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胃肠道糖脂转运体在代谢功能障碍相关脂肪性肝病中的研究进展

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摘 要

代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)已成为全球最常见的慢性肝病之一。胃肠道作为肝脏代谢底物输入和肠–肝信号传递的上游枢纽，其对葡萄糖、果糖、胆固醇、胆汁酸及脂肪酸的跨膜转运，与肝脂沉积、炎症反应和纤维化进展密切相关。近年来，随着MASLD/MASH命名更新、肠–肝轴研究深入及药物治疗证据不断累积，胃肠道糖脂转运体的研究内涵已由“营养吸收通道”拓展为“营养感知、代谢重编程、疾病分层与治疗靶向”的整合网络。本文围绕葡萄糖与果糖转运体、胆固醇与胆汁酸转运系统、脂肪酸转运相关蛋白3个方面，对SGLT1/SGLT2、GLUT2/GLUT5、NPC1L1、ABCG5/8、ASBT-FXR-FGF19轴、FATP、FABP及CD36等分子的研究进展进行综述，并结合近年来指南、系统评价和代表性临床试验，分析其在MASLD发生发展中的作用及转化价值。现有证据提示：SGLT2抑制剂可改善影像学脂肪变和部分非侵入性纤维化指标；GLUT5介导的果糖转运与胰岛素抵抗、肝纤维化风险及高果糖相关脂肪性肝病密切相关；NPC1L1是连接肠道胆固醇吸收与肝内胆固醇负荷的重要节点，但依折麦布对肝脂肪的直接改善作用有限；ASBT-FXR-FGF19轴是近年来胆汁酸转运研究的重要扩展；FATP5、FABP1和CD36则进一步揭示了脂毒性、炎症和纤维化与脂质递送之间的联系。未来应加强器官特异性干预、患者分层和联合治疗研究，以推动该领域由机制研究走向精准治疗。

关键词

MASLD，MASH，胃肠道转运体，SGLT，GLUT5

Research Progress of Gastrointestinal Glucose and Lipid Transporters in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most prevalent chronic liver disease worldwide. As an upstream hub for nutrient delivery and gut-liver signaling, the gastrointestinal tract influences hepatic steatosis, inflammation, and fibrosis through the transmembrane transport of glucose, fructose, cholesterol, bile acids, and fatty acids. With the recent update in disease nomenclature, expansion of gut-liver axis research, and rapid accumulation of therapeutic evidence, gastrointestinal transporters should no longer be viewed merely as "absorptive channels", but rather as an integrated network linking "nutrient sensing, metabolic reprogramming, disease stratification, and therapeutic intervention". This review summarizes recent advances in glucose and fructose transporters, cholesterol and bile-acid transport systems, and fatty-acid transport-related proteins, with a focus on SGLT1/SGLT2, GLUT2/GLUT5, NPC1L1, ABCG5/8, the ASBT-FXR-FGF19 axis, FATP, FABP, and CD36. Recent guidelines, meta-analyses, and representative clinical trials are incorporated to evaluate their mechanistic and translational relevance in MASLD. Current evidence indicates that SGLT2 inhibitors improve imaging-based steatosis and some non-invasive fibrosis indices; GLUT5-mediated fructose transport is closely associated with insulin resistance, fibrosis risk, and fructose-driven steatotic liver disease; NPC1L1 remains a key mechanistic bridge between intestinal cholesterol absorption and hepatic cholesterol burden, although ezetimibe has limited direct benefit on liver fat; the ASBT-FXR-FGF19 pathway represents a major post-2017 expansion of bile-acid transport research; and FATP5, FABP1, and CD36 further connect lipid delivery with lipotoxicity, inflammation, and fibrosis. Future studies should prioritize organ-specific intervention, patient stratification, and combination therapy to promote precision treatment in MASLD.

Keywords

MASLD, MASH, Gastrointestinal Transporters, SGLT, GLUT5

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1. 引言

代谢功能障碍相关脂肪性肝病(MASLD)是以肝脏脂肪变为基础、与代谢异常密切相关的一组疾病谱，严重类型可进展为代谢功能障碍相关脂肪性肝炎(MASH)、肝纤维化、肝硬化及肝细胞癌[1]-[4]。2023 年多学会 Delphi 共识将 NAFLD 更名为 MASLD，将 NASH 更名为 MASH，强调该病与心血管代谢危险因素之间的本质联系[1]。2024 年 EASL-EASD-EASO 指南进一步采用 MASLD 术语并完善了诊断与管理框架[5]。目前，全球 MASLD 患病率已超过 30%，且随时间呈持续上升趋势[3]。

