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肠道菌群在糖尿病肾病发生发展中的作用及机制

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摘　要

糖尿病肾病(Diabetic nephropathy, DN)是糖尿病(Diabetes mellitus, DM)最常见、最严重的并发症之一。近年来，肠肾轴在DN发生发展中的作用受到了越来越多的关注。DN患者肠道菌群多样性发生改变，并通过代谢物与宿主之间相互作用，在DN发病机制及治疗中起关键作用。本综述旨在讨论肠道菌群参与DN的关键机制及靶向肠道菌群的治疗策略，以期为DN的临床治疗提供新的见解。

关键词

糖尿病肾病，肠道菌群，肠肾轴，肠道菌群靶向疗法

The Role and Mechanism of Gut Microbiota in the Development of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is one of the most common and severe complications of diabetes mellitus (DM). In recent years, the role of the gut-kidney axis in the pathogenesis and progression of DN has garnered increasing attention. Patients with DN exhibit altered gut microbiota diversity, which, through interactions with the host via metabolites, plays a pivotal role in the pathogenesis and treatment of DN. This review aims to discuss the key mechanisms underlying the involvement of gut

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microbiota in DN and therapeutic strategies targeting the gut microbiota, with the intention of providing novel insights into the clinical management of DN.

Keywords

Diabetic Nephropathy, Gut Microbiota, Gut-Kidney Axis, Gut Microbiota Targeting Therapy

1. 引言

糖尿病肾病(Diabetic nephropathy, DN)是一种慢性肾脏病(Chronic kidney disease, CKD)，是糖尿病(Diabetes mellitus, DM)微血管病变最常见的并发症之一，也是终末期肾脏疾病(End-stage renal disease, ESRD)的主要原因[1]。约 30%~40%的 DM 患者可发展为 DN，DN 已成为我国 CKD 及 ESRD 的主要病因[2]。DN 患者易合并高血压、贫血、动脉硬化、心包炎、结肠炎和脑出血等疾病，严重影响患者生活质量及生存[3] [4]。DN 发病机制复杂，尚不完全清楚，这使得 DN 的治疗目前尚不具有特异性。现有研究表明，胰岛素抵抗((Insulin resistance, IR)、肾素－血管紧张素系统(Renin-angiotensin system, RAS)过度活跃、炎症反应和氧化应激等均参与 DN 的发生发展[5]-[7]。探索关键发病机制有助于进一步实现 DN 的靶向治疗。研究发现肠道菌群参与DN的发生发展，人类肠道微生物组被描述为调控人体健康的“第二基因组”，它通过基因、中间产物和代谢活动影响人体代谢和免疫功能[8] [9]。肠道菌群失调可影响 IR、血流动力学、炎症反应和免疫反应，与 DM 及 DN 密切相关[10]。因此，维持肠道菌群多样性和平衡对于调节宿主健康至关重要。在这篇综述中，我们总结了肠道菌群参与 DN 的重要发现，并描述了肠道菌群如何影响 DN 的发生发展和基于肠道菌群的相关靶向治疗，以期为 DN 的临床治疗提供新的见解。

2. 糖尿病肾病与肠道菌群

2.1. 肠肾轴

肠肾轴(Gut-kidney axis)是指肠道与肾脏之间的双向交流和相互影响。近年来，研究表明，肠道菌群在维持肠道和全身健康方面发挥着至关重要的作用[11]。越来越多的证据表明，肠道和肾脏之间存在双向串扰，即肠道或肾脏的病理生理变化可以相互影响，导致另一侧的病变[12]。一方面，尿毒症毒素的增加会影响 DN 患者肠道菌群的组成和功能。并且，在 DM 的情况下，高血糖症会促进肠道菌群失调，从而导致 DN 的发展[13]。肾脏疾病也会导致肠道菌群组成的改变，许多受损肾脏释放的含氮有机物可能会穿过肠道屏障并促进肠道病原体的生长[14]。不能由肾脏排泄的代谢废物容易进入肠腔，从而加剧肠道菌群失调[15]。另一方面，肠道菌群失调会破坏肠道屏障，增加上皮细胞的通透性，并导致脂多糖(Lipopolysaccharide, LPS)等代谢物暴露增加，最终加剧肾损伤[16]。敲除能够维持肠道微生态稳态的线粒体抗病毒信号蛋白(MAVS)的 DM 小鼠表现出更严重的肾小球和肾小管损伤，这表明肠道菌群紊乱可能导致 DN 的进展[17]。肾脏疾病的发生发展和肠道菌群紊乱会相互影响，形成恶性循环。阐明相互联系的潜在机制可能有助于了解疾病的病因和发病机制。

