

肝硬化门静脉血栓形成与肠道菌群及其代谢物的关系

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摘要

肝硬化是各种慢性肝病进展至晚期的常见结局, 其并发症门静脉血栓形成(PVT)显著增加患者病死率。本综述系统探讨了肠道菌群及其代谢产物在PVT发生发展中的作用机制。肝硬化状态下, 门脉高压导致肠道屏障功能受损, 菌群失调促使细菌脂多糖等病原相关分子模式易位, 通过激活TLR4/NF- κ B等信号通路诱发肝脏炎症与高凝状态, 进而促进PVT形成。此外, 肠道菌群代谢产物如短链脂肪酸(SCFAs)的减少、胆汁酸代谢紊乱、三甲胺-N-氧化物(TMAO)及硫酸吲哚酚等促血栓物质的增多, 共同调控凝血功能与内皮稳定性。当前PVT治疗以抗凝和经颈静脉肝内门体分流术(TIPS)为主, 而针对肠道微生态的干预策略(如益生菌、粪菌移植等)展现出通过恢复肠肝轴平衡以防治PVT的潜力。未来应进一步明确肠道菌群影响PVT的分子机制, 推动微生态治疗在临床中的应用。

关键词

肝硬化, 门静脉血栓, 肠道菌群, 肠道菌群代谢产物

The Relationship between Gut Microbiota, Gut Microbiota Metabolites, and Portal Vein Thrombosis in Cirrhosis

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Abstract

Cirrhosis represents the advanced stage of various chronic liver diseases, with portal vein thrombosis (PVT) as a serious complication that significantly increases mortality. This review systematically examines the role of gut microbiota and their metabolites in the pathogenesis of PVT. In cirrhosis, portal hypertension impairs intestinal barrier function, leading to gut dysbiosis and translocation of bacterial pathogen-associated molecular patterns such as lipopolysaccharide. These activate signaling pathways including TLR4/NF- κ B, inducing hepatic inflammation and a hypercoagulable state that promotes PVT development. Furthermore, gut microbiota-derived metabolites—including reduced levels of anti-inflammatory short-chain fatty acids (SCFAs), dysregulated bile acid metabolism, and elevated pro-thrombotic molecules such as trimethylamine N-oxide (TMAO) and indoxyl sulfate—collectively modulate coagulation and endothelial integrity. Current PVT management primarily involves anticoagulation and transjugular intrahepatic portosystemic shunt (TIPS), while interventions targeting the gut microbiome (e.g., probiotics, fecal microbiota transplantation) show promise in rebalancing the gut-liver axis for PVT prevention and treatment. Future studies should further elucidate the molecular mechanisms linking gut microbiota to PVT and advance microbiome-based therapies into clinical practice.

Keywords

Cirrhosis, Portal Vein Thrombosis, Gut Microbiota, Gut Microbiota Metabolites

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1. 引言

肝硬化是指各种原因导致的慢性肝病在长期炎症后进展,健康肝实质被纤维化组织及再生结节取代,导致门静脉高压的一种临床疾病[1]。作为一种晚期肝病,肝硬化会导致一系列严重并发症,其中门静脉血栓形成(Portal Vein Thrombosis)是肝硬化患者常见的并发症,尤其在失代偿肝硬化中更为突出[2]。PVT指门静脉主干或肝内门静脉分支内形成的血栓,可伴有肠系膜和脾静脉受累,表现为门静脉部分或完全闭塞。PVT常常发病隐匿,急性PVT易导致肠系膜缺血,甚至出现肠坏死;慢性PVT可引起门静脉海绵样变性或门静脉闭塞,从而继发门静脉高压[3]。

肝硬化合并门静脉血栓的发生率因研究对象、肝硬化程度、研究方案及诊断手段的不同而存在差异,且随着肝硬化病情的进展和病程的迁延,PVT的发生风险呈现逐步上升的趋势[4]。包括HCC在内的肝硬化患者的PVT发生率为22.7%~24.4% [5] [6],另有荟萃分析数据显示,在无肝细胞癌(HCC)或腹部手术、血管介入史的情况下,肝硬化患者中PVT的检出率可达10.42%。有研究表明,肝硬化合并PVT的发病率存在明显的地域差异,其中亚洲地区的统计数据最高,随后依次为非洲、欧洲及美洲[7]。

PVT的发生通常涉及多种因素共同作用,主要是由于Virchow三联征不同成分的变化,包括血流缓慢、局部血管损伤和血液高凝状态[8]。但PVT的确切发病机制尚未完全清楚,血管内皮改变的潜在作用尚未得到深入探讨,有关炎症反应或细菌移位在其中作用的相关研究数据也仍然有限[4]。肝脏和肠道通过肝门和胆道系统密切沟通,肠道微生物群通过肠-肝轴影响肝脏代谢。多项研究已证实肠道生态失调与肝硬化的进展有关[9],肠道菌群在调控宿主免疫、代谢和凝血功能方面具有重要作用[10],因此本综述

