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述评 EDITORIAL

间充质干细胞移植治疗消化系统疾病的进展

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Mesenchymal stem cell transplantation for treatment of digestive diseases

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Abstract

Treatment of diseases using mesenchymal stem cells (MSCs) has gained great breakthrough with the discovery of properties of MSCs since 1990s. So far, MSC transplantation in the treatment of digestive tract diseases is mainly focused on hepatic cirrhosis, liver failure, acute or chronic pancreatitis, inflammatory bowel disease and digestive tumors. In the current editorial, we rely primarily on the existing evidence to gain a comprehensive perspective toward this area.

Key Words: Mesenchymal stem cells; Hepatic cirrhosis; Pancreatitis; Inflammatory bowel disease; Digestive tumor

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摘要

自20世纪90年代以来, 间充质干细胞的特性被逐步发掘, 并在治疗临床疾病研究邻域陆续取得突破. 目前, 针对间充质干细胞移植治疗消化系统疾病的研究主要集中在肝硬化、肝衰竭、急慢性胰腺炎、炎症性肠病及消化系肿瘤等邻域, 其中部分研究已应用于临床. 本文就间充质干细胞移植治疗消化系统疾病的研究进展作一述评.

背景资料
间充质干细胞是一种具有自我更新及多向分化潜能的成体干细胞, 其具有迁移归巢、转分化、免疫调节、旁分泌细胞因子等特性, 因而起到损伤组织修复与再生的作用. 随着间充质干细胞在消化系统疾病的基础研究进展, 其临床应用研究也逐渐增多.

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研发前沿
在众多消化系统疾病中, 肝硬化和肝衰竭、急慢性胰腺炎、炎症性肠病及消化系肿瘤在间充质干细胞移植治疗过程中显示了良好的疗效, 但其相关的机制尚未阐明.

关键词: 间充质干细胞; 肝硬化; 胰腺炎; 炎症性肠病; 消化系肿瘤

核心提示: 间充质干细胞移植治疗消化系统疾病的研究主要集中在肝硬化和肝衰竭、急慢性胰腺炎、炎症性肠病及消化系肿瘤等领域, 其中部分研究已应用于临床. 本文总结了近年间充质干细胞移植治疗消化系统疾病的研究进展.

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0 引言

间充质干细胞(mesenchymal stem cells, MSCs)是一种具有自我更新及多向分化潜能的成体干细胞, 其具有迁移归巢、转分化、免疫调节、旁分泌细胞因子等特性, 因而起到损伤组织修复与再生的作用[1]. 自2000年以来, 越来越多的研究开始关注MSCs[2-4], MSCs作为理想的种子细胞也越来越多的运用于临床, 如移植物抗宿主反应、1型糖尿病、脊髓损伤等[5,6]. MSCs在消化系统疾病的应用也在逐渐开展, 并取得了一定的临床治疗效果. 目前的报道较多集中在肝硬化和炎症性肠病的基础及临床治疗方面, 在其他消化系统疾病中的应用尚需进一步开展. 本文就MSCs在消化系统疾病治疗的基础与临床研究作一述评.

相关报道
在肝硬化、肝衰竭领域, 已有28个临床试验开展, 通过自体移植间充质干细胞可以改善肝功能. 在炎症性肠病方面, 间充质干细胞可以降低72.7%的溃疡性结肠炎患者的炎症反应, 从而减少5-氨基水杨酸制剂及糖皮质激素的使用. 对于胰腺炎而言, 血管生成素-1基因修饰的间充质干细胞增加了胰腺微血管形成的同时, 改善了胰腺组织病理及血清酶学指标. 对于消化系肿瘤来说, 主要利用抗肿瘤基因修饰间充质干细胞并依赖其无免疫原性及归巢的特性, 在肿瘤局部发挥抗肿瘤作用.

