微生物学通报
Microbiology China
http://journals.im.ac.cn/wswxtbcn

Jul. 20, 2024, 51(7): 2271−2279
DOI: 10.13344/j.microbiol.china.230993

专论与综述

IgA 肾病与肠道微生态及肠黏膜免疫关系的研究进展

支文强，李亚峰*

山西医科大学第五临床医学院，山西 太原 030012

支文强, 李亚峰. IgA 肾病与肠道微生态及肠黏膜免疫关系的研究进展[J]. 微生物学通报, 2024, 51(7): 2271-2279.
ZHI Wenqiang, LI Yafeng. Advances in the relationship of IgA nephropathy with intestinal microecology and intestinal mucosal immunity[J]. Microbiology China, 2024, 51(7): 2271-2279.

摘　要：IgA 肾病(Immunoglobulin A nephropathy, IgAN)是一种多种机制共同参与免疫介导的肾小球疾病，是世界上最常见的原发性肾小球疾病。此外，许多疾病与 IgAN 的发生和进展相关(如炎症性肠病、肝炎及 HIV 病毒感染、干燥综合征等)，被称为继发性 IgAN。目前 IgAN 被广泛接受的发病机制是“多重打击学说”，该学说中 IgAN 发病的“扳机点”即为黏膜微生态失调导致的屏障功能破坏及免疫异常。肠道黏膜作为人体黏膜系统的重要组成部分，越来越多的研究表明肠道微生态失调、黏膜屏障功能受损及免疫调节异常在 IgAN 的发生发展中有重要作用，与此相关的治疗靶点也是目前的研究热点。本文就目前肠道微生态与肠黏膜免疫在 IgAN 发病机制中作用的研究进展进行综述，以期为未来从肠道微生态及免疫功能角度寻找 IgAN 新的治疗靶点提供思路。

关键词：IgA 肾病；肠道微生态；肠道菌群；肠黏膜免疫；代谢组学；发病机制

Advances in the relationship of IgA nephropathy with intestinal microecology and intestinal mucosal immunity

ZHI Wenqiang, LI Yafeng*

The Fifth Clinical Medical School, Shanxi Medical University, Taiyuan 030012, Shanxi, China

Abstract: Immunoglobulin A nephropathy (IgAN) is a common primary glomerular disease characterized by multifaceted, immune-mediated mechanisms. Additionally, several comorbidities, including inflammatory bowel disease, hepatitis, HIV infection, and Sjögren’s syndrome, are intricately linked to the genesis and progression of IgAN and collectively denoted

资助项目：国家自然科学基金(82170716)
This work was supported by the National Natural Science Foundation of China (82170716).
*Corresponding author. E-mail: yafengli@sxmu.edu.cn
Received: 2023-11-24; Accepted: 2024-01-28; Published online: 2024-03-21

as secondary IgAN. The multiple-hit hypothesis is currently the widely embraced pathogenesis framework for IgAN, positing mucosal dysbiosis-induced disruption of the barrier function and immune aberrations as pivotal triggers for IgAN pathogenesis. The intestinal mucosa, constituting a pivotal element of the mucosal system, is increasingly acknowledged for its substantive involvement in IgAN development. Perturbations in intestinal microbiota, compromised mucosal barrier integrity, and immune dysregulation are recognized as pivotal players in IgAN pathophysiology. Investigating the therapeutic targets associated with these facets currently represents a focal point in research. We comprehensively review the research advances in the roles of intestinal microecology and mucosal immunity in the pathogenesis of IgAN. This review aims to lay a foundation for exploring the novel therapeutic targets for IgAN from intestinal microbiota and immune functionality.

Keywords: Immunoglobulin A nephropathy; intestinal microecology; intestinal microbiota; intestinal mucosal immunity; metabolomics; pathogenesis

IgA 肾病(Immunoglobulin A nephropathy, IgAN)由病理学家 Berger 于 1986 年初次提出，他使用免疫荧光显微镜及电镜发现一组患者肾小球系膜的 IgA 沉积，并且发现这些患者的典型临床表现为反复发作的肉眼血尿合并上呼吸道感染[1]，这是最早关于 IgAN 的报道。IgAN 是目前世界上最常见的原发性肾小球疾病，确诊 IgAN 的患者 20 年后大约有 25%会发展为终末期肾病(end-stage renal disease, ESRD)并需要肾脏代替治疗，是全球公共卫生面临的重要问题[2]。相对而言，IgAN 在亚洲人中更常见，研究发现，患 IgAN 的亚洲人会比其他地区的人群临床表现更重，疾病进展风险更高[3-8]。

