肠道菌群介导的免疫反应与高血压和慢性肾脏病的关系研究进展

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[摘要] 肠道菌群被认为与多种疾病相关，其中，肠道菌群与高血压、慢性肾脏病发生及发展的相关性研究近年来取得了较大进展。高血压和慢性肾脏病的发生、发展破坏了原有的肠道菌群组成，进而又促进了高血压和慢性肾脏病的发展。高血压、慢性肾脏病与肠道菌群改变的因果关系及其确切机制仍需进一步探讨。该文回顾了高血压和慢性肾脏病患者的肠道微生物组成，重点总结了共生微生物影响宿主免疫对原发疾病进展的作用，阐述了肠道菌群介导的免疫反应与高血压、慢性肾脏病之间除细菌细胞壁及脂多糖外主要通过短链脂肪酸、血管紧张素Ⅱ、氧化三甲胺等相互联系，以期为寻找治疗高血压和慢性肾脏疾病的潜在方法提供参考。

[关键词] 慢性肾脏病；高血压；肠道菌群；免疫

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Research progress on the relationship of intestinal flora-mediated immune response to hypertension and chronic kidney disease

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[**Abstract**] Intestinal flora is increasingly considered to be associated with multiple diseases, such as insulin resistance, bile acid metabolism and inflammatory reaction. Research on the relationship of intestinal flora to the occurrence and development of hypertension and chronic kidney disease has made remarkable progress in recent years. The occurrence and development of hypertension and chronic kidney disease disrupt the original gut microbiota composition, further contribute to the advancement of hypertension and chronic kidney disease. So far, further discussion is needed on the causality and exact mechanism of intestinal flora to hypertension and chronic kidney disease. The composition of intestinal microorganisms in hypertension and chronic kidney disease has been reviewed in present paper, and focused on the role of symbiotic microorganisms in affecting the host immunity and the progress of the primary disease, and summarized the relationship of intestinal flora mediated immune response to hypertension and chronic kidney disease, mainly interlinked each other through short-chain fatty acids, angiotensin Ⅱ and trimethylamine oxide to provide the basis for finding potential treatment methods for hypertension and chronic kidney disease.

[**Key words**] chronic kidney disease; hypertension; intestinal flora; immunity

高血压是指以体循环动脉血压[收缩压和(或)舒张压]增高为主要特征(收缩压≥140 mmHg，舒张压≥90 mmHg)，可伴有心、脑、肾等器官功能或器质性损害的临床综合征。在我国，除糖尿病肾病和肾小球肾炎以外，高血压肾损害是最常见的终末期肾病(end stage renal disease，ESRD)病因(约占17%)。慢性肾脏病(chronic kidney disease，CKD)与高血压互为病因，相互关联。最近有大量研究表明，高血压、慢性肾脏病与肠道菌群所致免疫反应关系密切[1-4]，但具体的病理生理机制尚未阐明。因此，本文就肠道菌群所致免疫反应与高血压、慢性肾脏病相关性的最新研究进展进行综述，以期为寻找治疗高血压、慢性肾脏病的潜在方法提供参考。

1 肠道菌群

在健康人体肠道内，肠道菌群保持共生与拮抗的关系以维持相对稳态，并参与人体各种生理和病

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理过程，在肠道内外慢性疾病的发生、发展中起着至关重要的作用。肠道正常菌群构成机体肠道保护屏障的一部分，可抵抗有害微生物的侵入，保证肠道黏膜的完整性，影响机体的免疫力、胰岛素敏感性、体重，甚至影响大脑的思维觉醒功能[5-8]。在人的一生中，肠道菌群也是随着生长发育过程而发生改变的。有研究在胎盘和胎粪中检测到细菌，认为这是人体肠道菌群最早的出现时间[9-10]。随后，新生儿可通过分娩及母乳喂养获得母体的微生物，而此过程可受到一些因素如饮食、卫生、抗生素使用、疾病及运动的影响[11-14]。到两岁左右，更适应肠道环境的微生物在优胜劣汰的竞争中成为优势菌群，此时的肠道菌群比较接近于成年人。