1 肝硬化和肝衰竭

对于慢性乙型肝炎后肝硬化失代偿期或慢性肝衰竭等终末期肝病患者, 最有效的治疗手段是肝移植, 但由于供体肝的缺乏及移植后的排斥反应及昂贵的治疗费用限制了肝移植的广泛开展. 因此, 对于肝细胞修复或再生的研究成为当务之急, 而MSCs在肝硬化、肝衰竭等疾病模型中显示了潜在的疗效. MSCs治疗肝脏疾病的可能机制包括转分化为肝细胞样细胞、免疫调节及分泌多种细胞因子[7]. 首先, 体外实验表明MSCs在一定条件下可以转分化为肝细胞样细胞[8]. 在肝衰竭动物模型中, Sato等[9]证实MSCs可以转分化为肝细胞样细胞并取代已坏死的肝细胞. 尽管肝脏损伤微环境提供了MSCs定植与转分化的可能, 但其具体的信号传导机制尚不清楚. 其次, 炎症反应引起的肝脏损伤常伴有T细胞、B细胞及单核细胞的浸润, 而减少炎症可以促进肝细胞再生[10]. MSCs作为无免疫原性的细胞, 其表面不表达主要组织相容性复合体-Ⅱ(major histocompatibility complex Ⅱ, MHC-Ⅱ)、CD80、CD86及CD40, 因而在同种异体移植治疗过程中不会引起同种异体T细胞反应. 由于MSCs还具有抑制初始和记忆T细胞的活化、增殖和细胞毒性、增加调节性T细胞数量、抑制B细胞等免疫调节作用, 其通过减少肝脏损伤时的炎症反应从而促进肝脏再生[11]. 此外, MSCs分泌的多种细胞因子也参与了这一过程: 分泌白介素-10(interleukin-10, IL-10)、IL-1受体拮抗蛋白减少炎症[12,13]; 分泌肝细胞生长因子促进肝脏再生[14]; 分泌血管内皮生长因子、胰岛素样生长因子结合蛋白减少肝细胞凋亡[15,16]; 分泌肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)、神经生长因子减少星状细胞激活[17,18]; 分泌基质金属蛋白酶-9降解细胞外基质[19]. 目前, 已有28项临床试验(22项肝硬化和6项肝衰竭)开展, 通过自体移植MSCs可以改善肝功能(白蛋白、胆红素、凝血酶原时间), 显示出良好的临床疗效[7].

2 炎症性肠病

炎症性肠病作为一种病因尚未明确的慢性非特异性肠道炎性疾病, 主要包括溃疡性结肠炎和克罗恩病, 其具有终身复发倾向, 且重症患者迁延不愈, 预后不良. 现有的临床治疗方法主要针对于控制活动性炎症和调节免疫紊乱, 常用药物有5-氨基水杨酸类制剂、糖皮质激素、免疫抑制剂等, 对危重及难治性病例疗效有限, 且存在不良反应. MSCs用于治疗炎症性肠病的分子机制主要包括迁移归巢、免疫调节及损伤组织修复[20]. 前期的动物研究表明, MSCs可以明显降低促炎因子水平、改善肠道组织病理[21].

目前, MSCs用于治疗炎症性肠病的临床研究报道逐年增加. García-Olmo等[22]最早对5例克罗恩病合并瘘管患者行MSCs试验治疗, 除1例因细胞培养过程中细菌污染退出试验, 其余4例共8处瘘管均行自体MSCs局部注射, 随访12-30 mo(平均22 mo), 发现6处瘘管完全愈合(愈合率75%), 另2处瘘管部分闭合, 未有不良

