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文献综述 REVIEW

基质细胞衍生因子1对骨髓间充质干细胞的趋化作用

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■背景资料
近年来, 随着干细胞研究热潮的不断兴起, 骨髓间充质干细胞越来越受到重视, 他具有可塑性强、取材方便以及容易培养等优点, 但也存在很多问题尚待解决, 核心问题之一就是移植细胞在宿主体内的迁移和转化情况. 趋化因子SDF-1具有广泛的生物活性, 最初认为对造血干细胞的归巢有重要作用, 近年来研究发现其对骨髓间充质干细胞也有趋化作用.

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Chemotaxis of stromal cell-dirived factor-1 on bone marrow mesenchymal stem cells

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Abstract
Bone marrow stem cells (BMC) mainly include hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC). MSC not only have the potential capability of self-renewal and multi-directional differentiation, but also have a higher plasticity to differentiate into a variety of cells under the specific conditions. In addition, MSC can be easily obtained, and have been extensively studied in recent years. Many studies *in vivo* and *in vitro* have confirmed that some cytokines can influence the microenvironment of transplanted cells, resulting in the mobilization, migration and differentiation of BMC. Stromal cell-derived factor-1 (SDF-1) is a CXC-type chemokine with a wide biological activity, and it also has chemotaxis effect on BMC, which is reviewed in this article.

Key Words: Stromal cell-dirived factor-1; Bone mesenchymal stem cell; Chemotaxis

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摘要
骨髓干细胞主要由造血干细胞和间充质干细胞组成, 其中骨髓间充质干细胞除具有自我更新和多向分化的潜能外, 更具有很强的可塑性, 在一定的诱导条件下能向多细胞分化, 且其相对容易获得, 成为近年来研究的热点. 许多体内外试验证实, 细胞因子可以影响移植细胞的微环境, 进而影响骨髓干细胞的动员、迁移及分化. 基质细胞衍生因子1是一类对免疫细胞有趋化作用的小分子蛋白, 属于CXC趋化因子之一, 具有广泛的生物学活性, 对骨髓干细胞亦有趋化作用, 现就SDF-1对骨髓间充质干细胞的趋化作用作一综述.

关键词: 基质细胞衍生因子1; 骨髓间充质干细胞; 趋化作用

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0 引言
骨髓中主要包括两种多能干细胞, 即造血干细胞(hematopoietic stem cells, HSC)和间充质干细胞(mesenchymal stem cells, MSC). 其中, MSC是与HSC截然不同的一类干细胞, 除具有自我更新和多向分化的潜能外, 更具有很强的可塑性, 在一定的诱导条件下能分化为多种细胞, 且取材方便、培养容易、增殖较快. 近年来, 随着对干细胞的研究和应用热潮的不断兴起, 骨髓间充质干细胞越发受到重视. 众多体内外实验表明细胞因子可以影响干细胞移植的微环境[1-6], 进而影响骨髓间充质干细胞的动员、迁移及分化. 基质细胞衍生因子1(stromal cell-derived factor-1, SDF-1)是属于CXC趋化因子之一, 具有广泛的生物学活性, 在造血、神经、心血管系统发育以及人类免疫缺陷病毒(human immuno deficiency virus, HIV)感染中发挥重要作用. 本文就SDF-1对骨髓间充质干细胞的趋化作用作一综述.

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1 SDF-1及其受体

1.1 SDF-1 趋化因子是一类对免疫细胞有趋化作用的小分子蛋白质, M_r为8000-14 000, 可分为CXC、CC、C和CX3C这4个家族. Nagasawa *et al*[7]首先在小鼠骨髓基质细胞分泌的细胞因子中发现了SDF-1, 他包括SDF-1α和 SDF-1β, 两者的区别在于前者比后者少4个氨基酸[8]. 根据其氨基酸序列将其归类于趋化因子CXC亚家族, 命名为CXCL12. 现已知SDF-1在大脑、心、肺、肝、骨骼肌、胸腺、脾和肾等多种组织中都有表达[9]. SDF-1种群间保守性极强, 人源性SDF-1和鼠源性SDF-1同源性高达99%, 人源SDF-1基因定位已经明确, 其基因位于10号染色体长臂[10]. SDF-1其受体CXCR4(又称LESTR), 是一个有7个跨膜结构域的G蛋白耦联的受体, 在白细胞、$CD34^+$造血干细胞及$CD34^+$祖细胞表面都有广泛表达[11]. 最初认为CXCR4是SDF-1惟一的受体[12], 并将SDF-1与CXCR4特异性结合称为SDF-1/CXCR4轴. 近几年研究发现SDF-1的另一受体CXCR7, 曾称为孤儿受体RDC1[13], 他主要表达于许多肿瘤细胞系、活化的内皮细胞及胎肝细胞, 大多数正常细胞表面不表达, 但内部能检测到丰富的CXCR7[14].

