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肠道菌群在急性肾损伤中的作用机制研究进展

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摘　要

急性肾损伤(Acute Kidney Injury, AKI)作为临床常见病，病死率高，预后差。近年来，聚焦于肠道菌群与AKI的研究逐渐增多，提示了肠－肾轴可能是干预AKI的靶点。通过对肠道菌群及其失调对AKI的互相影响，如肠道屏障破坏、免疫反应被激活、肠道菌群代谢产物改变等方面进行综述，旨在为AKI的预防和治疗提供新靶点、新途径。

关键词

急性肾损伤，肠道菌群

Research Progress on the Mechanism of Intestinal Flora in Acute Renal Injury

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Abstract

Acute kidney injury (AKI) is a common clinical with mortality and poor prognosis. In recent years, studies focusing on the interaction between intestinal microbiota and AKI have gradually emerged, suggesting that the gut-kidney axis may be the target of intervention in AKI. This article reviews the interaction of intestinal microbiota and dysbiosis on AKI, such as the destruction of intestinal

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barrier, activation of immunity and the changes of intestinal metabolites, in order to provide new strategies for the prevention and treatment of AKI.

Keywords

Acute Kidney Injury, Gut Microbiota

1. 引言

急性肾损伤(Acute Kidney Injury, AKI)是一组异质性疾病，其特征是肾小球滤过率突然下降，表现为血清肌酐浓度升高或少尿[1]。据报道，AKI 发生在约 10%~15%的住院患者中，而重症监护室中的 AKI 发生率超过 50% [2]。肾功能的缓慢恶化或持续性肾功能障碍与肾细胞和肾单位的不可逆损失相关，这可能导致慢性肾脏病(Chronic Kidney Disease, CKD) [3]。近年来，肠道菌群与各种疾病之间的互相作用是一大研究热点，败血症[4]、动脉粥样硬化[5]、糖尿病[6]、肝炎[7]、肥胖症[8]等疾病都与肠道菌群及其代谢产物有着密不可分的关系。肾脏疾病和肠道菌群之间也存在重要关联，有研究发现约 36%~70%终末期肾病患者表现出肠道功能障碍[9] [10] [11]，证实慢性肾脏病患者的肠道菌群组成及结构改变，肠道屏障发生功能障碍，致使有害代谢物入血，导致炎症反应加剧[12] [13] [14] [15]。近年越来越多的研究证据表明肠道菌群及其代谢产物在 AKI 的发展过程中同样起到重要作用[16] [17] [18]。因此，肠道菌群对 AKI 之间的影响和作用有望成为治疗 AKI 的新方向。

2. 肠道菌群及其变化

正常人体肠道中有超过 1000 种微生物，而每个个体的微生物群落具有其独特性且是相对稳定的[19]。人类肠道中的大多数细菌属于四个门：厚壁菌、拟杆菌、变形杆菌和放线菌[16]。肠道菌群被认为是人体生理学中具有重要功能的虚拟器官[20]，肠道菌群参与营养素的消化、吸收和合成[21]，其过程中分解代谢产生的各种物质参与机体免疫调节[22]、能量代谢[23]、神经内分泌活动[24]等。而在病理状态下，肠道菌群的组成和稳定性将会发生改变，从而影响机体健康。

有研究发现在肾缺血再灌注(Ischemia Reperfusion, IR)模型小鼠中，肠道菌群的各个种属的丰度发生变化[25]，其特征主要是肠杆菌数量增加，乳杆菌和反刍球菌数减少[17]。在顺铂诱导的 AKI 大鼠中则同样发现乳杆菌减少，而梭菌、丹毒丝菌有增加[18]。这些研究的发现足以说明了肾脏疾病与肠道菌群之间存在密切关系。

