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文献综述 REVIEW

# 纤维化肝脏中肌成纤维细胞的来源

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■背景资料
肝纤维化是多种慢性肝病的共同结局, 包括病毒性肝炎, 自身免疫性肝病, 酒精性和非酒精性脂肪性肝病等. 其发病机制的研究对预后和治疗都有非常重要的意义.

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## Sources of myofibroblasts in liver fibrosis

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## Abstract
Myofibroblasts (MFBs) promote the accumulation of the extracellular matrix (ECM) by synthesis and secretion of collagen in the liver, leading to liver fibrosis. Activated hepatic stellate cells (HSC) are the major source of MFBs, and also play a key role in the development of liver fibrosis. Many studies indicate that hepatocytes and bile duct cells may undergo epithelial-to-mesenchymal transition (EMT) to MFBs; however, contrary conclusions have also been drawn in recent studies. In addition, other sources of MFBs have also been found, including portal fibroblasts, bone marrow cells, and hepatic progenitor cells. In this article we will review the sources of MFBs in liver fibrosis.



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## 摘要
肌成纤维细胞(myofibroblasts, MFBs)通过合成并分泌胶原促进肝脏细胞外基质(extracellular matrix)的累积, 导致肝纤维化的发生、发展, 其来源广泛. 肝损伤时肝纤维化发展中的关键细胞-活化的肝星状细胞(hepatic stellate cells)是MFBs的主要来源; 更有数据表明肝细胞和胆管上皮细胞在特定条件刺激下可以通过上皮-间质转分化(epithelial-to-mesenchymal transition)过程转变为MFBs, 但也有不少研究否定了该结论, 因此也成为目前的研究热点之一; 越来越多的研究表明, 来源细胞包括汇管区成纤维细胞、骨髓细胞、肝内祖细胞等. 因此本文就MFBs来源的研究进展做一综述.



关键词: 肝纤维化; 肌成纤维细胞

**核心提示**: 肌成纤维细胞通过合成胶原促进肝纤维化的发展. 活化的肝星状细胞是主要来源; 肝细胞和胆管上皮细胞是否可以通过上皮-间质转分化成为肌成纤维细胞仍存在争议; 其他来源包括汇管区成纤维细胞、骨髓细胞、肝祖细胞等.

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## 0 引言
肝纤维化是肝组织损害后的一种可逆的损伤修复反应, 以细胞外基质(extracellular matrix, ECM)的过度沉积为特点. 如果慢性炎症和ECM

沉积持续存在, 会导致肝实质结构逐渐被破坏, 由瘢痕组织代替, 从而形成肝硬化, 预后较差[1]. 肌成纤维细胞(myofibroblasts, MFBs)是典型的调节组织损伤修复的间质细胞, 通过合成胶原促进ECM累积, 表达α-平滑肌肌动蛋白(alpha smooth muscle actin, α-SMA), 具有收缩性[2]. 肝纤维化的持续存在主要是由肝脏MFBs维持[3]. MFBs是肝纤维化发生发展的重要细胞, 对其来源的探讨, 有助于阐明肝纤维化的发生发展机制, 也为肝纤维化治疗提供依据, 本文就MFBs来源的相关研究进展做一综述.

## 1 肝星状细胞

肝星状细胞(hepatic stellate cell, HSC)是肝纤维化形成的关键细胞, 也是目前研究最多的致纤维化细胞. 肝损伤过程中的多种病理反应因素, 包括氧化应激、缺氧、炎症和免疫反应、细胞凋亡、脂肪变性等, 均可使HSC活化, 获得肌成纤维细胞特征, 表达α-SMA, 合成大量ECM, 并且具有增殖、收缩、迁移以及促炎症反应等特点[4]. HSC活化分为启动和持续两个阶段. 启动阶段主要是损伤的实质细胞通过旁分泌作用激活HSC, 持续刺激导致进入持续阶段, HSC的活化在这一阶段则是由旁分泌和自分泌共同调节[5].

