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间充质干细胞治疗神经病理性疼痛的研究进展*

燕春州 综述 孟纯阳△ 审校
(济宁医学院临床医学院,济宁 272013;济宁医学院附属医院,济宁 272029)

摘 要 神经病理性疼痛(neuropathic pain,NP)是指由神经系统损害或功能障碍引起的慢性疼痛,表现为自发性疼痛、痛觉过敏、异常疼痛和感觉异常等临床特征。间充质干细胞是一类具有干细胞特征的非造血多功能成体干细胞。研究证实多种来源的间充质干细胞均能有效缓解 NP。间充质干细胞可通过抑制炎症反应、改善运动功能、缓解机械痛敏和热痛敏等方面治疗 NP。本文就间充质干细胞治疗 NP 的研究进展做一综述。

关键词 间充质干细胞; 神经病理性疼痛; 坐骨神经损伤
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Research progress of mesenchymal stem cells in the treatment of neuropathic pain

YAN Chunzhou, MENG Chunyang△
(*College of Clinical Medicine, Jining Medical University, Jining* 272013, *China*;
Affiliated Hospital of Jining Medical University, Jining 272029, *China*)

Abstract: Neuropathic pain (NP) refers to chronic pain caused by nervous system damage or dysfunction, which is characterized by spontaneous pain, hyperalgesia, abnormal pain and sensory abnormalities, etc. Mesenchymal stem cells are a kind of non-hemogenic pluripotent stem cells with stem cell characteristics. Studies have confirmed that mesenchymal stem cells from many sources can effectively alleviate NP. Mesenchymal stem cells play a role in the treatment of NP by inhibiting inflammatory response, improving motor function, and relieving mechanical and thermal hyperalgesia. A review of the research progress of mesenchymal stem cells in the treatment of NP is presented in this paper.

Keywords: Mesenchymal stem cell; Neuropathic pain; Spared nerve injury

神经病理性疼痛(neuropathic pain,NP)是通常由外伤、感染或局部缺血引起,神经系统的原发病变或功能障碍引发的进行性神经系统疾病。NP 特征是异常的感觉症状,如自发性疼痛、痛觉过敏和异常刺激痛[1]。多数 NP 在诱发因素消除或原发病治愈后仍长期存在,给患者带来极大的痛苦。现有药物对于治疗 NP 疗效均不理想,因此急需探寻新的治疗方法。干细胞作为一种治疗组织损伤的新策略,可为许多神经系统疾病提供有效的治疗选择。间充质干细胞广泛来源于骨髓、脐带、胎盘、羊水和脂肪组织等[2-3],具有自体移植、供体来源容易、移植方式相对灵活、易于体外扩增等优点[4-6]。间充质干细胞具有广泛的分化和迁移能力,注入损伤部位可促进组织和神经修复,并且可以通过释放神经营养因子以及抗炎蛋白,来调节小胶质细胞对促炎刺激的反应[7]。间充质干细胞为治疗 NP 带来了新的思路,具有广阔的研究前景。

1 NP 发病机制

NP 发生时,外周敏化、中枢敏化、促炎因子的释放以及痛觉受体表达上调等扮演着重要角色。外周敏化是指神经损伤发生后可促进巨噬细胞、淋巴细胞等分泌多种炎症介质,当这种炎症反应因 NP 而持续存在时,可导致初级传入伤害性感受器

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△[通信作者]孟纯阳,E-mail:chunyangmeng16@163.com

过度兴奋。中枢敏化是指脊髓背角神经元的超兴奋性,与 NP 的发生和维持密切相关[8]。中枢敏化可能关键取决于 N-甲基-D-天冬氨酸受体和谷氨酸代谢型受体激活引起的细胞内变化[9]。NP 时,伤害感受性神经元的可塑性,小胶质细胞活化和过度兴奋性(中枢敏化)可能导致中枢伤害感受性神经元的病理激活。近年来研究表明,中枢神经细胞和外周巨噬细胞中的非神经细胞和小胶质细胞分泌的多种促炎因子和趋化因子在 NP 中发挥重要作用[10-11]。此外,疼痛受体的表达上调(如 P2X3、P2X4、P2X7 受体)也在 NP 的发生和维持过程中发挥作用[12]。

