

基于“肠-肾轴”探讨肠道菌群参与肾脏疾病的研究进展

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摘要

肠道菌群与肾脏功能通过“肠-肾轴”构成紧密的双向调控网络, 肠道菌群失调不仅参与急性肾损伤(acute kidney injury, AKI)、慢性肾脏病(chronic kidney disease, CKD)等多种肾脏疾病的发生发展, 还在AKI向CKD的转归进程中发挥关键调控作用。近年来, 以肠道菌群为靶点的治疗策略已展现出显著的肾脏保护潜力。本文系统综述了健康状态下肠道菌群的组成特征与核心生理功能, 深入阐述了肠道菌群失调与各类肾脏疾病的关联及潜在分子机制, 全面总结了微生物疗法、天然产物干预、粪菌移植(fecal microbiota transplantation, FMT)等靶向治疗的研究进展, 并展望了该领域未来的研究方向, 旨在为肾脏疾病的预防与临床治疗提供新的思路 and 理论依据。

关键词

肠道菌群, 肠-肾轴, 肾脏疾病, 尿毒症毒素, 微生物治疗

Research Progress on the Involvement of Gut Microbiota in Kidney Diseases Based on the Gut-Kidney Axis

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Abstract

Gut microbiota forms a tight bidirectional regulatory network with renal function through the *gut-kidney axis*. Dysbiosis of gut microbiota is not only involved in the occurrence and development of various kidney diseases such as acute kidney injury (AKI), chronic kidney disease (CKD), but also plays a key regulatory role in the transition from AKI to CKD. In recent years, therapeutic strategies targeting gut microbiota have demonstrated significant renoprotective potential. This review systematically summarizes the compositional characteristics and core physiological functions of gut microbiota under healthy conditions, elaborates on the association between gut microbiota dysbiosis and various kidney diseases as well as the underlying molecular mechanisms, comprehensively reviews the research progress of targeted therapies such as microbial therapy, natural product intervention, and fecal microbiota transplantation (FMT), and prospects the future research directions in this field, aiming to provide new ideas and theoretical basis for the prevention and clinical treatment of kidney diseases.

Keywords

Gut Microbiota, Gut-Kidney Axis, Kidney Disease, Uremic Toxins, Microbial Therapy

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1. 引言

肾脏疾病已成为全球重大公共卫生问题，急性肾损伤(acute kidney injury, AKI)可快速进展为慢性肾脏病(chronic kidney disease, CKD)甚至终末期肾病(end-stage renal disease, ESRD) [1]，CKD 伴随多系统并发症，给医疗体系带来沉重负担[2]。肾脏纤维化是各类进展性肾病的共同终末结局[3]，涉及肾素-血管紧张素系统(RAS)、活性氧(ROS)、Toll 样受体 4 (TLR4)等多种分子通路的异常激活[4]。传统透析、肾移植等治疗手段难以从根本上阻断疾病进程[5]，探索肾脏疾病发病的新型分子机制并开发靶向治疗策略具有重要的临床意义。

近年来，随着微生物组学技术的快速发展，肠道菌群与肾脏疾病的关联被广泛关注。肠道菌群不仅参与营养物质的消化吸收，还在免疫稳态维持、代谢调控等方面发挥关键作用[6] [7]。肠道菌群失调可通过“肠-肾轴”引发代谢紊乱、炎症反应及肠道屏障损伤，进而促进肾脏病理损伤；而肾脏功能异常也会通过改变肠道微环境(如尿素蓄积、氮代谢障碍)反过来加剧菌群失调，形成恶性循环[8] [9]。大量研究证实，肠道菌群及其代谢产物在 AKI、CKD 等多种肾脏疾病中存在特征性改变[10] [11]，且靶向肠道菌群的干预策略可有效改善肾脏功能[12]。本文围绕肠道菌群参与肾脏疾病的研究进展展开系统综述，为相关领域研究及临床应用提供参考。