转化生长因子β1(transforming growth factor-β1, TGF-β1)可有效促使HSC活化为MFBs. 经典TGF-β1信号转导首先作用于TGF-β1受体(transforming growth factor-β receptor, TβR), 致其活化, 使下游效应器Smad2/3磷酸化(pSmad2/3), 后者与Smad4形成异寡聚复合体, 后转位至细胞核, 激活特异性靶基因的转录[6]; Smad7是TGF-β1信号通路的关键抑制分子, 通过负反馈环发挥其对TGF-β1信号转导的抑制作用[7,8]. 因此, 提高Smad7的表达, 有效抑制TGF-β1/Smad信号转导对肝纤维化的治疗至关重要. 另外, TGF-β1还可激活MAPK信号通路, 包括细胞外信号调节激酶(ERK)、p38 MAPK、c-Jun N-端激酶(JNK), 他们可以通过“串扰”(crosstalk)的方式对TGF-β1/Smad信号转导产生极大的影响[9]. 血小板衍生生长因子(platelet derived growth factor, PDGF)是HSC增殖的关键刺激源. PDGF与其受体PDGFR(platelet derived growth factor reporter)结合, 通过Ras激活下游Raf-1、MEK和ERK, 还可与磷脂酰肌醇(-3)激酶(phosphatidylinositol 3-kinase, PI3K)结合, 诱导HSC有丝分裂和趋化[10,11]. PDGF还可促进HSC的$Na^+/H^+$交换, 继而改变细胞内pH值[12], 抑制$Na^+/H^+$交换可以干扰细胞骨架重组的关键下游信号, 抑制PDGF诱导的细胞有丝分裂[9,13].

## 2 汇管区成纤维细胞

慢性肝损伤时, 位于胆管和血管周围结缔组织中的成纤维细胞(fibroblast)在TGF-β1/Smad作用下可以转化为α-SMA(+)的MFBs[14-16]. 汇管区成纤维细胞的促纤维化作用在胆汁淤积性纤维化中起主要作用[17], 胆汁淤积性肝损伤时, 仅有少数ECM来源于活化的HSC[14,18]. 胆管细胞受损后表达TGF-β2, 释放PDGF-BB亚型、IL-6和单核细胞趋化蛋白(monocyte chemo-attractant protein 1, MCP-1)等, 而这些生长因子和促炎因子都可促进成纤维细胞转化为MFBs[19]. 除此之外, 汇管区MFBs在其他以桥接样纤维化为特点的慢性肝病进展中也有重要作用, 包括病毒性的和酒精性的肝病[20,21]. 由此可见, 汇管区成纤维细胞在不同病因导致的慢性肝病中都发挥着重要作用, 然而其被激活的程度则可能是与胆管上皮损伤程度相关. 汇管区成纤维细胞分离方法的建立为进一步深入研究提供了方法学基础[22].

## 3 骨髓细胞

近年来, 干细胞移植成为肝纤维化治疗研究的热点, 然而越来越多的证据表明肝纤维化进程中的部分MFBs来源于骨髓干细胞, 这一点不利于干细胞治疗的应用. 研究证实, $CCl_4$处理的骨髓移植小鼠肝脏中, 30% α-SMA(+)的MFBs来源于骨髓[23]. 另一项类似的研究也发现纤维化肝脏中约70%合成Ⅰ型胶原(collagen Ⅰ)的MFBs来自骨髓[24]; 骨髓移植后肝硬化和肝移植后肝纤维化患者肝脏中6.8%-22.2% α-SMA(+)的MFBs由骨髓细胞提供[25]. 事实上肝纤维化早期即可发现骨髓来源的MFBs, 并且随着肝损伤的加重, 肝脏中骨髓衍生MFBs逐渐增多[26,27]. 上述数据显示骨髓来源的MFBs从6.8%到70%不等, 相差很大, 这有可能是由于损伤程度不同而造成的差异.

骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)可能是MFBs的来源之一. 将BMSCs移植入经部分肝切除和倒千里光碱(retrorsine)处理过的小鼠, 持续存在于肝组织中的BMSCs可以表达波形蛋白(vimentin)和α-SMA, 且其所在位置有胶原沉积[28]. 体外实验发现, BMSCs可以应答多种生长因子发生迁

**■研发前沿**
肝星状细胞活化被认为是肝纤维化发病过程中的关键环节, 随着研究的深入, 发现了其他可以分泌胶原、具有肌成纤维细胞特点的细胞. 但这些肌成纤维细胞的来源及促纤维化作用仍存在争议.

**■相关报道**
Lee等在2012年发表的“New insights into the regulation of epithelial-mesenchymal transition and tissue fibrosis”探讨了上皮间质转分化在多种组织纤维化中的作用, 包括肺脏、肾脏、肝脏、心脏等. 多领域的研究方法和研究进展值得我们学习和借鉴.