3. 肠道菌群与 AKI 的相互影响

3.1. 肠道屏障被破坏与 AKI 的相互影响

肠道黏膜上皮是分隔开肠道共生细菌与身体其他部分的屏障[26]，主要由肠道上皮细胞和细胞间的紧密连接(Tight Joint, TJ)如 ZO 蛋白、claudin 蛋白和连接粘附因子组成[18]。肠黏膜上皮屏障的完整性是肠道菌群发挥正常生理功能和宿主防御发育的重要保障[26]。在 CKD 大鼠中发现其结肠黏膜中 claudin-1、claudin-2 蛋白的表达显著下降，结肠固有层中单核细胞大量浸润，肠道屏障功能受损，导致全身炎症[27]。

而在 IR 小鼠中，同样发现 claudin 蛋白表达明显下降，肠黏膜上皮细胞凋亡数量增加以及 Th1、Th17 应答增强，炎症因子 TNF-α、IFN-γ 等分泌增加，这一系列改变导致肠道屏障完整性受损，进而引起内毒素水平上升，肠道通透性增加，更多肠源性毒素进入循环进一步加重肾脏损伤[17]。在败血症 AKI 期间，肠道黏膜屏障的破坏、肠道微生物菌群的改变会促进 AKI 的发展，当 AKI 进一步加重时，炎症介质和代谢产物的清除率降低则会进一步导致肠道损伤和黏膜屏障的破坏[4]。

3.2. 肠道菌群在 AKI 细胞免疫炎症反应中的作用

固有免疫和适应性免疫反应均可介导肾损伤以及 AKI 的恢复，树突状细胞、单核细胞/巨噬细胞、中性粒细胞、T 淋巴细胞和 B 淋巴细胞都在 AKI 的疾病发展过程中起到一定的作用[28]。除此之外，在肠道中，Tregs 细胞的功能受到微生物组成的严重影响[29]，同时也可以通过调节和诱导固有免疫应答和适应性免疫应答来影响肠道相关淋巴组织的发育和肠道免疫稳态[30]。

3.2.1. 固有免疫

单核细胞和巨噬细胞是固有免疫和炎症的关键效应器和调节器[31]，他们在体内维持稳态、监测、免疫应答以及组织损伤和修复中发挥关键作用[32]。活化的巨噬细胞有两种表型，促炎型 M1 巨噬细胞和抗炎型 M2 巨噬细胞[33]。Li 等人[34]在脓毒症 AKI 大鼠中发现，AKI 后 72 小时 M2 巨噬细胞明显增多，利用上调 IL-10 的表达和抑制 TNF-α 的分泌来减轻肾脏损害，在 M2 巨噬细胞被消耗后，这种肾脏保护作用消失且肾小管细胞增殖被显著抑制。而阿托伐他汀对肾缺血再灌注损伤的改善作用也是通过促进 M1 巨噬细胞转变为 M2 巨噬细胞得以实现[35]。F4/80 被认为是成熟驻留巨噬细胞的细胞表面标志物[36]，在 Emal 等人[37]的研究中发现，在利用抗生素进行肠道菌群耗竭后，小鼠肾脏驻留巨噬细胞和骨髓单核细胞中的 F4/80 和趋化因子受体 CX3CR1 和 CCR2 表达降低，肾脏损害、缺血得到改善，由此可见，肠道菌群的耗竭通过降低肾脏固有巨噬细胞的成熟来保护肾脏。CCR2/CCL2 轴在炎症性单核细胞募集和召集浸润巨噬细胞中起主要作用[38]。研究发现 IR 小鼠，肠道菌群耗竭后其单核细胞向 CX3CL1 和 CCL2 配体的迁移能力下降，说明肠道菌群耗竭可以通过降低骨髓单核细胞的成熟来保护肾功能[37]。

树突状细胞是免疫系统中的抗原提呈细胞，能够协调固有免疫和适应性免疫功能共同实现机体免疫功能[39]。在利用产短链脂肪酸(Short-chain fatty acids, SCFAs)的细菌处理 IR 诱导的 AKI 小鼠后发现，补充 SCFAs 可以调节炎症过程，降低树突状细胞的成熟，并抑制 CD4+和 CD8+T 细胞增殖的能力，减轻肾小管上皮细胞凋亡并促进其增殖[40]。

