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述评 EDITORIAL

肠道菌群失调——非酒精性脂肪肝病治疗新靶点

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背景资料

随着人们生活方式的改变, 非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)已成为全球公共健康问题. 但迄今为止, 其发病机制尚未明确, 也仍没有确切疗效的药物, 考虑到肝脏和肠道起源于同一胚层, 两者可相互影响, 且越来越多的文献也表明肠道菌群在NAFLD中起着举足轻重的作用, 可能会成为治疗NAFLD的重要靶点.

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Imbalance of intestinal flora: A new target for nonalcoholic fatty liver disease treatment

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a clinical pathologic syndrome characterized by steatosis and storage of hepatic parenchymal cells due to liver damage caused by factors other than alcohol. In recent years, with the change of people's lifestyle, NAFLD has become a global public health problem. The incidence of NAFLD is associated with obesity, type-2 diabetes and other metabolic syndromes. More and more studies indicate that intestinal flora is closely related with the occurrence and development of NAFLD: (1) Intestinal flora can promote the energy metabolism of the host; (2) Intestinal flora can induce the body lipid metabolism disorders and liver cell lipid accumulation; and (3) Intestinal flora can increase the intestinal mucosal permeability and activate inflammation. This article summarizes the relationship between NAFLD and intestinal flora imbalance, which may be a new target for NAFLD treatment.

Key Words: Non-alcoholic fatty liver disease; Intestinal flora; Energy metabolism; Lipid accumulation; Inflammation

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摘要

非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)是一种除饮酒以及其他肝损害因素外所致的以肝实质细胞脂肪变性

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及贮积为特征的临床病理综合征. 近年来, 随着人们生活方式的改变, NAFLD已成为全球公共健康问题, 其发生率与肥胖、2型糖尿病等代谢综合征相关. 越来越多文献表明肠道菌群与NAFLD的发生发展关系密切: (1)肠道菌群失调可促进宿主吸收更多的能量; (2)肠道菌群失调可诱导机体脂质代谢紊乱, 肝细胞脂质蓄积; (3)肠道菌群失调可增加肠黏膜通透性、促发炎症. 因此, 本文就肠道菌群与NAFLD关系进行整理, 为寻找治疗NAFLD的药物提供新靶点进行简要综述.

关键词: 非酒精性脂肪肝病; 肠道菌群; 能量代谢; 脂质蓄积; 炎症反应

核心提要: 越来越多文献表明肠道菌群失调在促进宿主能量吸收、脂质代谢、炎症反应中发生中起着举足轻重的作用, 而这些过程恰好是非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)发生发展中的重要环节, 本文参考大量文献来阐述肠道菌群失调在NAFLD中起着举足轻重的作用, 并通过调节肠道菌群的治疗表现, 如使用抗生素、益生元、益生菌等药物为大家打开NAFLD治疗的另一扇窗户, 并为研发治疗NAFLD药物寻找新靶点.

唐外姣, 周本杰. 肠道菌群失调——非酒精性脂肪肝病治疗新靶点. 世界华人消化杂志 2017; 25(22): 2000-2006 URL: http://www.wjgnet.com/1009-3079/full/v25/i22/2000.htm DOI: http://dx.doi.org/10.11569/wcjd.v25.i22.2000

0 引言

非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)是一种除饮酒以及其他肝损害因素外所致的以肝实质细胞脂肪变性及贮积为特征的临床病理综合征, NAFLD控制不佳可由单纯性脂肪肝进展为非酒精脂肪性肝炎(nonalcoholic steatohepatitis, NASH)、肝纤维化和脂肪性肝硬化, 甚至肝衰竭[1]. 研究[2]显示在西方国家有大约20%-30%的NAFLD患者, 其中2%-5%为NASH患者, 1%-2%NASH患者则有肝硬化的趋势. 因其高发病率, 各个国家投入治疗的经费高昂, 据悉美国为治疗NAFLD投入的经费大约为103千亿美元, 而英国、德国、法国以及意大利总共大约为35千亿欧元[3]. 西方国家NAFLD高发病率与其富含碳水化合物和脂肪的饮食有很大的关系. 越来越多的证据[4]也表明高脂饮食可诱导肠道菌群结构发生改变, 从而促进宿主能量吸收, 诱导患者出现肥胖、2型糖尿病等代谢综合征. 另一层面, 肝脏和肠道起源于同一胚层, 通常认为这两者可相互影响. 肝脏通过门静脉血液循环, 是肠道吸收营养物的首道防线, 反过来, 肝脏也是肠道菌群代谢产物的首次过滤器[5]. 有研究[6,7]指出慢性肝病患者常伴随着肠道菌群失调, 肝病越严重其肠道菌群失调程度越明显, 两者有一定的相关性. 在本文中, 我们将从能量吸收、脂质代谢、炎症反应以及通过调节肠道菌群的治疗表现, 如使用抗生素、益生元、益生菌等几个方面阐述已知的NAFLD发病机制中肠道菌群的作用.