肠道黏膜作为人体黏膜系统的重要组成部分，肠道微生态的作用不容忽视。如肠道菌群组成出现变化，有益菌减少及致病菌增多，引起促炎代谢物的增多，往往导致肠道黏膜炎症，通透性升高，而致病菌产生的各种毒素及抗原等进入血液循环，导致了自身免疫反应及各种疾病的发生。目前，IgAN 被广泛认可的发病机制“多重打击学说”即认为在有 IgAN 遗传倾向的个体中，感染、微生物失调或其他事件破坏了黏膜屏障防御功能，慢性刺激(如病原微生物)被抗原呈递细胞接收，从而激活 B 细胞，并以 T 细胞依赖性或非依赖性方式分化为分泌 IgA 的浆细胞，微生物紊乱还会导致黏膜屏障受损，从而导致大量半乳糖缺乏的 IgA1 (galactose deficient-IgA1, Gd-IgA1)释放入血，与特异性抗体结合后沉积在肾脏组织中，导致 IgAN 的发生(图 1)[9-11]。越来越多的研究表明，肠道微生态失调、黏膜屏障功能受损及免疫调节异常在 IgAN 的发生发展中起到了重要作用[12-14]。本文将从肠道菌群组成变化、肠道及血清代谢物变化、肠屏障及免疫功能变化等角度

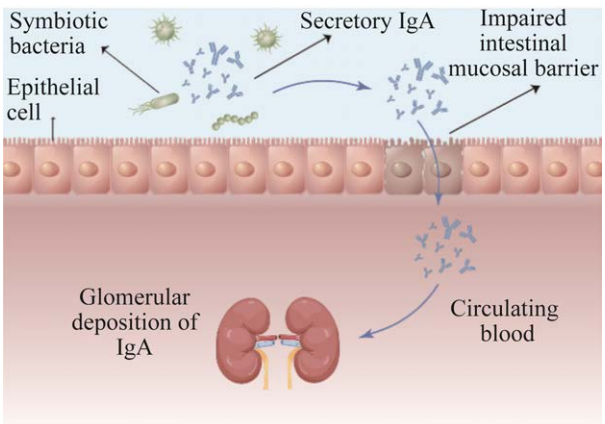

图 1 “多重打击”学说示意图

Figure 1 Schematic of the “multiple strike” doctrine.

分别阐述肠道微生态及肠黏膜免疫在IgAN发生发展中的作用,以期为未来从肠道微生态及免疫功能角度寻找 IgAN 新的治疗靶点提供思路。

1 IgAN 患者肠道菌群组成变化

肠道菌群作为肠道微生态的重要组成部分,对维持肠道微生态环境的稳定有重要作用。研究显示,与健康对照组相比,IgAN 患者存在菌群失调,肠道菌群多样性降低[15-17]。多项病例对照研究均发现IgAN组中志贺菌属(*Shigella*)及变形菌门(*Proteobacteria*)的相对丰度显著高于健康对照组[18-26]。而且志贺菌属丰度与估计肾小球滤过率(estimated glomerular filtration rate, eGFR)呈负相关,与尿白蛋白/肌酐(urinary albumin/creatinine ratio, uACR)呈正相关[19,23,26-27],动物研究也发现IgAN模型组肠道β变形菌目丰度显著增加[28]。研究还发现在 IgAN 患者组,肠道普雷沃氏菌(*Prevotella*)、粪球菌属(*Coprococcus*)、双歧杆菌(*Bifidobacterium*)丰度较低[23],基于数据库数据分析的生信研究也有相同结果[29],相关性分析显示,普雷沃氏菌丰度与 Gd-IgA1、脂多糖结合蛋白(lipopolysaccharide binding protein, LBP)、人可溶性 CD14 (soluble cluster of differentiation 14, sCD14)、细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1)、肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)水平呈负相关[20,24,26-27]。动物纵向研究也有类似发现,且双歧杆菌丰度降低与蛋白尿和血尿水平呈负相关,使用含双歧杆菌的益生菌处理IgAN小鼠可以显著缓解肠道菌群失调,表明双歧杆菌丰度降低可能与 IgAN 的严重程度有关[30]。然而也有一项临床研究显示 IgAN 患者组肠道中双歧杆菌丰度显著增加,这一不同结论可能与该研究纳入的IgAN患者限于疾病进展早期有关[27]。放线菌门(*Actinobacteria*)、肠道拟杆菌属(*Bacteroides*)、经黏液真杆菌属(*Blautia*)、瘤胃球菌属(*Ruminococcus*)等丰度的变化在先前的病例对照研究中得到了不同的结论。最新的孟德尔随机化研究结果显示放线菌丰度改变与IgAN患者白蛋白尿增加和预后较差之间存在关联[20-21,23-24,26-27,31-32]。值得注意的是,以上病例对照研究均来自中国人群。一项马来西亚的研究发现,与对照组相比,IgAN 组肠道梭杆菌门(*Fusobacteria*)显著增加,而广古菌门(*Euryarchaeota*)减少[33]。

