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文献综述 REVIEW

代谢组学在肝硬化及其并发症中的应用

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Application of metabolomics in liver cirrhosis and its complications

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Abstract

Liver cirrhosis is the end stage of a variety of liver diseases. Once liver cirrhosis progresses to the decompensated stage, various complications will develop, which will greatly reduce the quality of life and survival rate of patients. Metabolomics can reveal the metabolic changes closely related to the progression of liver cirrhosis by analyzing the metabolites in patients and provide new biomarkers for the early diagnosis and prognosis evaluation of liver cirrhosis and its complications, which is of importance in improving the prognosis of patients. This article reviews the recent advances in the application of metabolomics in liver cirrhosis and its complications.

Key Words: Liver cirrhosis; Metabolomics; Biomarker

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摘要

肝硬化是多种肝病的终末期阶段. 一旦肝硬化进展至失代偿期, 将会发生各种并发症, 降低患者生存质量及生存率. 代谢组学技术通过分析患者体内的代谢

物, 揭示了与肝硬化进展密切相关的代谢变化, 为肝硬化及其并发症的早期诊断和预后评估提供新的生物标志物, 对改善患者预后具有一定价值. 本文对代谢组学在肝硬化及其并发症中的应用进展作一综述.

关键词: 肝硬化; 代谢组学; 生物标志物

核心提要: 代谢组学技术通过分析代谢物揭示肝硬化的病理生理变化, 提供可用于早期诊断和预后评估的新生物标志物, 对改善患者预后具有重要意义, 本文着重回顾了代谢组学在肝硬化及其并发症中的应用, 以指导临床实践.

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0 引言

肝硬化是多种慢性肝病进展的终末期阶段, 表现为持续性肝脏炎症和损伤导致正常肝组织被纤维组织和再生结节替代, 肝脏结构和功能最终发生不可逆改变[1,2]. 据统计, 全球每年约有120万人死于肝硬化和79万人死于肝癌, 占总死亡人数的3.5%[3]. 肝硬化可被分为代偿期和失代偿期两个阶段. 代偿期患者一般无明显症状; 当肝硬化进展到失代偿期时, 患者可出现腹水、消化道出血以及肝性脑病等并发症, 甚至发展为慢加急性肝衰竭(acute-on-chronic liver failure, ACLF)和肝细胞癌(hepatocellular carcinoma, HCC)[4,5], 不仅严重影响患者的生活质量, 而且显著降低了患者的生存率[6]. 肝硬化的病因包括慢性病毒性肝炎、酒精性肝病(alcoholic liver disease, ALD)、非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)及自身免疫性肝炎(autoimmune hepatitis, AIH)等[7-9]. 各种病因的肝硬化患者存在共同的代谢紊乱特点, 包括糖代谢、脂质代谢、氨基酸代谢以及能量代谢紊乱[10-12]. 这些代谢紊乱常表现为胰岛素抵抗、糖异生增加、脂肪酸氧化受损、脂质合成与分解失衡、支链氨基酸及蛋白质生成减少、基础代谢率增加与能量利用效率降低等, 它们与疾病进展密切相关. 通过对代谢物变化的深入研究, 可以更好地理解肝硬化的病理生理机制, 进而开发出更有效的诊断与治疗策略.

