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·综 述·

脂肪间充质干细胞治疗缺血缺氧性脑病的研究进展

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[摘要] **目的** 脂肪间充质干细胞(adipose-derived mesenchymal stem cells,ADMSC)是一类具有多向分化潜能、免疫调控功能和自主更新能力的干细胞。与骨髓间充质干细胞(bone marrow mesenchymal stem cell,BMSC)相比,ADMSC具有脂肪组织来源丰富、提取率高、取材过程痛苦程度低等特点。缺血缺氧性脑病(hypoxic-ischemic encephalopathy,HIE)致死、致残率极高,但现有的治疗方法临床效果不佳。近年来的研究发现,ADMSC能通过归巢、旁分泌、免疫调节、神经样分化及内源性神经再生等机制减轻脑缺血缺氧引起的神经损伤,有望成为治疗HIE的新方法。本文综述了ADMSC治疗HIE的相关机制和已经开展的临床试验及其存在问题。

[关键词] 脂肪间充质干细胞;脑缺氧缺血;神经保护;间充质干细胞移植
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Research progress of adipose-derived mesenchymal stem cells in treatment of hypoxic-ischemic encephalopathy

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[**Abstract**] Adipose-derived mesenchymal stem cells (AMDSCs) isolated from adipose tissue are stem cells with a multilineage differentiation potential, immune regulation function and highly self-renewal capacity. Compared with bone marrow mesenchymal stem cells (BMSCs), AMDSCs have some unique advantages, including abundant resource in adipose tissue, high extraction rate, and are easy to acquire tissue and so on. Hypoxic-ischemic encephalopathy (HIE) has very high mortality and disability rates, and the clinical therapeutic effect is not very satisfactory. ADMSC can decrease neurological deficits and improve neurological function following HIE through multiple mechanisms, including homing, paracrine, immune modulation, neural differentiation and endogenous neurogenesis, and the ADMSC constitute a promising therapy for HIE treatment. This review summarized the related mechanisms, clinical trials and questions about ADMSC treatment.

[**Key words**] adipose-derived mesenchymal stem cells; brain hypoxic-ischemia; neuroprotection; mesenchymal stem cell transplantation

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缺血缺氧性脑病(hypoxic-ischemic encephalopathy,HIE)是由多种原因引起的局部或全脑血供不足而导致的缺血缺氧性脑损伤,常见于脑梗死、心跳骤停、卒中、窒息、溺水等疾病,表现为不同程度的神经功能障碍,如失语、偏瘫、认知能力下降、植物人状态,严重者甚至会死亡[1]。在常规治疗之外,亚低温治疗、高压氧治疗、药物治疗等方法相继应用在HIE的治疗中,取得了一些进展;但由于产生了不可逆的脑损伤,患者的出院率及生活质量仍然不高[2]。近年来,骨髓间充质干细胞(bone marrow mesenchymal stem cell,BMSC)在治疗HIE的研究中取得了良好效果,但也存在提取率低、取材过程痛苦、分化能力下降等不足[3]。脂肪间充质干细胞(adipose-derived mesenchymal stem cell,ADMSC)

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不仅具有与BMSC相似的生物学特性及多向分化潜能[4],而且具有脂肪组织来源丰富、提取率高、取材过程痛苦程度低等特点[5],使其具有替代BMSC成为再生医学新的干细胞来源的潜能。本文对ADMSC在HIE治疗中的应用进行综述。

1　ADMSC的生物学特性

ADMSC广泛存在于人体脂肪中,不仅取材方便,而且每1 g脂肪组织中可获得(0.5～2)×10^6个血管基质成分(stromal vascular fraction,SVF)细胞,SVF细胞经过培养分离可获得1%的ADMSC(0.5×10^4～2×10^5),其比例远高于骨髓分离。在免疫表型方面,与其他来源的间充质干细胞(mesenchymal stem cell,MSC)类似,ADMSC表达MSC特异性表面抗原,如CD90、CD105、CD73,不表达造血干细胞表面抗原,如CD45、CD34,不表达人类白细胞DR抗原(HLA-DR)[6-7]。同时,ADMSC具有多向分化能力,能分化为骨、软骨、脂肪,并且分化、增殖能力稳定,且不会随供者年龄增长出现明显下降趋势[3,8]。体外实验证实,ADMSC经多次传代后仍具有稳定的增殖能力,其增殖能力优于BMSC;ADMSC分泌的吲哚胺2,3二加氧酶活性水平明显优于BMSC,具有更强的免疫调节能力[9]。

