

脂质代谢紊乱在代谢功能障碍脂肪性肝病中的研究进展

刘成成, 黄 梦, 龚 欢, 赵婷婷, 贺 娜*

西安医学院第一附属医院消化内科, 陕西 西安

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摘 要

代谢功能障碍相关脂肪性肝病(MAFLD)已成为全球慢性肝病的主要病因, 其发生发展与脂质代谢紊乱密切相关。本文系统综述了脂质代谢异常在MAFLD发病机制中的作用, 重点阐述甘油三酯、游离脂肪酸、胆固醇及脂毒性介导肝脏损伤的分子机制, 并总结了靶向脂质代谢通路的潜在治疗策略。通过整合现有研究进展, 本文旨在为MAFLD的早期无创诊断及基于脂质代谢通路的治疗策略提供理论依据和新的研究视角。

关键词

脂质代谢, 代谢功能障碍相关脂肪性肝病, 胰岛素抵抗

Progress in Research on Lipid Metabolism Dysregulation in Metabolic Dysfunction-Associated Fatty Liver Disease

Chengcheng Liu, Meng Huang, Huan Gong, Tingting Zhao, Na He*

Department of Gastroenterology, The First Affiliated Hospital of Xi'an Medical University, Xi'an Shaanxi

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the leading cause of chronic liver disease worldwide, with its pathogenesis closely linked to disturbances in lipid

*通讯作者。

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metabolism. This review examines the role of lipid metabolic abnormalities in the onset and progression of MAFLD, with a particular focus on the molecular mechanisms by which triglycerides, free fatty acids, cholesterol, and lipotoxicity contribute to hepatic injury. Furthermore, it provides an overview of therapeutic strategies targeting lipid metabolic pathways. By integrating current research advances, this article aims to offer insights into the early non-invasive diagnosis of MAFLD and the development of lipid-based therapeutic approaches.

Keywords

Lipid Metabolism, MAFLD, Insulin Resistance

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1. 前言

代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD)是由遗传易感个体营养过剩和代谢功能障碍引起的脂肪性肝病。2020 年国际脂肪肝专家小组以新的术语“MAFLD”取代了既往的非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD) [1] [2]。术语的转变表明学界对此种疾病肝脏和全身致病途径机制新的认识,在遗传易感、营养过剩和胰岛素抵抗(insulin resistance, IR)等病因的基础上,强调了全身代谢功能紊乱在疾病发生发展中的作用[3]-[5]。MAFLD 疾病早期可逆,但其中大约 10%~30% 的 MAFLD 患者会进展为脂肪性肝炎和晚期肝病,2 型糖尿病(T2DM)和肥胖人群疾病发生、进展风险更高,预后更差。此外,其不仅影响肝脏,还与肝外疾病,如心血管疾病、慢性肾脏疾病和多种肝外肿瘤密切相关[6]-[8]。在全球范围内,MAFLD 影响超过 30% 的成年人,是成人健康体检肝功能异常的首要原因和最常见的慢性肝脏疾病;在中国,由于城市化、饮食结构西化和久坐少动的生活方式导致肥胖、2 型糖尿病人群逐年增加,以及随着病毒性肝炎防控策略的有效施行,MAFLD 已取代乙型病毒性肝炎成为我国慢性肝病的首要原因[9] [10]。目前 MAFLD 发病率仍逐年上升,已成为世界范围内肝移植手术及肝脏疾病花费增加的重要原因,被视为 21 世纪主要的健康负担之一[11]。