主要探讨肠道微生物在 PVT 形成中的潜在机制, 并探索潜在的治疗策略。

2. 肠道菌群及细菌成分与 PVT

肠道和肝脏通过门静脉系统紧密连接, 共同构成了“肠-肝轴”, 而作为这一复杂防御体系核心组成部分的“肠肝屏障”, 其主要由肠道屏障、血管及免疫屏障、肝脏屏障这三个关键部分构成, 在调控炎症反应和维持免疫稳态方面发挥着重要作用[11]。

在肝硬化病理状态下, 门静脉压力升高、肠道屏障受损以及肠黏膜渗透性增加[12], 使细菌相关分子模式(MAMPs)如脂多糖(LPS)、胞壁酰二肽(MDP)等物质渗入肝脏并刺激肝脏免疫细胞, 引发局部炎症反应[13], 进一步促进 PVT 的形成。有研究发现, LPS 可结合肝脏巨噬细胞及内皮细胞表面 Toll 样受体 4(TLR4), 激活 NF- κ B 通路和 MAPK 等炎症通路[14], 一方面导致 TNF- α 、IL-1 β 、IL-6 等炎症因子释放, 诱发肝脏局部高凝, 利于血栓形成[15], 另一面可诱导 E-选择素(CD62E)、黏附分子等表达, 使血小板更易附着在受损或活化的内皮表面, 进而加快 PVT 的形成进程。此外, LPS 还可进入细胞质结合 caspase4, 激活 NLRP3/ASC/caspase-1 炎症小体, 进而促进促炎细胞因子 IL-1 β 和 IL-18 的分泌[16]。通过特异性靶向抑制 LPS 信号通路, 可降低 LPS 水平[17], 从而减轻机体炎症反应, 抑制 PVT 的进展。

3. 肠道微生物代谢产物的调控作用

肠道菌群衍生的一系列代谢物, 不仅是其调节宿主生理的关键信使, 还能通过多种途径, 调控宿主的免疫应答、代谢稳态与凝血平衡。这些代谢产物构成了门静脉血栓形成的潜在调控网络[18]。

3.1. SCFAs

短链脂肪酸(SCFAs)是由五个及以下碳原子组成的饱和脂肪酸, 人类中最常见的 SCFAs 有乙酸、丙酸、丁酸。SCFAs 为肠道微生物核心代谢产物, 在调节肝脏炎症反应中发挥重要作用[19]。SCFAs 通过激活多种类型 G 蛋白偶联受体调控宿主免疫应答, SCFA 激活 GPCR43 可抑制核因子 κ B (NF- κ B)通路活性从而影响促炎性细胞因子(如肿瘤坏死因子 TNF、IL-1 β 、IL-6), 并抑制诱导型一氧化氮合酶(iNOS)的活性, 促进一氧化氮(NO)的产生, 从而减弱炎症反应, 降低 PVT 风险[20] [21]。SCFA 还可通过多种途径调节巨噬细胞功能, 包括激活 G 蛋白偶联受体(包括 GPCR41、GPCR43 和 GPCR109A)、抑制组蛋白脱乙酰化酶(HDAC)和调节 NLRP3 炎症小体, 从而增强巨噬细胞抗炎作用[22] [23]。而肝硬化患者肠道菌群失调, SCFAs 生物合成显著减少, 致使其抗炎效应衰减[24]。另一方面, SCFA 已被证实可增强肠道屏障功能, 通过口服和肠内丁酸盐、益生菌作为 SCFAs 补充剂, 可降低肠道通透性, 减少细菌移位及 LPS 入血[25], 从而降低 PVT 风险。

3.2. 胆汁酸

初级胆汁酸是由肝脏细胞以胆固醇为底物, 通过经典途径(由胆固醇 7 α -羟化酶 CYP7A1 介导)或替代途径(由甾醇 27-羟化酶 CYP27A1 催化)合成的羟基化甾醇。其通过 N-酰胺化与甘氨酸或牛磺酸结合成结合型胆汁酸, 随后排入近端小肠, 结合型胆汁酸需要膜转运蛋白才能进入细胞, 而游离胆汁酸在未带电时可跨膜渗透。主要发挥乳化膳食脂质、促进脂类及脂溶性营养素吸收的生理功能。胆汁酸在体内通过高效的肠肝循环得以循环利用: 超过 95%的胆汁酸在回肠末端通过主动及被动转运机制被重吸收, 经门静脉返回肝脏, 继而重新分泌入胆汁。仅少量(约 3%~5%)逃逸重吸收的胆汁酸进入远端肠道。在结肠中, 肠道微生物群(尤其是梭菌目物种)对胆汁酸进行广泛的生物转化, 包括去结合以及氧化、差向异构化和 7 α -脱羟基化等修饰反应, 由此生成次级胆汁酸, 并改变其生物物理与信号传导特性[11] [26]。

