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文献综述 REVIEW

骨髓干细胞定向分化为肝样细胞的研究进展

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■背景资料
干细胞独特的生物学特性决定其具有广泛的应用价值, 骨髓干细胞成为近几年的研究热点, 被认为是治疗一些临床终末期疾病的新途径.

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Research progress in directional differentiation from bone marrow stem cells into hepatocyte-like cells

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Abstract
Recent researches indicate that bone marrow stem cells not only can differentiate into bone, cartilage, fat, muscle cells and various blood cells, but also can differentiate into cells of trans-germinal layer, such as ectoderm original neuronal cells, endoderm original hepatocytes, insular cells, under suitable microenvironment. It is called "plasticity" or "trans-differentiation". This paper reviews the research advances that bone marrow stem cell differentiation into hepatocyte-like cells and their clinical application in liver disease treatment.

Key Words: Bone marrow stem cells; Cell differentiation; Cell transplantation; Liver disease

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摘要
近年来研究表明, 在适宜的微环境下, 骨髓干细胞不但可以分化为骨、软骨、脂肪、肌细胞和各种血细胞, 而且还可以跨越胚层向外胚层起源的神经元细胞及内胚层起源的肝细胞、胰岛细胞等分化, 称为"可塑性(plasticity)"或"横向分化(trans-differentiation)". 本文就骨髓干细胞分化为肝样细胞及其临床治疗肝系疾病做一综述.

关键词: 骨髓干细胞; 细胞分化; 细胞移植; 肝病

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0 引言
目前, 终末期肝病的治疗十分棘手, 原位肝移植一直被认为是最理想的方法, 但由于其缺乏供体、手术风险大、费用昂贵、存在免疫排斥反应等因素限制了其广泛应用[1-2]. 近年来, 干细胞研究为利用干细胞移植治疗终末期肝病提供了新的思路. 骨髓干细胞由于其可以跨越胚层横向分化为各种组织细胞[3-20], 包括向肝样细胞分化, 并且具备取材方便、体外培养技术成熟等优点, 使其自体细胞移植在治疗终末期肝病方面更具广阔的应用前景, 备受广大研究者的青睐.

1 骨髓干细胞向肝样细胞分化
骨髓干细胞(bone marrow stem cell, BMSC)是指骨髓起源的干细胞. 主要有两种: 造血干细胞(hemopoietic stem cells, HSCs)和间充质干细胞(marrow mesenchymal stem cells, MSCs). 分化研究主要分体外和体内研究两个方面.

1.1 体外分化研究 骨髓干细胞体外分化研究主要集中在利用组合不同生长因子、使用不同

的培养基、与肝细胞或肝非实质细胞共培养以及加入胆淤血清或肝衰竭患者血清等进行定向诱导. Oh *et al*[2]从大鼠骨髓中分离到表达c-Met mRNA及癌胚抗原mRNA的细胞, 加入肝细胞生长因子(hepatocyte growth factor, HGF)诱导培养21 d后, 该细胞表达肝细胞特异性标记如细胞因子8(cytokeratin, CK8)和CK18. Lee *et al*[22]在培养骨髓和脐血来源的MSCs时, 先加入表皮生长因子(epidermal growth factor, EGF)和成纤维细胞生长因子(fibroblast growth factor, FGF), 后加入烟酰胺、制瘤素M(oncostatin M, OSM)等进行诱导, 结果发现不同来源的MSCs均可分化为具有肝细胞功能的类肝样细胞. 鲁学恒 *et al*[23]和张瑞 *et al*[24]利用组合不同生长因子进行诱导, 得出类似结果. 应用不同培养基中也可以诱导出肝样细胞, Miyazaki *et al*[25]在HGM培养基中加入HGF和EGF, 将骨髓中表达AFP和c-Met同时表达造血干细胞特异性标记CD34、Thy-1及c-kit等的细胞诱导分化为成熟肝细胞. Kang *et al*[26]在低糖DMEM培养基中加入HGF和FGF-4, 可将大鼠骨髓MSCs分化为肝样细胞. 骨髓干细胞与肝细胞或与肝组织液共培养方面也有一些研究. Inderbitzin *et al*[27]从大鼠骨髓中分离出表达β2-微球蛋白-/Thy-1+的细胞亚群, 与肝细胞共培养, 结果发现该细胞亚群的氨代谢提高. Lange *et al*[28]将大鼠的MSCs与鼠肝细胞共培养, 诱导2 wk后, RT-PCR检测发现有肝特异标记ALB和CK-18的RNA表达. Jang *et al*[29]将雄性正常大鼠Fr25lin-PKH+HSC与雌性肝损伤大鼠的肝组织液共培养, 24 h后HSC表达肝转录因子(如AFP、GATA4)和成熟肝细胞标记(如CK18、ALB), FISH技术分析表明只有XYXY核型, 表明HSC参与受损肝脏的修复. 另据实验表明, 利用肝病患者血清进行诱导, 也取得相似结果. Yamazaki *et al*[30]用5-氮杂胞苷处理小鼠骨髓细胞, 12 h后与肝脏非实质细胞共培养, 再用肝衰竭患者血清、OSM、HGF、地塞米松诱导2 wk, 发现肝样细胞集落表达肝细胞标志物. Cai *et al*[31]研究发现含胆汁的血清也可以将骨髓MSCs诱导为肝细胞. 张淑芹 *et al*[32]将重型肝病患者血清与人骨髓MSCs共培养, 诱导后5 d、骨髓MSCs表现为肝细胞样细胞, 随着诱导培养时间的延长, 肝特异性标志物逐渐出现和成熟. AFP在7 d时表达水平最高, 培养14、21、28 d时表达逐渐减弱; Alb、CK-18和糖原随着诱导时间的延长, 表达逐渐增强. 其他学者也做了相关研究[33-35], 都可以表明体外适宜条件可以促进骨髓干细胞向功能性肝样细胞分化.

