作用. 在酒精灌胃大鼠ALD模型中, 鼠李糖乳杆菌GG(lactobacillus rhamnosus GG, LGG)显著减轻酒精性脂肪性肝炎、酒精诱导的肠道高通透性以及酒精诱导的肠、肝和全身的氧化应激[28]. 在乙醇暴露期间给予合生元可通过恢复肠道通透性和粪便菌群结构抑制血浆内毒素水平增高, 从而改善酒精性肝损伤[31]. 粪菌移植作为一种治疗方法的作用在艰难梭菌感染中体现出来[32]. 基于观察的研究表明, ALD中肠道菌群组成改变, 推测粪菌移植可改善ALD的预后或严重程度.

3 肠-肝轴与肝纤维化、肝硬化

肝纤维化是慢性肝脏炎症, 包括NAFLD、ALD、病毒性肝炎、胆汁淤积性肝病和自身免疫性肝病等引起的创伤愈合反应, 可导致终末期肝病或肝硬化, 最终破坏肝脏的代谢功能. 肝纤维化患者常无症状, 但是否进展为肝硬化是其发病率和死亡率的主要决定因素[33]. 肝硬化主要临床并发症是食管静脉曲张破裂出血和肝性脑病(hepatic encephalopathy, HE)、自发性腹膜炎、肝肾综合征等. 出现并发症的肝硬化患者预后较差, 往往提示是否需肝移植[34]. 一些研究[35-39]评估了肝硬化患者肠道菌群的种类组成, 发现肝硬化患者肠道菌群的一个共同特点是潜在的致病菌数目增加, 同时伴随着有益菌比例的减少. 不同病因所致肝硬化患者中粪便微生物群落是相似的. 因此, 终末期肝病的特征如胆汁流量减少可以决定肠道菌群的构成. 但基于16S rRNA基因的菌群测序, 与乙型肝炎肝硬化或健康人相比较, 酒精性肝硬化患者的粪便微生物群落以普雷沃氏菌科显著增加为主[35]. 病因特别是与酒精相关的, 似乎有助于终末期肝病患者肠道菌群构成的改变. 空肠穿刺细菌定量培养分析表明, 大多数肝硬化患者小肠细菌过度生长[40,41]. 与无肝硬化的人相比较, 肝硬化患者不仅微生物群落具有分类学上的差异, 肠道细菌负荷也增加. 导致肝硬化患者小肠细菌过度生长的因素包括: 小肠蠕动受损[42]、胆汁流量减少[43]以及免疫球蛋白A[43]和抗菌分子的分泌异常[44]. 在肝硬化伴有腹水和活菌移位至肠系膜淋巴结的大鼠, 潘氏细胞产生较低水平的防御素和Reg3分子, 对肠杆菌科的抗菌活性降低[44]. 潘氏细胞的功能在肝硬化进展过程中是如何损害的鲜为人知. 肠道的宿主防御受损可能因此促进终末期肝病肠道菌群的定性(失调)和定量(细菌过度生长)改变.

近年来, Bajaj等[36,37,45]发表了3项关于HE中致病性肠道菌群与不良认知和炎症关系的研究, 结果表明黏膜表面的重要过程如细菌移位、免疫功能障碍参与了HE的发病机制. 肝硬化患者粪便菌群随着Child-Turcotte-Pugh评分和终末期肝病模型评分的增加以及隐性或显性HE的发生而改变. 尽管粪便菌群没有差异, 但伴和不伴HE的肝硬化患者乙状结肠黏膜菌群显著不同[36]. 以原籍菌/有益菌与非原籍菌/致病菌比值作为肝硬化菌群失调率, 正常对照组和代偿期肝硬化患者的肝硬化菌群失调率显著高于失代偿期肝硬化患者[45].

非吸收性抗生素利福昔明净化肠道可减轻内毒素血症和肝病的严重性[46], 抑制肝纤维化小鼠TLR-4依赖性纤维连接蛋白和血管内皮细胞之间的交叉对话[47], 从而阻止肝纤维化的进展和门静脉高压的发生. 利福昔明治疗后, 轻微性HE患者的认知功能明显改善, 细菌种类与代谢产物如血氨、芳香族氨基酸, 以及氧化应激呈负相关, 但没有观察到明显的菌群改变[48], 表明利福昔明治疗引起细菌代谢功能而不是数量的变化, 其作用机制可能与改善认知相关菌群的代谢功能有关. 一项随机对照试验[49]表明, 益生菌VSL#3降低肝硬化患者因HE住院

应用要点

对于肠-肝轴概念的理解和深入的研究有助于大家重新认识疾病的治疗理念, 在临床工作中将肠道和肝脏这两大器官作为整体施治, 将有利于肠道及肝脏疾病治疗水平的提高.

名词解释
菌群: 在一个特定环境中寄居的微生物群落, 如皮肤或肠道的菌群; 失调: 体表或体内的微生物失衡, 常局限于肠道; 益生菌: 一种活的微生物, 被人类或动物摄入后对其健康有利.

的风险, 以及Child-Turcotte-Pugh评分和终末期肝病模型评分. 益生菌LGG可降低内毒素和TNF-α水平, 调节肠道菌群(肠杆菌科减少, 梭菌科和毛螺菌科相对丰度增加), 以及代谢产物/微生物相关的氨基酸、维生素和次级胆汁酸代谢改变[50]. 在四氯化碳诱导的肝纤维化大鼠模型中, 合生元调节肠道通透性和菌群结构变化, 改善肝脏炎症和纤维化[51]. 表明肠道菌群可作为肝损伤治疗的一个关键点.

4 结论

肠道菌群促进NAFLD和ALD的发生发展, 并介导了终末期肝病并发症的发生. 肠道菌群和肝病患者之间似乎存在关联, 但肠道菌群改变引起肝脏疾病主要在动物模型中体现出来, 很少与NAFLD和ALD患者的代谢和免疫特征相关联. 故进一步的研究应集中于肝病患者, 评估其微生物基因表达、蛋白和代谢产物, 提高对肠道及其微生物之间微妙平衡的理解可增加对肝病发病机制和治疗策略的新见解. 已有足够的证据证实调节肠道菌群治疗肝病的合理性和有效性, 最终的目标是修复肠屏障功能、恢复肠道内稳态, 进而延缓甚至阻止肝病进展.

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同行评价

本文就肠-肝轴失调在非酒精性脂肪性肝病、酒精性肝病及肝硬化中的作用研究和恢复肠道稳态在肝病防治中的潜在应用价值进行系统综述. 阐述严密, 论证充分, 结论合理. 对当前肝病的研究具有指导意义.

microbiota was assessed in cirrhotic patients with hepatitis B virus infection. Intestinal microbiota of HBV cirrhotic patients. *Microb Ecol* 2011; 61: 693-703 [PMID: 21286703 DOI: 10.1007/s00248-010-9801-8]

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