

# 骨髓干细胞在肝纤维化中的作用

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## Role of bone marrow stem cells in hepatic fibrosis

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### Abstract

Differentiation of bone marrow stem cells into hepatocytes and their curative roles in liver fibrosis have gained increasing popularity recently. However, further investigation has shown a opposite idea that the bone marrow stem cells don't have this ability. Some researchers have proposed that bone marrow stem cells can differentiate into stellate cells or fibroblasts, hence serving as a participator of hepatic fibrosis. This article aims to review the role of bone marrow cells in hepatic fibrosis.

**Key Words:** Bone marrow cell; Hepatic fibrosis; Hepatocyte; Stellate cell; Fibroblast

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### 摘要

近年来, 对骨髓干细胞向肝细胞分化, 并对肝纤维化的治疗作用的研究日益增多. 随着研究的不断深入有研究者也对这个观点提出反对意见, 认为骨髓干细胞没有这种能力, 同时还

有一些研究者提出骨髓干细胞可以分化成为星状细胞或者成纤维细胞, 从而参与肝纤维化的发生. 本文将骨髓干细胞在肝纤维化中的作用作一阐述.

**关键词:** 骨髓干细胞; 肝纤维化; 肝细胞; 星状细胞; 成纤维细胞

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### 0 引言

作为造血场所的骨髓, 其主要包括两大类的细胞: 造血细胞和骨髓基质细胞. 其中目前普遍比较认可的是骨髓干细胞中具有多向分化潜能的成体干细胞是造血干细胞和骨髓间充质干细胞<sup>[1-3]</sup>. 肝纤维化(hepatic fibrosis)是肝脏受到各种慢性损伤后发生的一种修复反应, 其特征是以胶原为主的细胞外基质(extracellular matrix, ECM)在肝内过多沉积. 在肝纤维化形成过程中, 肝细胞的相对体积、绝对数量均明显减少和肝星状细胞的激活、增殖, 是肝纤维化两个重要的方面<sup>[4-5]</sup>. 因此, 促进肝细胞再生及抑制肝星状细胞的激活和增殖也是逆转肝纤维化的重要途径<sup>[6-9]</sup>. 1999年Petersen首次提出骨髓干细胞在一定条件下可以向肝细胞横向分化, 对于骨髓干细胞的这种新特性的发现, 有些学者认为可以移植自身的骨髓干细胞, 使其向肝细胞分化, 促进肝细胞再生. 随着对这个论点研究的不断深入还有一些研究者提出骨髓干细胞在肝纤维化的过程中不具备横向分化成为肝细胞的能力. 同时, 另外还有一些研究者认为, 在一定条件下骨髓干细胞具有向造成肝纤维生成的细胞分化的能力, 如星状细胞, 成肌纤维细胞等, 是促进肝纤维化的一个重要原因, 治疗肝纤维化就要早期抑制骨髓向肝内移居. 本文将对近些年来, 骨髓干细胞在肝纤维化中的作用的研究作一综述.

### 1 骨髓干细胞在肝纤维化治疗中的作用

#### 1.1 骨髓干细胞向肝细胞分化的体内研究

### ■背景资料

骨髓干细胞是目前研究较多且较深入的一类成体干细胞. 早期的研究主要集中于血液学相关方面, 近年来对髓源干细胞分化潜能的研究层出不穷, 现已证实他不仅能分化为同胚层的细胞, 还能在一定条件下跨系、甚至跨胚层分化成多种组织细胞, 如神经细胞、心肌细胞、骨骼肌细胞等, 具有治疗相应脏器疾病的潜在价值.

### ■同行评议者

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■ 研发前沿  
干细胞是生命科学  
研究领域的  
一个热门话题。

Petersen *et al*<sup>[10]</sup>于1999年最早提出大鼠骨髓干细胞中的某个细胞群体具有转化为肝卵圆细胞,并能够进一步分化为肝细胞和胆管上皮细胞的潜能. Theise *et al*<sup>[11]</sup>对临床移植男性骨髓的女性患者和移植女性肝脏的男性患者的肝脏标本进行研究发现:约4%-43%的肝细胞和4%-38%的胆管细胞来源于骨髓干细胞的横向分化,并且他们发现这种骨髓来源的细胞最多的是1例肝移植后再发丙肝的患者. 对此其他的研究者在他们的研究中也发现了相同的发现<sup>[12-16]</sup>,并且Idilman *et al*<sup>[13]</sup>认为髓源性的肝细胞出现在肝脏损伤的过程的早期.

