

基于组学技术的中医药防治肝纤维化基础研究进展

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摘要: 肝纤维化是多种慢性肝病的关键共性病理环节, 可进展为肝硬化、肝癌等重大恶性疾病, 然而目前仍缺乏高效、靶向的治疗药物。传统中医药防治肝纤维化的临床疗效明确, 但复方成分的复杂性及作用机制欠明, 严重阻碍其临床精准应用和国际化推广。近年来, 多模态高通量组学技术快速发展, 凭借其系统性分析、大数据运算和靶点精准预测的集群优势, 为阐释中医药治疗重大疑难疾病的科学内涵提供了强大技术支撑。尤其是转录组学、蛋白质组学及代谢组学等多维整合策略, 可全景式解析中药复方及单体成分改善肝纤维化的关键信号通路群、细胞表型转化模式和细胞外基质代谢稳态的深层分子网络, 并助力中药有效成分群及新型生物标志物的筛选与评价。本文梳理了近5年应用多组学技术探讨中医药防治肝纤维化的基础研究进展, 通过汇总“药物-靶点-通路-表型”关联网以深度解析中药调控肝星状细胞活化等表型改变及逆转肝纤维化的核心机制。未来研究需进一步深入挖掘多组学技术的交叉融合与动态分析方法, 助力精准辨识中药调控核心靶标网络, 并系统解析复方配伍规律的科学内涵, 以期开发高效靶向抗肝纤维化药物及个体化诊疗策略提供理论依据。

关键词: 肝纤维化; 抗肝纤维化药(中药); 转录组学; 蛋白质组学; 代谢组学

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Advances in the basic research on traditional Chinese medicine for prevention and treatment of hepatic fibrosis based on omics technology

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Abstract: Hepatic fibrosis is the common key pathological link of various chronic liver diseases and can progress to malignant diseases such as liver cirrhosis and hepatocellular carcinoma; however, there is still a lack of effective targeted therapeutic drugs at present. Traditional Chinese medicine (TCM) has a marked clinical effect in the prevention and treatment of hepatic fibrosis, yet its precise clinical application and global promotion are greatly limited by the complex components of compound prescriptions and unclear mechanism of action. In recent years, multimodal high-throughput omics technology has achieved rapid development, providing strong technical support for elaborating on the scientific connotation of TCM in the treatment of complex diseases due to its advantages of systematic profiling, big-data analytics, and precise target prediction. In particular, integrated transcriptomic, proteomic, and metabolomic strategies comprehensively elucidate key signaling networks, cellular phenotypic transitions, and extracellular matrix metabolic homeostasis modulated by TCM compounds and monomers and assist in the screening and assessment

of effective component groups and novel biomarkers. This article systematically reviews the advances in basic research on TCM prevention and treatment of hepatic fibrosis based on multi-omics technologies in the past five years, summarizes the “drug-target-pathway-phenotype” regulatory network, and elaborates on the core mechanisms of TCM in regulating hepatic stellate cell activation and reversing hepatic fibrosis. Future studies should further delve into the interdisciplinary integration and dynamic analytical methodologies of multi-omics technologies, precisely identify the core regulatory target networks modulated by TCM, and systematically unravel the scientific connotation of compatibility rule in compound prescriptions, in order to provide a theoretical basis for developing efficient targeted drugs for hepatic fibrosis and individualized diagnosis and treatment strategies.

Key words: Hepatic Fibrosis; Anti-Hepato Fibrosis Agents (TCD); Transcriptomics; Proteomics; Metabolomics

