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文献综述 REVIEW

肝纤维化中表观遗传学调控的研究进展

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Advances in research of epigenetic regulation in liver fibrosis

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Abstract

Liver fibrosis is a pathological repair process in response to chronic injury caused by various etiologies in the liver. Imbalance between the expression of pro-fibrosis genes and anti-fibrosis genes play a pivotal role in hepatic fibrosis. The important path of reversing liver fibrosis is the early diagnosis and effective treatment. Epigenetic modifications have been considered an initial event in the development of hepatic fibrosis. Epigenetic regulatory mechanisms in liver fibrosis are intricate, including DNA methylation, histone modification, and microRNAs (miRNAs). Recently, many researchers have studied the effect of fibrosis-related gene expression at the epigenetic level on hepatic stellate cell activation and myofibroblast differentiation in hepatic fibrosis. This review discusses the epigenetic regulation in liver fibrosis, with an aim to provide new insights into the early non-invasive diagnosis, condition assessment and targeted therapy of this disease.

Key Words: Liver fibrosis; Epigenetics; Hepatic stellate cells; Myofibroblasts

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摘要

肝纤维化是机体对各种病因引起的肝脏的慢性损伤所产生的病理性修复的累积过程. 促纤维化与抗纤维化基因表达失衡, 是发生肝纤维化的中心环节. 早期诊断与有效治疗是逆转肝纤维化的重要途径. 表观遗传学改变被认为是肝纤维化发生过程中的早期事件. 肝纤维化的表观遗传学调控机制错综复杂, 主要包括DNA甲基化、组蛋白修饰、microRNAs(miRNAs)等. 近年来较多学者从表观遗传学水平探讨肝纤维化相关基因的表达及对肝星状细胞的活化、肌成纤维细胞的分化等的调控, 进一步揭示肝纤维化的发病机制. 本文就肝纤维化的表观遗传学调控作一综述, 为肝纤维化的诊断、病情评估及靶向治疗提供新思路.

关键词: 肝纤维化; 表观遗传学; 肝星状细胞; 肌成纤维细胞

核心提示: 表观遗传学主要通过影响纤维化相关基因表达、肝星状细胞(hepatic stellate cells)的活化、增殖、凋亡及肌成纤维细胞(myofibroblasts)分化来调控肝纤维的发生发展.

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■背景资料
肝纤维化是机体对各种病因引起的肝脏的慢性损伤所产生的病理性修复的累积. 目前认为肝纤维化是双向可逆的. 但其早期无创诊断及有效治疗仍是亟待解决的难题. 表观遗传学改变作为肝纤维化发生过程中的早期事件, 从DNA甲基化、组蛋白修饰、MicroRNAs三方面进行调控.

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■研发前沿
近年来研究证实, 表观遗传学参与并调控了肝纤维化的发生发展, 这些发现为肝纤维化的无创诊断、病情评估及靶向治疗提供了新的手段及思路.

0 引言

肝纤维化是机体对各种病因引起的肝脏的慢性损伤所产生的病理性修复的累积过程. 目前认为肝纤维化是双向可逆的. 但其早期无创诊断及有效治疗仍是亟待解决的难题. 近年来, 随着人类基因组计划的完成, 人们把视角由宏观转移到微观, 由遗传学转移到表观遗传学. 表观遗传学改变不涉及DNA序列的改变, 却与肿瘤及许多其他疾病的发生发展有着较为密切的联系. 表观遗传学的表型改变可能会遗传给子代, 影响子代基因的表达. 但庆幸的是, 表观遗传学水平的改变早于蛋白水平的改变, 且这种改变是可以逆转的. 因此, 近年来, 众多肝病学者关注于表观遗传学改变对纤维化相关基因表达及肝星状细胞(hepatic stellate cells, HSCs)的活化、肌成纤维细胞(myofibroblasts, MFs)分化的影响, 为肝纤维的无创诊断及逆转纤维化进程提供科学依据. 表观遗传学分子机制主要包括: DNA甲基化、组蛋白修饰、miRNAs、染色质重塑等. 其中以前三者与肝纤维化的相关研究较多. 本文就肝纤维化的表观遗传学调控作一综述.

近年来, 大多数研究用单一的表观遗传学改变解释其与肝纤维化发生发展的相关性, 也有学者提出在肝纤维化发生过程中, DNA甲基化、组蛋白乙酰化、miRNAs三者可能存在相互影响的潜在的联系[1-3]. 但肝纤维化中的表观遗传学改变, 是单一、串扰还是联合调控的确切机制仍不十分清楚.

