代谢功能障碍相关脂肪性肝病的小干扰RNA治疗

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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) 是当前全球最常见的慢性肝病。其发病机制复杂, 涉及脂质代谢紊乱、胰岛素抵抗、氧化应激、炎症反应、肠道菌群失调和遗传易感基因变异之间的相互作用。现有治疗手段主要依赖于全身给药, 其肝脏特异性或选择性有待提高。小干扰RNA (small interfering RNA, siRNA) 疗法通过精准沉默肝脏中的致病基因, 阻断异常蛋白的合成, 为MASLD治疗提供了全新策略。本文系统阐述了siRNA药物的作用机制和递送系统, 围绕MASLD的核心病理环节, 从遗传风险变异、脂质代谢调节及纤维化与炎症通路3个维度, 重点综述了各靶点siRNA药物的临床研发进展及作用机制, 旨在为MASLD的siRNA新药研发提供最新参考。

关键词: 代谢功能障碍相关脂肪性肝病; 肝脏靶向; 小干扰RNA; 基因沉默; 递送系统

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siRNA therapy for metabolic dysfunction-associated steatotic liver disease

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Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the most prevalent chronic liver disease worldwide. Its pathogenesis involves the interplay of lipid dysregulation, insulin resistance, oxidative stress, inflammation, gut microbiota dysbiosis, and genetic susceptibility variants. Current therapeutic interventions primarily rely on systemic administration, with their hepatic specificity or selectivity remaining to be improved. Small interfering RNA (siRNA) therapy offers a novel strategy by precisely silencing hepatic pathogenic genes to block aberrant protein synthesis. This review outlines the mechanisms of action and the delivery systems of siRNA therapeutics. Focusing on the core pathological drivers of MASLD, it details the clinical progress and mechanistic insights of siRNA therapeutics within three main areas: Genetic risk variants, lipid metabolism regulation, and fibrosis-inflammation pathways. This article provides an updated reference for siRNA drug development in MASLD.

Key words: metabolic dysfunction-associated steatotic liver disease; liver targeting; small interfering RNA; gene silencing; delivery system

代谢功能障碍相关脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD) 已成为全球范围内最常见的慢性肝病。最新流行病学数据显示, MASLD影响了全球约38%的成年人口, 且随着肥胖与2型糖尿病 (type 2 diabetes mellitus, T2DM) 患病率持续增加, 预计2040年这一比例将超

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过50%[1]。MASLD涵盖一系列肝脏疾病, 部分患者可由单纯脂肪变性进展为代谢功能障碍相关脂肪性肝炎 (metabolic dysfunction-associated steatohepatitis, MASH), 进而发展为肝纤维化、肝硬化乃至肝细胞癌 (hepatocellular carcinoma, HCC)[2]。鉴于其复杂的代谢病因, 2023年国际德尔菲共识正式将该疾病由非酒精性脂肪肝病 (nonalcoholic fatty liver disease, NAFLD)/非酒精性脂肪肝炎 (nonalcoholic steatohepatitis, NASH) 更名为MASLD/MASH, 以更准确地反映代谢功能障碍在疾病发展中的核心作用[3]。

MASLD和MASH发病机制复杂, 与遗传、环境和代谢因素密切相关[4]。“多重打击”学说认为, 胰岛素抵抗引发的机体脂质代谢紊乱是该疾病的关键致病因素[5]。外周游离脂肪酸大量内流和肝脏脂肪从头合成 (*de novo* lipogenesis, DNL) 异常增加, 共同导致了肝细胞内甘油三酯的过度蓄积[6]。这种脂质代谢失衡不仅会诱发严重的脂毒性, 还会引起线粒体功能障碍、氧化应激及内质网 (endoplasmic reticulum, ER) 应激, 进而激活机体免疫系统, 推动肝脏炎症及纤维化进程[7,8]。此外, 肠道菌群失调及遗传易感基因变异也参与了疾病进程[9-12]。

长期以来, 生活方式干预是MASLD和MASH的主要治疗方法, 通过饮食控制及运动实现5%～10%的体重减轻, 可有效改善肝脏脂肪变性和纤维化[13]。对于重度肥胖患者, 代谢减重手术可以显著改善其肝脏病理学改变[14]。近年来, 针对MASH的药物研发取得了一些实质性进展。2024年3月, 甲状腺激素受体β (thyroid hormone receptor beta, THR-β) 激动剂瑞美替罗获美国食品药品监督管理局 (FDA) 批准, 成为首个获批用于治疗非肝硬化MASH伴F2-F3期纤维化的药物[15]。2025年8月, 胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1) 受体激动剂司美格鲁肽注射剂获批新增适应症, 用于治疗MASH伴中重度肝纤维化的非肝硬化成人患者[16]。然而, 现有治疗手段主要以全身给药为主, 其肝脏特异性或选择性有待提高。传统小分子药物往往需较高的全身暴露量以维持肝脏内有效浓度, 但这也相应增加了患者出现不良反应的风险。因此, 开发能够精准调控肝脏致病基因表达的新型疗法具有重要临床价值。

小干扰RNA (small interfering RNA, siRNA) 技术为解决上述难题提供了全新的可能。siRNA通过诱导RNA干扰 (RNA interference, RNAi) 精准沉默靶基因mRNA, 在偶联肝脏特异性递送载体后, 能有效阻断肝细胞内致病蛋白的合成。与传统小分子药物相比, siRNA疗法具有显著的长效性优势, 单次给药疗效可持续3～6个月, 有效提升患者的治疗依从性。同时, siRNA高度特异性的作用机制也降低了药物脱靶效应所导致的系统性毒副作用。

本文将系统综述siRNA药物的作用机制与递送系统, 并重点介绍针对MASLD的siRNA药物研发进展及临床转化现状。

1 siRNA药物的基础与技术平台

1.1 siRNA药物的作用机制

siRNA是一种双链非编码RNA, 通常含有19～21个碱基对, 每条链的3'端有2个突出的碱基交错排列[17]。siRNA通过诱导RNAi抑制基因的表达来发挥作用[18]。当siRNA进入细胞后, 首先需要经历内体逃逸过程[19]。随后, 它与Argonaute 2 (Ago2) 和其他几种蛋白质组装形成RNA诱导的沉默复合物 (RNA-induced silencing complex, RISC)。Ago2蛋白根据siRNA双链的“热力学不对称性”进行链选择, 优先捕获5'端热力学稳定性较低的引导链, 利用核酸内切酶活性切割其非引导链, 从而完成RISC的激活[20,21]。激活后的成熟RISC根据Watson-Crick碱基互补配对原则识别并结合靶基因的mRNA, 通过催化mRNA磷酸二酯键水解将其切割, 从而阻止其翻译合成蛋白质, 最终降低靶蛋白的水平[22]。