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肝纤维化作为多种慢性肝病向肝硬化发展的关键病理进程,是中医药防治研究的关键领域。传统研究虽在揭示中药抗炎、抗氧化和抑制肝星状细胞(hepatic stellate cell, HSC)活化等作用机制方面取得进展,但对中药整体性、系统性抗肝纤维化调控网络的理解仍存在局限。近年来,转录组学、蛋白质组学及代谢组学等技术的飞速发展与深度整合,为中医药防治肝纤维化的基础研究提供了全新视角。这些高通量、系统性的技术手段显著拓展了对中药干预复杂病理过程的认知边界,揭示中药防治肝纤维化并非通过单一靶点的作用,而是涉及多靶点、多通路、多层次(包括基因表达、蛋白功能、代谢物谱、微生物群落及网络调控)协同互作的复杂调控体系。尤为重要的是,组学技术不仅为解析中医药药理核心机制提供了系统的分子证据与全局图谱,还能以前所未有的深度和广度持续鉴定潜在作用靶点、信号通路及具有诊断或疗效预测价值的生物标志物,从而深入阐释中药整体调节与多组分协同作用的科学内涵,为肝纤维化的现代化精准防治奠定坚实理论基础。

1 不同组学技术在中医药防治肝纤维化研究中的应用

组学技术体系涵盖转录组学、蛋白质组学及代谢组学等多维生物学领域,其核心优势在于通过系统性、高灵敏度分析获取海量数据,为深入挖掘肝纤维化病理靶点及作用机制提供技术支撑。

1.1 转录组学在中医药防治肝纤维化研究中的应用 基于转录组测序技术,近年多项研究系统揭示了中药通过调控相关基因群及生物过程改善肝纤维化的关键分子机制。Guo等^[1]通过转录组学分析发现三七皂苷R1可调控覆盖脂质分解等生物过程,尤其通过激活过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor gamma, PPAR- γ)信号通路,从而抑制TGF- β 1诱导的HSC活化并缓解小鼠肝纤维化损伤。此外,转录组

测序揭示养阴活血汤^[2]和圣草次苷^[3]均可上调PPAR- α 靶点。通过靶点相关性深入分析发现,养阴活血汤可同时下调脂肪酸合酶、脂肪酸去饱和酶2的表达,并激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路,改善脂质代谢与氧化应激,从而缓解CCl₄诱导的大鼠肝纤维化;而圣草次苷则通过上调PPAR- α 以抑制NLRP1(NOD样受体热蛋白结构域相关蛋白1)/NLRC4(NOD样受体含CARD结构域蛋白4)炎症小体及NET(中性粒细胞胞外诱捕网)形成,阻断HSC活化与巨噬细胞炎症因子释放,从而缓解硫代乙酰胺诱导的小鼠肝纤维化损伤。

TGF- β /Smad信号轴的异常激活直接参与肝纤维化发生、发展过程,是影响HSC活化的另一重要机制。基于RNA测序技术筛选315个靶点,研究证实,复方苦参注射液能稳定Smad7/TGF- β 1互作以再平衡Smad2/Smad3信号传导,抑制HSC活化及细胞外基质形成,从而缓解CCl₄注射和蛋氨酸-胆碱缺乏(methionine and choline deficient, MCD)饮食诱导的小鼠肝纤维化损伤,并延缓肝癌发生^[4]。通过前期对24个差异表达的microRNA(miRNA)靶点群进行系统分析与分子生物学实验验证,发现疏肝健脾方可通过上调miR-193a-3p以抑制其靶标TGF- β 2的表达,从而阻断HSC的活化、增殖和迁移,有效缓解CCl₄诱导的小鼠肝纤维化以及TGF- β 1活化的肝星状细胞系JS-1损伤^[5]。此外,借助mRNA测序技术的研究表明,芪甲柔肝方主要通过靶向抑制TGF- β 信号通路,并调控氧化还原、脂肪酸代谢和细胞黏附等多个生物学过程,从而显著逆转大鼠肝脏炎症暴发及纤维化进展^[6]。

在AMPK通路方面,除养阴活血汤外,益气柔肝汤借助转录组测序技术亦被证实能下调丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)/磷酸肌醇3-激酶(phosphoinositide 3-kinase, PI3K)-蛋白激酶B