胃肠道位于 MASLD 发生发展的上游。葡萄糖、果糖、胆固醇、胆汁酸和脂肪酸经小肠吸收后，直接决定门静脉与外周循环底物负荷，并通过肠促激素、胆汁酸信号、乳糜微粒装配及肠道菌群代谢产物等途径调节肝脏脂质代谢、炎症反应和纤维化进程。近年来，对胃肠道转运体的认识已从单一分子表达差异，逐渐转向“转运通量、信号网络与疾病表型”的整合框架。

2. 胃肠道糖脂转运网络与 MASLD 的概述

MASLD 的核心病理过程包括底物过剩、胰岛素抵抗、脂毒性、氧化应激、炎症反应和纤维化[6]。胃肠道在其中承担两类关键作用：其一，决定葡萄糖、果糖、胆固醇和脂肪酸等底物的进入速度与总量；其二，通过胆汁酸循环、肠道菌群及肠源性激素参与代谢信号调控。SGLT1、GLUT2 和 GLUT5 参与单糖跨膜转运；NPC1L1、ABCG5/8、ABCA1、ACAT2 与 apoB48/MTP 系统决定胆固醇的摄取、外排和乳糜微粒装配；ASBT-FXR-FGF19 轴连接回肠胆汁酸重吸收与肝脏代谢反馈；FATP、FABP 和 CD36 则共同影响脂肪酸摄取、胞内递送和脂毒性重塑(表 1) [7]。

Table 1. Overview of major gastrointestinal glycolipid transporters associated with MASLD and their research progress
表 1. 与 MASLD 相关的主要胃肠道糖脂转运体及其研究进展概览

类别	代表分子	主要部位/底物	与 MASLD 关系	潜在干预价值
葡萄糖转运	SGLT1	空肠刷状缘；葡萄糖/半乳糖	决定餐后糖吸收与肠促激素释放，影响肝脏底物负荷	适合作为营养感知与肠道局部干预靶点
葡萄糖转运	SGLT2	肾近曲小管；葡萄糖	临床药物证据显示可改善影像学脂肪变和部分纤维化指标	转化价值较强，但并非典型肠道局部靶点
果糖转运	GLUT5	小肠刷状缘；果糖	与高果糖饮食、胰岛素抵抗和纤维化风险相关性增强	近年最值得关注的肠道限制性治疗靶点之一
糖转运协同	GLUT2	顶膜/基底侧；葡萄糖、果糖	高糖负荷下顶膜插入增加，促进肠源性底物进入门静脉	更适合作为机制节点而非单独药物靶点
胆固醇转运	NPC1L1	小肠刷状缘；胆固醇	连接肠胆固醇吸收与肝内胆固醇负荷	依折麦布可验证机制，但直接肝脂获益有限
胆固醇外排	ABCG5/8、ABCA1	肠上皮顶膜/基底侧；甾醇外排	决定肠道胆固醇净通量并影响动脉粥样硬化风险	适合纳入组合分型与联合治疗研究
胆汁酸转运	ASBT-FXR-FGF19	回肠；胆汁酸反馈信号	调控胆汁酸合成、糖脂代谢及菌群－宿主互作	组织选择性干预前景突出
脂肪酸转运	FATP、FABP、CD36	肠上皮/肝细胞；长链脂肪酸	参与脂质递送、脂毒性、炎症和纤维化	具潜在成药性，但仍以机制研究为主

因此，胃肠道转运体并非单纯的“吸收通道”，而是将饮食暴露、肠道代谢状态与肝脏损伤表型连接起来的关键生物学接口。对这些转运体进行系统综述，有助于解释不同膳食负荷为何会诱发不同 MASLD 表型，也有助于理解近年来代谢药物何以能够通过重塑肠－肝通讯而带来肝脏获益。

需要指出的是，胃肠道糖脂转运体在 MASLD 中的作用并非彼此孤立，而是构成了由“底物转运—信号感知—代谢反馈”共同驱动的功能网络。不同转运系统之间的交联，首先体现在胆汁酸转运与糖、脂吸收之间的耦联。ASBT 介导的回肠胆汁酸重吸收不仅维持肠肝循环，也为回肠 FXR 激活及 FGF19 产生提供基础，从而参与肠—肝代谢反馈调控。该过程不仅影响胆汁酸稳态本身，还可通过改变胆汁酸池

