REVIEW

骨髓间充质干细胞治疗肝纤维化的研究进展

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: 2007- 07- 23　　: 2007- 11- 02

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Progress in research of treatment of liver fibrosis with mesenchymal stem cells

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Received: 2007-07-23　Revised: 2007-11-02

Abstract

Mesenchymal stem cells, a type of multipotent stem cells, can differentiate into heptocytes. Recently, more and more studies have shown that mesenchymal stem cells are anti-fibrotic and immune-tolerant when transplanted into liver fibrosis models, which brings about a new treatment strategy for liver fibrosis and cirrhosis.

Key Words: Mesenchymal stem cells; Liver fibrosis; Cell therapy; Gene therapy

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关键词:　　　;　　;
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0 引言

肝纤维化、肝硬化是多种慢性肝脏疾病的终末期病理表现, 目前传统的治疗手段难以从根本上修复肝脏的不可逆变化[1-3]. 肝脏原位移植是治疗各种终末期肝病的有效方法, 但是由于供体来源不足、操作复杂、移植后免疫排斥、治疗费用昂贵等问题, 限制了临床肝移植的发展[4-5]. 随着细胞移植技术的成熟, 肝细胞移植治疗有望从根本上治疗肝脏疾病. 而干细胞方面的研究为解决肝细胞来源问题带来了希望.

间充质干细胞(mesenchymal stem cells, MSCs)是一类具有自我增殖和分化潜能的多能干细胞. 由于骨髓来源的间充质干细胞易于取材, 未涉及伦理, 而被广泛应用于实验研究[6-10]. 现将骨髓来源的间充质干细胞(MSCs)治疗肝纤维化的实验进展及机制研究作一综述.

1 MSCs治疗肝纤维化的可行性

现在认为骨髓含有多种干细胞、祖细胞, 包括造血干细胞和间充质干细胞. 早期实验报道造血干细胞能高效植入肝脏, 并分化为肝细胞和胆管上皮细胞, 但最近发现这种现象发生几率很低. 核酸水平研究显示造血干细胞只表达少量肝细胞mRNA, 并不能高效地向肝细胞分化[11]. 而注入体内的MSCs则可广泛分布于肝脏、骨髓、脂肪组织等, 并且可特异地分化成相应的组织细胞[12-13]. MSCs不仅能分化成中胚层组织, 而且越来越多的体内外实验表明MSCs也向功能性肝细胞(非中胚层组织) "横向分化" [14-16]. 这种定位特性和分化潜力为MSCs局部治疗肝脏疾病提供了可行性.

2 MSCs治疗肝纤维化的实验研究

2.1 　　　通过骨髓MSCs体外培养和体内移植, 外源性的MSCs可替代机体骨髓的

MSCs的一部分, 进入正常的生物循环, 并且能掺入肝脏组织向该组织细胞分化[14-18]. 这为MSCs细胞治疗和基因治疗肝纤维化提供了细胞基础.

Peterson *et al*[16]用大鼠先后做了三个用不同细胞标记、性别交叉的骨髓移植实验, 证实移植的大鼠骨髓干细胞能够迁移到受损的肝脏组织中, 并能向肝脏实质细胞分化. 但Peterson所用干细胞并未明确为MSCs. Yamamoto *et al*[19]近年用Liv8-抗体分选骨髓干细胞. 由于Liv8-抗体可以结合E11.5小鼠胎肝上的造血祖细胞, 也可以结合骨髓内CD45阳性造血干细胞, 因此可将骨髓干细胞分成造血干细胞和非造血干细胞. 然后分别将Liv8-阳性和阴性的骨髓干细胞分别植入肝损伤的小鼠体内. 4 wk后, 对照发现Liv8-阴性亚群的骨髓干细胞(非造血干细胞)能更有效地向肝细胞方向分化.