MAFLD 的典型特征是肝脏细胞脂肪变性,这是由于甘油三酯(triacylglycerol, TG)在肝细胞蓄积,从早期脂肪变性进展到晚期纤维化甚至癌变是一个复杂的过程。其发生机制从“二次碰撞学说”发展到“多重打击学说”,众多学者提出多种致病因素平行作用于疾病的发生发展,包括遗传易感性、脂质代谢异常、胰岛素抵抗、肠道菌群稳态失调等[12]。其中脂质代谢紊乱对 MAFLD 的影响越来越受到学界重视,但是,它们之间关系复杂,尚不明确脂质代谢紊乱是否增加 MAFLD 的发生发展风险,以及纠正代谢紊乱对 MAFLD 治疗的影响。此外,有关脂质代谢在 MAFLD 的发病机制中的作用尚未完全明确。文章回顾并总结了脂质代谢紊乱和 MAFLD 的相关研究,描述脂质代谢对 MAFLD 发生、发展的影响及其基于脂质途径的分子治疗靶点,以期对 MAFLD 的诊疗提供一点思考。

2. MAFLD 的临床表现、组织学特征及发病机制特点

2.1. 临床表现

MAFLD 起病隐匿,发病缓慢,常无症状、少数患者可有乏力、肝区隐痛或上腹胀痛等非特异性症状。严重脂肪性肝炎可出现黄疸、食欲减退、恶心、呕吐等症状。部分患者可有肝大。进展至肝硬化及失代

偿表现与其他原因肝硬化表现相似。MAFLD 患者常在体检时发现血清转氨酶及 γ -GT 水平升高,其水平升高程度与 MAFLD 严重程度无关,但肝酶升高可能与肝脏相关死亡率增加有关[13]。此外,肝酶正常的个体也不应忽视,他们可能存在更严重的脂肪性肝炎,并已进展至纤维化晚期及肝硬化阶段[14]。同时,MAFLD 患者常存在血糖升高或高脂血症。当其进展为纤维化晚期、肝硬化或门脉高压阶段时可表现为血小板减少、凝血酶原时间增加[15]。MAFLD 患者出现血脂异常的可能性是非 MAFLD 患者的两倍,并且 MAFLD 患者的血脂亚组分更易发生动脉粥样硬化[16][17]。目前代谢组学的相关研究提示细胞角蛋白 18 片段、肠道菌群及其代谢物、SomaSignal 测试和 ADAPT 评分等可作为提示 MAFLD 发生及进展识别的新型生物学标志物,且多种代谢组分构成的评分模型优于单一血清生物学标志物[18]。

2.2. 组织学特征

肝活检作为 MAFLD 诊断及分期的金标准。组织学报告在诊断 MAFLD 时,需精准描述肝脏细胞脂肪变性、气球样变、炎症坏死、纤维化程度及位置分布,以及有无肝实质重建和假小叶形成等重要特征。活检标本按要求取得,高质量的切片及染色对于病理诊断也至关重要。MAFLD 患者送检样本在镜下表现为 $\geq 5\%$ 大泡或大泡为主的脂肪变性,若同时存在肝细胞气球样变和炎症时可诊断为 MASH,肝实质重建及假小叶形成常提示肝纤维化及肝硬化。在活检证实的 MAFLD 患者中,纤维化分期是肝脏相关死亡率和肝细胞肝癌风险的最强预测因子,其进展主要受到高龄(与患病时间更相关)、绝经后状态、2 型糖尿病、心脏代谢危险因素和严重程度及环境和遗传因素的影响[19][20]。纤维化简易诊断模型如 FIB-4、APRI、NFS、HFS、BRAD 等在临床实践中被广泛用于评估患者疾病纤维化进展程度。肝病科医生在接诊提示纤维化高级阶段患者时,应和病理科医生保持高度协作,此外考虑到 MAFLD 作为一种全身多系统疾病,必要时可多学科会诊,以期接近肝脏穿刺活检风险及收益的最佳平衡。同时,相较于单一病理医生诊断结果,结合组织学结果提出的 NAFLD 活动性积分及 SAF 评分可以减少病理医生间的诊断误差[21]。此外,使用人工智能和机器学习有助于提高病例医生对疾病诊断及分期判断的一致性[22]。