组成及肠道脂质吸收环境，进一步影响营养底物处理。已有研究提示，胆汁酸-FXR 信号可调节以 GLUT2 为代表的肠道葡萄糖转运，并影响餐后葡萄糖稳态；同时，肠道 FXR 活化还可通过改变胆汁酸组成和脂质吸收通量影响肝内脂质负荷[8]-[14]。进一步看，在高糖尤其高果糖饮食背景下，GLUT5 介导的果糖转运增强与 NAFLD/MASLD 及肝纤维化风险升高相关；动物研究进一步表明，肠道特异性抑制 GLUT5 可减轻高果糖诱导的脂肪性肝病表型。另一方面，CD36 等脂肪酸摄取相关分子的表达和功能还受到 LXR、PXR 和 PPARγ 等核受体网络调控。因此，MASLD 中的胃肠道转运异常更适合被理解为多类转运体共同参与的网络失衡，而不是若干独立分子的简单叠加[12]-[14]。

3. 葡萄糖与果糖转运体

3.1. SGLT1/SGLT2

SGLT 家族依赖钠离子电化学梯度主动转运单糖，其中 SGLT1 主要分布于小肠近端刷状缘，是膳食葡萄糖和半乳糖吸收的核心转运体；SGLT2 则主要表达于肾近曲小管，在肾糖重吸收中发挥主导作用[15]。从胃肠道转运角度看，SGLT1 直接决定餐后肠道糖负荷，而 SGLT2 的 MASLD 意义更多体现在系统代谢干预后的肝脏获益。

2024 年系统评价纳入 18 项随机对照试验、1330 例受试者，结果显示 SGLT2 抑制剂可改善受控衰减参数(CAP)、肝脏硬度测量值(LSM)、MRI-PDFF 及 FIB-4 等非侵入性指标(表 2) [16]。这提示 SGLT2 抑制剂的肝脏获益并非单纯来自降糖，而与体重下降、内脏脂肪减少、肝脏底物输入下降及氧化应激缓解等机制共同相关。然而，目前证据仍主要集中于合并 2 型糖尿病或肥胖的患者，且组织学终点和长期肝相关结局仍有待进一步验证。

3.2. GLUT2/GLUT5

LUT 家族属于易化扩散型转运体。GLUT2 参与肠上皮葡萄糖和果糖的双向转运，在高糖负荷下可发生顶膜插入；GLUT5 则是小肠刷状缘最重要的果糖转运体[17]。在高果糖膳食背景下，GLUT5 介导的果糖通量增加，可促进肠源性底物进入门静脉，继而诱导肝脏新生脂肪生成、尿酸生成、氧化应激和肠屏障损害。

De Vito 等[12]在人群研究中发现，NAFLD 患者十二指肠 GLUT5 水平升高，且与胰岛素抵抗和肝纤维化风险相关。进一步的机制研究显示，肠道特异性抑制 GLUT5 可减轻高果糖诱导的脂肪性肝病表型[13]。上述证据使 GLUT5 从“饮食危险因素相关分子”转变为有望用于患者分层和肠道限制性干预的候选靶点。相比之下，GLUT2 更适合作为糖负荷应答与肠源性底物转运的协同机制节点。

Table 2. Representative transformation evidence of MASLD related to gastrointestinal glucose and lipid transport
表 2. 胃肠道糖脂转运相关的 MASLD 代表性转化证据

靶点/干预	证据类型	主要发现	启示与局限
SGLT2 抑制剂	2024 系统评价[16]	18 项 RCT、1330 例受试者中，CAP、LSM、MRI-PDFF 和 FIB-4 等指标出现改善	临床转化价值较强，但组织学终点和长期肝结局仍需更多证据
GLUT5	2024 人群研究[12]	十二指肠 GLUT5 水平与 NAFLD 及纤维化风险相关	提示果糖转运具有患者分层价值，但尚缺成熟药物
GLUT5	2025 机制研究[13]	靶向肠道 GLUT5 可缓解高果糖诱导的脂肪性肝病	支持发展肠道限制性抑制剂，仍需进一步验证安全性与可转化性

续表

NPC1L1/依折麦布	随机试验再评价[18]	可降低胆固醇吸收和 LDL-C，但对 MRI-PDFF 改善有限	机制可靠，单药肝脏疗效有限，适合作为联合方案组成部分
FXR 激动剂	2025 系统评价[19]	可改善转氨酶和 MRI-PDFF，提示胆汁酸通路具治疗潜力	瘙痒和脂质相关不良反应仍是限制因素
Resmetirom	2024III期试验/FDA 批准[20]	改善 MASH 缓解及纤维化终点，成为首个获批 MASH 药物	验证了代谢重塑可改变肝组织学结局
Semaglutide	2025III期试验/AASLD 更新[21]	在 MASH 缓解和纤维化改善两项主要终点上均优于安慰剂	提示体重和代谢重塑可显著影响 MASH 结局