胆汁酸不仅调控宿主脂质代谢, 更通过与法尼醇 X 受体(FXR)及 TGR5 结合调节肝脏炎症反应, 其

在 PVT 形成中的作用具有双重性[27]。FXR 激活一方面可以通过阻止 NLRP3 与 caspase 1 的结合, 从而抑制促炎因子 IL-1 β 和 IL-18 的成熟, 物理性抑制 NLRP3 炎症小体的形成发挥抗炎特性。另一方面研究发现 FXR 激动作用可抑制转录因子 NF- κ B 与促炎基因(如 IL-1 β 、白细胞介素-6 (IL-6) 和肿瘤坏死因子 α (TNF α))的顺式调控 κ B 位点结合, 有助于降低 PVT 发生风险[15]。但肝硬化患者胆汁酸代谢紊乱导致次级胆汁酸比例升高, 此类代谢物通过激活炎症信号通路促进血栓形成[28]。

3.3. TMAO

三甲胺-N-氧化物(TMAO)同样是肠道微生物重要代谢产物之一, 其前体物质 TMA 由膳食来源的胆碱及左旋肉碱经肠道菌群代谢生成[28]。胆碱向 TMA 的转化过程在严格厌氧条件下进行[29], 左旋肉碱也可通过两步反应生成 TMA, 其中 γ -丁酰甜菜碱(γ BB)作为中间产物, 而将 γ BB 转化为 TMA 的第二步反应同样严格依赖厌氧环境, 并定位于肠道远端区域[30]。放线菌门和梭杆菌门, 以及厚壁菌门和变形菌门均可通过胆碱前体产生 TMA [31]。相比之下, 从肉碱生成 TMA 的基因簇存在于厚壁菌门和变形菌门[32]。TMA 经门静脉入肝, 通过肝脏含黄素单加氧酶(主要是 FMO1 和 FMO3)被氧化成 TMAO [33]。

已有大量研究表明 TMAO 可促动脉粥样硬化形成[34], 此外 TMAO 还可促进血栓形成。Witkowski 等[35]通过体内和体外实验表明, TMAO 通过增强组织因子和血管细胞黏附分子 1 的表达, 增加 PVT 形成风险。TMAO 能增强离体血小板对多种激动剂(ADP、凝血酶和胶原蛋白)的反应性, 促进细胞内钙释放[36]。TMAO 还可能通过促进内皮功能障碍增加血栓形成风险[37]。有研究表明, 用 TMAO 处理人脐静脉内皮细胞(HUVECs)会引发氧化应激并削弱细胞与细胞外基质的黏附能力。此外, TMAO 处理会上调血管细胞黏附分子 1 (VCAM1)的表达, 并增强体外单核细胞对 HUVECs 的黏附, 高 TMAO 水平通过下调抗炎因子 IL-10, 加剧炎症和氧化应激; 此外, TMAO 激活促炎通路, 如含核酸结合结构域、富含亮氨酸家族、NOD 样受体热蛋白结构域相关蛋白 3 (NLRP3)炎症小体, 并改变内皮一氧化氮合酶功能, 加剧血管内皮功能障碍[38]。在凝血机制方面, TMAO 可在体内诱导人微血管内皮细胞系(HMEC-1)和小鼠主动脉细胞表达组织因子。此外有研究表明 TMAO 增加 BA 合成并将肝脏 BA 组成转向 FXR 拮抗活性[39]。

3.4. 吲哚及其衍生物

吲哚由色氨酸代谢生成, 大多数色氨酸在肠嗜铬细胞中被宿主代谢, 产生神经递质血清素, 并且在免疫和上皮细胞中代谢, 导致产生神经毒性或神经保护性衍生物[40]。大量未被宿主吸收的色氨酸被肠道细菌代谢, 多种微生物能够代谢色氨酸并产生吲哚代谢物, 特别是拟杆菌属、副拟杆菌属、双歧杆菌属、梭状芽孢杆菌属、消化链球菌属和乳酸杆菌属, 产生具有免疫调节特性的生物活性吲哚[41]。

