

· 综述 ·

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线粒体丙酮酸载体抑制剂在代谢相关脂肪性肝炎治疗中的应用前景

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摘要: 代谢相关脂肪性肝炎(MASH)是一种复杂的肝脏疾病,其病理特征是肝脏中脂肪异常累积,伴随炎症和肝细胞损伤,可逐渐发展为肝纤维化、肝硬化甚至肝癌。MASH的发病机制复杂,涉及胰岛素抵抗、脂肪从头合成(DNL)增加、氧化应激和线粒体功能障碍等多个环节。近年来,线粒体丙酮酸载体(MPC)作为调控脂质代谢的关键分子靶点备受关注。本文系统综述了MPC在MASH中的作用机制,重点探讨抑制MPC表达如何通过减少DNL生成并调控腺苷一磷酸活化的蛋白质激酶-乙酰辅酶A羧化酶等信号通路来调节脂质合成代谢,最终改善肝脏炎症。此外,本文展望了MPC抑制剂在MASH治疗中的潜在应用前景,以期未来治疗MASH的临床研究提供新的思路。

关键词: 代谢相关脂肪性肝炎; 线粒体丙酮酸载体; 治疗学

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Application prospects of mitochondrial pyruvate carrier inhibitors in treatment of metabolic dysfunction-associated steatohepatitis

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Abstract: Metabolic dysfunction-associated steatohepatitis (MASH) is a complex liver disease characterized by abnormal fat accumulation in the liver, accompanied by inflammation and hepatocyte injury, and it can gradually progress to liver fibrosis, liver cirrhosis, and even hepatocellular carcinoma. MASH has a complex pathogenesis involving multiple links such as insulin resistance, de novo lipogenesis (DNL), oxidative stress, and mitochondrial dysfunction. In recent years, mitochondrial pyruvate carrier (MPC) has attracted wide attention as a key molecular target for regulating lipid metabolism. This article systematically reviews the mechanism of action of MPC in MASH, with a focus on how inhibiting MPC expression regulates lipid synthesis and metabolism by reducing DNL production and modulating signaling pathways such as AMPK-ACC, thereby improving liver inflammation. In addition, this article discusses the potential application prospects of MPC inhibitors in MASH treatment, in order to provide new ideas for future clinical research on MASH management.

Key words: Metabolic Dysfunction-Associated Steatohepatitis; Mitochondrial Pyruvate Carrier; Therapeutics

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代谢相关脂肪性肝炎 (metabolic dysfunction-associated steatohepatitis, MASH) 是一种以脂肪变性、肝小叶炎症、肝细胞气球样变、伴或不伴肝纤维化和肝硬化为病理体征的慢性肝脏疾病, 其与超重、肥胖、2型糖尿病、代谢综合征及其他因素引起的胰岛素抵抗 (insulin resistance, IR) 密切相关^[1-2]。据统计, MASH 的全球患病率为 3%~8%, 其中 5%~10% 的患者伴有严重的肝细胞炎症和纤维化, 15%~20% 的患者在 7.1~10 年内从 MASH 进展至晚期肝纤维化 (F3/F4); MASH 总病死率为 25.56/1 000 人年, 其中肝脏相关病死率为 11.77/1 000 人年^[3-4]。目前, MASH 已成为全球范围内最常见的慢性肝病之一, 也是健康体检肝生化指标异常和肝细胞癌的首要原因, 对人民健康及社会发展构成严重危害^[5-6]。

迄今为止, 尚无单一且有效的药物和方法能够应对 MASH 内在复杂的生理病理特点^[7-8]。因此, 围绕 MASH 发病的关键病理因素和个性化表型特征, 阻断肝脏脂质合成、代谢紊乱、IR、脂质过氧化及肝脏炎症反应关键病理环节, 研发成分明确、机制清晰和疗效确切的创新药物, 已成为 MASH 临床精准化治疗中突破核心瓶颈的关键技术和目标导向^[9-10]。