1 DNA甲基化

DNA甲基化是研究最早的表观遗传学修饰方式. DNA甲基化是DNA复制后的一种酶促反应, 一般从全基因组DNA甲基化水平及特定基因启动子区域的CPG岛5-氟胞嘧啶的甲基化状态这两方面来探讨甲基化的改变. 基因发生超甲基化后, 多下调该基因的表达, 反之, 基因的低甲基化多上调该基因的表达.

在肝纤维化中, 纤维化相关基因的甲基化状态及水平均表现出较明显的差异. 学者们在肝纤维化的动物实验及临床实验中, 发现*hMSH3*、*MGMT*、*RASSF1A*、*PTEN*、*GSTM3*、转化生长因子-β1(transforming factor β1, *TGF-β1*)等基因易发生超甲基化[4-8], 而*hMLH1*、*MSI*、*NORE1A*、*Spp1*则很少发生甲基化[5,7,9], *PPAR-γ*、*PTCH1*易出现表观沉默[4,10]. 特定基因的甲基化状态不仅能作为肝纤维的标志物, 还可以初步提示纤维化程度及疾病的病情. Qi等[6]指出*GSTM3*启动子甲基化可能与慢加急性乙型肝炎肝衰竭(acute-on-chronic hepatitis B liver failure, ACHBLF)的严重程度相关. HSCs的活化作为肝纤维化过程中的关键事件, 也与DNA甲基化状态密切相关. 学者研究指出PTEN的超甲基化可激活P13K/AKT与ERK通路, 参与HSCs的活化及肝纤维化形成的调控[8]. 肿瘤学学者在DNA甲基化方面研究显示, 多数肿瘤易同时伴随全基因组DNA甲基化水平的降低与抑癌基因、DNA修复基因的超甲基化改变. 在肝纤维化中也有类似的发现, Komatsu等[9]研究发现在肝纤维化动物模型中, 全基因组DNA甲基化水平降低, 同时纤维化相关基因*Spp1*出现低甲基化而其表达上调.

2 组蛋白修饰

组蛋白修饰主要包括乙酰化、甲基化、泛素化及磷酸化等方式. 在肝纤维化中, 目前以乙酰化与甲基化的研究较为多见. 组蛋白修饰多发生在转录后水平, 调控基因的表达. 组蛋白乙酰化一般使转录激活, 上调基因的表达; 而组蛋白甲基化则多引起基因的沉默, 下调基因的表达.

2.1 组蛋白去乙酰化抑制剂与肝纤维化 近年来, 组蛋白去乙酰化抑制剂越来越多的应用到动物及临床试验中, 从HSCs的活化、增殖和凋亡及MFs的分化等多条途径调控肝纤维化的发生发展过程. 其中, TSA可能通过抑制HSCs中肌动蛋白肌丝的生成及迁移, 从而阻止HSCs向MFs转化. Ⅱ类组蛋白去乙酰化酶抑制剂通过明显上调miR-29从而阻碍HSCs的活化[11]. 组蛋白去乙酰化抑制剂-辛二酰苯胺异羟肟酸(N-hydroxy-N-phenyloctanediamide, SAHA)抑制丙型肝炎病毒(hepatitis C virus, HCV)的复制, 可能用来治疗HCV相关的肝硬化或肝癌[12]. 2',4',6'-三(甲氧基甲氧基)查耳酮[2',4',6'-tris(methoxymethoxy) chalcone, TMMC]、尼洛替尼可能通过抑制组蛋白去乙酰化来诱导活化的HSCs发生凋亡和自噬性细胞死亡[13,14]. 组蛋白去乙酰化抑制剂可能通过抑制TGF-β1诱导的上皮间质转化, 阻断TGF-β1的自分泌环来减轻其诱导的胶原合成, 抑制血管内皮生长因子来降低血管生成, 表观沉默基质金属蛋白酶等途径, 从而阻止肝纤维化的发生、发展[15-18].