Lee *et al*[20]采用阴性免疫分选系统高效分离出hMSCs, 并且首次采用HGF和Oncostain M二步诱导法体外培养hMSCs. 4 wk后可以看到细胞呈立方形和肝细胞特异的基因标记, 并且具有正常肝细胞功能特性, 包括合成白蛋白、贮存糖原、分泌尿素、摄取低密度脂蛋白, 具有巴比妥诱导的细胞色素P450活性等. 将这些细胞注入肝损伤部位后, 是否也能发挥正常细胞的作用? Oyagi *et al*[21]在体外将MSCs和HGF共同培养2 wk, 然后将其注入CCl_4致肝损伤的大鼠体内. 4 wk后检测到体内白蛋白水平仍稳定, 转氨酶水平和纤维化程度均下降, 实验肯定了HGF诱导后MSCs的治疗作用.

最近, Oe *et al*[22]应用转染HGF和VEGF基因的重组腺病毒治疗肝损伤, 用*E.coli*的β-半乳糖苷基因对照. 结果与对照组相比, HGF和VEGF组的cyclin E表达增加, 显著加快肝卵圆细胞生成, 提高肝脏修复效率, 促进肝脏再生. Hung *et al*[23]用增强绿色荧光(EGFP)技术研究显示, 腺病毒(AdV)在hMSCs上具有很高的转导率(>90%), 并且转导AdV的hMSCs保持多向分化潜能, 4 wk后hMSCs亚群甚至分化成特化细胞系仍有转基因表达[23-25]. 可见, 骨髓间充质干细胞在体外传代后仍有多向分化潜力, 且分化后仍能稳定表达目的基因, 还可避免外源性转染载体进入受体产生的不良影响. 所以MSCs是理想的治疗基因载体[23].

那么是否可应用基因转染技术, 把HGF转染到其他代谢活跃组织让其表达, 以高效诱导

移植的骨髓MSCs向肝细胞分化? 由于MSCs被认为是良好的基因载体, 是否可以把HGF转染给MSCs, 从而发挥两者的修复肝损伤作用? 这些问题还有待进一步实验研究.

2.2　　　　　　　Theise *et al*[26]把男性的骨髓移植给2名女性患者, 又把女性的肝脏移植给4名男性患者. 结果发现男女患者的肝脏内均有Y染色体阳性的肝细胞和胆管细胞, 首次得出人骨髓干细胞同种移植后也能归巢分化为肝细胞的结论.

最近, Terai *et al*[27]报道了9名接受从周围静脉输注自体骨髓细胞治疗的肝硬化患者, 在移植24 wk后, 血清白蛋白、总蛋白水平明显改善($P<0.05$), 显著改善Child-Pugh分级($P<0.05$), 并未观察到任何副作用. 可见自体骨髓间充质干细胞移植可以作为肝纤维化肝硬化的一种新的治疗方法. 但MSCs治疗肝纤维化的临床实验证据颇少, 临床广泛应用尚存距离.

3 MSCs治疗肝纤维化机制

上述实验中MSCs治疗肝纤维化的具体机制尚不清楚, 当前推测主要有以下几个方面.

3.1 MSCs　　　　　　　　　　,

　　　　　　　维持人体正常肝脏功能约需$2.5×10^{10}$个肝细胞. 在肝纤维化特别是肝硬化时, 因过量纤维结缔组织增生挤压, 正常功能的肝细胞数量大为减少. MSCs通过体外诱导然后输注体内, 可随循环植入肝脏增殖分化成肝细胞[20]. Sakaida *et al*[28]实验也表明, 应用MSCs移植可补充大量的肝细胞和胆管细胞(4%-43%), 从而改善肝功能.

3.2 MSCs　　　　　　　／　　　、

　　　　MSCs分泌多种细胞因子和生长因子, 如HGF、ILs、SCF、SDF-1α、TGF-β、TNF-α等. 其中HGF不但具有诱导MSCs自身向肝细胞分化功能, 还抑制TGF-β1产生, 阻止肝脏纤维化, 抗肝细胞凋亡的活性, 从而提高存活率[22,29]. IL-10能破坏TNF的纤维化信号传导通路, 减少纤维化[30-31]. TGF-β1却促进肝星形细胞(hepatic stellate cells, HSCs)的纤维化反应[32], 是肝纤维化最主要的致病因子, 可以激活转录因子NF-κβ, 引起一系列靶基因的激活. 而Di *et al*[33]用骨髓细胞与异体树突状细胞或外周血淋巴细胞共同培养, 结果表达的TGF-β1和HGF显著抑制CD4^{+}和CD8^{+}细胞的增殖活性(65%±5%、75%±15%), 表明MSCs具有很强的抑制免疫排斥和炎症反

应作用.

