

间充质干细胞在消化系统疾病治疗中的应用进展

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背景资料

1970年, Friedenstein等首次从豚鼠骨髓中分离培养出间充质干细胞(mesenchymal stem cells, MSCs)。以后诸多研究证实, MSCs不仅来源于骨髓, 也来源于脂肪、骨骼肌、肝脏、脾脏、肾脏、肺、扁桃体、牙齿、脐带、包皮、滑膜等组织器官。MSCs在特定条件下可分化成肝细胞、心肌细胞、内皮细胞、神经细胞、成骨细胞、软骨细胞、脂肪细胞、成纤维细胞等。MSCs不仅主动趋向炎症组织、受损组织、肿瘤组织, 还具有免疫调节、多向分化及旁分泌功能。因此, MSCs被认为是组织工程、基因治疗的理想靶细胞。

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Application of mesenchymal stem cells in digestive system diseases

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Abstract

Mesenchymal stem cells (MSCs) have the capacity of multipotent differentiation and the property of immunomodulation. MSCs have been widely used in digestive system disease research because of their advantageous characteristics such as homing to areas of inflammation or tumour tissue, anti-inflammation, high plasticity, absence of immunologic rejection, being easy to be isolated, and being convenient for the

expression of exogenous genes. In this article, we will review the application of mesenchymal stem cells in digestive system diseases including caustic esophagus injury, reflux esophagitis, gastric ulcer, radioactive intestinal injury, severe acute pancreatitis, inflammatory bowel disease, nonalcoholic steatohepatitis, acute liver failure, hepatic fibrosis, autoimmune liver diseases, liver cirrhosis, esophageal cancer, gastric cancer, colon cancer, liver cancer, and pancreatic cancer.

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Key Words: Mesenchymal stem cells; Esophageal diseases; Gastric ulcer; Severe acute pancreatitis; Inflammatory bowel disease; Liver diseases; Gastrointestinal tumors; Therapy

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摘要

间充质干细胞(mesenchymal stem cells, MSCs)不仅具有多分化潜能, 还具有免疫调节功能。MSCs因具有主动趋向炎性或肿瘤组织、抗炎、可塑性、无免疫排斥、易于分离以及便于外源基因转染和表达等优点而被广泛用于消化系统疾病的研究。本文阐述了MSCs在腐蚀性食管损伤、反流性食管炎、胃溃疡、放射性肠损伤、重症急性胰腺炎、炎症性肠病、非酒精性脂肪性肝炎、急性肝衰竭、肝纤维化、自身免疫性肝病、肝硬化、食管癌、胃癌、结肠癌、肝癌以及胰腺癌等消化系统疾病治疗中的

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最新应用进展.

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关键词: 间充质干细胞; 食管疾病; 胃溃疡; 重症急性胰腺炎; 炎症性肠病; 肝病; 消化系肿瘤; 治疗

核心提示: 间充质干细胞(mesenchymal stem cells, MSCs)被认为是组织工程和基因治疗的理想靶细胞, 本文重点阐述了MSCs在消化系统疾病的最新应用进展.

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0 引言

间充质干细胞(mesenchymal stem cells, MSCs)是具有多种分化潜能的非造血干细胞, 因其易于从骨髓^[1]、脂肪组织^[1]、滑膜^[1]、骨膜^[1]、牙齿^[1]、胎盘^[1]、脐带^[2]等组织中分离, 并且具有高效分化潜能^[1,3]、营养活性、免疫调节特性以及巨大的供体池^[3], MSCs已引起干细胞治疗领域专家的浓厚兴趣^[1], 并被认为是细胞再生治疗的潜在工具^[3]. 尽管如此, MSCs的来源和净化程序对其治疗潜能仍至关重要, 最佳MSCs分离程序的标准化无疑有助于其最佳的临床应用^[4]. MSCs在其特定环境下不仅可分化为多种细胞谱系, 而且还具有使其成功进行同种异体移植的免疫抑制效能^[1]. 此外, MSCs在体内具有主动趋向炎性或肿瘤组织^[5]、促进血管形成^[4,6,7]等特性, 在体外具有易于分离培养扩增^[8]、易于被外源基因转染并稳定表达^[9]等优点. 因此, MSCs已成为组织工程与基因治疗的理想靶细胞而被广泛用于多种疾病的细胞治疗. 本文就MSCs在消化系统疾病治疗中的应用进展概述如下.