(protein kinase B, Akt)通路、上调PPAR/AMPK通路,改善内质网应激、细胞凋亡和自噬过程,从而缓解CCl₄诱导的大鼠肝纤维化损伤^[7]。此外,基于环状RNA(circular RNA, circRNA)测序技术,片仔癯报道可直接调控91个差异circRNA(其中上调基因58个,下调基因33个)网络表达谱,主要通过Bnip2(BCL2/腺病毒E1B 19 kDa相互作用蛋白2)、Plekho1(含pleckstrin同源结构域的蛋白O1)、Kn1(动粒支架蛋白1)及Acbd5(含酰基辅酶A结合结构域的蛋白5)等circRNA靶点调控TNF/PI3K-Akt/IL-17/MAPK信号通路及成纤维细胞增殖等生物过程,从而缓解CCl₄诱导的小鼠肝纤维化损伤^[8]。

基于转录组测序技术,研究者还发现龙胆水煎剂可有效上调线粒体自噬标志物帕金蛋白(parkin RBR E3 ubiquitin protein ligase, Parkin)表达并激活Parkin信号通路,抑制HSC活化和胶原沉积^[9]。笔者团队应用多组学技术筛选5个生物过程,发现四物汤主要抑制M2型巨噬细胞的激活以减少促纤维化细胞因子的释放,阻遏中性粒细胞激活及其胞外陷阱的形成,并调节Fas/FasL信号通路促进HSC凋亡,缓解胆管结扎诱导的小鼠肝纤维化损伤^[10]。Lan等^[11]借助转录组学测序筛选出天黄方中47个上调基因和225个下调基因,发现中药主要抑制CCL2(C-C趋化因子配体2)-CCR2(C-C趋化因子受体2)轴及其下游的MAPK/核因子 κ B(nuclear factor kappa B, NF- κ B)信号通路以减轻炎症和纤维化,缓解CCl₄和MCD饮食诱导的小鼠肝纤维化。

1.2 蛋白质组学在中医药防治肝纤维化研究中的应用 基于质谱的蛋白质组学技术,可全面解析蛋白质序列、表达丰度、功能、化学反应性及相互作用等信息,不仅为转录组学发现提供了关键的蛋白水平印证与翻译后修饰细节,更在揭示中药调控肝纤维化关键信号通路机制方面发挥核心作用。在调控PI3K/Akt信号通路及其相关网络方面,基于蛋白质组学技术发现,茵陈术附汤通过下调血小板衍生生长因子受体 β (platelet-derived growth factor receptor β , PDGFR β)表达并抑制PI3K/Akt信号通路(阻断黏着斑及细胞外基质受体互作),缓解3,5-二乙氧基羰基-1,4-二氢三甲基吡啶诱导的小鼠胆汁淤积性肝纤维化^[12]。同样聚焦于该通路及其介导的细胞外基质异常沉积过程,一项基于串联质谱标签定量蛋白质组学技术的研究揭示,余甘子低分子量活性组分可调控195种与细胞外基质组织、肌动蛋白结合及细胞外泌体相关的差异表达蛋白;进一步关联性分析比对发现,该组分能够通过下调I型胶原蛋白 α 2链、整合素 α V亚基、Toll

样受体2、血管紧张素转换酶以及PDGFR β 等5个关键靶点的表达,显著抑制细胞外基质-受体相互作用、局灶黏附及PI3K-Akt信号通路,从而有效缓解CCl₄诱导的大鼠肝纤维化损伤^[13]。而芪甲柔肝汤则通过抑制PI3K/Akt的重要下游Akt/mTOR通路,下调半胱天冬酶(Caspase)促凋亡蛋白、调控氧化还原及胶原合成过程,缓解CCl₄诱导的大鼠肝纤维化^[14]。此外,运用高效液相色谱-质谱技术,Zhang等^[15]揭示金银花-连翘药对的主要活性成分(槲皮素、山柰酚、木犀草素)通过下调 α -平滑肌肌动蛋白、环氧合酶-2、TGF- β 1等关键分子,并抑制炎症、氧化应激和胶原沉积等核心生物过程,缓解大鼠肝纤维化损伤。