代谢组学是对生物样本中所有小分子代谢物进行全面定性定量分析的组学技术, 用于揭示生物体内复杂的代谢网络和代谢过程[13,14]. 与其他组学技术相比, 代谢组学能够更直接地反映生物体的功能状态和生理变化[15-18]. 通过分析正常与疾病状态下的代谢物差异, 可以识别出潜在的生物标志物, 这对于疾病的早期诊断和治疗具有重要意义[19,20]. 代谢组学可分为靶向和非靶向代谢组学. 靶向代谢组学聚焦于特定代谢物或代谢途径, 主要用于特定代谢物的量化分析, 是研究特定代谢途径或生物标志物的首选方法[21]. 非靶向代谢组学是一种全面分析生物样本中所有可能存在的代谢物的方法, 通常用于探索疾病机制和新的生物标志物[22]. 代谢组学可以使用多种类型的生物样本, 包括血液、尿液、粪便、唾液、细胞和组织样本等[23,24]. 核磁共振(nuclear magnetic resonance, NMR)光谱法、气相色谱-质谱(gas chromatography-mass spectrometry, GC-MS)和液相色谱-质谱(liquid chromatography-mass spectrometry, LC-MS)是代谢组学中常用的三种技术[25,26]. NMR光谱法的优势在于不破坏样品、能提供丰富的结构信息, 且样品准备过程相对简单, 但局限性在于灵敏度较低且对复杂样品的解析能力有限[27]. GC-MS特别适用于分析挥发性小分子物质, 具有较高的灵敏度, 但分析非挥发性小分子物质时样本处理过程较为复杂[28]. LC-MS则适合分析非挥发性小分子物质, 常用于分析血液和尿液样本[29]. 代谢组学有助于识别肝硬化发生发展相关的代谢特征, 进一步探究肝硬化潜在的生物学机制及其诊断和预后的生物标志物[30-32]. 本文将对代谢组学在肝硬化及其并发症中的应用进展作一综述.

1 代谢组学在识别肝纤维化中的应用

持续的肝脏损伤会加剧肝纤维化的发展, 若不及时采取有效措施, 最终可能导致肝硬化[33,34]. 因此, 早期诊断肝纤维化是预防肝硬化的关键策略, 对于改善慢性肝病患者的预后至关重要[35]. 肝活检是诊断肝纤维化的金标准, 但存在侵入性、并发症风险和采样误差等不足. 近年来, 非侵入性诊断方法, 如瞬时弹性成像、天冬氨酸转氨酶与血小板比率指数(aspartate aminotransferase to platelet ratio index, APRI)、肝纤维化-4指数(fibrosis-4 index, FIB-4)等, 已广泛用于诊断肝纤维化, 但仍存在诊断准确性低等局限性[36,37]. 代谢组学通过分析患者血液或组织样本中的代谢物, 可用于发现敏感性和特异性更高的肝纤维化生物标志物. Xie等[38]利用牛磺胆酸、酪氨酸、缬氨酸和亚油酸等血清代谢物构建了机器学习模型, 用于区分早期和晚期肝纤维化患者, 该模型比APRI、FIB-4指数和天冬氨酸转氨酶/丙氨酸转氨酶等无创诊断方法的曲线下面积(area under the curve, AUC)更高, 敏感性和特异性也更高. He等[39]发现, 药物性肝损伤(drug-induced liver injury, DILI)相关肝纤维化患者体内多种代谢途径发生

了显著变化, 包括胆汁酸合成、脂质代谢和组氨酸代谢; 通过使用代谢组学方法鉴定出两组代谢指纹图谱, 一组可用于判断慢性DILI患者是否存在肝纤维化, 另一组可用于识别晚期纤维化, 在验证集中, AUC值分别为0.753和0.944. Gaggini等[40]揭示了脂质代谢障碍与丙型肝炎病毒(hepatitis C virus, HCV)感染患者的肝纤维化严重程度相关, 血清代谢物神经酰胺(18:1/22:0、18:1/24:0)、二酰甘油(42:6)和磷酸胆碱(40:6)的水平变化与肝纤维化严重程度相关. Batist等[41]利用血清^{1}H NMR谱建立代谢组学模型以预测HCV感染患者肝纤维化严重程度, 该模型比APRI和FIB-4等无创指标具有更高的敏感性和特异性, 预测中期和晚期肝纤维化的敏感性和特异性分别达到了97.6%和92.6%以及96.4%和95.1%. 代谢组学技术为肝纤维化的早期诊断提供了新的工具, 能够更准确地识别肝纤维化患者, 有助于早期采取针对性治疗, 以防止肝纤维化进展, 从而改善患者预后.