吲哚衍生物硫酸吲哚酚可通过促进内皮功能障碍诱导血栓炎症, 导致血小板高反应性和血栓形成。此外, 用硫酸吲哚酚预处理 HUVECs 通过上调粘附分子 E-选择素促进了它们与单核细胞的相互作用, 并增加了氧化应激, 硫酸吲哚氧基和吲哚 3-乙酸增加了内皮细胞和外周血单核细胞中与芳香烃受体(AHR)途径激活相关的组织因子和基因的表达。阻断 AHR 途径导致硫酸吲哚酚或吲哚-3-乙酸诱导的组织因子水平降低, 与内皮细胞促凝血活性降低相关[42]。

4. PVT 治疗

针对肝硬化门静脉血栓形成, 以抗凝为最主要治疗方案, 而溶栓治疗 PVT 的证据不足, 我国 TIPS 治疗肝硬化 PVT 与内镜联合普萘洛尔和抗凝药物治疗相比, TIPS 治疗能显著降低再出血率及提高 PVT 再通率, 但对生存率改善不明显[43]。

近年来, 针对肠道菌群组成及代谢功能的干预策略备受关注。临床研究证实, 补充特定益生菌(如双歧杆菌属、乳杆菌属)可重塑肠道微生态平衡, 增加 SCFAs 生成, 改善肝硬化炎症状态并降低 PVT 风险[44]。

在一项针对肝硬化患者的临床对照试验中[45], 施加益生菌干预组的丙氨酸氨基转移酶(ALT)和总胆红素水平明显低于非益生菌组治疗后的水平, 这表明在肝硬化患者中, 添加益生菌配合常规治疗, 有助于改善患者肝功能。此外, 在针对 NAFLD 患者的临床试验中, 使用益生菌干预 8 周后患者 TNF α 和 IL-6 显著降低[46]。靶向抗生素疗法, 如选用利福昔明等不吸收或吸收率低的抗生素, 可通过减少革兰阴性菌负荷降低脂多糖(LPS)水平[47]。已有研究表明, PVT 形成可加剧肝硬化患者菌群失调(致病菌增殖/有益菌衰减), 而调节拟杆菌属等特定菌群可延缓 PVT 进展[48]。此外, 粪菌移植用于从根本上重塑肠道菌群, 是具有前景的治疗及预防 PVT 形成的手段[49]。中药在 PVT 治疗上亦有报道, 目前主要使用黄芪、当归、水蛭等活血化瘀、补虚药物, 尚未发现中药干预对患者生存率的影响[50], 上述微生物干预策略虽为 PVT 防治提供新路径, 但其安全性及长期疗效有待验证, 需警惕益生菌、粪菌移植加重肠道菌群紊乱风险[51]。