2. 肠道菌群的生理功能与肠-肾轴的双向调控机制

2.1. 健康状态下的肠道菌群特征

健康成年人肠道菌群数量达 10^{14} CFU (菌落形成单位)以上，具有高度多样性和稳定性，核心菌门为厚壁菌门(79.4%)、拟杆菌门(16.9%)、放线菌门(2.5%)、变形菌门(1%)及疣微菌门(0.1%) [13]。各菌门协同

维持微生态平衡：厚壁菌门产短链脂肪酸(SCFAs)等抗炎产物，拟杆菌门形成防御屏障，放线菌门参与免疫调节，变形菌门致病菌过度增殖则与肠道炎症相关[9] [14] [15]。

2.2. 肠道菌群的核心生理功能

肠道菌群是机体稳态的重要调控者，其功能体现在三方面：一是代谢调节，发酵膳食纤维产生乙酸、丙酸等 SCFAs，参与氨基酸、脂质代谢，为肠道上皮细胞供能并调控全身代谢[9]；二是免疫平衡，促进免疫细胞成熟、抑制病原体定植，增强抗感染能力[16]；三是屏障维持，肠道菌群通过调节肠道黏膜紧密连接蛋白表达，减少肠道通透性，阻止毒素与病原体入血[17]。

2.3. 肠 - 肾轴的双向调控机制

肠 - 肾轴是连接肠道与肾脏的生理病理调控网络，其核心通过血液循环、免疫信号及代谢产物实现双向沟通[2]。生理状态下肠道菌群产生的 SCFAs 等有益代谢产物可通过抑制炎症反应、减轻氧化应激等方式保护肾脏功能[6] [11]；肾脏则通过调节体内水盐代谢、尿素排泄等维持肠道微环境稳定，保障菌群正常代谢[8]，二者形成相互依存的稳态平衡。病理状态下肾脏功能损伤会导致肠道内尿素蓄积、氮代谢障碍，改变肠道 pH 值及营养供应，引发菌群失调；而肠道菌群失调则会破坏肠道屏障完整性，导致尿毒症毒素，如吲哚硫酸盐(indoxyl sulfate, IS)、对甲酚硫酸盐(p-cresyl sulfate, PCS)、氧化三甲胺(trimethylamine N-oxide, TMAO)、细菌内毒素(lipopolysaccharide, LPS)等进入血液循环，通过激活炎症通路、加重氧化应激等方式加剧肾脏损伤，形成“肾损伤 - 菌群失调 - 肾进一步损伤”的恶性循环[11]。

3. 肠道菌群失调与各类肾脏疾病的关联

3.1. AKI 中的肠道菌群变化

AKI 的病因多样(如药物毒性、缺血再灌注损伤、脓毒症)，不同病因引发的肠道菌群失调具有特征性改变，其核心特征表现为微生物多样性降低、有益菌减少及致病菌增殖[18]；SCFAs 生成减少、尿毒症毒素(IS、PCS、TMAO)积累，同时肠道屏障完整性受损，LPS 及炎症因子进入血液循环，进一步加重肾脏炎症和氧化应激[19]。而 AKI 引发的炎症反应和缺血状态又会反过来加剧肠道菌群紊乱，形成恶性循环，加速疾病进展[20]。

3.2. CKD 中的肠道菌群变化

CKD 患者肠道菌群失调呈现显著的疾病特异性特征，且与疾病分期密切相关[21]。在 CKD 进展过程中乳杆菌属、粪杆菌属等有益菌丰度逐渐降低，埃格特菌属等致病菌丰度升高[22]。ESRD 患者菌群失调严重，产 SCFAs 菌丰度显著下降，尿毒症毒素产生菌增殖，毒素水平大幅升高[23]。菌群失调通过三条途径加速肾纤维化：① 肠道屏障受损导致细菌及毒素移位，引发内毒素血症；② 代谢产物(如 TMAO)促进血管损伤，增加心血管并发症风险；③ 毒素激活免疫系统，引发并维持全身性炎症[6]。