在肠道菌群组成方面,IgAN 组与健康对照表现出了明显的差异,IgAN 患者存在菌群多样性的降低,但不同研究中出现了一些菌属丰度的不同变化趋势,包括动物研究及不同人群的研究。目前大多数相关研究是在中国人群中进行的,这可以为我们进一步在中国人群中探究肠道微生态在 IgAN 发病机制中的作用提供相对坚实的证据,并可以为通过调节肠道菌群寻找 IgAN 新的治疗靶点(如粪菌移植、益生菌配方、抗生素疗法等)提供思路。粪菌移植(fecal microbiota transplantation, FMT)是指将健康供体的肠道菌群通过一定方式移植到患者肠道,期望通过直接改变肠道微生物群恢复肠道微生态并减轻炎症,获得治疗效益。目前已经在肠道感染、多种全身代谢及免疫性疾病中得到了应用[34-35]。动物研究显示 IgAN 小鼠经 FMT 治疗后,炎症因子表达降低,uACR 显著降低[36]。我们使用肠菌胶囊对 IgAN 患者进行 FMT,结果显示患者肠道菌群多样性增加,治疗 3 个月后,24 h尿蛋白定量显著降低,且无明显不良反应[37]。国内另一团队也对两名难治性 IgAN 患者进行了 FMT,结果显示治疗后两名患者均达到临床缓解[38]。这些结果需要更大规模的临床研究进一步论证,作者团队正在进行患者招募以进一步探索其疗效及安全性,相关研究已注册在

clinicaltrials.gov (NCT05182775)及中国临床试验注册中心(ChiCTR2100053206)。

2 IgAN 患者肠道屏障功能变化

肠道屏障主要由黏蛋白形成的黏液层、肠上皮细胞之间的紧密连接以及肠道微生物群形成的微生态屏障组成。有害细菌可诱导肠上皮细胞凋亡和炎症，使黏蛋白或紧密连接蛋白(tight junction protein, TJP)减少，肠黏膜屏障被破坏，导致 Gd-IgA1 等抗原及毒素入血[39-41]。动物研究显示 IgAN 模型组肠黏膜组织紧密粘连蛋白 1 (zonula occludens-1, ZO-1)、闭锁蛋白(occludin, OCLN)、黏蛋白 2 (mucin 2, MUC2)的 mRNA 表达量均显著降低，ZO-1、OCLN、D-乳酸(D-lactic acid, D-LA)、血清可溶性细胞间黏附分子-1 (soluble intercellular adhesion molecule-1, sICAM-1)、脂多糖(lipopolysaccharides, LPS)表达也降低，相反，血清二胺氧化酶(diamine oxidase, DAO)和 D-LA 水平升高，这些都是肠道通透性的生物标志物[42-43]。临床研究也发现 IgAN 患者血清中 DAO、D-LA、sICAM-1、LPS 等均升高，且与血清和尿液中 Gd-IgA1 水平呈正相关，与肠道微生物群中放线菌、双歧杆菌等的减少呈显著负相关[24]。另一项研究进一步验证了该结果，并讨论了该过程可能与 TLR4/NF-κB 通路激活有关[44]。以上研究均表明，IgAN 患者存在肠道屏障功能障碍，肠屏障功能受损可能在 IgAN 起重要的致病作用，且与肠道菌群失调相关，未来需要更多基础研究探索这一过程的具体机制。

3 IgAN 患者代谢组学变化

肠道微生物群的代谢活性对于维持宿主的稳态和健康也至关重要，微生物变化会引起代谢变化，继而影响宿主的健康状态[10,45-47]。动物研究中肠道微生物群功能分析显示异生素生物降解和代谢、α-亚麻酸代谢、醚脂质代谢和谷胱甘肽代谢在 IgAN 大鼠中上调，而辅因子和维生素代谢、氨基酸代谢、能量代谢、柠檬酸循环以及 D-谷氨酰胺和 D-谷氨酸代谢下调，血清中主要参与脂质代谢、信号转导、碳水化合物代谢、氨基酸代谢等的代谢物也显著改变，该研究还发现使用中药汤剂真武汤后，IgAN 大鼠的肠道微生物群及血清代谢谱均趋于接近正常大鼠，且肠黏膜组织病理改变较前缓解[28]。临床研究发现 IgAN 患者的肠道不饱和脂肪酸和脂肪酸衍生物水平显著降低，亚油酸和花生四烯酸代谢途径的异常导致促炎性代谢物花生四烯酸水平升高，保护性肠道代谢物(如前列腺素衍生物和环氧脂肪酸)水平普遍降低。IgAN 患者中大多数吲哚代谢物，如吲哚-3-乙酸和 3-吲哚丙酸均显著下调。这些吲哚代谢物是芳香烃受体(aryl hydrocarbon receptor, AhR)信号转导的主要配体，是肠黏膜免疫屏障的重要组成部分，可有效促进肠黏膜上皮的更新并维持肠黏膜的完整性[22,48]。血清非靶向代谢组学显示在 IgAN 组中，儿茶酚、壬二酸、扁豆酸和 L-色氨酸富集，且与血肌酐(blood creatinine, Scr)、血尿素氮(blood urea nitrogen, BUN)、尿酸(uric acid, UA)和 24 h 尿蛋白定量呈正相关，与 eGFR 和血清白蛋白(albumin, ALB)呈负相关[16]。针对 Gd-IgA1 产生相关酶的研究则发现，与对照组相比，β-半乳糖苷酶、β-N-乙酰己糖苷酶、α-半乳糖苷酶和 α-N-乙酰半乳糖苷酶在 IgAN 组中显著富集，而 α-半乳糖苷酶和 α-N-乙酰半乳糖胺酶是蛋白质糖基化的关键酶[23]。