研发前沿
肠道菌群失衡所导致的能量吸收差异及脂质代谢紊乱、内毒素等代谢产物的增多、肠黏膜通透性的增加及其分子机制在NAFLD发生发展的作用是目前该领域亟待研究的热点、重点.

1 肠道菌群可促进宿主能量吸收

肠道菌群与其人类宿主在几千年内发展出共生关系, 并在机体能量代谢方面发挥非常重要的作用. 一方面, 肠道菌群可将不被消化的植物多糖发酵为短链脂肪酸(short-chain fatty acids, SCFAs)如丙酸、丁酸等. SCFAs如丁酸盐可通过门静脉循环进入到肝脏, 并产生乙酰辅酶A进入柠檬酸循环, 加强糖原合成, 减少葡萄糖氧化和增加肝糖原储存, 从而建立膳食纤维消耗和葡萄糖耐量改善之间的联系[8]. 另一方面, SCFAs还可刺激肠激素的分泌, 如影响饱腹感的调节剂胰高血糖素样肽1(glucagon-like peptide-1, GLP1)和肽YY(peptide YY, PYY). GLP1和PYY的升高可改善宿主口服葡萄糖耐量, 胰岛素敏感性和瘦素水平[9]. Gordon小组[10]通过对无菌小鼠和肠道内定植正常菌群的普通小鼠进行对比, 发现在给予同样食物(57%碳水化合物, 5%脂肪)的情况下, 普通小鼠相较于无菌小鼠自身脂肪总量增加了42%, 而每天食物消耗却减少29%. Turnbaugh等[11]的研究表明, 将肥胖小鼠的肠道菌群移植到无菌小鼠体内, 2 wk后无菌小鼠就和肥胖小鼠一样, 体质量增加明显, 且排泄物中的能量更低, 具有更高的能量吸收效率. 与非肥胖患者相比, 肥胖患者体内的肠道菌群结构发生了失调, 进一步研究表明, 通过移植肥胖患者肠道菌群至健康志愿者, 可引起健康志愿者明显肥胖, 促进能量吸收[11-13]. 在测序研究中显示, NAFLD患者体内的肠道菌群结构发生了根本性改变. 与空

相关报道 比较新的观点是肠道菌群可将不被消化的植物多糖发酵为短链脂肪酸如丙酸、丁酸等. 而短链脂肪酸在NAFLD中起着举足轻重的作用.

白组相比, NAFLD患者具有较少比例的拟杆菌, 瘤胃菌科的比例也相对较低[14]. 另外, 有报道[15]称产甲烷古菌可通过对肠道代谢产物氢气的消耗加速细菌发酵膳食多糖. Basseri等[16]采用问卷形式对患者肠道症状严重度进行评分和检测患者呼吸气体中的甲烷含量, 结果发现呼出气甲烷检测阳性的患者体质量指数明显大于甲烷检测阴性的患者, 且甲烷检测阳性患者的便秘症状相较于阴性患者更严重, 该试验表明越肥胖的人群, 其体内肠道菌群中所含的产甲烷古菌可能更多. 进一步研究发现, 肥胖(ob/ob)小鼠肠道菌群基因组携带KEGG酶促反应路径中催化淀粉/蔗糖、半乳糖和丁酸盐代谢的酶等, 这些酶可催化人类自身无法利用的多糖裂解. 除此之外, 肠道菌群结构的改变如某种细菌的增多, 可能会导致机体在能量吸收方面产生差异, 如人们发现多形拟杆菌基因组就包含大量糖苷裂解酶和多糖裂解酶的编码基因, 这也使得多形杆菌可充分利用各种多糖进而促进机体能量吸收[17]. 这也提示我们, 饮食习惯的不同可以导致宿主肠道菌群结构的差异, 而产能多、效率高的菌群结构可使宿主得到更多的能量, 长期积累就可能进一步导致肥胖及相关代谢性疾病的产生.

