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文献综述 REVIEW

间充质干细胞移植治疗胰腺炎的研究进展

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背景资料
间充质干细胞(mesenchymal stem cells, MSCs)是存在于许多组织(如骨髓、脂肪组织、胎膜)的多功能细胞, 有免疫调节以及分泌抗炎细胞因子的作用. 急性胰腺炎(acute pancreatitis, AP)发病迅速, 病情进展快, 坏死性胰腺炎死亡率达30%. 慢性胰腺炎(chronic pancreatitis, CP)癌变率高, 如能得到良好诊治, 能极大的改善患者预后.

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Mesenchymal stem cell transplantation for treatment of pancreatitis

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Abstract

Mesenchymal stem cells (MSCs) are one of the main cell resources of regenerative medicine. Recently, MSCs have been used to treat many diseases, such as Alzheimer's disease, inflammatory bowel disease and cirrhosis, with certain curative effects achieved. MSCs can not only secrete a variety of anti-inflammatory cytokines, but also reduce the secretion of inflammatory factors. Therefore, acute pancreatitis (AP) and chronic pancreatitis (CP) can be treated with MSCs. Several studies have investigated the effect of MSC therapy on acute and CP. MSCs exert a therapeutic effect on AP perhaps *via* two pathways: anti-inflammatory pathway and anti-apoptotic pathway. However, the mechanism for the therapeutic effect of MSCs on CP is unclear. In this review, we will summarize the progress in MSC treatment of AP and CP.

Key Words: Mesenchymal stem cells; Acute pancreatitis; Chronic pancreatitis

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摘要

间充质干细胞(mesenchymal stem cells, MSCs)是再生医学重要的细胞来源之一, 近

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年来MSCs已应用于多种疾病的治疗: 例如阿尔茨海默病、炎症性肠病、肝硬化等等, 并取得了一定疗效. MSCs不仅可分泌多种有抗炎作用的细胞因子, 还可以减少炎症因子的分泌, 因此可用于治疗急性胰腺炎(acute pancreatitis, AP)与慢性胰腺炎(chronic pancreatitis, CP). 部分学者针对MSCs治疗AP和CP进行了一系列研究, MSCs治疗AP有抗炎和抗凋亡两种途径, 但治疗CP机制尚不明确. 我们将总结MSCs治疗AP和CP的研究进展作一综述.

关键词: 间充质干细胞; 急性胰腺炎; 慢性胰腺炎

核心提要: 间充质干细胞(mesenchymal stem cells, MSCs)目前已用于多种炎症性疾病的治疗, 对于急性胰腺炎(acute pancreatitis, AP)和慢性胰腺炎(chronic pancreatitis, CP)有广阔的研究前景. 本文就MSCs治疗AP、CP的研究进展进行总结, MSCs通过抗炎和抗凋亡两种途径治疗AP, 可能通过抑制胰腺星形细胞损伤治疗CP.

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0 引言

间充质干细胞(mesenchymal stem cells, MSCs)是存在于许多组织(如骨髓、脂肪组织、胎膜)的多功能细胞[1]. MSCs因其免疫调节作用以及分泌抗炎细胞因子等功能在再生医学领域取得了显著疗效[2]. MSCs没有人类主要组织相容性复合体II抗原, 即使同种异体移植也不会发生排异反应, 这也是其富有研究前景的一个先决条件. MSCs移植已经在多种胃肠道疾病及其他系统疾病的动物模型中得以成功开展: Onishi等[3]使用人羊膜提取的MSCs移植到大鼠肝脏纤维化模型中, 通过抑制肝脏库弗细胞和星形细胞的激活来改善肝脏纤维化. Ono等[4]同样使用人羊膜源性MSCs在治疗大鼠结肠炎, 发现MSCs减轻了肠道细胞损伤和炎症反应. Lee等[5]发现MSCs可以减轻心肌梗死的梗死面积.

急性胰腺炎(acute pancreatitis, AP)是一种有死亡风险的胰腺炎症性疾病, 且发病率逐年递增, 目前约为5-50/100000[6,7]. 目前已发现一些炎症因子与AP的发病相关[8,9]. AP发病急病情进展迅速, 约20%的急性水肿性胰腺炎可转变为死亡率高达20%的重症急性胰腺炎(severe acute pancreatitis, SAP). 发生器官衰竭和胰腺坏死的AP患者死亡率高达30%[10,11]. 慢性胰腺炎(chronic pancreatitis, CP)是各种原因引起的胰腺组织和功能不可逆改变, 并且以持续性炎性损害及纤维化为特征的慢性炎症性疾病, 发病率逐年增加, 且与胰腺癌存在一定关联. Etemad等[12]与Raimondi等[13]的研究显示CP癌变率高达13.3%. 至今仍没有发现有效治愈CP的治疗方法[14]. 全胰切除术并胰岛细胞自体移植是目前治疗CP的疗效较好的方法, 但受患者术后医从性差、生活治疗差和死亡率较高等因素限制也并未广泛开展[15,16]. AP与CP的治疗一直是临床与基础的研究重点. MSCs的抗炎症作用被认为是治疗AP和CP一种很有前途的治疗策略[17-19]. 在本综述中, 我们总结了当前MSCs治疗AP与CP的研究进展以及目前已发现的治疗相关的机制.