5. 总结与展望

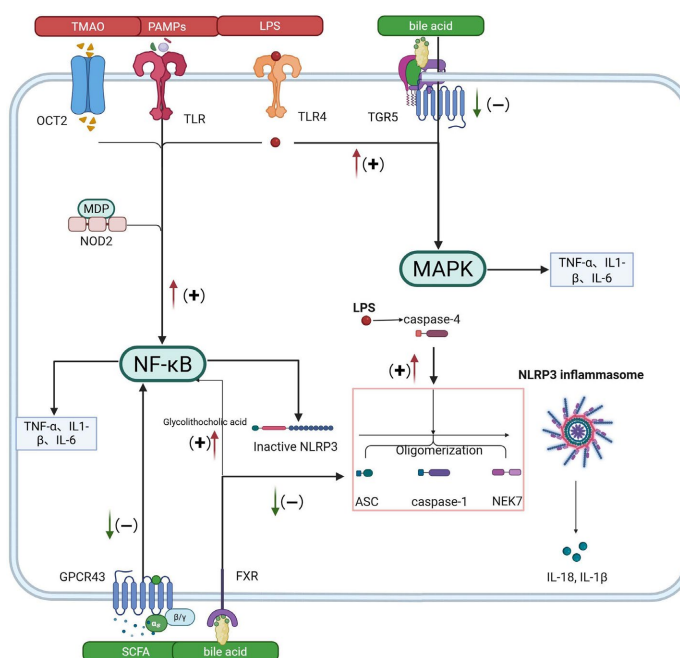


Figure 1. Gut microbiota-derived metabolites and inflammatory pathways

图 1. 肠道菌群代谢物与炎症通路

本综述系统探讨了肠道菌群及其代谢产物在肝硬化门静脉血栓形成中的关键作用(见图 1)。PVT 的发生是门静脉血流动力学改变、血管内皮损伤及血液高凝状态共同作用的结果, 而肠道微生态失衡通过“肠-肝轴”深度参与该过程。具体而言, 肝硬化门脉高压所致肠道屏障功能障碍, 导致细菌脂多糖等病原相关分子模式易位, 通过激活 TLR4/NF- κ B 等信号通路, 诱发肝脏局部炎症与高凝状态, 促进 PVT 形成。同时, 肠道菌群代谢产物, 如具有抗炎屏障作用的短链脂肪酸减少、具有复杂双向调控作用的胆汁酸代谢紊乱、以及促血栓形成的三甲胺-N-氧化物和硫酸吡啶酚等水平升高, 共同构成了影响 PVT 发生发展的关键微环境。现有临床治疗以抗凝和 TIPS 为主, 但针对肠道菌群的干预, 如益生菌、粪菌移植等, 已显示出通过调节微生态平衡、改善肠肝轴功能以防治 PVT 的潜力。尽管近年来不断有新的研究表明肠道菌群与门静脉血栓形成密切相关, 但其机制仍尚未完全阐明, 肠道代谢产物导致门静脉血栓形成的分子机制仍缺乏系统性, 将肠道菌群干预用于治疗 PVT 亦有诸多挑战。但随着未来微生物组学与代谢组学研究的不断深入, 肠道微生态治疗或将成为 PVT 治疗及预防的新方向。

参考文献

- [1] Ginès, P., Krag, A., Abraldes, J.G., Solà, E., Fabrellas, N. and Kamath, P.S. (2021) Liver Cirrhosis. *The Lancet*, **398**, 1359-1376. [https://doi.org/10.1016/s0140-6736\(21\)01374-x](https://doi.org/10.1016/s0140-6736(21)01374-x)
- [2] Hepatology, C.S.O. (2019) Chinese Guidelines on the Management of Liver Cirrhosis. *Journal of Clinical Hepatology*, **35**, 846-865.
- [3] Elkrief, L., Hernandez-Gea, V., Senzolo, M., Albillos, A., Baiges, A., Berzigotti, A., *et al.* (2024) Portal Vein Thrombosis: Diagnosis, Management, and Endpoints for Future Clinical Studies. *The Lancet Gastroenterology & Hepatology*, **9**, 859-883. [https://doi.org/10.1016/s2468-1253\(24\)00155-9](https://doi.org/10.1016/s2468-1253(24)00155-9)
- [4] Northup, P.G., Garcia-Pagan, J.C., Garcia-Tsao, G., Intagliata, N.M., Superina, R.A., Roberts, L.N., *et al.* (2021) Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients with Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*, **73**, 366-413. <https://doi.org/10.1002/hep.31646>
- [5] Serag, W.M., Mohammed, B.S.E., Mohamed, M.M. and Elsayed, B.E. (2020) Predicting the Risk of Portal Vein Thrombosis in Patients with Liver Cirrhosis and Hepatocellular Carcinoma. *Heliyon*, **6**, e04677. <https://doi.org/10.1016/j.heliyon.2020.e04677>
- [6] Zanetto, A., Senzolo, M., Vitale, A., Cillo, U., Radu, C., Sartorello, F., *et al.* (2017) Thromboelastometry Hypercoagulable Profiles and Portal Vein Thrombosis in Cirrhotic Patients with Hepatocellular Carcinoma. *Digestive and Liver Disease*, **49**, 440-445. <https://doi.org/10.1016/j.dld.2016.12.019>
- [7] Pan, J., Wang, L., Gao, F., An, Y., Yin, Y., Guo, X., *et al.* (2022) Epidemiology of Portal Vein Thrombosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis. *European Journal of Internal Medicine*, **104**, 21-32. <https://doi.org/10.1016/j.ejim.2022.05.032>
- [8] Intagliata, N.M., Caldwell, S.H. and Tripodi, A. (2019) Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients with and without Cirrhosis. *Gastroenterology*, **156**, 1582-1599.e1. <https://doi.org/10.1053/j.gastro.2019.01.265>