总之, 在肝损伤环境中MSCs分泌不同水平的细胞因子相互影响[29-39], 表现出抗纤维化、抗炎症反应作用.

3.3 MSCs 、

肝星形细胞是正常肝和纤维化时合成细胞外基质(extracellular matrix, ECM)的主要细胞. HSCs的过度激活导致肝纤维化的发生. 研究发现, HSCs与MSCs体外共培养后, HSCs增殖活性明显受抑制, 说明MSCs具有分泌细胞因子抑制HSCs增殖活性的潜能, 这在治疗肝纤维化中发挥作用[40]. Kim et al[34]认为其机制是MSCs可能通过HGF阻断细胞外信号调节激酶的磷酸化作用, 抑制α-SMA阳性细胞的增殖, 使门脉区成纤维细胞的生长抑制、凋亡增加, 从而缓解肝纤维化进展.

3.4 MSCs ,

卵圆细胞被认为是肝细胞的前体细胞. 当肝脏轻微损伤时肝脏可通过自身的肝细胞增殖修复, 严重时则通过卵圆细胞修复再生[16]. 最近发现, TGF-β/INF-α无论体内外都阻止肝细胞增殖, 而对于卵圆细胞增殖影响不大, 可能TGF/INF-α作用于两种细胞的信号转导机制不同. 实验发现, SDF-1α可以激活卵圆细胞, 在肝细胞再生过程中发挥作用. 因而MSCs在分泌上述细胞因子时起到激活卵圆细胞、促进肝细胞再生作用.

3.5 MSCs ECM

近年认为基质金属蛋白酶(MMPs)具有较强的降解ECM作用[31]. Zhao et al[41]发现肝纤维化时, MMP-2, MT-MMP-2的mRNA和相关抗原表达均升高, 而MMP-2和MT-MMP-2对肝纤维化的逆转起重要作用, 进一步研究证实MSCs是MMP-2和MT-MMP-2抗原的主要来源, 并且其表达水平与肝纤维化密切相关. Sakaida et al[28]实验表明, 骨髓干细胞通过表达高水平的MMPs特别是MMP-9, 降解胶原纤维, 减少实验小鼠的肝纤维化程度, 从而明显改善生存率.

4 目前MSCs应用中亟待解决的问题

4.1 MSCs ,

实施肝细胞移植的前提和关键在于获得大量功能正常的肝细胞, 并且不引发移植排斥反应. 维持人体正常肝脏功能约需2.5×10^{10}个肝细胞, 肝细胞的数量和体积约占肝实质的70%-80%. 然而MSCs在骨髓中含量极少, 大约每5万个骨髓单个核细胞中才有1个MSC. 因此需经过体外扩增才能满足

应用要求.

现在有人提出应用来源丰富的脂肪间充质干细胞[6], 但这一领域还有待深入研究.

4.2 MSCs

虽然Dominici et al[42]提出了间充质干细胞的界定标准, 但对其特征性的表面标志还不甚明了. SSEA-4抗原一直被用来鉴定人胚胎干细胞. 最近研究[43]发现他也可作为间充质干细胞的表面标志, 为提高MSCs的分离鉴定效率和特异性提供帮助. 正常肝细胞标记包括c-kit, CD34, OV6, CK7, CK19, chromogranineA, CD56等. 但因为他们并非特异性标记, 所以确定MSCs是否向肝细胞分化仍存困难.

4.3 MSCs

干细胞应用于临床治疗的一种风险就是可能导致干细胞的恶性增殖. 最近Wu et al[44]认为肝癌可能源自骨髓细胞的转分化. 骨髓干细胞可以分化为卵圆细胞, 卵圆细胞可以分化为肝细胞和胆管上皮细胞, 而不同阶段的肝干细胞的分化谱系都可能有肝癌细胞产生. Russo et al[45]提出MSCs还可能有促进肝纤维化的作用. 在他们的肝纤维化模型中, 骨髓间充质干细胞转分化为肝细胞的量很少(0.6%). 相比之下, 大部分转分化为肝星状细胞和肌成纤维细胞(68%, 70%). 所以对于骨髓细胞治疗的临床应用要慎重.

