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肠道菌群在急性肾损伤中作用的研究进展

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[摘 要] 急性肾损伤(acute kidney injury，AKI)是一个全球性的公共卫生问题，其发病率和病死率高、医疗费用昂贵且治疗手段有限。AKI可进一步转变为慢性肾脏病(chronic kidney disease，CKD)，最终进展为终末期肾病(end-stage renal disease，ESRD)。既往研究表明，创伤、药物的不良反应、手术等与AKI密切相关。随着进一步的深入探索，肠道菌群在AKI中的作用逐渐被揭示。AKI发生后，肠道菌群组成改变，肠道屏障破坏引发肠道免疫以及肠道细菌易位。同时，肠道菌群的代谢产物又可以加剧AKI的进展。因此，阐述肠道菌群参与AKI发生和发展的具体机制，有助于从肠道微生物角度为AKI的防治提供新思路。

[关键词] 急性肾损伤；肠道菌群；炎症；毒素；短链脂肪酸；益生菌；后生元；中药

Research progress in the role of gut microbiota in acute kidney injury

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ABSTRACT Acute kidney injury (AKI) remains a global public health problem with high incidence, high mortality rates, expensive medical costs, and limited treatment options. AKI can further progress to chronic kidney disease (CKD) and eventually end-stage renal disease (ESRD). Previous studies have shown that trauma, adverse drug reactions, surgery, and other factors are closely associated with AKI. With further in-depth exploration, the role of gut microbiota in AKI is gradually revealed. After AKI occurs, there are changes in the composition of gut microbiota, leading to disruption of the intestinal barrier, intestinal immune response, and bacterial translocation. Meanwhile, metabolites of gut microbiota can exacerbate the progression of AKI. Therefore, elucidating the specific mechanisms by

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which gut microbiota is involved in the occurrence and development of AKI can provide new insights from the perspective of intestinal microbiota for the prevention and treatment of AKI.

KEY WORDS acute kidney injury; gut microbiota; inflammation; toxins; short-chain fatty acids; probiotic; postbiotics; traditional Chinese medicine

急性肾损伤(acute kidney injury，AKI)是指患有或不患有慢性肾脏病(chronic kidney disease，CKD)的患者几小时或几天内出现严重的肾功能障碍，表现为尿液显著减少(少尿)或完全消除(无尿)，并伴有氮质产物积聚，水、电解质和酸碱平衡紊乱[1]。许多危险因素均可导致AKI的发生，常见原因包括药物引起的肾毒性损害[2]、肾外组织损伤[3]、感染[4]、缺血再灌注损伤(ischemia reperfusion injury，IRI)[5]等。已有研究表明：氧化应激[6]、内皮损伤[7]、线粒体损伤[8]和免疫功能紊乱[9]是导致AKI发生和发展的核心机制，并以此为支点开展了大量研究。目前，AKI的发病率和病死率仍然很高，这可能与AKI期间肾脏与远端器官(如心脏、大脑、肺、肠道、骨骼)或系统(如免疫系统)之间的串扰有关[10]。这些器官串扰会导致AKI后发生上消化道出血、脑卒中、骨折、恶性肿瘤等长期不良事件。

目前，肠道菌群和AKI的关系依然不甚明朗。因此，梳理和总结肠道菌群在AKI发生发展中的作用显得尤为重要。

1 AKI导致肠道微生态的改变

1.1 AKI与肠道菌群失调

健康人体的肠道中存在超过1 000余种、100万亿个微生物。在健康状态下，这些微生物与宿主共生，不仅可调节免疫系统，抵御病原体，还能调节碳水化合物和脂质的内源性代谢，从而有助于营养平衡。对肾脏IRI小鼠的粪便样本进行测序，结果显示：*Clostridium*、*Ruminococcus*丰度增加，而*Bifidobacterium*、*Saccharibacteria*丰度减少[11]。另一项研究[9]表明：小鼠肾脏IRI模型中肠道菌群生态失调主要表现为*Enterobacteriacea*的增加，*Lactobacilli*、*Ruminococacceae*的减少。张然等[12]发现：与同期健康体检的志愿者相比，AKI患者粪便肠道菌群中*Bifidobacterium*、*Bacteroides*明显增加，*Escherichia coli*、*Streptococcus*明显减少。在顺铂诱导的小鼠AKI模型中，*Lachnospiraceae NK4A136*、*Coriobacteriaceae_UCG_002*丰度降低，而*Allobaculum*、*Lactobacillus*、*Alloprevotella*、*Bacteroide*丰度相对升高[13]。