3.3. 特定类型肾脏疾病中的肠道菌群特征

3.3.1. 糖尿病肾病(Diabetic Kidney Disease, DKD)

DKD 是 ESRD 的首要病因[24]。DKD 患者肠道厚壁菌门/拟杆菌门比值降低，梭菌属及志贺菌属等致病菌丰度增加，有益菌属丰度降低[24] [25]。产 SCFAs 菌的减少与 DKD 患者尿蛋白/肌酐比值升高密切相关[26]。动物实验表明，菌群变化可通过激活 TLR4 炎症通路、加重氧化应激促进肾脏纤维化[26] [27]。

3.3.2. 膜性肾病(Membranous Nephropathy, MN)

MN 是成人肾病综合征的常见病因，核心病理特征为肾小球基底膜下免疫复合物沉积[28]。特发性膜性肾病(idiopathic membranous nephropathy, IMN)患者粪便中乳杆菌属、双歧杆菌属丰度降低，变形菌门、放线菌门丰度升高；动物模型则表现为厚壁菌门/拟杆菌门比值升高，脱硫弧菌属丰度增加，SCFAs 水平降低，尿毒症毒素前体生成增多[29]，菌群改变通过调节色氨酸代谢、激活芳香烃受体(AHR)通路等方式，促进肾脏炎症和纤维化[30]。

3.3.3. 免疫球蛋白 A 肾病(Immunoglobulin A Nephropathy, IgAN)

IgAN 是全球最常见的原发性肾小球肾炎[31]。IgAN 患者肠道菌群特征为厚壁菌门丰度升高，梭菌属、乳杆菌属等有益菌丰度降低，大肠杆菌 - 志贺菌属的分类链扩张，且该变化可通过免疫抑制治疗逆转[32]。其中双歧杆菌属丰度降低与 IgAN 患者蛋白尿、血尿水平呈负相关，通过补充双歧杆菌可通过抑制 NLRP3/ASC/Caspase-1 信号通路改善疾病症状[33]。

3.3.4. 其他肾脏疾病中的肠道菌群变化

局灶节段性肾小球硬化(focal segmental glomerulosclerosis, FSGS)患者肠道菌群多样性降低，拟杆菌门丰度升高、厚壁菌门丰度降低，菌群变化与足细胞损伤密切相关[34]。高血压肾病(hypertensive nephropathy, HN)患者肠道中克雷伯菌属丰度升高，链球菌属丰度与血尿素氮、蛋白尿水平呈正相关[35]。狼疮性肾炎(lupus nephritis, LN)患者肠道菌群多样性减少，瘤胃球菌属丰度升高，菌群失调通过破坏肠道屏障、激活全身免疫反应促进疾病进展[36]。

3.4. AKI 向 CKD 转归中的肠道菌群作用

部分 AKI 患者短期肾功能恢复后仍可能进展为 CKD，肠道菌群失调发挥关键调控作用[37]。老年 AKI 患者肠道微生物多样性降低，有益菌丰度减少，SCFAs 生成不足、肠道通透性增加，引发慢性低度炎症，促进 AKI 向 CKD 转归[37] [38]。此外，有动物实验证实缺血再灌注诱导的 AKI 小鼠肠道内有益菌丰度降低，肠杆菌属通过激活氧化应激和炎症通路，加重肾脏纤维化，加速 CKD 进展[38]。

3.5. 肾脏替代治疗与肾移植患者的肠道菌群改变

接受腹膜透析(peritoneal dialysis, PD)和血液透析(hemodialysis, HD)的患者肠道菌群均会发生显著重塑，SCFAs 生成减少，毒素水平升高，患者肠道屏障受损，促进内毒素移位和全身性炎症[39]。其中，PD 患者蛋白水解菌丰度升高，HD 患者拟杆菌门为主要优势菌门[39]-[41]。

肾移植受者肠道菌群同样存在异常。抗体介导的移植排斥患者菌群丰富度和多样性降低，胆酸类代谢产物异常[39]。肠道菌群失调可能通过影响免疫耐受、加重炎症反应等方式，影响移植肾存活[42]。不同肾脏疾病肠道菌群及代谢产物特征变化对比见表 1。

