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文献综述 REVIEW

# 骨髓间充质干细胞治疗急性胰腺炎的潜能

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■背景资料
急性胰腺炎是胰腺组织水肿、出血甚至坏死的炎症反应,目前缺乏特异性的治疗方法. 而骨髓来源的间充质干细胞作为一种具有多向分化潜能、修复及抗炎作用的细胞, 已证明有治疗急性胰腺炎的潜能.

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## Potential therapeutic effect of bone marrow-derived mesenchymal stem cells in acute pancreatitis

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## Abstract
Acute pancreatitis is an inflammatory disease with dropsical, hemorrhagic or even necrotic conditions of the pancreas caused by several factors. It has significant morbidity and mortality, but no specific therapy is available so far. Bone marrow-derived mesenchymal stem cells (BMSCs) have multiple differentiation potential. They can not only differentiate to form endoderm and ectoblast cells, but also participate in tissue regeneration, repair and anti-inflammation. Recent studies have demonstrated that BMSCs have potential therapeutical effect in acute pancreatitis. BMSCs can migrate to injury tissue, multiply, be transformed to pancreatic stem cells and then participate in the process of regeneration. They also renovate vascular endothelium to improve blood circulation, adjust and control the cytokines to decrease inflammation, and regulate immunization. Here we review the recent advances in understanding the role of BMSCs in the treatment of acute pancreatitis.

Key Words: Bone marrow; Mesenchymal stem cells; Acute pancreatitis; Therapy

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## 摘要
急性胰腺炎是多种病因导致的胰腺水肿、出血, 甚至坏死的炎症性疾病, 有较高的发病率及死亡率, 目前仍缺乏特异性的治疗方法. 而骨髓来源的间充质干细胞(marrow-derived mesenchymal stem cells, BMSCs)作为一种具有多向分化潜能的细胞, 可跨越中胚层向内、外胚层的其他组织细胞转化, 并具有再生、修复及抗炎的作用. 目前的研究已证明, BMSCs有治疗急性胰腺炎的潜能. 主要通过向损伤部位迁移并增殖, 转化为胰腺干细胞, 参与组织再生; 修复血管内皮, 改善血流; 调控炎症相关的细胞因子, 减轻炎症反应以及免疫调节功能来发挥其治疗作用, 为临床上急性胰腺炎的治疗提供了新的思路.

**关键词: 骨髓来源; 间充质干细胞; 急性胰腺炎; 治疗**

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## 0 引言
急性胰腺炎(acute pancreatitis, AP)是由多种病因导致的胰腺组织水肿、出血甚至坏死的炎症反应. 可按严重程度分为轻型(mild acute pancreatitis, MAP)和重型(severe acute pancreatitis, SAP). 其发病机制尚不完全清楚, 目前公认的是腺泡细胞分泌的酶原物质被激活, 导致胰腺组织的自身消化[1-4]. 急性胰腺炎作为胰腺常见的炎性组织环境, 因为其显著的发病率和死亡率, 成为临床工作中未解决的难题[1,5]. 酒精和胆结石(包括微结石)是AP最常见的发病原因[1,5,6], 其他少见的原因包括: 药物、毒素、感染、外伤、组

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织缺血、解剖变异、代谢异常(高钙血症及高脂血症)、自身免疫性疾病等等. 时至今日, 仍然没有治疗AP的特效方法. 目前的治疗主要局限于一般的支持治疗, 如液体疗法及营养支持、抗炎治疗以及通过ERCP治疗胆石性胰腺炎[5,7,8]. 因此, 开发一种能有效减少AP发病率及死亡率的方法迫在眉睫.

1987年Friedenstein等[9]发现在塑料培养皿中培养的贴壁的骨髓单个细胞在一定条件下可分化为多种类型的细胞, 而且经过20-30个培养周期仍能保持其多向分化潜能. 由于骨髓中的这种多能细胞能够分化为多种中胚层来源的间质细胞, 故称之为间充质干细胞(mesenchymal stem cells, MSCs). 目前研究已证明, MSCs在体内体外均表现出较强的可塑性, 能分化出3个胚层来源的多种组织细胞[10-12]. 近来研究表明, 骨髓来源的间充质干细胞(bone marrow-derived mesenchymal stem cells, BMSCs)在许多以炎症为基础病变的疾病的治疗中, 都发挥了潜在的再生、修复及抗炎作用[13-15]. Cui等[16]及滕春燕等[17]通过移植或回输BMSCs治疗SAP模型或胰腺损伤模型, 结果均显示血清淀粉酶水平明显低于对照组, 病理检查结果显示治疗组胰腺损伤程度亦轻于对照组, 提示BMSCs有助于减轻AP的病情.