在这些代谢物中，短链脂肪酸(short-chain fatty acid, SCFA)可能有重要作用。研究发现 IgAN 组中产 SCFA 细菌丰度低于健康对照，IgAN 组中的乙酸、丙酸、丁酸、异丁酸和己酸

水平显著降低，且与肾损伤相关指标(24 h 尿蛋白水平、BUN 等)呈负相关[15]。由于双歧杆菌是一种主要的产 SCFA 细菌，研究者在 IgAN 模型鼠组中进行了以双歧杆菌为主的益生菌补充实验，结果发现小鼠的肠道菌群结构改善，肾脏 IgA 沉积减少；研究者还对 IgAN 小鼠直接补充了 SCFA，结果发现，该组小鼠肾脏组织 IgA 荧光强度降低，尿蛋白水平降低，血清炎症因子 TNF-α 和 IL-1β 水平也降低[30]。以上研究表明，IgAN 患者存在多种肠道及血清代谢物的改变，相较于对照组，IgAN 组促炎性代谢物水平升高，吲哚代谢物及短链脂肪酸等保护性代谢物水平降低。动物研究表明益生菌及 SCFA 的补充可以缓解 IgAN 的进展，未来需要临床相关研究进一步论证。

4 IgAN 患者免疫功能变化

在“多重打击学说”中，Gd-IgA1 等炎症因子的产生在 IgAN 的发生发展中有重要作用。肠道活化的 B 细胞在病原体和黏膜炎症性疾病中起着核心作用，上皮来源的 B 细胞激活因子(B-cell activating factor, BAFF)是 B 细胞发育的主要调节剂，它在黏膜相关淋巴组织(mucosal-associated lymphoid tissue, MALT)的 IgA 类别转换和浆细胞存活中起关键作用。肠道菌群通过对黏膜树突状细胞的 Toll 样受体连接，可以诱导炎症和促炎细胞因子的产生，诱导黏膜上皮细胞中 BAFF mRNA 的过表达，BAFF 的上调与肠道高 IgA 和 IgA 免疫复合物在肾小球系膜中的沉积有关。一项使用抗生素利福昔明干预的动物研究发现，IgAN 组治疗后 TNF-α 和 BAFF 基因转录下调，肠道炎症减少[49]。临床研究也表明 IgAN 患者血清 BAFF 水平较对照组显著升高，Gd-IgA1 水平也显著升高，且与 24 h 尿蛋白定量水平正相关。流式细胞分析发现，IgAN 患者血清中的浆母细胞、CCR9/整合素 β7 调节 B 细胞、记忆 B 细胞和肠道 IgA 记忆 B 细胞显著升高，幼稚 B 细胞的百分比较低，提示炎症状态，且在其他肾小球肾炎患者中未发现这些变化[50]。以上研究证明肠道菌群改变导致黏膜免疫的变化在 IgAN 发病机制中起着核心作用。新近的临床研究发现，与对照组相比，IgAN 患者血清中的 Gd-IgA1、LBP、sCD14、ICAM-1、C-反应蛋白(C-reactive protein, CRP)、IL-6、IL-10、IL-22 和 TNF-α 水平明显升高，且这些指标的变化与肠道菌群、肠黏膜屏障损伤指标及肠道代谢物变化相关[20,24,48]。最新的动物研究也发现 IgAN 小鼠的肠道及肾脏组织中的 Toll 样受体 4 (Toll-like receptor 4, TLR4)、髓样分化因子(myeloid differentiation factor 88, MyD88)和核因子 κB (nuclear factor kappa-B, NF-κB)表达上调，肠道组织中 BAFF 和增殖诱导配体(a proliferation inducing ligand, APRIL)及血清中 TNF-α 和 IL-6 的表达也上调[43-44]。另一项动物研究使用 TLR4 抗体和谷氨酰胺肠溶胶囊治疗 IgAN 小鼠，治疗后肠道功能修复，炎症因子水平降低，结果支持了 IgAN 与 LPS/TLR4 通路调节肠系膜 B 细胞分泌 Gd-IgA1 之间存在关系的假设[51]。此外，我们前期的相关研究还发现辅助 T 细胞 17 (T helper cell 17, Th17)的分化可能介导 IgAN 患者的异常体液免疫，IgAN 患者肾小球中巨噬细胞增加，调节性 T 细胞减少，基于药物-基因相互作用数据库(drug-gene interaction database, DGIdb)预测分析发现岩藻糖可能是 IgAN 的潜在治疗分子，先前的研究发现岩藻糖可抑制巨噬细胞的活化，它是肠黏膜免疫的重要调节因子，但其在 IgAN 中的应用仍需要进一步验证[52-54]。