Table 1. Comparison of changes in gut microbiota and metabolic product characteristics among different kidney diseases
表 1. 不同肾脏疾病肠道菌群及代谢产物特征变化对比

疾病类型	核心菌群变化	代谢产物改变
AKI	菌群多样性降低； 有益菌减少、致病菌增殖	SCFAs 减少； IS、PCS、TMAO 蓄积
CKD (含 ESRD)	有益菌逐步减少； 毒素产生菌增殖； ESRD 产 SCFAs 菌显著下降	SCFAs 降低； IS、PCS、吲哚升高

续表

DKD	厚壁菌门/拟杆菌门比值降低； 致病菌升高、有益菌减少	SCFAs 降低
MN	IMN 有益菌降低、变形菌门升高； 模型大鼠厚壁菌/拟杆菌比值升高	SCFAs 降低； 毒素前体增多
IgAN	厚壁菌门升高；有益菌降低； 大肠杆菌 - 志贺菌属扩张	SCFAs 生成不足
肾移植排斥	丰富度和多样性降低	胆酸类代谢产物异常
透析患者	PD/HD 有益菌均降低； PD 蛋白水解菌升高； HD 拟杆菌门升高	SCFAs 降低； 尿毒症毒素升高

3.6. 现有研究中的矛盾结果及成因分析

上述不同肾脏疾病的菌群及代谢产物特征虽已初步明确，但现有研究中仍存在部分矛盾结果，如部分研究认为 CKD 患者厚壁菌门/拟杆菌门比值升高，部分则认为降低[6]；相同益生菌干预在不同 CKD 队列中疗效差异显著[2] [39] [43]。这些矛盾降低了研究结论的可重复性与临床转化价值。

导致矛盾的核心原因分为两类：一是研究设计异质性，多数研究为单中心小样本，易受随机误差影响；测序技术(16S rRNA/宏基因组)、分析方法及样本处理流程不统一，导致菌群检测结果差异[44]。二是研究对象异质性，地域饮食差异塑造不同的菌群结构，不同的疾病分期、合并症及治疗药物也会干扰菌群特征；同时，年龄、遗传、生活习惯等个体差异也会导致菌群表型不同。此外，抗生素、泻药等药物对菌群特征的干扰也是重要原因[14] [39] [45]。

4. 靶向肠道菌群的肾脏疾病治疗策略

4.1. 微生物疗法：益生菌、益生元与合生元

微生物疗法是靶向肠道菌群治疗肾脏疾病的核心手段之一[46]，动物实验证据充分，临床试验多为小样本单中心研究，整体证据等级中等。

1. 益生菌：动物实验证实，普拉梭菌可通过上调丁酸水平、降低 PCS 及 TMAO 等毒素浓度，发挥抗肾纤维化作用[47]。临床研究证实，益生菌补充可有效降低 CKD 患者血浆尿毒症毒素水平，改善肾功能核心指标，临床试验证据 II 级，但现有研究样本量小、菌株与疗程差异大，缺乏大样本随机对照试验(RCT)验证[43] [48]。安全性方面，其疗效具菌株特异性，盲目使用不同菌株的益生菌可能加剧肠道菌群失衡，免疫抑制患者中部分菌株可能成为条件致病菌，过量补充易致胃肠不适[48]。

2. 益生元：菊粉、低聚果糖等益生元在动物实验中可显著增加产 SCFAs 菌丰度，实现肾脏保护[49]，但临床研究较少，其对肾功能的长期改善效果尚未证实。

3. 合生元结合益生菌与益生元的协同优势，既直接补充有益菌，又为其增殖提供营养支持。动物实验证实合生元可通过修复肠黏膜屏障，延缓 CKD 模型大鼠肾功能衰退进程[50] [51]。临床研究显示其可改善 CKD 患者炎症状态及代谢紊乱，临床试验证据 II 级，但同样缺乏大样本 RCT 研究[52] [53]。

