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文献综述 REVIEW

肝纤维化的基因治疗

刘 娜, 张晓岚

■背景资料
肝纤维化的发生机制是机体对炎症的修复反应, 是多种慢性肝病共同的病理学基础, 是慢性肝病发展为肝硬化的中间环节. 如果能阻滞或逆转肝纤维化进展, 将会提高患者的生存质量, 在很大程度上改善肝病患者的预后.

刘娜, 张晓岚, 河北医科大学第二医院消化科 河北省石家庄市 050000
作者贡献分布: 文献检索、资料分析和论文撰写由刘娜完成, 选题和审校由张晓岚完成.
通讯作者: 张晓岚, 050000, 河北省石家庄市, 河北医科大学第二医院消化科. xiaolanzh@126.com
电话: 0311-66002951
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Gene therapy for hepatic fibrosis

Na Liu, Xiao-Lan Zhang

Na Liu, Xiao-Lan Zhang, Department of Gastroenterology, the Second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei Province, China
Correspondence to: Professor Xiao-Lan Zhang, Department of Gastroenterology, the Second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei Province, China. xiaolanzh@126.com
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Abstract
Hepatic fibrosis is a common pathological process of chronic liver diseases, characterized by increased synthesis and relatively low degradation of extracellular matrix (ECM) resulting from their dynamic imbalance. Recent progress in molecular biology techniques has made it possible to treat hepatic fibrosis with gene therapy. At present, the commonly used method is to induce the expression of exogenous genes by transducing enough therapeutic genes into injured liver to delay or cure liver fibrosis.

Key Words: Hepatic fibrosis; Gene; Therapy

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摘要
肝纤维化是慢性肝病共有的病理改变, 其本质是以胶原为主的细胞外间质(extracellular matrix, ECM)合成增多, 而降解相对减少, 两者失去动态平衡, 致使过多ECM沉积于肝内. 近年来随着分子生物学技术的发展, 肝纤维化的基因治疗成为可能. 目前, 常用的一般方法是将足够的治疗性基因导入受损的肝脏, 使外源基因得到表达调控, 达到延缓和治愈肝纤维化的目的.

关键词: 肝纤维化; 基因; 治疗

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■同行评议者
刘海林, 主任医师, 上海交通大学医学院附属第九人民医院消化内科

0 引言
肝纤维化是慢性肝病晚期的组织学变化, 是一种在损害因子持续作用下渐进的病理过程. 以细胞外间质(extracellular matrix, ECM)增加为特征, 同时伴有肝实质的广泛破坏和再生, 导致肝小叶和肝血管结构的紊乱, 最终可引起肝功能失代偿、腹水、上消化道出血等一系列并发症[1-2]. 近年来随着肝纤维化的分子机制逐渐阐明, 从而使肝纤维化的基因治疗成为可能[3-6]. 肝纤维化的形成是多种因素参与并长期相互作用的过程, 因此, 肝纤维化的基因治疗也应采取综合措施[7-12]. 本文针对目前肝纤维化的基因治疗进展作一综述.

1 细胞因子的作用
1.1 转化生长因子β(transforming growth factor, TGFβ) 是肝纤维化形成过程中的关键细胞因子之一. 可以促进肝星状细胞(hepatic stellate cell, HSC)分泌大量ECM, 抑制肝细胞增生, 诱导肝细胞凋亡, 抑制基质金属蛋白酶(matrix metalloprotainase, MMP)合成, 使ECM降解减少[13-14]. 因此, 阻断TGFβ信号转导通路就可以阻断肝纤维化进展[15-16]. 有人构建了表达TGFβⅡ受体细胞外区域的复制缺陷型腺病毒载体AdCAT-βTR, 通过门静脉注射实现其在肝脏的局部表达, 以阻断内源性TGFβ信号通路. 结果表明, 注射后大鼠肝脏纤维黏连蛋白(fibronectin, FN)、TGFβ1等与对照组比较显著减少, HSC及Kupffer细胞的活化被抑制, 显示出良好的抑制肝纤维化的作用. 更重要的是给予AdCAT-βTR后, 大鼠肝功能

■研发前沿
肝纤维化的基因治疗是慢性肝病研究的重点和热点, 近年的研究报道主要集中于TGFβ、HGF、ALR等细胞因子和HSC细胞活化、凋亡相关基因的表达调控.

逐渐恢复, 血清ALT、AST水平显著下降, 表明以腺病毒为载体将TGFβ基因转导入体内是治疗肝纤维化非常有效的方法. Ueno *et al*构建了表达TGFβⅡ型受体完整细胞外位点与人免疫球蛋白Fc片段融合蛋白的重组腺病毒载体, 可以表达一种可溶性的受体分子片段, 与TGFβ竞争性结合, 阻断TGFβ的生物学活性. 在接受腺病毒后的5-7 d达到高峰, 注射重组腺病毒的大鼠可以显著减轻二甲基亚硝胺诱导的肝纤维化的发生. 这些研究结果均证明阻断TGFβ信号传导通路, 可以有效阻断肝纤维化的形成和发展[17-19].