2.2. DN 患者肠道菌群失调

DN 患者肠道菌群组成、丰度和多样性失衡。迄今为止，多项研究调查了肠道菌群失调与 DN 之间的

关联。一项荟萃分析显示，与健康人群相比，DN 患者肠道菌群丰富度及多样性均降低，厚壁菌门相关菌属(*Hungatella*)和大肠埃希氏菌属(*Escherichia*)的富集，以及丁酸产生菌的减少[18]。与健康对照组相比，肠道菌群中可以产生 LPS 的变形菌门(*Proteobacteria*)和梭杆菌门(*Fusobacteria*)的水平明显更高[19]。Tao 等人也在 14 例确诊的 DN 病例中发现了高丰度的 *Proteobacteria* [20]。Shang 等发现，与健康对照组相比，180 例 DN 患者的肠道菌群中 *Proteobacteria* 和互养菌门(*Synergistota*)丰度增加，而拟杆菌门(*Bacteroidota*)和未分类细菌则丰度减少[21]。研究人员还发现，分析 DM、DN 患者和健康对照之间的菌群差异，普雷沃氏菌属(*Prevotella*)水平可以准确预测 DM 及 DN 个体[22]。总之，DN 患者的肠道菌群发生了特异性的改变，并且肠道菌群可以作为 DN 发生发展的预测因子，未来需要在种或菌株水平上进行进一步研究。

3. 肠道菌群及代谢物参与糖尿病肾病的作用及机制

3.1. 肠道菌群紊乱参与胰岛素抵抗

IR 是指身体对胰岛素的反应能力下降，导致血糖无法得到有效控制，IR 不仅与 DM 密切相关还能够驱动肾功能损伤影响 DN 的进展[23]。肠道菌群及其代谢物可以通过多种方式影响宿主 IR。研究发现肠道菌群组成以毛螺菌科(*Lachnospiraceae*)为主的人群往往 IR 水平和粪便单糖含量更高，而拟杆菌目(*Bacteroidales*)丰度较高人群 IR 程度和粪便单糖含量较低，因此，肠道中的 *Lachnospiraceae* 有潜力成为前驱 DM 的生物标志物[24]。特定菌群，如厚壁菌门(*Firmicutes*) 和拟杆菌门(*Bacteroidetes*)的比例失调能够通过介导胰高血糖素样肽-1 (GLP-1)的水平下降参与 IR [25]。狄氏副拟杆菌(*Parabacteroides distasonis*)可通过产生烟酸激活肠道中 G 蛋白偶联受体 109a (GPR109a)保护肠屏障功能并改善 IR [26] [27]。

肠道菌群的失衡可以通过代谢产物，如支链氨基酸(BCAA)、短链脂肪酸(SCFAs)、LPS 和胆汁酸(BA)，影响宿主的代谢和免疫反应，从而影响 IR [28]。IR 个体具有更高的 BCAA 生物合成潜力，同时产生 BCAA 的细菌丰度也增加，其中 *Prevotella* 和 *Bacteroides* 被确定为驱动 BCAA 生物合成的主要物种从而介导 IR [29]。SCFAs 通过与 G 蛋白偶联受体(如 GPR41 和 GPR43)结合，调节肠道激素分泌(如 GLP-1)，促进胰岛素分泌和提高胰岛素敏感性[30] [31]。LPS 通过 Toll 样受体 4 (TLR4)激活炎症信号通路，引起慢性低度炎症，这种炎症状态会干扰胰岛素信号通路，导致 IR [32]。初级 BA 被肠道细菌转化为次级胆汁酸(SBA)，后者可以通过与核法尼醇 X 受体(FXR)和膜结合的武田 G 蛋白偶联受体 5 (TGR5)来调节葡萄糖代谢，缓解 IR 并改善 DN [33] [34]。总之，肠道菌群及其代谢产物能够参与 IR 从而影响 DN 的发生发展[35]。

3.2. 肠道菌群紊乱参与炎症反应

炎症是 DN 发展中不可或缺的因素。在高血糖环境下，免疫细胞如巨噬细胞被激活，释放包括肿瘤坏死因子-α、白细胞介素-1β、白细胞介素-6 在内的炎症细胞因子，这些因子通过激活核因子 κB (Nuclear factor kappa-B, NF-κB)等炎症信号通路，加重肾脏损伤[36]。NF-κB 信号通路和免疫应答、炎性反应、细胞的增生转化以及细胞的凋亡等过程密切相关，NF-κB 是许多相互关联通路的中心，这些通路导致 DN 的结构和功能变化[37] [38]。一些研究表明，在 DN 大鼠模型中，代谢内毒素和 LPS 水平的失调导致 NF-κB 信号通路的激活，血液和肾脏中炎症细胞因子水平的增加，以及先天免疫系统的激活[39]。循环三甲胺氧化物(Trimethylamine n-oxide, TMAO)是肠道菌群代谢产物之一，其水平升高通过炎症小体 NLRP3 和 NF-κB 信号发挥促炎作用，导致 DN 患者肾间质纤维化和功能障碍[40]。而肠道菌群代谢物如 TMAO、IS、PCS 持续积累，也可激活补体 C5 刺激免疫系统，导致 DN 中炎症因子的过量产生和肾损害[41]。以上研究证明紊乱的肠道菌群能够刺激炎症因子的释放加重炎症反应从而促进肾功能的进展。