总之, 由于当前对骨髓间充质干细胞治疗肝纤维化的机制在很大程度上未知, 骨髓间充质干细胞的临床治疗存在疑虑和潜在的危险. 但是随着生物技术的发展, 利用MSCs的生物学特性, 在分子水平上将外源细胞因子和目的基因用于细胞归巢和定向分化的调控, 有望使骨髓间充质干细胞广泛应用于临床肝纤维化的治疗.

5 参考文献

1 Sobaniec-Lotowska ME, Lotowska JM, Lebensztejn DM. Ultrastructure of oval cells in children with chronic hepatitis B, with special emphasis on the stage of liver fibrosis: the first pediatric study. *World J Gastroenterol* 2007; 13: 2918-2922

2 Marra F, DeFranco R, Robino G, Novo E, Efsen E, Pastacaldi S, Zamara E, Vercelli A, Lottini B, Spirli C, Strazzabosco M, Pinzani M, Parola M. Thiazolidinedione treatment inhibits bile duct proliferation and fibrosis in a rat model of chronic cholestasis. *World J Gastroenterol* 2005; 11: 4931-4938

3 He YT, Liu DW, Ding LY, Li Q, Xiao YH. Therapeutic effects and molecular mechanisms of anti-fibrosis herbs and selenium on rats with hepatic fibrosis. *World J Gastroenterol* 2004; 10: 703-706

4 Noble-Jamieson G, Valente J, Barnes ND, Friend PJ, Jamieson NV, Rasmussen A, Calne RY. Liver

transplantation for hepatic cirrhosis in cystic fibrosis. *Arch Dis Child* 1994; 71: 349-352

5   Ben-Ari Z, Pappo O, Zemel R, Mor E, Tur-Kaspa R. Association of lamivudine resistance in recurrent hepatitis B after liver transplantation with advanced hepatic fibrosis. *Transplantation* 1999; 68: 232-236

6   Talens-Visconti R, Bonora A, Jover R, Mirabet V, Carbonell F, Castell JV, Gomez-Lechon MJ. Hepatogenic differentiation of human mesenchymal stem cells from adipose tissue in comparison with bone marrow mesenchymal stem cells. *World J Gastroenterol* 2006; 12: 5834-5845

7   Shu SN, Wei L, Wang JH, Zhan YT, Chen HS, Wang Y. Hepatic differentiation capability of rat bone marrow-derived mesenchymal stem cells and hematopoietic stem cells. *World J Gastroenterol* 2004; 10: 2818-2822

8   Chen LB, Jiang XB, Yang L. Differentiation of rat marrow mesenchymal stem cells into pancreatic islet beta-cells. *World J Gastroenterol* 2004; 10: 3016-3020

9   Zhao DC, Lei JX, Chen R, Yu WH, Zhang XM, Li SN, Xiang P. Bone marrow-derived mesenchymal stem cells protect against experimental liver fibrosis in rats. *World J Gastroenterol* 2005; 11: 3431-3440

10   Moriya K, Yoshikawa M, Saito K, Ouji Y, Nishiofuku M, Hayashi N, Ishizaka S, Fukui H. Embryonic stem cells develop into hepatocytes after intrasplenic transplantation in CCl4-treated mice. *World J Gastroenterol* 2007; 13: 866-873

11   Lian G, Wang C, Teng C, Zhang C, Du L, Zhong Q, Miao C, Ding M, Deng H. Failure of hepatocyte marker-expressing hematopoietic progenitor cells to efficiently convert into hepatocytes in vitro. *Exp Hematol* 2006; 34: 348-358

12   Liechty KW, MacKenzie TC, Shaaban AF, Radu A, Moseley AM, Deans R, Marshak DR, Flake AW. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. *Nat Med* 2000; 6: 1282-1286

13   Wu XH, Liu CP, Xu KF, Mao XD, Zhu J, Jiang JJ, Cui D, Zhang M, Xu Y, Liu C. Reversal of hyperglycemia in diabetic rats by portal vein transplantation of islet-like cells generated from bone marrow mesenchymal stem cells. *World J Gastroenterol* 2007; 13: 3342-3349

