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文献综述 REVIEW

小肠菌群与肠道及代谢性疾病

秦会平, 王学红

秦会平, 王学红, 中南大学湘雅二医院消化内科 湖南省长沙市 410011

秦会平, 在读硕士, 主要从事肠道微生态与肥胖的研究.

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作者贡献分布: 查找文献、写作由秦会平完成; 王学红审校.

通讯作者: 王学红, 副教授, 硕士生导师, 410011, 湖南省长沙市芙蓉区人民中路139号, 中南大学湘雅二医院消化内科. wxh05271@126.com
电话: 0731-85295149

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Relationship between small intestinal microbiota and bowel and metabolic diseases

Hui-Ping Qin, Xue-Hong Wang

Hui-Ping Qin, Xue-Hong Wang, Department of Gastroenterology, the Second Hospital of Xiangya, Central South University, Changsha 410011, Hu'nan Province, China

Correspondence to: Xue-Hong Wang, Associate Professor, Department of Gastroenterology, the Second Hospital of Xiangya, Central South University, 139 Renmin Middle Road, Furong District, Changsha 410011, Hu'nan Province, China. wxh05271@126.com

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Abstract

Microbiota plays a vital role in human health and diseases. Colonic microbiota has been deeply studied because it is abundant and easy to get. The small intestine is the main place where most nutrients are digested and absorbed, and the microbiota which dwells in the small intestine has also profound effects on the host. As it is difficult to obtain samples from the small intestine, small intestinal microbiota composition is seldom reported. A few recent studies show that a significant distinction exists in microbiota between the small intestine and colon. The small intestinal microbiota participates in energy storage, intestinal endocrine function and immune maturation of the host. Therefore, more and more studies are focusing on the small intestinal microbiota. This paper reviews recent advances in understanding the relationship between small intestinal microbiota and related diseases.

Key Words: Small intestinal microbiota; Inflammatory bowel disease; Irritable bowel syndrome; Celiac disease; Diabetes; Obesity

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摘要

肠道菌群对人类健康与疾病有重要作用. 结肠菌群因丰度高且标本易于获取而研究较为深入. 小肠是营养物质消化、吸收的主要场所, 聚居在其中的微生物也具有不容忽视

背景资料
小肠与结肠理化环境存在很大差异, 因此群落结构也不尽相同. 小肠解剖部位特殊, 标本不易获得, 故对其群落结构研究较少. 然而小肠菌群结构变化与疾病存在怎样的因果关系, 这也逐渐引起研究者的关注.

同行评议者
高泽立, 副教授, 周浦医院消化科, 上海交通大学医学院九院周浦分院

研发前沿
疾病状态下, 特殊细菌增加或减少, 当调节小肠菌群至正常, 疾病得到缓解. 因为个体差异, 菌群易受各种因素影响, 目前对于具体哪些菌种参与疾病发生、转归仍存在争议.

的功能. 但因小肠菌群标本难以获取而不易研究. 近年来, 有研究表明, 小肠菌群参与机体调节能量存储、肠内分泌、促进肠道免疫系统发育等, 小肠菌群与结肠菌群存在明显差异. 小肠菌群已越来越受研究者关注, 本文就小肠菌群与相关疾病关系研究进展进行综述.

关键词: 小肠菌群; 炎症性肠病; 肠易激综合征; 乳糜泻; 糖尿病; 肥胖

核心提示: 小肠是营养物质消化吸收的主要场所, 定居于小肠的微生物在促进能量吸收的同时也参与机体疾病的发生、发展和转归. 前人研究多集中于粪便和结肠菌群, 近年来, 部分学者注意到小肠菌群与消化道本身、代谢性疾病的关系.

