

· 综述 ·

间充质干细胞治疗重症急性胰腺炎的现状与展望

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【摘要】重症急性胰腺炎病情进展快、并发症多、病死率高, 目前临床治疗方法较为局限, 有效控制和减轻其导致的器官功能衰竭及远期并发症具有重要意义。间充质干细胞可以通过促进组织再生、抗氧化、调节自噬、分泌抗炎因子等途径发挥作用。本文总结目前间充质干细胞干预重症急性胰腺炎的相关研究, 展望外泌体的应用以及巨噬细胞极化的调控, 为重症急性胰腺炎的治疗提供新思路和新靶点。

【关键词】胰腺炎; 巨噬细胞; 外泌体; 间充质干细胞

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Research status and prospect on severe acute pancreatitis by mesenchymal stem cells treatment

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【Abstract】Severe acute pancreatitis progresses rapidly, with many complications and high mortality. Currently, the clinical treatment of severe acute pancreatitis is limited, so it is of great significance to control and treat the organ failure and long-term complications caused by severe acute pancreatitis. Mesenchymal stem cells play a beneficial role on severe acute pancreatitis therapy by promoting tissue regeneration, antioxidation, regulating autophagy and secreting anti-inflammatory factors. This paper summarized the current research status of mesenchymal stem cells on severe acute pancreatitis therapy and also showed the application of exosomes and the regulation of macrophage polarization, to provide new ideas and new targets for the treatment of severe acute pancreatitis.

【Key words】Pancreatitis; Macrophages; Exosomes; Mesenchymal stem cells

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急性胰腺炎(acute pancreatitis, AP)是由胰腺腺泡细胞内消化酶的过早激活引起的, 导致胰腺导管细胞的自我消化和炎症反应, 可继发全身炎症反应综合征^[1], 是急诊科常见消化系统急症之一。AP 伴有全身持续器官功能衰竭可发展为重症急性胰腺炎(severe acute pancreatitis, SAP)^[2], 病死率可达 13%~35%^[3], AP 中后期可因继发感染和脓毒症出现器官衰竭, 导致患者死亡^[4]。

尽管 SAP 发病后会启动胰腺再生修复, 但很多患者出院后持续存在胰腺内分泌和外分泌功能不足, 严重影响生活质量。研究显示, SAP 患者急性发作期后新发糖尿病约 39%, 高于 AP 患者的 23%^[5]。综上, 抑制全身炎症反应综合征以预防器官衰竭是改善 SAP 预后的关键。

间充质干细胞(mesenchymal stem cells, MSCs)是具有强大自我更新能力和多向分化潜能的成体干细胞^[6], 可以从成

熟的骨髓、脂肪组织、胎盘、头皮和多种胎儿组织中获得^[7]。得益于其独特的生物学特性, MSCs 在多种疾病的干预中都显示出巨大的潜力, 有望成为 SAP 治疗的重要手段。

一、MSCs 的生物作用

1. 促进组织再生: MSCs 可以通过迁移到损伤的胰腺组织中促进内源性胰岛 β 细胞再生, 还可以分泌多种细胞因子参与修复。2 型糖尿病模型大鼠单次或多次尾静脉注射 MSCs 后, 内源性胰岛 β 细胞再生和胰岛结构恢复, 逆转了大鼠的高血糖^[8-9]。研究表明, MSCs 分泌的微 RNA(microRNA, miR)-181a-5p 可通过人第 10 号染色体缺失的磷酸酶和张力蛋白同源物/蛋白激酶 B(protein kinase B, Akt)/转化生长因子-β(transforming growth factor-β, TGF-β)通路发挥抗凋亡作用, 促进 SAP 模型大鼠损伤的胰腺组织再生^[8]。SAP 大鼠尾静脉注射过表达 miR-9 的 MSCs 后, 全身炎症反应显著

降低,受损胰腺组织再生^[9]。MSCs 还可以通过基质细胞衍生因子/趋化因子受体轴上调血管内皮生长因子(vascular endothelial growth factor, VEGF)、血管生成素-1 的表达,促进血管新生来修复损伤的胰腺^[10]。

