

代谢相关脂肪性肝病发病机制的研究进展

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摘要

代谢相关脂肪性肝病(MAFLD)是全球范围内的常见肝病, 对全球健康产生巨大的危害。目前该病的发病机制尚不明确, 在治疗上也尚无特效药, 本文通过查阅相关文献对MAFLD的发病机制进行综述, 以期为临床上治疗MAFLD提供参考。

关键词

代谢相关脂肪性肝病, 发病机制, 诊断

Advances in the Pathogenesis of Metabolism-Related Fatty Liver Disease

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Abstract

Metabolism-associated fatty liver disease (MAFLD) is a common liver disease worldwide and poses a huge global health hazard. The pathogenesis of the disease is still unclear, and there is no specific drug in the treatment. In this paper, we review the pathogenesis of MAFLD by reviewing the relevant literature, with a view to providing a reference for the treatment of MAFLD in the clinic.

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Keywords

Metabolism-Associated Fatty Liver Disease, Pathogenesis, Diagnosis

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1. 引言

代谢相关脂肪性肝病(MAFLD)曾用名为非酒精性脂肪肝病(NAFLD),随着代谢综合征(Mets)、糖尿病、心血管疾病和其他慢性代谢疾病发病率的增加,MAFLD的发病率也在逐渐上升[1][2],影响着全球约1/3的人口健康,对社会造成了重大的经济负担[3]。NAFLD是一种排他性疾病,确诊NAFLD需要排除其他引起肝病的原因以及过量饮酒的病史,但由于不能确定过量饮酒的定义,且NAFLD可与其他肝病共存,故2020年国际专家小组提出了更简便的MAFLD诊断标准,该标准与饮酒量无关,可应用于任何临床患者[4]。研究表明,MAFLD是导致肝硬化、肝功能衰竭和肝癌风险增长最快的原因[5]。且MAFLD的危害不仅局限于肝病相关的高发病率和死亡率,更是一种全身代谢性疾病,与非MAFLD人群相比,MAFLD患者患心血管疾病、慢性肾脏疾病、其他肝外恶性肿瘤的发病率及死亡率均显著提高[6]-[8]。此外,MAFLD与胰岛素抵抗(IR)、睡眠呼吸暂停综合征、骨质疏松症、银屑病和其他内分泌疾病也有关。鉴于MAFLD的高发病率且与多种疾病密切相关,研究MAFLD的发病机制就显得尤为重要。

2. 诊断标准

MAFLD诊断标准是基于肝脏脂肪积聚(肝细胞脂肪变性)的组织学(肝活检)、影像学或血液生物标志物证据,同时合并以下三项条件之一:超重/肥胖、2型糖尿病(T2DM)、代谢功能障碍[4]。该规定明确指出满足腹型肥胖、高血压、血液甘油三酯水平升高、高密度脂蛋白水平下降、血糖升高但无糖尿病、IR指数升高、超敏C反应蛋白升高等指标中2项及以上者即为代谢功能障碍(图1)。

