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·文献综述·

间充质干细胞治疗胰腺炎的研究进展

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摘　要　目前胰腺炎的临床治疗仍以对症支持治疗为主，具有住院周期长、医疗费用高和高病死率，因此亟需寻找到一种新的治疗策略。间充质干细胞（MSCs）因其高度的自我更新、多向分化潜能、低免疫原性以及免疫调节功能等优势，已成为再生医学中组织或器官修复的理想种子细胞。近年来众多研究发现 MSCs 移植胰腺炎动物模型后，不但可归巢到损伤区域，而且可通过抗炎、抗凋亡、促血管新生及免疫调节作用等促进胰腺组织的修复，这表明 MSCs 有望成为治疗胰腺炎的新策略。笔者就 MSCs 在急、慢性胰腺炎治疗中的最新研究进展作一综述。

关键词　胰腺炎；间充质基质细胞；间质干细胞移植；综述文献
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Research progress of mesenchymal stem cell therapy for pancreatitis

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Abstract　At present, the clinical treatment of pancreatitis is mainly supportive, with long period of hospitalization, high medical expenses and high mortality. Therefore, it is urgent to find a new treatment strategy. Mesenchymal stem cells (MSCs) are considered to be ideal seed cells for tissue or organ repair in regenerative medicine, due to well-established self-renewal, multi-lineage differentiation potential, low immunogenicity, as well as immunomodulatory properties. In the last few years, several studies have found that MSCs can not only home to the damage area, but also promote the repair of pancreas injury through anti-inflammation, anti-apoptosis, angiogenesis and immune regulation. These studies suggest that MSCs therapy is a promising strategy for the treatment of pancreatitis. Here, the authors address the latest progress in MSCs therapy for acute and chronic pancreatitis.

Key words　Pancreatitis; Mesenchymal Stromal Cells; Mesenchymal Stem Cell Transplantation; Review
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急性胰腺炎（acute pancreatitis，AP）是指多种病因引起的胰酶异常激活，继以胰腺局部炎症反应为主要特征，伴或不伴有其他器官功能改变的疾病，其起病急、病程长及病情重。AP复发患者还具有发展为慢性胰腺炎（chronic pancreatitis，CP）的高风险，据统计约8%的AP患者在5年内会发展为CP[1]。CP是一种持续性胰腺炎症性疾病，其典型病理特征为胰腺纤维化和腺体萎缩，导致胰腺外分泌和内分泌功能不全[2-3]。目前临床上针对AP与CP的治疗仍是以对症处理为主，虽然CP患者可采取全胰切除联合自体胰岛移植（total pancreatectomy with islet auto-transplantation，TP-IAT）方案进行治疗[4]，但移植后的胰岛细胞存活率低[5]。

间充质干细胞（mesenchymal stem cells，MSCs）是干细胞家族的重要成员，其不但具有自我更新及多向分化潜能[6]，还具有来源方便、低免疫原性以及免疫调节功能[7-9]，因此备受再生医学研究者的青睐。MSCs具有广阔的临床应用前景，目前MSCs移植已在一些疾病中成功开展并取得了较好疗效，如移植物抗宿主病[10]、肝衰竭[11]、急性心肌梗死[12]、类风湿关节炎[13]、肝硬化[14]等。近年来，MSCs在治疗胰腺炎方面也取得了很多进展，研究发现MSCs移植胰腺炎动物模型后，不但可归巢到损伤区域，而且可通过抗炎、抗凋亡、促血管新生及免疫调节作用等促进胰腺组织的修复。笔者就MSCs治疗AP和CP的最新研究进展作如下综述。

1　MSCs 的生物学特性

MSCs具有多向分化潜能。MSCs作为干细胞，其在适宜的体内或体外环境下，可分化为成骨细胞、软骨细胞、脂肪细胞、肌细胞、神经细胞、内皮细胞等多种细胞[6-17]。

MSCs具有低免疫原性。MSCs表面中度表达主要组织相容性复合体I（major histocompatibility complex I，MHC-I）类分子，不表达MHC-II类分子，同时不表达或极低表达共刺激分子CD40、CD80（B7-1）和CD86（B7-2）[18-20]。因此当MSCs在活化T细胞时，由于缺乏共刺激分子传递的第二信号，因此不能有效激活T细胞，难以产生有效的排异反应。