1.3 代谢组学在中医药防治肝纤维化研究中的应用 代谢组学技术通过系统分析生物体液(如尿液、血清)的代谢物组成差异,不仅能够筛查肝纤维化的风险预测生物标志物,还可深入揭示疾病进程中复杂的代谢紊乱,并阐明中药通过调控关键代谢通路及网络所发挥的调节作用。在基础代谢调节方面,基于氢核磁共振和质谱的代谢组学技术,茵陈五苓散被证实可通过调节氨基酸代谢、糖代谢、甘油磷脂代谢及肠道菌群代谢(如促进尿素循环、降低血氨积累、减轻氧化应激),缓解小鼠肝纤维化^[16]。在肠道菌群代谢调控方面,借助气相色谱-质谱联用和液相色谱-质谱联用代谢组学技术发现,连翘脂素可通过促进肠道短链脂肪酸生成(乙酸、丙酸及丁酸)并恢复胆汁酸代谢稳态,修复肠上皮屏障及调控胆酸代谢基因表达,缓解CCl₄诱导的肝纤维化^[17]。在机制通路解析方面,运用代谢组学技术分析显示,五指毛桃及其关键成分芹素可通过调控谷胱甘肽/谷胱甘肽过氧化物酶4通路,诱导HSC铁死亡,从而缓解CCl₄/MCD诱导的肝纤维化^[18]。醋制莪术-三棱药对的乙酸乙酯提取物经研究证实,可靶向调控PI3K/Akt/eNOS和TGF- β 1/Smad信号通路,进而改善牛磺酸与次牛磺酸代谢,缓解CCl₄诱导的小鼠肝纤维化损伤^[19]。

2 多组学技术联合应用在中医药防治肝纤维化研究中的应用

多组学技术及其整合分析策略的快速发展,为系统解析中药复方复杂作用机制提供了全新研究范式。通过整合转录组学、蛋白质组学、代谢组学等多维度数据,并结合网络药理学等计算方法,显著提升了中药复方药理机制研究的系统性与可靠性。

转录组学与网络药理学相结合的研究表明,姜黄精油、逍遥散等能够通过抑制TGF- β 1/Smads、PI3K/Akt和

Akt/FoxO3信号通路,减轻肝纤维化相关的病理改变^[20-21]。进一步通过高通量测序与网络药理学等多组学分析发现,逍遥散还可靶向STAT3/NF- κ B/PPAR- γ 信号通路,调控细胞外基质沉积、炎症反应及脂代谢等肝纤维化相关病因环节^[22]。代谢组学联合网络药理学的应用证实,甘草-丹参药对及其关键活性成分槲皮素可通过调控戊糖/葡萄糖醛酸互变代谢过程,并抑制花生四烯酸代谢通路,从而缓解大鼠肝纤维化模型中的胶原沉积与炎症反应^[23]。此外,醋莪术及其活性成分(如呋喃二烯)通过抑制PI3K/Akt/mTOR通路的磷酸化,促进BAX/Caspase-3介导的HSC凋亡,进而延缓肝纤维化进程^[24]。基于色谱-质谱技术与网络药理学整合的研究揭示,鳖甲软肝胶囊的入血原型成分(包括金丝桃苷、土莫酸、常春藤皂苷元等)能够显著下调CDK2、CDK6和PIK3CG等关键靶蛋白的表达,抑制HSC增殖并缓解肝纤维化病理进展^[25]。类似地,其入肝活性成分可靶向下调PDGF-AA,抑制M2型巨噬细胞与HSC之间的交互作用,以减轻小鼠肝纤维化损伤^[26]。