1.2 SDF-1与其受体的相互作用 SDF-1具有广泛的生物学活性, 在维持造血、神经及心血管系统的发育、干细胞运动、血管形成、凋亡以及肿瘤发生、HIV感染中发挥重要的生物学作用, SDF-1与其受体结合, 是SDF-1发挥其生物学效应的基础. 目前SDF-1和CXCR4的结合动力学尚存争论, 大部分研究支持SDF-1和CXCR4相互作用的双位点模型(two site model), 即CXCR4 N端首先与SDF-1 N端第12-17位氨基酸(R-F-F-E-S-H)结合, 启动SDF-1和CXCR4构象的变化, SDF-1 N端处于无序状态的第1-11位氨基酸(K-P-V-S-L-S-Y-R-CPC-)形成特定构象, 并与CXCR4螺旋区的凹槽结合, 从而诱导CXCR4跨膜螺旋区的构象变化, G蛋白复合物中的Gα亚基和Gβγ亚基解离, Gβγ亚基结合和活化磷脂酶C、磷脂酰肌醇-3激酶和腺苷环化酶等, 引起一系列细胞内信号传递, 使细胞活化, 产生趋化运动, 细胞定向迁移至趋化因子浓度较高的组织器官部位[15]. 而SDF-1与CXCR7的作用机制尚不明确, 有研究认为CXCR7通过CXCR4对SDF-1进行信号转导[16], 也有人认为CXCR7和CXCR4相对独立的作用于SDF-1[17-18].

2 骨髓间充质干细胞

2.1 生物学特性 MSC又称骨髓基质干细胞(bone marrow stromal cells), 是一种存在于骨髓中的非造血干细胞, 具有自我更新、分化增殖和多向分化潜能, 在特定的微环境和适宜的细胞因子作用下可分化为中胚层和神经外胚层组织细胞, 如成骨细胞、软骨细胞、脂肪细胞、内皮细胞、肌肉细胞、心肌细胞和神经细胞等[19-23]. MSC在无诱导物的培养液中生长成纺缍状成纤维细胞样, 并表达SH2、SH3、CD29、CD44、CD27、CD90、CD105、CD106、CD166、CD120a和CD124[24-25], 而缺乏造血干细胞表面的CD34和白细胞表面的CD45标志.

2.2 免疫学特性 近年来不少研究发现将同种异体的或异种的MSC通过局部直接注射、蛛网膜下腔植入、动脉、静脉移植等途径植入后, 在受者体内并未发生免疫排斥, 表明MSC有特殊的免疫学特征: (1)MSC表达组织相容性复合物Ⅰ而不表达组织相容性复合物Ⅱ, 且缺乏共刺激因子的表达, 因此免疫原性较弱[26-27]. (2)MSC能直接或间接抑制T细胞的功能, 同时对$CD4^+$和$CD8^+$淋巴细胞也有抑制作用[28]. (3)MSC具有免疫调节的功能[29].