3.3. 肠道菌群紊乱参与氧化应激

氧化应激是指机体氧化与抗氧化失衡的状态[42]。当机体受到有害刺激时，会产生过多的活性氧(Reactive oxygen species, ROS)，导致氧化系统与抗氧化系统失衡，诱发氧化应激[43] [44]。氧化应激可通过激活 Ang II、转化生长因子-β 等信号分子引起肾脏损伤，反过来，这些信号分子的激活可以引起氧化应激，然后诱导肾损伤[45]。值得注意的是，氧化应激与炎症反应密切相关。在 DN 中，ROS 可激活 NF-κB 通路，诱导大量炎症介质，引发炎症反应，进而加重氧化应激损伤[46]。研究表明，肠道菌群失调可引发氧化应激，并在 DN 发病机制中发挥关键作用[47]。肠道微生物来源的尿毒症毒素循环水平的增加会引发氧化应激，增加 ROS 的产生，ROS 激活炎症小体 NLRP3，导致肾小球内皮细胞炎症反应，加重 DN 的肾功能障碍[48]。此外，通过 d-半乳糖致小鼠衰老动物模型，从调节肠道菌群的角度探讨 TFPS 降低炎症因子、降低氧化应激水平、抑制小胶质细胞氧化损伤的作用[49]。总之，肠道菌群可能在氧化应激和 DN 之间存在着重要的联系。

4. 靶向肠道菌群的糖尿病肾病疗法

4.1. 粪便微生物群移植治疗糖尿病肾病

粪便微生物群移植(Fecal microbiota transplantation, FMT)是一种新兴的治疗方法，它将健康供体的肠道菌群移植到病态微生物群患者的胃肠道中重建患者健康的肠道微生态[50]。已有证据表明 FMT 在消化系统疾病(艰难梭菌感染等)和非消化系统疾病(如 DM、儿童自闭症等)中具有优越的疗效和安全性[51]。在临床前研究中，将健康对照大鼠粪便给予 DN 大鼠进行 FMT 治疗，FMT 通过介导胆固醇稳态失调减轻 DN 大鼠小管间质损伤，FMT 显著降低大鼠血清醋酸盐水平，恢复胆固醇稳态，改善足细胞胰岛素敏感性，减轻小管间质和肾小球损伤[52]。FMT 可以通过调节微生物来影响 DN 小鼠的代谢，FMT 后马尿酸和胆酸等微生物来源的尿毒症溶质水平显着降低，肾脏损伤得到缓解[53]。值得注意的是，目前 FMT 在治疗 DM 方面取得了良好的疗效，并且已经在临床试验中得到了证实[54]。未来亟需更多高质量的前瞻性研究，为 FMT 治疗 DN 的临床应用提供安全性和有效性数据。

4.2. 益生菌治疗糖尿病肾病

益生菌是通过定殖在人体内，改变宿主某一部位菌群组成的一类对宿主有益的活性微生物[55]。益生菌通过调节宿主黏膜与系统免疫功能或通过调节肠道内菌群平衡，促进营养吸收保持肠道健康的作用，从而有助于人体健康，在治疗和预防疾病中具有重要作用[56]。复合益生菌能够通过调节 db/db 小鼠肠道菌群和诱导 GLP-1 分泌来缓解 2 型 DM [57]。在 DM 模型中，使用芒果苷和乳杆菌(*Lactobacillus*)组成的合生元处理大鼠，观察到(*Bifidobacterium*、*Lactobacillus*)的比例提高，且能够延缓大鼠的 DM 进展[58]。*Lactobacillus* 还可降低 STZ 诱导的 DM 大鼠的糖化血红蛋白和血糖水平，并抑制由高血糖引起的肾纤维化[59]。一项随机、双盲、安慰剂对照试验表明，摄入益生菌可以通过在肠道中产生 SCFAs 并减少过氧化氢自由基的产生减少症状因素，从而缓解肾脏炎症和纤维化[60]。以产丁酸的酪酸梭菌(*Clostridium butyricum*)为底盘菌，构建一株能够表达潜在高血压治疗药物 GLP-1 的工程益生菌，可通过重塑肠道菌群和释放 GLP-1 进而改善高血压[61]。

4.3. 饮食干预

饮食是支持人类生长、健康和繁殖的基础。DM 的进展与饮食营养习惯有很强的相关性，DN 的发生发展也可以通过合理的饮食干预来改变。饮食也被证明可以调节和维持肠道内共生肠道菌群[62]。高脂肪和高糖饮食会增加肠道中尿毒症毒素含量并使含有 LPS 的菌群比例升高，并诱导 IR [63]。高纤维饮食有