研发前沿
MSCs治疗AP有抗炎和抗凋亡两种方式, AP腺泡细胞死亡方式众多, 包括凋亡、坏死、自噬、坏死性凋亡以及可能存在的焦亡. MSCs是否对其余死亡方式有影响呢? 有待于进一步研究. MSCs治疗CP的详细机制尚不明确, 有待于进一步探索.

1 MSCs

MSCs于1976年被Friedenstein等[20]首次分离成功并描述. MSCs具有自我更新修复能力并能分化成多功能干细胞, 如软骨细胞、骨细胞、脂肪细胞和外胚层细胞[1]. MSCs可以从骨髓、脂肪组织和脐带中分离, 在体外很容易增殖培养. 一般来说, MSCs有以下特点: (a)标准培养条件下即可贴壁; (b)表达CD105、CD73、CD90, 不表达CD45、CD34、CD14、CD11b、CD79a、CD19或HLA-DR; (c)在不同诱导条件下MSCs体外可分化为成骨细胞、脂肪细胞、软骨细胞等[21].

早期对于MSCs的研究关注的是MSCs的多向分化能力. 一些研究[22]显示, 全身系统性的输注MSCs由于尺寸过大形成栓子卡在肺脏中. 而未分化MSCs有抑制炎症, 抗凋亡的作用. 在众多的间质纤维化疾病模型中也起到了抑制纤维化的作用[4,5]. 因此, 临床试验方向从MSCs多向分化方面转向MSCs对分子生物学、免疫方面的作用上[23-27]. MSCs移植在动物模型中已经进行了多项实验, 可以减轻多种炎症疾病的病情, 例如: 肝硬化、下肢缺血、心肌炎、肾

相关报道 Jung等认为MSCs对于胰腺腺泡细胞凋亡有抑制作用. Kawakubo等发现MSCs抑制了胰腺星形细胞中单核细胞趋化蛋白1和白介素-8的表达, 同时可以减轻PSC的炎性损伤.

炎、缺血再灌注引起的肾损伤, 移植物抗宿主病等等[28-33]. MSCs的抗炎作用近年研究较多, Teng等[34]的研究发现MSCs通过外泌体介导抗炎作用缓解心肌梗死. MSCs治疗较胚胎干细胞(embryonic stem cells, ES)和诱导多能干细胞(inducible pluripotent stem cells, iPS)治疗有一定优势, 后两者需要分化成特定的功能干细胞并进行靶组织移植; 此外, 采用ES和iPS细胞治疗方式时有一定概率形成畸胎瘤[35,36].

2 MSCs治疗AP

MSCs的来源较广, 包括骨髓、脐带、脂肪组织和胎膜[1]. AP是由早期腺泡细胞损伤导致的炎症性疾病, 病情加重与腺泡细胞持续受损伤的和释放促炎介质有关, 局部的炎症会使各种炎症细胞趋化导致进一步的腺泡细胞损伤, 导致不同的促炎细胞因子数量急剧增加, 如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α), 白介素(interleukin, IL)-1β和IL-6[37]. 血清促炎细胞因子水平与AP的严重程度相关. 有研究[38]发现促炎细胞因子受到抑制时AP病情则减轻. Jung等[39]在2009年第一次描述了MSCs治疗AP. 他们将人骨髓来源的MSCs移植到急性水肿型胰腺炎和坏死性胰腺炎大鼠模型中, 评估MSCs对胰腺的影响. 他们的实验结果显示MSCs可以降低胰腺组织的病理学评分, 减少炎症细胞因子在胰腺的表达以及减少血清转化生长因子-β、TNF-α和干扰素-γ的数量. 他们还发现$Foxp3^+$调节性T细胞(regulatery T cell, Treg细胞)在胰腺和临近淋巴结数量增多. 另一项研究报道, MSCs减少了胰腺$CD3^-$ Treg细胞的数量, 增加$Foxp3^+$ T细胞的数量[40]. 一些研究[39,41]认为MSCs可以抑制血清和胰腺的促炎细胞因子的释放, 并增加了抗炎细胞因子的数量. Yang等[42]发现MSCs移植的抗炎效果存在时间依赖性和剂量依赖性, 进行诱导AP后立即进行MSCs移植比诱导AP数小时后移植的抗炎效果明显. MSCs本身具有抗炎特性并且可以作为基因治疗的携带者. Hua等[43]报道, 经促血管生成素1转染的MSCs与普通MSCs相比, 对于AP大鼠抗炎作用更显著.