1.2 AKI与肠道免疫

炎症反应与AKI关系密切。发生AKI后，肠道内先天性和适应性免疫系统被激活。先天性免疫中的巨噬细胞和中性粒细胞，以及适应性免疫的白细胞介素(interleukin，IL)-17A是AKI诱导肠道菌群失调的关键因素。研究[9]表明：在小鼠肾脏IRI后，其结肠中巨噬细胞和中性粒细胞的数量显著增加。在结肠巨噬细胞亚群中，巨噬细胞极化，向M1表型转变，导致促进炎症反应的巨噬细胞百分比增加；同时诱生型一氧化氮合酶(inducible nitric oxide synthase，iNOS)表达增加，精氨酸酶表达减少[9]。这些变化表明肾脏IRI后，肠道炎症的发展。研究[14]发现：小鼠特异性缺失巨噬细胞中的低密度脂蛋白受体相关蛋白(low-denisity lipoprotein receptor-related protein，*LRP*)*5*和*LRP6*基因会加剧肾损伤；*LRP5/6*缺陷型巨噬细胞对Toll样受体(Toll-like receptors，TLR)配体高度反应，可能通过激活促分裂原活化的蛋白激酶(mitogenactivated protein kinase，MAPK)途径导致促炎因子和抗炎因子的失衡。此外，TLR识别抗原并激活中性粒细胞，从而触发多条细胞内途径，如c-Jun N末端激酶(c-Jun N-terminal kinase，JNK)、MAPK和核因子κB(nuclear factor kappa-B，NF-κB)，最终导致促炎因子和趋化因子的分泌[15]。另一方面，适应性免疫反应在AKI与肠道免疫之间也发挥了作用。AKI诱导小肠帕内特细胞合成和分泌IL-17A，通过向肝脏和全身递送IL-17A引发肠道、肾脏和肝脏的继发性损伤[16]。

1.3 AKI与肠道屏障和细菌易位

肠上皮由单层柱状上皮细胞构成，这些细胞通过紧密连接结合在一起，形成多功能复合物密封相邻肠道细胞间的空隙[17]，是抑制病原体和细菌易位的天然屏障。紧密连接复合物主要由闭锁小带蛋白-1(zonula occludens-1，ZO-1)、claudins、occludin等组成[18]。在脂多糖(lipopolysaccharide，LPS)诱导的AKI

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小鼠中，ZO-1和occludin表达降低[19]。益生菌可改善动物和人类的肠上皮屏障功能。发生AKI后，肠道菌群失调，益生菌尤其是*Bifidobacterium*丰度减少，导致紧密连接蛋白ZO-1和occludin表达下降[20-21]，从而增加肠道通透性。局部发生炎症时，细胞因子破坏连接蛋白的定位，诱导紧密连接蛋白的收缩和内吞作用，增加肠道上皮的通透性，影响上皮屏障的健康[22]。小鼠肾脏IRI后的第1天，肝组织中细菌16S rRNA显著增加，表明肾脏IRI后发生了细菌易位[9]。AKI后细菌易位的产生可能诱发肝肾综合征以及感染性休克等其他多种器官的损伤[23]。

2 肠道菌群失调加剧AKI发展

2.1 尿毒症毒素

尿毒症毒素可通过损伤肾小管细胞加速肾衰竭。其中，硫酸吲哚酚(indoxyl sulfate，IS)、硫酸对甲酚(p-cresol sulfate，PCS)、氧化三甲胺(trimethylamine-N-oxide，TMAO)、吲哚-3-乙酸、苯乙酰谷氨酰胺等被认为是与肠道微生物群相关的尿毒症毒素。肠道菌群失调导致肠源性尿毒症毒素过度分泌，进一步损害肾小管细胞[24]。选择性修饰微生物组可改变尿毒症毒素谱，如敲除消化道拟杆菌中的色氨酸酶基因后，小鼠体内几乎检测不到吲哚硫酸盐[25]。血清IS和PCS水平与血液透析患者的心血管事件发生率和病死率相关[26]。一项前瞻性队列研究[27]结果表明：血浆IS水平与医院获得性AKI的病死率及预后相关。唾液乳杆菌可对抗顺铂诱导小鼠发生AKI，唾液乳杆菌的这种保护肾脏的作用与其调节肠道微环境，抑制IS和PCS的生成，调节腺苷酸活化蛋白激酶(AMP-activated protein kinase，AMPK)和TLR4介导的紧密连接蛋白的组装有关[28]。TMAO是胆碱和左旋肉碱的肠道衍生代谢物，与心血管疾病和肾衰竭的较高发生风险相关[29]。目前，TMAO与AKI关系的研究还处于起步阶段。最新的一项研究[30]发现：二十二碳六烯酸酰化姜黄素双酯可以通过调节TMAO介导的磷脂酰肌醇-3-激酶(phosphatidylinositol3-kinase，PI3K)/蛋白激酶B(protein kinase B，PKB/AKT)/NF-κB信号通路，减少AKI后心血管疾病的发生。