健康成人的肠道菌群主要由拟杆菌门和厚壁菌门组成，但也包括少量的放线菌门、变形菌门和疣微菌门。成年人的肠道菌群相对稳定，但仍受抗生素、疾病等因素的影响。同时，肠道菌群失调可通过参与胰岛素抵抗、胆汁酸代谢、炎症反应来影响糖尿病、消化道疾病、心血管疾病及肥胖等的发生与发展。用16S rRNA检测高血压大鼠和高血压患者粪便发现，其肠道菌群的丰度和多样性明显下降，厚壁菌门/拟杆菌门(Firmicutes/Bacteroidetes，F/B)的比值增大，提示肠道菌群已发生紊乱[15]。Yang等[16]发现，无论是在动物模型还是人类患者中，高血压组的肠道菌群物种相对丰度较正常组明显下降；且在动物模型中进一步发现，自发性高血压大鼠(spontaneously hypertensive rats，SHR)的F/B比值是正常血压大鼠的5倍。在CKD疾病状态下，微生物蛋白水解产物的过度产生导致肠道菌群失调，这些产物的肾清除率降低可导致病情恶化甚至进展至尿毒症状态[17]。阿克曼氏菌是近年来研究的热门菌群，因其在预防肥胖、改善胰岛素抵抗、延缓早衰症及渐冻症等方面效果确切，故有望成为下一代益生菌。阿克曼氏菌水平与血压、成年人腰围及三酰甘油水平呈负相关[18]。与高血压前期受试者和原发性高血压受试者相比，健康受试者血液中含有更高水平的三氯乙醇葡萄糖醛酸苷，其含量与双歧杆菌和阿克曼氏菌菌群水平呈正相关，与普氏菌呈负相关[19]。

2 肠道菌群相关免疫反应

免疫应答分为固有免疫(先天性免疫)和适应性免疫(获得性免疫)，固有免疫系统主要由单核/巨噬细胞、树突细胞、粒细胞、自然杀伤细胞和全身性自然杀伤T细胞(natural killer T cell，NKT细胞)组成，而适应性免疫主要由T、B细胞参与。肠道菌群主要通过多聚糖A(polysaccharide，PSA)、鞭毛蛋白、肽聚糖及产生的代谢产物等诱导固有免疫应答。肠道细菌与病原体一样表达病原体相关的分子模式，可导致肠壁淋巴组织中淋巴滤泡的生成，最终激活免疫相关反应[20]。肠道菌群不仅可调节肠道免疫细胞的活化，还可调节骨髓中免疫祖细胞的分布[21-22]。同时，肠道微生物还可诱导宿主免疫成熟。叉头框(forkhead box，Fox)是脊椎动物叉头样转录因子的总称，是一个具有多种功能的转录因子大家族，其表达水平及功能与调节性T细胞(regulatory cell，Treg)密切相关。叉头状转录因子3(Foxp3)基因如发生突变，可影响Treg的发育成熟，是目前公认的最敏感的Treg标志物。已有研究证实肠道菌群可促进表达Foxp3的Tregs扩增或分化[23-24]。某些梭菌属细菌(如梭状芽孢杆菌)具有促进结肠Tregs的潜能，部分肠道菌群可控制黏膜、NKT细胞及淋巴样结构的发育和成熟[25-26]。另外，作为细菌细胞壁重要组成部分的肽聚糖具有调节外周免疫功能的潜力[27]。肠道细菌可与肠壁黏膜淋巴组织共同参与了机体的免疫反应。

3 与高血压、CKD的关系

3.1 与高血压的关系 免疫系统可通过介导的慢性炎性反应参与高血压的发生发展过程，其中单核巨噬系统可通过介导血管炎性反应、调节中枢交感神经系统及肾脏水盐代谢而参与血压调节。促炎性的单核及巨噬细胞可对未确定的危险信号做出免疫反应，从而促进血管收缩和钠潴留。McMaster等[28]发现，在高血压期间，树突细胞可增加活性氧(reactive oxygen species，ROS)的生成，导致脂质过氧化而形成异基酮(异黄酮或γ-酮醛)，后者一旦与树突细胞中的赖氨酸结合，即可被装载并作为非自身抗原呈递给T细胞。在抗原呈递过程中，还可刺激树突细胞中白细胞介素(interleukin，IL)-1β、IL-6及IL-23的表达，从而进一步促进活化T细胞释放效应细胞因子[29]。多个动物研究发现，原发性高血压可能是由树突细胞介导的抗原特异性的自身免疫性疾病[30-32]。在多种高血压动物模型中均观察到T细胞活化可使血压升高，但其机制尚不明确[33-35]。Rudemiller等[36]发现，高血压患者体内促炎性的$CD8^+$ T细胞比例增大，促炎因子分泌明显增多，表明T细胞介导的炎症反应在高血压发生中起到了一定作用。最近的研究发现，虽然B细胞不直接参与高血压的发生，但可在其发生过程中起协同作用[37]。