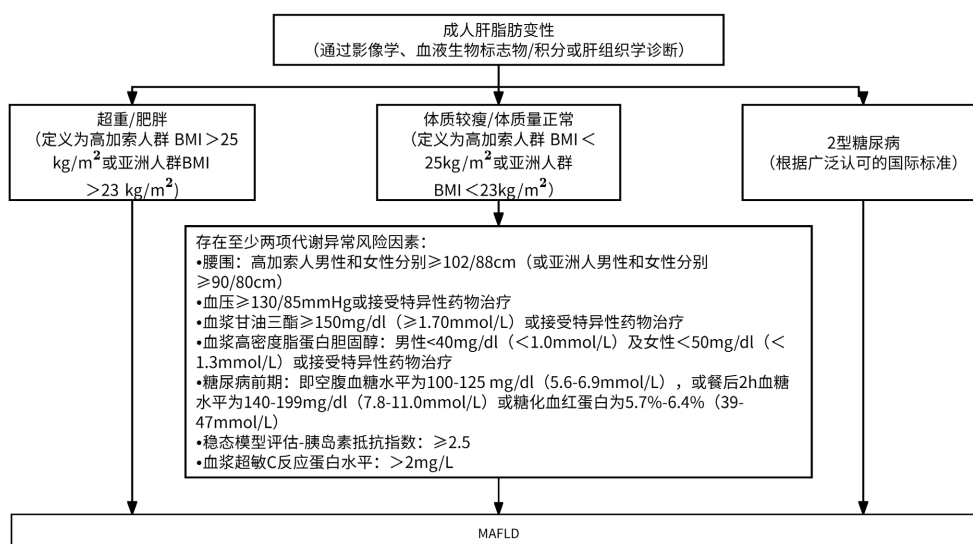


Figure 1. Diagnostic criteria for MAFLD

图 1. MAFLD 诊断标准

3. 发病机制

肝脏脂质代谢受脂肪酸的摄取和输出、新脂肪生成和 β 氧化对脂肪利用的共同调节。当这些途径之间的平衡发生改变时, 肝脏脂质开始堆积, 炎症和纤维化途径的长期激活可能会加重肝脏疾病[9]。

3.1. 脂肪酸摄取

肝脏通过主动转运和被动扩散从循环中摄取脂肪酸, 在 MAFLD 患者中, 59%的脂肪酸来自血液循环[10]。肝脏对脂肪酸的摄取会导致肝脏脂肪变性, 当摄取过量时可能会导致脂毒性, 从而促进 MAFLD 的进展。不同的蛋白质参与肝脏对脂肪酸的摄取, 包括脂肪酸转位酶 CD36、脂肪酸转运蛋白(FATPs)和脂肪酸结合蛋白(FABPs) [9] [10]。病态肥胖患者肝脏中 CD36mRNA 和蛋白水平升高, 并且与游离脂肪酸水平相关[11]。人类 MAFLD 患者肝脏中 CD36 表达上调, 且 CD36 过表达可以促进人肝癌细胞对脂肪酸的摄取[12]。肝脏过表达 CD36 增加了正常脂肪饮食小鼠的肝脂摄取和脂肪变性。FATP2 和 FATP5 是肝脏中存在的两种主要 FATP 亚型[13], 在小鼠中敲除 FATP2 可减少肝脏中脂肪酸的摄取, 并改善高脂肪饮食诱导的肝脂肪变性。FATP5 基因缺失可导致小鼠肝脏甘油三酯和游离脂肪酸含量降低, 并且脂质能够从肝脏重新分布到其他代谢组织。在人类中, FATP5 启动子的多态性导致 FATP5 表达增加, 这与男性 MAFLD 患者肝脏脂肪变性程度较高有关[14]。FABP1 是肝脏中高表达的 FABP 亚型, 能够促进脂肪酸及其酰基辅酶 A 衍生物的运输、储存和利用, 可通过结合具有细胞毒性的游离脂肪酸, 促进其氧化或添加到甘油三酯中来发挥对脂毒性的保护作用[15]。FABP1 水平可能因疾病严重程度而异, 与肥胖对照组相比, 肥胖伴脂肪变性患者的 FABP1 蛋白水平高表达, 但在轻度纤维化的非酒精性脂肪性肝炎(NASH)患者中降低, 在晚期纤维化的 NASH 患者中进一步下降[16]。

3.2. 从头脂肪生成(DNL)

乙酰辅酶 A 羧化酶(ACC)、脂肪酸合酶(FAS)和硬脂酰辅酶 A 去饱和酶-1(SCD1)在调节肝脏新生脂肪生成中发挥重要作用。首先, 乙酰辅酶 A 通过 ACC 转化为丙二酰辅酶 A, 然后通过 FAS 将丙二酰辅酶 A 转化为棕榈酸酯, SCD1 催化硬脂酰辅酶 A 和棕榈酰辅酶 A 生成油酸酯和棕榈油酸酯, 新生成的脂肪酸经过多种生物修饰, 如去饱和、伸长、酯化等, 最终以甘油三酯的形式储存或以极低密度脂蛋白(VLDL)颗粒的形式输出[9] [17] [18]。肝脏 DNL 是 MAFLD 患者肝内甘油三酯产生和肝内甘油三酯含量的重要贡献者, 在肝脏脂肪变性发病机制中具有重要作用[18]。DNL 升高可引起肝脏脂肪变性和高甘油三酯血症, 棕榈酸酯的产生增加可能通过炎症和细胞凋亡的增加而导致脂肪性肝炎。与对照组相比, MAFLD 患者的 DNL 增加; 与肝脏脂肪较低的超重/肥胖受试者相比, 肝脏脂肪含量高的 DNL 增强[19]。所以, 未能有效调节 DNL 可能是 MAFLD 患者肝脏脂质积累的主要原因之一。