2.2 短链脂肪酸

可溶性膳食纤维被肠道细菌发酵后可以合成短链脂肪酸(short-chain fatty acid，SCFA)。作为肠上皮细胞的重要燃料，SCFA具有调节肠上皮细胞增殖、分化，影响肠道蠕动，增强肠道屏障功能，以及改善宿主代谢的作用[31]。在SCFA家族中，丙酸盐、乙酸盐和丁酸盐目前已被证实在AKI中发挥着至关重要的作用[32]。发生AKI后，肠道菌群失调，肾脏保护性SCFA无法充分生成，使AKI恶化加速。丙酸盐主要参与糖异生，而乙酸盐和丁酸盐主要参与脂质的生物合成[33]。同时，丙酸和丁酸还可以诱导调节性T细胞(regulatory T cells，Treg)分化，通过组蛋白去乙酰化进一步抑制肠道炎症[34]。作为G蛋白偶联受体(G protein-coupled receptors，GPCR)的配体，SCFA可通过GPCR直接影响Treg细胞、中性粒细胞、单核细胞和肥大细胞[35]。在叶酸肾病小鼠模型中，SCFA可通过抑制组蛋白脱乙酰酶预防AKI的发生[36]。同时，SCFA还能通过抑制树突状细胞的成熟和$CD4^+$和$CD8^+$T细胞的增殖来调节炎症过程，改善肾上皮细胞缺氧，从而预防IRI引起的AKI[37]。口服益生菌*Lactobacillus casei Zhang*(*L. casei Zhang*)可通过增加血清和肾脏中的SCFA和烟酰胺，减轻肾小管上皮细胞损伤和肾脏炎症，延缓AKI向CKD的转变[38]。此外，在脓毒症诱发的AKI中，乙酸盐可能通过恢复T细胞的氧化-抗氧化平衡，发挥肾脏保护作用[39]。

3 基于肠道菌群的靶向治疗

3.1 益生菌

补充益生菌可以减轻AKI，延缓AKI的进展，减少远端器官的损伤。在肾脏IRI模型小鼠中[20]，益生菌*Bifidobacterium bifidum*(BGN4)可增加肠道微生物组的均匀度，阻止AKI标志性菌群*Enterobacteriaceae*和*Bacteroidacea*的扩张。BGN4的干预使得小鼠肾小管损伤评分、中性粒细胞和巨噬细胞数量以及肾脏*IL-6* mRNA的表达水平显著降低[20]。此外，BGN4还可以降低血浆中低密度脂蛋白、丙氨酸转氨酶、天门冬氨酸转氨酶的水平。在减轻肾脏IRI和AKI相关肝损伤方面表现出潜在价值[20-21]。

*L. casei Zhang*是从中国内蒙古地区的自然发酵酸马奶样品中分离出的众多乳酸菌中筛选而来的益生菌。*L. casei Zhang*在延缓AKI向CKD进展中发挥重大作用。在经*L. casei Zhang*预处理的小鼠中，*Allobaculum*和*unclassified_f_Prevotellacea*的丰度明显增加，由IRI引起的肠道微生物失调得到改善[38]。与其他益生菌一样，*L. casei Zhang*在改善肠道炎症和肠黏膜屏障损伤方面表现出优异的疗效[38]。*L. casei Zhang*可增强结肠中屏障连接蛋白occludin的表达[38]。研究[38]表明，*L. casei Zhang*通过下调纤维化相关基因和促纤维化细胞因子的表达，促进肾脏修复，减轻慢性肾间质纤维化。此外，*L. casei Zhang*可提