1 IR 引起的脂肪从头合成 (de novo lipogenesis, DNL) 是 MASH 进展为肝纤维化的关键环节

肥胖引起的 IR 和 DNL 增加, 是 MASH 肝脏炎症进展中的特征性病理改变和关键中心环节^[11-12]。在此状态下, 脂肪组织的分解加剧, 会释放大量的游离脂肪酸 (free fatty acids, FFA) 进入循环系统, 进而被肝脏摄取, 进一步加重肝脏的脂质累积, 并显著驱动肝脏 DNL 活动增强^[13]。DNL 是肝脏内源性脂质合成的主要途径^[14]。临床研究显示, MASH 患者肝脏 DNL 对脂质累积的贡献率高达 25%~30% (健康人群仅为 5%), 且 DNL 水平与疾病严重程度呈正相关^[15-16]。在分子机制层面, IR 状态下, 转录因子甾醇调节元件结合蛋白 (sterol regulatory element-binding protein, SREBP) 和碳水化合物反应元件结合蛋白 (carbohydrate responsive element binding protein, ChREBP) 被过度激活, 上调乙酰辅酶 A 羧化酶 (acetyl-

coA carboxylase, ACC) 和脂肪酸合成酶 (fatty acid synthase, FASN) 的表达, 促使过量碳水化合物转化为 FFA 和甘油三酯, 导致肝细胞脂质堆积, 从而引发脂毒性损伤。这些 FFA 及其衍生物 (如神经酰胺和 4-羟基壬烯醛等) 不仅直接损伤线粒体功能、诱发氧化应激, 还可通过激活核苷酸结合寡聚化结构域样受体蛋白 3 炎症小体和促炎因子 (如肿瘤坏死因子 α 、白细胞介素 1β 等), 加剧炎症反应。此外, DNL 生成的脂质介质 (如溶血磷脂酸) 通过旁分泌信号激活肝星状细胞 (hepatic stellate cell, HSC), 促进胶原沉积和肝纤维化进展。肝脏中过量堆积的脂质和 IR 可以诱导细胞内生成大量活性氧, 引起肝细胞氧化应激, 从而导致 FFA 吸收和 DNL 增加、促炎因子分泌、内质网应激反应和线粒体功能障碍, 形成“脂质累积-氧化损伤”的恶性循环^[17-18]。过度氧化应激、内质网应激反应和线粒体功能障碍可进一步导致肝细胞损伤、细胞凋亡和炎症反应, 并诱导 HSC 活化增殖, 从而导致 MASH 炎症加剧并进展为肝纤维化^[19-20]。

综上所述, DNL 增加是引发肝脏炎症反应、内质网应激、线粒体功能障碍及 HSC 活化的首要病理因素, 亦是 MASH 炎症向肝纤维化进展的关键中心环节。抑制 DNL 有望成为精准化治疗 MASH 创新药物研发的潜在靶点, 但其作用机制和分子靶点尚未明确。

2 抑制线粒体丙酮酸载体 (mitochondrial pyruvate carrier, MPC) 调控肝脏脂质合成与炎症的潜在机制

MPC 是由 MPC1 和 MPC2 亚基组成的异源二聚体蛋白复合物, 位于线粒体内膜, 作为连接糖酵解与三羧酸循环的关键代谢枢纽, MPC 负责将细胞质中糖酵解产生的丙酮酸转运至线粒体基质, 在机体整个能量代谢路径中发挥中枢核心作用^[21]。既往研究表明, MPC 不仅参与葡萄糖代谢, 还在脂质代谢平衡中发挥重要的调节作用^[22]。肥胖模型小鼠中, MPC1 的特异性敲除可降低肝脏糖异生水平, 胰岛素敏感性增加, 同时因线粒体丙酮酸通量下降导致 DNL 减少^[23]。在 MASH 患者肝脏中, MPC1 表达增高, 并与脂质沉积呈正相关, MPC1 基因敲除可通过调节肝细胞中的乳酸水平影响蛋白质乳酸化,