3 SDF-1对MSC的趋化作用

3.1 趋化作用 1997年, Aiuti *et al*[30]首次发现SDF-1是$CD34^+$造血干细胞的趋化因子, 提出$CD34^+$细胞可能沿SDF-1浓度梯度向骨髓迁移实现归巢. 随后, 大量的研究不断证实SDF-1在骨髓干细胞的细胞迁移中起重要作用, 并且发现来源于骨髓、脐血动员的外周血中的$CD34^+$造血干/祖细胞表面表达其相应受体CXCR4, 而SDF-1能特异性地对CXCR4产生趋化作用[12]. 研究证实, MSC可表达CXCR4[31], 但有人认为MSC只有少部分表达CXCR4. Wynn *et al*[32]通过流式细胞术检测显示活化的CXCR4仅表达于小部分MSC亚型的表面, 但经过Triton X-100处理后, MSC的CXCR4表达大量增加, 认为MSC内部有丰富的CXCR4表达, 应用抗体阻断CXCR4后发现MSC在循环中向骨髓的归巢行为大大减弱. 而在体外实验[33-34]中通过对MSC转染CXCR4基因, 增加MSC表面CXCR4的表达, 大大增加了SDF-1对MSC的趋化作用, 进而证实了SDF-1通过受体CXCR4对MSC产生趋化作用, 而SDF-1是否通过另一受体CXCR7作用于MSC尚不清楚.

SDF-1浓度梯度在MSC的迁移中发挥着重

■研发前沿
骨髓间充质干细胞可以向多细胞分化已成定论, 如何更有效的诱导分化及其分化机制尚不清楚. 趋化因子SDF-1可以通过其受体作用于骨髓间充质干细胞迁移归巢, 但如何更有效的应用SDF-1也不明确.

■相关报道
研究表明MSC不仅在神经、心血管系统的损伤修复以及器官移植中有较大的潜在价值，并且证实MSC可以转化为肝干细胞、类肝样细胞以及肝细胞，在一些细胞因子的诱导下可以促进MSC向肝脏迁移并向肝细胞分化.

要作用, 而当SDF-1或CXCR4被阻断后, 这种定向迁移也就被阻断[35]. 除了运用CXCR4及SDF-1抗体, 运用各种途径提高骨髓SDF-1的浓度也可以达到促进移植细胞归巢到骨髓的目的. 降低骨髓内SDF-1的浓度[36-37]或提高骨髓外SDF-1的浓度[38], 所产生的骨髓内、外SDF-1浓度梯度都可以促进骨髓干细胞的动员. Ji *et al*[31]当把SDF-1α注射到动物颅内神经损伤部位后, 通过局部提高SDF-1可以趋化MSC到达颅内, 且注射SDF-1α部位可见分化的神经细胞. 庄瑜 *et al*[39]在大鼠心肌梗区域给与注射SDF-1、SDF-1抗体及设置盐水对照组, 经尾静脉注射MSC, 发现注射SDF-1组MSC较其他组明显增多, 抗SDF-1组最少, 可见SDF-1对MSC的趋化作用与其浓度呈正相关. 但超过一定浓度时反而减弱趋化作用, 丁鹏 *et al*[40]通过Boyden小室法证实趋化因子SDF-1(5、50、500 μg/L)体外可以趋化MSC, 并且发现SDF-1浓度为50 μg/L时趋化作用达到高峰, 同时观察到抗SDF-1多克隆抗体可对抗SDF-1的趋化迁移作用, 从侧面证实了SDF-1对MSC体外迁移的特异性.

然而SDF-1对MSC的趋化作用还需要组织器官存在损伤区域. Abbott *et al*[41]发现无心肌梗死小鼠中无论有无SDF-1的表达, 都仅有少量的骨髓干细胞迁徙到心肌中, 但与心肌梗死组有明显差异; 提示骨髓干细胞归巢不只是需要SDF-1的趋化作用, 心肌梗死区域的存在本身就具有重要作用. 还有研究发现SDF-1在损伤器官的表达中存在一个时间窗, Ma *et al*[42]在大鼠急性心肌梗死模型中发现梗死后d 1梗死区SDF-1的含量显著升高并达到峰值, 随后逐渐下降, 并且发现利用SDF-1的效应进行有效的治疗, 需把握住这个时间窗或者重建梗死区SDF-1的表达[43].