1.2 siRNA药物临床转化的体内递送障碍

尽管RISC介导的基因沉默为siRNA提供了高度特异性的分子基础, 但裸露的siRNA分子并不具备成药性[23]。原因在于, 裸露的siRNA进入血液后极易被核酸酶降解, 并通过循环系统快速清除[24]。外源性双链RNA进入体内后可激活多种模式识别受体, 进而诱发先天性免疫应答[25,26]。此外, siRNA分子所携带的负电荷也阻碍了其透过细胞膜, 即使成功进入细胞也易被溶酶体所降解[27,28]。同时, siRNA的“脱靶效应”也是一个重要挑战。当siRNA序列与非靶基因存在部分互补时, RISC可能错误地识别非靶基因, 从而引发毒性反应[29]。因此, 合理的化学修饰及高效的递送系统已成为突破上述障碍、推动siRNA临床转化的关键策略。

1.3 siRNA药物的化学修饰及递送系统

1.3.1 化学修饰 根据核苷酸的天然化学结构, siRNA的化学修饰位点主要集中于磷酸骨架、核糖基团和碱基部分: ① 磷酸骨架修饰: 硫代磷酸酯 (phosphorothioate, PS) 修饰在siRNA药物中应用极为广泛。用硫原子替换磷酸二酯键中的非桥接氧原子, 不仅能增强siRNA抗核酸酶降解的能力, 还能在一定程度上增强其疏水性及血浆白蛋白结合能力, 延长体内半衰期[30,31]。但过度PS修饰可能引发毒性反应, 因

此PS键设计往往倾向于在链末端进行局部修饰, 而非全骨架替换[32,33]。② 核糖修饰: 糖环2'-位点修饰具有重要作用。2'-*O*-甲基 (2'-OMe) 和2'-氟 (2'-F) 修饰通常能够提高血清稳定性、提高RNAi效率并降低脱靶效应, 是siRNA药物开发中最为常用的修饰策略[34,35]。此外, 乙二醇核酸和解锁核酸通过引入柔性结构适度降低双链热力学稳定性, 促进引导链的RISC装载, 并减少种子区部分互补引发的脱靶效应[36]。锁核酸可增强热稳定性和碱基配对亲和力, 但可能影响RISC的装载, 因此多用于局部修饰[37]。③ 碱基修饰: 利用假尿嘧啶、5-甲基胞嘧啶等类似物替换天然碱基, 可进一步降低免疫识别风险。但目前制药企业仍以2'-修饰与骨架修饰为主, 保留天然碱基[38]。

随着化学修饰技术不断发展, siRNA药物从早期局部修饰发展为全长修饰的成熟体系。Alnylam公司早期提出的“标准模板化学”修饰策略通过PS键及交替的2'-F/2'-OMe修饰增强了siRNA的稳定性与亲和力[39]。出于对安全性的考虑[40], 该公司后续开发了“增强稳定化学” (enhanced stability chemistry, ESC) 策略, 实现了超长效的基因沉默效果[41]。Advanced ESC策略进一步降低2'-F的修饰比例以增加RISC装载和肝脏暴露量[41]。最新的ESC+设计在反义链种子区引入GNA修饰以有效阻断脱靶效应。此外, Arrowhead、Dicerna等企业也建立了多个特色技术平台。这些化学修饰策略的进步为开发高效、低毒且长效的siRNA治疗药物奠定了坚实基础[38]。

1.3.2 脂质纳米颗粒递送系统 脂质纳米颗粒 (lipid nanoparticles, LNP) 是最早成功应用于siRNA临床递送的技术平台之一[42]。LNP通常由4种关键组分构成, 通过电荷相互作用与siRNA自组装形成粒径约80～100 nm的纳米颗粒[43]。① 可电离阳离子脂质: 这是LNP的核心功能组分, 其酸解离常数通常在6.2～6.5之间[43]。在生理pH条件下, 该类脂质接近电中性, 减少了与血清蛋白的非特异性结合, 而在其被细胞内吞, 进入酸性内体后质子化而带有正电荷, 进而与内体膜上的负电磷脂相互作用, 破坏膜结构, 促进siRNA“内体逃逸”, 得以释放到细胞质中[44]。② 聚乙二醇–脂质: 该组分分布在LNP表面形成亲水层, 构成空间位阻, 有助于避免siRNA在血液循环过程中被免疫系统识别和清除, 延长体内循环时间。③ 胆固醇与辅助脂质: 作为结构脂质, 胆固醇能够调节膜的流动性并填充脂质间空隙, 辅助脂质有助于稳定双层膜结构, 二者共同维持LNP在体内的结构完整性[45]。2018年, 首个基于LNP递送的siRNA药物帕替司兰获FDA批准, 用于治疗遗传性转甲状腺素蛋白淀粉样变性, 这标志着LNP作为核酸药物递送平台的重大突破。

1.3.3 *N*-乙酰半乳糖胺偶联技术 *N*-乙酰半乳糖胺 (*N*-acetylgalactosamine, GalNAc) 是一种衍生自半乳糖的氨基糖, 目前已成为核酸药物领域肝脏靶向递送的“金标准”配体[46,47]。GalNAc递送技术的核心在于靶向肝实质细胞表面高表达的去唾液酸糖蛋白受体 (asialoglycoprotein receptor, ASGPR)。GalNAc-siRNA偶联物通过与ASGPR发生高亲和力结合, 经受体介导的内吞作用进入肝细胞。偶联物进入内体–溶酶体通路后经历逐步加工与代谢, 少量游离的siRNA能够成功逃逸至肝细胞的细胞质中[48-50]。进入胞质的siRNA会快速结合到RISC中, 以诱导持续的RNAi。在此过程中, ASGPR可在15 min内再循环至细胞膜表面, 持续捕获循环中的药物分子, 从而显著提升了药物在细胞内的积累效率[51,52]。这种高度特异的靶向机制不仅提高了肝细胞内的药物暴露量, 也有助于降低全身性脱靶风险 (图1)。