MSCs具有归巢特性。当机体组织发生损伤时，会释放多种炎性因子与趋化因子，如基质细胞衍生因子1（stromal cell derived factor 1，SDF-1）[21]、单核细胞趋化蛋白1（monocyte chemoattractant protein 1，MCP-1）[22]、肝细胞生长因子（hepatocyte-growth factor，HGF）[23]、肿瘤坏死因子α（TNF-α）[24]等，当这些因子与MSCs表面相应受体，如基质细胞衍生因子受体4（stromal cell derived factor receptor-4，CXCR4）、CCR-2、HGF受体、TNF-α受体等结合后，驱动MSCs向损伤部位迁移与定植。

MSCs具有较强的抗炎功能。MSCs能通过多种途径降低循环血液与损伤组织中促炎因子，如白细胞介素1（IL-1）、白细胞介素6（IL-6）、TNF-α、干扰素γ（IFN-γ）等的表达水平和增加抗炎因子如IL-10、IL-4、转化生长因子β（transforming growth factorβ，TGF-β）等的表达水平从而有效减轻局部或（和）全身炎症反应[25-27]。

MSCs具有促血管新生特性。MSCs通过直接分化为血管内皮细胞或（和）分泌促进血管新生因子，如血管内皮长因子（vascular endothelial growth factor，VEGF）、血管生成素1（angiopoietin 1，Ang-1）等促进血管新生，从而有利于损伤组织的修复[28-30]。

MSCs还具有较强的免疫调节能力。大量研究表明MSCs可通过分泌多种细胞因子，如前列腺素2（PGE2）、吲哚胺2，3-双加氧酶（IDO）、TGF-β1、HGF、一氧化碳（NO）等，或外泌体调节多种免疫细胞的增殖分化，如T淋巴细胞[9]、B淋巴细胞[31]、树突状细胞[32]、自然杀伤细[33]、巨噬细胞[34]等。

2　MSCs 与 AP

2.1　MSCs 向损伤部位迁移与定植的特性

MSCs在AP中有向损伤部位迁移与定植的特性。如Jung等[35]将荧光染料CM-DiI标记的人源性骨髓间充质干细胞（bone marrow-derived clonal MSCs，BMSCs）通过尾静脉输注到轻型急性胰腺炎（mild acute pancreatitis，MAP）与重症急性胰腺炎（severe acute pancreatitis，SAP）组及正常对照组大鼠体内，与正常对照组相比，MAP组与SAP组大鼠的胰腺组织检测到更多CM-DiI标记的BMSCs，且SAP组检测到CM-DiI标记的BMSCs多于MAP组，此外还发现输注后的BMSCs主要定植

在胰腺，而肺与肝脏中BMSCs的定植相对较少。后来，大量研究[36-39]也都证实体外输注的MSCs有向损伤的胰腺组织迁移与定植的特性。但关于AP动物模型中输注的MSCs主要向损伤胰腺迁移与定植而较少在肺与肝等器官定植这一观点存在争议。如He等[40]研究发现BMSCs通过尾静脉输注到SAP小鼠体内72 h后，输注的BMSCs主要定植在肺与肝脏，而胰腺部位仅检测到极少量的BMSCs。关于这种不同实验结果的原因还不得而知，或许是因为不同实验室使用的MSCs生物活性不同或实验动物不同（前者用的是大鼠，而后者用的是小鼠）或其他原因。

目前关于MSCs向损伤部位迁移与定植机制的研究还较少。在一项AP动物模型的研究中，发现SDF-1/CXCR4轴在调节BMSCs向损伤的胰腺部位迁移与定植的过程中发挥重要作用[41]。但SDF-1/CXCR4轴是否也参与调节其他类型MSCs向胰腺损伤部位迁移还有待进一步研究。