BMSCs因取材方便, 骨髓穿刺即可获得, 创伤小, 无伦理道德影响, 属于前体干细胞, 免疫原性小, 方便体外扩增及分离, 成为近来研究的热点. 本文主要讨论BMSCs在急性胰腺炎中起到的修复胰腺损伤、抑制炎症反应及免疫调节功能方面的作用.

## 1 BMSCs向损伤部位的迁移与增殖

BMSCs发挥治疗作用的关键是到达损伤的部位. 已有研究表明, 骨髓间充质干细胞可随血液循环到达全身其他器官组织[16,18,19], 参与生理更新和病理损伤修复. 更有叶海清等[20]、陆奕等[21]、王建祥等[22]及Jung等[23]的实验显示, 相比于其他组织, 被标记BMSCs多出现在被损伤的胰腺组织中. 在Jung[23]的实验中还发现, 重度胰腺炎的胰腺组织中比中度胰腺炎发现更多的BMSCs聚集. 此结果与早前Prockop[24]的研究一致, 即组织损伤可以促进骨髓干细胞的迁入, 可能因为损伤部位产生的细胞因子可引导干细胞到达该部位, 类似于白细胞的趋化移动. 赵航等[25]的实验证明, 急性坏死性胰腺炎(acute necrotizing pancreatitis, ANP)大鼠在12 h内骨髓BMSCs的克隆形成率显著高于对照组, 证明ANP时BMSCs的增殖能力增强.

## 2 BMSCs在病损部位转化为胰腺干细胞, 并修复血管内皮

胰腺组织有自我修复的能力, 提示胰腺中可能存在具有分裂及分化功能的细胞. Bonner-weir等[26]切除大鼠90%胰腺后, 残存的胰腺组织明显增殖, 形成新的胰岛和胰腺外分泌组织, 提示胰腺存在能分化成具有特异功能的细胞. Ishiwata等[27]在L-精氨酸诱导的胰腺炎的胰腺组织内检测到nestin阳性细胞, 而一般认为nestin、c-Kit、CK19和vimentin可能是胰腺成体干细胞的表面标志物[28,29], 故提示胰腺成体干细胞参与了胰腺的再生. 但是生理条件下, 胰腺干细胞数目少, 再生和分化能力差, 分离纯化较困难, 限制了其应用.

BMSCs有转化为胰腺干细胞参与受损胰腺组织修复的能力. Ianus等[30]通过将带有GFP基因的骨髓移植给雌鼠后发现, 骨髓可以掺入胰腺中, 并且分化为有功能的内分泌细胞, 而且排除该分化是由细胞融合引起, 提示骨髓有可能是胰腺干细胞的另一个居所[31]. 在江学良等[32,33]的2个实验中, BMSCs移植组均出现了CK19荧光染色阳性的细胞. CK19是胰腺干细胞的分子标志物之一, 有研究发现, CK19阳性细胞能转分化为具有内分泌功能和外分泌功能的细胞, 故CK19在胰腺导管上皮细胞中有明显的表达, 在胰岛细胞中CK19表达很少, 在腺泡细胞中CK19无表达[34]. 这表明BMSCs在病损的胰腺组织停留下来, 完成了“本地化”, 成为胰腺干细胞, 参与胰腺组织的修复. 在坏死性胰腺炎大鼠的肠组织中也出现荧光标记阳性的细胞, 说明BMSCs是机体多种组织干细胞的共同前体细胞, 从而证明了骨髓是干细胞库之一.

已有研究结果表明, 间充质干细胞在适当的条件下可向包括内皮祖细胞在内的多细胞分化[35-40], 而内皮祖细胞可促进血管新生, 改善血流[41,42]. 在陈强等[43]的实验中, 将体外培养后, 用EGFP标记的BMSCs注射至动物胰腺损伤区与完好区交界处, 24 h后冰冻切片, 共聚焦显微镜观察, 组织片中未见荧光标记, 仅在片中出现一环状荧光图像, 经专家鉴定为小循环系统管腔组织. 由此可见间充质干细胞首先到达受损组织的循环系统血管内皮, 使小循环修复, 改善血

■研发前沿
目前关于骨髓间充质干细胞对急性胰腺炎病程的干预作用成为研究的热点, 包括其迁移、转化、修复、调控炎症反应以及免疫调节功能. 骨髓间充质干细胞的分离、培养及其特征的研究是仍需努力的方向.

■相关报道
Jung等的研究将重点放在骨髓间充质干细胞对炎症因子的调控及免疫调节方面, 提示骨髓间充质干细胞能显著减少促炎因子TNF-α, IL-1β, IL-6的表达, 增加抗炎因子IL-4或IL-10的产生, 并能产生调节性T细胞, 并抑制T细胞增殖, 减少组织中T细胞的渗入. 这是目前研究中比较新颖的内容.