2 代谢组学在识别HBV肝硬化中的应用

随着乙型肝炎病毒(hepatitis B virus, HBV)疫苗接种的普及与高效抗病毒药物的出现, 全球范围内由慢性HBV感染引起的肝硬化发病率及死亡率均有所降低. 值得注意的是, 慢性肝炎病毒感染导致的肝硬化在某些地区的死亡率依然很高[3]. HBV感染可能会导致肝功能损伤, 进而引起脂质代谢变化. Arain等[42]发现, 与健康受试者相比, HBV肝硬化患者体内饱和脂肪酸与单不饱和脂肪酸水平升高, 而多不饱和脂肪酸水平降低. Yu等[43]也发现, 乙肝病毒复制活跃的患者的血清花生四烯酸水平显著降低. Fan等[44]发现, 对抗病毒治疗有反应的乙肝患者的花生四烯酸水平较高, 同时, 肝星状细胞中过氧化物酶体增殖物激活受体(peroxisome proliferators-activated receptors, PPAR)γ的表达上调. 花生四烯酸可能通过调节PPARγ的表达从而改善肝纤维化. Wu等[45]发现在慢性乙型肝炎发展为HBV肝硬化甚至肝癌的过程中, 溶血磷脂酰胆碱的水平逐渐降低. 在慢性乙型肝炎患者体内, 溶血磷脂酰胆碱合成减少, 同时更多地转化为溶血磷脂酸, 后者通过刺激细胞增殖和抑制细胞凋亡从而推动疾病进展. Xue等[46]发现, 乙酸、山梨醇、D-乳酸、己酸、α-萘胺、丁酸、磷酸、D-山梨醇和葡萄糖等代谢物可用于区分慢性HBV与HBV肝硬化患者. Zheng等[47]发现, 慢性HBV与HBV肝硬化患者的血清代谢物特征存在显著差异, 乙酸盐、甲酸盐、丙酮酸和谷氨酰胺等代谢物可以作为区分这两组患者的潜在生物标志物, 进一步证明了代谢组学在HBV肝硬化诊断中的应用价值.

3 代谢组学在识别酒精相关肝硬化中的应用

随着酒精消费的持续增长, ALD已成为发达国家中肝硬化的主要原因[9,48], 酒精相关肝硬化患者的病情通常比慢性肝炎病毒感染引起的肝硬化更为严重[49,50]. 酒精性肝硬化患者体内存在显著的代谢紊乱, 主要表现为脂质代谢紊乱、氨基酸代谢异常以及能量代谢失衡. Huang等[51]发现了与酒精性肝硬化进展相关的两组代谢指纹图谱, 分别包括38种和64种代谢物, 这些代谢物主要与脂质代谢、氨基酸代谢和三羧酸循环中间代谢产物相关, 并揭示了细胞能量供应相关代谢障碍是酒精性肝硬化进展的关键机制. 酒精代谢导致NADH/NAD$^+$比值增加, 进而抑制三羧酸循环中的关键酶, 干扰能量代谢, 这种变化还促使脂肪酸氧化转向脂质合成, 从而导致脂肪堆积和肝脏损伤. 此外, 酒精也会影响胆汁酸的合成与分泌, 石胆酸及其衍生物的蓄积将进一步加剧氧化应激及肝脏炎症, 从而导致肝损伤和纤维化. Meyer等[52]发现, ALD患者体内的鞘磷脂酶与自分泌运动蛋白活性增加, 导致鞘磷脂与磷脂酰胆碱水平降低, 可能影响细胞膜的完整性, 引发慢性炎症及干扰细胞信号传导. 此外, 磷脂酰胆碱在肝脏中参与脂质运输和代谢, 其水平降低可能导致肝脏脂肪堆积. 因此, 血清鞘磷脂、磷脂酰胆碱及溶血磷脂酰胆碱水平变化有助于识别酒精性肝硬化患者. Ascha等[53]发现, 酒精性肝硬化的患者肝脏再生S-腺苷甲硫氨酸能力受损, 这影响了甜菜碱-同型半胱氨酸甲基转移酶通路, 导致甜菜碱水平升高. 通过检测血清中的甜菜碱和瓜氨酸水平能够有效识别酒精性肝硬化患者(AUC = 0.84). Calzadilla等[54]发现, 与ALD非肝硬化患者相比, 肝硬化患者血清中甲基化核苷酸、γ-谷氨酰氨基酸、胆汁酸、犬尿氨酸和菜油甾醇水平升高, 而支链氨基酸、5-羟色胺和黄尿酸水平降低, 这些代谢物可作为判断疾病严重程度的生物标志物. Suciu等[55]发现, N-月桂基甘氨酸在酒精性肝硬化的诊断中显示出了极高的敏感性(100%)以及较高的阴性预测值(90%), 提供了一种潜在的高效诊断标志物. Yang等[56]发现, 胰高血糖素样肽-1和成纤维细胞生长因子21水平升高可能与酒精性肝硬化的进展相关.

