•综述•

肝脏去唾液酸糖蛋白受体1在代谢疾病中的作用及药物研究进展

吴 敏, 冯存玉, 郝思铭, 雷 蕾*, 环 奕*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室, 北京 100050)

摘要: 在代谢性疾病的防治领域, 肝脏作为核心代谢器官, 其功能状态对疾病的发展和治疗策略选择具有重要影响。近年来, 随着对肝脏受体分子的深入研究, 去唾液酸糖蛋白受体1 (asialoglycoprotein receptor 1, ASGR1) 因其在糖蛋白识别、脂质代谢调节及免疫调控等方面的作用, 逐渐受到关注。尽管已有研究提示ASGR1功能紊乱与多种代谢性疾病密切相关, 但将其直接作为治疗靶点尚存在较大争议, 需要进一步研究其作为肝脏靶点的可行性和疗效。另一方面, 基于ASGR1介导的肝靶向递送系统已在多个药物开发中展现出临床应用潜力。本文系统梳理了ASGR1的生理功能及其在代谢疾病中的研究进展, 重点讨论其分子调控机制与药物应用前景, 以期为肝脏相关代谢疾病的诊疗策略提供参考。

关键词: 去唾液酸糖蛋白受体1; 肝脏; 胆固醇; 代谢疾病

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2026)01-0075-09

The role of liver asialoglycoprotein receptor 1 in metabolic diseases and the research progress of drugs

WU Min, FENG Cun-yu, HAO Si-ming, LEI Lei*, HUAN Yi*

(*State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*)

Abstract: In the field of prevention and treatment of metabolic diseases, liver is the core metabolic organ, and its functional status has an important impact on the development of diseases and the selection of treatment strategies. In recent years, with the in-depth study of liver receptor molecules, asialoglycoprotein receptor 1 (ASGR1) has gradually attracted attention because of its role in glycoprotein recognition, lipid metabolism regulation, and immune regulation. Although studies have suggested that ASGR1 dysfunction is closely related to a variety of metabolic diseases, it is still controversial to directly use ASGR1 as a therapeutic target, and further studies are needed to explore the feasibility and efficacy of ASGR1 as a liver target. On the other hand, ASGR1-mediated liver-targeted delivery systems have shown clinical application potential in multiple drug development. This article systematically reviews the physiological functions of ASGR1 and its research progress in metabolic diseases, focusing on its molecular regulatory mechanisms and drug application prospects, in order to provide reference for the diagnosis and treatment strategies of liver-related metabolic diseases.

Key words: asialoglycoprotein receptor 1; liver; cholesterol; lipid metabolism

代谢性疾病是一类因体内糖、脂肪、蛋白质、嘌呤、水−电解质等代谢过程紊乱或代谢产物异常积聚所导致的病理状态[1], 其病理机制涉及能量代谢调控异常、慢性炎症反应和器官间交互作用失调等多个层面[2]。这类疾病涵盖高血压、2型糖尿病、血脂异常、肥胖症及代谢相关性脂肪性肝病等多个慢性疾病[3-6], 各疾病间不仅共享遗传易感性、营养过剩和体力活动不足等

收稿日期: 2025-06-26; 修回日期: 2025-09-01.
基金项目: 国家自然科学基金青年科学基金项目 (82200883); 国家自然科学基金面上项目 (82373922).
*通讯作者 Tel: 86-10-63165194,
E-mail: huany@imm.ac.cn; dlei228@imm.ac.cn
DOI: 10.16438/j.0513-4870.2025-0731

危险因素, 更通过复杂的代谢−炎症网络产生协同效应[7-12]。

去唾液酸糖蛋白受体 1 (asialoglycoprotein receptor 1, ASGR1) 是肝细胞表面特异性表达的 C 型凝集素受体 (C-type lectins receptors, CLRs)[13], 与去唾液酸糖蛋白受体 2 (asialoglycoprotein receptor 2, ASGR2) 共同构成去唾液酸糖蛋白受体 (asialoglycoprotein receptor, ASGPR)[14-16], 可特异性结合含半乳糖 (galactose, Gal) 或 N-乙酰半乳糖胺 (N-acetylgalactosamine, GalNAc) 的糖蛋白, 介导配体内吞及溶酶体降解[17]。基于此特性, ASGR1 在代谢性疾病中的作用机制备受关注。本综述将总结 ASGR1 的生物学功能及在代谢性疾病中的作用机制, 并调研其靶向治疗的临床研究, 展望其在以上疾病中的应用前景。

1 ASGR1 的发现

ASGR1 的发现可以追溯到 20 世纪 60 年代, Morell 等[18]和 Ashwell 等[19]在研究哺乳动物血浆铜蓝蛋白的过程中, 意外发现了一种可以特异性结合去唾液酸糖蛋白的受体, 不仅为糖蛋白的代谢研究开辟了新的道路, 也为后续的脂质代谢研究奠定了基础。由于这一重要发现, 该受体被命名为“Ashwell-Morell 受体”, 以纪念两位科学家的贡献。

2 ASGR1 结构特征

ASGR1 分为 3 个主要功能结构域: 胞质结构域、跨膜结构域、胞外结构域[20,21] (图 1)。胞质结构域位于细胞内侧, 含有 40 个氨基酸残基, 参与 ASGR1 的细胞内信号传导和与其他蛋白的相互作用。跨膜结构域由约 20 个氨基酸构成, 负责将 ASGR1 锚定于肝细胞膜上。胞外区域则由茎区和碳水化合物识别结构域 (carbohydrate recognition domain, CRD) 组成。茎区含约 80 个氨基酸残基, 连接跨膜结构域与 CRD, 并为 CRD 提供必要的空间结构支持, 增强其稳定性。CRD 是 ASGR1 最关键的功能区域, 约含 140 个氨基酸残基, 专职识别和结合特定的去唾液酸糖蛋白配体。该结构域属于 C 型凝集素超家族, 具有 3 个高度保守的分子内二硫键, 这些二硫键对于维持 CRD 的三维构象和识别功能至关重要[22]。