1.2 骨髓干细胞向肝细胞分化体外研究 在体内实验研究的基础上,日本学者Oh *et al*<sup>[17]</sup>于2000年骨髓干细胞进行了体外诱导. 他们利用加入肝细胞生长因子(hepatocyte growth factor, HGF)的诱导体系,体外诱导3 wk后发现骨髓干细胞转化成为可以表达白蛋白、CK-8和CK-18的一类肝细胞样细胞,同时他们通过RT-PCR的方法检测出大鼠骨髓干细胞中存在这一群表达AFP和c-met的细胞,故认为骨髓中可能包含一些肝脏祖细胞,而这些细胞在HGF的诱导下可转化为肝细胞. 但是这群细胞只表达部分肝细胞标志,只能说明是肝细胞样细胞,于是他们利用加入HGF和表皮生长因子(epidermal growth factor, EGF)的HGM培养大鼠的骨髓干细胞,发现了肝细胞形态样细胞的出现,而且这些细胞表达肝细胞分化终末阶段标志色氨酸-2, 3-二氧合酶(tryptophan-2, 3-dioxygenase, TO)和酪氨酸氨基转移酶(trypsin aminotransferase, TAT)<sup>[18]</sup>. Schwartz *et al*<sup>[19]</sup>在进一步的研究中发现,在一定的条件下,这种来源于骨髓的CD44<sup>+</sup>、CD45<sup>+</sup>、HLA I型<sup>+</sup>、HLA II型<sup>+</sup>和cKit<sup>+</sup>的成体多能干细胞(multipotent adult progenitor cells, MAPCs)可以转化为肝细胞,而这种转化来的肝细胞不仅具有肝细胞的形态和超微结构,同时还表达AFP, ALB, CK18等肝细胞标志,并具有合成糖原,尿素,蛋白等多种肝细胞的功能. 并且通过建立不同的诱导体系,发现骨髓细胞有向肝细胞分化的能力<sup>[20-26]</sup>.

1.3 肝纤维环境是骨髓分化成为肝细胞的适宜环境 Theise *et al*<sup>[27]</sup>对在没有肝损伤的情况下,采用同种异性小鼠间进行骨髓移植,移植后2-6 mo,发现移植存活的小鼠肝脏内大约有2%的骨髓来源的肝细胞. 而McTaggart *et al*<sup>[28]</sup>通过对CCl<sub>4</sub>诱导的小鼠肝纤维化模型和无肝纤维化对

照组小鼠,从尾静脉移植1×10<sup>5</sup>个经绿色荧光蛋白(green fluorescent protein, GFP)标记的骨髓干细胞,1 d后GFP阳性标记细胞的BMC定植在肝小叶门脉周围,4 wk后肝脏中有25%的细胞是GFP阳性标记细胞,而无肝硬化的对照组中却没有GFP阳性的细胞出现. 骨髓移植组的血清白蛋白明显高于非骨髓移植组. 实验结果提示,肝纤维化的环境是骨髓干细胞分化的适宜环境. 董学君 *et al*<sup>[29]</sup>通过在体外,利用损伤肝脏条件培养液成功诱导骨髓干细胞分化成为肝细胞,并在进一步的研究中证明了骨髓间充质干细胞是参与骨髓干细胞分化成为肝细胞的主要细胞之一<sup>[30]</sup>. 由此可以看出骨髓干细胞向肝细胞分化需要具备一定的条件,而肝纤维化可能正是其所需要的条件<sup>[31-33]</sup>.

1.4 骨髓干细胞对肝纤维化的治疗作用 肝纤维化是一个可逆的过程,肝细胞再生是使肝纤维化逆转的一个重要途径. 由于骨髓干细胞具有横向分化的能力,并且在肝纤维化的环境中适宜骨髓干细胞向肝细胞分化,所以有的研究者认为可以利用骨髓干细胞这种分化来逆转肝纤维化<sup>[34-38]</sup>. Sakaida *et al*<sup>[39]</sup>通过对比造成肝纤维化模型后给予骨髓移植处理的小鼠和单纯造成肝纤维化模型小鼠的肝脏中羟脯氨酸(hydroxyproline)的含量,证实了骨髓干细胞移植能够明显的减轻肝纤维化,并且在此研究的基础上发现还可以通过评估血清中的载脂蛋白A1(apolipoprotein A1, apoA1),预见这种骨髓移植的方法对肝纤维化减轻的程度<sup>[40]</sup>. 进而其他的研究者在他们的研究中也发现了相同的发现<sup>[34,41-45]</sup>,且Ishikawa *et al*<sup>[45]</sup>的研究发现成纤维生长因子-2(fibroblast growth factor-2, FGF-2)联合骨髓移植一起给药时,可以使肝纤维化的程度得到更好的改善.

1.5 对骨髓干细胞这种横向分化成为肝细胞能力的质疑 虽然目前有越来越多的实验证明骨髓干细胞可以横向分化成为肝细胞,从而达到逆转肝纤维化的目的,但是还是有研究者对骨髓干细胞的这项能力提出了质疑. Wagers *et al*<sup>[46]</sup>通过移植GFP<sup>+</sup>骨髓造血干细胞到受致死剂量作用的普通小鼠的研究发现,虽然造血干细胞重建了外周血,但在肝脏中分化成为肝细胞的水平却非常低,仅为1/70 000. 而后,日本学者Kanazawa *et al*<sup>[47]</sup>将GFP转基因鼠[TgN(ActbEGFP)]和β-半乳糖苷酶转基因鼠[TgN(MtnLacZ)]的骨髓干细胞分别移植给3个不同的模型: (1)经过放射线处理