2 肠道菌群可促进脂质代谢

Bäckhed等[10]的研究认为肠道菌群可促进机体对多糖的吸收并上调碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, ChREBP)/固醇反应元件结合蛋白(sterol regulatory element binding protein, SREBP)的表达, 有文献证实ChREBP作用的靶基因主要是控制脂质合成及糖酵解等, Iizuka等[18]敲除ob/ob小鼠体内的*ChREBP*基因后, 发现小鼠体质量明显下降且脂肪肝有明显改善. SREBP主要是在肝脏和脂肪细胞中表达, SREBP表达过度可引起机体糖脂代谢紊乱[19]. 而这两者同时过表达可促进机体脂质代谢紊乱[20], 导致甘油三酯在肝细胞中蓄积, 从而增加宿主肝脏脂肪合成; 同时, 肠杆菌的增加可抑制禁食诱导脂肪因子的表达, 进一步减少脂蛋白脂肪酶(lipoprteinlipase, LPL)抑制物生成, 从而使LPL生成过多, 促进脂质在细胞中沉积, 诱发机体的脂质代谢紊乱[21-23]. 另外, Spencer等[24]发现在胆碱缺乏时, 人体肠道菌群和肝脂肪水平直接相关. 众所周知, 胆碱是一种重要的细胞膜的磷脂组成成分, 也是肝脏脂肪代谢中的关键成分, 由极低量的脂蛋白装配而成. 肠道菌群能通过将膳食性胆碱转化为肝毒性的三甲胺N-氧化物, 降低宿主自身对胆碱的利用, 以致极低密度脂蛋白分泌减少、肝脏甘油三酯蓄积, 促进NAFLD的发生[10]. 同时, 最近有研究[25]发现富含脂肪的饮食可使宿主胆汁酸的成分改变, 同时伴随着宿主肠道菌群组成改变. 而胆汁酸主要由胆固醇转变过来, 他可促进机体对脂肪和脂溶性维生素的吸收、转运和分配等, 并可作为一种信号分子激活法尼酯衍生物X受体(farnesoid X receptor, FXR)继而调节脂质代谢[26,27]. 肠道菌群还可上调胆汁酸膜受体(G protein coupled bile acid receptor 5, TGR5)活性进而刺激胆汁酸, 降低肝脏脂质水平[28,29]. 以上文献结果表明肠道菌群可通过调节胆汁酸代谢和FXR/TGR5信号传导, 进一步促进NAFLD的进程[30].

3 调节肠黏膜通透性、促发炎症

非酒精性脂肪肝患者往往伴随着小肠细菌过度生长(small intestinal bacterial overgrowth, SIBO)[31], Shanab等[32]报道了80例NASH和32例健康志愿者乳果糖呼气试验的结果, 发现NASH患者组SIBO的患病率明显高于健康志愿者(77.8% *vs* 31.3%). Fan等[33]及Wu等[34]发现给高脂饮食诱导的NASH大鼠口服乳果糖或庆大霉素, 大鼠体内血清转氨酶和肝组织炎症的坏死程度可显著减轻. 上述研究提示SIBO可能是NAFLD“二次打击”的重要因素. 另外, Cani等[35]和Muccioli等[36]发现高脂饮食会增加革兰阴性菌的比例, 并因此增加脂多糖(lipopolysaccharide, LPS)的释放, 使其血浆内毒素浓度增加2-3倍, 到达代谢性内毒素血症的阈值. 而机体内毒素的增加可激活肠道黏膜细胞中的腺苷环酶, 进而导致肠黏膜上皮细胞水肿、坏死、脱落等, 继而损伤肠黏膜层, 造成肠黏膜通透性升高[37]. Miele等[38]的实验显示在NAFLD患者中, 肠道通透性明显与肝脏脂肪变的严重情况成正相关, 同时伴随着血清炎症因子显著上升.

研究进一步发现高脂饮食可上调CD14受体并促进LPS的分泌, 从而产生全身性胰岛素抵抗, 这与单独给予小鼠注射LPS只产生肝脏

胰岛素抵抗不同, 高脂饮食改变小鼠肠道菌群结构可能是这其中的关键因素[39]. 益生元可促进肠道有益细菌生长, 增进宿主健康. 有文献指出益生元能够促进革兰阳性菌的生长, 抑制高脂饮食导致的革兰氏阴性杆菌的生长, 从而缓解肝脏炎症及胰岛素抵抗产生[35].

4 肠道菌群可代谢产生肝毒性物质–乙醇

NAFLD与酒精性脂肪性肝病在病理上非常相似, 而乙醇已被充分证明其对肠道菌群失调以及炎症反应有影响. 乙醇暴露的环境可从根本上改变了机体肠道菌群结构, 如肠杆菌科和变形菌门数量增多, 而拟杆菌的水平下降[40,41]. Zhu等[42]发现, NASH患者肠道菌群所含大肠埃希菌数量及血乙醇浓度均显著高于与单纯肥胖及健康志愿者(P<0.01). 另有研究[43]指出大肠埃希菌可刺激机体产生更多的内源性乙醇. 内源性乙醇在机体内代谢为乙醛, 而一旦机体内乙醛脱氢酶活性降低, 就会导致肠源性乙醇/乙醛在机体内蓄积[44]. 肠源性乙醇/乙醛可通过门静脉血流进入肝脏, 继而诱发肝细胞脂肪变性; Le Poul等[45]研究还发现乙醛能改变小肠上皮细胞之间的紧密连接, 从而增加肠黏膜通透性. 且乙醛进入肝细胞内能够破坏线粒体功能, 使肝细胞易出现氧化损伤[46]. 由此可见, NAFLD患者体内可因肠道菌群结构改变从而导致内源性乙醇产生过多, 诱导及加重NAFLD的发生发展.