1.2 体内分化研究 体内实验研究表明, 骨髓细胞或纯化后的骨髓干细胞可在体内转化为肝前体细胞或肝样细胞, 并能发挥肝细胞的部分功能. 一些学者通过骨髓交叉移植方法证实动物肝脏中确实存在骨髓源性的成熟肝细胞[36-39]. Lagasse *et al*[40]将正常小鼠骨髓干细胞移植到延胡索酸乙酰乙酸羟化酶基因缺陷(fumarylace toacetate hydrolase gene, FAH)小鼠体内, 发现肝功能明显改善, 分化的肝细胞具有正常功能. Avital *et al*[41]利用免疫磁珠法分选出人和大鼠骨髓β2m-/Thy-1+细胞, 通过门静脉植入同系胆汁淤积大鼠肝内, 电镜下发现植入细胞具有与成熟肝细胞类似的细胞器超微结构, 并表达ALB、AFP、CK-18等肝细胞特异性标志, 而且能将氨转化为尿素. 在肝损伤动物模型体内的分化研究也比较多, Wang *et al*[42]研究发现, 肝损伤时造血干细胞也可向肝细胞横向分化, 而rhHGF对分化起促进作用. Yamamoto *et al*[43]利用mAb从GFP转基因大鼠骨髓中分选出anti-Liv8阴性细胞, 经尾静脉移植入到持续性肝损伤的小鼠模型体内, 4 wk后发现多数移植细胞集中于门静脉周围的肝实质内, 同时表达Liv2和ALB. Sato *et al*[44]研究发现人骨髓MSCs可以在烯丙醇大鼠肝损伤模型体内表达AFP、ALB、CK18/19和去唾液酸糖蛋白受体(asialoglycoprotein recptor, ACPR), FISH技术分析发现, 细胞中人Y染色体杂交信号阳性, 大鼠染色体杂交信号阴性. 终末期肝病模型动物体内骨髓干细胞同样可以分化为肝样细胞. 展玉涛 *et al*[45]向肝纤维化模型大鼠体内自体移植骨髓Thy+CD3-CD45RA-细胞并进行间接荧光免疫组化和PKH26-GL标记, 结果发现标记细胞可以表达ALB、CK8. Abdel Aziz *et al*[46]将雄性大鼠骨髓中CD29+ MSCs通过尾静脉移植入肝纤维化模型♂大鼠体内, RT-PCR检测证实雌性大鼠肝组织中Y染色体阳性, 肝功能检测血清ALB显著增加, 肝胶原基因表达显著下降, 羟脯氨酸下降. 提示, MSCs在体内可以分化为肝样细胞, 并通过减少胶原沉积来发挥其抗纤维化作用. Terai *et al*[47]在肝硬化小鼠体内注入GFP标记的骨髓细胞, 1 d后发现GFP阳性标记细胞定植在肝小叶门脉周围, 4 wk后肝脏中有25%的细胞为阳性标记细胞, 血清ALB明显升高. 以上表明, 体内环境和肝脏本身微环境是促进骨髓干细胞向肝样细胞转化的关键因素, 分

■研发前沿
现阶段骨髓干细胞研究主要集中在特定条件下促使其向特定方向分化. 而临床应用方面的研究尚处于起步阶段, 有待于进一步深入.

■创新盘点
本文就骨髓干细胞体内外向肝样细胞分化及其在肝系疾病治疗方面的研究, 进行一定的总结.

■应用要点
骨髓干细胞分化为肝样细胞的研究为临床干细胞治疗终末期肝病提供新的思路, 而自体骨髓干细胞移植更具实用价值.

