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肠道菌群及益生菌干预: 慢性肾脏病治疗的新视角

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摘要 肠道是"隐形"的免疫器官, 具有调节机体营养代谢、生理和免疫等重要功能. 近年来, 肠道菌群被认为参与了慢性肾脏病(chronic kidney diseases, CKD)的发生发展过程. CKD患者肠道功能屏障受到破坏, 一些肠源性代谢毒素和细菌移位进入体循环, 从而加重CKD全身炎症反应, 促进其心脑血管并发症的发生. 而益生菌治疗作为调节肠道菌群的主要干预措施, 可能通过调节肠稳态, 减少肠源性尿毒症毒素而延缓CKD的进展. 由于益生菌对生理功能的调节具有菌株特异性, 因此根据他们的功能特性选择适当的益生菌菌株干预是至关重要的. 益生菌治疗更新了以往探讨疾病发生发展的分子机制的理念, 为临床疾病的治疗提供了更开阔的视野. 本文主要概述了CKD患者肠道菌群的变化以及益生菌在CKD治疗中的功效和可能作用机制.

关键词 肠道菌群, 益生菌, 慢性肾脏病

人体肠道含有超过100万亿细菌, 不同菌群共生形成了独特的肠道微生态环境. 肠道超过90%细菌属于厚壁菌门(Firmicutes)、拟杆菌门(Bacteroidetes)、放线菌门(Actinobacteria)等[1,2]. 不同的菌种在肠道不同的位点栖息, 发挥不同的功能. 肠道菌群与宿主的营养、代谢、生理、免疫功能密切相关. 而肠道菌群也受到多种因素的影响, 例如饮食、药物、生活方式、生理状态、环境和基因等[3]. 因此, 正常的肠道菌群对维持人体健康是至关重要的. 近年来, 随着宏基因组学、宏转录组学以及代谢组学等技术的应用和发展, 大量的研究开始探讨肠道菌群的组成结构和功能变化与疾病的关系. 越来越多研究表明, 肠道菌群失调与炎症性肠病、糖尿病、高血压、肥胖、肿瘤、心血管疾病、神经系统疾病、过敏性疾病、风湿免疫性疾病、慢性肾脏病等多种疾病发生发展过程相关[4~9]. 本文主要概述了慢性肾脏病(chronic kidney diseases, CKD)患者肠道菌群的变化以及益生菌在CKD治疗中的功效和可能作用机制.

1 肠道菌群失调与慢性肾脏病

流行病学调查结果表明, 全球范围内CKD的发病率为8%~16%[10,11]. 我国多中心调查结果也显示, 成人CKD总患病率为10.8%, CKD已成为全球公共健康问题[12]. CKD如未能得到及时有效的治疗, 将持续进行性发展, 最终进入到终末期肾衰竭(end-stage renal disease, ESRD), 则需长期肾脏替代治疗. ESRD并发症多, 心血管事件发生率显著增加, 远期预后差, 对个人及社会造成了巨大的经济负担. 越来越多研究表明, 肾脏病患者存在明显肠道菌群紊乱[13~16], 临床研究显示, CKD患者肠道菌群丰度和组成发生变化, ESRD患者肠道菌群中存在19种优势菌, 其中合成硫酸吲哚酚(indoxyl sulfate, IS)的菌种有3种, 硫

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酸对甲酚(p-cresyl sulfate, PCS)的2种, 而乳酸杆菌科(Lactobacillaceae)等益生菌显著减少[14,17,18]. 胃肠道内的致病菌(包括条件致病菌在内)的数量增多到一定程度时, 将会诱发或者加重尿毒症毒素和相关细菌毒素的积累, 加速CKD进程及并发症的发生; 同时肠道益生菌减少也同样会对CKD患者产生不利影响[14,17,19,20]. Vaziri等人[18]采取肾切除手术构建大鼠肾损伤模型, 发现肾切除大鼠的肠道菌群种类明显减少, 说明肾损伤可以直接影响肠道菌群的种类和数量. 我国最新研究发现, 中国ESRD患者肠道菌群(肠型)会从普氏菌属(*Prevotella*)为主转换为拟杆菌属(*Bacteroides*)为主, 这种转变与产丁酸菌的减少有关[15]. 尽管导致CKD患者肠道菌群紊乱的因素仍未明确, 一些学者认为限制性的饮食、磷结合剂、抗生素和吸附剂等药物的使用以及CKD本身的疾病状态在其中起着重要作用[21~23].