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0 引言

人类是由自身和共生微生物组成的“超级生物体”, 肠道内聚居的微生物种类就超过1000种, 数量达10-100万亿, 相当于人体自身细胞总数的10倍[1,2], 拥有3.3百万独特基因, 是人类基因数的150倍[3]. 硬壁菌门、拟杆菌门、变形菌门、放线菌门是四种主要的肠道细菌, 硬壁菌门、拟杆菌门比例占90%以上[2]. 肠道菌群数量庞大、功能复杂, 能将宿主不能消化的多糖酵解为单糖和短链脂肪酸(short chain fat acid, SCFA), 增加宿主能量吸收, 促进肠上皮细胞增殖分化和肠道免疫系统的发育成熟, 抵御病原微生物入侵[4]. 肠道微生物与人类健康疾病息息相关, 动物或人类的结肠、粪便菌群分析表明, 肠道菌群与炎症性肠病(inflammatory bowel disease, IBD)、肠易激综合征(irritable bowel syndrome, IBS)、乳糜泻(celiac disease, CD)、肥胖、糖尿病、脂肪肝、中枢神经系统疾病有关[4]. 小肠是人类营养物质消化吸收的主要场所, 几乎所有的蛋白质、脂质、单糖(如葡萄糖)、部分二糖(乳糖、蔗糖)和淀粉在小肠被吸收, 而结肠吸收的营养只占10%[5]. 肠道不同节段菌群种类和丰度差异很大, 由于肠道蠕动速度快、肠分泌杀菌物质导致小肠菌群数量较少(10^4/mL-10^8/mL)[6], 但小肠菌群具有调节免疫、代谢、内分泌等功能, 对宿主健康有多方面影响[7]. 由于小肠位置特殊, 标本不易获得, 目前研究疾病与菌群关系的标本绝大多数取自结肠或粪便, 对小肠菌群研究不多. 本文就近年来小肠菌群与相关疾病关系研究进行综述.

1 小肠菌群概述

小肠菌群与结肠菌群存在明显差异, 且易受环境、饮食、时间影响, 具有波动性大、不稳定性、物种多样性较低、有独特优势菌等特点[8,9]. 培养、非培养方法均被用于小肠菌群检测. Hayashi使用末端限制性片段长度多样性(terminal restriction fragment length polymorphism, T-RFLP)方法对空肠、回肠样本菌群测序显示小肠菌群大部分为需氧菌和兼性厌氧菌, 链球菌属、乳酸杆菌属、γ变形菌纲的肠球菌属、拟杆菌属在小肠中比例均较高[10]. Zilberstein等[11]对健康人小肠标本进行培养, 观察到十二指肠主要菌是韦荣氏菌属、乳酸杆菌属、梭菌属, 空肠、回肠仍主要为拟杆菌属、变形杆菌属. Wang等[12]通过聚合酶链式反应(PCR)方法发现空肠链球菌占60%以上, *Clostridium clusters XIVa*和*IV*均是远端回肠的优势菌. 对健康人群十二指肠样本进行Illumina高通量测序, 观察到较高比例的蓝藻菌门、放线菌门[13]. 很多证据表明小肠微生物含量低于结肠, 物种丰富性也较低, 但最近有研究者得到与前人相反结果, 454高通量测序小鼠不同肠段菌群, 证实十二指肠物种多样性与结肠相当, 空肠回肠物种多样性稍低, 同样的检测方法观察到十二指肠物种多样性高于直肠[14,15]. 目前研究表明, 链球菌属、韦荣氏菌属、乳酸菌杆菌属是小肠主要菌群, 已有研究[16]证实人类小肠分离出的链球菌属、韦荣氏菌属、肠球菌属、乳酸菌杆菌属参与小肠免疫调节.

2 小肠菌群与肠道疾病

2.1 小肠菌群与IBD IBD是一种慢性、自发性、反复发作的胃肠道炎症性疾病, 主要包括溃疡性结肠炎和克罗恩病[17]. IBD是环境、个体易感性及肠道菌群相互作用的结果[18]. 共生菌和

