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肠道菌群在肾性贫血中作用机制的研究进展

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【摘要】 肾性贫血是慢性肾脏病（chronic kidney disease，CKD）的常见并发症。人类肠道微生物群参与人体代谢、免疫等功能，对人类的健康调节起着至关重要的作用。研究表明肠道菌群紊乱与肾性贫血的发生、发展有着密切的关联。在CKD患者中肠道菌群紊乱可以通过促红细胞生成素生成减少、铁代谢紊乱、炎症和骨髓造血微环境紊乱等方式加重肾性贫血。而膳食纤维等益生元可以调节肠道微环境进而改善肾性贫血。本文综述了肠道菌群影响肾性贫血的作用机制及膳食纤维在其中的调节作用。

【关键词】 肾性贫血；肠道菌群；膳食纤维；慢性肾脏病
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Research advances on the mechanism of gut microbiota in renal anemia

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【Abstract】 Renal anemia is a common complication of chronic kidney disease (CKD). Human gut microbiota participates in human metabolism, immunity and other functions, playing vital roles in the regulation of human health. Numerous studies have demonstrated that any disorder of gut microbiota is closely correlated with the occurrence and development of renal anemia. Gut microbiota disorder may aggravate renal anemia through lower erythropoietin production, iron metabolism disorder, aggravating inflammation and bone marrow hematopoietic microenvironment disorder. Such probiotics as dietary fiber regulates intestinal microenvironment and improves renal anemia. This review focused upon the mechanism of the effect of gut microbiota on renal anemia and its regulatory role of dietary fiber.

【Key words】 Renal anemia; Gut microbiota; Dietary fiber; Chronic kidney disease

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肾性贫血是慢性肾脏病(chronic kidney disease, CKD)最具挑战性的多因素并发症之一,其发病机制包括促红细胞生成素(erythropoietin, EPO)的缺乏、铁代谢紊乱、慢性炎症以及骨髓造血微环境紊乱等[1]。目前对于肾性贫血的治疗方法主要包括应用红细胞刺激因子(erythropoiesis stimulating agents, ESAs)、低氧诱导因子脯氨酰羟化酶抑制剂(hypoxia-inducible factor prolyl hydroxylase inhibitor, HIF- PHI)和铁剂等[2]。肠道菌群是人类肠道中高度多样化的微生物群落,它们由400多种不同的菌种组成,主要包括5个门:疣微菌门、拟杆菌门、放线菌门、厚壁菌门、变形杆菌门,不同细菌门之间的相互作用形成了一个完整和平衡的细菌生态系统[3-5]。越来越多的研究表明肠道菌群紊乱会导致EPO缺乏、铁代谢紊乱、慢性炎症以及造血微环境紊乱等,进而促进了肾性贫血的发生。而应用膳食纤维(dietary fiber, DF)等益生元调节肠道微生物群已成为治疗肾性贫血的新策略。

一、肠道菌群紊乱导致EPO生成减少

在贫血中氧转运减少导致组织缺氧、激活缺氧诱导因子(hypoxia-inducible factor, HIF)系统、刺激EPO的产生。EPO是红细胞生成的主要激素调节因子,而肾脏是产生EPO的主要部位[7]。在CKD患者中肠道菌群介导的肠道生化环境的改变,会导致大量炎症细胞的产生和炎症因子的释放[8-9]。研究表明,在炎症大鼠模型中,白细胞介素1β(interleukin-1β, IL-1β)通过肿瘤坏死因子的间接作用,抑制肾EPO的产生。在慢性肾功能不全急性加重模型中,肿瘤坏死因子可通过核因子-κB(nuclear factor-kappa B, NF-κB)途径抑制EPO的转录[7]。CKD患者中蛋白质被肠道菌群发酵,优先转化为吲哚硫酸盐(indole sulfate, IS)等尿毒症毒素[10-11],而另一项研究发现,IS可显著抑制EPO mRNA的表达。在HepG2细胞中,IS处理减少了缺氧后HIF-α蛋白的核积聚,并抑制了缺氧反应元件荧光素酶的活性[12],进一步导致了EPO的生成减少,加重了肾性贫血。

因此肠道菌群紊乱介导的炎症状态会通过肿瘤坏死因子抑制EPO的生成,而IS等尿毒症毒素可通过抑制HIF系统,进而减少EPO的生成,最终加重肾性贫血。

二、肠道菌群紊乱导致铁代谢紊乱

饮食中的非血红素铁摄入肠道后,在十二指肠上皮细胞色素B(duodenal cytochrome B, DcytB)的催化下,铁(Fe^{3+})被还原为亚铁(Fe^{2+}),Fe^{2+}通过二价金属转运蛋白1(divalent metal tansporter 1, DMT1)被吸收到细胞内,而血红素铁则通过血红素载体蛋白被吸收。必要时,铁可通过细胞膜上的膜铁转运蛋白(ferroportin, FPN)释放到血液中[13],然后,血浆转铁蛋白和血清铁被输送到红细胞膜表面,与转铁蛋白受体结合进入细胞释放铁。细胞内的铁与线粒体中的铁卟啉结合形成血红蛋白,完成红细胞的成熟[14]。