助于肠道菌群的重建。DM 小鼠在高纤维饮食后，小鼠肠道厚壁菌门(*Firmicutes*)减少，*Bacteroides* 增多，*Prevotella* 和 *Bifidobacterium* 增多，SCFAs 的产生增加[64]。低碳水化合物饮食也可使产 SCFAs 细菌 *Roseburis* 丰度增加，这导致血清和粪便中 SCFAs 浓度增加，从而增强胰岛素敏感性和 GLP-1 分泌，还可通过先天免疫、炎症和巨噬细胞募集的关键途径延缓 DN 的进展[65]。上述结果表明，调整饮食可通过改善肠道菌群来预防或延缓 DN 的发生，值得进一步探讨。

5. 小结

本综述总结了肠道菌群及其相关代谢产物在 DN 进展及治疗中的机制及应用。紊乱的肠道菌群及其代谢产物参与 DN 患者 IR、RAS 激活、炎症反应及氧化应激影响肾功能的进展。通过 FMT、益生菌以及调整饮食结构，提高肠道菌群的稳定性、改善糖代谢并减少相关代谢物的产生可以延缓 DN 的进展。肠道菌群有望成为 DN 治疗的新靶点。

然而，先前大多数研究为横断面研究，未能反映 DN 不同疾病进展阶段的肠道菌群特异性变化。因此，目前仍缺乏对肠道菌群与 DN 之间机制的深入探索。基于肠道菌群治疗 DN 的大型临床试验尚未开展，评估肠道菌群及其代谢物作为 DN 的治疗策略仍需要广泛的临床研究进行验证，未来还需要更多研究深入探索。

利益冲突

所有作者均声明不存在利益冲突。

作者贡献声明

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参考文献

[1] Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., *et al*. (2023) Erratum to “IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045” [Diabetes Res. Clin. Pract. 183 (2022) 109119]. *Diabetes Research and Clinical Practice*, **204**, Article ID: 110945. https://doi.org/10.1016/j.diabres.2023.110945

[2] Afkarian, M., Zelnick, L.R., Hall, Y.N., Heagerty, P.J., Tuttle, K., Weiss, N.S., *et al*. (2016) Clinical Manifestations of Kidney Disease among US Adults with Diabetes, 1988-2014. *JAMA*, **316**, 602-610. https://doi.org/10.1001/jama.2016.10924

[3] Wal, P., Tyagi, S., Pal, R.S., Yadav, A. and Jaiswal, R. (2023) A Strategic Investigation on Diabetic Nephropathy; Its Conceptual Model and Clinical Manifestations: A Review. *Current Diabetes Reviews*, **19**, e260422204036. https://doi.org/10.2174/1573399818666220426091238

[4] Jiang, G., Luk, A.O.Y., Tam, C.H.T., Xie, F., Carstensen, B., Lau, E.S.H., *et al*. (2019) Progression of Diabetic Kidney Disease and Trajectory of Kidney Function Decline in Chinese Patients with Type 2 Diabetes. *Kidney International*, **95**, 178-187. https://doi.org/10.1016/j.kint.2018.08.026

[5] D’Alessandro, V.F., Takeshita, A., Yasuma, T., Toda, M., D’Alessandro-Gabazza, C.N., Okano, Y., *et al*. (2022) Transforming Growth Factorβ1 Overexpression Is Associated with Insulin Resistance and Rapidly Progressive Kidney Fibrosis under Diabetic Conditions. *International Journal of Molecular Sciences*, **23**, Article No. 14265. https://doi.org/10.3390/ijms232214265

[6] Ricciardi, C.A. and Gnudi, L. (2021) Kidney Disease in Diabetes: From Mechanisms to Clinical Presentation and Treatment Strategies. *Metabolism*, **124**, Article ID: 154890. https://doi.org/10.1016/j.metabol.2021.154890

[7] Jha, J.C., Banal, C., Chow, B.S.M., Cooper, M.E. and Jandeleit-Dahm, K. (2016) Diabetes and Kidney Disease: Role of Oxidative Stress. *Antioxidants & Redox Signaling*, **25**, 657-684. https://doi.org/10.1089/ars.2016.6664

[8] Noecker, C. and Turnbaugh, P.J. (2024) Emerging Tools and Best Practices for Studying Gut Microbial Community Metabolism. *Nature Metabolism*, **6**, 1225-1236. https://doi.org/10.1038/s42255-024-01074-z

[9] Heintz-Buschart, A. and Wilmes, P. (2018) Human Gut Microbiome: Function Matters. *Trends in Microbiology*, **26**,