移, 如PDGF[29]、胰岛素样生长因子(insulin-like growth factor, IGF)[30], 表皮生长因子(epidermal growth factor, EGF)[31]和肝细胞生长因子(hepatocyte growth factor, HGF)[32]等. 另外有实验证实BMSCs归巢至损伤的肝脏, 可能还与鞘氨醇-1-磷酸盐(sphingosine 1-phosphate, S1P)有关[33], 肝损伤时, 肝组织和血循环中的S1P增加, 而骨髓中的S1P保持不变, 这种梯度差促进肝组织募集骨髓细胞, 这一过程中, S1P受体(S1P3/S1P2)是关键介质, 阻断S1P3可以抑制纤维化进展[34]; 而S1P2的活化可以抑制BMSCs的迁移[35].

另外, 骨髓中包含一类CD45(+)collagen Ⅰ(+)的纤维细胞(fibrocytes-like cells), 有人发现胆管结扎(bile duct ligation, BDL)小鼠的肝脏中存在这类细胞, 经TGF-β刺激后可转化为α-SMA(+)desmin(+)有合成胶原能力的MFBs, 促进纤维化发展[36]. 在硬化性胆管炎模型小鼠肝脏中发现了类似的CD34(+)desmin(+)纤维细胞, 能够表达collagen Ⅰ, 并且在体外实验中得到验证[37]. 纤维细胞的募集过程受到趋化因子受体(chemokine receptor, CCR)1和CCR2调节, $CCR1^{-/-}$和$CCR2^{-/-}$小鼠纤维细胞迁移分别减少25%和50%; TGF-β和脂多糖(lipopolysaccharide, LPS)也可以诱导骨髓释放CD45(+)collagen Ⅰ(+)纤维细胞, 迁移至肝脏和脾脏; 此外, 骨髓纤维细胞的迁移可能还与年龄有关, 老年小鼠在没有损伤和应激的情况下, 也可发生骨髓纤维细胞的迁移[38]. 虽然体内外实验均发现骨髓纤维细胞可以分化为MFBs, 但减少纤维细胞的迁移对肝脏纤维化程度并没有影响[34].

然而有研究认为骨髓细胞并不会分化为MFBs, 骨髓细胞移植小鼠肝脏中出现的大量CD45(+)细胞是由于炎性细胞浸润, 这些炎性细胞促进了HSC的活化[39]. 而且, 某些骨髓细胞亚群移植后能够取得良好效果, 并已应用于临床[40,41]. 上述差异可能与细胞亚群不同有关. 骨髓细胞移植有可能成为肝细胞再生的有效手段之一, 在治疗肝硬化方面具有潜在优势, 已成为目前的研究热点之一. 但骨髓细胞分化的多向性, 特别是在肝硬化病理状态下分化为MFBs, 逐渐成为治疗肝纤维化的障碍. 如何诱导骨髓细胞向有利的方向分化是研究的关键. 某些中药可有效改善肝硬化病理环境, 促进肝细胞再生, 所以骨髓干细胞移植联合中药治疗具有良好的研究前景.

## 4 上皮-间质转分化

上皮-间质转分化(epithelial-to-mesenchymal transition, EMT)是指细胞逐渐失去上皮细胞特性, 获得间质细胞特征的细胞转分化过程[42]. 上皮和间质表型转换是胚胎发育的关键, 也是成熟细胞应答损伤的关键, 这一过程为损伤组织的修复提供MFBs[43]. 有研究证明肾纤维化和肺纤维化中均存在EMT现象[44,45]. 然而肝纤维化进展中是否存在EMT仍存在一些争议.