的C57BL/6小鼠, 移植后给予CCl<sub>4</sub>造成非选择性的肝损伤; (2)经放射线处理的白蛋白-酪氨酸转基因小鼠[TgN(Alb1Plau)]; (3)经放射线处理的乙肝转基因鼠[TgN(Alb1HBV)]. 通过对每只鼠的 $1.5 \times 10^6$ 肝细胞GFP表达的检测及整个肝脏 $\beta$ -半乳糖苷酶的表达情况进行鉴定, 结果并没有在肝脏中发现骨髓来源的细胞存在. Dahlke *et al*<sup>[48]</sup>认为在使用倒千里光碱(retrorsine)抑制内源性肝细胞再生和CCl<sub>4</sub>联合给药时, 骨髓干细胞对肝脏没有重建的作用. Fogt *et al*在对人体和体外的研究中有相同的发现<sup>[49-51]</sup>.

## 2 骨髓干细胞参与肝纤维化的研究

**2.1 骨髓干细胞向星状细胞的分化** 2004年Forbes *et al*<sup>[52]</sup>在人体的研究中发现, 不同的肝病都有起源于肝外来源的成肌纤维细胞存在, 从而导致肝纤维化的发生. Baba *et al*<sup>[53]</sup>通过把GFP<sup>+</sup>转基因小鼠的骨髓移植给年龄匹配的经过致死剂量放射线照射的普通小鼠, 使其造血系统重建, 再采用密度梯度离心的方法分离星状细胞, 在骨髓移植后12 wk发现有30%的星状细胞来源于骨髓, 这些细胞经过7 d的培养几乎都表达 $\alpha$ -平滑肌肌动蛋白( $\alpha$ -smooth muscle actin,  $\alpha$ -SMA), 同时他们对另外一批接受骨髓移植的小鼠进行CCl<sub>4</sub>注射, 使肝脏受损, 发现在肝纤维化的区域出现了GFP<sup>+</sup>的细胞, 并且这些细胞表达 $\alpha$ -SMA. 因此他们认为在肝纤维化过程中, 肝星状细胞可能来源于骨髓, 并且这种髓源性的星状细胞无论是在静止还是在活化的状态, 都有星状细胞的特点. 而后, Russo *et al*<sup>[54]</sup>提出了骨髓干细胞可以促进肝纤维化发生的这个观点, 他们发现在CCl<sub>4</sub>受损的小鼠肝脏中68%的星状细胞和70%的成肌纤维细胞直接起源于骨髓, 而骨髓来源的肝实质细胞却很少(0.6%), 并且还提出了不同的观点, 认为一部分成肌纤维细胞是直接起源于骨髓, 并且具有产生细胞外基质的能力. Miyata *et al*<sup>[55]</sup>在进一步研究中发现, 骨髓干细胞中表达Lin<sup>-</sup>、Sca-1<sup>+</sup>、c-kit<sup>+</sup>、CD34<sup>+</sup>的造血干细胞在CCl<sub>4</sub>造成肝损伤的情况下, 可以分化成为肝星状细胞.

**2.2 骨髓干细胞向成纤维细胞的分化** 损伤肝组织内的成肌纤维细胞(myofibroblast, MF)合成大量的胶原为主的ECM, 并沉积于肝脏组织内. 正常肝组织并无成肌纤维细胞存在, 可由星状细胞或者门静脉周围的成纤维细胞转化而来<sup>[56]</sup>. Kisseleva *et al*<sup>[57]</sup>采用胆管结扎的造模方式, 在损

伤的肝脏中发现了一群起源骨髓并且合成胶原I型的成纤维细胞, 这些细胞不表达 $\alpha$ -SMA或者结蛋白(desmin), 而是CD45<sup>+</sup>, 而且这些细胞在添加转化生长因子- $\beta$ (transforming growth factor beta, TGF- $\beta$ )的培养基中能够分化成为成肌纤维细胞. 所以他们认为这种骨髓起源的成纤维细胞参与了肝纤维化的发生. Asawa *et al*<sup>[58]</sup>通过他们的研究发现, 在胆管结扎造成的急性肝损伤的早期(7 d)就会有来源于骨髓的成纤维细胞或者成肌纤维样细胞出现在汇管区的纤维化处, 并且他们认为早期阻断胆汁型肝纤维化就应该抑制骨髓向肝中迁移.

## 3 结论

造血干细胞和间充质干细胞作为重要的髓源性多能成体干细胞, 在一定条件下能够跨系、甚至跨胚层分化成多种组织细胞, 但是这种跨系跨胚层的分化是需要一定条件下诱导产生. 那么肝纤维化的这种体内环境是否适于骨髓干细胞的分化, 不同方式造成的肝纤维化环境是否会使骨髓细胞有向不同方向分化的能力? 而且如果存在着可以向肝细胞或者造成纤维化生成的细胞分化的骨髓细胞, 那么这些细胞是否是同一群体的细胞? 这些都将是有待解决和值得讨论的问题.

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## ■创新盘点

本文从体内研究到体外研究两方面论证了骨髓干细胞能否向肝细胞分化.



## ■同行评价

本文选题新颖, 参考文献较新, 具有一定的可读性。

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