· 综述 ·

代谢相关脂肪性肝病合并抑郁障碍发病机制的研究进展

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DOI：10.3969/j.issn.1009-6574.2025.08.011

【摘要】 研究表明，代谢相关脂肪肝病与抑郁障碍常共同发生。为深入探讨两者之间的关系及其交织的病理生理机制，现回顾近年来关于两者发病机制的相关研究，涵盖神经递质失衡、系统性炎症、胰岛素抵抗、肠道微生物群失调、大脑结构变化、内分泌干扰物以及饮食习惯等方面，旨在分析这些潜在的机制联系，并展望未来的研究方向。

【关键词】 抑郁障碍； 代谢相关脂肪性肝病； 发病机制； 综述

基金项目：“脑科学与类脑研究”重大项目（2021ZD0202000）；甘肃省自然科学基金（25JRRA618）；兰州大学第二医院萃英学子科研培育计划项目（CYXZ2023-55）

Research progress on the pathogenesis of metabolism associated fatty liver disease combined with depressive disorder

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【**Abstract**】 Numerous studies have shown that metabolism associated fatty liver disease and depressive disorders often occur together. In order to delve deeper into the relationship between the two and their intertwined pathophysiological mechanisms, this article reviews recent studies on the pathogenesis of the two, covering neurotransmitter imbalance, systemic inflammation, insulin resistance, gut microbiota dysbiosis, structural changes in the brain, endocrine disrupters, and dietary habits, with the aim of analyzing these potential mechanistic links and looking ahead to the future research direction.

【**Key words**】 Depressive disorder; Metabolic associated fatty liver disease; Etiology; Review

Fund programs: Brain Science and Brain-like Research Major Program (2021ZD0202000); Natural Science Foundation of Gansu Province of China (25JRRA618); Cuiying Scholar Research Incubation Planning Project of the Second Hospital of Lanzhou University (CYXZ2023-55)

代谢相关脂肪性肝病（metabolic associated fatty liver disease，MAFLD）和抑郁障碍是现代社会中常见的疾病，两者之间存在复杂的相互关联[1]。MAFLD是指在代谢综合征（metabolic syndrome，MetS）的背景下，肝细胞发生脂肪变性，且排除了乙醇、病毒性肝炎、自身免疫或药物等已知原因导致的肝脏疾病[2]。MetS主要表现为胰岛素抵抗、高血压、血脂异常、肥胖和糖尿病等代谢紊乱。抑郁障碍则以持续的悲伤、兴趣丧失、疲乏无力、睡眠障碍、食欲改变、注意力不集中和自我评价低为主要症状的心理障碍[3]。

目前多项研究表明，MAFLD的存在及其严重程度与抑郁症状显著相关[1,4-5]。荟萃分析和孟德尔随机化研究显示，抑郁障碍会增加MAFLD的患病风险[6]。与非抑郁障碍受试者相比，抑郁障碍患者患MAFLD的可能性高出1.6～2.2倍[7]。在MAFLD女性患者中，抑郁障碍的风险增加约40%[8]。此外，MAFLD患者中常见的非肝脏疾病之一即为抑郁障碍[9]。在确诊的170例MAFLD患者中，约1/4存在抑郁障碍，且这一比例明显高于非MAFLD受试者。即便在控制了混杂因素后，MAFLD仍然被认为是新发抑郁和焦虑的独立危险因素[10]。一项大型队列研究发现，特别是在肥胖人群中，基线时患有抑郁障碍的人群在后续超声诊断中更易出现肝脂肪

变性及更严重的肝纤维化风险[11]。系统回顾与荟萃分析还发现，糖尿病、体重指数(body mass index，BMI)、女性、吸烟史及肺部疾病史等风险因素与MAFLD患者中抑郁障碍的高患病率相关[12]。尽管MAFLD与抑郁障碍之间的因果关系尚不明确，但存在多种可能的共病病理生理机制。本文通过概述现有证据，旨在探讨MAFLD与抑郁障碍之间的潜在发病机制联系。

一、神经递质失衡

神经递质是神经元之间传递信息的化学物质，能够激活或抑制目标神经元的功能。大量研究表明，抑郁障碍与5-HT、去甲肾上腺素(norepinephrine，NE)、多巴胺、GABA和谷氨酰胺等神经递质的失衡密切相关[13]，在MAFLD患者中也发现了类似的神经递质变化。因此，神经递质失衡可能是加重MAFLD患者抑郁水平的重要因素之一。