总之，异常的黏膜免疫反应在 IgAN 的发生发展中有重要作用，且可能与 T 细胞、巨噬细胞的激活及 TLR4/NF-κB 通路有关。通过调节肠

道免疫功能治疗IgAN的代表性药物肠道靶向释放的布地奈德即定向作用于肠道相关淋巴系统来调节免疫功能，研究显示该药物可以显著降低IgAN患者的尿蛋白水平[55]。

5 总结与展望

目前对于IgA肾病仍无特异有效的治疗办法，肾素血管紧张素系统抑制剂仅为支持治疗；免疫抑制剂与激素的副作用较大，不良事件发生率高；扁桃体切除为侵入性手术，患者接受度不高，在我国研究较少。肠道靶向释放的布地奈德期望通过调节肠道免疫达到治疗效果，但缺乏亚洲人群相关研究。因此，揭示IgAN发病机制、寻找疾病靶向治疗方案成为IgA肾病诊治的当务之急。

本文总结了目前关于肠道微生态在IgAN发病机制及相关治疗策略的研究进展，现有的研究证据表明肠道菌群组成的变化、肠黏膜屏障功能的破坏、肠道和血清代谢物的变化及异常的黏膜免疫反应在IgAN的发病及进展过程中发挥了重要作用，提示相关研究可作为未来进一步研究的重点。特别是大多数关于IgAN患者肠道菌群组成的研究均来自中国人群，这为我们在中国人群中进行下一步研究提供了更充分的证据。但目前的研究仍存在一定不足：首先，先前的研究样本量较少，对于IgAN肠道菌群组成及代谢物的改变，小样本的研究不能得出统一的结论，未来需要进行大规模的临床研究进一步验证；其次，目前针对IgAN肠道微生态治疗IgAN的策略仅肠道靶向释放的布地奈德实现了临床应用，尚缺乏在亚洲人群中的研究证据，其他策略如FMT、益生菌配方、TLR4抗体、消化道黏膜保护剂等干预措施目前只进行了动物研究，FMT治疗有个案报告初步显示了其有效性及安全性，仍需更大规模的临床研究进一步验证，而通过生物信息学发现的岩藻糖等潜在治疗分子也需实验进行验证。

REFERENCES

[1] FEEHALLY J, CAMERON JS. IgA nephropathy: progress before and since Berger[J]. American Journal of Kidney Diseases, 2011, 58(2): 310-319.

[2] JARRICK S, LUNDBERG S, WELANDER A, CARRERO JJ, HÖIJER J, BOTTAI M, LUDVIGSSON JF. Mortality in IgA nephropathy: a nationwide population-based cohort study[J]. Journal of the American Society of Nephrology, 2019, 30(5): 866-876.

[3] LI L. End-stage renal disease in China[J]. Kidney International, 1996, 49(1): 287-301.

[4] KOYAMA A, IGARASHI M, KOBAYASHI M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research group on progressive renal diseases[J]. American Journal of Kidney Diseases, 1997, 29(4): 526-532.

[5] SZETO CC, LAI FM, TO KF, WONG TY, CHOW KM, CHOI PC, LUI SF, LI PK. The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria[J]. The American Journal of Medicine, 2001, 110(6): 434-437.

[6] GUTIÉRREZ E, ZAMORA I, BALLARÍN JA, ARCE Y, JIMÉNEZ S, QUEREDA C, OLEA T, MARTÍNEZ-ARA J, SEGARRA A, BERNIS C, GARCÍA A, GOICOECHEA M, de VINUESA SG, ROJAS-RIVERA J, PRAGA M, de ESTUDIO de ENFERMEDADES GLOMERULARES deLa SOCIEDAD ESPAÑOLA de NEFROLOGÍA (GLOSEN) G. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria[J]. Journal of the American Society of Nephrology, 2012, 23(10): 1753-1760.

[7] YU GZ, GUO L, DONG JF, SHI SF, LIU LJ, WANG JW, SUI GL, ZHOU XJ, XING Y, LI HX, LV JC, ZHANG H. Persistent hematuria and kidney disease progression in IgA nephropathy: a cohort study[J]. American Journal of Kidney Diseases, 2020, 76(1): 90-99.

[8] ZHANG H, BARRATT J. Is IgA nephropathy the same disease in different parts of the world?[J]. Seminars in Immunopathology, 2021, 43(5): 707-715.

[9] COPPO R. The gut-kidney axis in IgA nephropathy: role of microbiota and diet on genetic predisposition[J]. Pediatric Nephrology, 2018, 33(1): 53-61.