GalNAc-siRNA偶联物分子量小、水溶性好, 适用于皮下注射[53,54]。有研究表明, 相比于静脉输注, 皮下注射能实现更好的体内药效[46]。这可能是皮下注射的siRNA需要穿过结缔组织、毛细血管及淋巴管内皮细胞才能进入循环系统, 这一过程改变了GalNAc-siRNA的药代动力学特征, 在较长时间内维持了较低的血药浓度, 有效避免了因血浆药物峰浓度过高而导致的快速肾脏清除, 最终显著提升了药物的肝脏递送效率, 并延长了作用时间。同时, 与脂质体可能引发细胞膜有害相互作用相比, ASGPR所介导的天然内吞途径更为安全[55]。更为重要的是, 当GalNAc结合了优化的化学修饰 (如ESC或ESC+) 后, 这些偶联物能够实现超长效的基因沉默效果, 支持每季度或每半年给药一次的治疗方案[56,57], 改善了慢性病患者的治疗依从性。

目前全球已获批上市的8款siRNA药物中, 除首个获批药物帕替司兰采用LNP静脉输注给药以外[58], 其余7款药物均采用了GalNAc偶联递送技术, 并实现了皮下注射给药[59-61]。从LNP静脉输注到GalNAc皮下注射的技术转变, 确立了GalNAc作为当前肝脏靶向siRNA递送体系的首选策略。

1.3.4 其他递送策略 LNP和GalNAc是目前临床应用最为广泛的递送技术。同时, 针对非肝实质细胞及肝外组织靶向递送等新型递送策略也在持续探索。其中具有代表性的递送技术发展是动态多聚偶联物向靶向RNAi分子的迭代[62,63], 该技术摒弃了聚合物骨架, 采用siRNA与高亲和力配体直接共价偶联的设计, 显著降低了载体相关的免疫原性和蓄积毒性[64]。此外,

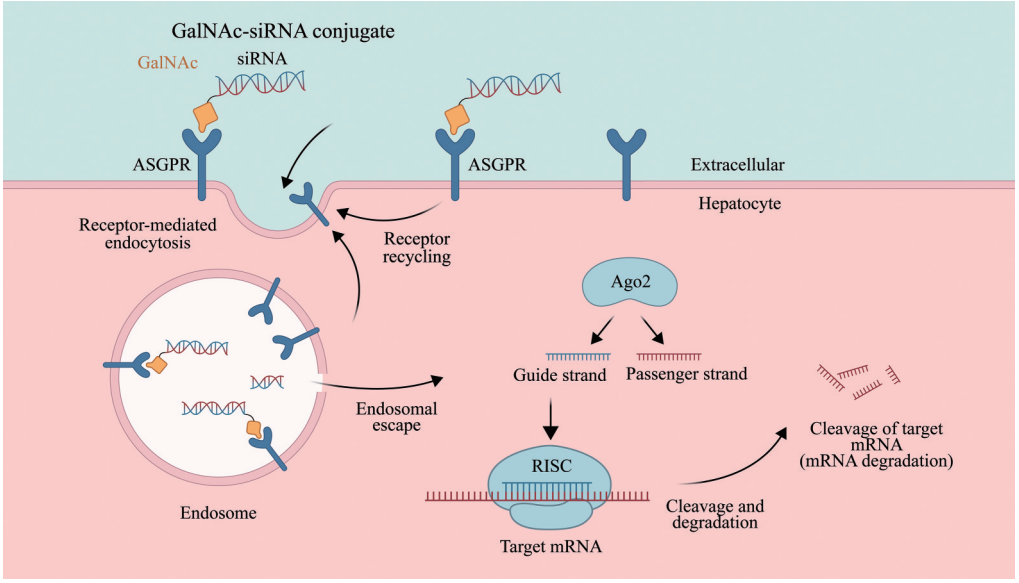


Figure 1 The mechanism of targeted hepatic delivery of GalNAc-siRNA conjugates. Following subcutaneous administration and entering the systemic circulation, the GalNAc ligand binds with high affinity to the ASGPR on the hepatocyte surface, triggering receptor-mediated endocytosis. Upon internalization, ASGPR recycles to the plasma membrane within approximately 15 min, enabling continuous uptake. Intracellularly, the siRNA payload undergoes endosomal escape into the cytoplasm, where it is loaded into RISC to facilitate specific cleavage of target mRNA, ultimately mediating sustained and potent gene silencing. siRNA: Small interfering RNA; GalNAc: *N*-Acetylgalactosamine; ASGPR: Asialoglycoprotein receptor; Ago2: Argonaute 2; RISC: RNA-induced silencing complex

无载体递送技术不依赖递送载体，通过对siRNA进行精细的化学修饰，使其适用于眼部等局部给药场景[23,65]。LODER系统利用聚乳酸–羟基乙酸共聚物基质包裹siRNA实现药物在肿瘤内的持续缓释[66,67]。外泌体等生物源性载体具有低免疫原性及易跨越生物屏障的优势[68,69]。金纳米颗粒[70,71]、介孔硅[72]、氧化铁[73]等无机纳米材料，凭借其可控的理化性质和易于修饰的表面，在实现siRNA高效递送的同时兼具成像诊断功能，推动了诊疗一体化的发展。

2 治疗MASLD的siRNA核心靶点与药物研发进展

随着肝脏靶向递送技术的成熟，siRNA药物凭借高特异性的基因沉默优势，已成为MASLD治疗领域的重要研发方向。本章节将围绕MASLD的核心病理环节，从遗传风险变异、脂质代谢调节以及纤维化与炎症通路3个维度，重点综述各靶点siRNA药物的临床研发进展及作用机制（图2）。