563-574. https://doi.org/10.1016/j.tim.2017.11.002

[10] Yang, G., Wei, J., Liu, P., Zhang, Q., Tian, Y., Hou, G., *et al*. (2021) Role of the Gut Microbiota in Type 2 Diabetes and Related Diseases. *Metabolism*, **117**, Article ID: 154712. https://doi.org/10.1016/j.metabol.2021.154712

[11] Giordano, L., Mihaila, S.M., Eslami Amirabadi, H. and Masereeuw, R. (2021) Microphysiological Systems to Recapitulate the Gut-Kidney Axis. *Trends in Biotechnology*, **39**, 811-823. https://doi.org/10.1016/j.tibtech.2020.12.001

[12] Vallianou, N.G., Kounatidis, D., Panagopoulos, F., Evangelopoulos, A., Stamatopoulos, V., Papagiorgos, A., *et al*. (2023) Gut Microbiota and Its Role in the Brain-Gut-Kidney Axis in Hypertension. *Current Hypertension Reports*, **25**, 367-376. https://doi.org/10.1007/s11906-023-01263-3

[13] Thaiss, C.A., Levy, M., Grosheva, I., Zheng, D., Soffer, E., Blacher, E., *et al*. (2018) Hyperglycemia Drives Intestinal Barrier Dysfunction and Risk for Enteric Infection. *Science*, **359**, 1376-1383. https://doi.org/10.1126/science.aar3318

[14] Wang, X., Yang, S., Li, S., Zhao, L., Hao, Y., Qin, J., *et al*. (2020) Aberrant Gut Microbiota Alters Host Metabolome and Impacts Renal Failure in Humans and Rodents. *Gut*, **69**, 2131-2142. https://doi.org/10.1136/gutjnl-2019-319766

[15] Graboski, A.L. and Redinbo, M.R. (2020) Gut-Derived Protein-Bound Uremic Toxins. *Toxins*, **12**, Article No. 590. https://doi.org/10.3390/toxins12090590

[16] Linh, H.T., Iwata, Y., Senda, Y., Sakai-Takemori, Y., Nakade, Y., Oshima, M., *et al*. (2022) Intestinal Bacterial Translocation Contributes to Diabetic Kidney Disease. *Journal of the American Society of Nephrology*, **33**, 1105-1119. https://doi.org/10.1681/asn.2021060843

[17] Han, S., Chen, M., Cheng, P., Zhang, Z., Lu, Y., Xu, Y., *et al*. (2022) A Systematic Review and Meta-Analysis of Gut Microbiota in Diabetic Kidney Disease: Comparisons with Diabetes Mellitus, Non-Diabetic Kidney Disease, and Healthy Individuals. *Frontiers in Endocrinology*, **13**, Article ID: 1018093. https://doi.org/10.3389/fendo.2022.1018093

[18] Salguero, M., Al-Obaide, M., Singh, R., Siepmann, T. and Vasylyeva, T. (2019) Dysbiosis of Gram-Negative Gut Microbiota and the Associated Serum Lipopolysaccharide Exacerbates Inflammation in Type 2 Diabetic Patients with Chronic Kidney Disease. *Experimental and Therapeutic Medicine*, **18**, 3461-3469. https://doi.org/10.3892/etm.2019.7943

[19] Tao, S., Li, L., Li, L., Liu, Y., Ren, Q., Shi, M., *et al*. (2019) Understanding the Gut-Kidney Axis among Biopsy-Proven Diabetic Nephropathy, Type 2 Diabetes Mellitus and Healthy Controls: An Analysis of the Gut Microbiota Composition. *Acta Diabetologica*, **56**, 581-592. https://doi.org/10.1007/s00592-019-01316-7

[20] Shang, J., Cui, W., Guo, R., Zhang, Y., Wang, P., Yu, W., *et al*. (2022) The Harmful Intestinal Microbial Community Accumulates during DKD Exacerbation and Microbiome-Metabolome Combined Validation in a Mouse Model. *Frontiers in Endocrinology*, **13**, Article ID: 964389. https://doi.org/10.3389/fendo.2022.964389

[21] Huang, H., Luo, Y., Lu, P., Huang, C., Lin, K., Lee, M., *et al*. (2023) Gut Microbiota Composition Can Reflect Immune Responses of Latent Tuberculosis Infection in Patients with Poorly Controlled Diabetes. *Respiratory Research*, **24**, Article No. 11. https://doi.org/10.1186/s12931-023-02312-w

[22] Tervaert, T.W.C., Mooyaart, A.L., Amann, K., Cohen, A.H., Cook, H.T., Drachenberg, C.B., *et al*. (2010) Pathologic Classification of Diabetic Nephropathy. *Journal of the American Society of Nephrology*, **21**, 556-563. https://doi.org/10.1681/asn.2010010010