肠道菌群失调会导致全身的炎症状态[8-9]。炎症通过白细胞介素6(interleukin-6, IL-6)、转录激活蛋白3(activator of transcription 3, STAT3)途径和骨形态发生蛋白(bone morphogenetic protein, BMP)-SMAD途径促进肝脏分泌铁调素[15-18]。铁调素与单核吞噬细胞和十二指肠细胞膜上铁转运体结合,促进FPN的内化和降解,导致单核巨噬细胞和十二指肠细胞铁输出受阻[19]。同时,研究发现铁调素能抑制DMT1和DcytB的功能,从而影响肠道铁的吸收[20]。这些因素导致血清铁不足,无法满足红细胞生成所需的铁而导致贫血。

三、肠道菌群紊乱促进炎症状态

CKD患者往往合并慢性微炎症状态,炎症因子的释放会加重肾性贫血。炎性细胞因子白细胞介素33(interleukin-33, IL-33)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和干扰素-α(interferon-α, IFN-α)等对骨髓中红系前体细胞的增殖和分化有抑制作用[22]。IL-1和TNF等细胞因子可通过干扰GATA-2或HNF4的转录,损伤产生EPO的肾上皮细胞等方式,抑制EPO的产生[21]。此外炎症状态下氧化应激增加导致红细胞膜脂质过氧化,同时炎性细胞因子促进巨噬细胞吞噬功能[23],共同导致红细胞寿命缩短。

肠道菌群紊乱可通过多种途径加重炎症。一方面,在CKD患者中因为肾小球滤过率降低,人体内尿素浓度随之

升高，导致其大量进入胃肠道。在肠腔内，尿素被肠道微生物脲酶水解形成大量的氨，进一步转化为氢氧化铵[10]。氢氧化铵会提高腔液的pH值，引起黏膜刺激，使结肠黏膜紧密连接Claudine-1、occludine和ZO1蛋白明显减少[24]。肠黏膜通透性的增加，导致巨噬细胞、树突状细胞和淋巴细胞的激活，促炎细胞因子和趋化因子的释放、炎症细胞的渗透，进而导致局部和全身的炎症[8]。另一方面，结肠上皮细胞分泌大量的尿酸和草酸，引起肠道生化环境改变，使产生短链脂肪酸（short chain fatty acid，SCFA）的有益菌群（包括乳杆菌科和普氏菌科）丰度减少[25]，导致其他微生物种群的过度生长和一些病原微生物的肠道易位[26]。细菌和内毒素的易位会通过NF-κB途径刺激免疫系统细胞（如巨噬细胞和树突状细胞），产生大量促炎细胞因子，导致全身炎症[9]。而SCFA特别是丁酸盐，可直接激活G蛋白偶联受体，抑制组蛋白脱乙酰酶，具有抗炎特性[27-28]。所以产SCFA菌群的减少也会加重全身的炎症[29]。

因此，肠道菌群水解尿素产生的代谢产物和肠道中的尿酸会改变肠道的生化环境，破坏肠道的紧密连接、导致细菌和内毒素的异位、SCFA的减少，引起炎症因子的大量释放。炎症因子通过抑制骨髓中红系细胞增殖分化、抑制EPO的生成、促进氧化应激、促进巨噬细胞吞噬功能，最终加重肾性贫血。

四、肠道菌群紊乱导致骨髓造血微环境的破坏

在大多数脊椎动物中，骨髓是造血的主要部位。除了造血细胞外，骨髓还具有有助于骨髓造血微环境稳态的细胞，包括间充质干细胞（mesenchymal stem cell，MSCs）、骨祖细胞、成骨细胞等[30]。MSCs和间充质祖细胞能产生多种支持造血干细胞的因子，包括血管周围趋化因子受体12（CXCL12）、血管生成素和干细胞因子。成骨细胞也能发挥相似的作用，产生多种支持造血干细胞的因子，包括血小板生成素和CXCL12[31]。

肠道菌群紊乱在尿毒症毒素的产生中起着重要的作用。CKD患者肠道菌群中含有促进IS和对甲酚硫酸盐（para-cresol sulfate，PCS）合成酶的细菌丰度更高[32]，蛋白质被肠道病原体发酵，优先转化为IS、PCS和氧化三甲胺等尿毒症毒素[10-11]。有研究表明，IS、PCS等尿毒症毒素会抑制MSC的增殖分化[33]，将MSCs置于尿毒症患者的血清中培养，细胞培养上清液中骨桥蛋白、骨钙素和I型胶原的水平增加而BMP-2和茜素红染色减少，表明骨破坏大于骨吸收[34]。同时基因表达分析显示ALPL、BGLAP和SPP1基因部分上调，COL1A1水平显著降低。I型胶原α1链的下调可能是最终成骨潜能降低的原因[33]。

