Advances in Clinical Medicine 临床医学进展, 2026, 16(5), 881-886
Published Online May 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1651884

Hans汉斯

肝纤维化研究进展：机制、诊断与治疗

杜豪杰[1]，刘　涛[2*]

[1]湖北民族大学医学部，湖北　恩施
[2]恩施土家族苗族自治州中心医院肝胆胰脾外科，湖北　恩施

收稿日期：2026年4月12日；录用日期：2026年5月6日；发布日期：2026年5月13日

摘　要

肝纤维化是多种慢性肝病进展为肝硬化及肝癌的关键病理过程，其核心机制为肝星状细胞(HSCs)活化及细胞外基质(ECM)异常沉积。研究表明，TGF-β1/Smad等信号通路、代谢重编程、非编码RNA及免疫细胞相互作用共同参与HSCs的调控，推动纤维化进展。流行病学上，病毒性肝炎仍为主要病因，而非酒精性脂肪性肝病相关纤维化呈上升趋势。诊断方面，非侵入性检测技术不断发展，但肝活检仍为金标准。治疗上，抗纤维化药物、中药活性成分及靶向分子治疗取得一定进展，基因编辑等新技术展现出潜在应用前景。

关键词

肝纤维化，肝星状细胞，机制研究，诊断与治疗

Research Progress in Hepatic Fibrosis: Mechanisms, Diagnosis and Therapy

Haojie Du[1], Tao Liu[2*]

[1]Health Science Center, Hubei Minzu University, Enshi Hubei
[2]Department of Hepatopancreatobiliary Surgery, The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi Hubei

Received: April 12, 2026; accepted: May 6, 2026; published: May 13, 2026

Abstract

Hepatic fibrosis is a critical pathological process in which various chronic liver diseases progress to liver cirrhosis and hepatocellular carcinoma. Its core mechanism lies in the activation of hepatic

*通讯作者。

文章引用: 杜豪杰, 刘涛. 肝纤维化研究进展: 机制、诊断与治疗[J]. 临床医学进展, 2026, 16(5): 881-886.
DOI: 10.12677/acm.2026.1651884

stellate cells and abnormal deposition of extracellular matrix. Studies have demonstrated that signaling pathways such as TGF-β1/Smad, metabolic reprogramming, non-coding RNAs, and crosstalk with immune cells are jointly involved in the regulation of HSCs, thereby promoting fibrogenesis. Epidemiologically, viral hepatitis remains the leading etiology, while fibrosis associated with non-alcoholic fatty liver disease is on the rise. In terms of diagnosis, non-invasive detection techniques have been continuously developed, yet liver biopsy is still the gold standard. In treatment, certain progress has been made in anti-fibrotic drugs, active ingredients of traditional Chinese medicine, and targeted molecular therapy, and novel technologies such as gene editing have shown promising application potential.

Keywords

Hepatic Fibrosis, Hepatic Stellate Cells, Mechanistic Research, Diagnosis and Therapy

1. 肝纤维化基础理论

1.1. 肝纤维化的流行病学特征

肝脏疾病世界负担重，每年死亡率占全球死亡人数的 3.5% [1]，其中作为肝纤维化晚期阶段的肝硬化死亡率位列第 11 位[2]。病毒性肝炎仍是肝纤维化主要病因。一项关于印度难民的调查显示，人群 HBsAg 阳性率达 8.9%，其中 HBeAg 阳性率高达 60.7% [3]。此外，HCV 感染在全球影响约 7100 万人，其中 23% 的感染者存在晚期纤维化或肝硬化[4]。与此同时，非酒精性脂肪性肝病(NAFLD)相关肝纤维化的流行率持续上升，已成为发达国家慢性肝病的首要原因[5]。这些数据表明，肝纤维化的流行病学特征具有地域和人群异质性，病毒性肝炎仍是发展中国家的主要病因，而 NAFLD 相关纤维化在发达国家和代谢综合征人群中快速增长。