此外,转录组学常与蛋白质组学、代谢组学等其他组学技术联合应用,共同揭示基因表达-蛋白质功能-代谢表型之间的调控网络关系。通过转录组测序和非靶向代谢组学技术,Wu等^[27]发现桃红四物汤的肝脏保护作用主要与调控脂代谢途径相关,可显著上调49种代谢物及下调151种代谢物,其中主要通过抑制ACSL4(长链酰基辅酶A合成酶4)的表达并促进线粒体自噬,从而缓解硫代乙酰胺诱导的小鼠脂代谢紊乱及肝纤维化损伤。基于转录组测序与蛋白质组学联合技术的研究表明,片仔癀可通过调控928个差异转录本和138个差异蛋白,增强免疫过程,抑制炎症细胞浸润与胶原沉积,从而缓解小鼠肝纤维化损伤^[28]。在传统转录组-蛋白质组-代谢组多组学联合的基础上,随着单细胞测序和空间代谢组学等新兴技术的引入,中医药抗肝纤维化机制研究实现了从分子网络到细胞微环境的跨越式突破。例如,通过整合转录组与单细胞测序技术发现,肝纤方能够抑制CCL2介导的巨噬细胞招募,阻断Trem2⁺CD9⁺巨噬细胞亚群的扩增及PDGFR α ⁺PDGFR β ⁺肌成纤维细胞的活化,并调控TGF- β /EGFR、PDGFB/PDGFR α 等配体-受体相互作用,从而减轻CCl₄诱导的大鼠肝纤维化损伤^[29]。此外,综合空间代谢组学、蛋白质组学及代谢组学的分析显示,黄芩甲醇提取物的关键入肝成分黄芩素和汉黄芩素,能够直接抑制胞质磷脂酶A2活性,阻断花生四烯酸代谢及其下游NF- κ B炎症通路,同时改善甘油磷脂代谢紊乱,最终缓解CCl₄诱导的小鼠肝纤维化^[30]。

基于中药活性成分可通过菌群-宿主互作网络调控宿主代谢与基因表达的特性,微生物组学与代谢组学的整合分析策略在揭示中医药抗肝纤维化机制方面展现出独特优势。例如,通过16S rRNA肠道菌群测序与非靶向代谢组学联用技术的研究发现,二氢杨梅素能够通过重塑肠道菌群结构、改善宿主肝脏代谢紊乱,并下调TNF- α 和IL-1 β 等炎症因子表达,从而缓解小鼠肝纤维化损伤^[31]。茵陈五苓散则通过调节*Barnesiella*、*Ruminococcus*和*Christensenella*等关键菌属,增加丁酸盐产生菌(如*Bifidobacterium*、*Coprococcus*、*Anaerostipes*),进而改善精氨酸生物合成、鞘脂代谢及丙氨酸-天冬氨酸-谷氨酸代谢通路,减轻大鼠肝纤维化损伤^[32]。芪甲柔肝汤通过改善肠道紧密连接蛋白表达、调控*Turicibacter*等核心肠道菌群及宿主代谢物,修复肠道屏障功能,调节肠道菌群代谢轴,从而缓解大鼠肝纤维化损伤^[33]。鳖甲煎丸则通过降低厚壁菌门丰度、提高拟杆菌丰度并影响菌群代谢物,调控肠道菌群代谢轴,抑制TMA-FMO3-TMAO生成,阻断TMAO激活的PI3K/Akt信号通路,进而减轻胆管结扎诱导的HSC活化及大鼠肝纤维化^[34]。此外,综合运用16S rRNA测序、非靶向与靶向代谢组学技术的研究表明,当归芍药散可通过调控肠道菌群(如*Veillonella*等),促进短链脂肪酸生成,改善胆汁酸代谢并修复肠道屏障,以减轻大鼠肝纤维化损伤^[35]。而基于宏基因组学与非靶向代谢组学的研究揭示,益气健脾方能够抑制TGF- β /Smad3信号通路、促进巨噬细胞向M2表型极化、降低氧化应激与炎症反应,并通过重塑肠道菌群稳态(如抑制*Calditerrivibrio_nitroreducens*降解18 β -甘草次酸),缓解小鼠肝纤维化损伤^[36]。

3 总结与展望

包括转录组学、蛋白质组学、代谢组学及微生物组学在内的多组学技术,系统性揭示了中药抗肝纤维化的多靶点协同机制。转录组学主导发现中药复方及成分(如养阴活血汤、三七皂苷R1、圣草次苷)通过激活PPAR- γ / α 通路抑制TGF- β 1诱导的HSC活化,或通过调控miR-193a-3p/circRNA靶向TGF- β /Smad、MAPK/PI3K-Akt等通路。蛋白质组学进一步补充揭示了关键蛋白相互作用的精细模式,如茵陈术附汤抑制PI3K/Akt介导的细胞外基质形成及沉积过程;芪甲柔肝汤阻断Akt/mTOR促凋亡信号转导。代谢组学则深入阐释了中药调节代谢稳态与新型作用机制,如茵陈五苓散调控尿素循环重编程、连翘脂素恢复胆汁酸稳态及鳖甲煎丸抑制TMA-FMO3-TMAO代谢轴以调控