1 MSCs与食管疾病

1.1 MSCs与腐蚀性食管损伤 腐蚀性物质的摄入可致食管狭窄和食管的干细胞破坏, MSCs可分化成特殊的细胞谱系, 有归巢受损部位的能力^[10]. Kantarcioglu等^[10]对腐蚀性食管损伤的大鼠模型采用MSCs移植治疗, 并通过正电子发射断层扫描(positron emission tomography, PET)观察标记MSCs的生物学分布情况. 结果

显示, 食管损伤部位存在MSCs归巢行为, Dil标记的上皮细胞和肌肉细胞均源于移植的MSCs^[10]. 此研究^[10]表明, MSCs移植对腐蚀性食管损伤可能是一种有益的治疗模式. Tan等^[11]对犬模型组织工程食管的研究也证实, MSCs移植可促进受损食管的上皮、血管及肌肉组织再生.

1.2 MSCs与反流性食管炎 反流性食管炎(reflux esophagitis, RE)可致Barrett食管, 最终引发食管腺癌而危及生命^[12]. Lee等^[13]认为, MSCs移植提供了RE临床应用的可能性. Mazzanti等^[14]采用胃食管肌切术(esophagogastric myotomy, MY)建立RE大鼠模型, 并于MY处局部注射骨髓MSCs(bone marrow mesenchymal stem cells, BM-MSCs), 采用组织学和功能分析评估肌肉再生、收缩能力及不同移植时间点受损处绿色荧光蛋白(green fluorescent protein, GFP)阳性BM-MSCs(BM-MSC-GFP⁺)的表达情况. 结果显示, BM-MSCs促进肌肉再生、增加食管下括约肌(lower esophageal sphincter, LES)收缩功能. 移植BM-MSC-GFP⁺于受损处滞留达30 d. 免疫组织化学分析显示, MSCs维持其表型, 任何时间点均未显示趋向平滑肌或横纹肌的变异. 此研究^[14]表明, 自体BM-MSCs移植即可促进LES再生, 也可以控制术后的胃食管反流.

2 MSCs与胃部疾病

2.1 MSCs与胃溃疡 MSCs因具有高效分化和促进细胞再生潜能, 已被用于胃溃疡治疗的实验研究^[15]. Chang等^[16]将羧基荧光素琥珀酰亚胺酯(carboxyfluorescein diacetate succinimidyl ester, CFDA SE)标记的BM-MSCs注入胃溃疡大鼠体内发现, 移植48、72 h后, CFDA SE标记细胞散在分布于受损胃黏膜组织, 移植72 h后, BM-MSCs组平均溃疡指数为 12.67 ± 2.16 , 赋形剂处理对照组为 17.33 ± 1.97 ($P < 0.01$). BM-MSCs组胃黏膜血管内皮生长因子(vascular endothelial growth factor, VEGF)、表皮生长因子受体(epidermal growth factor receptor, EGFR)的表达显著升高. 此研究^[16]表明, 自体BM-MSCs移植可促进大鼠模型的胃溃疡愈合. Hayashi等^[17]研究认为, BM-MSCs移植加速胃溃疡愈合, 可能与胃黏膜分泌VEGF诱导血管形成有关, MSCs的优势在

■ 研究前沿

MSCs移植的相关研究仍大多集中于基础或动物实验阶段, 如何提高MSCs的靶向移植是目前的研究热点和难点, 也是将MSCs移植应用于临床的最重要阻碍.

■ 相关报道

最近, Gazouli等对包括MSCs在内的干细胞移植在炎症性肠病(inflammatory bowel disease, IBD)的潜在靶向治疗作用进行了阐述, 认为干细胞移植治疗可能会在不久的将来替代传统治疗成为IBD治疗的新方法。