AP病程中由于体液缺失、血容量减少、内脏血管收缩、局部缺血再灌注损伤造成微循环障碍, 会引起小肠损伤. Tu等[44]报道, AP通过MSCs移植可以使水通道蛋白-1(aquaporin-1, AQP-1)表达上调, 降低肠道黏膜通透性, 促使内皮细胞自我修复, 保持肠道黏膜稳定性, 进而改善AP造成的肠道损伤. Tu等[45]的研究发现MSCs移植可以减少血清丙二醛、超氧化物歧化酶、IL-6、IL-10、TNF-α的含量, MSCs可减弱肠膜损伤, 促进SAP大鼠肠道黏膜修复. Lu等[46]的研究发现MSCs可以上调AQP-1表达, 减轻小肠毛细血管内皮屏障损伤.

MSCs治疗AP的另一个机制是抗凋亡作用[47,48]. MSCs通过基质细胞衍生因子(SDF)1/CXC趋化因子受体4型趋化因子受体CXCR4轴促进修复和血管生成[49]. He等[50]报道, MSCs分泌的TNF-α刺激基因6因子能够明显减少炎性细胞的浸润, 抑制炎性因子的表达. Yin等[38]表明MSCs分泌的微泡能减弱AP带来损伤. 部分研究发现MSCs可以迁移和植入多个器官, 其中就包括胰腺[39,50,51]. 其中作用的具体机制有待于进一步研究.

腺泡细胞死亡方式一直是AP研究的热点, AP细胞死亡方式众多, 包括凋亡、坏死、自噬、程序性凋亡[52-57]. 我们在初步试验中发现AP存在焦亡的现象[58]. Kawakubo等[48]已经证明MSCs存在抗凋亡的作用, 可以减轻AP病情. Naji等[59]在铟锡氧化物造成的呼吸系统疾病中发现, MSCs可以通过抑制NLRP3-ASC-caspase-1炎症小体进一步抑制焦亡. 炎症小体在AP腺泡细胞多种细胞死亡方式中起重要作用[60]. 我们在此提出一个假设, MSCs可以通过抑制炎症小体减轻腺泡细胞凋亡和焦亡等细胞死亡方式. 我们在后续实验中会对MSCs对凋亡和焦亡的作用进行研究. 关于MSCs治疗AP的深层机制仍有待于后续实验揭示.

3 MSCs治疗CP

与AP相比, 只有极少数实验研究了MSCs在CP模型中的作用. 胰腺星状细胞(pancreatic stellate cells, PSC)在CP的发病机制发挥关键作用[61,62]. 在正常胰腺中PSC已经被认为是“静止的”. 然而在由各种原因引起的胰腺损伤或炎症反应刺激下, PSC发生形态和功能改变—成纤维细胞样细胞. 激活的PSC可加重胰腺炎症反应、促进由α-平滑肌肌动蛋白、细胞因子、趋化因子和细胞黏附分子导致的血管生成和纤维化形成[63]. Zhou等[64]报道, 从脐带分离的MSCs通过抑制胰腺中炎性细胞因

子, 可以减少诱导胰腺纤维化主要物质—二氯化物. Kawakubo等[48]已经证明人类羊膜提取的MSCs能减少单核细胞趋化蛋白1(monocyte chemotactic protein-1, MCP-1)在胰腺的表达. 胰腺星型细胞是纤维化的主要载体. Kawakubo等[48]发现人类羊膜提取的MSCs抑制了胰腺星形细胞中MCP-1和IL-8的表达, 同时可以减轻PSC的炎性损伤. MSCs在CP扮演的角色和作用的确切机制仍然未知, 有待于进一步揭示.

4 结论

许多动物模型研究已经证实了MSCs的治疗潜力. 当MSCs细胞治疗进入临床研究后, 出于安全考虑, 只能使用自身来源或者配型匹配后的MSCs, 从而制约了MSCs的应用[65,66]. MSCs的临床应用存在MSCs的质量不佳和活体捐献及其伦理学方面的问题. MSCs移植的细胞数量、移植方式都需要统一规划, 接受治疗的患者主体也需进行限制.

总之, MSCs可以通过抑制巨噬细胞的活性减轻CP的炎症反应, 通过减少腺泡细胞的损伤和抗凋亡来减轻AP的炎症反应. 虽然目前没有临床试验用MSCs治疗AP或CP, 但不可否认的是MSCs治疗AP和CP存在广阔前景.

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■创新盘点

本文较全面地介绍了MSCs在治疗AP和CP的研究进展.

■应用要点
目前AP的临床治疗取得了极大的成果, 对于部分治疗效果不佳的AP患者, MSCs治疗可能有不错的效果. CP治疗一直是临床难题. MSCs能为CP治疗提供新思路.

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名词解释

*TSG-6*基因: 一个保护性的炎性反应性基因, 在多种炎症性疾病或类似炎症的过程中呈高表达, 通过与透明质酸等物质集合介导炎性细胞的迁移黏附, 参与细胞外基质重塑, 调节蛋白酶网络.

■同行评价
本文具有一定的新颖性和科学性, 内容较充实, 行文较流畅.

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•消息•

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var. glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.