研究表明，高氨血症可能导致MAFLD患者体内5-HT和多巴胺的变化[14]。正常人的胃肠道细菌通过尿素酶对尿素的作用产生氨，而生成的氨在肝脏的尿素循环中被利用。然而，MAFLD患者存在尿素循环失调，可能导致高氨血症[15]。高氨血症会损害大脑内5-HT和多巴胺的生成，氨与多巴胺竞争性结合多巴胺转运体，减少多巴胺的再摄取，导致突触间隙中多巴胺水平升高；同时，氨也与NE和5-HT的合成酶竞争性结合，减少这2种神经递质的合成，从而增加MAFLD患者罹患抑郁障碍的风险[16]。GABA是大脑中主要的抑制性神经递质，而谷氨酰胺是主要的兴奋性神经递质。为了维持大脑的正常功能，GABA的抑制作用和谷氨酰胺的兴奋作用之间必须保持微妙的平衡。研究发现，MAFLD患者因肝脏脂肪变性，使得产生GABA的能力下降[17]，这可能导致GABA水平降低，前额叶皮层和枕叶皮层中的GABA能神经元减少，谷氨酸水平异常以及谷氨酸受体表达改变[18]。当GABA水平降低时，前额叶皮层和枕叶皮层中的GABA能神经元数量也会减少，进一步导致抑制性调控的减弱。这种变化可能导致大脑中兴奋性神经递质(如谷氨酸)水平异常增高，且谷氨酸受体的表达发生改变，其GABA和谷氨酰胺水平失衡则会导致神经兴奋性和抑制性失衡，从而影响情绪和行为。

色氨酸和酪氨酸是多种单胺类神经递质(如5-HT、NE、多巴胺)的前体，能够调节认知功能、情绪和情感。抑郁障碍患者体内肠道微生物群(gut microbiome，GM)的变化也会影响色氨酸代谢，导致色氨酸水平下降[19]。如前所述，抑郁障碍的特征是单胺类神经递质的缺乏，而L-色氨酸的生成减少在MAFLD相关抑郁障碍的发病机制中发挥作用。GM对MAFLD小鼠模型的生化分析表明，肠道菌群变化，色氨酸水平下降，导致单胺类神经递质缺乏，从而加重抑郁障碍。此外，色氨酸还具有调节肝细胞变性的作用，其水平的下降进一步加重了MAFLD的病情[20]。

总之，神经递质失衡是MAFLD和抑郁障碍之间关联的重要机制之一。MAFLD相关的肝脏炎症和纤维化可能导致神经递质的合成、释放、转运、降解和受体功能异常，从而影响神经递质在脑内的平衡，并导致抑郁症状的发生与发展。

二、胰岛素抵抗(insulin resistance，IR)

IR是指机体对胰岛素的敏感性降低，需要更多的胰岛素才能维持正常的血糖水平。IR是MetS的主要特征之一，也是许多慢性疾病(如MAFLD和抑郁障碍)的独立风险因素[21]。

IR是MAFLD的一个主要特征，导致肝细胞对葡萄糖的摄取和利用减少，从而促进脂肪堆积和肝脏炎症，最终形成肝纤维化和肝硬化。胰岛素敏感性的降低阻碍了其抑制肝脏葡萄糖和游离脂肪酸产生的关键作用，这种抵抗促使过量游离脂肪酸流入肝脏，引起肝脂肪变性[22]。此外，肝脏的结构性病变也会导致胰岛素信号传导受损。IR进一步加重MAFLD患者的肝脏脂肪堆积，加剧系统性炎症和纤维化[23]。MAFLD与IR之间形成相互影响的恶性循环。MAFLD患者存在的IR还会产生能穿过血脑屏障的神经毒性脂质(如神经酰胺、亚硝胺)，主要影响海马和前额叶皮质，加重神经退行性病变和认知功能障碍[24]。研究发现，IR对抑郁障碍有预测作用，可能是由于IR在大脑中诱导线粒体和多巴胺功能障碍，导致抑郁行为。在一项研究中，通过破坏小鼠大脑组织中的胰岛素受体评估IR在抑郁障碍中的作用，结果显示小鼠脑中IR逐渐诱导纹状体和伏隔核中的线粒体功能障碍和氧化应激，并提高单胺氧化酶水平，导致多巴胺清除率增加和多巴胺水平降低，从而引发抑郁行为[25]。同时，在抑郁障碍患者的大脑中，纤溶酶原激活物抑制剂-1水平升高会导致神经递质平衡受损，进一步加重患者的IR水平[26]。探讨IR是否作为抑郁障碍与MAFLD之间的中介因素的研究表明，抑郁障碍与IR相关，这意味着IR可能是驱动抑郁障碍患者MAFLD风险增加的原因[27]。