自身免疫系统在IBD中起重要作用, 肠道菌群细胞成分与TLRs作用激活核因子-κB(nuclear factor-κB, NF-κB)信号通路, 促炎症因子、黏附分子、主要组织相容性抗原分泌增加引起IBD, 肠道菌群能破坏肠上皮细胞完整性而加剧炎症[19]. 许多研究[20,21]表明肠道菌群与IBD相关, 拟杆菌门、硬壁菌门减少, 变形菌门、放线菌门增加. 侵袭性大肠杆菌、艰难梭菌、脆弱类拟杆菌、鸟分枝杆菌副结核亚种(*Mycobacterium avium subsp. Paratuberculosis*, MAP)加剧肠道炎症[17], 柔嫩梭菌能改善IBD患者炎症状态[22]. 肠道菌群与IBD关系的研究样本多数来自于结肠或粪便, 对于小肠菌群变化了解较少. Suchodolski等[18,23]分析IBD动物模型的小肠活检样本菌群, 发现十二指肠菌群门水平变形菌门增加, 拟杆菌门、硬壁菌门和梭杆菌门减少, 属水平以*Diaphorobacter*和不动杆菌属增加为主, 一些参与SCFA代谢且具有保护肠道作用的菌群如瘤胃球菌科、韦荣氏球菌科和毛螺菌科减少. IBD患者手术获取小肠标本, 与非IBD患者相比, 前者小肠变形菌门明显增加, 芽孢杆菌纲丰度较低, 拟杆菌门、毛螺菌科无明显差异[20]. 小肠菌群与IBD关系密切, 但仍需进一步深入研究, 为IBD诊治提供相关理论依据.

2.2 小肠菌群与IBS IBS是一种以腹痛、腹部不适、腹胀和大便性状改变(腹泻、便秘或两者交替出现)为主要表现的疾病, 全球发病率为4%-30%, 肠道菌群在IBS病理生理及临床症状出现中起重要作用[24,25]. 许多粪便菌群研究揭示IBS患者存在肠道菌群失调, 如变形菌门增加, 尤以包含多种致病菌的未分类肠杆菌纲增加明显, 韦荣氏球菌属、多形拟杆菌、铜绿假单胞菌、*Ruminococcus productus-Clostridium coccoides*增多可能与肠上皮细胞炎症及腹胀等症状相关, 而具有抗炎、保护肠黏膜作用的柔嫩梭菌、益生菌如双歧杆菌、乳酸菌减少[26,27]. IBS患者常合并有小肠细菌过度生长综合征[24], 因此近年来小肠菌群变化与IBS关系引起学者关注. 对比IBS患者与健康人群十二指肠菌群发现, IBS患者双歧杆菌比例明显减少, *B. catenulatum*减少最显著, 提示调节小肠*B. catenulatum*水平可能对IBS患者有益[28]. 使用变性梯度凝胶电泳(denaturing gradient gel electrophoresis, DGGE)方法分析IBS患者十二指肠菌群, 假单胞菌属、克雷伯杆菌属比例最多, 而健康对照组主要为沙雷氏菌属、不动杆菌属、泛生菌属和未培养的梭菌目, IBS患者假单胞菌、克雷伯菌属明显增加, 可能与IBS病理生理有关[29]. 然而也有学者比较35例IBS患者与16名健康人小肠菌群, 结果出乎意料, 他们观察到IBS患者小肠菌群门水平及属水平主要菌群与健康人群无明显差异, 普雷沃氏菌是主要的小肠菌[30]. 小肠菌群与IBS发病及转归是否相关仍存在争议, 如果相关, 那么哪些菌促进IBS进展呢? 这都需要研究者进一步探索.

2.3 小肠菌群与CD CD是一种自身免疫性疾病, 患者对食物中麦麸不耐受, 摄入的麦麸引起炎症反应导致小肠绒毛萎缩、肠壁渗透性增加, 有研究[31,33]表明易感基因HLA DQ2/DQ8, 免疫细胞Th1、Th17, 细胞因子等参与CD的病理生理过程. 微生物感染和肠道菌群失调也与CD的发生有关[32], 一项分析CD患者粪便及小肠菌群研究发现, CD患者粪便、小肠的革兰氏阴性菌(大肠杆菌和葡萄球菌)较对照组高, 革兰氏阳性菌(双歧杆菌)则减少[34]. 活动期与缓解期CD患者小肠菌群存在差异, 对十二指肠黏膜菌群测序表明, 活动期CD患者变形菌门丰度高于缓解期CD组和正常组, 而硬壁菌门呈相反趋势, 活动期CD组产酸克雷伯杆菌(肠杆菌科), 表皮葡萄球菌和巴氏葡萄球菌(链球菌科)也明显多于正常组[35]. 经过治疗并且严格坚持无麦麸饮食仍有持续存在症状的CD患者, 症状持续存在可能与肠道菌群失调有关. 比较治疗后仍有症状的CD组和无症状CD组十二指肠菌群, 与无症状组相比, 有症状组十二指肠变形菌增多而硬壁菌门、拟杆菌门、普雷沃氏菌属丰度减低, 物种多样性也减少, 补充益生菌改善肠道菌群失调可能缓解CD症状[36].