功能性的 ASGPR 通常由 ASGR1 和其同源亚基 ASGR2 组成异源寡聚体, 二者通过茎段形成稳定的卷曲螺旋结构完成寡聚化[16], 典型形式为 2∶2 异源四聚体[23], 该结构显著增强了 ASGPR 对配体的亲和力和特异性, 是其功能和稳定性的基础。尽管 ASGPR 的完整功能通常需要 ASGR1 与 ASGR2 协同构建, 但已有研究表明, ASGR1 为该复合物中介导配体识别和内吞作用的主要功能亚基, 在 ASGR2 缺失的条件下, ASGR1 仍可维持部分功能[24]。因此, 本文后续主要聚焦于 ASGR1 的生物学作用及其在代谢性疾病发生发展中的潜在作用与靶向研究进展。

3 ASGR1 生物学功能

ASGR1 最核心的生物学功能是介导去唾液酸糖蛋白的特异性识别与清除, 这一过程构成其在代谢调控、疾病防御及靶向治疗中的基础机制。ASGR1 的胞外 CRD 结构域具有高度糖链特异性, 能够精准识别血液循环中去唾液酸化糖蛋白上暴露的 Gal 和 GalNAc 残基, 尤其是三天线或四天线型 N-连接糖链的末端结构[25,26]。与配体结合后, ASGR1 通过受体介导的内吞作用将糖蛋白内吞至肝细胞内, 并经内体−溶酶体通路完成降解[27], 最终代谢为可再利用的小分子营养成

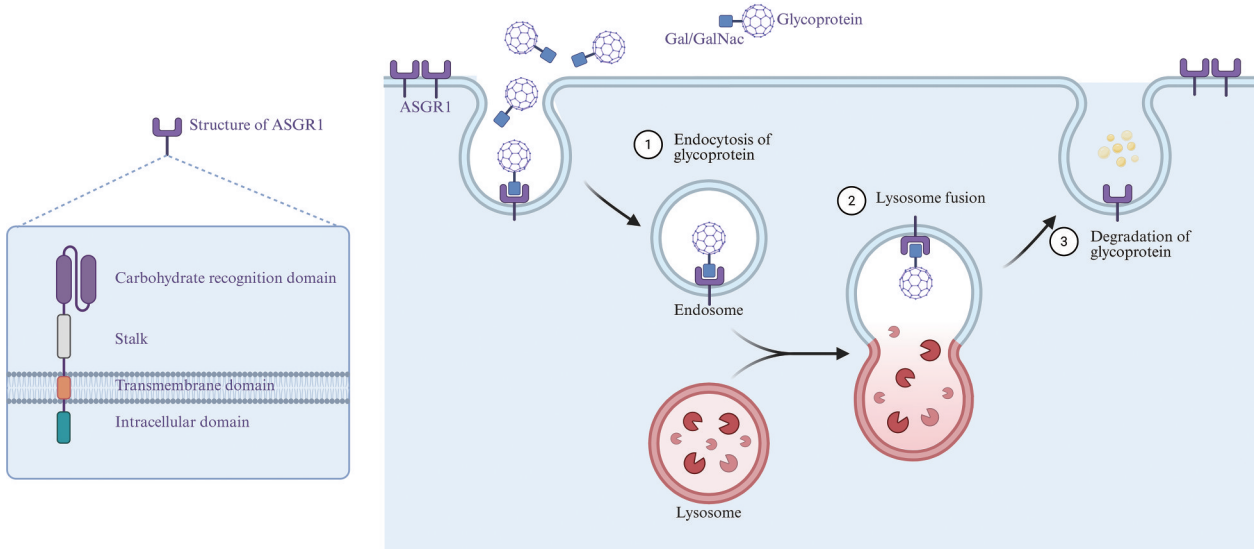


Figure 1 The structure of ASGR1 and ASGR1 mediates the specific recognition and clearance of glycoproteins. ASGR1: Asialoglycoprotein receptor 1; Gal: Galactose; GalNAc: N-Acetylgalactosamine. Created with BioRender.com

分 (图1)。该功能对于维持血浆糖蛋白稳态至关重要, 可有效清除老化或异常糖基化蛋白, 避免其在体内蓄积引发免疫或代谢紊乱[25]。同时, ASGR1对特定糖结构的高度识别性也为其在肝脏靶向递药中提供了理论基础[28], 后续多种代谢疾病相关功能和治疗策略均建立在这一机制之上。

4　ASGR1与代谢性疾病

4.1　ASGR1与高血脂　脂质是参与生物能量代谢的重要化学物质[29], 脂质代谢异常通常会导致内分泌激素紊乱, 并进一步发展为肥胖、高脂血症和其他内分泌疾病[30]。近年来, 多项研究表明ASGR1在脂质代谢中扮演着关键角色 (图2)。ASGR1功能缺失型变异 (如del12及W158X) 可显著降低血非高密度脂蛋白胆固醇 (non-high density lipoprotein cholesterol, non-HDL-C) 水平[31], 且携带者心血管事件风险降低26%[32]。ASGR1-LOF变异通过抑制甾醇调节元件结合蛋白 (sterol-regulatory element binding protein, SREBP) 通路 (减少胆固醇合成) 和增强低密度脂蛋白受体 (low density lipoprotein receptor, LDLR) 稳定性 [促进低密度脂蛋白胆固醇 (low density lipoprotein cholesterol, LDL-C) 清除] 实现降脂效应 (图2)。此外, Xie等[33]研究发现ASGR1缺失可抑制胆固醇合成限速酶HMG-CoA还原酶 (3-hydroxy-3-methyl glutaryl coenzyme A reductase, HMGCR) 的活性, 减少肝脏胆固醇的从头合成, 进一步降低non-HDL-C水平。