4.2. 天然产物干预

天然产物(含中药复方、植物提取物及天然化合物)凭借多靶点、低毒副作用的优势，通过调节肠道菌群平衡，展现出潜在的肾脏疾病治疗价值，其作用核心在于重塑肠道微生态与调控下游致病通路[45] [54]。

整体以动物实验证据为主, 临床试验稀缺(III~IV级), 证据等级偏低。

动物实验证实, 琼玉膏、黄芪丹参复方等中药可增加有益菌丰度、降低毒素水平, 减轻肾损伤[45]; 新橙皮苷、金针菇多糖等可调节菌群结构、抑制氧化应激[54]。但临床研究多为小样本观察, 仅少量研究证实中药可改善患者菌群失调。并且天然产物成分复杂, 部分传统中药可能含马兜铃酸等潜在肾毒性成分, 可能与临床常规治疗药物发生相互作用, 剂量过高易引发菌群紊乱及肝肾功能损伤[55]。

4.3. 粪菌移植(Fecal Microbiota Transplantation, FMT)

粪菌移植通过将健康捐赠者的功能完整肠道菌群转移至患者体内, 实现肠道微生态的快速重塑, 是治疗菌群失调相关性肾脏疾病的新颖干预手段[11], 其疗效已在不同类型肾脏疾病中得到验证。

动物实验中, FMT 可减轻肾脏病理损伤、降低化疗药物肾毒性、延缓 CKD 进展[56]; 临床试验(证据等级 II 级)显示, FMT 可恢复患者菌群多样性、降低蛋白尿和毒素水平, 但研究仍处于探索阶段, 样本量小、缺乏长期随访, 标准化操作流程尚未形成[44]。安全性方面, 供体筛选不严可能会传递条件致病菌、多重耐药菌等, 从而增加免疫抑制患者的感染风险[23] [57] [58]。

4.4. 其他辅助治疗策略

以饮食调整为核心的辅助策略临床证据充分(I级), 是维持肠道菌群平衡、间接保护肾脏功能的基础手段。增加膳食纤维摄入可促进产 SCFAs 菌增殖, 减轻肾脏炎症损伤[49]; 合理限制蛋白质摄入可减少肠道内尿素生成, 缓解肠道菌群失调[49]。同时, 避免抗生素滥用、规律运动、戒烟限酒等, 均可通过维持肠道菌群稳态间接发挥肾脏保护作用[59]。

5. 总结与展望

肠道菌群失调是各类肾脏疾病发生发展的重要诱因, 肠-肾轴双向调控机制在病理进程中发挥核心作用。肠道菌群可通过代谢产物失衡、肠道屏障损伤、炎症激活等途径调控肾脏功能, 而肾脏疾病状态又会反作用于肠道菌群, 加剧失调并形成恶性循环。此外, AKI 与 CKD 的肠道菌群特征存在特异性差异, 为肾脏疾病的无创诊断提供了潜在标志物; 靶向肠道菌群的干预策略(如微生物疗法、FMT、天然产物干预)也展现出良好的临床应用前景。然而, 该领域仍面临诸多挑战: ① 菌群标志物的临床转化受限于样本量小、检测标准不统一; ② 益生菌菌株的特异性选择、FMT 的安全性及长期疗效尚未明确; ③ 天然产物的作用机制仍需深入阐明; ④ 个性化治疗方案缺乏系统的理论支持与临床验证。因此未来研究应进一步开展多中心、大样本前瞻性队列研究, 筛选高特异性肠道菌群标志物, 通过多学科交叉(微生物组学、分子生物学、临床医学)来深入阐明肠-肾轴的精准调控机制, 从而优化靶向治疗策略, 明确益生菌、FMT 及天然产物的最佳使用剂量、疗程及适用人群, 提升治疗的安全性与有效性。最终推动肠道菌群靶点在肾脏疾病临床防治中的转化应用, 改善肾脏疾病患者的生存质量。

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