反应, 显示了MSCs对克罗恩病合并瘘管有良好的治疗作用. Ciccocioppo等[23]同样对10例克罗恩病合并瘘管患者行自体MSCs局部注射, 最终7例达到完全愈合. Lee等[24]在Ⅱ期的临床试验中证实MSCs局部注射可以使克罗恩病合并瘘管患者的临床缓解率达到82%(27/33). 对于难治性克罗恩病患者, Duijvestein等[25]将9例患者静脉注射自体MSCs(1×10^6-2×10^6个细胞/kg体质量), 间隔7 d, 最终3例患者达到临床缓解(33%). 新近的研究[26]对15例难治性克罗恩病患者行连续自体MSCs(2×10^6个细胞/kg体质量)静脉注射4 wk, 将临床缓解率提升至47%. MSCs用于治疗溃疡性结肠炎的研究多来自俄罗斯研究团队, 在长达两年的随访期间, 他们发现MSCs可以降低72.7%的溃疡性结肠炎患者的炎症反应, 从而减少5-氨基水杨酸制剂及糖皮质激素的使用[27]. 尽管目前MSCs用于治疗炎症性肠病显示了良好的疗效及临床运用前景, 但其标准的治疗剂量、治疗周期尚未达成共识, 且治愈率仍有待提高. 另外, 还未见到较大规模的多中心研究结果.

3 胰腺炎

急性胰腺炎是临床常见的急腹症之一, 在其病理生理过程中, 过度激活的白细胞及瀑布样反应的炎性因子释放加速了病情的恶化, 增加了治疗的难度. 其中10%-20%的患者可发展为重症急性胰腺炎(severe acute pancreatitis, SAP). SAP病情凶险, 预后差, 临床病死率高[28]. 目前, 临床上对SAP的治疗仍以抑制胰酶的合成与分泌, 预防性应用抗生素, 营养支持等保守治疗为主, 缺乏特异有效的治疗方法. 近年的研究提示MSCs在胰腺组织修复中有重要价值, 其自我更新、多向分化潜能、独特的低免疫原性和免疫调节及促进新生血管形成等作用可能为SAP提供一种全新的治疗方法. 动物模型研究显示, 用人来源的MSCs移植入大鼠SAP模型可以显著改善胰腺组织病理、降低血清淀粉酶和脂肪酶水平、降低血清促炎因子水平、升高血清抗炎因子水平, 并发现MSCs移植可以显著增加胰腺组织$Foxp3^+$调节性T细胞数量[29-32]. Tu等[33,34]同样证实MSCs可以改善大鼠SAP模型的胰腺组织病理和血清酶学指标, 并发现MSCs移植后, SAP相关的肠道黏膜损伤好转. 我们的前期研究[35,36]则证实基质细胞衍生因子-1/CXC趋化因子受体4轴(stromal cell-derived factor-1/C-X-C chemokine receptor type 4, SDF-1/CXCR4)在MSCs的迁移归巢中起了重要作用, 阻断这一轴, 则MSCs无法起到治疗SAP的作用. 新近的研究[37]发现, 血管生成素-1基因修饰的MSCs增加了胰腺微血管形成的同时, 更进一步改善胰腺组织病理及血清酶学指标, 表明胰腺组织修复过程中胰腺微血管再生亦起到重要作用. 此外, 在SAP相关的肺损伤模型中, 移植MSCs可以提高水通道蛋白1和5水平、减轻肺水肿、降低肺部炎症以减轻肺损伤[38]. MSCs亦可以减轻SAP相关肾损伤时对肾间质毛细血管内皮屏障的破坏从而减轻肾损伤[39]. 这些研究对临床SAP可能出现的呼吸窘迫综合症及肾功能不全等多脏器功能不全进行模拟, 说明了MSCs治疗重症胰腺炎的可能性, 但临床研究尚未见报道.

慢性胰腺炎是由于各种不同病因引起的胰腺组织和功能持续性损害, 最终导致胰腺内外分泌功能永久性丧失. 目前治疗上仍采取止痛、内外分泌不足的替代、手术等治疗措施[40]. Marrache等[41]将标记的MSCs静脉注射移植入小鼠慢性胰腺炎模型并进行示踪, 发现MSCs参与构成5.12%的胰腺星状细胞并对胰腺组织的修复起作用. 为进一步研究MSCs在治疗慢性胰腺炎中的作用, Qin等[42]将抑制核因子-κB(nuclear factor-κB, NF-κB)转录因子的基因*IκBαM*转染MSCs后移植入大鼠慢性胰腺炎模型, 他们发现IκBαM-MSCs不仅可以抑制促炎因子, 还通过抑制胰腺星状细胞激活、促进其凋亡来减轻胰腺纤维化. 新近的研究也表明, 脐带华通氏胶来源的MSCs可以向纤维化的胰腺“归巢”, 抑制胰腺星状细胞激活并减轻胰腺纤维化[43]. 虽然目前MSCs抑制胰腺星状细胞激活的具体机制尚不明确, 但为今后MSCs用于治疗慢性胰腺炎提供了研究方向.