- [9] Manzoor, R., Ahmed, W., Afify, N., Memon, M., Yasin, M., Memon, H., *et al.* (2022) Trust Your Gut: The Association of Gut Microbiota and Liver Disease. *Microorganisms*, **10**, Article 1045. <https://doi.org/10.3390/microorganisms10051045>
- [10] Di Vincenzo, F., Del Gaudio, A., Petito, V., Lopetuso, L.R. and Scaldaferri, F. (2024) Gut Microbiota, Intestinal Permeability, and Systemic Inflammation: A Narrative Review. *Internal and Emergency Medicine*, **19**, 275-293. <https://doi.org/10.1007/s11739-023-03374-w>
- [11] Pabst, O., Hornef, M.W., Schaap, F.G., Cerovic, V., Clavel, T. and Bruns, T. (2023) Gut-Liver Axis: Barriers and Functional Circuits. *Nature Reviews Gastroenterology & Hepatology*, **20**, 447-461. <https://doi.org/10.1038/s41575-023-00771-6>
- [12] Chopyk, D.M. and Grakoui, A. (2020) Contribution of the Intestinal Microbiome and Gut Barrier to Hepatic Disorders. *Gastroenterology*, **159**, 849-863. <https://doi.org/10.1053/j.gastro.2020.04.077>
- [13] Hsu, C.L. and Schnabl, B. (2023) The Gut-Liver Axis and Gut Microbiota in Health and Liver Disease. *Nature Reviews Microbiology*, **21**, 719-733. <https://doi.org/10.1038/s41579-023-00904-3>
- [14] Wei, J., Zhang, Y., Li, H., Wang, F. and Yao, S. (2023) Toll-Like Receptor 4: A Potential Therapeutic Target for Multiple Human Diseases. *Biomedicine & Pharmacotherapy*, **166**, Article 115338. <https://doi.org/10.1016/j.biopha.2023.115338>
- [15] Luo, M., Xu, Y., Li, J., Luo, D., Zhu, L., Wu, Y., *et al.* (2023) Vitamin D Protects Intestines from Liver Cirrhosis-Induced Inflammation and Oxidative Stress by Inhibiting the TLR4/MyD88/NF- κ B Signaling Pathway. *Open Medicine*, **18**, Article 20230714. <https://doi.org/10.1515/med-2023-0714>
- [16] De Chiara, S., De Simone Carone, L., Cirella, R., Andretta, E., Silipo, A., Molinaro, A., *et al.* (2025) Beyond the Toll-Like Receptor 4. Structure-Dependent Lipopolysaccharide Recognition Systems: How Far Are We? *ChemMedChem*, **20**, e202400780. <https://doi.org/10.1002/cmdc.202400780>
- [17] Kumar, P., Schroder, E.A., Rajaram, M.V.S., Harris, E.N. and Ganesan, L.P. (2024) The Battle of LPS Clearance in Host Defense vs. Inflammatory Signaling. *Cells*, **13**, Article 1590. <https://doi.org/10.3390/cells13181590>
- [18] 武雅荣, 张永强, 郑英, 等. 肝硬化门静脉血栓形成机制研究进展[J]. 协和医学杂志, 2025, 16(2): 439-447.
- [19] Mann, E.R., Lam, Y.K. and Uhlig, H.H. (2024) Short-Chain Fatty Acids: Linking Diet, the Microbiome and Immunity. *Nature Reviews Immunology*, **24**, 577-595. <https://doi.org/10.1038/s41577-024-01014-8>
- [20] Liu, T., Li, J., Liu, Y., Xiao, N., Suo, H., Xie, K., *et al.* (2012) Short-Chain Fatty Acids Suppress Lipopolysaccharide-Induced Production of Nitric Oxide and Proinflammatory Cytokines through Inhibition of NF- κ B Pathway in RAW264.7 Cells. *Inflammation*, **35**, 1676-1684. <https://doi.org/10.1007/s10753-012-9484-z>