3.3. 脂肪酸氧化(FAO)

脂肪酸在线粒体中被氧化, 为肝细胞提供 ATP 和 NADH, 以促进糖异生并产生乙酰辅酶 A。抑制脂肪酸氧化, 会引起脂肪在肝脏中沉积, 从而诱发脂肪肝或脂肪变性[20]。FAO 功能受损会导致脂质堆积、活性氧(ROS)生成过多和氧化损伤, 从而引发 MAFLD [21]。ROS 和炎症引起的氧化应激(OS)是导致肝细胞死亡和组织损伤的重要机制。线粒体异常、多种抗氧化酶下调、谷胱甘肽(GSH)耗竭和依赖 GSH 的抗氧化剂活性降低、白细胞聚集和肝脏炎症是 MAFLD 中 ROS 过量产生的主要来源[22]。FAO 受肝脏中过氧化物酶体增殖物激活受体 α (PPAR α) 的调节, 脂肪酸通过激活 PPAR α 而刺激线粒体 β 氧化[23] [24]。肉碱棕榈酰转移酶 1 (CPT1)包含 CPT1A、CPT1B 和 CPT1C 3 种亚型, 其中 CPT1A 是线粒体脂肪酸 β 氧化的关键限速酶, 催化 β 氧化的限速步骤[25] [26]。CPT1 位于线粒体外膜, 它将酰基肉碱基

团与脂质偶联在一起,并促进线粒体外膜的转运。酰基肉碱转运后,定位于线粒体内膜的 CPT2 会从脂质分子上移除肉碱基团,进而进行脂肪酸的 β 氧化[27]。组蛋白脱乙酰酶 Sirtuin 6 可以通过激活 PPAR α 或抑制 miR-122 促进脂肪酸氧化,还能够直接调节酰基辅酶 A 合成酶长链家族成员 5(ACSL5)的脂肪酸氧化活性[28]。饮食中补充猪去氧胆酸(HDCA)可通过激活依赖于 PPAR α 的 FAO 途径来改善雄性野生型小鼠饮食诱导的 MAFLD,而在 PPAR α 基因敲除小鼠中,补充 HDCA 未观察到抗 MAFLD 作用[29]。相比于野生型小鼠,PPAR α 基因敲除小鼠在高脂饮食后,肝脏炎症恶化明显伴随促炎 M1 巨噬细胞群明显改变,血浆中甘油三酯和脂蛋白 B100 水平更高,而 β -羟基丁酸含量较低,过氧化物酶体基因功能显著下降[30]。在 MAFLD 中,PPAR α 通过上调脂质氧化和线粒体生物合成,以及抑制炎症基因转录而发挥保护作用[31]。一些 PPAR α 特异性激动剂,如 Wy14643 和非诺贝特,已被应用于 Mets 的治疗。

3.4. 脂质输出

除 FAO 外,肝脏以极低密度脂蛋白(VLDL)颗粒的形式分泌甘油三酯到外周组织,是降低肝脏脂质含量的另一个重要途径。载脂蛋白 B100(apoB 100)和微粒体甘油三酯转移蛋白(MTTP)是肝脏分泌 VLDL 和维持肝脂质稳态的关键成分。在内质网中,MTTP 催化 apoB100 的脂质化,形成原始的 VLDL 颗粒,原始颗粒被转移到高尔基体,通过与高尔基体融合进一步脂质化形成成熟的 VLDL 颗粒,随后通过 apoB 100 介导的机制分泌到血液中[32] [33]。VLDL 组装和分泌缺陷是 MAFLD 发病机制的关键促成因素之一。apo B 基因遗传缺陷(低 β 脂蛋白血症)和 MTTP 基因遗传缺陷(无 β 脂蛋白血症),与进行性肝病关系密切。肝脏中 MTTP 特异性缺失,可引起肝脂肪变性,并且完全抑制乳糜微粒和 VLDL 的分泌。在 MAFLD 小鼠遗传模型中,使用载体诱导肝脏 MTTP 的表达,可减少肝脏甘油三酯的积累,改善 VLDL 的分泌和输出[34]。总体而言,MTTP 和 apoB 100 的改变,尤其是在脂质超载的情况下,可能导致脂肪变性和脂毒性,从而促进 MAFLD 的进展。