综上，IR是MAFLD的主要特征，同时与抑郁障碍密切相关。IR可作为中介因素影响MAFLD和抑郁障碍。

三、GM

GM是人体肠道的正常微生物，能够合成多种人体生长发育所必需的维生素，利用蛋白质残渣合成必需氨基酸，并促进铁、镁、锌等矿物元素的吸收。然而，在MAFLD患者中，GM常常出现失衡[28]。已有大量研究证实GM失衡与MAFLD纤维化程度和抑郁障碍水平密切相关[29-30]。

抑郁障碍患者的肠道菌群数量显著减少[31]，其中粪杆菌的数量与抑郁症状的严重程度呈负相关[32]。将抑郁障碍患者的GM转移到经过抗生素预处理的正常小鼠中，观察到小鼠出现类似抑郁行为[33]。在MAFLD患者中，GM正常组成发生改变，GM失调导致GM介导的局部黏膜炎症加剧，从而促进黏膜免疫功能障碍，进一步加重肝脏炎症和MAFLD的发展[34]。这些GM衍生的介质包括脂多糖、短链脂肪酸(short-chain fatty acids，SCFAs)、胆汁酸、胆碱和乙醇，其通过某些途径参与MAFLD和抑郁障碍的进展。LPSs诱导的IL-6和TNF-α水平升高，会影响大脑发育，并对行为和神经内分泌功能产生长期影响；同时，LPSs诱导的5-HT能神经元降解会导致焦虑和抑郁情绪的产生[35]。LPSs还会激活肝脏中的库普弗细胞和星状细胞受体，刺激MAFLD的炎性反应[36]。GM失衡会影响SCFAs的产生，而SCFAs含量下降会导致肠道屏障和线粒体功能受损，增加细菌和内毒素进入血液循环的风险[37]。此外，SCFAs含量下降会导致调节GABA受体和谷氨酸受体的表达与功能下降，增加抑郁风险[38]。研究证实，补充SCFAs可降低难治性抑郁症患者的焦虑和抑郁水平[39]，并能降低MAFLD患者的纤维化水平，对肝脏具有保护作用[40]。GM与胆汁酸的代谢有关，GM失调会导致胆汁酸水平升高[41]，而高胆汁酸水平可以增加血脑屏障通透性，促进细菌和内毒素进入大脑，引发神经炎症和抑郁障碍[42]；同时，MAFLD肝纤维化程度会影响胆汁酸水平，从而加重抑郁障碍，通过调节GM失衡可减少MAFLD患者的纤维化程度[43]。

总体而言，GM失调可能是MAFLD与抑郁障碍之间的重要中介因素。GM失调可导致系统性炎症、脂质代谢紊乱和IR，从而促进MAFLD的发展；而肝脏炎症又会进一步影响GM组成，形成恶性循环。此外，GM失调还会导致神经递质代谢紊乱、神经炎症和神经可塑性受损，从而促进抑郁障碍的发生和发展，改善GM失调有助于缓解MAFLD患者的肝纤维化程度与抑郁障碍水平。

四、大脑与系统性炎症

前额叶皮层是大脑中负责调节情绪、认知和行为的关键区域。在抑郁障碍中，前额叶皮层是受损最为显著的区域之一，其结构和功能的改变对抑郁障碍患者的治疗和预后产生重要影响[44]。研究发现，抑郁障碍患者的前额叶皮层通过正电子发射断层扫描显示出体积减小[45]。同样，MAFLD患者的前额叶皮层也检测到灰质萎缩，这可能导致其抑郁水平升高和认知能力下降[46]。

在抑郁障碍和MAFLD患者中均观察到前额叶皮层的灰质萎缩，表明前额叶皮层的结构改变可能是两者共病的中介因素。此外，研究指出，这种大脑结构变化可能源于MAFLD相关的肝脏脂肪变性引发的肝脏炎症和纤维化，进而导致全身炎性反应，而炎性抑制剂可能有助于减轻MAFLD患者大脑结构的变化[47]。系统性炎症与抑郁障碍之间也存在关联[48]，抑郁障碍患者的血液和脑脊液中炎性细胞因子水平升高，且炎性反应的激活程度与抑郁症状的严重性相关。系统性炎症可能导致星形胶质细胞因子的释放和氧化应激，从而影响前额叶皮层及其他脑区的功能，引发抑郁障碍[49]。炎性反应可导致细胞因子的释放和氧化应激，其中细胞因子能够穿过血脑屏障，影响神经细胞的功能和神经可塑性，从而损害前额叶皮层的功能[50]。此外，系统性炎症还可能引起海马体的萎缩，这一区域与学习、记忆及情绪调节密切相关，其损伤与抑郁障碍显著关联[51]。