目前肠道菌群与CKD的关联主要体现在以下3个方面:

(1) 肠源性尿毒症毒素合成. CKD患者肠道菌群失调导致肠源性尿毒症毒素例如IS, PCS和氧化三甲胺(trimetlylamine oxide, TMAO)等生成增加, 并且肠道菌群失调可以破坏肠道上皮的紧密连接, 增加肠道通透性, 导致细菌和毒素的移位, 而肠源性尿毒症毒素的聚集又会进一步加重肠道菌群紊乱, 促进致病菌生长, 从而形成恶性循环. IS和PCS是不易被透析清除的蛋白结合毒素, 已有研究表明, ESRD患者肠道菌群中含有促进IS和PCS合成酶的细菌丰度更多[14]. IS和PCS与CKD的进展和心血管并发症的发生密切相关. IS, PCS可通过激发炎症和氧化应激反应, 损伤血管内皮细胞, 增加血管通透性, 增加CKD血透患者的致死率[24~26]. 然而, 并不是所有的研究都认同这一观点, 最近一项关于1273名透析患者的大型队列研究认为, IS和PCS和心血管事件并无显著相关性, 只有在低血清白蛋白透析患者的亚组中, PCS与心血管事件显著相关, 这表明其他因素可能会改变IS和PCS与心血管事件之间的关系[27]. TMAO是肠道菌群分解食物中胆碱和左旋肉碱的代谢副产物, 它被认为是心血管事件的独立危险因素, 可直接导致动脉粥样硬化、缺血性心脏病等, 大量研究表明CKD患者血清中TMAO含量升高可以明显增加患者心血管事件风险和全因死亡率[28~33]. 动物实验和临床试验也都证明, CKD中血清TMAO升高与肠道菌群失调直接相关[13].

(2) 肠道菌群引起的炎症反应. 肠道菌群失调可促进肠道免疫炎症, 进而参与CKD的全身免疫炎症调节, 炎症反应贯穿了CKD发生发展的全过程. 最新的人体及动物实验均表明, CKD患者肠道菌群紊乱伴随有全身系统性炎症反应, 这主要与肠道菌群紊乱导致肠道黏膜屏障功能失调引发的细菌移位和毒素入血密切相关[21]. Andersen等人[23]研究发现, Collagen type *4α3*(*Col4α3*)基因缺失小鼠构建CKD模型可表现出全身炎症反应, 内毒素血症和肠道菌群失调, 应用抗生素剔除兼性厌氧菌群, 可阻止细菌移位, 减少血清内毒素, 逆转全身炎症标志物. 然而, 目前仍缺乏大规模的临床试验证实CKD患者发生肠道菌群紊乱的同时, 也存在肠道炎症和细菌移位.

(3) 营养代谢紊乱. 肠道菌群宏基因组测序发现CKD患者肠道菌群中厚壁菌门增加而拟杆菌门减少, 这与肥胖患者的变化极为相似, 因此认为肠道菌群可能诱发胰岛素抵抗和营养代谢紊乱进而影响CKD[34~36]. 藉此, Meijers等人[37]提出了CKD进展和干预的"肠-肾轴"理论(the theory of gut-kidney axis), 它是指胃肠道与肾脏相互作用, 包括胃肠道与肾脏任何一方发生变化都会通过能量物质代谢、免疫炎症、肠道黏膜和肠道菌群等多方面影响另一方, 并可互为因果. 总之, 肠道与肾脏之间可以通过代谢依赖性和免疫2种路径构成"肠-肾轴"而相互影响[38]. "肠-肾轴"介导的延缓CKD进展的理论成为近年国内外肾病领域研究的热点之一. 总而言之, 肠道菌群紊乱会进一步引发一系列代谢紊乱, 包括尿毒症毒素的产生、炎症反应、氧化应激和免疫抑制等, 最终也将促进CKD的进展和心血管疾病等并发症的发生.