1.2 肝细胞生长因子的作用 在肝纤维化形成过程中, 肝细胞的相对体积和绝对数量都显著减少. 因此, 刺激、促进肝细胞的再生也是防治肝纤维化的重要策略和措施. 肝细胞生长因子(hepatic growing factor, HGF)是一种多功能细胞因子, 能刺激多种类型细胞分化、增殖及迁移, 对肝再生具有强大的促进作用[20-21]. Xia *et al*[22]将裸露HGF表达质粒静脉注射到经胆总管结扎引起肝硬化的大鼠中, 发现肝脏Ⅰ、Ⅲ型胶原沉积明显减少, TGFβ1的表达受到抑制, 肝纤维化程度明显减轻. 随后, 人们利用一些缺陷病毒如逆转录病毒、腺病毒等作为基因的载体, 也取得了一定的效果[23]. 还有学者通过腺病毒介导将HGF和截短型TGFβⅡ型受体联合转入肝硬化大鼠体内, 发现肝纤维化明显好转, 肝脏功能恢复, 肝细胞再生旺盛[24]. 提示HGF在体内可刺激肝细胞有丝分裂, 促进肝细胞增殖, 可以作为肝纤维化基因治疗的有效靶点[25].

1.3 肝再生增强因子(augmenter of liver regeneration, ALR) 比HGF具有更强的促肝细胞分裂活性, 对CCl_4诱发的肝损伤有明显的保护作用. 研究表明, ALR通过上调γ干扰素的表达, 抑制自然杀伤细胞的活性, 去除抑制肝再生的因素, 达到促进肝再生和逆转肝纤维化的目的. 有人构建了ALR真核表达质粒, 以基因治疗的方式观察对急性肝损伤的保护作用, 发现急性肝衰竭大鼠的存活率显著高于对照组, 并显著降低外周血ALT和AST水平[26].

1.4 白介素-10(interleukin-10, IL-10) 是肝纤维化间质炎症的重要炎症介质因子[27-28], 并对肝纤维化发生起调节作用, 因而是阻断肝纤维化过程基因治疗的重要靶点[29-32]. 研究证实, 肝星状细胞表达IL-10水平的下降可能是肝纤维化形成的重要原因[33-35]. 用含有大鼠IL-10基因的腺病毒载体通过尾静脉转染CCl_4肝损伤大鼠, RT-PCR检测HSC的Ⅰ、Ⅳ型胶原mRNA表达和分泌明显低于空载体组和空白对照组, 证实IL-10可以抑制HSC表达和分泌Ⅰ、Ⅳ型胶原, 对肝纤维化起负调节作用. 利用电穿孔技术将外源IL-10基因导入CCl_4肝损伤大鼠, 结果证实胶原Ⅰα、TGFβ1、FN均明显下降, 肝纤维化程度减轻[36]. 将外源IL-10基因导入硫代乙酰胺肝损伤大鼠, 结果同样证实胶原Ⅰα、TGFβ1、TNFα明显下降[35]. IL-10的基因治疗为肝纤维化提供了良好的应用前景. 如能把IL-10基因导入肝脏, 使之在肝脏局部高效长时间表达, 则有望抑制肝纤维化发展[37-39].

1.5 其他细胞生长因子 多种细胞生长因子, 如血小板衍生生长因子(platelet-derived growth factor, PDGF)[40], 角质细胞生长因子(karatinocyte growth factor, KGF), 胰岛素样生长因子(insulin-like growth factor, IGF)[41-43]等也可以促进HSC增殖, 加速肝脏纤维化. 研究证实KGF可以显著促进HSC增殖, 促进细胞由G_0/G_1期进入S期, KGF刺激后, cyclin D1蛋白表达明显升高, P21waf1蛋白表达下降, 表明KGF对HSC有显著促增殖作用, 在肝纤维化的发生中有重要意义. 而重组新型人KGF异构体(K102)可以抑制肝纤维化大鼠成纤维细胞增殖、分化, 显著降低ALT、AST水平, 肝组织胶原蛋白染色可见胶原纤维明显减少[44]. IGF与肝纤维化的关系也非常密切, 应用低剂量重组IGF于肝硬化大鼠, 发现肝细胞功能、门静脉高压、肝纤维化均显著改善, 肝硬化相关的肝外表现也得到改善[45]. 随机临床对照实验表明, IGF1替代疗法可以提高肝硬化患者血清白蛋白水平, 改善能量代谢状态, 但仍需要进一步的临床实验证实[46].