14   Zhang Y, Fan Y, Zhao L, Tang H. Differentiation of mouse bone marrow mesenchymal stem cells into hepatocyte in vivo. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 2005; 22: 521-524

15   Chen M, Wang GJ, Diao Y, Xu RA, Xie HT, Li XY, Sun JG. Adeno-associated virus mediated interferon-gamma inhibits the progression of hepatic fibrosis in vitro and in vivo. *World J Gastroenterol* 2005; 11: 4045-4051

16   Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS, Greenberger JS, Goff JP. Bone marrow as a potential source of hepatic oval cells. *Science* 1999; 284: 1168-1170

17   Lange C, Bruns H, Kluth D, Zander AR, Fiegel HC. Hepatocytic differentiation of mesenchymal stem cells in cocultures with fetal liver cells. *World J Gastroenterol* 2006; 12: 2394-2397

18   Li W, Liu SN, Luo DD, Zhao L, Zeng LL, Zhang SL, Li SL. Differentiation of hepatocytoid cell induced from whole-bone-marrow method isolated rat myeloid mesenchymal stem cells. *World J*

19   Yamamoto N, Terai S, Ohata S, Watanabe T, Omori K, Shinoda K, Miyamoto K, Katada T, Sakaida I, Nishina H, Okita K. A subpopulation of bone marrow cells depleted by a novel antibody, anti-Liv8, is useful for cell therapy to repair damaged liver. *Biochem Biophys Res Commun* 2004; 313: 1110-1118

20   Lee KD, Kuo TK, Whang-Peng J, Chung YF, Lin CT, Chou SH, Chen JR, Chen YP, Lee OK. In vitro hepatic differentiation of human mesenchymal stem cells. *Hepatology* 2004; 40: 1275-1284

21   Oyagi S, Hirose M, Kojima M, Okuyama M, Kawase M, Nakamura T, Ohgushi H, Yagi K. Therapeutic effect of transplanting HGF-treated bone marrow mesenchymal cells into CCl4-injured rats. *J Hepatol* 2006; 44: 742-748

22   Oe H, Kaido T, Mori A, Onodera H, Imamura M. Hepatocyte growth factor as well as vascular endothelial growth factor gene induction effectively promotes liver regeneration after hepatectomy in Solt-Farber rats. *Hepatogastroenterology* 2005; 52: 1393-1397

23   Hung SC, Lu CY, Shyue SK, Liu HC, Ho LL. Lineage differentiation-associated loss of adenoviral susceptibility and Coxsackie-adenovirus receptor expression in human mesenchymal stem cells. *Stem Cells* 2004; 22: 1321-1329

24   Abbas Z, Moatter T, Hussainy A, Jafri W. Effect of cytokine gene polymorphism on histological activity index, viral load and response to treatment in patients with chronic hepatitis C genotype 3. *World J Gastroenterol* 2005; 11: 6656-6661

25   Tsui TY, Lau CK, Ma J, Glockzin G, Obed A, Schlitt HJ, Fan ST. Adeno-associated virus-mediated heme oxygenase-1 gene transfer suppresses the progression of micronodular cirrhosis in rats. *World J Gastroenterol* 2006; 12: 2016-2023

26   Theise ND, Nimmakayalu M, Gardner R, Illei PB, Morgan G, Teperman L, Henegariu O, Krause DS. Liver from bone marrow in humans. *Hepatology* 2000; 32: 11-16

27   Terai S, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujii Y, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006; 24: 2292-2298

28   Sakaida I, Terai S, Nishina H, Okita K. Development of cell therapy using autologous bone marrow cells for liver cirrhosis. *Med Mol Morphol* 2005; 38: 197-202

29   Shi MN, Huang YH, Zheng WD, Zhang LJ, Chen ZX, Wang XZ. Relationship between transforming growth factor beta1 and anti-fibrotic effect of interleukin-10. *World J Gastroenterol* 2006; 12: 2357-2362

30   Shi MN, Zheng WD, Zhang LJ, Chen ZX, Wang XZ. Effect of IL-10 on the expression of HSC growth factors in hepatic fibrosis rat. *World J Gastroenterol* 2005; 11: 4788-4793