2.1 基于遗传风险变异的药物靶点

2.1.1 PNPLA3 在MASLD复杂的致病因素中，编码含patatin样磷脂酶结构域蛋白3（patatin-like phospholipase domain-containing 3, PNPLA3）的基因，是经全基因组关联研究（genome-wide association study, GWAS）确证的最为关键的遗传易感基因之一[74]。*PNPLA3*基因的常见错义突变（rs738409 C>G）可导致其编码蛋白第148位异亮氨酸被蛋氨酸取代（I148M），是MASLD发生发展中重要的遗传风险因素[75]。该风险等位基因与肝脏脂肪含量升高呈显著正相关，还会促进MASLD向MASH、肝纤维化、肝硬化乃至HCC进展，且该效应独立于肥胖、T2DM等代谢危险因素[76]。在生理状态下，野生型PNPLA3蛋白具有甘油三酯水解酶活性，参与肝细胞脂滴的脂质重塑过程。而I148M突变导致其水解酶功能丧失，突变蛋白也因此在肝细胞脂滴表面异常蓄积，进而竞争性抑制脂肪甘油三酯脂肪酶（adipose triglyceride lipase, ATGL）活性，导致肝内脂质蓄积[77]。此外，该变异通过影响视黄醇代谢、激活炎症通路等机制，协同促进疾病进展[78]。

基于*PNPLA3*在MASLD发病机制中的核心驱动作用，开发靶向沉默该基因的siRNA药物已成为MASLD精准治疗的重要策略。目前临床进展最快的代表药物ARO-PNPLA3，是由Arrowhead公司开发的一款GalNAc-siRNA偶联药物[79]。该药物已完成两项针对携带I148M纯合子或杂合子MASH患者的I期临床试验，结果显示其具有预期的药代动力学特征，包括肝脏特异性摄取、血浆半衰期短及低免疫原性。药效学数据显示，在携带I148M纯合子受试者中，单次皮下给药即可实现肝脏脂肪含量的剂量依赖性下降，其中最高剂量组（400 mg）在给药12周后肝脏脂肪含量降低了46%。但在所有研究剂量下，杂合子受试者的肝

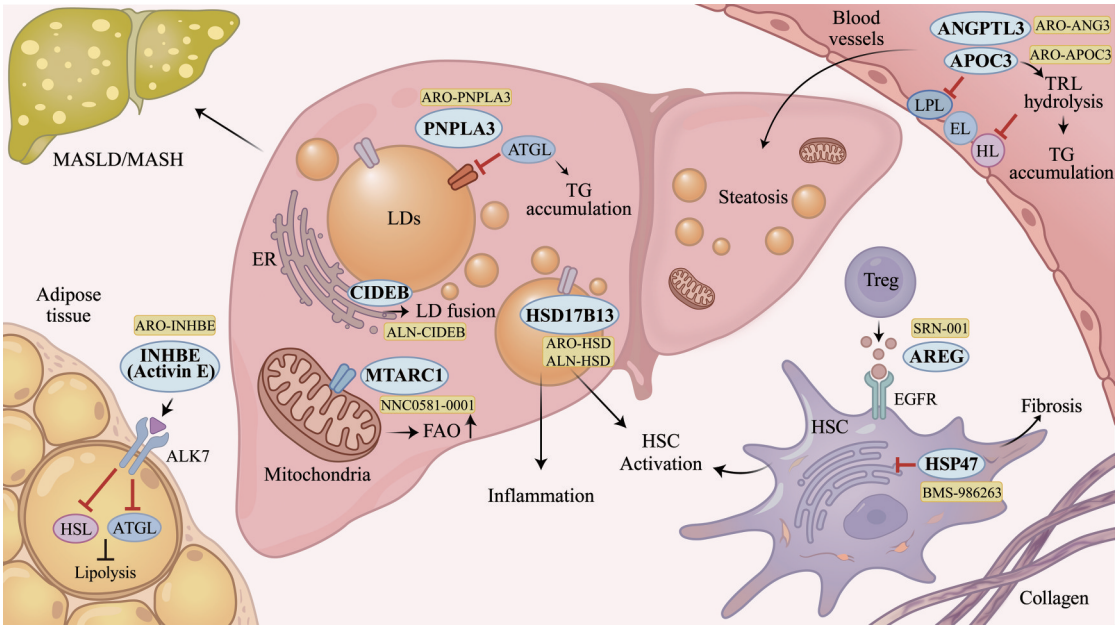


Figure 2 MASLD/MASH pathogenesis and RNA interference targets. Genetic and metabolic factors drive hepatic steatosis and fibrosis *via* inter-organ crosstalk and intracellular signaling pathways. In hepatocytes, the PNPLA3 I148M variant and CIDEB promote aberrant lipid droplet fusion, while MTARC1 modulates fatty acid oxidation. HSD17B13 and Treg-derived AREG trigger HSC activation. In adipose tissue, INHBE suppresses lipolysis, while circulating ANGPTL3/APOC3 impair triglyceride hydrolysis, thereby exacerbating hepatic lipid accumulation. Upon HSC activation, HSP47 facilitates procollagen folding and collagen deposition. These integrated pathways drive disease progression from simple steatosis to MASH and advanced fibrosis. HSC: Hepatic stellate cells; ER: Endoplasmic reticulum; FAO: Fatty acid beta-oxidation; LD: Lipid droplet; TG: Triglyceride; TRL: Triglyceride-rich lipoprotein; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; CIDEB: Cell death-inducing DFFA-like effector b; MTARC1: Mitochondrial amidoxime reducing component 1; HSD17B13: Hydroxysteroid 17-beta dehydrogenase 13; INHBE: Inhibin subunit beta E; ANGPTL3: Angiopoietin-like protein 3; APOC3: Apolipoprotein C-III; HSP47: Heat shock protein 47

脏脂肪含量均未出现明显改善。此外, 该药物显示出良好的安全性和耐受性, 目前已进入以肝组织学改善为主要终点的 IIb 期临床试验[80]。除 ARO-PNPLA3 外, 多家制药企业也推进了靶向 *PNPLA3* 的 siRNA 研发, 如 Alnylam 和 Regeneron 公司合作开发的 ALN-PNP[81,82], 以及 Lilly 和 Dicerna 公司合作开发的 LY-3849891[83], 两者目前均处于针对携带 PNPLA3 I148M 突变患者的 I 期临床试验阶段。