于其不仅能分化为胃间质细胞, 还可以提供血管生成因子。

2.2 MSCs与胃穿孔 MSCs可促进受损组织的组织修复, 但MSCs局部注射是否会加速胃穿孔缝合处的修复仍不清楚^[18]。Liu等^[18]对胃穿孔缝合大鼠局部注射MSCs或局部喷洒含有MSCs的纤维蛋白凝胶治疗, 分别评估3、5、7 d胃穿孔缝合处的愈合情况。结果显示, 局部注射MSCs显著促进胃穿孔的愈合。MSCs注射组不仅胃穿孔缝合处炎症减轻、颗粒状增生及上皮再生, 且缝合处白介素-6(interleukin 6, IL-6)表达减少, 转化生长因子 β 1(transforming growth factor β 1, TGF- β 1)及上皮细胞增殖核抗原(proliferating cell nuclear antigen, PCNA)表达增加。此研究^[18]表明, 局部注射MSCs能有效通过抗炎、促进细胞再生及颗粒化的早期启动而促进胃穿孔缝合处的愈合。

3 MSCs与放射性肠损伤

放射性肠损伤是急性放射综合征(acute radiation syndrome, ARS)的重要组织损伤类型, 也是腹部肿瘤放疗或核辐射事件导致的重要并发症之一, 严重危及患者生命, 目前尚缺乏确切有效的治疗措施^[19]。Eaton等^[19]认为, 体内外实验证实, 通过培养肠残留隐窝干细胞的生长, MSCs治疗能有效促进肠上皮的修复, 其机制可能在于局部分泌的上皮生长因子和趋化信号诱导上皮祖细胞趋向受损组织^[19]。腹部辐射和全身辐射的临床前模型证实, MSCs注射伴随肠隐窝细胞再生、干细胞利基恢复、木糖吸收增加, 其生存率亦增加, 血清肠辐射防护因子[R-Spondin1、角质细胞生长因子(keratinocyte growth factor, KGF)、血小板源性生长因子(platelet derived growth factor, PDGF)、成纤维细胞生长因子(fibroblast growth factor, FGF)]含量和抗炎性细胞因子水平增加, 炎症性细胞因子则被抑制^[19]。目前, MSCs治疗放射性肠损伤的临床资料仍极为有限^[19]。Voswinkel等^[20]对前列腺癌患者意外过度放疗导致的放射性肠损伤采用同种异体MSCs注射后发现, 其腹痛、腹泻、出血、炎症等症状明显缓解, 提示MSCs能有效治疗放射性肠损伤。Eaton等^[19]认为, 基因修饰的MSCs因具有干细胞治疗和细胞生长因子治疗的双重优势, 这可能为放射性肠损伤的治疗提供新的途径。

4 MSCs与重症急性胰腺炎

MSCs对组织的修复功能与其自身的免疫调节机制有关, 包括抑制T细胞增殖、影响树突细胞的成熟和功能、抑制B细胞增殖和终末分化、免疫调节NK细胞和巨噬细胞等^[21]。动物实验证实, MSCs移植对重症急性胰腺炎(severe acute pancreatitis, SAP)的组织修复作用和抗炎效果均十分显著^[21]。基因修饰的MSCs对上皮细胞的生存、血管稳定以及血管的形成也十分重要^[22]。Hua等^[22]将含有ANGPT1(血管生成素)基因慢病毒载体的人脐带MSCs从尾静脉注入SAP大鼠体内, 依据SAP严重程度评分、血清淀粉酶、脂肪酶、炎症细胞因子[肿瘤坏死因子 α (tumor necrosis factor α , TNF- α)、 γ 干扰素(interferon- γ , IFN- γ)、IL-1 β 、IL-6]的水平下降, MSCs能显著减少胰腺损伤和炎症反应。ANGPT1基因转染的MSCs不仅进一步减少胰腺损伤和炎症细胞因子水平, 还能促进胰腺血管生成^[22]。基质细胞衍生因子-1(stromal cell-derived factor-1, SDF-1)、SDF-1受体及CXC趋化因子受体-4(CXC chemokine receptor-4, CXCR4)对BM-MSCs移植具有重要的调节作用^[23]。Gong等^[23]对SAP大鼠研究发现, SDF-1在受损胰腺组织中的表达显著增加, SDF-1诱导的剂量依赖BM-MSCs移植几乎完全被AMD3100(CXCR4拮抗剂)和抗CXCR4抗体抑制, 通过加强CM-Dil标记BM-MSCs移植, SDF-1/CXCR4轴可以促进受损胰腺的修复, 此效应则被抗CXCR4抗体抑制。此结果表明, BM-MSCs局部生成的SDF-1与CXCR4之间的相互作用对BM-MSCs趋向SAP的受损胰腺组织具有重要的调节作用^[23]。SAP是胰腺的急性炎症性疾病, 并可累及多个远隔组织和器官^[24]。一些动物实验^[24-26]表明, MSCs移植除明显促进胰腺组织的修复外, 还可显著缓解SAP导致的肺损伤^[25]、肾损伤^[26]以及促进肠黏膜屏障^[24]的修复。此外, Jung等^[27]研究证实, 人BM-MSCs也可以有效缓解SAP的胰腺损伤。