针对CKD的致病原因和临床表现, 在CKD的治疗中, 传统有一类治疗主要针对代谢废物的堆积, 包括减少代谢废物的产生, 如减少蛋白质的摄入或者优质低蛋白饮食加α-酮酸治疗以及减少蛋白质的吸收; 还有碳吸附剂(AST-120等), 或者增加肾脏废物清除率, 主要指肾替代治疗, 包括透析和肾移植[39~41]. 以上肾脏病治疗措施可以改善或者延缓肾脏病的进展, 但其伴随着的副作用, 比如胃肠道症状、激素性副作用、治疗费用昂贵等也限制了这些治疗措施在临床上的广泛应用. 因此, 开发一种新型的, 副作用更少、更无害、价格更便宜的治疗药物在临床上减少尿毒素堆积, 延缓慢CKD的进展具有重

要意义.

2 益生菌在CKD中的应用

益生菌作为主要调节肠道菌群的干预措施，目前在疾病中的研究十分火热. 益生菌是对人体有益的一类活性微生物的总称，它能存活于胃酸、胆汁等生理性体液中，通过分泌一些特异性功效的酶等增加结肠某些共生菌浓度，对机体产生有益作用[42,43]. 大量研究证明，益生菌可以改变肠道微生态环境、抑制炎症反应、减少肠道黏膜损伤、修复受损的肠道上皮细胞间连接并改善肠道物理屏障功能. 同时益生菌可以竞争性增强营养物质的吸收，减少尿毒症毒素和铵盐类产物的堆积，改善水电解质紊乱和酸碱紊乱. 此外，益生菌还可以通过其占位效应，减少病原体或病理性抗原与肠道黏膜受体的结合，减轻外源性致病体的入侵和内源性致病体的激活，增强机体免疫防御能力[44,45].

已有大量临床试验证实，某些益生菌、益生元以及合生元可以减少CKD患者血清中IS和PCS等尿毒症毒素的水平，同时减少炎症介质的释放，减轻结肠上皮紧密连接的损害，从而改善患者内毒素血症，提高生存质量[46~49]. 然而，益生菌在临床CKD患者的治疗仍处于试验阶段，益生菌作用于CKD的具体分子机制，益生菌对CKD患者的长期效应等未得到解决. 目前，益生菌在CKD中的前期研究也主要集中在3个方面：减少尿毒性毒素在机体的堆积、改善慢性炎症、改善机体代谢.

(1) 减少尿毒性毒素在机体的堆积. 益生菌可以重构肠道菌群平衡，稳定肠道黏膜屏障，减少肌酐、尿素氮以及肠源性尿毒症毒素的产生和堆积，提高宿主免疫防御能力. 同时改善患者生存质量，延缓CKD患者的进展. 大量研究已经证明，益生菌可以减少尿毒症毒素的堆积，减少血清肌酐和尿素氮水平，在一定程度上改善了肾功能. 通过给尿素症大鼠喂养巴氏生孢八叠球菌(*Sporosarcina pasteurii*)发现，该种益生菌具有尿素靶向性，可以直接水解尿素，减轻血清尿素水平，延缓小鼠CKD的进展，延长生存期[50]. 为了研究益生菌在人体的作用及可能作用机制，Ranganathan等人[51]开展了一个双盲的多中心的临床试验，对42例CKD-III期患者采取益生菌混合或安慰剂疗法. 试验中发现，益生菌治疗的患者期血清尿素水平显著下降，其中12名患者肾小球滤过率下降速率减缓. 同时，在一组血液透析患者的临床试验中发现，血液透析只能轻微改善患者酚类的排泄，而血透加口服干酪乳杆菌(*Lactobacillus casei*)Shirota (*LcS*)5周的患者，其酚类和吲哚类尿毒症毒素的产生明显减少[52]. 在另一组试验中，口服嗜酸乳杆菌(*L. acidophilus*)的CKD患者，其产生二甲胺和亚硝基二甲胺的水平也下降[53]. 最近研究还表明，益生菌联合益生元使用，可改变CKD患者肠道菌群，减少尿毒症毒素的产生，从而阻碍CKD的进展及心血管疾病发生[47]. 以上试验均证实了益生菌可以减少尿毒症毒素的产生和堆积，改善机体水电解质以及代谢紊乱. 值得关注的是，只有肠溶性的益生菌试剂能减少尿毒症毒素的产生. 前面我们提到在CKD患者肠道中，乳酸杆菌科含量明显减少，因此这一类益生菌最常被用于CKD的临床干预试验中.