3.2 与CKD的关系 CKD及ESRD患者免疫系统功能发生异常后，易出现感染并发症，是该人群除心血管疾病外的主要死亡原因。Gupta等[38]发现，慢性肾功能不全患者的炎症标志物与肾功能指标(如

肾小球滤过率或血清胱抑素C)及蛋白尿的程度呈负相关。CKD中存在的免疫缺陷主要是由抗原呈递树突细胞、T细胞和B细胞的减少，以及单核细胞和多形核白细胞的吞噬能力改变引起的。树突细胞可通过增强吞噬作用、分泌促炎细胞因子和趋化因子等加速肾组织的损伤。树突细胞在CKD患者的免疫平衡受损中可能发挥主要作用，而免疫平衡受损则与CKD患者心血管风险增加明显相关[39-40]。树突细胞刺激自然杀伤细胞后可释放细胞因子，促进肾脏疾病的进展[28,41-42]。巨噬细胞可促进抗炎细胞因子IL-1、IL-6、IL-23、ROS等的分泌，这些细胞因子与肾损伤密切相关。巨噬细胞还可释放基质金属蛋白酶引起肾纤维化。细胞毒性T淋巴细胞可被特定的肾组织抗原激活，造成局部的损伤和炎症，而$CD8^+$ T细胞释放的肾表面特异性抗原进一步加重了肾损伤。有研究发现，B淋巴细胞增多可加重肾损伤，反之则可延缓肾损伤[43]。CKD患者体内补体的激活可诱导部分促炎细胞因子及促纤维化介质的释放，使肾脏细胞功能发生改变，从而导致慢性肾损伤。CKD患者体内的尿毒症毒素还可通过破坏细胞间接触来损害内皮屏障功能和修复能力，这与血管内皮细胞钙黏蛋白和闭锁小带蛋白1的表达降低有关[44-45]。尿毒症毒素中的尿素被含脲酶的细菌(主要为梭菌、肠球菌、志贺氏菌和大肠埃希菌)代谢为氨，可使胃肠道pH值升高及胃肠道上皮细胞紧密连接减少，从而增加胃肠道通透性，导致细菌移位或细菌产物进入体循环。在CKD炎症反应过程中，某些炎性因子的产生又进一步促进了肾功能损害和炎症的发生。线粒体ROS介导的嗜中性白细胞碱性磷酸酶3(neutrophilic alkaline phosphatase 3，NALP3)炎性小体激活增加了醛固酮引起的肾小管细胞损伤[46]。肾上皮细胞通过表达Toll样受体(Toll-like receptors，TLR)如TLR1、TLR6促进肾脏炎症的发生。因此，CKD患者中普遍存在炎症反应，这也是判断其预后的重要标准。

4 高血压、CKD与肠道菌群相关的免疫反应

微炎症状态在多种慢性疾病(如高血压、CKD等)的发生和发展过程中起关键作用。肠道菌群可通过介导多种炎性因子的产生参与机体的微炎症状态。高血压患者肾脏中T细胞浸润的炎性环境可促进部分细胞因子如IL-17A、γ干扰素(IFN-γ)和肿瘤坏死因子α(TNF-α)的分泌，改变钠的代谢，促进肾脏损伤，并最终引发高血压肾损害[47]。慢性肾衰竭患者体内尿毒症毒素的蓄积可导致循环内炎症反应，影响血管张力，从而影响机体的血压水平。Desai等[48]发现，纤维剥夺或无纤维饮食可致部分降解黏蛋白的细菌过度生长，从而使黏液屏障厚度降低。由于结肠黏液层是病原体入侵的早期障碍，因此，黏液的降解可促进病原体定植，增强细菌易位性，并可能加剧肾脏的炎症状态和损害，加快高血压的进程。肠道细菌除可通过细菌细胞壁及脂多糖诱发机体产生免疫反应参与高血压和CKD的发生和发展外，还通过细菌的代谢产物如短链脂肪酸(short chain fatty acids，SCFAs)、血管紧张素Ⅱ(angiotensin Ⅱ，Ang Ⅱ)、氧化三甲胺(trimetlylamine oxide，TMAO)等产生的免疫反应介导高血压和CKD的疾病进展。