31   Zheng WD, Zhang LJ, Shi MN, Chen ZX, Chen YX, Huang YH, Wang XZ. Expression of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 in hepatic stellate cells during rat hepatic fibrosis and its intervention by IL-10. *World J Gastroenterol* 2005; 11: 1753-1758

32   Fang B, Shi M, Liao L, Yang S, Liu Y, Zhao RC.

Systemic infusion of FLK1(+) mesenchymal stem cells ameliorate carbon tetrachloride-induced liver fibrosis in mice. *Transplantation* 2004; 78: 83-88

33 Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, Gianni AM. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood* 2002; 99: 3838-3843

34 Kim WH, Matsumoto K, Bessho K, Nakamura T. Growth inhibition and apoptosis in liver myofibroblasts promoted by hepatocyte growth factor leads to resolution from liver cirrhosis. *Am J Pathol* 2005; 166: 1017-1028

35 Prosser CC, Yen RD, Wu J. Molecular therapy for hepatic injury and fibrosis: where are we? *World J Gastroenterol* 2006; 12: 509-515

36 Kang XQ, Zang WJ, Bao LJ, Li DL, Song TS, Xu XL, Yu XJ. Fibroblast growth factor-4 and hepatocyte growth factor induce differentiation of human umbilical cord blood-derived mesenchymal stem cells into hepatocytes. *World J Gastroenterol* 2005; 11: 7461-7465

37 Song SL, Gong ZJ, Zhang QR, Huang TX. Effects of Chinese traditional compound, JinSanE, on expression of TGF-beta1 and TGF-beta1 type II receptor mRNA, Smad3 and Smad7 on experimental hepatic fibrosis in vivo. *World J Gastroenterol* 2005; 11: 2269-2276

38 Jiang W, Yang CQ, Liu WB, Wang YQ, He BM, Wang JY. Blockage of transforming growth factor beta receptors prevents progression of pig serum-induced rat liver fibrosis. *World J Gastroenterol* 2004; 10: 1634-1638

39 Lange C, Bassler P, Lioznov MV, Bruns H, Kluth D, Zander AR, Fiegel HC. Liver-specific gene expression in mesenchymal stem cells is induced by liver cells. *World J Gastroenterol* 2005; 11: 4497-4504

40 Parekkadan B, van Poll D, Megeed Z, Kobayashi N, Tilles AW, Berthiaume F, Yarmush ML. Immunomodulation of activated hepatic stellate cells by mesenchymal stem cells. *Biochem Biophys Res Commun* 2007; 363: 247-252

41 Zhao ZH, Xin SJ, Zhao JM, Wang SS, Liu P, Yin TY, Zhou GD. Dynamic expression of matrix metalloproteinase-2, membrane type-matrix metalloproteinase-2 in experimental hepatic fibrosis and its reversal in rat. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi* 2004; 18: 328-331

42 Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; 8: 315-317

43 Gang EJ, Bosnakovski D, Figueiredo CA, Visser JW, Perlingeiro RC. SSEA-4 identifies mesenchymal stem cells from bone marrow. *Blood* 2007; 109: 1743-1751

44 Wu XZ, Chen D. Origin of hepatocellular carcinoma: role of stem cells. *J Gastroenterol Hepatol* 2006; 21: 1093-1098

45 Russo FP, Alison MR, Bigger BW, Amofah E, Florou A, Amin F, Bou-Gharios G, Jeffery R, Iredale JP, Forbes SJ. The bone marrow functionally contributes to liver fibrosis. *Gastroenterology* 2006; 130: 1807-1821

• 消息 •

本刊讯 世界华人消化杂志要求所有署名人写清楚自己对文章的贡献. 第一方面是直接参与, 包括: (1)酝酿和设计实验, (2)采集数据, (3)分析/解释数据. 第二方面是文章撰写, 包括: (1)起草文章, (2)对文章的知识性内容作批评性审阅. 第三方面是工作支持, 包括: (1)统计分析, (2)获取研究经费, (3)行政、技术或材料支持, (4)指导, (5)支持性贡献. 每个人必须在第一至第三方面至少具备一条, 才能成为文章的署名作者. 世界华人消化杂志不设置共同第一作者和共同通信作者.