2.2 组蛋白甲基化与肝纤维化 近几年来, 组蛋白的甲基化修饰也越来越受到广泛重视, 肝纤维

表 1 肝纤维化相关miRNAs

抗纤维化相关miRNAs	促纤维化相关miRNAs	
miR-132[3]	miR-328[21]	miR-9[41]
miR-26a[21]	miR-299-5p[21]	miR-125b[41]
miR-122[21,22,46]	miR-34a[23,34,35]	miR-128[41]
rno-miR-878[23]	miR-571[27]	miR-27a/b[47]
miR-29a/b[24,25,39,49,50]	miR-199a/b[28,29]	miR-221[48]
miR-19b[26]	miR-200a/b[28,29,34]	miR-222[48]
miR-652[27]	miR-615-5p[30]	
miR-449a[38]	miR-106b[31]	
miR-146a[40,51]	miR-181a/b[31,32]	
miR-15b[42]	miR-506[33]	
miR-16[42]	miR-155[34]	
miR-194[43]	miR-29c[34]	
miR-150[43,45]	miR-92a[37]	
miR-335[44]	miR-20a[37]	

化相关的组蛋白甲基化修饰的相关研究也开始崭露头角. Perugorria等[19]发现组蛋白甲基转移酶ASH1直接绑定于活化的HSCs中α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)、Ⅰ型胶原、金属基质蛋白酶组织抑制因-1(tissue inhibitor of metalloproteinase-1, TIMP-1)、TGFβ1所在区域, ASH1的消失会极大地抑制纤维化基因的表达. 甲基化CpG岛结合蛋白2(methyl-CpG-binding protein 2, MeCP2)正调控ASH1的表达, 提出ASH1作为MeCP2表观遗传学调控通路中的一个关键的转录活性成分共同调节多个纤维化相关基因的表达. Krämer等[20]发现组蛋白H3K27的三甲基化通过激活成纤维细胞来诱导纤维化的发生.

3 miRNAs

miRNAs是一类分布广泛的内源性非编码小RNA, 也在转录后水平调控基因的表达. 越来越多的研究表明肝纤维化与miRNAs密切相关. 目前, 发现与肝纤维化相关的miRNAs约30多个, 多呈差异性表达. 肝纤维化中, 促纤维化相关的miRNAs多发生上调, 抗纤维化相关的miRNAs多发生下调.

3.1 miRNAs在肝纤维化中的差异性表达 在多项肝纤维化研究中, 组织或血标本中miR-122、miR-26a、rno-miR-878、miR-29、miR-19b、miR-652多发生下调, 与肝纤维化呈负相关[21-27]; 而miR-328、miR-299-5p、miR-34家族、miR-199家族、miR-200家族、miR-615-5p、miR-106b、miR-181b、miR-571、miR-506、miR-29c、miR-155多发生上调, 与肝纤维化呈正相关[21,23,27-34], 如表1. miRNAs水平的高低在一定程度上提示肝纤维化的严重程度, 对评估病情、治疗效果的判断等有一定的指导意义. Waidmann等[22]研究发现肝硬化失代偿期患者的miR-122水平较代偿期患者低, 且伴有腹水、自发性细菌性腹膜炎、肝肾综合征等并发症患者的miR-122水平较不伴这些并发症患者的明显降低. 提出血清miR-122可能提示肝纤维化患者的生存. Murakami等[29]研究发现肝纤维化的进展与miR-199家族及miR-200家族的过表达密切相关. Pogribny等[34]研究指出NASH的进展与miR-29c、miR-34a、miR-155、miR-200b表达的改变密切相关. 单个miRNA的改变可能不足以诊断肝纤维化, 学者Chen等[31]研究指出miR-106b和miR-181b同时出现可作为肝纤维化的生物学标志物. 同一家族中miRNA在疾病中可能表现出一致性或者差异性表达, miR-34家族、miR-199家族、miR-200家族的表达在肝纤维化中较一致地发生上调, 而多位学者研究显示miR-29a/b与肝纤维化成负相关[24,25,35-37], Pogribny等[34]研究发现miR-29c却与肝纤维化呈正相关. Wang等[32]研究表明肝硬化患者血清中miR-181b水平较正常对照明显增高, 但miR-181a水平在两组患者中无显著差异.

3.2 miRNAs与肝纤维化的病因 近年来, 肝纤维化起病的相关因素如乙醇、HCV、丁型肝炎病毒(hepatitis D virus, HDV)等与miRNAs的研究的也有部分报道. miR-34a可能与乙醇摄入相关, 在酒精性肝纤维化中miR-34a的表达上调[38]. Bae等[39]研究结果显示miR-101-1与miR-101-2的遗传变异与HBV所致的肝硬化和肝癌显著相关. HCV感染相关肝病患者中miR-20a、miR-92a的表达出现上调[40], 而miRNA-449a出现了下调[41]. Zhang等[35]研究指出雌激素作为肝纤维化的保护性因素, 可能通过诱导miR-29的表达来抑制四氯化碳引起的肝损伤, 发现雄性肝纤维化小鼠中miR-29a、miR-29b水平显著降低, 而在雌性鼠中没有统计学差异.