在胆固醇外排方面, ASGR1缺失通过抑制雷帕霉

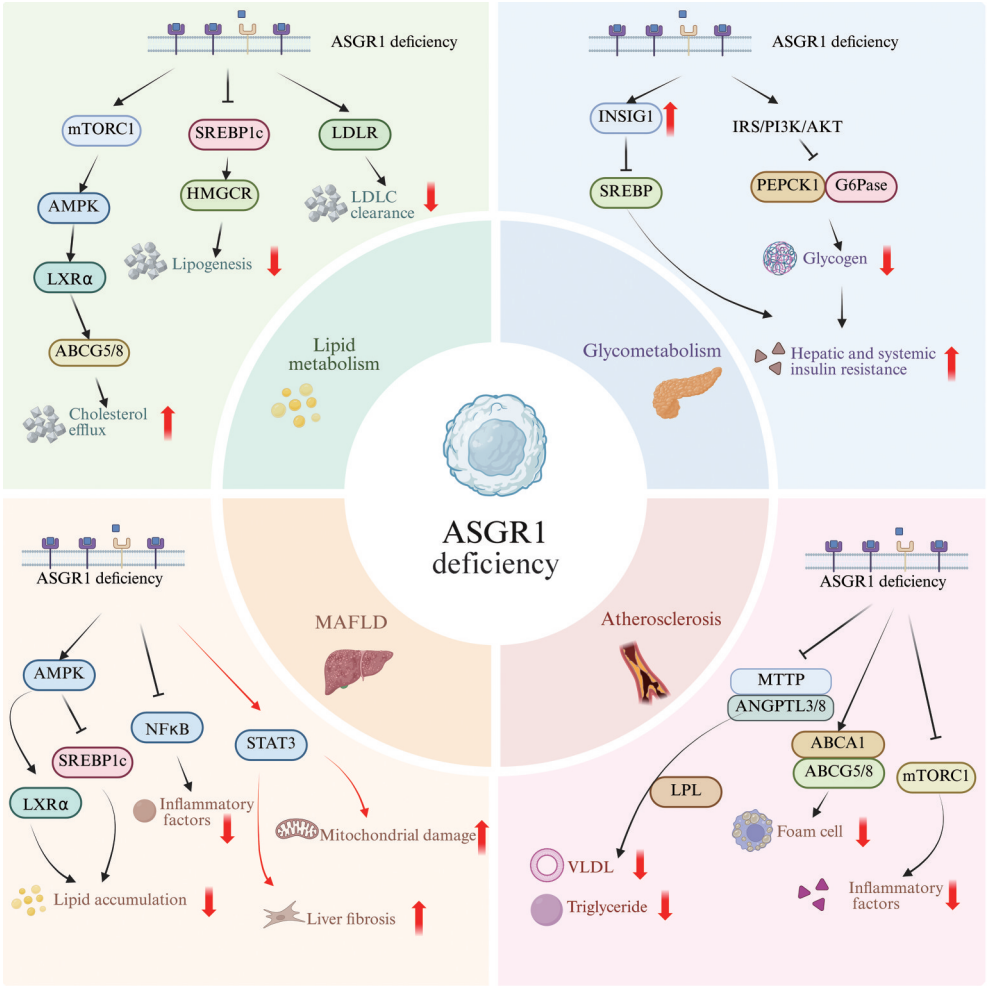


Figure 2　The ASGR1 signaling in metabolic diseases. mTORC1: Mechanistic target of rapamycin complex 1; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; LXRα: Liver X receptor α; ABCG5: ATP binding cassette subfamily G member 5; ABCG8: ATP binding cassette subfamily G member 8; SREBP1C: Sterol-regulatory element binding protein 1C; HMGCR: 3-Hydroxy-3-methyl glutaryl coenzyme A reductase; LDLR: Low density lipoprotein receptor; LDL-C: Low-density lipoprotein cholesterol; INSIG1: Insulin-induced gene 1; IRS: Insulin receptor substrate; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; MAFLD: Metabolic associated fatty liver disease; STAT3: Signal transducer and activator of transcription 3; MTTP: Microsomal triglyceride transfer protein; ANGPTL3/8: Angiopoietin-like 3/8; LPL: Lipoprotein lipase; VLDL: Very low-density lipoprotein; ABCA1: ATP-binding cassette transporter A1. Created with BioRender.com

素靶蛋白复合体 1 (mechanistic target of rapamycin complex 1, mTORC1) 并激活 AMP 依赖的蛋白激酶 [adenosine 5'-monophosphate (AMP) -activated protein kinase, AMPK], 下调泛素连接酶乳腺癌易感蛋白 1 (breast cancer susceptibility protein-1, BRCA1) 或BRCA1 关联的 RING 域 1 (BRCA1 associated RING domain 1, BARD1), 进而稳定肝 X 受体 α (liver X receptor α, LXRα), 最终促进胆固醇外排蛋白 ATP 结合盒转运体 G5 (ATP binding cassette subfamily G member 5, ABCG5) 和 ATP 结合盒转运体 G8 (ATP binding cassette subfamily G member 8, ABCG8) 的表达, 增加胆汁和粪便中胆固醇的排泄[27]。同时, ASGR1 缺失抑制 SREBP 活性, 减少脂肪酸合成, 改善脂质代谢紊乱[27,34,35]。

综上, ASGR1 通过调节 LDLR、LXRα、HMGCR 和 SREBP 等关键分子, 在胆固醇代谢中发挥核心作用。ASGR1 作为治疗高胆固醇血症的新型靶点, 其缺失或抑制展现出显著的降脂和动脉保护效果。但需注意, 胆固醇外排增强导致的胆汁酸合成代偿性上调可能打破胆汁酸池稳态, 引起肝损伤[33,36,37]与肝细胞脂质堆积[38], 因此, 抑制 ASGR1 以治疗高血脂是否安全有效仍需进一步研究。

4.2 ASGR1 与代谢相关脂肪性肝病 代谢相关脂肪性肝病 (metabolic associated fatty liver disease, MAFLD) 是全球最普遍的慢性肝病, 由国际专家组于 2020 年提出, 强调以代谢功能障碍为核心, 取代了传统的非酒精性脂肪肝概念[39]。MAFLD 包括从单纯性肝脂肪变性到伴炎症的脂肪性肝病, 并可进展为肝纤维化、肝硬化及肝细胞癌[40]。ASGR1 在其发生发展中具有复杂的功能表现, 既参与肝脏脂质代谢紊乱和炎症反应的调控, 也与肝纤维化及肝硬化的进展密切相关 (图 2)。