[10] VISCONTI A, Le ROY CI, ROSA F, ROSSI N, MARTIN TC, MOHNEY RP, LI WZ, de RINALDIS E, BELL JT, VENTER JC, NELSON KE, SPECTOR TD, FALCHI M. Interplay between the human gut microbiome and host metabolism[J]. Nature Communications, 2019, 10: 4505.

[11] PATTRAPORNPISUT P, AVILA-CASADO C, REICH HN. IgA nephropathy: core curriculum 2021[J]. American Journal of Kidney Diseases, 2021, 78(3): 429-441.

[12] HE JW, ZHOU XJ, LI YF, WANG YN, LIU LJ, SHI SF, XIN XH, LI RS, FALCHI M, LÜ JC, ZHANG H. Associations of genetic variants contributing to gut microbiota composition in immunoglobin A nephropathy[J]. mSystems, 2021, 6(1): e00819-20.

[13] AI SN, LI YK, TAO JY, ZHENG HJ, TIAN L, WANG YX, WANG Z, LIU WJ. Bibliometric visualization analysis of gut-kidney axis from 2003 to 2022[J]. Frontiers in Physiology, 2023, 14: 1176894.

[14] WANG JY, WANG X, CAI XT, PAN DK. Global trends and hotspots in IgA nephropathy: a bibliometric analysis and knowledge map visualization from 2012 to 2023[J]. International Urology and Nephrology, 2023, 55(12): 3197-3207.

[15] CHAI LX, LUO Q, CAI KD, WANG KY, XU BB. Reduced fecal short-chain fatty acids levels and the relationship with gut microbiota in IgA nephropathy[J]. BMC Nephrology, 2021, 22(1): 209.

[16] DONG YJ, CHEN JJ, ZHANG YD, WANG ZH, SHANG J, ZHAO ZZ. Development and validation of diagnostic models for immunoglobulin A nephropathy based on gut microbes[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 1059692.

[17] HAN SS, SHANG L, LU Y, WANG Y. Gut microbiome characteristics in IgA nephropathy: qualitative and quantitative analysis from observational studies[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 904401.

[18] DONG RJ, BAI M, ZHAO J, WANG D, NING XX, SUN SR. A comparative study of the gut microbiota associated with immunoglobulin a nephropathy and membranous nephropathy[J]. Frontiers in Cellular and Infection Microbiology, 2020, 10: 557368.

[19] HU XF, DU J, XIE YH, HUANG Q, XIAO Y, CHEN J, YAN SY, GONG ZC, OUYANG SX. Fecal microbiota characteristics of Chinese patients with primary IgA nephropathy: a cross-sectional study[J]. BMC Nephrology, 2020, 21(1): 97.

[20] ZHONG ZX, TAN JX, TAN L, TANG Y, QIU ZC, PEI GQ, QIN W. Modifications of gut microbiota are associated with the severity of IgA nephropathy in the Chinese population[J]. International Immunopharmacology, 2020, 89(Pt B): 107085.

[21] SHAH NB, NIGWEKAR SU, KALIM S, LELOUVIER B, SERVANT F, DALAL M, KRINSKY S, FASANO A, TOLKOFF-RUBIN N, ALLEGRETTI AS. The gut and blood microbiome in IgA nephropathy and healthy controls[J]. Kidney360, 2021, 2(8): 1261-1274.

[22] WU HW, TANG DE, ZHENG FP, LI SS, ZHANG XZ, YIN LH, LIU FN, DAI Y. Identification of a novel interplay between intestinal bacteria and metabolites in Chinese patients with IgA nephropathy via integrated microbiome and metabolome approaches[J]. Annals of Translational Medicine, 2021, 9(1): 32.

[23] LIANG XL, ZHANG SM, ZHANG DF, HU L, ZHANG L, PENG Y, XU Y, HOU HJ, ZOU C, LIU XS, CHEN Y, LU FH. Metagenomics-based systematic analysis reveals that gut microbiota Gd-IgA1-associated enzymes may play a key role in IgA nephropathy[J]. Frontiers in Molecular Biosciences, 2022, 9: 970723.

[24] TANG YY, ZHU YF, HE HD, PENG YS, HU P, WU JJ, SUN WQ, LIU P, XIAO Y, XU XD, WEI MG. Gut dysbiosis and intestinal barrier dysfunction promotes IgA nephropathy by increasing the production of Gd-IgA1[J]. Frontiers in Medicine, 2022, 9: 944027.

[25] ZHAO J, BAI M, NING XX, QIN YL, WANG YW, YU ZX, DONG RJ, ZHANG YM, SUN SR. Expansion of *Escherichia-shigella* in gut is associated with the onset and response to immunosuppressive therapy of IgA nephropathy[J]. Journal of the American Society of Nephrology, 2022, 33(12): 2276-2292.

[26] CAI FT, ZHOU CF, JIAO N, LIANG XL, YE ZM, CHEN W, YANG QQ, PENG H, TANG Y, NIU CQ, ZHAO GP, WANG ZF, ZHANG GQ, YU XQ. Systematic microbiome dysbiosis is associated with IgA nephropathy[J]. Microbiology Spectrum, 2023, 11(3): e0520222.