首先, 胆管细胞可能通过EMT作用为肝纤维化进展提供MFBs. BDL肝纤维化小鼠中发现了α-SMA和细胞角蛋白(cytokeratin, CK)19(胆管细胞标记)共染的胆管上皮细胞, 且细胞周围存在collagen Ⅰ; 体外培养的人胆管上皮细胞经TGF-β刺激后可表达α-SMA和纤连蛋白, 而CK19表达下降[46]. 胆道闭锁和其他一些胆管增生性疾病的患者肝组织中, 胆管上皮细胞共表达CK19和多种间质细胞标记物, 包括FSP1(fibroblast-specific protein 1)、HSP47(heat shock protein 47)、vimentin和转录因子Snail[47]. 另一个以CK7作为胆管细胞标记的类似实验发现, 胆管闭锁患者胆管上皮细胞高表达α-SMA和FSP1, 同时具备成纤维细胞样形态学表现[48]. 其次, 肝细胞也可能成为是肝纤维化中MFBs的一个来源. Kaimori等[49]用原代小鼠肝细胞和小鼠肝细胞株同时证实了肝细胞可以合成collagen Ⅰ. Zeisberg等[50]发现$CCl_4$诱导的肝纤维化模型中Alb(+)(肝细胞标记)的肝细胞可以转分化为Alb(-) FSP1(+) α-SMA(-)的成纤维细胞; 高达45%的成纤维细胞来源于肝细胞, 高达60%的FSP1(+)细胞同时表达Alb, 后者可能是肝细胞EMT过程的中间阶段, 提示纤维化肝脏中相当多数量的FSP1(+) α-SMA(-)的成纤维细胞来自肝细胞. 另外, 在肺、心、肾纤维化发病中发现一种新的细胞分化类型, 内皮-间质转分化(endothelial to mesenchymal transition, EndoMT), 也可能是MFBs的一个来源, 由TGF诱导发生[51]. 然而肝纤维化中是否存在EndoMT, 目前尚无定论.

TGF-β、EGF、IGF-Ⅱ以及成纤维细胞生长因子(fibroblast growth factor, FGF)-2等细胞因子均可诱导EMT的发生, 其中研究较为深入的是TGF-β/Smad信号通路[52,53]. 沉默Smad4或高表达Smad7使TGF-β信号下调, EMT减少, 间质胶原聚集减少[54]. 只有逃避了促凋亡作用的肝细胞才可以被TGF-β刺激发生EMT, 这些存活的肝

细胞由MAPK非依赖转向MAPK依赖的细胞存活途径[55], 在TGF-β的刺激下过量表达Snail, 获得了抵制程序性细胞死亡的能力, 因此Kaimori等[49]认为肝细胞EMT取决于凋亡和存活机制. 缺氧也可诱导肝细胞发生EMT, Copple等[56]发现置于缺氧环境中的原代肝细胞表达α-SMA、vimentin、Snai和FSP1增加; 而缺氧诱导因子(hypoxia inducible factors, HIFs)-1β缺失的肝细胞在低氧环境中不发生EMT, 同样HIF-1α缺失的BDL小鼠FSP1表达并未增多, 提示HIF在这一过程中发挥重要作用.

虽然有较多实验证明胆管上皮细胞和肝细胞在特定环境下转分化为MFBs, 但也有研究得出相反的结论, 即在BDL、$CCl_4$和3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)3种动物模型中, 肝细胞和胆管上皮细胞均未发现表达间质标记FSP1、vimentin、α-SMA以及collagen Ⅰ前体等[57,58]. Taura等[59]发现, 虽然正常小鼠原代肝细胞在体外经TGF-β刺激可以产生collagen Ⅰ, 具有MFBs形态, 但是并没有表达其他间质细胞的标记物; 而$CCl_4$处理的小鼠原代肝细胞, 不论纤维化等级如何, 都没有发现α-SMA, FSP1或vimentin, 也不产生collagen Ⅰ, 因此认为肝细胞EMT是体外培养和TGF-β联合作用的人为产物. Rygiel等[60]也给出了类似的实验证据, 人原代肝内胆管上皮细胞经TGF-β诱导后具备成纤维细胞表型, 表达FSP1和α-SMA显著增加, 并且具有迁移性, 可以认为其转分化为成熟的MFBs; 但是原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)、原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)以及肝内胆管结石[61]患者肝组织活检并未发现胆管上皮细胞表达α-SMA, 然而Rygiel等并未因此否认EMT, 而是认为原代细胞和活检组织的不一致可能是因为胆管上皮细胞在表达α-SMA之前发生了迁移, 证据是汇管区纤维化处有α-SMA表达.