靶向 *PNPLA3* 的 siRNA 疗法具有显著降低肝脏脂质水平的效果, 为后续改善肝脏炎症和纤维化奠定了基础。但是, 该策略也存在明显的局限性, 这类药物更适用于携带 PNPLA3 I148M 纯合子患者, 其在非携带者人群中的临床获益仍需要后续临床试验数据确定[84]。对于携带 I148M 突变的患者, 靶向 *PNPLA3* 的 siRNA 药物可能会成为一种高特异性、高效的治疗选择。

2.1.2 HSD17B13 羟基类固醇 17-β 脱氢酶 13 (hydroxysteroid 17-beta dehydrogenase 13, HSD17B13) 是近年来基于人类遗传学证据验证的、与肝脏炎症和纤维化进展密切相关的关键靶点。GWAS 数据显示, *HSD17B13* 功能缺失突变对 MASLD 等慢性肝病进展至纤维化、肝硬化及 HCC 具有显著的保护效应[85,86]。HSD17B13 是一种肝脏特异性表达并定位于脂滴表面的蛋白, 可能通过调控视黄醇代谢、调节脂滴分解等途径, 在肝脏炎症和纤维化进程中发挥重要作用[87]。*HSD17B13* 功能缺失的肝脏保护效应主要体现在减轻肝细胞炎症、抑制肝星状细胞活化与纤维化进展上, 但其功能缺失对肝脏脂肪变性的直接调控作用较弱[85]。因此, 靶向 *HSD17B13* 的治疗策略核心功能是阻断 MASLD 向 MASH 及肝纤维化病程进展[88]。

目前, 多款靶向 *HSD17B13* 的 GalNAc-siRNA 药物已进入临床试验阶段。其中, 由 Arrowhead 与 GSK 公司合作开发的 ARO-HSD 进展较快, 其 I/IIa 期临床试验结果显示, 在 MASH 受试者中, 200 mg 剂量皮下给药可实现肝内 *HSD17B13* mRNA 水平下调约 93.4%, 蛋白水平降低 82.7%, 并伴随血清丙氨酸氨基转移酶 (alanine aminotransferase, ALT) 水平下降 42.3%。尽管该药物对肝脏磁共振质子密度脂肪分数无显著影响, 但部分受试者的肝硬度得到改善[89]。该药物耐受性良

好, 目前已进入一项为期52周的IIb期PK/PD肝活检研究, 主要评估其对肝脏纤维化改善和MASH组织学消退的长期疗效[90]。ALN-HSD是由Alnylam与Regeneron公司合作开发的另外一款靶向*HSD17B13*的GalNAc-siRNA药物, 其I期临床数据证实, 该药物能够在MASH受试者中剂量依赖性敲低*HSD17B13*表达, 最高剂量组 (400 mg) 单次皮下给药6个月后, 肝内*HSD17B13* mRNA水平下降78%[91]。国内研发管线方面, 维亚臻生物开发的VSA006可显著降低肝脏*HSD17B13* mRNA和蛋白水平, 同时有效改善患者的ALT水平, 目前正处于国内II期临床试验阶段[92]。

靶向*HSD17B13*的siRNA研发基于人类遗传学证据, 现有临床研究证实, 该疗法具有高效的靶点沉默效率和良好的安全性, 对肝脏炎症和纤维化相关生物标志物的改善作用显著, 使其有望成为针对MASH核心病理特征——肝纤维化的治疗药物之一。不过, 该类药物对肝脏脂肪变性的改善效果有限, 可能更适用于未携带*HSD17B13*天然保护性变异且已出现明显肝脏炎症和/或纤维化的患者[93]。

2.1.3 MTARC1 线粒体酰胺肟还原成分1 (mitochondrial amidoxime reducing component 1, MTARC1)是一种锚定于线粒体外膜的含钼酶。*MTARC1*基因的常见错义突变rs2642438 (p.A165T)与MASLD患病率降低、肝脏脂肪含量减少、血清转氨酶水平下降及肝硬化风险降低密切相关[94,95]。临床研究进一步显示, 携带该保护性变异的人群, 肝脏炎症和纤维化程度明显降低[96]。从机制上看, 该保护性变异会显著降低MTARC1蛋白稳定性, 加速其降解[94,97]。抑制或下调*MTARC1*功能可通过多种途径发挥肝细胞保护作用。首先, 下调*MTARC1*可激活脂肪酸代谢、氧化磷酸化及三羧酸循环相关通路, 增加线粒体脂肪酸氧化, 促进脂肪酸分解; 其次, 该靶点表达下调可显著减少细胞内活性氧和线粒体超氧化物生成, 并上调铁死亡抑制蛋白, 减轻细胞损伤[97]; 此外, 降低*MTARC1*表达能有效抑制胶原蛋白形成相关基因表达和细胞外基质重塑, 延缓肝脏纤维化进程[98]。临床前研究证实, 在MASH小鼠模型中, 给予靶向*MTARC1*的GalNAc-siRNA干预可有效敲低肝脏内*MTARC1*表达, 并显著降低肝脏甘油三酯含量, 但同时观察到血浆甘油三酯含量升高的现象[95]。针对该靶点的代表性在研药物主要有Novo Nordisk公司开发的GalNAc-siRNA药物NNC0581-0001, 根据ClinicalTrials.gov临床试验登记平台信息, 该药物目前处于I期临床试验阶段[99], 截至目前尚未公开披露该药物的详细临床试验数据。