2　间充质干细胞在 NP 治疗中的应用

2.1　*骨髓间充质干细胞*(bone marrow mesenchymal stem cells,BM-MSC)与 NP

Yoo 等[13]采用不同的注射方法注射 BM-MSC,鞘内注射(intrathecal,IT) 和腹膜内注射(intrapaw,IP)均可降低小鼠的胶质纤维酸性蛋白(glial fibrillary acidic protein,GFAP)的表达,NP 小鼠模型的机械性异常性疼痛得到改善。BM-MSC 也可通过抑制蛋白激酶 C(protein kinase C,PKC)和背角神经元中环磷酸腺苷反应元件结合蛋白(cAMP response element binding protein,CREB)的表达改善小鼠运动功能和机械异常性疼痛[14]。在炎症因子方面,BM-MSC 可以减少坐骨神经损伤模型(spared nerve injury,SNI)小鼠前额叶皮层中神经半乳糖苷酶的过度活化以及减少星形胶质细胞和小胶质细胞的活化,同时降低 SNI 小鼠脊髓中白细胞介素 1β(IL-1β)和白细胞介素 17(IL-17)水平,提高小鼠白细胞介素 10(IL-10)水平[15]。在信号通路方面,Yang 等[16]发现脊髓背角小胶质细胞 TLR2/MyD88/NF-κB 通路为靶点,通过肿瘤坏死因子-α 刺激基因 6 蛋白(tumor necrosis factor alpha stimulated gene-6 protein,TSG-6)的分泌减轻 NP。BM-MSC 可通过抑制核因子 κB,(nuclear factor-κB,NF-κB)信号通路的同时,通过产生胶质细胞源性神经营养因子(glialcellline-derivedneurotrophicfactor,GDNF)促进 PI3K/AKT 信号通路的激活以减轻 NP[17]。在基因修饰方面,经鞘内注射经人前脑啡肽原(human preproenkephalin ,HPPE)基因修饰的 BM-MSC 显著减少了大鼠坐骨神经慢性压迫模型(chronic constrictive injury,CCI)引起的机械异常性疼痛和热痛觉过敏的发生。经 HPPE 修饰的 BM-MSC 分泌的亮氨酸脑啡肽(leu-enkephalin,L-EK)与对照组相比显著增加[18]。在临床实验方面,通过腰椎穿刺将 BM-MSC 置入患者蛛网膜下腔,发现患者 NP、运动能力、括约肌功能障碍均表现出不同程度的临床改善[19]。

2.2　*脐带间充质干细胞*(umbilical cord mesenchymal stem cell,UC-MSC)与 NP

连续鞘内注射 UC-MSC 外泌体可通过减弱脊髓神经结扎诱导的神经元活化和神经胶质细胞激活,降低肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)和 IL-1β 的表达,提高 IL-10 表达水平、脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)和 GDNF 的表达;减轻神经结扎引起的疼痛[20]。BM-MSC 和 UC-MSC 在大鼠模型中均能促进神经功能恢复、改善痛觉和痛觉过敏,并且二者在改善痛觉和痛觉过敏方面无显著性差异[21]。UC-MSC 可通过减少炎症因子 IL-6 和 TNF-α 的分泌,上调 GDNF 的表达来增强受损脊髓组织的修复并发挥对 NP 的镇痛作用[22]。

2.3　*羊水间充质干细胞*(human amniotic fluid derived mesenchymal stem cells ,hAFMSCs)与 NP

尾静脉对大鼠 CCI 模型注射人 hAFMSCs 能够通过减少蛋白基因产物 9.5(protein gene product 9.5,PGP9.5)、突触囊泡蛋白和 TNF-α 以及脊髓背角 OX-42 的表达来减轻 NP[23]。在细胞水平上,hAFMSCs 与背根神经节细胞共培养也可减少 TNF-α、IL-1β 和突触囊泡蛋白的表达。

2.4　*脂肪间充质干细胞*(adipose mesenchymal stem cells,AD-MSC)与 NP

Forouzanfar 等[24]研究发现通过尾静脉注射经成纤维细胞生长因子 1(Fibroblast growth factor1,FGF1)基因转染的 AD-MSC 可改善大鼠 CCI 模型引所起的机械和热超敏反应,TNF-α 和 GFAP 的表达水平明显降低,大鼠脊髓结构改变和细胞凋亡也显著减少。Liu 等[25]实验表明,大鼠 BM-MSC 和大鼠 AD-MSC 中,两种间充质干细胞在大鼠 CCI 模型中静脉和鞘内移植均安全有效,均能显著减轻 NP。

综上所述,间充质干细胞通过改善大鼠模型机

械痛敏和热痛敏症状、降低促炎因子的表达和小胶质细胞的活化治疗 NP。同时间充质干细胞可通过多种方式进行移植,在实验中可灵活运用,包括鞘内注射、腹膜内注射、尾静脉注射等,均能缓解大鼠 NP。但由于其分子机制尚不清楚,未来间充质干细胞治疗 NP 的分子机制将成为研究热点。间充质干细胞治疗 NP 虽取得一定进展,但大多数还仅存在于动物实验,对人体实验还相对较少。对于间充质干细胞的人体实验,还存在较多问题和局限性,如间充质干细胞注射的剂量和浓度、间充质干细胞注射是否具有潜在危险性、最优的注射的方法和途径是否会影响治疗效果和如何评判治疗成功等尚未在医学界形成共识,实验人数较少且缺少随机对照实验等,还需进一步探究。

3 小结与展望

由于 NP 的发病机制尚不清楚,而临床治疗 NP 的药物效果不理想,而且价格不菲,给患者和家庭都带来沉重负担。间充质干细胞作为干细胞的一员,在治疗 NP 中取得一定的成果。近来研究表明间充质干细胞外泌体也具有治疗 NP 的作用,仍需对间充质干细胞及其外泌体分泌的多种活性物质进一步探究,从而阐明其治疗 NP 的分子机制。随着未来间充质干细胞及其应用的大规模的实验研究,间充质干细胞有望成为安全性高、耐受性良好和高效治疗 NP 的新方法。

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