尽管某些实验否认肝纤维化进展中存在EMT来源的MFBs, 但多数实验观察到了这一现象, 体内外结果的矛盾需要优化实验条件和扩大临床样本来明确. 胆管上皮细胞和肝细胞来源的MFBs对ECM合成的贡献度也需要进一步的研究.

## 5 肝内祖细胞

肝内祖细胞属于肝脏干细胞, 具有分化潜能, 有研究发现这类细胞群也可能成为MFBs的来源. 最近一项临床研究结果显示, 肝祖细胞的活化促进了非酒精性脂肪性肝病的进展[62]. 猕猴肝脏上皮祖细胞(rhesus monkey liver epithelial progenitor cells, mLEPCs)经TGF-β刺激后, 转变为成纤维细胞, 失去上皮细胞标记物CK8及相关基因(*E-Cadherin*、*ZO-1*、*CK18*、*occludin*), 表达间质细胞相关基因(*snail*、plasminogen activator inhibitor 1、*collagen* Ⅰ); 60%以上的成纤维细胞样细胞表达α-SMA、vimentin和N-Cadherin[63]. 另外, 肝脏卵圆细胞是一种肝内祖细胞群, 原代大鼠Thy-1.1(+)肝卵圆细胞可以同时表达上皮和间质细胞标记物, 分化为具有MFBs表型的细胞[64]. 此外, 有人发现了一个表达祖细胞标记CD133的HSC亚群, 说明HSC有可能来源于成熟肝脏的肝祖细胞, 对于这一发现也有人认为HSC可能是肝卵圆细胞转分化过程中的过渡细胞[65,66]. 但是最近有研究利用二乙酰氨基芴(AAF)/$CCl_4$模型证实, 肝祖细胞没有分化为MFBs, 而是通过表达TGF-β促进HSC的聚集[67]. 因此肝内祖细胞与MFBs的关系仍需进一步研究, 并且肝内祖细胞具有干细胞特性, 其存在的问题与骨髓干细胞类似, 抑制肝内祖细胞向MFBs分化, 促进其向肝实质细胞分化是我们需要努力的方向.

## 6 其他

CD14(+)的外周血单核细胞亚群能分化的纤维细胞, 在多种器官中参与损伤修复[68]. 肺纤维化和肾纤维化过程均有其参与, 他的分化过程受到单核-刺激因子(colony-stimulating factor, CSF), MCP-1以及其他趋化因子、生长因子、分化因子的影响; 虽然这些细胞因子可以由活化的HSC和其他一些肝内细胞分泌, 但外周血单核细胞在肝纤维化中的作用尚未得到证实[52].

肝脏中的大量巨噬细胞(即Kupffer细胞), 在肝纤维化中发挥双向作用, 纤维化进展期, 促进其发展, 而在纤维化消退期, 他又能促进纤维化消退[5]. 最近的一项研究在肝脏巨噬细胞的一个亚群中发现了间质细胞标记FSP1[69], 这可能是Kupffer细胞发挥其促纤维化作用的另一个方面.

## 7 结论

肝纤维化时, MFBs合成大量ECM, 促进纤维化进展, 其主要来源是活化的HSC, 另外越来越多的MFBs的其他来源逐渐被发现, 包括汇管区成纤维细胞、骨髓细胞、肝细胞和胆管细胞EMT

**■创新盘点**

全面系统综述了近年来该领域的研究, 内容不但包括基础性的实验研究, 还涉及到多项临床研究, 客观评述了某些存在争议的内容, 对研究热点进行了深入的探讨.

**■应用要点**
这些不同来源的肌成纤维细胞在纤维化进程中的作用不容忽视, 并有可能成为抗肝纤维化的治疗靶点. 其来源的广泛性及对肝纤维化进程的影响程度仍需进一步研究.

以及肝内祖细胞等. 这些不同来源的细胞在纤维化进程中的作用不容忽视, 并有可能成为抗肝纤维化的治疗靶点. 但是另一方面, MFBs来源的广泛性仍存在争议, 胆管上皮细胞和肝细胞是否可以通过EMT促进纤维化, 以及除HSC外的其他来源的MFBs对肝纤维化进程的影响程度仍需要进一步研究.

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**■同行评价**

本文较全面深入地总结该领域的研究进展, 为同行者提供参考.

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