尤其是FASN的K673位点乳酸化修饰能够显著抑制其活性,而乳酸是ChREBP的天然抑制剂,能直接抑制ChREBP的转录活性并下调其表达水平;与此同时,抑制MPC导致的三羧酸循环改变,可能减少磷酸戊糖途径中间产物(如木糖醇-5-磷酸)的生成,这些代谢物是ChREBP的激活剂,其减少会进一步削弱ChREBP的活性^[24]。由于ChREBP是控制葡萄糖/碳水化合物反应性脂肪生成基因(如ACC、FASN)转录的主开关,其活性被抑制后,可在转录水平方面下调DNL,从而显著减轻肝细胞脂质沉积。虽然MPC1敲除会导致乳酸积累,但线粒体功能的维持与巨噬细胞极化的正向调控,共同介导了炎症水平的变化^[25-26]。此外,线粒体内丙酮酸匮乏会导致乙酰辅酶A生成减少,使得依赖其合成的柠檬酸向细胞质输出量下降,从源头上切断了DNL的关键底物——细胞质乙酰辅酶A的供应^[27],此时,细胞间平衡状态被破坏,腺苷三磷酸(adenosine triphosphate, ATP)水平下降,腺苷一磷酸(adenosine monophosphate, AMP)/ATP比值升高^[28],激活细胞能量代谢的核心传感器,即AMP活化的蛋白质激酶(AMP-activated protein kinase, AMPK)。一方面,活化的AMPK通过磷酸化并抑制雷帕霉素靶蛋白复合物1的活性,由此下调SREBP-1c;而SREBP-1c作为FASN、ACC等脂肪酸合成关键基因的转录启动因子,其功能受到抑制会直接减少丙二酰辅酶A的生成,从而减缓脂肪酸合成^[29];另一方面,解除丙二酰辅酶A对肉毒碱棕榈酰转移酶1A的抑制,促进脂肪酸进入线粒体进行 β -氧化,实现对脂质生物合成通路的抑制作用,进而降低甘油三酯的胞内沉积,进一步改善脂质堆积^[30]。SREBP-1c和ChREBP共同控制ACC、FASN及硬脂酰辅酶A去饱和酶1等所有DNL关键酶的转录^[31]。MPC抑制通过上述机制同时下调这两大主调控因子,相当于关闭了肝脏脂肪合成的“总开关”,从而在基因表达层面实现对DNL的强力抑制。因此,通过这一通路,MPC抑制能够有效阻断MASH从“脂肪变性”向“炎症”进展的核心病理进程。

3 抑制MPC调控MASH炎症进展为肝纤维化的机制

在MASH中,HSC的活化是肝纤维化的关键环节。在正常肝脏中,HSC处于静止状态;但在肝损伤或炎症时,HSC会被激活,转化为促纤维化的细胞,分泌细胞外基质成分,导致肝纤维化。研究表明,抑制MPC表达可以减少HSC活化标志物(如 α -平滑肌肌动蛋白和胶原蛋白I)的表达,提示MPC在HSC活化中发挥关键作用。

动物实验显示,高脂饮食喂养44周后,小鼠肝脏炎症、纤维化和HSC活化均显著减轻,特异性敲除MPC的肝细胞可显著减少HSC活化,这可能与两种细胞间旁分泌通讯有关,肝细胞分泌的因子可以调节HSC的活化状态。例如,肝细胞分泌的转化生长因子 β 是激活HSC的主要因子之一^[32]。抑制原代HSC中的MPC表达可使HSC活化标志物表达下降,表明抑制MPC表达可调节肝细胞分泌的旁分泌因子,从而抑制HSC活化,或可诱导HSC凋亡^[33]。MPC是丙酮酸进入线粒体的关键载体,其功能缺失会抑制三羧酸循环和氧化磷酸化,导致ATP生成减少和活性氧积累。HSC依赖低水平的氧化代谢维持静息状态,而MPC抑制可能打破该平衡,触发凋亡从而改善MASH炎症和纤维化^[34]。因此,MPC已被作为阻断MASH炎症进展为肝纤维化、糖尿病和依赖线粒体代谢癌症等慢性疾病的潜在作用分子靶点^[35]。