[23] Mohandes, S., Doke, T., Hu, H., Mukhi, D., Dhillon, P. and Susztak, K. (2023) Molecular Pathways That Drive Diabetic Kidney Disease. *Journal of Clinical Investigation*, **133**, e165654. https://doi.org/10.1172/jci165654

[24] Lambie, M., Bonomini, M., Davies, S.J., Accili, D., Arduini, A. and Zammit, V. (2021) Insulin Resistance in Cardiovascular Disease, Uremia, and Peritoneal Dialysis. *Trends in Endocrinology & Metabolism*, **32**, 721-730. https://doi.org/10.1016/j.tem.2021.06.001

[25] Takeuchi, T., Kubota, T., Nakanishi, Y., Tsugawa, H., Suda, W., Kwon, A.T., *et al*. (2023) Gut Microbial Carbohydrate Metabolism Contributes to Insulin Resistance. *Nature*, **621**, 389-395. https://doi.org/10.1038/s41586-023-06466-x

[26] Greenhill, C. (2015) Firmicutes and Bacteroidetes Involved in Insulin Resistance by Mediating Levels of Glucagon-Like Peptide 1. *Nature Reviews Endocrinology*, **11**, Article No. 254. https://doi.org/10.1038/nrendo.2015.40

[27] Sun, Y., Nie, Q., Zhang, S., He, H., Zuo, S., Chen, C., *et al*. (2023) Parabacteroides Distasonis Ameliorates Insulin Resistance via Activation of Intestinal Gpr109a. *Nature Communications*, **14**, Article No. 7740. https://doi.org/10.1038/s41467-023-43622-3

[28] Pedersen, H.K., Gudmundsdottir, V., Nielsen, H.B., Hyotylainen, T., Nielsen, T., Jensen, B.A.H., *et al*. (2016) Human Gut Microbes Impact Host Serum Metabolome and Insulin Sensitivity. *Nature*, **535**, 376-381. https://doi.org/10.1038/nature18646

[29] Aggarwal, H., Gautam, J., Kumari, D., Gupta, S.K., Bajpai, S., Chaturvedi, K., *et al*. (2024) Comparative Profiling of Gut Microbiota and Metabolome in Diet-Induced Obese and Insulin-Resistant C57BL/6J Mice. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Cell Research*, **1871**, Article ID: 119643. https://doi.org/10.1016/j.bbamcr.2023.119643

[30] Facchin, S., Bertin, L., Bonazzi, E., Lorenzon, G., De Barba, C., Barberio, B., *et al*. (2024) Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implications. *Life*, **14**, Article No. 559. https://doi.org/10.3390/life14050559

[31] Saad, M.J.A., Santos, A. and Prada, P.O. (2016) Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. *Physiology*, **31**, 283-293. https://doi.org/10.1152/physiol.00041.2015

[32] Guo, Y., Xie, G. and Zhang, X. (2023) Role of FXR in Renal Physiology and Kidney Diseases. *International Journal of Molecular Sciences*, **24**, Article No. 2408. https://doi.org/10.3390/ijms24032408

[33] She, J., Tuerhongjiang, G., Guo, M., Liu, J., Hao, X., Guo, L., *et al*. (2024) Statins Aggravate Insulin Resistance through Reduced Blood Glucagon-Like Peptide-1 Levels in a Microbiota-Dependent Manner. *Cell Metabolism*, **36**, 408-421.e5. https://doi.org/10.1016/j.cmet.2023.12.027

[34] Naaman, S.C. and Bakris, G.L. (2023) Diabetic Nephropathy: Update on Pillars of Therapy Slowing Progression. *Diabetes Care*, **46**, 1574-1586. https://doi.org/10.2337/dci23-0030

[35] Jaworska, K., Koper, M. and Ufnal, M. (2021) Gut Microbiota and Renin-Angiotensin System: A Complex Interplay at Local and Systemic Levels. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **321**, G355-G366. https://doi.org/10.1152/ajpgi.00099.2021

[36] Liu, W., Tan, Z., Geng, M., Jiang, X. and Xin, Y. (2023) Impact of the Gut Microbiota on Angiotensin II-Related Disorders and Its Mechanisms. *Biochemical Pharmacology*, **214**, Article ID: 115659. https://doi.org/10.1016/j.bcp.2023.115659

[37] Lohia, S., Valkenburg, S., Stroggilos, R., Lygirou, V., Makridakis, M., Zoidakis, J., *et al*. (2024) Investigation of the Human-Gut-Kidney Axis by Fecal Proteomics, Highlights Molecular Mechanisms Affected in CKD. *Heliyon*, **10**, e32828. https://doi.org/10.1016/j.heliyon.2024.e32828

[38] Karbach, S.H., Schönfelder, T., Brandão, I., Wilms, E., Hörmann, N., Jäckel, S., *et al*. (2016) Gut Microbiota Promote Angiotensin II-Induced Arterial Hypertension and Vascular Dysfunction. *Journal of the American Heart Association*, **5**, e003698. https://doi.org/10.1161/jaha.116.003698