ASGR1 通过调控溶酶体氨基酸感知和代谢信号通路, 影响肝脏脂质动态平衡。当 ASGR1 功能缺失时, 去唾液酸化糖蛋白的内吞和溶酶体降解受阻, 导致溶酶体内氨基酸水平下降, 进而抑制 mTORC1 信号并激活 AMPK[27,35]。激活的 AMPK 通过双重机制改善脂质代谢: ① 通过抑制转录因子 SREBP1c 减少脂肪酸和甘油三酯的合成[26]; ② 通过稳定 LXRα, 上调胆固醇外排蛋白 ABCG5/G8 的表达, 促进胆固醇经胆汁排泄, 从而缓解肝脏脂质蓄积[27,41]。此外, ASGR1 缺失可抑制炎症相关通路 (如 NF-κB), 减少促炎因子的释放, 减轻肝脏炎症微环境[36,42]。这种抗炎作用进一步通过改善胰岛素敏感性和脂质氧化能力, 协同改善代谢紊乱。

然而, ASGR1 缺陷对肝脏稳态的影响存在显著矛盾性。一方面, 其缺失可通过 AMPK 等通路改善脂质代谢和胰岛素敏感性; 另一方面, 也可能诱导多种有害信号。Zhu 等[43]报道, ASGR1 缺陷可显著激活信号转导和转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 通路, 导致促炎因子和纤维化相关因子表达升高, 促进慢性炎症和肝纤维化发生。此外, 研究提示 nemo 样激酶 (nemo-like kinase, NLK) 可增强 STAT3 活性, 从而进一步加速纤维化进程。Zhang 等[37]研究表明, ASGR1 缺失还可能通过上调 GP73 表达, 诱导内质网应激反应并加重肝损伤。因此, ASGR1 功能丧失可能通过多途径破坏肝脏稳态, 促进纤维化恶性转化。

ASGR1 的“双刃剑”机制揭示了其在脂质代谢与炎症调控网络中的重要地位。临床数据显示, MAFLD 及肝硬化患者的组织中 ASGR1 表达显著降低, 其表达水平与疾病严重程度呈负相关[37]。机制矛盾性 (如代谢获益与 STAT3 驱动的损伤并存) 则部分解释了 MAFLD 向终末期肝病进展的复杂性[44-47]。值得注意的是, ASGR1 还参与促进各类肝炎病毒进入细胞, 如甲型肝炎病毒 (hepatitis A virus, HAV)[48,49]、乙型肝炎病毒 (hepatitis B virus, HBV)[50,51]、丙型肝炎病毒 (hepatitis C virus, HCV)[52]、戊型肝炎病毒 (hepatitis E virus, HEV)[53]及严重急性呼吸综合征冠状病毒 2 (severe acute respiratory syndrome coronavirus-2, SARS-CoV-2)[54,55], 提示其可能通过调控病毒侵袭性和免疫反应而间接介导肝脏损伤过程[56,57]。未来靶向 ASGR1 的治疗策略需精准调控其下游效应分子, 从而在改善代谢的同时规避纤维化风险。

4.3 ASGR1 与动脉粥样硬化 动脉粥样硬化是一种慢性炎症性血管疾病, 其病理特征为脂质在动脉内膜异常蓄积, 伴随免疫细胞浸润形成斑块[58], 已被广泛认定为全球心脑血管疾病主要的病理生理基础[59]。ASGR1 通过多维度调控脂质代谢与炎症反应, 在动脉粥样硬化 (atherosclerosis, AS) 的病理进程中发挥关键作用 (图 2)。

脂质代谢环节, ASGR1 功能缺失通过抑制微粒体甘油三酯转运蛋白 (microsomal triglyceride transfer protein, MTTP) 和血管生成素样蛋白 3/8 (angiopoietin-like 3/8, ANGPTL3/8) 表达, 减少极低密度脂蛋白 (very low-density lipoprotein, VLDL) 的合成与分泌, 并增强脂蛋白脂肪酶 (lipoprotein lipase, LPL) 活性以加速甘油三酯的降解, 从而显著降低血浆 LDL-C 及极低密度脂蛋白胆固醇 (very low-density lipoprotein cholesterol, VLDL-C) 水平[38]。上述脂蛋白的减少直接降低脂质在动脉内膜的沉积, 延缓脂纹形成。同时, ASGR1 缺失上调肝脏 LDLR 表达促进 LDL 清除[35], 并通过激活 AMPK/mTORC1 信号轴进一步抑制 SREBP

介导的脂质合成通路改善脂质谱 (如升高HDL-C)[27,34], 协同减轻血管壁损伤。

炎症调控方面, 肝细胞ASGR1特异性缺失被报道可通过抑制mTORC1活性减少促炎因子释放[35], 进而减轻血管内皮炎症反应; 全身性ASGR1缺失则通过上调胆固醇外排蛋白如ATP结合盒转运体A1 (ATP-binding cassette transporter A1, ABCA1)及ABCG5/G8, 促进巨噬细胞胆固醇逆向转运, 减少斑块内泡沫细胞形成及脂质蓄积[38]。动物实验显示[38], ASGR1全身敲除可使西方饮食饲养小鼠斑块面积减少大于50%, 血浆总胆固醇和甘油三酯水平显著下降, 证实其抗AS的显著效果。同时进一步研究证明ASGR1功能缺陷通过增强内皮屏障功能, 减少脂质浸润及炎症细胞迁移, 从而抑制斑块进展。