4 消化系肿瘤

目前, 手术仍是根治消化系恶性肿瘤的唯一方法. 虽然对于失去手术机会的肿瘤患者, 有化疗、放疗或同步化放疗等治疗方式, 但总体疗效仍不令人满意, 且有一定不良反应. 近年, MSCs用于治疗消化系肿瘤越来越成为研究热

创新盘点

本文详细综述了与间充质干细胞移植治疗消化系统疾病相关的文献, 对相应文献的机制和临床数据进行提炼、比较, 对此领域的研究进展及不足进行了点评.

应用要点
本文对今后间充质干细胞治疗消化系统疾病的研究方向及应用前景提供理论基础.

点. 将抗肿瘤基因修饰MSCs并利用其无免疫原性及归巢的特性, 在肿瘤局部发挥抗肿瘤作用[44]. Cousin等[45]研究发现MSCs在体外及体内试验通过影响细胞周期抑制胰腺肿瘤细胞增殖及诱导细胞凋亡. Zischek等[46]将胸苷激酶基因修饰的MSCs移植于小鼠Pan02原位胰腺癌模型中发现其可以抑制胰腺肿瘤的生长, 减少转移的发生. Kidd等[47]将干扰素-β(interferon β, IFN-β)修饰的MSCs移植入小鼠原位PANC-1移植瘤模型, 发现MSCs同样明显抑制肿瘤细胞的生长. 在胃癌方面, Wang等[48]在小鼠模型上移植MSCs发现可以降低胃异型增生, 延缓胃癌的进展. 然而, Song等[49]则发现MSCs会促进人胃癌细胞的增殖和转移. 在MSCs治疗肝癌研究中, 同样存在相互矛盾的结论[50]. 这主要是由于抗肿瘤基因(包括*TRAIL*、*HSV-Tk*、*IFN-β*等)修饰的MSCs具有抗肿瘤作用, 而单纯未用基因修饰的MSCs有致瘤潜能[44]. 因此, 在开展临床试验之前, 利用基因修饰的MSCs治疗消化系肿瘤尚需进一步探索.

5 结论

经过10余年的研究, MSCs在治疗肝硬化、炎症性肠病方面均取得了很大的成果, 但其相关的机制仍未完全阐明. 在治疗急慢性胰腺炎方面, 动物实验均证实了MSCs的治疗效果, 尚需进一步临床试验的验证与推广. MSCs在消化系肿瘤方面的应用尚存争议, 目前主要的机制是利用MSCs作为抗肿瘤基因的载体而发挥肿瘤局部靶向治疗效应, 其生物学特性及相应的靶向基因需进一步探索. 相信随着对MSCs研究的不断深入, MSCs用于消化系统疾病会有明显进展.

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名词解释

基质细胞衍生因子-1/CXC趋化因子受体4轴: 趋化因子受体CXCR4是趋化因子SDF-1的唯一受体, SDF-1/CXCR4这一生物学轴的功能主要为介导免疫及炎症反应、调控干细胞迁移及归巢、参与恶性肿瘤的浸润和转移等.

同行评价

该文从间充质干细胞移植治疗肝硬化、炎性肠病、急慢性胰腺炎、消化系肿瘤等方面的研究进展进行了详细评述, 展望了其在这四个领域的潜在治疗优势, 为间充质干细胞移植治疗这一新的治疗方法进一步深化研究奠定了一定基础. 该文具有一定前瞻性、新颖性.

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