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供部分独立于原始肠道菌群的肾脏保护作用[38]。

*Lactobacillus*通过减轻炎症反应，降低氧化应激水平来预防AKI。*Lactobacillus salivarius* BP121主要通过影响依赖AMPK和TLR4的紧密连接蛋白组装，抑制IS和PCS等尿毒症毒素的产生发挥肾脏保护作用[28]。与BP121相比，*Lactobacillus acidophilus* ATCC 4356的抗氧化应激效果更好。ATCC 4356可激活抗氧化应激的重要通路——核因子红细胞系2相关因子2(nuclear factor erythroid 2-related factor 2，Nrf2)/血红素加氧酶-1(heme oxygenase-1，HO1)轴，降低丙二醛(malondialdehyde，MDA)的表达并促进超氧化物歧化酶(superoxide dismutase，SOD)和Nrf2的表达[40]。ATCC 4356还通过调节PI3K/Akt信号通路发挥抗炎作用[40]。

Ikeda等[41]从水果和蔬菜中分离出2种新型益生菌，补充这2种益生菌可通过调控*Akkermansia muciniphila*的数量，减轻氧化应激和AKI。在脓毒症继发AKI的患者中，服用益生菌治疗后，病死率呈下降趋势，但对肾功能恢复无明显影响[42]。此外，益生菌联合内皮祖细胞移植能显著改善肠道微环境，促进SCFA的生成和血管内皮细胞的有效增殖，为临床早期防治AKI和肾纤维化提供了新靶点[43]。

3.2 后生元

2019年，国际益生菌和益生元科学协会将后生元定义为对宿主健康有益的无生命微生物和/或其成分的制剂[44]。后生元对肠道微生物群和宿主可产生积极的影响，并在改善AKI患者预后方面显示出较好的效果。在大鼠肾脏IRI模型和缺氧复氧损伤的HK-2细胞模型中，丁酸钠通过下调外源发状分裂相关增强子-1(hairy and enhancer of split 1，Hes 1)，促进过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor alpha，PPARα)的转录，抑制氧化应激、炎症和细胞凋亡[45]。乙酸盐可促进肾上皮细胞的增殖和抑制凋亡基因*Bcl-2*表达，减少肾组织中凋亡细胞的数量；增加自噬途径相关蛋白ATG-7的表达，激活细胞自噬[37]。乙酸钠可显著减少AKI后活性氧的生成，减轻肾纤维化[46]。端粒缩短、活性氧生成增加、沉默信息调节因子2相关蛋白1(silent information regulator 2-related protein 1，SIRT1)和Klotho蛋白质表达减少以及炎症等均可促进p16/p-Rb和p53/p21/p-Rb通路的激活[47]。乙酸钠可以通过调节p16/p-Rb和p53/p21/p-Rb通路改善肾脏衰老[46]。*D*-丝氨酸可抑制肾小管损伤并促进肾小管增殖，从而减轻IRI引起的肾损伤[11]。然而，AKI中*D*-丝氨酸代谢的确切机制尚未明确，可能与肾小管细胞衰老途径中的一般性调控阻遏蛋白2(general control nonderepressible 2，GCN2)相关[11]。

3.3 中药

近年来，许多中药被证实可以通过调节肠道菌群来改善AKI。大黄素是中药大黄的主要活性成分，其可减少肠源性尿毒素的蓄积，加快肠源性尿毒素的清除速度，缓解肠黏膜损伤，改善肾功能[48]。在通过盲肠结扎穿孔术建立的脓毒症AKI小鼠模型中，中药复方凉血活血方可通过调节肠道菌群，恢复肠道屏障，抑制NLRP3/caspase-1/GSDMD信号通路的活化，减少肾上皮细胞焦亡[49]。茯苓水粉可以逆转AKI后嘌呤代谢异常，增加次黄嘌呤和黄嘌呤，有助于恢复肠上皮细胞的能量代谢，修复顺铂引起的肠道损伤；此外，茯苓水粉还可能通过重建肠道微生物群来调节不饱和脂肪酸的生物合成，改善肠黏膜免疫系统功能，发挥保护作用[50]。黄芩苷等对AKI显示出很好的疗效，但是否通过肠道菌群发挥作用仍需要进一步研究[51-52]。