2.1.4 CIDEB 细胞死亡诱导DNA片段化因子α亚基 (DFFA)样效应子b (cell death-inducing DFFA-like effector b, CIDEB)是MASLD/MASH领域中经遗传学验证且具有明确抑制方向的核心治疗靶点。*CIDEB*功能缺失变异与更低的ALT水平、更低的肝脏疾病及肝硬化发病风险相关, 提示其失活可能具有肝脏保护效应[100]。在MASLD患者肝组织中, *CIDEB*体细胞失活突变能增强肝细胞在脂毒性环境中的存活能力, 并呈现选择性富集与克隆扩增[101]。CIDEB蛋白定位于内质网与脂滴接触位点, 其C端结构域可以折叠成四聚体β-桶状结构, 通过内部疏水通道促进不饱和脂肪酸的转移与积累, 进而促进小脂滴融合[102]。抑制*CIDEB*功能可阻断这一过程, 减少大脂滴形成, 降低脂毒性。同时其蛋白水平下调能够降低关键转录因子固醇调节元件结合蛋白-1c (sterol regulatory element-binding protein-1c, SREBP-1c)及其下游靶基因的表达水平, 抑制肝脏DNL。并且该靶点表达下调能够激活ATGL和过氧化物酶体增殖物激活受体α (peroxisome proliferator activated receptor α, PPARα), 增强线粒体脂肪酸氧化。这不仅能够改善肝脏脂肪变性、炎症及纤维化病理表型, 还能增加全身能量消耗, 改善机体葡萄糖代谢及胰岛素抵抗[102,103]。临床前研究证实, GalNAc-siRNA药物可在小鼠体内实现肝脏特异性、持续性的*CIDEB*沉默, 降低肝脏甘油三酯和总胆固醇水平, 改善脂质代谢紊乱并有效缓解肝脏炎症和纤维化[104,105]。目前, 由Alnylam和Regeneron公司联合开发的靶向*CIDEB*的siRNA药物ALN-CIDEB已进入I期临床试验阶段, 该研究旨在评估其安全性、耐受性、药代动力学特征及对肝脏脂肪含量的影响, 截至目前该药物详细临床疗效数据尚未公布[106]。

2.2 基于脂质代谢调节的药物靶点

2.2.1 ANGPTL3 血管生成素样蛋白3 (angiopoietin-like protein 3, ANGPTL3)是一种主要由肝脏合成和分泌的循环蛋白, 通过抑制循环系统中脂蛋白脂肪酶 (lipoprotein lipase, LPL)和内皮脂肪酶 (endothelial lipase, EL)活性, 调控机体甘油三酯和低密度脂蛋白胆固醇 (low-density lipoprotein cholesterol, LDL-C)代谢。抑制*ANGPTL3*功能可增强LPL与EL活性, 促进肝细胞脂肪酸氧化, 减少甘油三酯合成, 从而减轻肝脏脂质堆积[107,108]。同时, *ANGPTL3*还参与肝脏果糖代谢的调控, 过量果糖摄入与MASLD发展密切相关。*ANGPTL3*是肝脏果糖代谢的细胞外调节因子, 敲低*ANGPTL3*会显著下调肝脏果糖转运体8和果糖分解酶水平, 减少肝脏对果糖的摄取[109]。目前, 全球多款靶向*ANGPTL3*的siRNA药物已进入临床试验阶段, 主要包括ARO-ANG3、LY-3561774和BW-00112等。在

混合型高脂血症患者中开展的IIb期临床试验结果显示, ARO-ANG3每季度皮下给药一次, 可使受试者空腹血浆甘油三酯水平降低50%～63%、LDL-C水平降低14%～20%、残余胆固醇水平降低82%, 且在治疗过程中未观察到肝脏脂肪含量或血清肝酶水平异常升高[110]。LY-3561774的II期临床试验同样证实了该药物具有显著的血脂调控效果[111]。现有数据显示, 靶向*ANGPTL3*的siRNA疗法对混合型高脂血症疗效显著。但基于其对脂质代谢和果糖代谢的双重调控机制, 该疗法也可能适用于血脂异常的MASLD患者。

2.2.2 APOC3 载脂蛋白C-III (apolipoprotein C-III, APOC3)主要由肝脏分泌产生, 通过抑制LPL和肝脂酶 (hepatic lipase, HL)活性, 延缓富含甘油三酯脂蛋白 (triglyceride-rich lipoprotein, TRL)的水解与清除, 调控机体甘油三酯代谢稳态。*APOC3*表达异常升高会导致循环甘油三酯蓄积, 增加高甘油三酯血症及相关代谢并发症的发病风险[112,113]。靶向*APOC3*的siRNA疗法可特异性降解*APOC3* mRNA, 解除对LPL和HL的抑制, 恢复甘油三酯正常代谢, 减轻肝脏脂质负荷[114]。该靶点的核心代表药物为ARO-APOC3 (普乐司兰钠), 这是由Arrowhead公司开发的一款GalNAc-siRNA药物, 于2025年11月获FDA批准上市。ARO-APOC3的III期临床试验结果显示, 25和50 mg剂量组每季度皮下给药一次, 在治疗10个月时, 持续乳糜微粒血症患者空腹甘油三酯水平分别下降了80%和78%, 循环系统中APOC3蛋白水平分别下降了93%和96%, 且疗效可持续至给药后12个月。同时, 治疗组患者急性胰腺炎发生率显著低于安慰剂组, 药物安全性良好[60]。此外, 还有多款靶向*APOC3*的siRNA药物正处于临床研发进程中。苏州瑞博公司基于自主研发的RIBO-GalSTAR肝靶向递送技术开发的RBD5044, 目前已进入II期临床试验阶段[115]; Alnylam与Regeneron公司合作开发的ALN-APOC3处于I期临试验床阶段[116]。目前, 此类疗法的获批适应症及已开展的临床研究主要聚焦于高甘油三酯血症、高乳糜微粒血症的患者亚群, 针对MASLD/MASH人群以肝脏组织学改善为终点的临床获益仍需进一步补充验证。

2.2.3 INHBE 抑制素亚基β-E (inhibin subunit beta E, INHBE)蛋白二聚化形成激活素E (Activin E), Activin E通过与脂肪组织高表达的活化素受体样激酶7 (Activin receptor-like kinase 7, ALK7)结合, 抑制脂肪分解关键酶激素敏感性脂肪酶 (hormone-sensitive lipase, HSL)与ATGL的表达, 最终抑制脂肪组织的脂解过程。当前INHBE/Activin E在MASLD/MASH中的调控作用仍存在不同解释: 一方面, 有研究认为*INHBE*缺失会促进脂解、增加脂肪酸流入肝脏, 加重肝脂负荷[117]; 另一方面, 也有研究认为其过表达可导致内脏脂肪异常堆积与脂肪细胞肥大, 参与肝脏纤维化的病理进程[118]。在药物开发方面, 多款靶向*INHBE*的siRNA药物已进入临床试验阶段。Wave Life Sciences公司研发的WVE-007在I期INLIGHT研究中显示, 在超重或肥胖受试者中, 240 mg单剂量皮下给药3个月后, 受试者内脏脂肪减少9.4%, 瘦组织增加3.2%, 血清Activin E水平持续降低超过75%, 药效持续时间支持每年1或2次的给药方案, 且药物整体安全性良好[119]。Arrowhead公司研发的ARO-INHBE I期临床研究显示, 400 mg单剂量给药后16周, 肥胖患者内脏脂肪减少9.9%、肝脏脂肪降低38%; 其与葡萄糖依赖性促胰岛素多肽/GLP-1双受体激动剂替尔泊肽联合应用于2型糖尿病肥胖患者时, 替尔泊肽单药组体重降幅为4.8%, 联合给药组体重降幅达9.4%, 减重效果较单药组提升约一倍[120]。该类药物在有效减少内脏与肝脏脂肪的同时, 能够保持甚至增加患者瘦组织, 并且其长效作用支持低频给药。基于现有证据, 靶向*INHBE*的治疗策略可能尤其适用于以内脏型肥胖为主的MASLD患者、合并T2DM的MASH患者, 以及需要长期体重维持的治疗人群。