2 抑制HSC活化和促进HSC的凋亡

HSC活化、增殖是肝纤维化发生发展的中心环节[47-49]. 因此, 最为有效的抗肝纤维化基因治疗还是针对HSC的基因治疗途径[50-52]. 用携带外源Smad7基因的重组复制缺陷型腺病毒AdSmad7感染大鼠原代HSC, 结果显示AdSmad7可在HSC中高效表达, TGFβ1对HSC的活化作用被有效阻断[53].

在HSC凋亡的调节中, 可溶性Fas配体(sFasL)与Fas系统是细胞凋亡调节过程中的重要因素. 对sFasL诱导的HSC细胞凋亡研究发现, sFasL诱导的HSC凋亡是一种蛋白和RNA合成依赖性的过程. 如果以环磷酸胺阻断蛋白的合成或者以放线菌素D阻断RNA的合成, sFasL诱导

■应用要点
肝纤维化的基因治疗是国内外研究的热点, 近年来取得飞速发展, 逐渐成为最有希望逆转肝脏纤维化的治疗方法, 具有广阔的应用前景.

的HSC细胞凋亡即受到抑制. 对HSC表达的细胞凋亡抑制基因*bcl-2*和*bcl-xl*的水平进行半定量测定, 发现早期的HSC表达水平显著高于晚期培养的HSC活化而成的成纤维细胞. 因此, 从HSC的细胞凋亡入手, 也是探索肝纤维化基因治疗的重要途径[54-59].

3 端粒酶在肝纤维化中的作用

端粒是真核细胞染色体末端特殊的帽状结构, 端粒本身维持一定的长度对于细胞的染色体末端的稳定性、正常的有丝分裂过程都是必须的. 端粒长度的维持主要依赖端粒酶的活性. 大量的证据表明, 在纤维化的肝脏中, 端粒酶的活性变得不稳定或显著降低. 以表达端粒酶蛋白亚单位的重组表达载体转染人的成纤维细胞系, 可以使端粒酶阴性的细胞系继续维待细胞的正常状态. Rudolph *et al*[60]将端粒酶的mRNA转入端粒功能不良的肝细胞中, 结果显示可以减轻肝纤维化的病理损害, 恢复肝功能. 当用表达端粒酶基因的腺病毒载体感染小鼠肝细胞时, 小鼠出现腹水消失、体质量增加、血清ALT水平下降和肝细胞增殖活性升高. 研究还发现, 端粒酶RNA基因能部分抑制TGFβ的功能, 提高其抗纤维化效果. 提示通过表达端粒酶的基因治疗措施是慢性肝脏疾病包括肝纤维化基因治疗的重要途径[61].

4 RNA干扰技术在治疗肝纤维化中的应用

RNA干扰(RNA interference, RNAi)是新近发展起来的一种快速、简洁、经济的新技术, 可同时阻断多个基因表达, 不仅可用于研究基因功能, 而且可高效、靶向性阻断目的基因的复制和表达, 而不干扰其他基因的转录, 达到治疗目的[62-64]. 由于其针对性强, 且无严重的不良反应, 在肝病治疗方面无疑将具有非常广阔的应用前景, RNAi将有望为抗肝纤维化治疗带来新希望. 靶位选择是RNAi研究的关键环节. 抑制介导HSC活化的关键细胞因子结缔组织生长因子(connective tissue growth factor, CTGF)及TGFβ也是针对肝纤维化基因治疗较理想的靶位. 经门静脉注射肝纤维化大鼠CTGF siRNA发现, 治疗组大鼠肝组织CTGF mRNA及蛋白表达显著下调, 肝组织炎症、坏死及纤维化显著减轻[65-66]. 将TGFβ1 siRNA用于CCl_4肝损伤大鼠模型同样发现, 肝脏表达TGFβ1、α-SMA、Ⅰ型胶原含量均明显下降[67]. 随着对RNAi认识的不断深化, RNAi技术必将对肝纤维化的治疗起到不可估量的作用[68-69].

5 结论

肝纤维化的基因治疗在短短几年中的飞速发展, 给人们展现了治疗慢性肝病的美好前景[70]. 我们相信, 随着基因治疗技术的日趋成熟, 基因治疗将更加有效、安全、经济. 肝纤维化基因治疗也将由单基因治疗向着多基因治疗的方向发展, 治疗的最终目标是逆转纤维化、重建正常肝小叶, 恢复正常肝功能.

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■名词解释

RNA干扰(RNAi): 是指在进化过程中高度保守的、由双链RNA (dsRNA)诱发的、同源mRNA高效特异性降解的现象.

■同行评价
本文内容详实, 层次分明, 具有一定的理论意义和学术价值.

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