2.2 MSCs 抗炎作用

大量研究表明MSCs能有效减轻AP局部与全身炎症反应。如Jung等[35]首次证实BMSCs能有效减轻 MAP与SAP大鼠炎症反应与组织损伤。MSCs输注后能显著降低AP动物模型血清与胰腺组织中促炎因子（TNF-α、IL-1β、IL-6、IFN-γ）的表达水平，增加血清与胰腺组织中抗炎因子（IL-4、IL-10、TGF-β）的表达水平[36-44]。此外，笔者前期工作也证实人脐带间充质干细胞（umbilical cord-derived MSCs，UCMSCs）能有效减轻SAP大鼠胰腺损伤与炎症程度[45]。关于MSCs减轻AP炎症的机制也进行了相关研究。如He等[40]研究表明BMSCs能通过分泌肿瘤坏死因子α刺激蛋白6（tumor necrosis factor-α-stimulated gene/induced protein 6，TSG-6）显著抑制核苷酸结合寡聚化结构域样受体蛋白3（nucleotide binding oligo merization domain like receptor protein 3，NLRP3）炎性体活性与核因子κB（nuclear factor-kappa B，NF-κB）信号通路来减轻SAP炎症程度与组织损伤。Qian等[42]研究发现BMSCs能产生microRNA-9作用于NF-κB1/p50基因并抑制NF-κB信号通路（p-P65↓、NF-κB1/p50↓、IκBα↑、IκBβ↑）减轻AP胰腺组织损伤程度，减轻局部或全身炎症反应。虽然以上众多研究都已证实MSCs能降低循环血液与胰腺、肺等器官中促炎因子表达水平，增加抗炎因子表达水平，但是关于MSCs减轻AP炎症机制的了解依旧甚少，因此还需进一步探讨其作用机制。

2.3 MSCs 对腺泡细胞保护作用

胰腺腺泡细胞损伤或坏死在AP发生发展中起十分重要作用，因此减少腺泡细胞损伤或坏死或许能减AP炎症。研究发现MSCs能有效减少AP中腺泡细胞的损伤与坏死。如Meng等[46]发现UCMSCs在SAP中能减少胰腺腺泡细胞的凋亡与坏死，维持其结构与功能的完整性。Kawakubo等[44]发现人羊膜MSCs（human amnion-derived MSCs，hAMSCs）能减少牛蛙素诱导的腺泡细胞损伤或坏死。Jung等[35]发现BMSCs也能减少AP大鼠腺泡细胞的凋亡。Tu等[47]为证实MSCs对腺泡细胞有保护作用，将腺泡细胞与BMSCs在体外进行共培养，发现BMSCs能提高牛黄胆酸钠诱导后腺泡细胞的存活率，降低淀粉酶分泌率与乳酸脱氢酶泄露率。以上研究证实MSCs确实能降低AP中腺泡细胞凋亡与坏死，但关于MSCs减少腺泡细胞凋亡与坏死的机制还缺乏相关研究。

2.4 MSCs 促血管新生

MSCs在AP中能促进损伤胰腺血管新生。Qian等[48]研究发现BMSCs 通过SDF-1α/CXCR4轴在SAP中促进血管新生（VEGF↑、ANG-1↑、HGF↑、TGF-β↑、CD31↑）来促进损伤胰腺组织修复。促进损伤胰腺血管新生，能够有效改善胰腺血液循环，加速修复，因此增强MSCs的促血管新生能力，或许能更有效修复损伤胰腺。

2.5 MSCs 分化为腺泡样细胞

有研究发现MSCs在AP中可分化为胰腺腺泡样细胞。如Qu等[39]将荧光染料PKH26标记的BMSCs输注到AP大鼠体内，在胰腺部位发现PKH26标记BMSCs表面表达胰腺腺泡细胞表面分子标记（如Pax-4、Ngn3、Nkx-6）。

2.6 MSCs 免疫调节作用

研究表明大量免疫细胞也参与胰腺炎的发生发展，如巨噬细胞[49]、树突状细胞[50]、肥大细胞[51]、T细胞[52]等。MSCs对免疫细胞增殖分化有调节作用，如研究发现MSCs输注后能减少AP胰腺组织中$CD3^+$T细胞数，增加$Foxp3^+$调节性T细胞数量[35-36]。但关于MSCs在AP中对巨噬细胞、肥大细胞、树突状细胞的调节还缺少相关研究。

2.7 MSCs 对胰腺外器官的保护作用

MSCs在AP中对胰腺外器官也有保护作用。研究表明MSCs移植能减轻AP相关肠损伤，MSCs移

植后水通道蛋白1（aquaporin 1，AQP-1）表达上调，减少小肠毛细血管内皮屏障损伤，降低肠道黏膜通透性，促进损伤内皮修复[53-54]。笔者前期研究也发现UCMSCs移植后增加了肠角质细胞生长因子（keratinocyte growth factor，KGF）的表达，改善肠屏障功能（d-乳酸、内毒素和细菌易位减少，紧密连接蛋白occludin、ZO-1表达增加）[45]。此外，也有研究[55-56]证实MSCs移植能减轻AP所致的肺损伤。如Wang等[56]发现BMSCs能过降低TNF-α与P物质减轻AP相关肺损伤。Chen等[57]证实MSCs能通过改善肾间质毛细血管内皮屏障功能和上调AQP1的表达来减轻AP相关肾损伤。