2.3. 发病机制特点

MAFLD 的发生与肝脏能量代谢失衡密切相关,肝脏是机体能量代谢的中枢器官,MAFLD 是机体能量代谢失衡导致脂肪蓄积在肝脏的表现。外周脂肪组织功能障碍及其相关胰岛素抵抗是导致平衡被打破的重要原因,脂肪组织功能障碍迫使肝脏储存过多的脂肪酸,进而影响肝细胞正常功能及胰岛素敏感性[23]。在对 MAFLD 的发病机制研究中已经注意到种族差异,双胞胎研究表明 MAFLD 遗传率为 50% [24]。全基因组关联研究表明多个关键基因位点与 MAFLD 进展有关,其中 PNPLA3 通过影响脂质代谢途径导致疾病进展[25]。同时,遗传学研究也显示在胰岛素抵抗和血脂异常相关的遗传位点与脂肪组织的功能状态相关,这表明脂肪组织功能障碍与胰岛素抵抗和血脂代谢紊乱密切相关[26]。脂肪组织功能障碍及其相关胰岛素抵抗和低度炎症反应引起肝脏甘油三酯合成增多及其氧化利用和肝外转运减少,导致肝脏脂肪沉积;肠道菌群紊乱、糖脂毒性等附加打击则通过诱发线粒体功能障碍、内质网应激、脂质过氧化损伤等机制导致肝脏炎症损伤和星状细胞活化,从而导致疾病的进展及恶化[27]。MAFLD 患者常伴发肥胖、代谢综合征、2 型糖尿病,它们之间呈密切的双向关系[28][29]。它们不仅是 MAFLD 发生的危险因素,而且可能是发展的结局,在 MAFLD 患病数年后,肥胖、代谢综合征及 2 型糖尿病的发病风险几乎增加一倍[30][31]。此种现象可能是由于脂肪沉积的肝脏通过全身胰岛素抵抗、糖脂代谢改变、氧化应激和炎症损伤等途径参与肥胖、代谢综合征和 2 型糖尿病的发病,从而形成此种恶性循环[32][33]。

3. 脂质、脂质代谢及其紊乱

3.1. 脂质的定义、功能分类

3.1.1. 定义

脂质化学家将脂质定义为是一类完全或者部分由硫酯的碳负离子缩合(脂肪酸、聚酮化合物等)或由异戊二烯的碳正离子缩合(异戊烯醇、固醇类等)产生的疏水性或两亲性的小分子。脂质是两亲性分子,既有亲水部分,又有疏水部分。机体甘油三酯、胆固醇、胆固醇酯除了羟基或碳基集团外,主要呈疏水性,故其在体内运输需要载脂蛋白协助[34]。血脂是血液内脂类物质的统称,包括甘油三酯、磷脂、胆固醇、胆固醇脂和游离脂肪酸等。

3.1.2. 功能分类

根据脂质在机体生命活动中的主要功能[35],脂质可分为:

膜脂质,主要用于构成细胞膜且含量相对较高。几乎所有极性脂质及其代谢中间产物都是细胞膜的组分,其中代谢中间体的含量非常低,但其对膜结构和功能的调节至关重要。胆固醇是非极性脂质,但细胞膜特别是质膜中富含胆固醇。膜结构作为细胞的隔室屏障,膜脂含量和组成变化用于调控膜的通透性和流动性,进而影响细胞通讯和细胞内离子分布微环境;能量脂质,通常与能量储存和代谢相关。当参与能量代谢的脂质过量就会将能量储存起来,在机体需要时提供能量。这些脂质包括甘油二酯、甘油三酯(Triacylglycerol, TAG)、非酯化脂肪酸/游离脂肪酸等。这些脂质的变化通常交织在一起,它们在动物和人体内积累通常被称为“脂毒性”,会导致肥胖和 IR;生物活性脂质,作为脂质第二信使,通常含量极低。在任何生物信号中,大量的脂质都作为信号分子。生物体中,涉及脂质的信号途径主要有两种类型。一种类型是脂质直接与蛋白靶标(例如受体、激酶或磷酸酶)结合后将其激活,介导特定细胞功能。另一类是脂质的变化可影响膜结构并影响膜蛋白与膜双层的相互作用。脂质是机体的能量仓库,构成细胞膜的重要组成部分,也是信号通路调控的重要分子,在机体生命活动稳态中起到重要作用。