运情况, 从而使受损组织得到供血供氧, 达到修复损伤的目的.

## 3 BMSCs对炎症反应的调控

在急性胰腺炎的病理学过程中, 炎症反应发挥了极其重要的作用. 在AP的发病过程中释放的促炎因子及抗炎因子的活动介导着疾病的临床表现[44], 故患者血浆中的许多种细胞因子的活动受到越来越多的关注. 主要的促炎因子有TNF-α、IL-1β和IL-6[45-47]. Ishibashi等[48]的实验说明发生SAP时TNF-α及IL-6的水平增加. Masamune等[49]曾报道抗促炎因子TNF-α、IL-1β及IL-6治疗对AP动物模型有保护作用. 与促炎因子相反, IL-4及IL-10是阻碍炎症发生的抗炎因子[50-52], 尽管此结论存在争议.

Zhang等[53]及Guo等[54]的报道提示, 人类齿龈来源的MSCs能使结肠炎及心肌梗塞患者体内的TNF-α、IL-1β、IL-6、IFN-γ及IL-17水平衰减; Lee SH等[55]在应用BMSCs移植治疗博来霉素引起的肺损伤时, 发现BMSCs能下调肺组织中促炎因子的水平. 另外, 研究证明BMSCs能够分泌高水平的IL-1受体拮抗剂[56], 而IL-1受体拮抗剂能直接阻断IL-1α的作用及抑制活化的巨噬细胞产生TNF-α、IL-1、IL-6等细胞因子. 在抗炎因子方面, 有报道称[57]BMSCs能够分泌IL-10; Semedo等[58]报道, MSCs可增强肾损伤患者血浆中IL-4及IL-10的水平; 李德泉等[59]的实验中, BMSCs治疗组较胰腺炎组各时间点的血清淀粉酶及TNF-α和IL-6明显降低, IL-10无明显下降. 在Jung KH等[23]的实验中, 对AP大鼠移植BMSCs能显著减少TNF-α, IL-1β, IL-6的表达, 增加抗炎因子IL-4或IL-10的产生. 间充质干细胞合成分泌抗炎因子可能与细胞内NF-κB活性改变, 促进相关基因表达有关. Kang等[60]在研究NF-κB与胚胎干细胞的关系时发现, 干细胞未分化时干细胞内NF-κB的表达和活性都相当低, 而当干细胞分化时NF-κB的表达和活性明显增加, 但这一机制的具体细节目前仍然不清楚. 此外, MSCs还可以抑制NK细胞增殖, 减低其细胞毒性作用, 减少其细胞因子产生.

## 4 BMSCs的免疫调节功能

MSCs具有免疫调节作用, 这也是供体MSCs在受体中可以存活的原因之一[61], 他可以抑制过度活跃的免疫细胞的活性[62]. 有研究表明, MSCs能够产生抑制炎症相关性疾病的调节性T细胞[63-66], 且近来研究的焦点集中在MSCs调控许多炎症介质的能力上, 这些炎症介质可通过转录因子3$^+$调节性T细胞来抑制免疫反应[64,67], 并且转录因子3$^+$调节性T细胞也可以诱导嗜中性粒细胞及CD4$^+$T细胞的凋亡[68,69](也有研究报道MSCs可以抑制中性粒细胞的凋亡[70]). 因此, 我们推测BMSCs是否有可能诱导转录因子3$^+$调节性T细胞的表达及T细胞的凋亡, Jung等[23]的实验揭示了BMSCs能够引起调节性T细胞的产生, 并通过凋亡来抑制T细胞增殖, 从而减少胰腺组织中T细胞的渗入, 从某种程度上证实了我们的推测. 详细的机制还需要将来进一步的探讨.

## 5 结论

BMSCs在干预AP的病程中发挥着重要作用. 他参与了胰腺干细胞的转化, 血管内皮组织的修复, 炎症相关的细胞因子的调控, 以及免疫调节等过程, 充分显示了治疗急性胰腺炎的潜能. 未来研究的重点应集中在BMSCs标准化的分离、培养方法及其特征的研究上, 还包括AP发生过程中的内源性机制以及细胞的活化等方面. BMSCs是未来治疗AP极有吸引力的崭新途径, 在应用于临床前还需要深入地进行评估和实践.

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**■创新盘点**
本文创新性的总结了骨髓间充质干细胞干预急性胰腺炎病程转归的机制及途径, 其中免疫调节方面是近来研究的焦点.

**■同行评价**
本文总结了近年来骨髓间充质干细胞治疗急性胰腺炎研究, 显示了其将来的治疗潜能, 选题新颖,条理清楚, 有较好的学术价值.


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