4 结 语

越来越多的研究证明肠道菌群在AKI中的作用，改变肠道菌群组成可能会给AKI患者带来更好的结局。随着人们对肠道菌群的进一步了解，更多创新的治疗策略将被应用于AKI的治疗，缓解AKI向CKD的进展，减少相关远端器官不良事件的发生。但是，由于实验方法、民族、年龄等的差异，部分菌群在AKI中的改变缺乏一致性，为以肠道菌群为基础的靶向治疗带来了挑战。益生菌、后生元等的补充治疗目前还处于实验室阶段，是否能为临床所用依然存疑。AKI发生急，进展快，同时伴随诸多其他器官、系统的改变，通过改善肠道微生态治疗AKI能否在短期发挥疗效值得进一步深入的研究。

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参考文献

[1] Kellum JA, Romagnani P, Ashuntantang G, et al. Acute kidney injury[J]. Nat Rev Dis Primers, 2021, 7: 52. https://doi. org/10.1038/s41572-021-00284-z.

[2] Morales-Alvarez MC. Nephrotoxicity of antimicrobials and antibiotics[J]. Adv Chronic Kidney Dis, 2020, 27(1): 31-37.

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https://doi.org/10.1053/j.ackd.2019.08.001.

[3] Messerer DAC, Halbgebauer R, Nilsson B, et al. Immunopathophysiology of trauma-related acute kidney injury [J]. Nat Rev Nephrol, 2021, 17(2): 91-111. https://doi. org/10.1038/s41581-020-00344-9.

[4] Ozrazgat-Baslanti T, Loftus TJ, Mohandas R, et al. Clinical trajectories of acute kidney injury in surgical sepsis: a prospective observational study[J]. Ann Surg, 2022, 275(6): 1184-1193. https://doi.org/10.1097/SLA.0000000000004360.

[5] Watchorn J, Huang DA, Bramham K, et al. Decreased renal cortical perfusion, independent of changes in renal blood flow and sublingual microcirculatory impairment, is associated with the severity of acute kidney injury in patients with septic shock [J]. Crit Care, 2022, 26(1): 261. https://doi.org/10.1186/s13054-022-04134-6.

[6] Thomas K, Zondler L, Ludwig N, et al. Glutamine prevents acute kidney injury by modulating oxidative stress and apoptosis in tubular epithelial cells[J/OL]. JCI Insight, 2022, 7 (21): e163161[2023-11-01]. https://doi.org/10.1172/jci. insight. 163161.

[7] Rane MJ, Zhao YG, Cai L. Krüppel-like factors (KLFs) in renal physiology and disease[J]. EBioMedicine, 2019, 40: 743-750. https://doi.org/10.1016/j.ebiom.2019.01.021.

[8] Aranda-Rivera AK, Cruz-Gregorio A, Aparicio-Trejo OE, et al. Mitochondrial redox signaling and oxidative stress in kidney diseases[J]. Biomolecules, 2021, 11(8): 1144. https://doi. org/10.3390/biom11081144.

[9] Yang J, Kim CJ, Go YS, et al. Intestinal microbiota control acute kidney injury severity by immune modulation[J]. Kidney Int, 2020, 98(4): 932-946. https://doi. org/10.1016/j. kint. 2020. 04.048.

[10] Lee SA, Cozzi M, Bush EL, et al. Distant organ dysfunction in acute kidney injury: a review[J]. Am J Kidney Dis, 2018, 72 (6): 846-856. https://doi.org/10.1053/j.ajkd.2018.03.028.

[11] Nakade Y, Iwata Y, Furuichi K, et al. Gut microbiota-derived D-serine protects against acute kidney injury[J/OL]. JCI Insight, 2018, 3(20): e97957[2023-11-01]. https://doi. org/10.1172/jci. insight.97957.

[12] 张然, 张晗. 急性肾损伤患者血清KLF8和CXCL8水平与肠道菌群的关系研究[J]. 中国病原生物学杂志, 2023, 18(6): 713-716. https://doi.org/10.13350/j.cjpb.230618.
ZHANG Ran, ZHANG Han. Study on the relationship between serum KLF8 and CXCL8 levels and intestinal flora in patients with acute renal injury[J]. Journal of Pathogen Biology, 2023, 18(6): 713-716. https://doi.org/10.13350/j.cjpb.230618.