4. 胆固醇与胆汁酸转运系统

4.1. NPC1L1

NPC1L1 位于小肠刷状缘，是膳食胆固醇和胆汁来源胆固醇摄取的关键蛋白，也是依折麦布的经典靶点[22]。进入肠上皮的胆固醇可经 ACAT2 酯化，并在 apoB48 和微粒体甘油三酯转运蛋白(MTP)参与下形成乳糜微粒进入循环。因此，NPC1L1 所代表的并非单一分子事件，而是肠道胆固醇输入通量的重要阀门。

临床上，MOZART 随机试验显示，依折麦布虽能降低胆固醇吸收和 LDL-C，但在 MRI-PDFF 测得的肝脂降低方面并未显著优于安慰剂[18]。这提示“机制正确”并不等同于“单药疗效充分”。尽管如此，NPC1L1 仍是解释胆固醇敏感型 MASLD 的重要节点。近期研究还显示，限制肠道胆固醇摄取及相关转运基因表达可减轻肝脂肪变和纤维化[23]，说明肠胆固醇通量在疾病进展中仍具有关键作用。

4.2. ABCG5/8、ABCA1 与乳糜微粒

ABCG5 和 ABCG8 以异源二聚体形式促进甾醇外排，对抗 NPC1L1 介导的摄取；ABCA1 参与胆固醇向 apoA1 外排，影响逆向胆固醇转运[24]。进入肠上皮的胆固醇若进一步经 ACAT2 酯化并装配至 apoB48/MTP 复合体，则更易形成乳糜微粒并进入循环。由此可见，真正决定肝脏胆固醇暴露的，是“摄取、外排、酯化与装配”整条通路的净效应，而非单一分子水平的高低。

4.3. ASBT-FXR-FGF19

回肠胆汁酸转运体(ASBT)介导胆汁酸重吸收，随后可激活肠 FXR 并诱导 FGF19 (啮齿类为 Fgf15)产生，后者反馈抑制肝脏胆汁酸合成，并调节糖脂代谢与能量稳态。该通路兼具“物质转运”和“信号反馈”双重属性，是近年来胃肠道转运体研究与肠–肝轴研究相互融合的代表。

2025 年系统评价提示，FXR 激动剂可改善 ALT、AST、GGT 和 MRI-PDFF 等指标，但瘙痒及脂质相关不良反应仍限制其广泛应用[25]。与此同时，动物研究显示，回肠 FXR 敲低可通过改变胆汁酸谱和肠道菌群而缓解 MASLD [26]；另一项研究则提示，菌群改变所驱动的 FXR-FGF19 激活可能参与代谢改善过程[27]。这些结果表明，胆汁酸通路干预需要区分肝脏 FXR 与肠道 FXR、区分胆汁酸再吸收与系统性受体效应，未来更可能走向组织选择性和通路精细化调控。

5. 脂肪酸转运相关蛋白

5.1. FATP 家族

FATP 家族兼具脂肪酸转运和酰基辅酶 A 合成功能。早期研究更多关注 FATP4 在小肠刷状缘对膳食

脂肪吸收的重要性，而近年的研究视角则逐步转向器官特异性 FATP 网络及其对脂质组成和脂毒性的影响[28]。2025 年的研究显示，FATP5 缺失可通过重塑肝脏脂质组成、降低促铁死亡脂质并抑制相关氧化损伤，从而减轻 MASH 表型[29]。这说明 FATP 分子不仅影响脂肪酸输入量，还会深刻影响脂质分子谱和细胞损伤易感性。

5.2. FABP 家族

FABP 家族参与长链脂肪酸的胞内递送、定位和代谢信号整合。FABP1 在肝内高度表达，FABP2 则主要见于小肠上皮[30]。近年来，FABP1 的成药性受到更多关注。2025 年报道的新型 FABP1 抑制剂在前临床 MASH 模型中对降低脂质蓄积、炎症和纤维化显示出较好效果[31]。因此，FABP1 有望兼具生物标志物和治疗靶点双重价值。