因此，肠道菌群失调产生的IS和PCS可介导细胞毒性并抑制人MSCs的增殖，多种支持造血干细胞的因子减少，最终影响造血干细胞的造血功能，加重肾性贫血。

五、肠道菌群稳定HIF

HIF于1992年被发现是一种低氧诱导的转录因子，负责调节EPO基因的表达。HIF的转录活性主要由其降解速率控制，降解速率受氧感受器——脯氨基羟化酶结构域蛋白（prolyl hydroxylase domain proteins，PHD）的调节[35]。在常氧条件下，PHD可诱导HIF降解，但在缺氧或PHD抑制剂存在的情况下，PHD失活，HIF诱导其靶基因表达。HIF作用于肾脏和肝脏中产生EPO的细胞，从而诱导内源性EPO的产生和随后的造血，并且HIF还可以调节与铁代谢和利用有关分子的基因[36]。

人体肠道中的细菌、拟杆菌和梭状芽胞杆菌簇可将DF转化为短链脂肪酸[37]。单链脂肪酸刺激丙酮酸脱氢酶激酶，使丙酮酸脱氢酶复合体失活。灭活的丙酮酸脱氢酶复合物不能将丙酮酸转化为乙酰辅酶A来满足细胞的能量需求。因此，结肠细胞开始通过SCFA的β氧化产生乙酰辅酶A。增加氧化呼吸导致生理性缺氧、PHD失活，进而趋于稳定HIF[38]。HIF-1α可以调节肠上皮屏障的完整性，改善肠上皮屏障可以进一步减少细菌和内毒素的异位减少炎症的产生，从而改善肾性贫血[39]。HIF-2a是顶端和基底外侧铁转运蛋白的主要肠道转录调节因子，对细胞铁和氧水平很敏感。HIF-2a通过直接转录激活铁吸收，在缺铁和缺氧条件下的红细胞需求过程中，介导铁吸收的适应性增加[40]，进而纠正铁代谢紊乱，改善肾性贫血。

六、DF改善肠道菌群

DF是一种不被消化也不被吸收的碳水化合物聚合物，分为不可溶性DF和可溶性DF。不可溶性DF的主要作用是促进肠道蠕动、改善便秘。而参与宿主机体调节作用的主要是可溶性DF。可溶性DF在胃肠道中被细菌发酵，从而影响肠道细菌群落的组成以及微生物的代谢活动，进而影响宿主的健康[41]。DF可使结肠微生物的发酵活动从蛋白水解发酵转变为糖化发酵，进而通过肠腔内的糖酵解作用，使碳水化合物转化为乙酸、丁酸、丙酸等SCFA[42]。SCFA对人类宿主有多种影响，也是结肠细胞的重要营养物质。SCFA会导致管腔pH的降低，促进铁的溶解性，将铁还原到亚铁状态。重要的是，通过刺激上皮细胞的增殖，增强吸收表面[48]。同时肠道pH的降低导致微生物种群的改变，抑制了革兰阴性杆菌包括常见的病原体沙门菌和大肠杆菌的生长，使有益菌如乳杆菌和双歧杆菌的数量增加[44]，有研究发现，随着低聚半乳糖浓度的升高，乳酸杆菌属和双歧杆菌属的组分都逐渐升高。同时，肝脏处转铁蛋白受体、十二指肠处DMT1表达量增高促进了铁的吸收，进而改善肾性贫血[49]。

SCFA可以改善肠道菌群、增加益生菌的数量，而益生菌可维持肠上皮细胞的完整性，并使蛋白质发酵减少和相关多肽衍生有毒代谢物减少[34,45]。一方面，部分益生菌会产生物理屏障，通过定殖性抵抗和对有限生态位的竞争减少病原体复制的场所[46]。益生菌也可通过上调紧密连接蛋白-1的表达或阻止上皮紧密连接蛋白的再分布来增加细胞间顶端上皮紧密连接，从而维持肠道屏障的完整性[47]。最近的研究发现，SCFA可以通过稳定HIF增强肠道屏障功能[6]。肠道屏障结构与功能的正常可以减轻炎症因子的释放，也可以减少内毒素和细菌的易位，从而减少全身炎症

的产生，缓解肾性贫血。另一方面，代谢毒物的减少可进一步减轻对EPO分泌和骨髓造血微环境的影响。益生菌还可以降低尿毒症患者血清或粪便中吲哚-3-乙酸-O-葡萄糖醛酸苷、3-胍基丙酸和1-甲基肌苷的滞留溶质的丰度，从而减轻肾性贫血[43]。

七、展望

肠道菌群是人体中重要的组成部分，承担着不可或缺的作用。在CKD患者中，肠道菌群紊乱是导致肾性贫血加重的重要原因之一。DF作为一种通过饮食摄取的益生元，其所产生的不良反应和花费较少，与药物相比有很大优势，如何结合DF调节肠道菌群的作用综合治疗，进一步改善CKD患者的贫血仍待研究。这或许可以为肾性贫血的改善提出新的治疗方向。

利益冲突 所有作者均声明没有利益冲突

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