[13] Zou YT, Zhou J, Zhu JH, et al. Gut microbiota mediates the protective effects of traditional Chinese medicine formula Qiong-yu-Gao against cisplatin-induced acute kidney injury[J/OL]. Microbiol Spectr, 2022, 10(3): e0075922[2023-11-01]. https://doi.org/10.1128/spectrum.00759-22.

[14] Manoharan I, Swafford D, Shanmugam A, et al. Genetic deletion of LRP5 and LRP6 in macrophages exacerbates colitis-associated systemic inflammation and kidney injury in response to intestinal commensal microbiota[J]. J Immunol, 2022, 209(2): 368-378. https://doi.org/10.4049/jimmunol.2101172.

[15] Wang YH, Zhang YG. Kidney and innate immunity[J]. Immunol Lett, 2017, 183: 73-78. https://doi.org/10.1016/j.imlet. 2017.01.011.

[16] Park SW, Kim M, Kim JY, et al. Paneth cell-mediated multiorgan dysfunction after acute kidney injury[J]. J Immunol, 2012, 189(11): 5421-5433. https://doi. org/10.4049/ jimmunol.1200581.

[17] Usuda H, Okamoto T, Wada K. Leaky gut: effect of dietary fiber and fats on microbiome and intestinal barrier[J]. Int J Mol Sci, 2021, 22(14): 7613. https://doi.org/10.3390/ijms22147613.

[18] Mishra SP, Wang B, Jain S, et al. A mechanism by which gut microbiota elevates permeability and inflammation in obese/diabetic mice and human gut[J]. Gut, 2023, 72(10): 1848-1865. https://doi: 10.1136/gutjnl-2022-327365.

[19] Xiang H, Wang Y, Yang L, et al. Novel MAGL inhibitors alleviate lps-induced acute kidney injury by inhibiting nlrp3 inflammatory vesicles, modulating intestinal flora, repairing the intestinal barrier, and interfering with serum metabolism[J]. Molecules, 2023, 28(21): 7245. https://doi: 10.3390/ molecules28217245.

[20] Yang J, Ji GE, Park MS, et al. Probiotics partially attenuate the severity of acute kidney injury through an immunomodulatory effect[J]. Kidney Res Clin Pract, 2021, 40(4): 620-633. https:// doi.org/10.23876/j.krcp.20.265.

[21] Kim MG, Cho WY, Chung SM, et al. Altered gut microbiome plays an important role in AKI to CKD transition in aged mice [J]. Front Med, 2023, 10: 1238960. https://doi. org/10.3389/ fmed.2023.1238960.

[22] Chen YY, Chen DQ, Chen L, et al. Microbiome-metabolome reveals the contribution of gut-kidney axis on kidney disease [J]. J Transl Med, 2019, 17(1): 5. https://doi. org/10.1186/ s12967-018-1756-4.

[23] Gupta K, Bhurwal A, Law C, et al. Acute kidney injury and hepatorenal syndrome in cirrhosis[J]. World J Gastroenterol, 2021, 27(26): 3984-4003. https://doi. org/10.3748/wjg. v27. i26.3984.

[24] Nakano T, Watanabe H, Imafuku T, et al. Indoxyl sulfate contributes to mTORC1-induced renal fibrosis via the OAT/NADPH oxidase/ROS pathway[J]. Toxins, 2021, 13(12): 909. https://doi.org/10.3390/toxins13120909.

[25] Devlin AS, Marcobal A, Dodd D, et al. Modulation of a circulating uremic solute via rational genetic manipulation of the gut microbiota[J]. Cell Host Microbe, 2016, 20(6): 709-715. https://doi.org/10.1016/j.chom.2016.10.021.

[26] Rydzewska-Rosołowska A, Sroka N, Kakareko K, et al. The links between microbiome and uremic toxins in acute kidney injury: beyond gut feeling-a systematic review[J]. Toxins, 2020, 12(12): 788. https://doi.org/10.3390/toxins12120788.

[27] Wang WJ, Hao GH, Pan Y, et al. Serum indoxyl sulfate is associated with mortality in hospital-acquired acute kidney injury: a prospective cohort study[J]. BMC Nephrol, 2019, 20

©Journal of Central South University (Medical Science). All rights reserved.

(1): 57. https://doi.org/10.1186/s12882-019-1238-9.

[28] Lee TH, Park D, Kim YJ, et al. *Lactobacillus salivarius* BP121 prevents cisplatin-induced acute kidney injury by inhibition of uremic toxins such as indoxyl sulfate and p-cresol sulfate via alleviating dysbiosis[J]. Int J Mol Med, 2020, 45(4): 1130-1140. https://doi.org/10.3892/ijmm.2020.4495.