3　MSCs与CP

复发性或持续性AP可发展成CP，且CP与胰腺癌的发生有一定关联[58-59]，因此要积极控制胰腺炎症。研究[60-61]发现胰腺星状细胞（pancreatic stellate cells，PSCs）在CP纤维化和炎症进展中起关键作用。PSCs在正常情况下处于“静止状态”，当胰腺受到损伤处于炎症状态时，PSCs可演变成一种成纤维样细胞，活化的PSCs加重胰腺炎症反应与纤维化[62]。

Kawakubo等[44]发现hAMSCs能抑制PSCs产生单核细胞趋化蛋白1（monocyte chemotactic protein 1，MCP-1）和IL-8。而另一项研究表明抑制PSCs产生MCP-1能降低胰腺纤维化程度[63]。一项研究[64]表明将荧光染料CFSE 标记的UCMSCs输注到CP大鼠体内，在胰腺部位检测到CFSE 标记的UCMSCs，UCMSCs治疗组胰腺组织学评分及纤维化程度均低于对照组，同时也抑制了PSCs的活性。此外，Sun等[65]发现脂肪间充质干细胞（adipose derived MSCs，ADMSCs）在CP小鼠中，能减轻炎症、胰腺纤维化程度，并能分化为腺泡样细胞。

全胰切除联合自体胰岛移植（TP-IAT）是目前治疗复发性AP伴腹痛的CP且接受规范化内科、内镜或常规手术治疗无效者的一种有效方法[66]，但移植后的胰岛细胞存活率低。Song等[67]在进行ADMSCs联合胰岛移植实验时，发现ADMSCs能通过上调胰岛素样生长因子1（insulin like growth factor 1，IGF-1）的表达量改善胰岛细胞存活率与功能。后来，Wang等[68]在CP患者中进行全胰切除术后的自体BMSCs联合胰岛移植，在BMSCs输注后没有发生与其直接相关的不良事件。与对照组相比，BMSCs输注后的患者对胰岛素的需求量降低，12个月后的空腹血糖相对降低，生活质量得到更好改善。这初步证明自体MSCs联合胰岛移植可能是一种安全、有效改善移植胰岛功能的策略。

4　问题与展望

尽管大量动物实验已证实MSCs在治疗胰腺炎时的有效性与安全性，然而MSCs的临床应用却依旧受到诸多问题的阻碍。如来源与培养方式的不同可能导致MSCs质量与疗效的不同，这是由于MSCs作为一种活细胞，其生物活性的强弱直接影响治疗效果。关于MSCs输注剂量与时间，目前尚无统一的定论。但Yang等[69]发现UCMSCs治疗大鼠SAP具有时间依赖性和剂量依赖性，他们认为在SAP发生后越早输入UCMSCs治疗效果越好，且适当的大剂量输入能取得更好疗效。此外，关于MSCs治疗胰腺炎时MSCs在胰腺炎动物模型体内存活时间等还缺少系统研究。因为MSCs要发挥治疗作用，其必须要能在体内存活以分泌活性因子或通过直接接触发挥作用。

在治疗胰腺炎的种子细胞选择方面，目前大都聚焦在BMSCs与UCMSCs上，而对胎盘间充质干细胞（placental MSCs，PMSCs）与胰腺炎的研究较少[70-71]。大量研究表明PMSCs也具有抗炎与免疫调节等MSCs具有的特性，并且表现出一定的优势。如PMSCs相对BMSCs更易大量获取，因为PMSCs取自分娩后胎盘，其获取过程不会给捐赠者带来不适，且胎盘MSCs含量远多于骨髓。一项通过提取来自同一捐赠者PMSCs和UCMSCs的研究，发现PMSCs比UCMSCs表现出更强的免疫调节能力[72]。

总之，MSCs移植能有效减轻胰腺炎的炎症程度与组织损伤，因此MSCs有望成为治疗胰腺炎的新策略。但其作用机制尚不完全清楚，仍需要大量研究来进一步探究其作用机制，以推进MSCs能够早日进入胰腺炎的临床治疗。

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