尽管ASGR1作为动脉粥样硬化治疗靶点的潜力已被多项研究证实, 但其临床应用仍面临胆固醇过多排泄及影响肝脏代谢等挑战。

4.4　ASGR1与糖尿病　糖尿病 (diabetes mellitus, DM)是一种以血糖升高为主要特征的慢性代谢性疾病, 由不同程度的胰岛素抵抗 (insulin resistance, IR)和胰岛素分泌功能障碍引起[60]。如图2所示, ASGR1可通过调控肝细胞的胰岛素敏感性, 在机体糖代谢稳态中发挥关键作用。Yu等[61]发现, ASGR1缺陷可激活胰岛素受体底物 (insulin receptor substrate, IRS)-磷酸肌醇3激酶 (phosphatidylinositol 3-kinase, PI3K)-蛋白激酶B (protein kinase B, AKT)通路, 促进AKT磷酸化, 抑制糖异生关键酶的表达, 从而减少肝脏葡萄糖生成 (hepatic glucose production, HGP)并改善系统性胰岛素抵抗; ASGR1缺陷还能上调胰岛素诱导基因1 (insulin-induced gene 1, INSIG1)抑制SREBP的加工与转运, 减少脂肪酸及胆固醇合成从而增强肝脏胰岛素信号。除此之外, 临床数据[62]显示ASGR1在2型糖尿病合并冠心病患者外周血单核细胞中表达下调, 提示其在代谢紊乱相关疾病中可能存在功能改变, 进一步突显了其在不同代谢环境下功能的复杂性和多面性。因此, ASGR1作为糖脂代谢调控的重要因子, 有望成为代谢性疾病干预的新靶点。

5　ASGR1靶向治疗的临床研究进展

近年来, ASGR1作为肝脏特异性受体, 其靶向治疗在代谢性疾病及肝病领域受到广泛关注。随着学术界的不断投入, 其抗体类抑制剂和药物递送系统为动脉粥样硬化、代谢相关脂肪性肝病及肝纤维化等疾病的精准治疗提供了新的策略和希望。

5.1　靶向ASGR1的抗体类抑制剂　单克隆抗体是ASGR1抑制剂的主要类型之一。由武汉大学宋保亮团队[27]开发的4B9抗体能够高亲和力结合ASGR1的胞外结构域, 阻断其与配体的相互作用, 同时与他汀类药物联用可协同抑制胆固醇合成与外排, 进一步优化降脂效果。另一代表性单克隆抗体AMG 529[63] (由Amgen开发)已完成I期临床试验, 数据显示其耐受性良好, 并能剂量依赖性地降低健康受试者的总胆固醇和LDL-C水平, 提示其潜在的临床应用价值 (表1)。

双特异性抗体是抗体类抑制剂的重要拓展方向。SZN-043[64]是一种同时靶向ASGR1和Wnt信号通路相关蛋白的双特异性抗体, 其通过ASGR1介导的肝细胞靶向作用, 激活Wnt/β-catenin信号通路, 其设计基于ASGR1在肝细胞再生[36]和免疫微环境调节[65,66]中的双重作用。临床前研究表明, SZN-043在肝纤维化模型中显著减少胶原沉积并改善肝功能, 目前已进入I期临床试验, 用于治疗酒精性肝炎和肝硬化。此外, 基于ASGR1识别病原体糖蛋白的天然功能[54,67,68], 免疫偶联物如ASGR1-TLR8偶联物SBT8230[69]通过靶向递送免疫调节分子至肝脏, 激活局部抗病毒或抗肿瘤免疫反应, 为慢性乙肝和肝癌的治疗提供了新策略。

5.2　靶向ASGR1的药物递送系统　靶向ASGR1的药物递送系统是基于该受体在肝细胞表面特异性高表达的特性而设计的精准治疗策略。ASGR1能够特异性识别并内吞含有Gal或GalNAc的糖蛋白, 这一特性使其成为肝脏靶向递送的理想靶点。

GalNAc共轭递送系统是靶向ASGR1的核心技术之一。GalNAc作为ASGR1的天然配体, 可通过化学偶联与核酸药物 [如小干扰RNA (small interfering RNA, siRNA)[70]、反义寡核苷酸 (antisense oligonucleotides, ASO)[71]或微小RNA (microRNA, miRNA)[72]] 结合, 形成稳定的复合物。临床药物如siRNA和反义核苷酸等已经通过GalNAc递送系统实现了肝脏靶向治疗 (表2)。如Alnylam公司开发的GalNAc-siRNA技术已成功应用于多款获批药物, 包括治疗淀粉样变性多

Table 1　Antibodies targeting ASGR1

Type	Program	Indication	Phase
Monoclonal antibody	AMG529	Hypercholesterolemia	Phase I completed
Monoclonal antibody	4B9	Hypercholesterolemia	Preclinical
Bispecific antibody	SZN-043	Alcoholic hepatitis, cirrhosis	Phase I
Antibody-immunomodulator conjugate	SBT8230	Chronic hepatitis B, hepatocellular carcinoma	Preclinical

Table 2 Approved nucleic acid drugs based on the GalNac delivery system. ASO: Antisense oligonucleotides; hATTR: Abstract hereditary transthyretin amyloidosis

Type	Program	Delivery system	Indication	FDA approval	Company
siRNA	RIVFLOZA® (nedosiran)	GalXC™-RNAi platform	Primary hyperoxaluria type 1	2023	Novo Nordisk
siRNA	AMVUTTRA® (vutrisiran)	GalNAc-siRNA	hATTR amyloidosis with polyneuropathy	2022	Alnylam
siRNA	LEQVIO® (inclisiran)	GalNAc-siRNA	Hypercholesterolemia	2021	Alnylam
siRNA	OXLUMO® (lumasiran)	GalNAc-siRNA	Primary hyperoxaluria type 1	2020	Novartis
siRNA	GIVLAARI® (givosiran)	GalNAc-siRNA	Acute hepatic porphyria	2019	Alnylam
ASO	Tryngolza™ (olezarsen)	GalNAc-ASO	Familial chylomicronemia syndrome	2024	Ionis

发性神经病的 vutrisiran (Amvuttra)[73]、治疗急性肝卟啉症的 givosiran (Givlaari)[74,75]及靶向前蛋白转化酶枯草溶菌素 9 (proprotein convertase subtilisin/kexin type 9, PCSK9) 治疗高胆固醇血症的 inclisiran (Leqvio)[76]。这些药物通过 ASGR1 介导的内吞作用进入肝细胞后, siRNA 在胞内释放并沉默靶基因表达, 从而实现对疾病相关通路的精准调控。此外, GalNAc 共轭技术还被拓展至 CRISPR-Cas9 基因编辑系统, 如 Intellia Therapeutics 开发的 NTLA-2001[77], 其通过 GalNAc-LNP 递送系统靶向肝脏, 用于治疗遗传性转甲状腺素蛋白淀粉样变性, 目前已进入临床试验阶段。值得注意的是, 虽然目前获批药物主要针对罕见肝病, 但它们验证了 GalNAc-ASGR1 递送系统在肝脏靶向沉默致病基因的有效性和安全性, 为该系统应用于更广泛的代谢性疾病如高胆固醇血症、代谢相关脂肪性肝病、2 型糖尿病奠定了坚实基础。