[29] Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders[J]. Gut, 2021, 70(6): 1174-1182. https://doi. org/10.1136/gutjnl-2020-323071.

[30] Shi HH, Chen LP, Wang CC, et al. Docosahexaenoic acid-acylated curcumin diester alleviates cisplatin-induced acute kidney injury by regulating the effect of gut microbiota on the lipopolysaccharide- and trimethylamine- *N*-oxide-mediated PI3K/Akt/NF-κB signaling pathway in mice[J]. Food Funct, 2022, 13(11): 6103-6117. https://doi.org/10.1039/d1fo04178a.

[31] Martin-Gallausiaux C, Marinelli L, Blottière HM, et al. SCFA: mechanisms and functional importance in the gut[J]. Proc Nutr Soc, 2021, 80(1): 37-49. https://doi.org/10.1017/S0029665120006916.

[32] Gong J, Noel S, Pluznick JL, et al. Gut microbiota-kidney cross-talk in acute kidney injury[J]. Semin Nephrol, 2019, 39 (1): 107-116. https://doi.org/10.1016/j.semnephrol.2018.10.009.

[33] Ríos-Covián D, Ruas-Madiedo P, Margolles A, et al. Intestinal short chain fatty acids and their link with diet and human health [J]. Front Microbiol, 2016, 7: 185. https://doi. org/10.3389/fmicb.2016.00185.

[34] Chou YT, Kan WC, Shiao CC. Acute kidney injury and gut dysbiosis: a narrative review focus on pathophysiology and treatment[J]. Int J Mol Sci, 2022, 23(7): 3658. https://doi. org/10.3390/ijms23073658.

[35] Schlatterer K, Peschel A, Kretschmer D. Short-chain fatty acid and FFAR2 activation - A new option for treating infections? [J]. Front Cell Infect Microbiol, 2021, 11: 785833. https://doi.org/10.3389/fcimb.2021.785833.

[36] Liu YZ, Li YJ, Loh YW, et al. Fiber derived microbial metabolites prevent acute kidney injury through G-protein coupled receptors and HDAC inhibition[J]. Front Cell Dev Biol, 2021, 9: 648639. https://doi.org/10.3389/fcell.2021.648639.

[37] Andrade-Oliveira V, Amano MT, Correa-Costa M, et al. Gut bacteria products prevent AKI induced by ischemia-reperfusion [J]. J Am Soc Nephrol, 2015, 26(8): 1877-1888. https://doi.org/10.1681/ASN.2014030288.

[38] Zhu H, Cao CJ, Wu ZC, et al. The probiotic *L. casei Zhang* slows the progression of acute and chronic kidney disease[J/OL]. Cell Metab, 2021, 33(10): 1926-1942. e8[2023-11-01]. https://doi.org/10.1016/j.cmet.2021.08.015.

[39] Al-Harbi NO, Nadeem A, Ahmad SF, et al. Short chain fatty acid, acetate ameliorates sepsis-induced acute kidney injury by inhibition of NADPH oxidase signaling in T cells[J]. Int Immunopharmacol, 2018, 58: 24-31. https://doi. org/10.1016/j.intimp.2018.02.023.

[40] Zhang P, Han XW, Zhang X, et al. *Lactobacillus acidophilus* ATCC 4356 alleviates renal ischemia-reperfusion injury through antioxidant stress and anti-inflammatory responses and improves intestinal microbial distribution[J]. Front Nutr, 2021, 8: 667695. https://doi.org/10.3389/fnut.2021.667695.

[41] Ikeda Y, Suga N, Matsuda S. Efficacy of life protection probably from newly isolated bacteria against cisplatin-induced lethal toxicity[J]. Microorganisms, 2023, 11(9): 2246. https://doi.org/10.3390/microorganisms11092246.

[42] Chávez-Íñiguez JS, Ibarra-Estrada M, Gallardo-González AM, et al. Probiotics in septic acute kidney injury, a double blind, randomized control trial[J]. Ren Fail, 2023, 45(2): 2260003. https://doi.org/10.1080/0886022X.2023.2260003.