3.2. 脂质代谢及紊乱

脂质代谢是指机体内各种脂质在相关酶作用下的合成、运输、利用及调控系列代谢过程,其受遗传、神经体液、酶及肝脏等组织器官调节。脂质代谢途径包括内源性和外源性代谢途径[36]。内源性脂质代谢途径的中枢器官是肝脏,胆固醇的合成调控及脂蛋白的合成转化都在肝脏进行,以 VLDL-LDL 轴为主,受胰岛素、SREBP 等调控,与能量代谢和胆固醇稳态密切相关。外源性脂质指的是饮食摄入的脂质在消化道的酶吸收及转运、利用过程,其中主要乳糜微粒起到重要协助转运及调控作用[37]。

脂质代谢紊乱是指上述脂质代谢过程某一环节或多环节障碍,导致脂质在体内的分布水平或功能受损的异常状态,进而影响正常机体内环境稳态[38]。脂质代谢紊乱常表现为血脂异常及脂质积累所致“脂毒性”器官损害。脂质代谢是维持机体能量稳态、细胞结构稳定及生命活动信号传递核心生理过程,其调控失衡可引发系列疾病[39]。

4. MAFLD 和脂质代谢紊乱

MAFLD 本身作为一种全身代谢性疾病在肝脏的表现,其典型组织学表现为 TG 在肝细胞的蓄积。同时,MAFLD 患者常伴类似于粥样硬化性血脂异常,具体表现为高甘油三酯、高 LDL 及低 HDL,这是因为 TG 除了蓄积于肝细胞外,还可以结合 VLDL 转运至肝外,继而导致血脂异常[40]。脂质代谢紊乱与 MAFLD 的发生、发展密切相关。

4.1. 甘油三酯和 MAFLD

MAFLD 的典型组织学特征是 TG 脂滴蓄积于肝细胞, 肝细胞内脂滴的直径约为 50 nm 至 1 μm , 由中性脂质和单层磷脂膜构成的疏水核心以及执行生物学功能的蛋白构成[41][42]。TG 除了蓄积于细胞外, 还可以结合 VLDL 转运至肝外, 导致血脂紊乱。VLDL 含量降低会减轻血脂异常的严重程度, 但会加剧 MAFLD 的进展, 这凸显了 VLDL 在脂质代谢类疾病发生中的复杂作用[43]。只是单纯 TG 在肝脏的积累不足以发展至肝脏乃至全身的 IR, 肝细胞中 TG 的积累本身无害, 甚至被认为是一种能防止游离脂肪酸诱导脂毒性的保护因素[44]。但是, 存在代谢紊乱患者往往存在 TG 合成、储存与清除的失衡, 导致过量的 TG 负荷会刺激肝脏细胞 ROS 损害, 致脂毒性损害增强[45]。

4.2. 游离脂肪酸和 MAFLD

机体游离脂肪酸(free fatty acids, FFA)主要来源于三个方面: 脂肪组织动员、膳食摄入以及肝脏脂肪酸从头合成(de novo lipogenesis, DNL) [46]。其中, 脂肪组织内储存的甘油三酯是 FFA 的主要来源。甘油三酯在脂肪酶作用下逐步水解, 释放脂肪酸和甘油, 随后被外周组织利用。肝脏中 FFA 的清除主要通过两种途径完成, 即线粒体内脂肪酸 β -氧化以及以极低密度脂蛋白(VLDL)形式转运至外周组织。脂肪酸氧化(fatty acid oxidation, FAO)是机体在饥饿和应激状态下的重要能量供给方式, 在长期禁食条件下, 几乎所有组织均依赖 FAO 维持能量需求。MAFLD 患者普遍存在外周组织及肝脏的胰岛素抵抗(insulin resistance, IR)。外周脂肪组织 IR 的典型特征是在空腹状态下脂肪分解增强, 脂肪细胞释放 FFA 增加, 并随疾病进展进一步加重[47]。此外, 由于长期营养过剩及 IR 状态, MAFLD 患者外源性脂肪酸摄入增加, 同时肝脏 DNL 显著增强。IR 促进肝细胞内中性脂质积聚, 最终导致肝细胞脂肪变性。脂肪酸氧化增强可诱导活性氧(reactive oxygen species, ROS)过量生成, 当 ROS 损伤线粒体电子传递链时, 可形成恶性循环。ROS 及脂质过氧化产物不仅损伤线粒体 DNA, 还可引起线粒体肿胀及胆固醇转运障碍, 从而进一步加重线粒体功能紊乱[48]。此外, MAFLD 的肝外表现, 如与 IR 和肥胖相关的并发症(高血糖、糖尿病、心脏脂肪变性及亚临床炎症等), 亦可能通过全身代谢紊乱参与疾病进展的调控[20]。