肾脏疾病与炎症密不可分，而炎症的发展离不开巨噬细胞、树突状细胞、淋巴细胞等免疫细胞与肾实质细胞的相互作用[41]。Jang 等人[42]在 IR 小鼠模型中发现，无菌小鼠的正常肾脏中存在更多的 NKT 细胞和更低的 IL-4 水平，而在 IR 后，肾脏中出现更多的 CD8+T 细胞且肾脏损伤更严重，显而易见，肠道微生物可以影响肾脏淋巴细胞的表型和细胞因子的表达，且对 IR 后的肾损害有一定影响。

3.2.2. 适应性免疫

有研究显示无菌小鼠中的 Tregs 细胞比例降低了数倍，肠道菌群可以诱导 Tregs 细胞参与维持对肠道抗原的耐受性[43]。Yang 等人的研究中发现口服抗生素消除肠道微生物可以防止缺血/再灌注损伤，其保护肾脏的作用与 Th17、Th1 反应降低以及 Tregs 细胞和 M2 巨噬细胞的扩张有关[17]。有研究利用高盐饮食喂养 AKI 大鼠后发现，其肾脏中 Th17 细胞明显增加，间质纤维化被加快，加速了向 CKD 的转变[44]。在抗中性粒细胞胞浆抗体(ANCA)相关性肾小球肾炎患者中存在大量的 Th17 细胞，同时在小鼠中发现 Th17 细胞以 S1P 受体依赖的方式从肠道排出，又经过 CCL20/CCR6 轴迁移到肾脏，而耗竭肠道 Th17 细胞可以改善肾脏病情[45]。有研究表明免疫细胞中的 IL-17 在干扰素 1 (Interferon-I, IFN-I)诱导的新月体肾

炎过程中对于巨噬细胞肾脏浸润所必需的趋化因子的表达至关重要[46]。Sang 等人[47]在小鼠 AKI 模型中发现，在 AKI 后，小肠 Paneth 细胞增加了 IL-17A 的合成和释放，同时带来了严重的肠细胞凋亡和炎症，而在门静脉和全身循环中 IL-17A 也明显增加。IL-23 在慢性炎症和 Th17 细胞活化中起着关键作用，从而导致 IL-17 的分泌[48]。在 IL-23 受体缺陷型小鼠中发现，T 细胞产生的 IL-2 数量增加，IL-17 数量减少[49]。由此可见，Th17 细胞的增殖和维持有赖于 IL-23，而抗 IL-23 的单克隆抗体如 Guselkumab、Ustekinumab 可以阻断这个过程[50] [51]。而 IL-17 同样可以被单克隆抗 IL-17A 抗体如 Brodalumab，Secukinumab 和 Ixekizumab 破坏[52]。

IL-10、IL-4 等细胞因子在肾脏损伤中有一定保护作用。IL-10 可以保护 IR 后的无菌小鼠肾脏炎症的发生，在利用药物阻断 IL-10 后无菌小鼠出现了显著的死亡率和致死率[53]。在对正常小鼠进行双侧肾脏的 IR 之后发现，IL-4、IL-10 的水平较无菌小鼠更高，肾脏损伤程度更轻[42]。Marques 等人[54]研究发现，IL-4 敲除小鼠在 IR 后肾小管损伤和细胞再生受损明显。

多个研究证明，通过调节肠道菌群可减少炎症因子的产生，从而起到保护肾脏的作用。Haro 等人[55]在 LPS 诱导的内毒素 AKI 小鼠模型中发现，予以预防性干酪乳杆菌治疗通过降低促炎细胞因子、TNF-α、IL-6 的表达影响炎症发展。而在顺铂诱导的 AKI 猪中，添加乳杆菌混合物可以减少 TNF-α、IL-6 的产生，同时防止肾小管细胞凋亡[56]。唾液乳杆菌 BP121 抑制肠源毒素的产生，调节 5’AMP 活化蛋白激酶(5’AMP-activated protein kinase, AMPK)和 Toll 样受体 4 (Toll-like receptor) TLR4 依赖性 TJ 组装，下调肾脏炎症介质和减少氧化应激来保护顺铂诱导的下肾损害的发生[18]。