5 MSCs与炎症性肠病

炎症性肠病(inflammatory bowel disease, IBD)的发病机制可能与自身免疫有关, 治疗十分棘手, 严重影响患者的生活质量^[28,29]。MSCs具有抑制T细胞增殖、影响树突细胞成熟、抑制B细胞增殖和分化、调节NK细胞和巨噬

细胞等免疫调节功能^[21], SDF-1、CXCR4则参与MSCs趋向IBD受损肠黏膜组织的免疫调节作用^[30]. MSCs除具有细胞高效分化、促进组织再生潜能以及营养活性外^[28,29], MSCs(自体或同种异体)还具有较低的免疫原性^[28]. 基于其上述特性, MSCs有望于不久的将来用于IBD的治疗^[21,28,29]. Abdel Salam等^[31]将MSCs注入IBD小鼠模型体内发现, 其粪便性状、体质量及组织学变化均显著改善, 炎症标志物的基因表达也明显低于对照组. 提示MSCs对IBD有潜在治疗效果. IBD相关的肠神经系统损伤可能持久改变肠道的功能, MSCs通过归巢炎症区域、增强神经保护、抗炎及免疫调节特性可对神经退行性病变的衰减提供治疗^[32]. Robinson等^[32]采用三硝基苯磺酸(trinitrobenzene-sulfonic acid, TNBS)灌肠诱导肠神经病变和功能紊乱的豚鼠IBD模型, 通过组织形态学、免疫组织化学及肠动力分析评估MSCs对肠神经元的治疗效果. 结果显示, MSCs治疗不仅可阻止炎症相关的体质量减轻、结肠形态学损伤, 降低结肠壁的炎症浸润程度和肌间神经节水平, 还可以阻止肠肌层的神经元缺失和神经损伤进程, 缓解结肠的运动功能紊乱. 但Nam等^[33]对IBD小鼠模型采用腹腔注射MSCs后发现, MSCs并不能阻止IBD小鼠的结肠炎症进展, 也不能减轻其临床病理学的严重程度, MSCs治疗组与对照组之间的存活率或疾病活动指数评分差异并无统计学意义. 因此, Nam等^[33]认为, MSCs腹腔注射对IBD的治疗效果十分有限, MSCs的功能提升有待于进一步研究. 此外, Gonçalves Fda等^[34]对IBD小鼠模型的对比研究也发现, MSCs静脉注射对IBD结肠炎症的治疗效果明显优于腹腔注射.

6 MSCs与肝脏疾病

6.1 MSCs与非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)

NASH是以肝细胞丧失、脂肪变性、气球样变、炎症坏死及纤维化形成特征的病理状态^[35]. 体内外的一些研究证实, MSCs能分化成肝细胞样细胞而作为肝细胞的替代细胞来源^[36,37]. 此外, MSCs还有抗炎和促进细胞再生特性, 从而有助于NASH的肝细胞恢复^[37]. Winkler等^[37]对饮食诱导的NASH小鼠模型采用人BM-MSCs移植治疗7 d后发现,

实验小鼠肝实质内可见人肝细胞样细胞分布, 肝组织中的甘油三酯含量下降, 而血中的含量则恢复正常, 急性期蛋白(血清淀粉样蛋白A)、炎症相关标志物[脂质运载蛋白2(lipocalin 2, Lcn2)]、炎症细胞因子(如TNF- α)的表达下降提示肝细胞炎症减轻, 宿主肝细胞的增殖表明接受MSCs移植肝脏的再生能力增强. Ezquer等^[38]对NASH小鼠模型研究也发现, MSCs移植可阻止肥胖小鼠形成NASH.