FFA 是介导脂质代谢紊乱和炎症损伤的关键分子。血清 FFA 水平升高与 MAFLD 进展密切相关, 并被认为是疾病进行性纤维化的重要标志之一。其潜在分子机制可能与硬脂酰辅酶 A 去饱和酶 1(SCD1)表达或活性下降有关, 导致肝细胞对过量脂肪酸的适应能力受损, 从而促进疾病进展[49]。过量 FFA 在肝细胞内蓄积可引起线粒体超负荷, 诱发线粒体功能障碍并激活细胞凋亡通路。同时, FFA 可通过激活肝脏巨噬细胞表面的模式识别受体, 如 Toll 样受体 4 (TLR4), 启动下游炎症信号通路(NF- κ B 通路), 从而促进炎症因子如 IL-6 和 TNF- α 的释放, 放大肝脏炎症反应。凋亡肝细胞形成的凋亡小体可被 Kupffer 细胞和肝星状细胞吞噬, 促使肝星状细胞向成纤维样表型转化, 增强胶原蛋白合成并触发促纤维化反应。胶原沉积的增加通常伴随基质金属蛋白酶(如 MMP-9)表达上调, 进一步推动肝纤维化进展。鉴于 FFA 在 MAFLD 发生发展中的核心作用, 深入阐明过氧化物酶增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)的调控机制及其在 MAFLD 治疗中的潜在价值具有重要意义[50]。

4.3. 胆固醇和 MAFLD

胆固醇通过调节肝脏的炎症反应, 促使 MAFLD 疾病进展。其发生机制可能与肝脏中游离胆固醇的积累通过激活 JNK1 引起肝细胞凋亡、坏死。细胞内游离胆固醇浓度升高结晶, 含有胆固醇结晶的坏死肝细胞进一步激活 Kupffer 细胞聚集成“冠状结构”的过程, 最终转化为活化泡沫细胞。胆固醇稳态受几种核转录因子的调控, 包括固醇调节元件结合蛋白(SREBP-2)、FXR 和肝 X 受体(LXR) [46] [51]。SREBP-2 是一种检测膜胆固醇和 FA 含量的转录因子, 可以改变参与胆固醇合成的基因转录过程。SREBP-2 转录因子的

过表达破坏了胆固醇代谢稳态。持续激活的 SREBP-2 破坏了细胞有关胆固醇调节的负反馈机制,导致胆固醇的合成增加。此外,除了促进胆固醇合成增加通路外,其可能通过影响患者 CYP7A1 及转运蛋白 ABCA1 的表达,导致胆固醇排泄减少。另外,游离胆固醇在造血干细胞中的积累也会加重肝纤维化,此间过程中内溶酶体网络在胆固醇稳态维持中起到核心介导作用[52]。此外,Liu Lei 等人的队列研究表明基线水平或累计残余胆固醇升高与新发 MAFLD 独立相关,其可作为 MAFLD 预防策略的一部分[53]。