尽管靶向 ASGR1 的递送系统在肝病治疗中展现出显著优势, 其临床应用仍面临递送速率[24]、受体脱敏[27,37]和生物相容性[78]等问题。未来研究需聚焦于开发新型配体, 探索多靶点协同递送策略, 并结合人工智能技术优化递送系统设计。随着基因编辑和核酸药物技术的快速发展, 靶向 ASGR1 的递送系统有望在精准医学领域实现更广泛的应用。

6 结语与展望

综上所述, ASGR1 作为肝脏细胞重要膜受体, 在代谢疾病中发挥着糖蛋白识别、脂质代谢调节及免疫调控等重要作用, 相关分子调节机制涉及多种信号通路和调控因子, 其功能的改变与多种代谢性疾病的发展密切相关, 同时基于 ASGR1 的递送系统也为肝靶向治疗提供了新的思路和方向。

尽管已有研究显示, ASGR1 缺陷在部分疾病模型中表现出保护作用, 但也有研究提示其在其他代谢紊乱状态下可能加重病情, 这种功能的双重性提示 ASGR1 在不同疾病模型和病理阶段中可能具有不同的生物学效应。因此, 未来研究应聚焦于 ASGR1 在组织特异性表达与时序性调控等维度的机制解析, 并探索相应的精准干预策略, 为 ASGR1 相关靶向药物的研发与优化提供理论基础与实践指导。

作者贡献: 吴敏负责组织文章的框架、文章的撰写及修改; 环奕负责文章的思路指导和审阅; 冯存玉、郝思铭和雷蕾对稿件进行了完善。

利益冲突: 所有作者均声明不存在利益冲突。

References

[1] Giangregorio F, Mosconi E, Debellis MG, et al. A systematic review of metabolic syndrome: key correlated pathologies and non-invasive diagnostic approaches [J]. J Clin Med, 2024, 13: 5880.

[2] Sethi JK, Hotamisligil GS. Metabolic messengers: tumour necrosis factor [J]. Nat Metab, 2021, 3: 1302-1312.

[3] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report [J]. Circulation, 2002, 106: 3143-3421.

[4] Duseja A, Singh SP, Saraswat VA, et al. Non-alcoholic fatty liver disease and metabolic syndrome-position paper of the Indian National Association for the Study of the Liver, Endocrine Society of India, Indian College of Cardiology and Indian Society of Gastroenterology [J]. J Clin Exp Hepatol, 2015, 5: 51-68.

[5] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [J]. Circulation, 2005, 112: 2735-2752.

[6] Ng CH, Wong ZY, Chew NWS, et al. Hypertension is prevalent in non-alcoholic fatty liver disease and increases all-cause and cardiovascular mortality [J]. Front Cardiovasc Med, 2022, 9: 942753.

[7] Golabi P, Paik JM, AlQahtani S, et al. Burden of non-alcoholic fatty liver disease in Asia, the Middle East and North Africa: data from global burden of disease 2009-2019 [J]. J Hepatol, 2021, 75: 795-809.

[8] GBD 2019 Diabetes Mortality Collaborators. Diabetes mortality and trends before 25 years of age: an analysis of the global burden of disease study 2019 [J]. Lancet Diabetes Endocrinol,

2022, 10: 177-192.

[9] Toh JZK, Pan XH, Tay PWL, et al. A meta-analysis on the global prevalence, risk factors and screening of coronary heart disease in nonalcoholic fatty liver disease [J]. Clin Gastroenterol Hepatol, 2022, 20: 2462-2473.

[10] Chew NW, Figtree GA, Kong G, et al. Hepatic steatosis and advanced fibrosis are independent predictors of mortality in acute myocardial infarction without standard modifiable risk factors [J]. Diabetes Obes Metab, 2022, 24: 2454-2458.

[11] Tay PWL, Ng CH, Lin SY, et al. Placebo adverse events in non-alcoholic steatohepatitis clinical trials: a pooled analysis of 2 944 participants [J]. Am J Gastroenterol, 2023, 118: 645-653.

[12] Kong G, Chin YH, Chong B, et al. Higher mortality in acute coronary syndrome patients without standard modifiable risk factors: results from a global meta-analysis of 1 285 722 patients [J]. Int J Cardiol, 2023, 371: 432-440.

[13] Drickamer K. C-type lectin-like domains [J]. Curr Opin Struct Biol, 1999, 9: 585-590.

[14] Spiess M, Lodish HF. Sequence of a second human asialoglycoprotein receptor: conservation of two receptor genes during evolution [J]. Proc Natl Acad Sci U S A, 1985, 82: 6465-6469.

[15] Spiess M, Schwartz AL, Lodish HF. Sequence of human asialoglycoprotein receptor cDNA. An internal signal sequence for membrane insertion [J]. J Biol Chem, 1985, 260: 1979-1982.

[16] Henis YI, Katzir Z, Shia MA, et al. Oligomeric structure of the human asialoglycoprotein receptor: nature and stoichiometry of mutual complexes containing H1 and H2 polypeptides assessed by fluorescence photobleaching recovery [J]. J Cell Biol, 1990, 111: 1409-1418.

[17] Stockert RJ. The asialoglycoprotein receptor: relationships between structure, function, and expression [J]. Physiol Rev, 1995, 75: 591-609.

[18] Morell AG, Irvine RA, Sternlieb I, et al. Physical and chemical studies on ceruloplasmin. V. Metabolic studies on sialic acid-free ceruloplasmin *in vivo* [J]. J Biol Chem, 1968, 243: 155-159.

[19] Ashwell G, Harford J. Carbohydrate-specific receptors of the liver [J]. Annu Rev Biochem, 1982, 51: 531-554.