6.2 MSCs与急性肝衰竭(acute liver failure, ALF)

ALF是以肝功能突然丧失为特征的致命性疾病, 常因过量应用对乙酰氨基酚所致^[39]. Liu等^[39]对ALF小鼠模型采用人脐带MSCs静脉注射发现, MSCs显著提高小鼠的生存率和肝脏相对质量, 血清天冬氨酸转氨酶(aspartate aminotransferase, AST)、丙氨酸转氨酶(alanine aminotransferase, ALT)及总胆红素水平显著降低. MSCs的护肝潜能通过旁分泌途径介导, 包括抗氧化剂(谷胱甘肽、超氧化物歧化酶)、炎症因子(如TNF- α 、IL-6)下降和血清肝细胞生长因子(hepatocyte growth factor, HGF)水平升高. 通过这些旁分泌作用, 静脉注射MSCs可减少肝细胞坏死/凋亡、促进肝细胞再生. 此研究表明, 人脐带MSCs可有效治疗ALF. Stock等^[40]采用人脐带MSCs对急性肝损伤(acute liver injury, ALI)小鼠模型的治疗也得出了与Liu等^[39]相似的结论. 但Briquet等^[41]的研究结果却迥然不同, 他们发现, 人骨髓MSCs、脐带MSCs以及肝MSCs对四氯化碳诱导的ALI小鼠模型均无治疗效果. 此外, Cai等^[42]采用大鼠BM-MSCs注入ALI大鼠模型体内发现, MSCs治疗组的血清ALT、AST水平显著降低, 线粒体依赖通路相关因子Bcl-2相关X蛋白(Bcl-2 associated X protein, Bax)表达下降, B细胞淋巴瘤基因-2(B cell lymphoma 2, Bcl-2)表达增加, 血清甲胎蛋白(α -fetoprotein, AFP)、磷脂酰肌醇蛋白聚糖(glypican-3, GPC3)的mRNA水平及增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)的表达均显著增加. 提示, BM-MSCs移植对肝脏功能的显著恢复可能与MSCs抑制肝细胞凋亡、促进再生有关, 减少细胞凋亡似乎与线粒体依赖通路相关^[42]. BM-MSCs的靶向移植安全有效, MSCs不会混乱移至其他器官^[43]. MSCs对急性肝损伤小鼠移植剂量及途径的优化可通过生物发光成像技术评估^[44].

■ 创新盘点

本文综合大量国内外新近文献, 全面系统阐述了MSCs移植在消化系统疾病应用中的最新进展, 提供了大量有价值的信息.

应用要点

本文详尽阐述了MSCs在消化系统疾病治疗中的最新进展, 内容丰富, 涉及广泛, 为该领域的进一步研究提供了大量信息, 有重要的学术价值。

6.3 MSCs与肝纤维化 Berardis等^[45]认为, MSCs治疗能减轻肝纤维化并改善其肝脏功能. Park等^[46]首次将人扁桃体MSCs(tonsil-derived mesenchymal stem cells, T-MSCs)注入四氯化碳诱导的肝纤维化小鼠模型发现, T-MSCs可分化成肝细胞样细胞, 并通过自噬激活和下调TGF- β 以减轻肝纤维化. 提示T-MSCs可作为新的细胞来源对肝纤维化进行治疗^[46]. 过度表达HGF的转基因MSCs是否可增强肝纤维化疗效尚不清楚^[47]. Kim等^[47]将携带HGF编码cDNA的腺病毒转染MSCs(MSCs/HGF)注入肝纤维化大鼠模型发现, MSCs/HGF因其具有抗纤维化活性, 更能显著改善肝纤维化的治疗效果. 因此, MSCs/HGF是一种有前途的肝纤维化治疗方法^[47]. Yu等^[48]研究发现, 脂肪MSCs移植不仅能阻止肝星状细胞的增殖和活化, 还能阻止肝纤维化大鼠的纤维化形成. Tang等^[49]研究显示, FGF明显促进脂肪MSCs增殖、分化及HGF表达. 提示FGF通过旁分泌HGF促进脂肪MSCs对肝纤维化大鼠的治疗效果^[49].