4 代谢组学在识别代谢相关肝硬化中的应用

NAFLD作为一种与生活方式密切相关的代谢相关性肝脏疾病, 近期也被更名为代谢功能障碍相关脂肪肝病或代谢功能障碍相关性脂肪性肝病, 其在所有肝硬化病因中的占比相对较低, 但由于肥胖和2型糖尿病患者数量的持续增加, NAFLD相关肝硬化比重正逐年上升[9,57]. NAFLD是一种涉及氨基酸代谢、抗氧化物质平衡以及能量代谢等多种代谢途径紊乱的肝脏疾病[58]. 在NAFLD的不同阶段, 患者体内代谢物变化模式存在显著差异. Masarone等[58]发现, 从脂肪肝进展为非酒精性脂肪性肝炎乃至肝硬化的过程中, 患者体内脂肪酸氧化和氨基酸

代谢增强, 甘氨胆酸、牛磺胆酸、苯丙氨酸以及支链氨基酸等代谢物的水平普遍升高. 此外, NAFLD患者体内氧化应激反应显著增加, 导致谷胱甘肽(glutathione, GSH)大量消耗. 同时, 由于肝脏功能的受损, 合成GSH的能力下降, 削弱了肝脏对抗氧化损伤的能力, 氧化应激通过损伤肝细胞并激活炎症进一步加重了肝损伤[59].

5 代谢组学在识别药物相关肝硬化中的应用

DILI是常见的药物不良反应, 其临床表现缺乏特异性, 可能仅表现为无症状的肝功能异常, 也可能表现为急性肝衰竭[60,61]. DILI大多为急性, 通常预后较好, 但有相当部分患者可发展为慢性DILI, 甚至可能迁延为肝硬化甚至肝癌, 预后较差. DILI引起的肝硬化与TCA循环受阻、胆汁酸过量累积以及氨基酸代谢紊乱等多种代谢途径异常有关[62]. 某些药物及其代谢产物能够抑制三羧酸循环中的关键酶, 导致循环中间体的累积, 阻碍细胞的正常能量代谢, 进而影响线粒体功能, 增加活性氧的生成, 导致氧化应激加剧和细胞损伤, 从而使肝脏更易受到药物毒性作用的影响[62]. Chen等[62]对DILI伴或不伴肝硬化患者的血清进行代谢组学分析, 发现一组与肝硬化密切相关的代谢指纹图谱. 该指纹图谱联合APRI能够更准确地区分肝硬化和非肝硬化患者(AUC = 0.914), 明显优于单独使用APRI(AUC = 0.573).

6 代谢组学在识别自身免疫相关肝硬化中的应用

AIH是一种由自身免疫介导的炎症性肝病[63]. 在持续的肝脏炎症损伤下, AIH可能进展为肝硬化[64]. 在AIH相关肝硬化进展中存在明显能量代谢障碍, 主要表现为脂肪分解和蛋白质分解增加[65]. Li等[65]发现了一组特定的代谢指纹图谱, 能够有效的区分AIH相关肝硬化与非肝硬化患者, 其诊断效能优于APRI; 从这组指纹图谱中筛选出中胆红素原和6-羟基烟酸这两种关键代谢物, 并基于它们的强度比值, 构建了一个新的诊断参数, 其在诊断AIH相关肝硬化患者中具有较高的准确性(AUC = 0.865).