3.3 miRNAs对肝纤维的调控机制 较多研究显示, HSCs的激活与MFs的分化被认为是肝纤维化发生过程中的必要非充分条件. 研究发现越来越多的miRNAs通过参与MFs的分化与HSCs的活化、增殖和凋亡来调控肝纤维化的纤维生成. 在MFs的分化过程中, miR-146a表达出现下调[42], 而miR-9、miR-125b、miR-128的表

■相关报道
肝纤维化中特定基因的DNA甲基化、组蛋白乙酰化与甲基化、MicroRNAs均呈现差异性表达, 并调控HSCs的活化、增殖、凋亡及MFs的分化.

■创新盘点
本文对DNA甲基化、组蛋白修饰、microRNAs在肝纤维中的纤维化相关基因的差异性表达及其作用机制做一综述, 为进一步探究表观遗传学如何调控并逆转肝纤维化提供新的着眼点.

达均明显增高[43]. Guo等[44]研究发现HSCs的激活与21个miRNA相关, 其中有12个miRNA发生上调, 9个miRNA产生下调. 其中miR-15b和miR-16通过Bcl-2及Caspase信号通过诱导HSCs的凋亡. 诸多研究发现miR-150、miR-194、miR-335、miR-122[45-48]与HSCs的活化呈负相关, 而miR-27a、miR-27b、miR-221、miR-222、miR-29[36,37,49,50]与HSCs的活化成正相关. miR-27a、miR-27b、miR-146a、miR-181a可诱导的HSCs的增殖, 增加HSCs的凋亡[32,49,51].

4 结论

肝纤维化的发病机制, 需要大量深入的基础及临床研究才能为我们对其有较充分的认识提供足够的科学证据. 近年来, 学者们积极探索肝纤维化中表观遗传学水平的调控, 为肝纤维化的靶向治疗提供了思路. 再者肝纤维化诊断的金标准是有创的肝组织病理学检查, 且因所取组织的局限性、并发症的发生风险及患者的合作度不够满意等, 使大家更期待血液学指标能作为早期无创的诊断、病情评估的标准. 表观遗传学改变作为一个信使, 为我们开启了肝纤维化的无创诊断及靶向治疗的希望之门.

在近年来的研究中, 我们发现甲基化水平的高低在一定程度上反映了肝纤维化的进程, 致纤维化相关基因或细胞因子大多出现异常超甲基化, 而抗纤维化相关基因则较易出现异常低甲基化. 这为肝纤维化的无创诊断及病情评估提供了手段, 同时为应用去甲基化治疗肝纤维化提供了理论依据. 组蛋白乙酰化与miRNA都在转录后水平积极地参与了HSCs的增殖、活化和凋亡及MFs的分化的调控. 在较多的基础及临床研究中, 组蛋白去乙酰化抑制剂可能作为潜在的抗肝纤维化药物得到应用. 在肝纤维化发生过程中, 近期发现越来越多的miRNAs呈差异性表达. 目前, 发现纤维化相关的miRNAs多达30多个. 在肝纤维化中, miRNAs通过多种细胞因子和信号通路调控胶原及细胞外基质的产生. miRNAs可能作为信号分子为肝纤维化的诊断及病情评估提供新的无创手段, 可作为治疗靶点为逆转肝纤维化提供广泛的前景.

总之, 肝纤维化中表观遗传学调控得到了广泛的关注. 近年来, 越来越多的肝病学家积极探讨表观遗传学改变在肝纤维化中的影响, 特定基因的甲基化、乙酰化及miRNAs的差异性表达均可能作为肝纤维化的信号分子, 在诊断肝纤维化及初步评估其严重程度方面发挥不可估量的作用. 但肝纤维化的表观遗传学调控机制尚不清楚, DNA甲基化、组蛋白乙酰化、miRNAs之间的联系仍不明确. 三者之间可能存在串扰或相互促进, 进而启动或参与肝纤维化的纤维化进程. 故仍需大量的相关研究来进一步阐明肝纤维化中表观遗传学水平的调控机制, 进一步为肝纤维化的早期的无创诊断及靶向治疗提供新视野.

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■应用要点
表观遗传学改变作为肝纤维化的早期事件，为肝纤维化的无创诊断、病情评估及靶向治疗提供新的手段与思路，为临床决策者提供参考.

■同行评价
本文对临床有一定的指导意义.

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