2. 抗氧化及细胞保护作用:在 SAP 早期阶段,胰腺腺泡细胞内发生氧化应激,协同还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶的活化导致大量活性氧释放,激活核因子- κ B 信号通路,加重炎症反应^[11]。

与 MSCs 共培养 48 h 后,胰岛细胞活力更高,凋亡更少,活性氧、一氧化氮和超氧离子水平降低,提示 MSCs 对胰岛细胞氧化应激诱导的细胞损伤的保护作用^[12]。MSCs 通过清除氧自由基,增强抗氧化能力、增强线粒体功能来减少氧化损伤,保护受损的细胞^[13]。MSCs 通过尾静脉注射到 SAP 大鼠体内,检测到脂质过氧化物、一氧化氮合酶活性均下降^[14],髓过氧化物酶和活性氧含量下降,超氧化物歧化酶活性增加^[15]。

3. 调节自噬:SAP 早期,胰腺腺泡细胞内自噬激活,与自噬相关的自噬体、自噬标记蛋白等表达显著上调^[16],但自噬体与溶酶体融合障碍,不能完成自噬过程,自噬受损。自噬紊乱与氧化应激、炎症及免疫功能障碍等相互促进进一步加重 SAP^[17]。MSCs 可以有效降低自噬标记蛋白的表达,调节腺泡细胞自噬紊乱,在早期抑制 SAP 的进展(结果待发表)。

4. 缓解炎症:SAP 中局部炎症会导致炎症细胞趋化,促炎细胞因子数量增加,MSCs 移植后可以分泌抗炎因子来缓解局部炎症。MSCs 能通过分泌肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、肿瘤坏死因子- α 刺激蛋白-6 和 miR-9 显著抑制核因子- κ B 信号通路来缓解 SAP^[18-19]。尾静脉输注 MSCs 后可以下调 SAP 大鼠胰腺组织及周围淋巴结中 CD3⁺T 淋巴细胞比例,上调调节性 T 细胞比例,以减轻胰腺局部炎症^[20]。

二、MSCs 治疗 SAP 的现状

迄今为止,几乎所有实验研究均证实 MSCs 可减轻 SAP 胰腺损伤,降低胰腺炎症因子的表达以及血清炎症因子的水平,且 MSCs 对 SAP 的干预具有一定的时效性和量效性。发病时尽快给予 MSCs 干预可以更加有效地降低病死率,缓解胰腺损伤,降低胰外器官损伤发生率^[21]。

尽管已有理论及数据支持 MSCs 用于 SAP 治疗,但仍有诸多问题有待解决。既往报道中,MSCs 来源不一,且均为单次输注,不同组织来源的 MSCs 存在差异,有待探索 MSCs 的最佳来源以及最佳输注次数,并进一步关注胰外器官损伤的治疗和胰腺的再生修复情况,为制定最优临床治疗方案奠定理论基础。

目前国内外临床应用 MSCs 极少。黄少雄等^[22]利用 MSCs 治疗 10 例 SAP 患者,与常规治疗的 10 例患者相比,MSCs 治疗组患者血清 TNF- α 、白细胞介素(interleukin, IL)-6、IL-8、血小板活化因子、淀粉酶、白细胞、C 反应蛋白、CT 征象等得到显著改善,住院时间也明显缩短。韩国一项拟纳入

39 例 SAP 患者评估 MSCs 治疗 SAP 的安全性及疗效的临床研究已备案(NCT04189419)。

三、展望

1. 调控巨噬细胞极化:巨噬细胞可塑性较强,可以针对微环境的信号分化为具有不同表型和功能的亚型,此过程称为极化^[23]。极化的巨噬细胞可分为经典活化的 M1 型和选择性活化的 M2 型。M1 型巨噬细胞多由 γ -干扰素或脂多糖诱导分化,分泌 IL-6、IL-8、TNF- α 等促炎因子,引起机体的免疫炎症反应。M2 型巨噬细胞多由 IL-4、IL-1、Toll 样受体诱导分化,上调 IL-10、肿瘤坏死因子- β 等抗炎因子的表达和 VEGF 的释放,促进细胞生长和组织修复。