3.2 作用机制 目前SDF-1趋化MSC的机制尚不明确, 较多研究表明, SDF-1通过其受体激活细胞内多个信号传导途径, 并受多种调节因子影响. SDF-1与CXCR4结合后通过第二信使如NO, IP3, Ca^{2+}等引起的细胞内一系列相关积激酶的磷酸化, 某些核转录因子如NFκB, ELK-1等磷酸化使核内的某些核蛋白磷酸化, 改变骨髓干细胞的遗传信息, 产生肌动蛋白快速、短暂聚合等生物效应[44]. 这可能是SDF-1诱导细胞迁移的分子基础. 蛋白激酶B、细胞外信号调节蛋白-2和JAK/STAT家族成员JAK2也参与了SDF-1-CXCR4信号传导途径[45].

另外SDF-1能够充当骨髓干细胞定向迁移的化学引诱物[35,46], 同时他也可以增强骨髓干细胞的运动能力[47], 这可能是SDF-1趋化MSC的机制. 骨髓干细胞到达靶器官后, 首先要黏附到血管内皮上, SDF-1能够促进细胞黏附于纤维蛋白原、纤维连接蛋白、间质和内皮细胞[48-50], 而这种促进作用主要通过激活靶细胞表面的各种黏附分子, 如淋巴细胞功能相关抗原-1(LFA-1)、晚期活原-4(VLA-4)和晚期活化抗原-5(VLA-5)等来实现[49]. 黏附到血管内皮的细胞随后要穿过血管壁从而进入靶器官, 在SDF-1的作用下, 可以分泌更多的基质金属蛋白酶-9(MMP-9)、一氧化氮和某些促进血管生长的因子, 如血管内皮细胞生长因子(VEGF)[51-52], 这些因子和酶都参与辅助细胞穿过血管壁的基底膜到达靶器官.

SDF-1还可能通过一些间接的途径趋化MSC, 如促进其他生长因子分泌等. Mbemba *et al*[53]发现, SDF-1具有聚糖和葡糖胺聚糖特性, 能增加整合素ICAM-1和VCAM-1等多对受/配体间相互作用. 其他细胞因子如SCF、HGF、IGF-1等, 在干细胞动员、迁移中的作用也与SDF-1相关. SCF可以通过增加CXCR4的表达而增强SDF-1引起干细胞迁移[46]. HGF可以SDF-1可以促进MSC向受损器官迁移[54]. IGF-1可以增加CXCR4在MSC中的表达, 并且促进MSC向SDF-1迁移的反应能力[55].

总之, 随着干细胞领域基础研究的迅速进展, 各种来源的干细胞已经广泛应用到各器官疾病治疗的基础研究和早期临床实验中. 以往的研究表明MSC不仅在神经、心血管系统的损伤修复以及器官移植中有较大的潜在价值[56-60], 并且证实MSC可以转化为肝干细胞、类肝样细胞以及肝细胞[61-63], 在一些细胞因子的诱导下可以促进MSC向肝脏迁移并向肝细胞分化[64], 这为肝脏疾病的细胞治疗[65-67]提供了一条新方法. 近年来国内外对晚期严重肝病的细胞治疗是将供体肝细胞通过介入通道输入体内或将其用于生物人工肝的细胞成分, 但由于肝细胞来源有限, 体外增殖困难且易丧失活性、永生化困难并有癌变危险, 一直难以推广, MSC取材方便, 体外扩增快速, 且适合于自体移植, 具有对病灶的趋化特性, 是良好的转基因治疗的靶细胞. 能否通过SDF-1来调控MSC向靶组织的迁移分化, 有望为今后的研究提供新的思路. 有研究认为SDF-1与肿瘤的发生有关[68-69], 对于如何更有效的应用SDF-1、SDF-1应用的安全性及MSC的调控机制仍有待于进一步的研究.

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■应用要点

MSC取材方便, 体外扩增快速, 适合于自体移植, 且具有对病灶的趋化特性, 是良好的转基因治疗的靶细胞, 鉴于其在神经、心血管系统以及肝脏的损伤修复中的潜在价值, SDF-1有望为肝脏疾病的细胞治疗提供了一条新方法.

■同行评价
本文结构清晰, 条理清楚, 具有一定的科学性和可读性, 是一篇较好的综述.

progenitor cells and provides a new mechanism to explain the mobilization of CD34+ progenitors to peripheral blood. *J Exp Med* 1997; 185: 111-120
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• 消息 •

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