[27] 包文晗, 唐雯. 初诊 IgA 肾病患者的肠道菌群及其与疾病进展因素的相关分析[J]. 北京大学学报(医学版), 2023, 55(1): 124-132.
BAO WH, TANG W. Change of gut microflora in newly diagnosed IgA nephropathy patients and its correlation with clinical risk factors[J]. Journal of Peking University (Health Sciences), 2023, 55(1): 124-132 (in Chinese).

[28] LI JC, CAO YW, LU RR, LI HL, PANG Y, FU HX, FANG GX, CHEN QH, LIU BH, WU JB, ZHOU Y,

ZHOU JY. Integrated fecal microbiome and serum metabolomics analysis reveals abnormal changes in rats with immunoglobulin A nephropathy and the intervention effect of Zhen wu Tang[J]. Frontiers in Pharmacology, 2020, 11: 606689.

[29] HU XL, FAN R, SONG WZ, QING JB, YAN XY, LI YH, DUAN Q, LI YF. Landscape of intestinal microbiota in patients with IgA nephropathy, IgA vasculitis and Kawasaki disease[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 1061629.

[30] TAN JX, DONG LQ, JIANG Z, TAN L, LUO XY, PEI GQ, QIN AY, ZHONG ZX, LIU X, TANG Y, QIN W. Probiotics ameliorate IgA nephropathy by improving gut dysbiosis and blunting NLRP3 signaling[J]. Journal of Translational Medicine, 2022, 20(1): 382.

[31] WANG F, LI N, NI SM, MIN Y, WEI K, SUN HB, FU YQ, LIU YL, LV D. The effects of specific gut microbiota and metabolites on IgA nephropathy-based on Mendelian randomization and clinical validation[J]. Nutrients, 2023, 15(10): 2407.

[32] REN FH, JIN QB, LIU TT, REN XL, ZHAN YL. Causal effects between gut microbiota and IgA nephropathy: a bidirectional Mendelian randomization study[J]. Frontiers in Cellular and Infection Microbiology, 2023, 13: 1171517.

[33] SUGURMAR ANK, MOHD R, SHAH SA, NEOH HM, CADER RA. Gut microbiota in immunoglobulin A nephropathy: a malaysian perspective[J]. BMC Nephrology, 2021, 22(1): 145.

[34] WANG JW, KUO CH, KUO FC, WANG YK, HSU WH, YU FJ, HU HM, HSU PI, WANG JY, WU DC. Fecal microbiota transplantation: review and update[J]. Journal of the Formosan Medical Association, 2019, 118(suppl 1): S23-S31.

[35] DANNE C, ROLHION N, SOKOL H. Recipient factors in faecal microbiota transplantation: one stool does not fit all[J]. Nature Reviews Gastroenterology & Hepatology, 2021, 18: 503-513.

[36] LAURIERO G, ABBAD L, VACCA M, CELANO G, CHEMOUNY JM, CALASSO M, BERTHELOT L, GESUALDO L, de ANGELIS M, MONTEIRO RC. Fecal microbiota transplantation modulates renal phenotype in the humanized mouse model of IgA nephropathy[J]. Frontiers in Immunology, 2021, 12: 694787.

[37] ZHI WQ, SONG WZ, ABDI SAED Y, WANG Y, LI YF. Fecal capsule as a therapeutic strategy in IgA nephropathy: a brief report[J]. Frontiers in Medicine, 2022, 9: 914250.

[38] ZHAO J, BAI M, YANG XX, WANG Y, LI R, SUN SR. Alleviation of refractory IgA nephropathy by intensive fecal microbiota transplantation: the first case reports[J]. Renal Failure, 2021, 43(1): 928-933.

[39] ROSTOKER G, WIRQUIN V, TERZIDIS H, PETIT-PHAR M, CHAUMETTE MT, DELCHIER JC, BELGHITI D, LANG P, DUBERT JM, MEIGNAN M. Mucosal immunity in primary glomerulonephritis. III. study of intestinal permeability[J]. Nephron, 1993, 63(3): 286-290.

[40] KOVÁCS T, METTE H, PER B, KUN L, SCHMELCZER M, BARTA J, JEAN-CLAUDE D, NAGY J. Relationship between intestinal permeability and antibodies against food antigens in IgA nephropathy[J]. Orvosi Hetilap, 1996, 137(2): 65-69.

[41] KLOSTER SMERUD H, FELLSTRÖM B, HÄLLGREN R, OSAGIE S, VENGE P, KRISTJÁNSSON G. Gastrointestinal sensitivity to soy and milk proteins in patients with IgA nephropathy[J]. Clinical Nephrology, 2010, 74(5): 364-371.