总之，前额叶皮层损伤和系统性炎症是MAFLD与抑郁障碍之间关联的重要机制。这些机制可能通过多种途径相互影响，导致MAFLD患者抑郁障碍的发展。

五、外环境与饮食

内分泌干扰化学物质(endocrine-disrupting chemicals，EDCs)是一类广泛存在于环境中的化合物，能够模拟或干扰生物体内的自然激素，进而影响正常的内分泌功能[52]。研究表明，EDCs与MAFLD和抑郁障碍之间存在相关性[53-54]。

EDCs可激活与脂肪细胞分化相关的基因，增加脂肪细胞的数量和体积，干扰脂肪代谢，从而导

致脂肪在肝脏中异常积累，加速MAFLD的发生与发展[55]。EDCs通过抑制脂肪分解的关键酶(如激素敏感性脂肪酶)减少脂肪的氧化和能量释放，从而导致脂肪堆积[56]。此外，EDCs还与IR和系统性炎症有关。其与胰岛素受体结合，影响胰岛素信号通路，阻断正常的胰岛素信号传导[57]；同时，EDCs通过激活小胶质细胞释放炎性因子，可能破坏血脑屏障的完整性，使得炎性细胞和因子更容易进入大脑，影响大脑的发育和功能，促进抑郁障碍的发生[58]。EDCs还影响神经递质(如5-HT和多巴胺)的合成、释放和再摄取，这些神经递质与情绪调节密切相关[59]。

高胆固醇饮食是MAFLD和抑郁障碍的主要风险因素之一，会刺激MAFLD患者从简单的脂肪变性发展到非酒精性脂肪肝炎和肝硬化[60]，同时也增加了抑郁的发病率。相反，水果和蔬菜的高消费则被证实可以降低抑郁的发病率[61]。研究发现，高胆固醇饮食可能通过上调大脑中Toll样受体4(Toll-like receptor 4，Tlr4)的表达而引起抑郁和焦虑样行为[62]。

综上所述，EDCs可能在MAFLD与抑郁障碍之间起到桥梁作用。一方面，EDCs通过诱导脂肪肝和IR等代谢紊乱间接增加抑郁障碍的风险；另一方面，EDCs直接作用于中枢神经系统，可能导致或加剧抑郁症状。此外，高胆固醇饮食可能促进MAFLD与抑郁障碍的进展。因此，减少EDCs的暴露和控制其体内水平以及改善饮食结构可能有助于预防和治疗MAFLD和抑郁障碍。

六、总结与展望

系统性炎症、IR和GM失调通过神经递质失衡加重这两种疾病的严重程度。大脑结构的改变可能是系统性炎症的表现，同时内分泌干扰物和饮食习惯可能通过这些因素间接影响这两种疾病。因此，理解这些机制的相互作用对于揭示MAFLD和抑郁障碍之间的病理关系至关重要。

已有大量研究揭示了MAFLD和抑郁障碍之间的紧密联系，但未来的研究仍需进一步探索其共病机制，并进一步阐明两者共病的具体分子通路。鉴于MAFLD和抑郁障碍之间的密切关联，早期诊断和干预对于改善患者预后至关重要。未来的研究应致力于开发针对神经递质失衡、IR和GM失调的早期生物标志物，并设计个性化的治疗方案，以减少两者的共病发生率。此外，MAFLD和抑郁障碍的共病机制涉及多个系统和器官的相互作用。因此，未来的研究应加强多学科交叉合作，结合神经科学、内分泌学、微生物学和心理学等领域的知识，共同揭示这些复杂的病理机制。未来的研究应致力于开发针对MAFLD和抑郁障碍共病的综合治疗方案，特别是针对神经递质失衡、IR和GM失衡的联合干预措施。

综上所述，MAFLD与抑郁障碍之间的相互作用为探索代谢性疾病与精神障碍共病机制提供了重要的窗口。通过未来的深入研究和临床应用，可改善两者的预后。

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(收稿日期: 2024-10-19)
(本文编辑: 王影)