6.4 MSCs与自身免疫性肝病(autoimmune liver diseases, AILDs) AILDs包括自身免疫性肝炎(autoimmune hepatitis, AIH)、原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)和原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)^[50]. AIH是一种免疫介导的肝脏炎症性疾病^[51]. Chen等^[52]将BM-MSCs从尾静脉注入AIH小鼠模型体内发现, BM-MSCs治疗组的肝损伤程度明显减轻, IL-17表达显著下调, 而程序性死亡配体1(programmed death ligand 1, PD-L1)和IL-23的表达则显著上调. 此研究^[52]结果表明, BM-MSCs移植可通过其免疫抑制作用缓解AIH的肝细胞损伤. PBC是一种免疫介导的胆汁淤积性肝病, BM-MSCs移植可通过调节免疫反应, 促进PBC小鼠肝脏的炎症恢复^[53]. Wang等^[54]通过对C57BL/6小鼠注射聚肌胞-聚肌胞苷酸钠(poly I :C)建立PBC动物模型, 并观察BM-MSCs移植6 wk后对PBC小鼠的疗效. 结果显示, 血清转氨酶和自身免疫性抗体下降, HE染色示胆管周围单核细胞浸润显著缓解. 流式细胞仪分析显示, MSCs治疗组血液及淋巴结中CD4(+)Foxp3(+)调节性T细胞含量显著增加. 血清TGF- β 1增加, 但IFN- γ 显著下降. 此研究^[54]表明, BM-MSCs移植可调节全身免疫反应, 促进PBC小鼠肝脏炎症恢复, 为MSCs治

疗早期PBC患者的临床应用提供了可能.

6.5 MSCs与肝硬化 Li等^[55]将MSCs注入四氯化碳诱导的肝硬化小鼠模型发现, MSCs显著缓解肝硬化小鼠的肝纤维化、门静脉高压及钠潴留, 受损肝组织中TGF- β 1水平下降, 骨成型蛋白7(bone morphogenetic protein 7, BMP7)水平升高, MSCs显著增加BMP7表达水平, 清除BMP7的MSCs则完全丧失对肝硬化小鼠模型的治疗作用. 此研究^[55]表明, MSCs治疗肝硬化的作用机制可能与其生成的BMP7抵抗TGF- β 1致受损肝脏纤维化有关. 尽管MSCs移植对肝硬化动物模型的治疗效果较好, 但MSCs移植对终末期肝硬化患者的疗效尚不清楚^[56]. Xue等^[56]将人脐带MSCs移植至50例肝硬化失代偿期患者的肝组织中发现, 术后2-3 wk, 患者食欲增加, 腹胀、尿少、水肿症状显著减轻, 术后24 wk, 终末期肝病模型(model for end stage liver disease, MELD)评分显著增加, 血清白蛋白、前白蛋白水平显著增加, 但血清AFP无显著增加, 凝血指标也无显著下降, 门静脉、脾静脉的血流动力学无显著变化, 乙型肝炎病毒性肝炎与其他病因所致肝硬化之间的肝功及凝血酶功能差异亦无统计学意义.

7 MSCs与消化系统肿瘤

7.1 MSCs与食管癌 MSCs因在体内具有主动趋向原发及转移肿瘤组织的特性, 因此被认为是肿瘤基因治疗的理想载体细胞^[5]. TNF相关凋亡诱导配体(TNF-related apoptosis-inducing ligand, TRAIL)能通过与死亡受体结合选择性诱导肿瘤细胞系的凋亡, 被认为是一种有希望的候选癌基因治疗^[57]. Li等^[57]采用表达TRAIL的腺病毒载体转染MSCs, 并观察这些转染后的MSCs对食管癌细胞Eca-109的凋亡诱导活性. 结果显示, 转染TRAIL的MSCs在体外不仅能抑制Eca-109细胞增殖、诱导细胞凋亡, 在体内也能阻止Eca-109移植瘤小鼠模型的肿瘤生长. 此结果^[57]表明, 采用转染TRAIL的MSCs基因治疗策略对提高食管癌的疗效具有广泛的潜在价值. Wang等^[58]研究发现, 人脐带MSCs与食管癌细胞融合能诱导癌细胞凋亡并使之向良性细胞转化. 但Yang等^[59]研究显示, 人脐带MSCs在体内均能促进食管癌细胞生长. 因此, 应谨慎采用人脐带MSCs作为食管癌新的治疗策略^[59].