2　ADMSC治疗HIE的相关机制

2.1　*归巢机制*　归巢是指MSC在多种因素作用下,定向性迁移越过血管内皮细胞到达靶向组织,并定植存活的过程。在大鼠大脑中动脉闭塞模型(middle cerebral artery occlusion,MCAO)中,通过颈内动脉或外周静脉注射ADMSC,发现ADMSC能穿越血脑屏障迁移至脑损伤区域[10-11],其机制可能与基质细胞衍生因子1α(stromal cell-derived factor 1α,SDF-1α)和趋化因子受体4(C-X-C chemokine receptor type 4,CXCR4)轴有关。SDF-1α是促进ADMSC迁移的关键因子,损伤部位SDF-1α表达增加或者ADMSC过表达SDF-1α都能促进ADMSC向损伤部位的迁移[12],而CXCR4抑制剂AMD3100能抑制迁移能力[13]。在细胞信号通路方面,激活丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)通路、PI3K/Akt通路、Ras同源基因家族、血小板衍生生长因子BB/血小板衍生生长因子受体β通路都能加强ADMSC的迁移能力,促进归巢[14]。

2.2　*旁分泌功能*　ADMSC能分泌多种营养因子,这些因子多为水溶性物质,能在脑损伤部位发挥保护及修复作用。其中,脑源性神经生长因子(brain-derived neurotrophic factor,BDNF)和神经生长因子(nerve growth factor,NGF)具有促进新的神经元分化及强大的保护受损神经元的作用[15-16];血管内皮生长因子(vascular endothelial growth factor,VEGF)和肝细胞生长因子(hepatocyte growth factor,HGF)是促进血管再生的关键因子,能促进损伤部位的血管再生,为损伤部位恢复血液供应[17-18]。研究发现ADMSC上清液含有多种因子,在大鼠HIE模型中注射上清液,发现神经细胞凋亡减少,胶质细胞增殖减轻,新生血管形成,脑功能改善[19]。不同来源的MSC分泌的因子存在差异,ADMSC分泌某些蛋白(成纤维细胞生长因子、干扰素γ等)的能力优于BMSC[9]。

2.3　*免疫调节*　在脑损伤后数小时内,就会出现大量的黏附于受损部位的内皮细胞神经炎症介质,这些介质能加重已存在的神经损伤或者在神经修复中起积极作用。体外实验证实,ADMSC能抑制单核细胞增殖,并调节白介素(IL)6、转化生长因子1的浓度[20]。动物实验表明,ADMSC既能下调促炎因子(IL-18、TNF-α、Toll样受体4等),也能上调抗炎因子(IL-8、Bcl-2蛋白等),从而减轻炎症反应[10,21]。其潜在作用机制目前尚不明确,可能是ADMSC通过与细胞的直接接触及分泌可溶性因子共同作用而发挥一系列效应。

2.4　*神经样分化*　ADMSC除了能向中胚层组织分化,还具有跨胚层向神经细胞分化的能力,即横向分化能力,其分化机制可能与细胞所处的微环境有关。Safford等[22]发现,在一定环境下ADMSC(传代4～5代)可分化成类神经元样细胞,并表达神经巢蛋白、核蛋白等神经表型,在开始诱导后1～3 h,ADMSC就可以出现阳性神经表型。体外实验发现,多种因素及条件(富含血小板的血清[23]、人参皂苷Rg1[24]、神经营养因子[25]、催产素[26])均可诱导AMDSC向神经样细胞分化。在动物实验中,无论

进行颅内定位或外周血管注射都会在脑损伤区域发现 ADMSC，并表达巢蛋白、核蛋白等神经表型[11,27]，说明 ADMSC 产生了神经样分化。上述研究表明，多种物质均能诱导 ADMSC 向神经样细胞分化，而这些物质可能通过激活或失活某些细胞内与细胞增殖分化相关的信号通路来诱导神经样分化[28]，激活 MAPK/ERK 通路、Wnt 通路并促进 ADMSC 神经样分化[28-29]。

2.5　内源性神经再生　成人大脑的侧脑室室下区（subventricular zone，SVZ）及海马齿状回颗粒下层（subgranular zone，SGZ）的神经细胞仍保持着一定的神经再生能力，在 HIE 发生 2 周内 SVZ 的神经干细胞增殖现象明显[30]，提示如果能够大量激活 SVZ、SGZ 的神经干细胞，就可以通过加强内源性神经再生促进神经修复。注射 ADMSC 1 周后，SVZ 神经干细胞增殖、分化增多，出现了大量 BrdU、DCX 双阳性细胞，并且向脑损伤区域迁移，说明 ADMSC 能促使 SVZ 的神经干细胞向神经细胞分化[10,31]。BDNF 能调控中枢神经细胞存活、增殖，以及神经分化[32]，ADMSC 促进内源性神经再生可能与其大量分泌 BDNF、NGF 多种营养因子有关[33]。