3.3. 肠道菌群相关代谢产物对 AKI 的影响

3.3.1. 肠源性内毒素合成增加和潴留

IS 可以损伤线粒体代谢活性并诱导细胞肥大，激活内质网应激，并且促进促纤维化和促炎因子的分泌，抑制肾小管上皮细胞增殖，促进细胞凋亡和肥大[57]。肠道菌群代谢产物有硫酸吲哚酚(Indoxyl Sulfate，IS)、硫酸对甲酚(P-cresyl sulfate, PCS)、氧化三甲胺(Trimethylamine Oxide, TMAO)等，其中 IS 和 PCS 由色氨酸、芳香氨基酸和酪氨酸的细菌发酵产生，在肝脏或肠黏膜中硫酸化[58]，不能通过血液透析有效去除[59]。IS、PCS 等尿毒症毒素可以加速肾小球硬化、肾小管间质损伤甚至是肾功能丧失[60]。IS、PCS 浓度与心血管疾病、透析患者死亡率以及 CKD 的发生相关[59] [61] [62]。在顺铂诱导的 AKI 大鼠中同样发现其血清 IS、PCS 水平升高[18]，随着 AKI 程度的加重，IS、PCS 浓度逐渐升高[63]。研究发现，在接受 5/6 肾切除术的大鼠中，可能是由于微生物种群改变和 IS 本身破坏肠道屏障引起血清 IS 和 PCS 水平增加[64]。Wang 等人[65]发现，AKI 患者中血清 IS 升高与其预后死亡风险增加相关。IS 可以通过 C/EBP 同源蛋白(CHOP)的增加来诱导近端管状细胞内质网应激，口服肠道毒素吸附剂可以降低 CKD 大鼠的血清 IS 浓度，同时减低免疫组织化学中 CHOP 的管状表达[66]。内皮细胞表达的有机阴离子转运蛋白(Organic anion transporter, OAT)参与 IS 和 PCS 的转运[47]。在顺铂诱导的 AKI 大鼠中 IS、PCS 水平明显升高，利用口服活性炭吸附剂 AST-120 可以降低其水平，并改善大鼠肾基底外侧有机离子转运蛋白 OAT1、OAT3 的表达和功能[67]。在对接受 5/6 肾切除术的大鼠连续予以 4 周的 PCS 给药后发现其肾小管损伤明显，可能是由于细胞内积聚 PCS，导致 NADPH 氧化酶(Nicotinamide adenine dinucleotide phosphate, NADPH)活性和活性氧(Reactive oxygen species, ROS)产生增加，进而引发参与肾纤维化的炎性细胞因子的诱导[68]。

TMAO 通过转化生长因子 β (transforming growth factor β, TGF-β)/Smad3 信号通过引起肾小管间质纤维化和功能障碍[69]。TMAO 由肠道菌群从饮食营养物质和肉碱中合成的[70]，可以通过透析去除[71]。随着肾功能下降，血清 TMAO 浓度显著增加[72]，其与进展性肾纤维化和功能损害的风险较高以及长期生存率较低有关[69]。在一项对高脂饮食(High-fat diets, HFD）诱导的肥胖小鼠模型中发现，TMAO 在循

环中升高，促进肾脏氧化应激和炎症而导致肾间质纤维化和功能障碍[73]。在顺铂诱导的小鼠 AKI 中发现，予以二十二碳六烯酸酰化姜黄素酯可以明显降低肾小管的损伤，其可能的机制是通过降低脂多糖和 TMAO 水平，阻止 LPS 和 TMAO 诱导的 PI3K/Akt/NF-κB 信号通路实现的[74]。