5 肠道菌群可作为新靶点寻找防治NAFLD的药物

如前所述, 肠道菌群能从多个方面参与宿主能量代谢的调控, 是一种可诱发宿主发生代谢性疾病的具有遗传特性的环境因子. 因此, 以肠道菌群为靶点寻找防治NAFLD的药物具有重要意义, 可调控宿主肠道菌群的抗生素、益生菌及中药等药物, 成为防治NAFLD的研究热点. Carvalho等[47]发现给予高脂喂养小鼠抗生素后, 体质量下降, 肠道菌群也发生了改变, 伴随着小鼠体内血液内毒素水平减少, 肝脏组织的炎症水平降低, 同时长期高脂饮食所致的机体胰岛素抵抗也得到了改善.

各种研究[48,49]已经证明乳杆菌可减轻机体炎症反应, 并且对内毒素血症是有益的. 益生菌同样证实可通过调节细胞炎症从而改善肝细胞脂肪变性和葡萄糖耐量. Fan等[33]在高脂饲料诱发的NASH大鼠模型中发现乳果糖可以降低大鼠肝脏炎症和门静脉LPS水平. 其他的NAFLD模型也证实低聚果糖具有阻止肝脏脂肪变性的有益作用[50]. Xu等[51]发现在动物饲料中添加益生菌可以降低NAFLD动物肝脏内的脂肪含量. 同时, Vajro等[52]发现, 给予20例NAFLD患儿服用乳杆菌, 8 wk后患者的AST、ALT改善. Aller等[53]也发现联合使用乳杆菌和链球菌, 可观察到NAFLD患者AST、ALT下降. 临床试验也表明双歧杆菌联合果寡聚糖可改善NAFLD患者内毒素血症和肝细胞脂肪变性[54]. 在试验中给予NASH患者服用益生菌及益生元、维生素B及叶酸组成的混合物2 mo后, NASH患者体内相应的肝损伤指标水平均比治疗前明显降低[55].

传统中医药因其成分多, 在治疗NAFLD时具有不良反应小、作用靶点多的特点. 中药通常以汤剂形式口服给药, 经过机体消化道在局部或全身起作用, 而消化道(尤其是肠道)是机体微生物寄生的最主要场所, 与肠道菌群的关系十分密切[56]. 目前已知的可通过调控肠道菌群而防治NAFLD的中药成分主要有: 生物碱、黄酮类、皂苷、多糖等[57]. 研究[58]发现含有异喹啉生物碱的盐酸小檗碱可通过调控机体肠道菌群从而起到防治NAFLD的作用. 绿茶中含有茶多酚及皂苷类成分从而具有抗氧化作用, Liu等[59]发现绿茶茶汤可调节肠道菌群结构及改变其多样性从而起到减脂效果.

6 结论

肠道细菌种类结构的变化可影响机体能量的生成及吸收, 这种微小的能量差长期累积可诱导肥胖等代谢性疾病的产生, 同时, 肠道菌群代谢产物如肠源性内毒素LPS、内源性乙醇的合成, 使得机体肠黏膜通透性增高和肠道菌群移位, 继而诱发肝细胞脂肪蓄积及促进肝脏炎症发生. 另外, 文献也证实一些抗生素、益生菌、益生元及中药可通过调控肠道菌群起到延缓NAFLD进展的作用, 因此, 肠道菌群可作为寻找防治NAFLD药物的新靶点.

创新盘点

本文系统阐述了肠道菌群失衡所导致的宿主能量吸收差异、脂质代谢紊乱和炎症反应在NAFLD进展中的作用.

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应用要点

本文探讨肠道菌群失调是否可作为NAFLD治疗的新靶点，并寻找与此相关的治疗药物.

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名词解释

胰高血糖素样肽1(GLP1): 回肠内分泌细胞分泌的一种脑肠肽, 目前主要作为2型糖尿病药物作用的靶点. 由于GLP-1可抑制胃排空, 减少肠蠕动, 故有助于控制摄食, 减轻体质量;
肽YY(PYY): 近年新发现的一种胃肠道肽类激素, 他主要由结肠、回肠黏膜的内分泌细胞分泌. 其生物学作用包括: 收缩血管、减少胰腺外分泌、抑制胃肠运动和胃酸分泌等.

同行评价

本文具有一定的先进性和可读性, 较好地反映了当前国内外对肠道菌群与NAFLD相关研究的重要进展.

Lactobacillus casei Shirota protects from fructose-induced liver steatosis: a mouse model. *J Nutr Biochem* 2013; 24: 531-538 [PMID: 22749137 DOI: 10.1016/j.jnutbio.2012.01.014]

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