1.2. 肝纤维化的病理机制

肝纤维化的核心病理过程是肝细胞损伤后，HSCs 从静息态向肌成纤维细胞表型活化，大量分泌 ECM 如 I 型胶原，导致肝脏结构重构[6]。HSCs 活化受多种信号通路调控，其中 TGF-β1/Smad 通路是经典的促纤维化通路。研究发现，钙结合蛋白 S100A11 通过与 SIRT6 竞争性结合 Smad2/3，抑制其去乙酰化，从而激活 TGF-β1 信号通路，促进 HSC 活化和 ECM 沉积[7]。代谢重编程在 HSC 活化中扮演关键角色：CPT1A 是线粒体脂肪酸 β-氧化的限速酶，在 NASH 患者的 HSCs 中表达显著升高，且与纤维化程度正相关；抑制 CPT1A 可通过降低线粒体活性，抑制 TGF-β1 诱导的 HSCs 活化[8]。非编码 RNA 也参与 HSCs 功能调控，如长链非编码 RNA lnc-ADD3-AS1 在胆道闭锁患者的肝组织中高表达，可促进 HSCs 的增殖、迁移并抑制其凋亡[9]。免疫细胞与 HSCs 的交互作用同样重要，巨噬细胞表面的 MerTK 被 Gas-6 激活后，分泌的可溶性介质可促进 HSCs 的迁移、增殖及 α-平滑肌肌动蛋白表达[10]；而 B 淋巴细胞在 NAFLD 模型中具有双向作用，抗体缺陷的 IgMi 小鼠可完全免受肝脂肪变性和纤维化，提示致病性抗体的关键作用[11]。肝淋巴系统的功能紊乱也参与纤维化进展，其可通过影响门静脉高压、腹水形成等过程，促进肝纤维化发展[12]。这些研究表明，肝纤维化是多细胞、多通路协同激活 HSCs 的结果。

1.3. 肝纤维化的分子生物学研究进展

肝纤维化的分子生物学机制涉及基因表达调控及信号通路激活等多个层面。转录组学研究发现，肝纤维化患者中多个基因表达异常，如 CXCL9、THBS2、MGP 等在肝纤维化中呈现表达变化[13]；而在 NAFLD 模型中，高糖高脂饮食和蛋氨酸胆碱缺乏饮食诱导的基因表达谱存在差异，蛋氨酸胆碱缺乏饮食模型更易诱导纤维化相关基因表达[14]。信号通路的异常激活是肝纤维化的核心分子事件。TGF-β1/Smad 通路是经典的促纤维化通路[15]，S100A11 通过调控 Smad3 的去乙酰化激活 TGF-β1 信号[7]。此外，Wnt/β-catenin 通路、Notch 通路、TNFα 通路等也参与 HSC 活化[16]。综上，肝纤维化的分子机制是多层面、多通路协同作用的结果。

2. 肝纤维化的临床诊断技术

2.1. 非侵入性肝纤维化诊断技术

非侵入性诊断技术因避免肝活检的创伤性和取样误差，已成为肝纤维化诊断的重要手段。血清标志物组合模型如 FIB-4、APRI、GPR、Kings Score 等在不同病因的肝纤维化中表现出不同的诊断效能。在慢性乙肝患者中，GPR、Kings Score 和 S-Index 对显著纤维化(≥F3)、晚期纤维化(≥F4)和肝硬化的诊断均有显著作用，其中 GPR 的诊断效能优于 APRI 和 FIB-4 [17]。

2.2. 影像学在肝纤维化诊断中的应用

影像学技术在肝纤维化诊断中扮演关键角色。基于影像学的非侵入性技术如瞬时弹性成像(TE)、声辐射力脉冲成像(ARFI)等广泛应用于临床[18] [19]。剪切波弹性成像(SWE)在肝纤维化诊断中也表现出良好的效能，灵敏度和特异性分别为 80.7%和 70.4% [20]。

此外，多模态超声弹性成像结合算法可同时分级诊断肝纤维化、炎症和脂肪变性，优于单一临床指标[21]。CT 技术如低剂量双能 CT 灌注成像可通过测量脾脏血流动力学参数预测高危食管静脉曲张[22]。MR 弹性成像(MRE)的诊断准确性最高。MRE 在慢性乙肝患者中诊断显著纤维化(≥F2)优于 TE 和 ARFI [18]。

2.3. 生物标志物在肝纤维化诊断中的作用

生物标志物在肝纤维化诊断中具有重要价值，可分为直接标志物和间接标志物。直接标志物如III型胶原前肽(PRO-C3)、VI型胶原前肽(PRO-C6)在 NAFLD 患者中与肝纤维化程度显著相关[23]。间接标志物如 FIB-4、APRI 也有一定的诊断肝硬化价值[24]。