[39] Wang, L., Zhu, Q., Lu, A., Liu, X., Zhang, L., Xu, C., *et al*. (2017) Sodium Butyrate Suppresses Angiotensin II-Induced Hypertension by Inhibition of Renal (Pro)renin Receptor and Intrarenal Renin-Angiotensin System. *Journal of Hypertension*, **35**, 1899-1908. https://doi.org/10.1097/hjh.0000000000001378

[40] Deng, F., Zhang, L., Wu, H., Chen, Y., Yu, W., Han, R., *et al*. (2022) Propionate Alleviates Myocardial Ischemia-Reperfusion Injury Aggravated by Angiotensin II Dependent on Caveolin-1/Ace2 Axis through Gpr41. *International Journal of Biological Sciences*, **18**, 858-872. https://doi.org/10.7150/ijbs.67724

[41] Campbell, C., Kandalgaonkar, M.R., Golonka, R.M., Yeoh, B.S., Vijay-Kumar, M. and Saha, P. (2023) Crosstalk between Gut Microbiota and Host Immunity: Impact on Inflammation and Immunotherapy. *Biomedicines*, **11**, Article No. 294. https://doi.org/10.3390/biomedicines11020294

[42] Ni, Y., Zheng, L., Nan, S., Ke, L., Fu, Z. and Jin, J. (2022) Enterorenal Crosstalks in Diabetic Nephropathy and Novel Therapeutics Targeting the Gut Microbiota. *Acta Biochimica et Biophysica Sinica*, **54**, 1406-1420. https://doi.org/10.3724/abbs.2022140

[43] Mosterd, C.M., Kanbay, M., van den Born, B.J.H., van Raalte, D.H. and Rampanelli, E. (2021) Intestinal Microbiota and Diabetic Kidney Diseases: The Role of Microbiota and Derived Metabolites Inmodulation of Renal Inflammation and Disease Progression. *Best Practice & Research Clinical Endocrinology & Metabolism*, **35**, Article ID: 101484. https://doi.org/10.1016/j.beem.2021.101484

[44] Rysz, J., Franczyk, B., Ławiński, J., Olszewski, R., Ciałkowska-Rysz, A. and Gluba-Brzózka, A. (2021) The Impact of CKD on Uremic Toxins and Gut Microbiota. *Toxins*, **13**, Article No. 252. https://doi.org/10.3390/toxins13040252

[45] Zhou, W., Wu, W., Si, Z., Liu, H., Wang, H., Jiang, H., *et al*. (2022) The Gut Microbe Bacteroides Fragilis Ameliorates Renal Fibrosis in Mice. *Nature Communications*, **13**, Article No. 6081. https://doi.org/10.1038/s41467-022-33824-6

[46] Zhong, C., Dai, Z., Chai, L., Wu, L., Li, J., Guo, W., *et al*. (2021) The Change of Gut Microbiota-Derived Short-Chain Fatty Acids in Diabetic Kidney Disease. *Journal of Clinical Laboratory Analysis*, **35**, e24062. https://doi.org/10.1002/jcla.24062

[47] Srivastava, A., Tomar, B., Sharma, D. and Rath, S.K. (2023) Mitochondrial Dysfunction and Oxidative Stress: Role in Chronic Kidney Disease. *Life Sciences*, **319**, Article ID: 121432. https://doi.org/10.1016/j.lfs.2023.121432

[48] Su, S., Ma, Z., Wu, H., Xu, Z. and Yi, H. (2023) Oxidative Stress as a Culprit in Diabetic Kidney Disease. *Life Sciences*, **322**, Article ID: 121661. https://doi.org/10.1016/j.lfs.2023.121661

[49] Samsu, N. (2021) Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. *BioMed Research International*, **2021**, Article ID: 1497449. https://doi.org/10.1155/2021/1497449

[50] Winiarska, A., Knysak, M., Nabrdalik, K., Gumprecht, J. and Stompór, T. (2021) Inflammation and Oxidative Stress in

Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists. *International Journal of Molecular Sciences*, **22**, Article No. 10822. https://doi.org/10.3390/ijms221910822

[51] Tan, Y., Wang, Y., Feng, H., Guo, Z., Li, X., Nie, X., *et al*. (2022) Host/Microbiota Interactions-Derived Tryptophan Metabolites Modulate Oxidative Stress and Inflammation via Aryl Hydrocarbon Receptor Signaling. *Free Radical Biology and Medicine*, **184**, 30-41. https://doi.org/10.1016/j.freeradbiomed.2022.03.025

[52] Chao, C. and Chiang, C. (2015) Uremic Toxins, Oxidative Stress, and Renal Fibrosis: An Interwined Complex. *Journal of Renal Nutrition*, **25**, 155-159. https://doi.org/10.1053/j.jrn.2014.10.010