7 代谢组学在识别失代偿期肝硬化中的应用

肝硬化一旦进展到失代偿期, 患者的肝脏代谢功能将显著下降, 主要表现为氨基酸和脂质代谢紊乱. Fischer等[66]发现, 失代偿期肝硬化患者的脂质代谢途径与代偿期肝硬化患者存在显著差异, 包括磷脂酰胆碱、酰基肉碱、硬脂酸衍生物和15-羟基十五碳五烯酸等代谢物. 其中, 9-己烯酰基肉碱和15-羟基十五碳五烯酸是区分二者的重要代谢物. Chen等[62]发现了一组与肝硬化失代偿相关的代谢指纹图谱, 可准确区分代偿期和失代偿期肝硬化(AUC = 0.954). Li等还发现溶血磷脂酸(8:0/0:0)和7α-羟基胆固醇这两种代谢物可准确区分代偿期和失代偿期肝硬化, 并展现出较高的准确性(AUC = 0.792). 此外, 失代偿期肝硬化患者体内蛋白质分解显著增加, 血清中蛋白质分解标志物及蛋白质分解不完全产物水平显著升高.

此外, 随着肝硬化进展到失代偿期, 患者的死亡风险将明显增加. 因此, 准确评估患者从代偿期向失代偿期的进展风险至关重要. 肝静脉压力梯度(hepatic venous pressure gradient, HVPG)>10 mmHg的代偿期肝硬化患者进展为失代偿期肝硬化的风险较大, 但测量HVPG是一种侵入性操作, 存在一定局限性[67]. Nicoară-Farcău等[68]利用靶向代谢组学对代偿期肝硬化患者的血清进行分析, 在发生肝硬化失代偿及肝脏相关死亡事件的患者中, 神经酰胺(d18:1/22:0)水平较低, 而蛋氨酸水平较高; 这两种代谢物可以有效识别发生肝硬化失代偿及肝脏相关死亡风险较高的肝硬化患者. 使用HVPG、Child-Pugh评分和治疗类型构建的模型C指数为0.748, 在此基础上加入这两种代谢物后, 模型的预测准确性显著提高, C指数提高至0.808; 将这两种代谢物与Child-Pugh评分和治疗类型联合的模型C指数为0.785, 这与基于HVPG的模型有着相似的预测效果. 综上, 代谢组学有助于区分肝硬化代偿期和失代偿期患者, 且可利用代谢物构建预测模型, 评估肝硬化患者进展至失代偿期的风险.

8 代谢组学在识别HCC中的应用

HCC是全球范围内癌症相关死亡的主要原因之一[69]. 代谢组学可用于探索HCC的生物标志物, 对于HCC的早期诊断具有重要意义[70,71]. 氨基酸与脂质代谢途径紊乱是HCC的一个显著特征[72-74]. 目前已发现一系列与HCC相关的潜在生物标志物, 如鹅脱氧胆酸、甘氨胆酸等[75]. Ressom等[76]发现, HCC患者血清中鞘磷脂和磷脂酰胆碱相关代谢物水平显著高于肝硬化患者. 同时, HCC患者血清中参与胆汁酸生物合成的代谢物水平显著降低. Nenu等[77]发现, 与代偿期肝硬化患者相比, HCC患者血清中1,25-二羟基胆固醇、肉豆蔻酸棕榈酸酯、25-羟基维生素D2、12-酮脱氧胆酸、溶血磷脂酰胆碱(21:4)和溶血磷脂酰乙醇胺(22:2)水平更高, 神经酰胺水平更低.

Han等[75]通过分析HCC、肝硬化患者及健康对照组的血清, 识别出HCC相关的特征代谢物, 包括鹅脱氧胆酸、甘氨胆酸、溶血磷脂酰胆碱(20:5)、溶血磷脂酰乙醇胺(18:0)、琥珀酰腺苷和尿苷. 基于这些代谢物构建的诊断模型, 在区分HCC与肝硬化方面展现出高于甲胎蛋白(alpha-fetal protein, AFP)的诊断性能(AUC = 0.938), 敏感性为93.3%, 特异性为86.7%. Di Poto等[78]进一步探讨了HCC患者血清中代谢物的变化, 发现HCC患者血清中缬