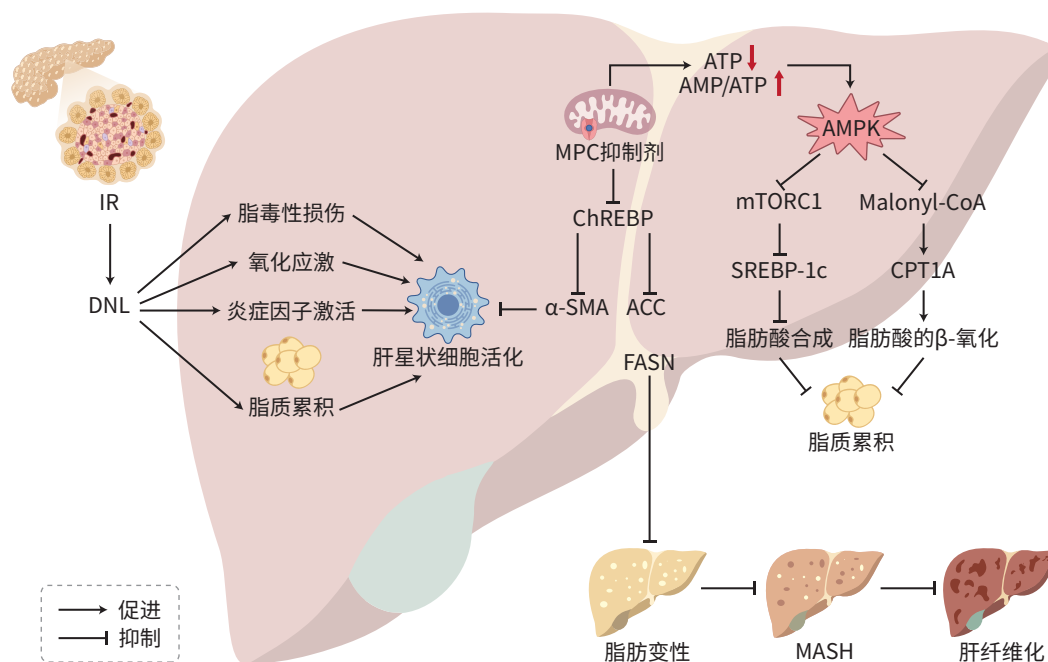
4 小结与展望

现有研究已经明确MPC作为脂质代谢的枢纽,在MASH的病理进程中发挥核心调控作用。本文系统阐述了抑制MPC表达可减少线粒体丙酮酸的摄入,下调DNL,同时激活AMPK-ACC信号通路,增强脂肪酸氧化,抑制脂质合成的关键酶活性,从而缓解肝细胞脂质累积,抑制氧化应激及炎症反应,并通过抑制HSC活化以阻止肝纤维化进程,为MPC抑制剂在MASH防治中的潜在价值以及调控机制提供了理论依据(图1)。

目前,已有部分MPC抑制剂进入临床试验阶段,其中进展最快的是MSDC-0602K,其通过抑制MPC以靶向作用于肝脏代谢过程,从而多重影响MASH的核心病理环节,包括改善肝脏IR、减少脂肪生成,并发挥抗炎和抗纤维化效应。该抑制剂的突出优势是安全性和耐受性良好,并可精准定位于2型糖尿病的MASH患者^[36]。未来研究应进一步探索MPC调控的精确分子机制,不仅需从基础研究领域入手,还要针对MASH的形成机制开展多靶点干预探索,加速实现MASH治疗方案的突破与临床转化,以期推动MASH的治疗从“对症治疗”过渡到“机制干预”。

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注:IR,胰岛素抵抗;DNL,脂肪从头合成;ACC,乙酰辅酶A羧化酶;FASN,脂肪酸合成酶;MPC,线粒体丙酮酸载体;ChREBP,碳水化合物反应元件结合蛋白; α -SMA, α -平滑肌肌动蛋白;ATP,腺苷三磷酸;AMP,腺苷一磷酸;AMPK,AMP活化的蛋白质激酶;mTORC1,雷帕霉素靶蛋白复合物1;SREBP-1c,甾醇调节元件结合蛋白-1c;Malonyl-CoA,丙二酰辅酶A;CPT1A,肉毒碱棕榈酰转移酶1A;MASH,代谢相关脂肪性肝炎。

图1 MPC抑制剂治疗MASH的分子机制

Figure 1 The molecular mechanism of MPC inhibitors in treating MASH

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