3 小肠菌群与代谢性疾病

3.1 小肠菌群与糖尿病 糖尿病是一组以高血糖为表现的代谢性疾病, 可造成多器官损害的远期并发症, 如糖尿病肾病、糖尿病视网膜病变、糖尿病周围神经病变等. 世界卫生组织(World Health Organization, WHO)2014年统计结果显示, 全世界糖尿患者人口已达34.7亿[37]. Ⅰ型糖尿病、Ⅱ型糖尿病是两种主要糖尿病

相关报道 有学者报道小肠双歧杆菌、产丁酸盐菌减少, 假单胞菌、链球菌增加与肠易激综合征、炎症性肠病、乳糜泻有关. 小肠丁酸盐菌霍氏真杆菌增加可改善胰岛素抵抗. 最近也有研究表明, 肥胖患者小肠菌群种类与正常人无明显差异.

创新盘点

2011年国外学者曾对小肠菌群与肠道本身疾病关系进行综述, 国内并未见这方面综述. 本文在前人综述基础上增加小肠菌群与肠道本身疾病最新的研究进展, 并首次对小肠菌群与代谢性疾病进行综述.

类型, 很多证据表明肠道菌群对两型糖尿病发生起重要作用. Ⅰ型糖尿病患者放线菌门、硬壁菌门减少, 拟杆菌门明显增加, 梭菌属、拟杆菌属、韦荣氏菌属增加, 乳酸杆菌属、双歧杆菌属、*Blautia coccoides/Eubacterium rectale*和*Prevotella*减少. 血糖水平与双歧杆菌属、乳酸菌属和硬壁菌门/拟杆菌门呈明显负相关, 而与梭状芽孢杆菌属呈正相关[38]. Ⅱ型糖尿病患者粪便菌群硬壁菌门、梭状芽孢杆菌纲减少, 尤其是一些产丁酸菌如柔嫩梭菌、罗氏菌属减少, 革兰氏阴性菌β变形菌纲、乳酸菌属增加, 拟杆菌门/硬壁菌门、*Bacteroides-Prevotella/C.coccoides-E. rectale*、β变形菌纲与血糖水平高度正相关, 乳酸菌属与血糖、糖化血红蛋白水平呈正相关[39,40]. 小肠菌群参与肠道黏膜免疫形成、营养物质吸收, 因此其与糖尿病关系密切. 比较脲链霉素诱导的Ⅰ型糖尿病小鼠、胰岛素治疗后及正常对照组小鼠十二指肠、回肠菌群差异, 发现十二指肠菌群丰度、多样性在各组间差异不明显. 3组间回肠菌群差异显著, 糖尿病组、对照组主要菌均为硬壁菌门、变形菌门和乳酸杆菌属, 但对照组变形菌门主要为埃希氏杆菌属和志贺菌属, 而糖尿病组变形菌门中克雷伯杆菌最多, 且硬壁菌门中链球菌和放线菌门的棒状杆菌属丰度高于对照组. 胰岛素治疗后回肠菌群拟杆菌门、放线菌门比例升高显著, 双歧杆菌替代棒状杆菌属, 虽*Firmicutes*总数变化不明显, 但梭菌属和消化链球菌属取代了乳酸杆菌属, 克雷伯菌是常见的引起肠道炎症细菌, 胰岛素治疗后克雷伯菌几乎观察不到, 可能因此减轻糖尿病的炎症反应[41]. 绿茶和植物乳杆菌(green tea powder+*Lactobacillus plantarum*, GT+*Lp*)能促进小鼠小肠乳酸菌生长, 缓解高脂饮食诱导的炎症反应, 虽然黏膜降解菌*Akkermansia*在GT+*Lp*组与高脂组间无明显差异, 但小肠*Akkermansia*与一些糖尿病危险因子相关的代谢参数如胰岛素、血糖、甘油三酯水平呈负相关, GT+*Lp*治疗后小鼠小肠细菌群落多样性也明显增加[42]. 将正常人粪便菌群经十二指肠注射移植给代谢综合征患者, 6 wk后患者胰岛素敏感性增加, 同时取十二指肠活检样本检测菌群组成, 发现产丁酸盐菌霍氏真杆菌增加[43]. 十二指肠菌群通过改变丁酸盐产量而调节胰岛素敏感性.