[43] 姚颖, 张和平, 曾锐, 等. 益生菌联合内皮祖细胞移植延缓肾脏病进展的关键技术及其应用[Z]. 武汉: 2018. http://www.whkx.org.cn/news_show.aspx?id=43538.
YAO Ying, ZHANG Heping, ZENG Rui, et al. Key technologies and applications of probiotics combined with endothelial progenitor cell transplantation to delay the progression of kidney disease[Z]. Wuhan: 2018. http://www.whkx.org.cn/news_show.aspx?id=43538.

[44] Salminen S, Collado MC, Endo A, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics [J]. Nat Rev Gastroenterol Hepatol, 2021, 18(9): 649-667. https://doi.org/10.1038/s41575-021-00440-6.

[45] Wang Q, Ma XY. Gut microbial sodium butyrate alleviates renal ischemia-reperfusion injury by regulating HES1/PPARα [J]. Mol Immunol, 2022, 150: 20-28. https://doi. org/10.1016/j.molimm.2022.07.009.

[46] Zheng JY, Wang SC, Tang SC, et al. Sodium acetate ameliorates cisplatin-induced kidney injury *in vitro* and *in vivo* [J]. Chem Biol Interact, 2023, 369: 110258. https://doi. org/10.1016/j.cbi.2022.110258.

[47] Zhou B, Wan Y, Chen R, et al. The emerging role of cellular senescence in renal diseases[J]. J Cell Mol Med. 2020 Feb;24 (3): 2087-2097. https://doi: 10.1111/jcmm.14952.

[48] 孙蒋, 罗静雯, 姚文杰, 等. 大黄素对急性肾损伤大鼠肠道菌群的调节作用[J]. 中国中药杂志, 2019, 44(4): 758-764. https://doi.org/10.19540/j.cnki.cjcmm.20181105.002.
SUN Jiang, LUO Jingwen, YAO Wenjie, et al. Effect of emodin on gut microbiota of rats with acute kidney failure[J]. China Journal of Chinese Materia Medica, 2019, 44(4): 758-764. https://doi.org/10.19540/j.cnki.cjcmm.20181105.002.

[49] 周旻, 杨磊, 卓玉珍, 等. 凉血活血方对脓毒症急性肾损伤小鼠肠道菌群及NLRP3/caspase-1/GSDMD焦亡通路的影响[J]. 中华危重病急救医学, 2023, 9(3):250-255. https://doi.org/10.3760/cma.j.cn121430-20221122-01018.
ZHOU Min, YANG Lei, ZHUO Yuzhen, et al. Effect of Liangxue Huoxue decoction on intestinal flora and NLRP3/caspase-1/GSDMD signaling pathway in mice model of sepsis-induced acute kidney injury[J]. Chinese Critical Care Medicine, 2023, 9(3): 250-255. https://doi. org/10.3760/cma. j.cn121430-20221122-01018.

[50] Zou YT, Zhou J, Wu CY, et al. Protective effects of *Poria*

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cocos and its components against cisplatin-induced intestinal injury[J]. J Ethnopharmacol, 2021, 269: 113722. https://doi.org/10.1016/j.jep.2020.113722.

[51] 刘雪, 秦振志, 管陈, 等. 野黄芩苷通过CCN1介导抑制核转录因子-κB信号通路改善脂多糖诱导的肾损伤[J]. 中华危重病急救医学, 2022, 34(4): 400-406. https://doi. org/10.3760/cma.j.cn121430-20210401-00767.
LIU Xue, QIN Zhenzhi, GUAN Chen, et al. Scutellarin alleviates lipopolysaccharide-induced renal injury via mediating cysteine-rich protein 61-connective tissue growth factor-nephroblastoma overexpressed gene 1 expression to inhibit nuclear factor-κB signaling pathway[J]. Chinese Critical Care Medicine, 2022, 34(4): 400-406. https://doi. org/10.3760/cma.j.cn121430-20210401-00767.

[52] 乐健伟, 樊恒, 孙敏, 等. 黄芩苷对脓毒症小鼠急性肾损伤的保护作用及机制研究[J]. 中华危重病急救医学, 2021, 33(7): 866-870. https://doi. org/10.3760/cma. j. cn121430-20201204-00756.
LE Jianwei, FAN Heng, SUN Min, et al. Protective effect and mechanism of Baicalin on acute kidney injury in septic mice [J]. Chinese Critical Care Medicine, 2021, 33(7): 866-870. https://doi.org/10.3760/cma.j.cn121430-20201204-00756.

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