3.3.2. 短链脂肪酸生成减少

SCFAs 是一组由肠道微生物群发酵的代谢产物，其包括乙酸、丙酸、丁酸等。SCFAs 的减少与很多疾病的发生有关，包括有炎症性肠病、肥胖症、糖尿病、多发性硬化症、结肠癌等[75]，在 IR 诱导的 AKI 小鼠粪便中同样发现 SCFAs 水平显著降低[17]。SCFA 在 AKI 和 CKD 中的保护作用主要通过抑制组蛋白乙酰酶(Histone Deacetylases, HDAC)活性、阻止 TGF-β1 信号通路、减少细胞外调节蛋白激酶(Extracellular regulated protein kinases, ERK)的磷酸化来实现[75] [40] [76]。SCFA 的信号传导主要是通过激活 G 蛋白偶联受体 GPR41 和 GPR109A 实现的[76]。研究发现，利用 SCFA 治疗 IR 小鼠，其血清肌酐和尿素水平明显降低[40]。Al-Harbi 等人[77]在脓毒症 AKI 中发现，给予小鼠 SCFA 后其肾脏损伤得以恢复，主要是因为 SCFA 减弱了 HDAC 活性，对 NOX2/ROS 信号传导产生抑制作用，改善了氧化与抗氧化之间的平衡。在造影剂肾病的大鼠的研究中同样发现，丁酸可以通过抑制 NF-κB 活化减少炎症因子，同时降低血清肌酐水平[78]。而近年多个关注于益生菌或益生元改善 AKI 的研究中均发现，其作用主要是通过改善肠道微生物，增加 SCFA 的产生得以实现的[79] [80] [81]。

3.3.3. 氨基酸代谢紊乱

小鼠肠道内含有丰富的来源于肠道菌群的 D-氨基酸，D-氨基酸氧化酶(D-Amino acid oxidase, DAO)对 D-氨基酸进行氧化脱氨基作用产生 H_2O_2，从而保护小肠黏膜表面免受病原体侵害[82]。Sasabe 等人[83]发现在肾脏 IR 之后小鼠血清中 D-丝氨酸水平升高，而 L-丝氨酸水平降低。在肾缺血再灌注 AKI 小鼠粪便中可检测到多种氨基酸，但只有 D-丝氨酸在肾脏中被检测到，同时在无菌小鼠粪便中没有找到 D-氨基酸，这表明肾损伤小鼠肠道菌群对 AKI 损伤做出反应产生 D-丝氨酸，并运送至肾脏[25]，而给予口服 D-丝氨酸可减轻 IR 损伤小鼠的肾小管损伤[25]。除此之外，在 AKI 患者中同样观察到 D-丝氨酸/L-丝氨酸比值与肾功能相关，提示 D-丝氨酸可能是 AKI 潜在的生物标志物[25]。Yasunori 等人[84]研究发现在 IR 小鼠模型中，D-丙氨酸通过 NMDA (N-methyl-d-aspartate)受体信号传导抑制 ROS 产生并提高线粒体膜电位，减少缺氧刺激引起的肾小管上皮细胞坏死。

4. 展望

目前对于 AKI 仍没有明确的药物治疗，作为临床常见病、高发病，AKI 有着不可忽视的高病死率，同时 AKI 后发展为 CKD 的可能性大大增加，带来的透析等长期护理的费用仍然十分沉重。随着近年来关于肠道菌群这一研究热点的出现，AKI 的防治似乎出现了新的转机，肠道菌群与肾脏之间是双向作用的，在疾病的发展过程中相互影响。多个研究表明通过干预肠道菌群或可改善肾脏疾病预后，但目前对于 AKI 与肠道菌群的研究多建立于顺铂诱导或缺血再灌注损伤模型下，并且多为动物研究，虽然已经有部分研究涉及临床应用，但多为慢性肾脏病或者单一的研究，不具有普适性。除此之外，AKI 的病因多种多样，肠道菌群及其代谢产物在不同病因 AKI 中的作用机制仍需要进一步研究，有望为 AKI 的预防和治疗提供新的转机。

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