[53] Porcari, S., Benech, N., Valles-Colomer, M., Segata, N., Gasbarrini, A., Cammarota, G., *et al*. (2023) Key Determinants of Success in Fecal Microbiota Transplantation: From Microbiome to Clinic. *Cell Host & Microbe*, **31**, 712-733. https://doi.org/10.1016/j.chom.2023.03.020

[54] Yadegar, A., Bar-Yoseph, H., Monaghan, T.M., Pakpour, S., Severino, A., Kuijper, E.J., *et al*. (2024) Fecal Microbiota Transplantation: Current Challenges and Future Landscapes. *Clinical Microbiology Reviews*, **37**, e0006022. https://doi.org/10.1128/cmr.00060-22

[55] Hu, Z.B., Lu, J., Chen, P.P., Lu, C.C., Zhang, J.X., Li, X.Q., *et al*. (2020) Dysbiosis of Intestinal Microbiota Mediates Tubulointerstitial Injury in Diabetic Nephropathy via the Disruption of Cholesterol Homeostasis. *Theranostics*, **10**, 2803-2816. https://doi.org/10.7150/thno.40571

[56] Wang, H., Lu, Y., Yan, Y., Tian, S., Zheng, D., Leng, D., *et al*. (2020) Promising Treatment for Type 2 Diabetes: Fecal Microbiota Transplantation Reverses Insulin Resistance and Impaired Islets. *Frontiers in Cellular and Infection Microbiology*, **9**, Article No. 455. https://doi.org/10.3389/fcimb.2019.00455

[57] Ding, D., Yong, H., You, N., Lu, W., Yang, X., Ye, X., *et al*. (2022) Prospective Study Reveals Host Microbial Determinants of Clinical Response to Fecal Microbiota Transplant Therapy in Type 2 Diabetes Patients. *Frontiers in Cellular and Infection Microbiology*, **12**, Article ID: 820367. https://doi.org/10.3389/fcimb.2022.820367

[58] Yang, Y., Yan, J., Li, S., Liu, M., Han, R., Wang, Y., *et al*. (2023) Efficacy of Fecal Microbiota Transplantation in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Endocrine*, **84**, 48-62. https://doi.org/10.1007/s12020-023-03606-1

[59] Singh, R.P., Shadan, A. and Ma, Y. (2022) Biotechnological Applications of Probiotics: A Multifarious Weapon to Disease and Metabolic Abnormality. *Probiotics and Antimicrobial Proteins*, **14**, 1184-1210. https://doi.org/10.1007/s12602-022-09992-8

[60] Meng, F., Zhang, F., Meng, M., Chen, Q., Yang, Y., Wang, W., *et al*. (2023) Effects of the Synbiotic Composed of Mangiferin and *Lactobacillus reuteri* 1-12 on Type 2 Diabetes Mellitus Rats. *Frontiers in Microbiology*, **14**, Article ID: 1158652. https://doi.org/10.3389/fmicb.2023.1158652

[61] Lu, Y., Yin, L., Chang, W. and Huang, J. (2010) Effect of *Lactobacillus reuteri* GMNL-263 Treatment on Renal Fibrosis in Diabetic Rats. *Journal of Bioscience and Bioengineering*, **110**, 709-715. https://doi.org/10.1016/j.jbiosc.2010.07.006

[62] Ross, P. (2022) Expression of Concern: Metabolic and Genetic Response to Probiotics Supplementation in Patients with Diabetic Nephropathy: A Randomized, Double-Blind, Placebo-Controlled Trial. *Food & Function*, **13**, 4229-4229. https://doi.org/10.1039/d2fo90024f

[63] Ma, J., Lyu, Y., Liu, X., Jia, X., Cui, F., Wu, X., *et al*. (2022) Engineered Probiotics. *Microbial Cell Factories*, **21**, Article No. 72. https://doi.org/10.1186/s12934-022-01799-0

[64] Wang, X., Chen, W., Jin, R., Xu, X., Wei, J., Huang, H., *et al*. (2022) Engineered Probiotics Clostridium Butyricum-pMTL007-GLP-1 Improves Blood Pressure via Producing GLP-1 and Modulating Gut Microbiota in Spontaneous Hypertension Rat Models. *Microbial Biotechnology*, **16**, 799-812. https://doi.org/10.1111/1751-7915.14196

[65] Hu, H., Luo, J., Liu, Y., Li, H., Jin, R., Li, S., *et al*. (2023) Improvement Effect of a Next-Generation Probiotic L. Plantarum-pMG36e-GLP-1 on Type 2 Diabetes Mellitus *via* the Gut-Pancreas-Liver Axis. *Food & Function*, **14**, 3179-3195. https://doi.org/10.1039/d3fo00044c