3.2 小肠菌群与肥胖 肥胖症是世界性疾病, 是全球死亡率升高的重要危险因素, 其病因复杂, 涉及环境、饮食、生活方式、遗传因素等[44]. 肠道菌群失调是肥胖发生的重要病理生理因素, 他们通过增加能量吸收储存、影响肠道激素分泌、破坏肠壁完整性促进脂多糖吸收入血、调节内源性大麻素系统等方式参与肥胖的发生发展[44]. 结肠及粪便样本已被许多学者用于研究肠道菌群与肥胖关系. 遗传性肥胖小鼠(ob/ob)肠道拟杆菌门比例较瘦型小鼠增加50%, 硬壁菌门比例相应减少, 硬壁菌门/拟杆菌门比例升高[45,46], 肥胖小鼠古生菌(*Euryarcheota*和*Crenarcheota*)比例较瘦型鼠高[46]. 将ob/ob小鼠和瘦型小鼠粪便移植给无菌小鼠, 接受ob/ob小鼠粪便组肠道硬壁菌门丰度高于接受瘦型小鼠粪便组[46], 以*Erysipelotrichi*、*Clostridium innocuum*、*Eubacterium dolichum*、*Catenibacterium mitsuokai*和*Bacilli*增多明显, 而拟杆菌门比例减少[47]. 肥胖的根本在于能量收支失衡, 小肠是营养物质吸收主要场所, 小肠菌群在能量吸收、储存过程中起重要作用, 可能是肥胖发生发展的重要因素. 高脂组小鼠空肠*Lactobacillus/Enterococcus*(*LAB*)增多, *Bacteroides/Prevotella*(*BAC*)减少, *LAB/BAC*比例升高, 体质量、外周脂肪组织也增加[48]. 添加益生菌饮食的肥胖小鼠, 与对照组相比, 益生菌组小鼠小肠硬壁菌门和*Clostridium cluster XIVab*丰度减低, 拟杆菌门量无明显变化, 硬壁菌门/拟杆菌门减低, 同时小鼠体质量增长减慢, 肥胖相关代谢指标下降[49]. 使用Illumina MiSeq平台对5例肥胖患者和5名健康志愿者十二指肠菌群测序, 结果显示肥胖组和健康组十二指肠门水平主要为硬壁菌门、放线菌门、变形菌门, 而拟杆菌门比例较少, 且除*Rubrobacter*外, 其余在门、属、种水平主要菌无明显差异[50]. 肥胖组十二指肠厌氧菌比例、乙酰辅酶A脱氢酶基因较健康组增加, 而需氧菌和蔗糖磷酸酶和1-4α葡萄糖支链酶减少[50]. 目前研究表明结肠菌群通过各种机制参与肥胖及相关代谢性疾病的形成, 但小肠菌群与肥胖关系仍存在争议, 值得进一步研究.

4 结论

小肠菌群与肠道本身病变、代谢性疾病、自

身免疫性疾病等可能存在千丝万缕的联系. 技术限制、标本来源困难等限制了对小肠菌群的研究, 但研究者们在小肠菌群与IBD、IBS、CD、糖尿病、肥胖等关系探索中取得重要进展. 应用益生菌、益生元、抗生素等调节小肠菌群, 应用小肠粪便移植等都有研究表明对疾病治疗有益. 认识小肠菌群与疾病关系, 合理利用小肠菌群将为人类对抗疾病提供又一有力武器. 小肠菌群作为消化道菌群重要组成部分, 在人类健康与疾病中扮演重要角色, 其相关研究仍然存在很多未知之谜, 有待进一步深入探讨.

应用要点

本文引起科研临床工作者注意, 希望更多学者加入对小肠菌群与疾病关系研究, 更加透彻理解小肠菌群在疾病的发生、发展、转归机制, 研发并利用小肠微生态制剂治疗更多疾病.

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同行评价

小肠菌群是消化道菌群重要组成部分, 在人类健康与疾病中起重要作用. 目前研究疾病与菌群关系标本绝大多数取自结肠或粪便, 综述引用较新参考文献, 就近年来小肠菌群与疾病关系相关研究进行综述.

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