- [21] Liu, P., Wang, Y., Yang, G., Zhang, Q., Meng, L., Xin, Y., *et al.* (2021) The Role of Short-Chain Fatty Acids in Intestinal Barrier Function, Inflammation, Oxidative Stress, and Colonic Carcinogenesis. *Pharmacological Research*, **165**, Article 105420. <https://doi.org/10.1016/j.phrs.2021.105420>
- [22] Duan, H., Wang, L., Huangfu, M. and Li, H. (2023) The Impact of Microbiota-Derived Short-Chain Fatty Acids on Macrophage Activities in Disease: Mechanisms and Therapeutic Potentials. *Biomedicine & Pharmacotherapy*, **165**, Article 115276. <https://doi.org/10.1016/j.biopha.2023.115276>
- [23] Xie, Q., Li, Q., Fang, H., Zhang, R., Tang, H. and Chen, L. (2024) Gut-Derived Short-Chain Fatty Acids and Macrophage Modulation: Exploring Therapeutic Potentials in Pulmonary Fungal Infections. *Clinical Reviews in Allergy & Immunology*, **66**, 316-327. <https://doi.org/10.1007/s12016-024-08999-z>
- [24] Fu, K., Ma, C., Wang, C., Zhou, H., Gong, L., Zhang, Y., *et al.* (2022) Forsythiaside Alleviated Carbon Tetrachloride-Induced Liver Fibrosis by Modulating Gut Microbiota Composition to Increase Short-Chain Fatty Acids and Restoring Bile Acids Metabolism Disorder. *Biomedicine & Pharmacotherapy*, **151**, Article 113185. <https://doi.org/10.1016/j.biopha.2022.113185>
- [25] Pohl, K., Moodley, P. and Dhanda, A. (2022) The Effect of Increasing Intestinal Short-Chain Fatty Acid Concentration on Gut Permeability and Liver Injury in the Context of Liver Disease: A Systematic Review. *Journal of Gastroenterology and Hepatology*, **37**, 1498-1506. <https://doi.org/10.1111/jgh.15899>
- [26] Ridlon, J.M. and Gaskins, H.R. (2024) Another Renaissance for Bile Acid Gastrointestinal Microbiology. *Nature Reviews Gastroenterology & Hepatology*, **21**, 348-364. <https://doi.org/10.1038/s41575-024-00896-2>
- [27] Moon, A., Briand, F., Breyner, N., Song, D., Madsen, M.R., Kim, H., *et al.* (2024) Improvement of NASH and Liver Fibrosis through Modulation of the Gut-Liver Axis by a Novel Intestinal FXR Agonist. *Biomedicine & Pharmacotherapy*, **173**, Article 116331. <https://doi.org/10.1016/j.biopha.2024.116331>
- [28] Reusswig, F., Reich, M., Wienands, L., Herebian, D., Keitel-Anselmino, V. and Elvers, M. (2024) The Bile Acid Receptor TGR5 Inhibits Platelet Activation and Thrombus Formation. *Platelets*, **35**, Article 2322733. <https://doi.org/10.1080/09537104.2024.2322733>
- [29] Zhu, Y., Li, Q. and Jiang, H. (2020) Gut Microbiota in Atherosclerosis: Focus on Trimethylamine N-Oxide. *APMIS*, **128**, 353-366. <https://doi.org/10.1111/apm.13038>
- [30] Martínez-del Campo, A., Bodea, S., Hamer, H.A., Marks, J.A., Haiser, H.J., Turnbaugh, P.J., *et al.* (2015) Characterization and Detection of a Widely Distributed Gene Cluster that Predicts Anaerobic Choline Utilization by Human Gut Bacteria. *mBio*, **6**, e00042-15. <https://doi.org/10.1128/mbio.00042-15>
- [31] Buffa, J.A., Romano, K.A., Copeland, M.F., *et al.* (2022) The Microbial GBU Gene Cluster Links Cardiovascular Disease Risk Associated with Red Meat Consumption to Microbiota l-Carnitine Catabolism. *Nature Microbiology*, **7**, 73-86.
- [32] Wang, Z., Klipfell, E., Bennett, B.J., Koeth, R., Levison, B.S., DuGar, B., *et al.* (2011) Gut Flora Metabolism of Phosphatidylcholine Promotes Cardiovascular Disease. *Nature*, **472**, 57-63. <https://doi.org/10.1038/nature09922>
- [33] Nebieridze, A., Abu-Bakr, A., Nazir, A., Ghosson, A., Minova, A. and Uwishema, O. (2025) Microbiome and Cardiovascular Health Unexplored Frontiers in Precision Cardiology: A Narrative Review. *Annals of Medicine & Surgery*, **87**, 4255-4261. <https://doi.org/10.1097/ms9.0000000000003430>
- [34] Zhu, W., Gregory, J.C., Org, E., Buffa, J.A., Gupta, N., Wang, Z., *et al.* (2016) Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell*, **165**, 111-124. <https://doi.org/10.1016/j.cell.2016.02.011>
- [35] Witkowski, M., Witkowski, M., Friebel, J., Buffa, J.A., Li, X.S., Wang, Z., *et al.* (2021) Vascular Endothelial Tissue Factor Contributes to Trimethylamine N-Oxide-Enhanced Arterial Thrombosis. *Cardiovascular Research*, **118**, 2367-2384. <https://doi.org/10.1093/cvr/cvab263>
- [36] Szegedi, I., Bomberák, D., Éles, Z., Lóczi, L. and Bagoly, Z. (2025) Cardiovascular Disease and Microbiome: Focus on Ischemic Stroke. *Polish Archives of Internal Medicine*, **135**, Article 17088. <https://doi.org/10.20452/pamw.17088>
- [37] Chen, H., Li, J., Li, N., Liu, H. and Tang, J. (2019) Increased Circulating Trimethylamine N-Oxide Plays a Contributory Role in the Development of Endothelial Dysfunction and Hypertension in the RUPP Rat Model of Preeclampsia. *Hypertension in Pregnancy*, **38**, 96-104. <https://doi.org/10.1080/10641955.2019.1584630>
- [38] Tan, X., Liu, Y., Long, J., Chen, S., Liao, G., Wu, S., *et al.* (2019) Trimethylamine n-Oxide Aggravates Liver Steatosis through Modulation of Bile Acid Metabolism and Inhibition of Farnesoid X Receptor Signaling in Nonalcoholic Fatty Liver Disease. *Molecular Nutrition & Food Research*, **63**, e1900257. <https://doi.org/10.1002/mnfr.201900257>
- [39] Park, J., Lee, S.R., Dhennezel, C., Taylor, N., Dame, A., Kadoki, M., *et al.* (2025) Elucidating the Role of *Campylobacter concisus*—Derived Indole Metabolites in Gut Inflammation and Immune Modulation. *Proceedings of the National Academy of Sciences*, **122**, e2514071122. <https://doi.org/10.1073/pnas.2514071122>
- [40] Agus, A., Planchais, J. and Sokol, H. (2018) Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host & Microbe*, **23**, 716-724. <https://doi.org/10.1016/j.chom.2018.05.003>