2.4. 肝纤维化诊断的“金标准”与局限性

肝纤维化的病理诊断被广泛认为是评估肝脏健康状况的金标准。肝活检作为一种历史悠久的诊断方法，自 1883 年首次由 Paul Ehrlich 进行以来，经过技术的不断改进，已成为诊断多种肝脏疾病的重要工具[25]。尽管非侵入性方法在肝纤维化的诊断中取得了显著进展，肝活检仍然是评估肝纤维化的最终标准。其在组织学分析中的准确性和可靠性使其在许多研究中被用作对比的基准[26]。但是，肝脏组织学检查也存在一定局限性，肝活检作为一种侵入性操作，具有创伤风险和穿刺部位不准确等问题，这些因素限制了其广泛应用[27] [28]。此外，肝活检的取样误差和观察者间的变异性也对结果的准确性产生影响[29]。

2.5. 新型肝纤维化检测技术

新型检测技术的发展显著提高了肝纤维化诊断的准确性和可及性。血清学技术如血清二硫苏糖醇氧

化能力可作为排除显著纤维化的生物标志物[30]；而基于胶原代谢产物的 ADAPT 评分(年龄、糖尿病、PRO-C3、血小板计数)在 NAFLD 患者中判断肝硬度也有一定意义[23]。分子成像技术如 PET/CT 使用碳-11 标记的氨基甘油探针，可通过检测水甘油通道蛋白的表达，诊断肝纤维化[31]。肝最大容量测试通过测量肝功能酶活性，诊断肝纤维化的效能优于 TE 和血清标志物[32]。这些新型技术的应用为肝纤维化的早期诊断和预后评估提供了更多选择。

3. 肝纤维化的治疗策略

3.1. 抗纤维化药物的临床试验

抗纤维化药物的研发聚焦于抑制 HSCs 活化、调节胶原代谢及抗炎等靶点。扶正化瘀片通过抑制 TGF-β1/Smad 通路，减轻硫代乙酰胺诱导的肝纤维化；而三草颗粒通过调控 TGF-β1 信号通路发挥抗纤维化作用[15]。在 HCV 相关纤维化患者中，PPARγ 激动剂可通过降低 PRO-C3 水平抑制纤维化进展[33]。尼达尼布作为多靶点酪氨酸激酶抑制剂，在特发性肺纤维化中表现出抗纤维化作用，在肝纤维化中的应用值得探索[34]。中药成分如柴胡皂苷通过 caspase-3 依赖和非依赖途径诱导 HSCs 凋亡，从而抑制肝纤维化[35]；而小檗碱通过抑制自噬诱导 HSCs 凋亡，其机制与 miR-30a-5p/ATG5 轴相关[36]。

3.2. 基因编辑技术在肝纤维化治疗中的潜力

基因编辑技术为肝纤维化治疗提供了新的策略。CRISPR/Cas9 技术可编辑 HSCs 中的关键基因，如敲除 CPT1A 可抑制 HSCs 活化和肝纤维化[8]；而编辑 IL-10 基因的间充质干细胞可通过抑制炎症和 HSCs 活化，减轻肝纤维化[37]。然而，该技术在应用于肝纤维化治疗时仍面临一些挑战，如靶点和非靶点位点的结构变异以及靶向递送效率等问题[38]。TALEN 技术可在间充质干细胞中插入 IL-10 基因，其分泌的 IL-10 可抑制 HSC 活化和胶原合成[37]；而锌指核酸酶技术可编辑 α1-抗胰蛋白酶基因，逆转 α1-抗胰蛋白酶缺乏相关的肝纤维化[39]。这些技术为肝纤维化的治疗带来了新的希望，但在递送效率、特异性和安全性方面仍需进一步研究[40]。

4. 肝纤维化的未来展望

未来肝纤维化研究应聚焦通路交叉、细胞互作与精准靶点三大方向开展深度突破：以 TGF-β1/Smad、Wnt/β-catenin、Hippo/YAP 信号串扰为核心，解析 S100A11、CPT1A 介导的代谢–信号耦联调控网络；以巨噬细胞 MerTK/Gas-6 轴、B 淋巴细胞与肝星状细胞交互为切入点，挖掘纤维化微环境关键调控节点；围绕 lnc-ADD3-AS1、CPT1A 等特异性分子，结合 CRISPR/Cas9、ZFN 等基因编辑技术，开发靶向肝星状细胞的精准干预策略，推动肝纤维化可逆性调控与临床转化。

但是，肝纤维化领域仍存在诸多争议和挑战。非侵入性技术的标准化制定仍需解决，抗纤维化药物的疗效和安全性仍需大规模临床验证。此外，肝纤维化的异质性如不同病因和阶段的纤维化机制差异，给精准治疗带来挑战。未来需加强基础研究与临床转化的结合，推动肝纤维化诊断和治疗的标准化和个性化。

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