(2) 改善慢性炎症. 益生菌可以改善患者慢性炎症状态. 大量研究发现，益生菌可以通过调控某些信号通路，抑制促炎因子的分泌，减轻机体炎症反应. 临床试验也证实，益生菌可以有效地减少CKD腹透患者血清TNF-α和IL-6的水平，减少维持性血透患者C反应蛋白水平，抑制炎症反应[54,55]. 然而，至今仍少有关于益生菌在非透析CKD患者中的抗炎作用的研究，益生菌在CKD患者群体的广泛使用仍缺乏更充分的实验基础. 此外，益生菌分泌抑菌肽降低胃肠消化道的细菌易感率，对于CKD患者具有特别的意义. 临床CKD患者对艰难梭菌(*Clostridium difficile*)比普通病人具有更高的易感性，因此，CKD患者更易发生*C. difficile*相关性腹泻[56]，加重患者水电解质平衡紊乱. 益生菌的抑菌作用可以减少CKD患者*C. difficile*的感染，减少肠炎以及腹泻的发生[18]. 同时益生菌可以改善便秘，减少毒素的吸收和蓄积，溶解草酸石，改善尿石症患者病情.

(3) 改善机体代谢. 大量研究表明，益生菌可以增加胆盐水解酶的活性，调节肝脏胆固醇的合成，减轻肝脏脂肪变性. 鼠李糖乳杆菌(*L. rhamnosus*)通过下调脂质代谢转录基因的表达抑制胆固醇和甘油三酯合成，同时增加脂肪酸水平[57]. 益生菌(*LcS*)尚能改善食源性胰岛素抵抗[58]. 益生菌也是产生短链脂肪酸的主力军，尤其是乳酸菌属. 其中短链脂肪酸含量最丰富的主要为乙酸、丙酸和丁酸等，而短链脂肪酸不仅仅局限于肠道，维持肠道上皮的正常功能，它还可以通过扩散作用进入血液发挥作用. 益生菌

通过增加短链脂肪酸水平发挥抗炎作用是其产生保护效应的机制之一, Maslowski等人[59]研究发现肠道菌群通过分泌短链脂肪酸结合GPR43受体发挥抗炎效应. 已有研究报道CKD患者肠道菌群紊乱, 其中产生尿素、酚类等毒素的肠道菌群增加, 而产生短链脂肪酸的肠道细菌减少[14]. 也有研究证实双歧杆菌(*Bifidobacteria*)可以通过分泌乙酸改善肠道紧密连接抑制缺血/再灌注(ischemia/reperfusion, I/R)诱导后的细菌移位[60]. 最新研究也认为, 膳食纤维通过选择性调节肠道促短链脂肪酸分泌菌群, 改变短链脂肪酸含量, 进而改善2型糖尿病[61]. Andrade-Oliveira等人[62]最新研究也发现乙酸可以减轻I/R诱导的急性肾损伤(acute kidney injury, AKI).