氨酸、丝氨酸、异亮氨酸、α-D-氨基葡萄糖1-磷酸和亚油酸等代谢物水平较高. 利用LASSO回归选择了与HCC相关的一组代谢物和临床协变量构建模型, 诊断HCC的准确性优于AFP(AUC = 0.808 *vs* AUC = 0.723). 此外, 利用这些代谢物与临床协变量构建的支持向量机模型展现了更优的性能(AUC = 0.857). Kim等[79]通过蛋氨酸、脯氨酸、鸟氨酸、庚酰肉碱和辛酰肉碱五种代谢物构建模型, 诊断HCC的准确性优于AFP(AUC = 0.82 *vs* AUC = 0.75). 上述研究表明, 利用代谢组学构建的模型有助于提高HCC诊断的准确性, 显示了代谢组学在HCC诊断方面的潜力.

9 代谢组学在识别ACLF中的应用

ACLF是一种表现为肝功能急剧恶化、凝血功能障碍以及多器官功能衰竭的临床综合征[80,81]. ACLF通常是在慢性肝病的基础上, 由感染、酒精以及药物等一系列急性诱因所导致的[82,83]. ACLF的短期死亡率很高[84], 因此, 探索能够预测ACLF进展和预后的新型生物标志物尤为重要. Bajaj等[83]通过代谢组学分析发现, 微生物来源的化合物(包括芳香族化合物、次级或磺化胆酸和苯甲酸)和雌激素代谢物水平升高以及磷脂水平降低与ACLF的进展、住院以及30天内死亡相关. López-Vicario等[85]通过代谢组学发现了16种与疾病状态显著相关的脂质介质, 其中, 白三烯E4水平变化与疾病进展一致, 能够区分不同严重程度的ACLF; 白三烯E4、脂氧素A5以及环氧酮十八烯酸与患者的短期死亡率相关; LTE4和12-羟基十二烷酸可作为区分ACLF和非ACLF患者的生物标志物. Amathieu等[86]通过比较肝硬化患者与ACLF患者血清中的代谢物, 发现ACLF患者血清中乳酸、丙酮酸、酮体、谷氨酰胺、苯丙氨酸、酪氨酸和肌酐等代谢物水平升高, 揭示了ACLF患者存在能量和氨基酸代谢异常. 代谢组学不仅揭示了ACLF患者的代谢变化, 并且能够利用这些代谢物构建模型用于预测疾病进展. Zhang等[87]发现了与ACLF患者疾病进展及90天死亡率显著相关的代谢物, 并据此构建了预测模型, 在验证集中展示出良好的预测性能(AUC = 0.88, AUC = 0.83). Weiss等[88]利用4-羟基-3-甲氧基苯乙醇硫酸盐、半乳糖醛酸和己酰肉碱三种血清代谢物构建了预测ACLF患者短期死亡的模型, 相比于MELD-Na评分, 代谢物模型能更准确地预测ACLF患者的短期死亡. 代谢组学技术能够揭示ACLF患者中复杂的代谢变化, 为理解ACLF的病理生理特征、识别早期生物标志物和构建预测模型提供新的见解.

10 结论

综上所述, 代谢组学为不同病因肝硬化的早期诊断和监测疾病进展提供了新的生物标志物, 并揭示了HCC和ACLF特有的代谢组学特征. 与传统诊断方法相比, 基于代谢物的诊断模型显示出更高的诊断准确率. 然而, 代谢组学在实际应用中仍存在一些局限性[89,90]: 首先, 代谢组学研究需要多种技术平台进行分析, 分析成本较高; 其次, 代谢物易受到外界环境因素的影响, 若样本未及时处理或储存不当, 可能会导致代谢物发生变化, 从而影响最终的分析结果. 尽管如此, 代谢组学在未来的医学研究和临床应用中仍具有巨大的潜力, 随着分析技术的改进、样品处理方法的优化以及分析成本的减少, 代谢组学的应用门槛正在逐渐降低, 已成为探索疾病生物标志物不可或缺的工具之一.

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