[20] Meier M, Bider MD, Malashkevich VN, et al. Crystal structure of the carbohydrate recognition domain of the H1 subunit of the asialoglycoprotein receptor [J]. J Mol Biol, 2000, 300: 857-865.

[21] Chiacchia KB, Drickamer K. Direct evidence for the transmembrane orientation of the hepatic glycoprotein receptors [J]. J Biol Chem, 1984, 259: 15440-15446.

[22] Hoober JK. ASGR1 and its enigmatic relative, CLEC10A [J]. Int J Mol Sci, 2020, 21: 4818.

[23] Bider MD, Wahlberg JM, Kammerer RA, et al. The oligomerization domain of the asialoglycoprotein receptor preferentially forms 2∶2 heterotetramers *in vitro* [J]. J Biol Chem, 1996, 271: 31996-32001.

[24] Willoughby JLS, Chan A, Sehgal A, et al. Evaluation of GalNAc-siRNA conjugate activity in pre-clinical animal models with reduced asialoglycoprotein receptor expression [J]. Mol Ther, 2018, 26: 105-114.

[25] Svecla M, Nour J, Bladergroen MR, et al. Impact of asialoglycoprotein receptor and mannose receptor deficiency on murine plasma N-glycome profiles [J]. Mol Cell Proteomics, 2023, 22: 100615.

[26] Svecla M, Da Dalt L, Moregola A, et al. ASGR1 deficiency diverts lipids toward adipose tissue but results in liver damage during obesity [J]. Cardiovasc Diabetol, 2024, 23: 42.

[27] Wang JQ, Li LL, Hu A, et al. Inhibition of ASGR1 decreases lipid levels by promoting cholesterol excretion [J]. Nature, 2022, 608: 413-420.

[28] Debacker AJ, Voutila J, Catley M, et al. Delivery of oligonucleotides to the liver with GalNAc: from research to registered therapeutic drug [J]. Mol Ther, 2020, 28: 1759-1771.

[29] Xu L, Yang Q, Zhou J. Mechanisms of abnormal lipid metabolism in the pathogenesis of disease [J]. Int J Mol Sci, 2024, 25: 8465.

[30] Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease [J]. Nat Rev Endocrinol, 2019, 15: 507-524.

[31] Nioi P, Sigurdsson A, Thorleifsson G, et al. Variant ASGR1 associated with a reduced risk of coronary artery disease [J]. N Engl J Med, 2016, 374: 2131-2141.

[32] Ali L, Cupido AJ, Rijkers M, et al. Common gene variants in ASGR1 gene locus associate with reduced cardiovascular risk in absence of pleiotropic effects [J]. Atherosclerosis, 2020, 306: 15-21.

[33] Xie B, Shi X, Li Y, et al. Deficiency of ASGR1 in pigs recapitulates reduced risk factor for cardiovascular disease in humans [J]. PLoS Genet, 2021, 17: e1009891.

[34] Xu Y, Tao J, Yu X, et al. Hypomorphic ASGR1 modulates lipid homeostasis *via* INSIG1-mediated SREBP signaling suppression [J]. JCI Insight, 2021, 6: e147038.

[35] Zhao W, Xu S, Weng J. ASGR1: an emerging therapeutic target in hypercholesterolemia [J]. Signal Transduct Target Ther, 2023, 8: 43.

[36] Shi R, Wang J, Zhang Z, et al. ASGR1 promotes liver injury in sepsis by modulating monocyte-to-macrophage differentiation *via* NF-κB/ATF5 pathway [J]. Life Sci, 2023, 315: 121339.

[37] Zhang Z, Leng XK, Zhai YY, et al. Deficiency of ASGR1 promotes liver injury by increasing GP73-mediated hepatic endoplasmic reticulum stress [J]. Nat Commun, 2024, 15: 1908.

[38] Zhang Y, Jiang X, Wang W, et al. ASGR1 deficiency inhibits atherosclerosis in western diet-fed ApoE$^{-/-}$ mice by regulating lipoprotein metabolism and promoting cholesterol efflux [J]. Arterioscler Thromb Vasc Biol, 2024, 44: 2428-2449.

[39] Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international

expert consensus statement [J]. J Hepatol, 2020, 73: 202-209.

[40] Wei S, Wang L, Evans PC, et al. NAFLD and NASH: etiology, targets and emerging therapies [J]. Drug Discov Today, 2024, 29: 103910.

[41] Xia Y, Xu Y, Liu Q, et al. Glutaredoxin 1 regulates cholesterol metabolism and gallstone formation by influencing protein S-glutathionylation [J]. Metabolism, 2023, 145: 155610.

[42] Chen S, Gan H. Analysis and verification of glycosylation characteristics of septic acute kidney injury [J]. J Inflamm Res, 2023, 16: 5881-5897.

[43] Zhu X, Song G, Zhang S, et al. Asialoglycoprotein receptor 1 functions as a tumor suppressor in liver cancer *via* inhibition of STAT3 [J]. Cancer Res, 2022, 82: 3987-4000.

[44] Niu L, Thiele M, Geyer PE, et al. Noninvasive proteomic biomarkers for alcohol-related liver disease [J]. Nat Med, 2022, 28: 1277-1287.

[45] Shi B, Abrams M, Sepp-Lorenzino L. Expression of asialoglycoprotein receptor 1 in human hepatocellular carcinoma [J]. J Histochem Cytochem, 2013, 61: 901-909.

[46] Witzigmann D, Quagliata L, Schenk SH, et al. Variable asialoglycoprotein receptor 1 expression in liver disease: implications for therapeutic intervention [J]. Hepatol Res, 2016, 46: 686-696.

[47] Roa-Colomo A, López Garrido M, Molina-Vallejo P, et al. Hepatocellular carcinoma risk-stratification based on ASGR1 in circulating epithelial cells for cancer interception [J]. Front Mol Biosci, 2022, 9: 1074277.

[48] Dotzauer A, Gebhardt U, Bieback K, et al. Hepatitis A virus-specific immunoglobulin A mediates infection of hepatocytes with hepatitis A virus *via* the asialoglycoprotein receptor [J]. J Virol, 2000, 74: 10950-10957.