肠道菌群。多组学整合分析更有助于系统性解析中药的整体作用靶点网络(如发现鳖甲煎丸通过“菌群-TMAO-PI3K/Akt轴”抑制HSC活化),并证实中药可同时影响免疫调节(抑制Trem2⁺CD9⁺巨噬细胞)、代谢稳态、细胞凋亡/自噬等多个生物学层面协同作用,从而缓解肝纤维化进程。

此外,不同组学技术在阐释中药药效机制方面展现出高度互补性。转录组学擅长系统性揭示中药如何影响具体基因表达调控网络,例如miRNA/circRNA调控TGF- β 相关通路;蛋白质组学能够提供中药调控翻译后修饰及功能蛋白互作证据,如中药影响PI3K/Akt通路及其磷酸化水平改变;代谢组学则可直接反映药物介入下病理代谢表型转变情况,例如影响脂质/氨基酸代谢紊乱。针对同一通路改变时,转录组与蛋白质组数据往往呈现一致性变化,例如复方苦参注射液对Smad7/TGF- β R1的调控在mRNA和蛋白水平均得到验证;而代谢组学可补充相关蛋白介入的下游代谢效应,如醋莪术对牛磺酸代谢的改善。不同中药虽可共性靶向核心通路群(如TGF- β 、PI3K/Akt等),但其作用特性各不相同,如疏肝健脾方强于miRNA调控,茵陈五苓散侧重肠道菌群代谢轴修复,五指毛桃独擅诱导铁死亡影响肝纤维化进程,这一现象生动体现了“同通路异环节”或“同病理异机制”的中药干预策略。

目前,组学技术在中医药研究中的应用仍存在一定的局限性,主要体现在以下两个方面。(1)技术挑战。样本异质性(如病变肝组织不同病理分区存在分子特征差异)影响组学数据获取的可靠性,且多组学整合算法仍不成熟,尤其跨组学关联分析技术尚不完善,例如转录组-蛋白质组-代谢组等多组学技术之间的多维动态调控网络;此外,中药成分复杂,药物多组分间存在协同或拮抗作用,以及药物在体内可能通过代谢转化为其他成分发挥作用,导致目标活性物质的追踪与功能解析较为困难。(2)机制验证深度不足。当前研究虽运用多组学技术揭示了TGF- β /Smad、PI3K/Akt等通路对肝纤维化进程的关键作用,但新兴机制如特定非编码RNA(circKn1)、菌群-宿主共代谢物(丁酸盐/TMAO)及铁死亡等过程,需通过单细胞或空间组学进一步验证细胞特异性、微空间分布及靶点网络之间互作模式。因此,未来中医药组学研究领域应进一步融合先进技术并深度分析,例如应用单细胞组学解析肝纤维化微环境细胞互作模式(巨噬细胞-HSC对话),利用空间代谢组学定位药效成分在组织中的精确分布,并引入类器官模型模拟人源化病理微环境以验证组学发现。同时,可通过精准检测患者体内多

组学生物标志物水平(如细胞外基质蛋白、炎症相关代谢物等),对患者群体进行科学分型。在此基础上,结合个体化辨证分析,运用针对不同靶标网络的中药复方组合对患者实施精准干预,实现从中西医结合防治肝纤维化的经验医学向精准医学的范式转变。

当前,多组学技术已成为系统解析中药“多成分-多靶点-多通路”协同抗肝纤维化作用机制的关键研究策略。然而,面对中药成分间复杂相互作用及靶点动态调控网络等科学问题,现有组学技术在机制解析的深度与精度方面仍存在一定局限。未来可通过开发高覆盖度的新型组学检测技术、建立动态药效-靶点互作分析平台,并优化多组学数据整合算法模型,助力提升中医药抗肝纤维化机制研究的系统性和精准性,为中药现代化发展提供强有力的技术支撑。

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