巨噬细胞的极化过程涉及较多的信号通路和转录调控。MSCs 可通过抑制核因子- κ B 通路和激活信号转导及转录激活蛋白 3 通路^[24],分泌 TGF- β 激活 Akt/FoxO1 通路^[25],分泌正五聚蛋白 3 激活有丝分裂原及应激活化的蛋白激酶 1 信号通路^[26],分泌血小板应答蛋白 1^[27]等途径促进巨噬细胞 M2 极化。

巨噬细胞作为 SAP 期间浸润胰腺的主要白细胞,当病原体相关的分子模式被受体识别后,巨噬细胞被激活并分化为 M1 表型,产生大量的促炎介质放大炎症反应和招募额外的免疫细胞,并可引起全身炎症反应综合征^[28]。SAP 后期胰腺迅速启动再生修复,为了减轻过度的炎症反应,巨噬细胞发生凋亡或极化为 M2 表型,以保护宿主免受过度损伤,促进伤口愈合^[29]。MSCs 对巨噬细胞的调节作用是近年来研究的热点,在多种急性损伤或慢性炎症疾病模型中,如急性心肌梗死^[30]、脓毒症^[31]、急性肝损伤^[32]、2 型糖尿病^[33]、胰腺炎相关肺损伤^[34]中均证实 MSCs 可诱导促炎 M1 型巨噬细胞转变为抗炎 M2 型巨噬细胞,从而减轻炎症,改善组织器官功能。

2. 外泌体:大量研究表明,MSCs 的免疫调节作用大多归因于其旁分泌作用^[35],外泌体就是其中一种。外泌体是脂质囊泡(大小 30~100 nm),包含信使 RNA、miR、长链非编码 RNA 和蛋白质等,在细胞间的信息传递中发挥重要作用^[36]。

外泌体可通过传递 miR-223^[37]、miR-let7^[38]、miR-21-5p^[39]等促进巨噬细胞 M2 型极化,外泌体可通过抑制核因子- κ B 和诱导型一氧化氮合酶信号转导,减少 TNF- α 、IL-1 和 IL-6 的产生,缓解炎症并促进巨噬细胞向 M2 型极化^[40]。

与 MSCs 相比,外泌体由于避免了分化过程而拥有稳定性、安全性、低免疫排斥等优点^[41],外泌体的组成可以通过 MSCs 的体外预处理来调节,从而产生疾病特异性且基于 MSCs 的免疫抑制产物,因此有望作为一种新型无细胞治疗手段^[42]。

3. 预处理:已有文献表明,通过细胞因子、药物、缺氧等多种方式预处理可显著增强 MSCs 的生物学功能,如药物预处理小鼠骨髓来源的 MSCs 可以提高其 IL-6 依赖的促巨噬细胞 M2 极化的潜力^[43]。红景天甙预处理一方面抑制了高血糖诱导的 MSCs 细胞内活性氧水平,降低细胞凋亡率,另一方面改善了高血糖条件下受损的 MSCs 迁移能力,促进了

糖尿病小鼠伤口愈合^[44]。在大鼠糖尿病模型中,与 MSCs 干预组相比,氟西汀预处理后的 MSCs 干预组大鼠组织中 VEGF 表达增加,坐骨神经切片显示神经元结构基本恢复正常,说明预处理可以增强 MSCs 对糖尿病神经病变的干预作用^[45]。将 MSCs 通过尾静脉输注到 SAP 大鼠体内,与未预处理组相比,血管紧张素 II 预处理的 MSCs 显著抑制胰腺损伤,胰腺炎严重程度、血清淀粉酶和血清脂肪酶水平改善^[46]。

四、总结

目前,SAP 的临床治疗策略以支持和抗炎治疗为主,并不能有效纠正过度炎症导致的免疫失衡。控制疾病进展同时促进胰腺再生修复,改善患者远期生活质量是当前 SAP 治疗的重点。本文展望了 MSCs 在 SAP 治疗中的应用前景,其中 MSCs 对巨噬细胞极化的调节是干预的关键靶点,对于炎症组织的修复至关重要^[47]。此外,预处理 MSCs 可以增强其生物学功能,外泌体有望成为治疗 SAP 的新方法。

利益冲突 所有作者均声明不存在利益冲突

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