[49] Dotzauer A, Brenner M, Gebhardt U, et al. IgA-coated particles of hepatitis A virus are translocalized antivectorially from the apical to the basolateral site of polarized epithelial cells *via* the polymeric immunoglobulin receptor [J]. J Gen Virol, 2005, 86: 2747-2751.

[50] Zhang X, Lin SM, Chen TY, et al. Asialoglycoprotein receptor interacts with the preS1 domain of hepatitis B virus *in vivo* and *in vitro* [J]. Arch Virol, 2011, 156: 637-645.

[51] Owada T, Matsubayashi K, Sakata H, et al. Interaction between desialylated hepatitis B virus and asialoglycoprotein receptor on hepatocytes may be indispensable for viral binding and entry [J]. J Viral Hepat, 2006, 13: 11-18.

[52] Saunier B, Triyatni M, Ulianich L, et al. Role of the asialoglycoprotein receptor in binding and entry of hepatitis C virus structural proteins in cultured human hepatocytes [J]. J Virol, 2003, 77: 546-559.

[53] Zhang L, Tian Y, Wen Z, et al. Asialoglycoprotein receptor facilitates infection of PLC/PRF/5 cells by HEV through interaction with ORF2 [J]. J Med Virol, 2016, 88: 2186-2195.

[54] Yang X, Zheng X, Zhu Y, et al. Asialoglycoprotein receptor 1 promotes SARS-CoV-2 infection of human normal hepatocytes [J]. Signal Transduct Target Ther, 2024, 9: 42.

[55] Hoffmann M, Pöhlmann S. Novel SARS-CoV-2 receptors: ASGR1 and KREMEN1 [J]. Cell Res, 2022, 32: 1-2.

[56] Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests [J]. J Hepatol, 2020, 73: 566-574.

[57] Zhang D, Guo R, Lei L, et al. Frontline science: COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes [J]. J Leukoc Biol, 2021, 109: 13-22.

[58] Kong P, Cui ZY, Huang XF, et al. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention [J]. Signal Transduct Target Ther, 2022, 7: 131.

[59] Soehnlein O, Libby P. Targeting inflammation in atherosclerosis-from experimental insights to the clinic [J]. Nat Rev Drug Discov, 2021, 20: 589-610.

[60] Niu F, Liu W, Ren Y, et al. *β*-Cell neogenesis: a rising star to rescue diabetes mellitus [J]. J Adv Res, 2024, 62: 71-89.

[61] Yu X, Tao J, Wu Y, et al. Deficiency of ASGR1 alleviates diet-induced systemic insulin resistance *via* improved hepatic insulin sensitivity [J]. Diabetes Metab J, 2024, 48: 802-815.

[62] Hamledari H, Sajjadi SF, Alikhah A, et al. ASGR1 but not FOXM1 expression decreases in the peripheral blood mononuclear cells of diabetic atherosclerotic patients [J]. J Diabetes Complications, 2019, 33: 539-546.

[63] Aniszewski M, Sohn W, Su C, et al. A randomized, placebo-controlled, double-blind, ascending single-dose, phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 529, a novel anti-ASGR1 monoclonal antibody, in healthy subjects [J]. J Am Coll Cardiol, 2019, 73: 1755.

[64] Surrozen. Surrozen presents preliminary results from phase 1a study of SZN-043 [EB/OL]. South San Francisco: Surrozen, 2024-06-10 [2025-07-21]. https://investors. surrozen. com/news-releases/news-release-details/surrozen-presents-preliminary-results-phase-1a-study-szn-043.

[65] Sun Y, Tong H, Chu X, et al. Notch1 regulates hepatic thrombopoietin production [J]. Blood, 2024, 143: 2778-2790.

[66] Gu D, Jin H, Jin G, et al. The asialoglycoprotein receptor suppresses the metastasis of hepatocellular carcinoma *via* LASS2-mediated inhibition of V-ATPase activity [J]. Cancer Lett, 2016, 379: 107-116.

[67] Lee D, Yoon CH, Choi SY, et al. Transcriptome analysis identifies altered biological processes and novel markers in human immunodeficiency virus-1 long-term non-progressors [J]. Infect Chemother, 2021, 53: 489-502.

[68] Jiang Y, Tang Y, Hoover C, et al. Kupffer cell receptor CLEC4F is important for the destruction of desialylated platelets in mice [J]. Cell Death Differ, 2021, 28: 3009-3021.

[69] Silverback Therapeutics. Silverback therapeutics presents preclinical data for SBT8230 at AASLD the liver meeting 2021 [EB/OL]. Seattle: Silverback Therapeutics; 2021-11-12 [2025-07-21]. https://www. businesswire. com/news/home/20211112005354/en/Silverback-Therapeutics-Presents-Preclinical-Data-for-SBT8230-at-AASLD-The-Liver-Meeting-2021.

[70] Thangamani L, Balasubramanian B, Easwaran M, et al. GalNAc-siRNA conjugates: prospective tools on the frontier of anti-viral therapeutics [J]. Pharmacol Res, 2021, 173: 105864.

[71] Huang Y. Preclinical and clinical advances of GalNAc-decorated nucleic acid therapeutics [J]. Mol Ther Nucleic Acids, 2017, 6: 116-132.

[72] Maestro S, Weber ND, Zabaleta N, et al. Novel vectors and approaches for gene therapy in liver diseases [J]. JHEP Rep, 2021, 3: 100300.

[73] Nie T, Heo YA, Shirley M. Vutrisiran: a review in polyneuropathy of hereditary transthyretin-mediated amyloidosis [J]. Drugs, 2023, 83: 1425-1432.

[74] Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria [J]. N Engl J Med, 2020, 382: 2289-2301.

[75] Scott LJ. Givosiran: first approval [J]. Drugs, 2020, 80: 335-339.

[76] Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol [J]. N Engl J Med, 2020, 382: 1507-1519.

[77] Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 *in vivo* gene editing for transthyretin amyloidosis [J]. N Engl J Med, 2021, 385: 493-502.

[78] Szyk P, Czarczynska-Goslinska B, Mlynarczyk DT, et al. Polymer-based nanoparticles as drug delivery systems for purines of established importance in medicine [J]. Nanomaterials (Basel), 2023, 13: 2647.