2.3 基于纤维化和炎症通路的药物靶点

2.3.1 HSP47 热休克蛋白47 (heat shock protein 47, HSP47)是定位于内质网的胶原蛋白特异性分子伴侣, 主要参与调节胶原蛋白正确折叠、组装和分泌。在MASH相关肝纤维化的病理进程中, 激活的肝星状细胞 (hepatic stellate cells, HSCs)是纤维化肝脏中细胞外基质的主要来源, HSCs中*HSP47*的mRNA和蛋白表达水平显著上调, 且其表达量与胶原蛋白沉积程度和肝纤维化分期呈正相关[121,122]。编码HSP47的基因本身并非MASLD的主要遗传易感基因, 但PNPLA3 I148M等遗传风险变异的致病效应最终会汇聚到胶原生物合成这一共同病理过程, 而胶原的正确折叠与分泌依赖其分子伴侣HSP47, 因此*HSP47*被视为一个重要的抗纤维化干预靶点。由于活化的HSCs具有特异性摄取和储存维生素A的生理特性, 靶向*HSP47*的siRNA多采用带有维生素A修饰的脂质纳米颗粒递送系统, 以提高对活化HSCs的递送效率, 特异性降解*HSP47* mRNA[123]。*HSP47*缺失导致前胶原蛋白无法正确折叠, 进而引发ER应激并激活促凋亡转录因子C/EBP同源蛋白, 最终诱导HSCs凋亡[121]。

目前该靶点进展较为成熟的候选药物是BMS-986263, 该药物最初由Nitto Denko公司研发, 后Bristol Myers Squibb公司通过独占许可获得全球开发

与商业化权利。该药物的II期临床试验结果显示, 在61例已治愈的丙型肝炎相关晚期肝纤维化 (F3-F4期) 患者中, 90 mg单剂量静脉给药后, 21%的受试者实现肝纤维化METAVIR分期改善 ≥ 1期, 71%受试者肝组织*HSP47* mRNA水平显著降低[124]。该研究在人体中证实了*HSP47*靶点沉默与肝组织学改善的相关性, 但其逆转晚期纤维化的有效性仍需更大规模、更长随访周期的临床试验进一步确认。同时需要明确的是, 丙型肝炎与MASH相关纤维化在致病病因、肝脏免疫微环境、HSCs激活调控通路及纤维化进展机制上存在明显差异。目前该药物尚未在MASH患者中开展临床试验, 其在MASH人群中的疗效与安全性仍需要针对性临床试验验证。基于现有临床证据, 靶向*HSP47*的siRNA疗法对存在显著纤维化 (F2-F4期) 的MASH患者具有潜在应用价值, 但该疗法对肝脏脂肪变性和炎症的直接改善作用有限, 单药治疗可能无法全面控制MASH疾病进展, 未来或需与代谢调节类药物联合使用以实现协同治疗。

2.3.2 AREG 双调蛋白 (amphiregulin, AREG) 是表皮生长因子 (epidermal growth factor, EGF) 家族的分泌型功能蛋白, 在调节细胞增殖、凋亡和迁移过程中发挥重要作用。*AREG*的表达和释放可受炎症因子、细胞因子和生长因子等多种信号刺激, 通过与表皮生长因子受体 (epidermal growth factor receptor, EGFR) 特异性结合激活下游信号通路, 在组织发育、损伤修复中发挥关键调控作用。在MASH患者肝脏中, 浸润的调节性T细胞 (regulatory T cells, T_{reg}) 是AREG的主要来源之一, T_{reg}来源的AREG通过激活HSCs表面的EGFR信号促进HSCs活化与增殖, 进而促进肝脏纤维化进程。同时, 该通路的异常激活还与机体葡萄糖耐量异常相关, AREG介导HSCs表面EGFR信号激活后, 诱导HSCs分泌白细胞介素-6, 白细胞介素-6作用于肝细胞促进肝脏糖异生, 导致机体糖耐量异常并加重胰岛素抵抗[125]。siRNAgen Therapeutics公司开发的SRN-001是一种靶向*AREG*的siRNA药物, 采用基于SAMiRNA自组装胶束平台构建的纳米递送体系实现体内递送。在肾纤维化和肺纤维化临床前模型中, SRN-001均能显著降低纤维化标志物的表达水平, 减轻组织胶原沉积[126]。尽管该药物尚未在MASLD/MASH人群中开展临床试验, 但其在多器官纤维化模型中展现出的抗纤维化疗效, 结合AREG在肝纤维化中明确的致病机制, 使其成为具有一定转化潜力的候选药物。

3 总结与展望

siRNA疗法通过RNAi机制特异性降解靶基因mRNA, 在转录后水平阻断致病蛋白的合成。与传统小分子或抗体药物相比, siRNA疗法具有高度特异性、长效性等优势。近年来, 化学修饰技术的持续推进和肝脏靶向递送载体的不断发展, 有效克服了裸siRNA体内应用面临的核酸酶降解、肾脏快速清除、免疫系统识别及内体逃逸效率低等多重递送障碍。其中siRNA与GalNAc偶联载体结合后, 可特异性识别并结合肝细胞表面高表达的ASGPR, 实现向肝细胞的高效递送, 显著提升肝脏组织药物暴露量, 为肝脏靶向siRNA药物的临床转化提供了技术支撑。在MASLD领域, 围绕疾病核心致病环节, 包括遗传风险变异、脂质代谢调节及肝脏纤维化与炎症通路, 开发出多款靶向不同通路的siRNA候选药物。这些进展表明, siRNA疗法在MASLD领域初步建立起多层次的治疗体系 (表1)。