4.1 SCFAs SCFAs(乙酸、丙酸和丁酸等)是由盲肠及结肠中的厌氧菌产生的，可作为机体及肠道细菌的能量来源。其中，丁酸不仅是结肠细胞的主要能量来源，而且还可通过抗炎作用保持肠动态平衡[49]。Andrade-Oliveira等[50]发现，SCFAs可减轻局部及全身的炎症反应，降低氧化应激及细胞凋亡水平，从而改善肾功能不全、降低血压水平。目前认为，SCFAs主要通过两个机制调节机体炎症反应：(1)组蛋白去乙酰基酶类的抑制；(2)细胞表面G蛋白偶联受体(G protein-coupled receptors，GPCR)如GPR41、GPR43、GPR109a及嗅觉受体78(olfactory receptors78，Olfr78)的激活。SCFAs可通过GPCR诱导前列腺素E_2的释放及抗炎细胞因子IL-10的表达，从而抑制人类单核细胞的炎症反应。SCFAs中的丁酸可通过外源性的GPR109a在结肠细胞系及离体小鼠结肠中抑制脂多糖诱导的核因子-κB(nuclear factor kappa-B，NF-κB)活化。SCFAs中的乙酸盐可通过GPR43途径刺激人结直肠腺癌细胞及正常结肠细胞中的钾流出和超极化，使NLRP3炎性小体激活。在Ang Ⅱ诱导的高血压模型中补充丁酸盐，可改变肠道微生物群的组成，促进黏液周转，使肠道上皮屏障更完整；并可降低平均动脉压，改善心脏压力感受器反射，使心脏交感神经张力降低，从而恢复内皮功能[51]。炎性细胞(如中性粒细胞、巨噬细胞、树突细胞和T细胞)可表达GPR41和GPR43，并对SCFAs做出反应以减轻炎症反应[49]。有研究发现，粪便SCFAs排泄量较低的受试者肠道中富含有益微生物，包括嗜黏蛋白阿克曼菌、克里斯滕森菌科、甲烷短杆菌属及颤螺菌属；而粪便中较高的SCFAs水平则与较低的肠道微生物群多样性指标、较高的肠道通透性、全身炎症、高血糖、血脂异常、肥胖及高血压相关[52]。

4.2 Ang Ⅱ Ang Ⅱ在肾内的多种活性可通过与Ang Ⅱ1型受体(angiotensin type 1 receptor，AT1R)的结合诱导，AT1R位于肾小动脉、肾小球系膜细胞和近端肾小管细胞膜上，肾小球中AT1R的激活

可加速肾损伤和炎症反应。Ang Ⅱ-AT1R结合产生的影响包括收缩肾小球传入和传出小动脉，促进系膜细胞收缩，并减少肾髓质血流。最近的研究表明，Ang Ⅱ介导的血浆和粪便代谢产物的变化完全依赖于肠道菌群，揭示了肠道微生物群在响应Ang Ⅱ的代谢组学改变中的重要作用[53]。近年来的新发现拓宽并超越了传统肾素-血管紧张素系统(renin-angiotensin system，RAS)的观念[53-54]。与循环RAS相比，肾脏中血管紧张素转换酶2(angiotensin converting enzyme 2，ACE2)可调节Ang 1-7产生更有效的靶点。ACE2在肾小管上皮细胞中呈高表达，可通过促进局部Ang Ⅱ的降解来改善肾病，而ACE2缺乏可加重Ang Ⅱ诱导的肾纤维化和炎症反应。此外，ACE2可调节肠道氨基酸稳态、抗菌肽的表达及肠道菌群的平衡状态，其缺乏会损害色氨酸的稳态，使肠道微生物组成发生改变，进而改变肠道对炎症的易感性。