3　ADMSC 治疗 HIE 的临床研究

3.1　ADMSC 的临床试验　2016 年 12 月 16 日从 *www.clinicaltrials.gov* 查询到使用 ADMSC 治疗 HIE 的临床试验共 4 项，见表 1。已开展的试验侧重于对 ADMSC 治疗缺血性卒中的有效性及安全性评价，研究对象均为 60～80 岁脑梗死患者，注射剂量为 1×10^6 细胞/kg，注射方式为静脉注射或颈内动脉注射，注射时间为卒中后 1～14 d，观察时间6～24 个月。Regenerative Stem Cell Therapy for Stroke in Europe（NCT02849613）试验是 2016 年在欧洲开展的多中心、大样本（400 例）临床研究，研究对象为 18 岁以上的缺血性卒中患者，设置安慰剂对照组，观察静脉注射 ADMSC 治疗缺血性卒中的有效性和安全性，预计在 2020 年 9 月完成。该试验缺乏对心搏骤停、窒息、失血等原因引起的全脑缺血的研究，因此需要进一步开展针对全脑缺血的大样本、多中心临床试验，验证 ADMSC 在治疗 HIE 中的有效性和安全性。

表 1　应用 ADMSC 治疗 HIE 的临床试验[a]

Tab 1　Clinical trials of HIE treated with ADMSCs[a]

Identifier	Disease	Intervention	Phase	Research center
NCT02813512	Ischemic stroke	ADMSCs	Phase 1	Single center
NCT01678534	Ischemic stroke	ADMSCs/placebo	Phase 2	Single center
NCT02849613	Ischemic stroke	ADMSCs/placebo	Phase 2，3	Multicenter
NCT01453829	Ischemic stroke	ADMSCs	Phase 1，2	Multicenter

[a]：From *www.clinicaltrials.gov*. ADMSC：Adipose-derived mesenchymal stem cell；HIE：Hypoxic-ischemic encephalopathy

3.2　ADMSC 体内应用的安全性　ADMSC 不表达 HLA-DR，不会引起效应 T 细胞介导的免疫排斥反应，因此目前无论在异体还是异种 ADMSC 移植实验中，均未发现存在排异反应。ADMSC 具有归巢、多向分化、分泌营养因子的特点，因此致瘤性是其安全性研究的焦点。ADMSC 是否会定向迁移至病灶，分泌生长因子，促进肿瘤细胞增殖、浸润及远处转移，是否会诱发新生肿瘤，目前尚存争议。Feng 等[34]发现，ADMSC 会向胶质细胞瘤迁移，但在体外不会分化为肿瘤相关的成纤维细胞，在体内也不具有致瘤性。但也有研究认为，ADMSC 通过分泌 IL-6 激活肿瘤细胞内的 JAK2/STAT3 信号通路，可能促进乳腺肿瘤、结肠癌发生[35]，ADMSC 能促进与肥胖相关肿瘤（如子宫内膜癌）的生长[36-37]。目前关于 ADMSC 安全性的研究较少，缺乏长时间的观察及相关机制的探讨。

3.3　ADMSC 临床应用的瓶颈

3.3.1　供体选择　ADMSC 移植包括自体移植和异体移植。自体移植是指从患者体内抽取脂肪，需要传代 3～6 次才能获得临床治疗需要的细胞，准备时间长达 4 周。ADMSC 低表达 MHC Ⅰ类抗原，不表达 MHC Ⅱ类抗原和共刺激分子 CD40、CD80y、CD86，具有免疫调节和免疫豁免的特性，此特点使异体甚至异种移植成为可能。研究发现，人

来源的 ADMSC 对大鼠 HIE 具有较好的治疗效果[38],且与同种来源 ADMSC 治疗效果无明显差异[17],为临床异体移植提供了理论支持。从健康供者抽取脂肪进行培养和传代,准备时间可缩短至 7 d。此外,脂肪的类型、脂肪采集的部位、采集的方法、供者的体质量、健康状态等多种因素都可能影响 ADMSC 的质量,因此需要对供者进行筛选,对采集过程进行规范。

3.3.2　注射途径　注射途径主要有颅内定位注射、鞘内注射和静脉注射 3 种。颅内定位注射 ADMSC 的归巢细胞数多,但存在不能大剂量注射、易引起继发性损伤等缺点[39]。鞘内注射相对风险较小,但存在操作烦琐、容易导致脊髓损伤等不足。静脉注射安全、快捷,可大剂量注射,但存在 ADMSC 归巢数量少、部分细胞被肺毛细血管网捕获的缺点[39]。临床上,需要结合患者的特点,选择合适的注射途径。

3.3.3　治疗时间窗　研究发现,在 HIE 发生后 30 min 注射 ADMSC,24 h 内就能减轻神经损伤,且在观察期(14 d)内也一直有脑保护作用[40]。也有研究表明,在脑损伤后 30 d 注射 BMSC,没有观察到症状好转[41]。上述差异表明,早期注射能通过多个环节保护脑神经,但有效的时间窗需要新的研究来确认。

4　小　结

ADMSC 能够通过归巢、旁分泌、免疫调节、神经样分化、内源性神经再生等多个环节减轻 HIE 的脑损伤,在动物实验中取得了较好的效果,并开展了初步的临床试验。但从临床应用角度而言,目前仍存在一些问题有待解决,如最佳注射途径、治疗的时间窗、作用机制、与肿瘤关系等。随着研究的不断深入,ADMSC 有望成为治疗 HIE 的理想策略。

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