[42] ZHOU N, SHEN Y, FAN LR, SUN Q, HUANG CX, HAO J, LAN JC, YAN HM. The characteristics of intestinal-barrier damage in rats with IgA nephropathy[J]. The American Journal of the Medical Sciences, 2020, 359(3): 168-176.

[43] TANG YY, XIAO Y, HE HD, ZHU YF, SUN WQ, HU P, XU XD, LIU Z, YAN ZW, WEI MG. Aberrant gut microbiome contributes to barrier dysfunction, inflammation, and local immune responses in IgA nephropathy[J]. Kidney and Blood Pressure Research, 2023, 48(1): 261-276.

[44] 唐余燕, 孙蔚倩, 贺海东, 胡屏, 金玫萍, 刘萍, 黄鲁生, 徐旭东. 肠黏膜 TLR4/NF-κB 通路激活与伪无菌 IgA 肾病小鼠肾损害有关[J]. 细胞与分子免疫学杂志, 2023, 39(10): 865-871.
TANG YY, SUN YQ, HE HD, HU P, JIN MP, LIU P, HUANG LS, XU XD. Activation of intestinal mucosal TLR4/NF-κB pathway is associated with renal damage in mice with pseudo-sterile IgA nephropathy[J]. Chinese Journal of Cellular and Molecular Immunology, 2023, 39(10): 865-871 (in Chinese).

[45] TURNBAUGH PJ, LEY RE, MAHOWALD MA, MAGRINI V, MARDIS ER, GORDON JI. An obesity-associated gut microbiome with increased capacity for energy harvest[J]. Nature, 2006, 444: 1027-1031.

[46] CLAUS SP, TSANG TM, WANG YL, CLOAREC O, SKORDI E, MARTIN FP, REZZI S, ROSS A, KOCHHAR S, HOLMES E, NICHOLSON JK. Systemic multicompartmental effects of the gut microbiome on mouse metabolic phenotypes[J]. Molecular Systems Biology, 2008, 4: 219.

[47] WIKOFF WR, ANFORA AT, LIU J, SCHULTZ PG, LESLEY SA, PETERS EC, SIUZDAK G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites[J]. Proceedings of the National Academy of Sciences of the United States of America, 2009, 106(10): 3698-3703.

[48] WU HW, TANG DE, YUN MH, LIU HP, HUANG SX, YUN C, HOCHER B, ZHANG XZ, LIU FN, YIN LH, DAI Y. Metabolic dysfunctions of intestinal fatty acids and tryptophan reveal immuno-inflammatory response activation in IgA nephropathy[J]. Frontiers in Medicine, 2022, 9: 811526.

[49] Di LEO V, GLEESON PJ, SALLUSTIO F, BOUNAIX C, Da SILVA J, LORETO G, BEN MKADDEM S, MONTEIRO RC. Rifaximin as a potential treatment for IgA nephropathy in a humanized mice model[J]. Journal of Personalized Medicine, 2021, 11(4): 309.

[50] SALLUSTIO F, CURCI C, CHAOUL N, FONTÒ G, LAURIERO G, PICERNO A, DIVELLA C, Di LEO V, de ANGELIS M, BEN MKADDEM S, MACCHIA L, GALLONE A, MONTEIRO RC, PESCE F, GESUALDO L. High levels of gut-homing immunoglobulin A+ B lymphocytes support the pathogenic role of intestinal mucosal hyperresponsiveness in immunoglobulin A nephropathy patients[J]. Nephrology Dialysis Transplantation, 2021, 36(3): 452-464.

[51] HE H, SHEN M, TANG Y, SUN W, XU X. LPS/TLR4 pathway regulates IgA1 secretion to induce IgA nephropathy[J]. Alternative Therapies in Health and Medicine, 2024, 30(1): 419-425.

[52] LITVINOVA EA, BETS VD, FEOFANOVA NA, GVOZDEVA OV, ACHASOVA KM, ALPERINA EL, KOZHEVNIKOVA EN. Dietary fucose affects macrophage polarization and reproductive performance in mice[J]. Nutrients, 2021, 13(3): 855.

[53] QING JB, HU XL, LI CQ, SONG WZ, TIRICHEN H, YAIGOUB H, LI YF. Fucose as a potential therapeutic molecule against the immune-mediated inflammation in IgA nepharopathy: an unrevealed link[J]. Frontiers in Immunology, 2022, 13: 929138.

[54] QING JB, LI CQ, HU XL, SONG WZ, TIRICHEN H, YAIGOUB H, LI YF. Differentiation of T helper 17 cells may mediate the abnormal humoral immunity in IgA nephropathy and inflammatory bowel disease based on shared genetic effects[J]. Frontiers in Immunology, 2022, 13: 916934.

[55] BARRATT J, LAFAYETTE R, KRISTENSEN J, STONE A, CATTRAN D, FLOEGE J, TESAR V, TRIMARCHI H, ZHANG H, EREN N, PALIEGE A, ROVIN BH, INVESTIGATORS NT. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy[J]. Kidney International, 2023, 103(2): 391-402.