7.2 MSCs与胃癌 NK4是一种肝细胞生长因子受体拮抗剂,在胃癌组织中常被异常激活,因此被认为是有益的候选靶向治疗^[60]。Zhu等^[60]将带有NK4互补DNA或增强GFP的慢病毒载体转染MSCs注入胃癌BALB/C裸小鼠模型体内发现, MSCs-NK4显著抑制胃癌裸鼠模型的移植瘤生长, 迁移并聚集于肿瘤组织, 移植瘤微血管密度下降, 肿瘤细胞凋亡也被显著诱导。此研究表明, 转染NK4的MSCs基因治疗能明显阻止胃癌移植瘤的生长, MSCs是较慢病毒更好的NK4基因治疗载体^[60]。Li等^[61]研究发现, 儿童包皮MSCs是一种新的MSCs来源, 在体内外均可抑制胃癌细胞生长。Wang等^[62]研究发现, 人脐带MSCs促进裸鼠胃癌模型的移植瘤生长, 但采用IL-6预处理的人脐带MSCs则抑制胃癌细胞增殖, 并显著诱导胃癌细胞凋亡。

7.3 MSCs与结肠癌 高迁移率族蛋白B1(high mobility group box 1 proteins, HMGB1)是一种核DNA结合蛋白, 常见于肿瘤组织中, 被认为与肿瘤细胞无限增殖、血管生成、凋亡等因素有关^[63]。Kikuchi等^[63]将转染HMGB1拮抗剂的MSCs注入结肠癌小鼠模型体内发现, 移植瘤肿块体积明显缩小。提示, 转染分泌HMGB1拮抗剂的MSCs具有抗肿瘤治疗的潜力^[63]。Harati等^[64]将带有Lcn2的转染MSCs注入结肠癌裸鼠模型体内发现, MSCs-Lcn2不仅抑制结肠癌肝转移, 而且使肝组织中VEGF表达下调。这些转染MSCs为结肠癌的基因靶向治疗提供了新的思路。

7.4 MSCs与肝癌 前已述及, TRAIL被认为是一种有希望的肿瘤基因治疗的候选基因^[57]。Deng等^[65]研究发现, 转染TRAIL的MSCs可促进热休克蛋白预处理的肝癌细胞凋亡, 并抑制肝癌裸鼠模型的移植瘤生长。Li等^[66]将人MSCs注入肝癌裸鼠模型体内发现, MSCs移植后第3周, 肿瘤抑制率最高, 并随时间进展而逐渐下降, MSCs移植不仅下调肿瘤细胞的转移潜能, 也进一步诱导其细胞凋亡。提示肿瘤细胞增殖能力的下降可能导致其转移能力的下降^[66]。

7.5 MSCs与胰腺癌 NK4为肝细胞生长因子受体拮抗剂, 常被作为候选靶向治疗^[60]。Sun等^[67]将带有NK4的腺病毒转染MSCs后发现, NK4-MSCs不仅对胰腺癌细胞有明显趋向性, 而且强烈抑制胰腺癌细胞株SW1990的增殖和迁移。此外, Moniri等^[68]研究发现, 转染TRAIL的

MSCs也显著抑制胰腺癌细胞的生长。这些研究表明, MSCs可以作为胰腺癌靶向基因治疗的载体^[67,68]。

8 结论

尽管MSCs在消化系统疾病中的基础研究已取得较大进展, 但仍处于初始研究阶段, 尚有诸多问题需要解决。目前所熟知的MSCs生物学特性均是在细胞培养扩增状态下, 而对原始状态MSCs的生物学功能却知之甚少。此外, 如何选择最佳的MSCs类型、移植途径、移植细胞数等问题仍有待解决。随着MSCs研究的不断深入, 将有助于我们进一步认识MSCs在替代治疗中的利弊, 并最终为MSCs在消化系统疾病中的临床应用提供依据。

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■名词解释

干细胞: 是一类未分化的祖细胞, 具有自我更新、分化成多种功能细胞的潜能, 分胚胎干细胞和成体干细胞两种。

同行评价

本文结合最新的国内外文献资料, 全面阐述了MSCs在胃肠道、肝脏以及胰腺等消化系统疾病的应用进展, 为进一步的临床研究和应用提供了很好的理论依据。

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