然而, siRNA疗法在MASLD临床应用中仍存在诸多挑战。首先, 最佳治疗靶点的选择与成药性验证存在不确定性。*PNPLA3*、*HSD17B13*等核心遗传靶点虽在临床前研究中表现出肝脏病理改善潜力, 但这些靶点效应强度在不同个体与人群间存在差异[127-130]。MASLD发病涉及脂质代谢异常、胰岛素抵抗、炎症及纤维化等多条通路的相互作用, 单一靶点干预能否实现疾病的长期有效控制仍需要长期临床试验数据验证。其次, MASLD患者在遗传背景、代谢表型、疾病进展阶段等方面存在显著个体差异, 且多数患者合并肥胖、T2DM等代谢综合征, 目前仍缺乏可精准预测治疗反应的生物标志物[130,131]。此外, 尽管GalNAc偶联技术显著提高了siRNA的肝脏靶向递送效率, 但长期重复给药的潜在安全性问题仍需密切监测[93,132,133]。

尽管面临诸多挑战, siRNA疗法在MASLD领域仍具有广阔发展前景。siRNA与GLP-1受体激动剂、THR-β激动剂等代谢调节剂的联合应用, 可能在基因转录调控与代谢改善层面实现协同作用, 为不同类型的患者提供更全面的治疗方案。此外, siRNA与中医药的联合应用也展现出较大的临床转化潜力。中药天然活性产物或经典复方可通过减轻肝脏脂肪变性、改善胰岛素抵抗、调节肠道菌群等途径, 发挥多靶点、多通路的治疗优势, 弥补siRNA疗法单一靶点治疗的不足[134,135]。现有研究表明, 利用活性中药成分构建递送载体, 不仅能提高siRNA的沉默效率, 载体自身还可发挥调节免疫微环境、缓解肝脏纤维化的协同作用[136,137]。当然, 此类联合策略还需关注药代动力学相互作用、长期安全性、代谢干扰及治疗成本等现实问题, 其长期临床获益仍需更多临床试验验证。近年来, 我国siRNA药物研发发展迅速, 为突破国际专利壁垒, 国内多家企业已自主研发出多款具有自主知识

Table 1 Promising siRNA therapeutics for MASLD/MASH treatment

Drug name	Target	Mechanism of action	Clinical trial (NCT) number	Study phase	Company	Ref.
ARO-PNPLA3	*PNPLA3*	Genetic risk variants	NCT05039710; NCT04844450	II	Arrowhead	[79]
ALN-PNP	*PNPLA3*	Genetic risk variants	NCT05648214; NCT06024408	I	Alnylam/Regeneron	[81, 82]
LY3849891	*PNPLA3*	Genetic risk variants	NCT05395481	I	Lilly/Dicerna	[83]
ARO-HSD	*HSD17B13*	Genetic risk variants	NCT04202354	II	Arrowhead/GSK	[89, 90]
ALN-HSD	*HSD17B13*	Genetic risk variants	NCT04565717; NCT05519475	II	Alnylam/Regeneron	[91]
VSA006	*HSD17B13*	Genetic risk variants	NCT06322628	II	Visirna	[92]
NNC0581-0001	*MTARC1*	Genetic risk variants	NCT05599945	I	Novo Nordisk	[99]
ALN-CIDEB	*CIDEB*	Genetic risk variants	NCT06836609	I	Alnylam/Regeneron	[106]
ARO-ANG3	ANGPTL3	Lipid metabolism regulation	NCT03747224; NCT05217667; NCT04832971	III	Arrowhead	[110]
LY-3561774	*ANGPTL3*	Lipid metabolism regulation	NCT04644809; NCT05256654; NCT07269210	II	Lilly/Dicerna	[111]
ARO-APOC3	*APOC3*	Lipid metabolism regulation	NCT06822790; NCT05089084; NCT06347003; NCT06347016; NCT06347133; NCT06880770	FDA approval	Arrowhead	[60]
RBD5044	*APOC3*	Lipid metabolism regulation	NCT05539651; NCT06797401	II	Suzhou Ribo Life Science	[115]
ALN-APOC3	*APOC3*	Lipid metabolism regulation	NCT06784349	I	Alnylam/Regeneron	[116]
WVE-007	*INHBE*	Lipid metabolism regulation	NCT06842186	I	Wave Life Sciences	[119]
ARO-INHBE	*INHBE*	Lipid metabolism regulation	NCT06700538	II	Arrowhead	[120]
BMS-986263	*HSP47*	Fibrosis-inflammation pathways	NCT04225936; NCT03142165; NCT04267393; NCT03420768	II	Bristol Myers Squibb	[124]
SRN-001	*AREG*	Fibrosis-inflammation pathways	NCT07407543; NCT05984992	I	siRNAgen Therapeutics	[126]

产权的修饰技术与递送系统。如苏州瑞博生物的RIBO-GalSTAR肝靶向递送平台, 以及圣诺医药基于多肽纳米颗粒PNP的递送技术。随着全球研发趋势的演变, 国内企业研发布局逐渐从乙型肝炎向慢性病领域拓展, 但目前多数小核酸药物仍处于早期临床阶段。

在递送技术优化方面, 除完善现有GalNAc偶联技术外, 开发特异性靶向肝脏内不同细胞类型的新型配体也具有重要意义。脂质纳米颗粒和外泌体等新型递送载体的技术迭代, 也为MASLD患者的治疗提供了更多技术可能。随着更多siRNA药物获批上市, 该类疗法有望成为MASLD治疗体系中的重要组成部分, 适用人群将进一步扩大, 不仅局限于携带特定遗传变异的患者, 而是拓展至基于疾病进展阶段、代谢表型、炎症和纤维化程度等多维度评估制定个体化方案的广泛患者群体。尽管目前siRNA疗法难以完全取代MASLD传统治疗手段, 但其凭借独特的作用机制和精准治疗潜力, 为这一全球性公共卫生挑战提供了新的治疗策略。随着基础研究、临床试验和递送技术创新的持续推进, siRNA疗法将在MASLD治疗中发挥日益重要的作用。

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