5.3. CD36

CD36 既参与长链脂肪酸摄取，又与氧化脂质识别、炎症放大和细胞应激相关。经典研究表明，CD36 是 LXR、PXR 和 PPARγ 等核受体共同调控的下游靶点，可促进肝脂沉积[32]；其在 MASH 中的上调还与细胞凋亡、炎症和纤维化密切相关[33]。当前对 CD36 的认识更加细化，即其致病效应与组织分布、细胞类型和亚细胞定位密切相关。因此，未来若考虑靶向 CD36，更合理的策略可能是限制其特定组织和病程阶段中的致病性功能，而非简单进行全身性抑制。

6. 临床转化与治疗前景

近年来真正改变 MASLD/MASH 治疗格局的药物，往往并非直接针对某一胃肠道转运体，而是通过重塑肠－肝代谢网络而间接影响相关通路。2024 年，resmetirom 基于 III 期试验结果获 FDA 批准，用于伴中重度纤维化的 MASH 患者，成为首个获批的 MASH 治疗药物[34] [35]。2025 年，semaglutide 在 ESSENCEIII 期试验中同时达到 MASH 缓解和纤维化改善两项主要终点，随后 FDA 批准其用于 MASH，AASLD 亦发布了针对 semaglutide 治疗 MASH 的实践指导更新[36] [37]。

这些进展提示，MASLD 的有效干预不必拘泥于“单一转运体直接命中”，而更应强调以患者主导病理机制为基础的分层治疗。

进一步而言，所谓“患者分层”不应仅停留于临床表型层面，而应尽可能结合与特定转运通路相关的候选生物标志物进行机制分型。对于胆汁酸转运及 FXR-FGF19 相关通路，可考虑以循环 FGF19、血清 7α-hydroxy-4-cholesten-3-one(C4)以及血清或粪便胆汁酸谱作为候选指标，用于反映胆汁酸合成—回收反馈状态。已有研究显示，MASLD/NAFLD 患者，尤其伴纤维化进展者，存在血清和粪便胆汁酸谱及 C4 的异常；但 FGF19 在不同研究中的分层稳定性并不一致，因此更适合与胆汁酸代谢谱联合解读，而非单独作为分层依据[38]-[42]。对于肠道胆固醇吸收通路，可考虑以 campesterol、sitosterol 等非胆固醇甾醇标志物识别“高吸收表型”，为 NPC1L1 相关干预提供机制分型依据；但现有研究提示，这类指标虽能反映胆固醇吸收状态，其对依折麦布等药物反应的预测价值仍不稳定[42] [43]。对于果糖转运通路，高果糖暴露特征及十二指肠 GLUT5 表达升高可作为探索性分层线索；已有临床与动物研究分别提示，GLUT5 升高与 NAFLD 及肝纤维化风险增加相关，肠道特异性抑制 GLUT5 则可减轻高果糖诱导的脂肪性肝病表型[12] [13] [44]。总体而言，这些指标目前更适合作为未来前瞻性研究和患者富集设计中的候选标志物，而尚不足以作为成熟的临床用药预测工具。

在此基础上，对于高果糖暴露和果糖转运活跃的患者，可关注 GLUT5 相关策略；对胆固醇负荷突出者，可考虑 NPC1L1 及胆汁酸通路；对合并肥胖或 2 型糖尿病者，SGLT2 抑制剂、GLP-1 受体激动剂和

THR-β 激动剂则更具现实意义。需要指出的是，生活方式干预仍是 MASLD 治疗基础。AASLD 指南指出，减重 3%~5%即可改善脂肪变，而显著改善 MASH 和纤维化通常需要超过 10%的体重下降[4]。

7. 结语

综上所述，胃肠道糖脂转运体研究已由传统的吸收生理学问题，拓展为 MASLD 机制解释、患者分层和治疗转化的重要交叉领域。SGLT1/SGLT2、GLUT5、NPC1L1 以及 ASBT-FXR-FGF19 轴分别对应糖负荷、果糖暴露、胆固醇输入和胆汁酸反馈等不同上游通路；FATP、FABP 和 CD36 则进一步揭示了脂质递送与脂毒性、炎症和纤维化之间的联系。未来研究应在三个层面继续推进：一是开展基于肠组织、生物标志物、代谢组及非侵入性影像的患者分层研究；二是加强组织特异性和局部作用型干预策略开发，降低全身副作用；三是探索转运体靶向策略与现有获益药物之间的联合应用模式。只有在“底物输入、胆汁酸信号、菌群代谢、肝脏重编程”的整体框架下理解这些分子，胃肠道转运体研究才能真正走向精准治疗。

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