- [41] Dodd, D., Spitzer, M.H., Van Treuren, W., Merrill, B.D., Hryckowian, A.J., Higginbottom, S.K., *et al.* (2017) A Gut Bacterial Pathway Metabolizes Aromatic Amino Acids into Nine Circulating Metabolites. *Nature*, **551**, 648-652. <https://doi.org/10.1038/nature24661>
- [42] Khuu, M.P., Paeslack, N., Dremova, O., Benakis, C., Kiouptsi, K. and Reinhardt, C. (2024) The Gut Microbiota in Thrombosis. *Nature Reviews Cardiology*, **22**, 121-137. <https://doi.org/10.1038/s41569-024-01070-6>
- [43] 祁兴顺, 杨玲. 肝硬化门静脉血栓管理专家共识(2020 年, 上海) [J]. 临床肝胆病杂志, 2020, 36(12): 2667-2674. <http://gffgx1d182c2ce1904ac7s9kn6fuvkwc9q6uww.zzzz.cwlib.cqmu.edu.cn/CNKI:SUN:LCGD.0.2020-12-010>
- [44] Song, M., Liu, Y., Huang, X., Ding, S., Wang, Y., Shen, J., *et al.* (2020) A Broad-Spectrum Antibiotic Adjuvant Reverses Multidrug-Resistant Gram-Negative Pathogens. *Nature Microbiology*, **5**, 1040-1050. <https://doi.org/10.1038/s41564-020-0723-z>
- [45] Wu, Z., Zhou, H., Liu, D. and Deng, F. (2023) Alterations in the Gut Microbiota and the Efficacy of Adjuvant Probiotic Therapy in Liver Cirrhosis. *Frontiers in Cellular and Infection Microbiology*, **13**, Article 1218552. <https://doi.org/10.3389/fcimb.2023.1218552>
- [46] Sepideh, A., Karim, P., Hossein, A., Leila, R., Hamdollah, M., Mohammad E, G., *et al.* (2015) Effects of Multistrain Probiotic Supplementation on Glycemic and Inflammatory Indices in Patients with Nonalcoholic Fatty Liver Disease: A Double-Blind Randomized Clinical Trial. *Journal of the American College of Nutrition*, **35**, 500-505. <https://doi.org/10.1080/07315724.2015.1031355>
- [47] Nie, G., Zhang, H., Xie, D., Yan, J. and Li, X. (2024) Liver Cirrhosis and Complications from the Perspective of Dysbiosis. *Frontiers in Medicine*, **10**, Article ID: 1320015. <https://doi.org/10.3389/fmed.2023.1320015>
- [48] Huang, X., Zhang, Y., Yi, S., Lei, L., Ma, T., Huang, R., *et al.* (2023) Potential Contribution of the Gut Microbiota to the Development of Portal Vein Thrombosis in Liver Cirrhosis. *Frontiers in Microbiology*, **14**, Article ID: 1217338. <https://doi.org/10.3389/fmicb.2023.1217338>
- [49] Xing, Y., Ou, Y., Wang, Y., Hou, L. and Zhu, J. (2025) New Insights into Gut-Liver Axis in Advanced Liver Diseases: A Promising Therapeutic Target. *Biochemical Pharmacology*, **242**, 117284. <https://doi.org/10.1016/j.bcp.2025.117284>
- [50] 郭亚楠, 顾宏图, 赵长青, 等. 中医药对肝硬化门静脉血栓的干预作用及用药特点分析[J]. 临床肝胆病杂志, 2023, 39(2): 345-351.
- [51] DeLeon, O., Mocanu, M., Tan, A., Sidebottom, A.M., Koval, J., Ceccato, H.D., *et al.* (2025) Microbiome Mismatches from Microbiota Transplants Lead to Persistent Off-Target Metabolic and Immunomodulatory Effects. *Cell*, **188**, 3927-3941.e13. <https://doi.org/10.1016/j.cell.2025.05.014>