3 目前存在的问题

综上所述, 肠道菌群已经成为慢性肾脏病的治疗新靶点, 益生菌干预也打开了慢性肾脏病治疗的新视角. 但是益生菌在慢性肾脏病中的推广应用仍存在一定问题亟待解决. 大量体内实验已经证实了口服益生菌可以到达并黏附在肠道上皮细胞, 存活并发挥抗菌作用[63]. 然而尿毒症患者由于大量毒素堆积, 肠道微环境改变, 口服益生菌后肠道益生菌的生存率以及抗菌效应均有改变, 因此还需要更多的实验来确认益生菌在尿毒素患者中的变化和效应. 目前也有一些方法可以提高益生菌在肠道定植的数量及活性[64], 如抗胃酸材料制备的胶囊或者粪菌移植等, 但其长远效应仍需大量实验验证. 另外, 目前报道的益生菌对肠道微生态环境的效应评估主要通过粪便中菌群的种类和数量来检测, 其他一些指标也包括粪便中相关酶的活性、短链脂肪酸的含量、内毒素浓度及肠道pH等. 但至今极少有研究用三代测序技术证实ESRD患者肠道菌群中菌种的变化趋势和功能分析以及服用益生菌后肠道有益菌种的变化情况. 虽然关于益生菌对机体的保护作用已有大量研究, 然而对于益生菌的副作用, 或者其长期应用效应, 研究数据甚少, 仍需要高质量的大型临床试验证实[65]. 此外, 并不是所有的益生菌都能产生理想的效果, 个别实验发现, 大量菌落的形成可以产生碱性分子, 损伤肠道上皮细胞间紧密连接, 促进炎性分子脂多糖的产生并进入血液循环, 扩散到全身. 在一项动物研究中, 评估5种不同的益生菌组合对尿毒症大鼠的作用, 只有巴氏芽孢杆菌(*Bacillus pasteurii*)和芽孢乳杆菌(*L. sporogenes*)能够降低血清尿素氮和肌酐. 某些益生菌可以产生尿素和尿素酶, 导致上皮细胞电阻丢失, 紧密连接蛋白缺陷, 促进尿毒症毒素和内源性毒素的吸收, 加重尿毒症毒素在体内的蓄积, 加重内环境紊乱[66]. 因此, 益生菌在慢性肾脏病中研究之路仍然漫长, 建立临床大样本研究, 评估益生菌的长效性及安全性, 并探讨不同特性益生菌对肾脏疾病的影响具有重要意义.

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Summary for “肠道菌群及益生菌干预: 慢性肾脏病治疗的新视角”

Gut microbiota and probiotics intervention: A new therapeutic target for management of chronic kidney disease

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Epidemiological investigation showed that the prevalence of chronic kidney disease (CKD) is 8%−16%. A multi-center survey in China also showed that the total prevalence of CKD in adults is 10.8%, which demonstrated that CKD has become a global public health problem. Failed timely and effective treatment of CKD leads to progressive deterioration, and eventual development of end-stage renal disease (ESRD), which requires long-term renal replacement therapy. ESRD is accompanied by several complications and poor long-term prognosis, imposing a heavy economic burden on individuals and society. Therefore, delaying the progression of CKD and reducing the occurrence of ESRD is an urgent issue and currently is a trending research topic for nephrologists.

The intestinal tract can be compared to an “invisible” immune organ, capable of influencing nutrition, metabolism, physiology, and immune function in the host. Intestinal homeostasis refers to the dynamic balance between the host’s mucosal barrier and intestinal microecology (including the intestinal microflora, nutritive and metabolic products, etc). The intestinal microflora is influenced by a multitude of factors such as an individual’s external environment, lifestyle, eating habits, medicine intake and surgeries, etc. In recent years, gut microbiota have been considered to be involved in the occurrence and development of chronic kidney diseases (CKD). CKD is associated with impaired intestinal barrier function. Preliminary evidence indicates that toxic products generated by a dysbiotic gut microbiome and bacterial translocation may contribute to CKD progression and cardiovascular and cerebrovascular complications. The interplay between the accumulation of uremic toxins, inflammatory responses and metabolic disorders produces a vicious circle, as all three factors influence intestinal homeostasis and are crucial risk factors in the development of CKD. Therefore, it is imperative to find effective intervention measures to effectively regulate these three factors and improve intestinal homeostasis to prevent CKD progression. Probiotics, as a main intervention measure to regulate intestinal flora, may alleviate CKD progression by regulating intestinal homeostasis and reducing enteral uremic toxin. As the regulatory capacity of physiological processes by probiotics is strain specific, it is essential to choose appropriate probiotic strains according to their functional properties. Probiotics present as a new therapeutic target for management of chronic kidney disease. This review mainly summarizes the role of intestinal flora in CKD and the effect and mechanism of action of probiotics in CKD.

gut microbiota, probiotics, chronic kidney disease

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