3.5. 胰岛素抵抗(IR)

MAFLD 常与肥胖、T2DM、Mets 等疾病伴随出现,并且与一种或多种 Mets 相关,如高血压、向心性肥胖、血脂异常、IR 等。IR 是指机体葡萄糖利用障碍,循环中胰岛素水平代偿性增加,造成高胰岛素血症。IR 和 MAFLD 关系密切,IR 在肝脂肪变性和脂肪性肝炎中起着关键作用,多达三分之二的 T2DM 患者存在 MAFLD,MAFLD 患者罹患 T2DM 的风险是非 MAFLD 人群的 2 倍多[35]。肝脏 DNL 加重 MAFLD 患者的脂肪变性,DNL 发生率与全身和肝脏胰岛素敏感性之间存在很强的负相关关系[18]。IR 和 DNL 升高都能促进 NASH 的进展[36] [37]。多种酶介导 IR 过程,包括 κ 激酶 β 抑制剂(IKK-b)、c-Jun-N 末端激酶(JNK-1)和蛋白激酶 C(PKC),它们都会促进胰岛素受体底物(IRS)的丝氨酸磷酸化,从而减少葡萄糖摄取、糖原合酶活化以及叉头盒蛋白 O(FOXO)磷酸化,进而刺激肝脏葡萄糖生成,这在 MAFLD 相关的胰岛素信号转导中至关重要。游离脂肪酸、氧化应激(OS)和脂肪细胞介导的改变,是 IKK-b、JNK-1 和 PKC 影响 IRS 1/2 信号转导抑制的主要原因[35]。肿瘤坏死因子 α (TNF- α)、白细胞介素 1- β (IL-1 β) 和白细胞介素 6(IL-6)等炎性细胞因子可通过 JNK-1、IKK-b、S6K 和哺乳动物雷帕霉素靶蛋白(mTOR)诱导 IRS 1 丝氨酸磷酸化而引发 IR。脂肪细胞分泌脂联素,脂联素是已知的与 IR、脂质积累、炎症和 MAFLD 呈负相关的脂联因子,具有促进 FAO,葡萄糖利用和抑制脂肪酸合成作用[38] [39]。在 MAFLD 患者中,过量的游离脂肪酸通过下调 IRS 1 信号,减少外周葡萄糖利用和促进肝葡萄糖产生来促进 IR,而持续升高的葡萄糖和高胰岛素血症又会通过上调 SREBP1c 和 ChREBP 来刺激游离脂肪酸的 DNL,因此在 IR 和游离脂肪酸之间形成一个恶性循环。

4. 总结

MAFLD 作为全球高发的慢性肝病,与代谢综合征、心血管疾病及肝外恶性肿瘤密切相关,严重威胁人类健康。尽管近年来其发病机制研究取得显著进展,但病理过程复杂且尚未完全阐明。本文从脂质代谢失衡、炎症反应及 IR 等核心环节,系统综述了 MAFLD 的关键机制:包括脂肪酸摄取蛋白(CD36、FATP2/5)异常介导的肝内脂质蓄积、DNL 关键酶(ACC、FAS、SCD1)活性上调、线粒体 β 氧化(PPAR α /CPT1A 轴)功能抑制、VLDL 分泌缺陷(MTTP/apoB100 功能障碍)以及 IR 驱动的脂质-糖代谢恶性循环。目前,针对 PPAR α 激动剂、CD36 抑制剂及 MTTP 调控等潜在靶点的研究为 MAFLD 治疗提供了新方向,但临床仍缺乏特效药物。其异质性特征要求个体化干预策略,而现有临床研究在患者分层、疗效评价及长期随访方面存在局限性。未来可以进一步整合遗传易感性、表观调控及肠-肝轴交互作用等机制,借助多组学技术解析疾病分子网络;同时优化临床试验设计,提升治疗靶点验证的可靠性和转化效率,最终实现 MAFLD 的精准诊疗,改善患者预后及生活质量。

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