化的肝样细胞能够对损伤肝脏起到一定的修复作用.

关于分化机制存在很多说法. 一些学者认为骨髓干细胞主要通过转分化为不同组织来源的细胞, 从而修复损伤组织[48-51]. 另一些学者认为肝损伤时BMSC主要通过细胞融合产生肝细胞, 而不是分化的结果[52-55]. 还有学者持否定态度, 认为肝脏再生和修复时确实存在BMSC分化而来的肝细胞, 但对肝脏再生作用不大[56-57]. 但是, 大量研究还是倾向于BMSC能够分化为肝样细胞, 并参与了损伤肝脏的修复, 尽管分化机制目前尚不明确.

2 临床应用现状及存在问题

目前, 骨髓干细胞自体移植在临床治疗终末期肝病方面的研究尚处起步阶段, 但已呈现出巨大应用前景. 曾伟导 *et al*[58]对肝硬化失代偿期患者采集自体骨髓125 mL, 提取干细胞总数约8.43×10^6, 经肝动脉注入肝内, 结果发现症状明显好转, 肝性脑病得到控制, 肝功指标恢复正常, 腹水、胸水减少. 姚鹏 *et al*[59]通过肝动脉插管对重症肝病患者进行自体MSCs移植, 结果发现患者肝功能和凝血功能明显改善, 临床症状明显好转, 无并发症. Ivantes *et al*[60]对259例做过骨髓干细胞移植的丙型肝炎患者进行研究, 移植后10年发现, 有91例存活, 而携带丙肝抗体患者的肝纤维化发生率降低. 曹葆强 *et al*[61]对20例肝硬化门静脉高压症患者进行脾切除、断流术或内镜食道曲张静脉套扎术时, 埋置“门静脉导管-皮下药盒”, 术后3-4 wk经移植通道输注自体骨髓细胞, 后每隔1 mo输注1次, 共3次, 第3次输注后1 mo进行疗效评价, 结果发现肝脏功能和肝纤维化血清学指标都得到显著改善, 无不良反应和并发症. 尽管自体骨髓干细胞移植临床应用现状喜人, 但仍有一些问题急需解决: (1) 如何进一步完善骨髓干细胞的体外分离、培养、鉴定等技术, 确保其更好向肝细胞定向分化和扩增; (2)移植方式、部位、最佳时机的选择以及移植细胞的最佳数量有待进一步探讨; (3)需要建立一个有效的体内跟踪体系, 以便更好地观察骨髓干细胞在体内的归巢和定位; (4)在细胞因子等调控下骨髓干细胞向肝细胞诱导分化的分子机制需进一步研究; (5)自体骨髓干细胞移植的长期疗效和安全性还有待进一步观察.

3 结论

干细胞在各个领域都逐步发挥出他无与伦比的潜力. 在终末期肝病治疗方面, 自体骨髓干细胞移植具有取材方便、体外培养扩增容易、不易受病毒、肿瘤污染, 无移植免疫排斥反应、创伤小, 价格低廉等优点, 与原位肝移植、生物人工肝等相比更具显著优势, 因而具有更为广阔的应用前景. 虽然发现BMSC具备向肝样细胞分化的潜能和有一些初步的临床观察结果, 但涉及临床应用, 目前还有许多基础理论和技术问题需要解决, 比如移植治疗细胞的来源、数量和活性问题, 细胞进入组织的途径和机制, BMSC向肝样细胞分化的调控机制, 体内不同疾病状态下的微环境条件对BMSC迁移、定居、分化和功能的影响, 长期疗效和可控性、安全性等. 只有在解决基础理论问题的基础上, 才有可能建立适于临床应用的技术方法. 随着细胞工程、蛋白组学、基因工程、糖基工程和相关技术的发展及其在BMSC研究中的应用, BMSC横向分化为肝细胞的研究将逐步深入, 骨髓干细胞自体移植技术将逐步完善, 相信骨髓干细胞最终能够获得真正意义上向肝细胞分化, 并达到病变肝的有效功能替代, 结果将为临床治疗终末性肝病患者带来新的希望.

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■**名词解释**

1 细胞融合: 又称细胞杂交(cell hybridization), 是指两个或两个以上的细胞融合成一个细胞的现象. 2 自体干细胞移植: 在大剂量放、化疗前采集自体造血干细胞, 使之免受大剂量放、化疗造成的损伤, 并在大剂量放、化疗后回输. 自体造血干细胞可取自骨髓, 亦可取自外周血, 前者称自体骨髓移植,后者称自体外周血干细胞移植, 统称“自体干细胞移植”.

■同行评价
本文对骨髓干细胞定向分化为肝样细胞的研究状况进行了综述, 文笔流畅, 表述较清晰, 选题有一定新颖性, 有一定的学术价值.

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