4.4. 有关脂质代谢途径的 MAFLD 目前治疗药物研究

基于脂质代谢通路的 MAFLD 治疗研究近年来取得重要进展,相关药物主要集中于调控脂质代谢关键环节的靶向策略。1) PPAR 激动剂(如吡格列酮)可通过增强脂肪酸氧化、改善胰岛素抵抗并降低脂毒性,从而有效改善肝脏脂肪变性和炎症反应[54]。2) SCD1 抑制剂作为调控脂肪酸去饱和化的重要策略,其作用机制在于减少单不饱和脂肪酸(MUFA)的生成,降低甘油三酯合成,从而减轻由神经酰胺、DAG 等代谢产物介导的脂毒性损害;研究提示,在脂质类型失衡的背景下,MUFA 消耗不足与疾病进展风险增高相关,SCD1 抑制剂因此成为潜在治疗靶点[49] [55]。3) 选择性甲状腺激素受体 β (THR- β)激动剂 resmetirom 通过提升肝脏脂质代谢、降低肝脂水平并改善胰岛素抵抗,在 III 期临床试验中显著改善 MASH 的炎症与纤维化,是首个获得 FDA 批准用于治疗 MAFLD/MASH 纤维化进展的靶向药物[56]。4) FXR 激动剂(如奥贝胆酸)通过调控胆汁酸代谢、抑制从头脂肪酸合成(DNL)并减少肝脏炎症,为 MAFLD 的治疗提供了另一重要方向,但其临床应用仍受瘙痒、血脂升高等副作用限制。在非药物干预方面,生活方式调控仍是基础治疗策略。通过热量限制及抗炎饮食模式(如地中海饮食)可显著减少肝脂肪含量;规律运动可通过激活 AMPK 通路促进脂肪酸氧化[32]。其背后的机制是由于饮食中的膳食纤维经肠道微生物分解生成短链脂肪酸(SCFAs),可激活脂肪组织中 GPR43 信号,从而抑制脂肪在肝脏和脂肪组织中的堆积[57]。超重肥胖难以通过生活方式干预及药物治疗纠正患者可考虑通过外科手术干预,以期纠正脂质代谢紊乱改善脂质代谢紊乱,从而延缓改善疾病发生进展。

尽管目前多种药物展现出潜在疗效,但大部分仍聚焦于单一靶点。未来研究应强调多通路联合调控,以提高治疗效率并改善长期预后。此外,随着代谢组学、机器学习和人工智能的发展,基于脂质代谢特征的患者分层和个体化精准治疗将成为 MAFLD 药物研发的关键方向。

5. 结论和展望

近年来,随着 MAFLD 在全球范围内流行并逐渐成为慢性肝病研究的热点领域,相关研究迅速增长。脂质代谢作为生命活动的重要组成部分,其紊乱被认为是 MAFLD 发生和进展的核心机制之一。肝脏在脂质“输入与合成增加、输出与氧化减少”之间的动态失衡,导致脂质在肝内异常蓄积,并通过脂毒性产物生成、氧化应激增强、炎症信号激活、细胞器功能障碍以及肠-肝轴紊乱等多重机制,引发肝细胞损伤、胰岛素抵抗和肝纤维化,最终推动 MAFLD 向进展性阶段发展。基于上述机制,MAFLD 的疾病干预与药物研发亟需围绕脂质代谢的关键调控节点(如抑制肝内新生脂肪生成、促进 VLDL 分泌)及其下游病理效应通路(包括抗炎和抗氧化反应)开展系统性调控。尽管多种靶向脂质代谢的治疗策略已显示出一定潜力,但其长期疗效及安全性仍有待进一步验证。未来研究有必要在整合多组学技术与临床表型数据的基础上,深入解析患者特异性的脂质代谢谱,重点关注特定脂质亚类(如具有特定脂肪酸链长或饱和度特征的甘油三酯)在区分惰性脂肪肝与进展性 MASH 中的作用,从而为 MAFLD 的风险分层、精准干预和新型治疗靶点的发现提供更加明确的理论依据和研究方向。

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