mTOR可调节抗菌肽的表达，从而影响肠道微生物群的组成。厄贝沙坦可抑制应激诱导的AT1通路的激活，从而减少肠道ROS的累积和炎症反应，使ACE2/B0AT-1的表达升高，恢复mTOR和p70S6K的活性，抑制色氨酸代谢紊乱[55]。在益生菌发酵过程中，ACE抑制肽可被释放并产生降压作用[56]。在机体的消化过程中，部分细菌如隐球菌等会产生ACE抑制剂、肾素抑制剂和抗氧化分子[57]；而当此类细菌数量减少时，则可改变肾素-血管紧张素-醛固酮系统，使血压升高[58]。

4.3 TMAO 机体摄入含有胆碱、甜菜碱、左旋肉碱或三甲胺结构的食物(如红肉、鸡蛋等)后，在肠道菌群(主要为法氏杆菌和双歧杆菌)的协助下转化成三甲胺，在黄素单加氧酶作用下转化为TMAO。越来越多的证据表明，血浆中的TMAO水平升高可促进高血压的发生与发展[59-61]。TMAO是影响肾脏预后的重要尿毒症毒素之一，不仅参与肾脏纤维化进程，还可通过促进动脉粥样硬化、高血压、糖尿病、炎症等病理过程加重肾脏损害。多项研究表明，当血浆TMAO水平升高时，促炎细胞因子的表达增加，TMAO的血浆浓度与微炎症状态呈正相关[62-64]。Eckardstein等[64]的研究表明，当血浆TMAO水平升高时，血浆TNF-α、sTNF-R p75及sTNF-R p55也较高。Chou等[62]发现，TMAO水平与IL-1β和超敏C反应蛋白水平呈正相关。值得注意的是，有研究发现较高的TMAO水平可诱导NLRP3的活化[65]。NLRP3炎性小体是由模式识别受体激活形成的多蛋白复合物，活化的NLRP3炎性小体可促进IL-18及IL-1β的成熟和分泌，并引发炎症和免疫反应。固有免疫系统通过一系列模式识别受体识别病原体，促使免疫细胞做出反应并分泌炎性细胞因子。有证据表明，TMAO可能与炎症相关的标志物(如IL-6、TNF-α及C反应蛋白等)及内皮功能障碍相关的标志物[如内皮素-1(ET-1)]的表达升高相关，进而导致蛋白和脂多糖水平升高[65-66]。TMAO参与炎性标志物如IL-6、TNF-α的表达，可能与NF-κB激活的B细胞κ轻链增强p65转录因子的核内定位有关[67]。TMAO可通过促进NF-κB磷酸化来调节炎性相关基因如IL-6、TNF-α的表达[66]。有研究发现，给小鼠饲喂高脂饮食可使TMAO水平升高，从而加重肾小管间质纤维化及胶原蛋白沉积，并使SMAD3蛋白磷酸化增加，肾损伤分子-1、血浆胱抑素C、NAAPH氧化酶及TNF-α等炎症相关指标上升，而三甲胺形成抑制剂3,3-二甲基-1-丁醇可阻止这些作用[68]。

5 总结与展望

综上所述，肠道细菌所致的免疫反应与高血压及CKD紧密相关，且在疾病的诊治过程中取得了一定成就，但仍存在不足之处：(1)目前的研究多局限于动物实验，缺乏大量的临床试验支持；(2)虽然已经明确肠道菌群所致的免疫反应与高血压及CKD的发生、发展具有相关性，但因果关系尚不清楚；(3)肠道菌群所致的免疫反应参与高血压及CKD发生、发展的确切机制尚不明确。基于这些研究，益生菌、益生元、SCFAs及口服抗生素被认为是治疗CKD和高血压的新方案。尽管这些疗法尚未在临床实践中广泛应用，但在部分人体试验或动物研究中被证实有效。粪便菌群移植(FMT)是指将经过处理的健康者的粪便溶液直接植入受者的肠道以改变其肠道微生物构成的方法，目前已成为一种高效的治疗方法，并有望成为一种恢复肠道营养不良的途径。

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