

干细胞来源的外泌体治疗中枢神经系统疾病的研究进展

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【中图分类号】 R742 【文献标识码】 A 【文章编号】 1007-0478(2023)02-0224-06

【DOI】 10.3969/j.issn.1007-0478.2023.02.021

中枢神经系统疾病包括缺血性脑卒中(Ischemic stroke, IS)、阿尔兹海默病(Alzheimer's disease, AD)和帕金森病(Parkinson's disease, PD)等,其氧化应激、神经炎症和细胞凋亡是促进疾病进展的重要病理机制^[1]。小胶质细胞也在中枢神经系统疾病病理过程中发挥重要作用。有研究表明,小胶质细胞可以响应不同的环境刺激被激活为 M1 或 M2 表型;前者产生大量促炎细胞因子并加剧脑损伤;后者通过分泌各种抗炎细胞因子来发挥对大脑的保护作用^[2]。干细胞来源的外泌体具有抑制氧化应激、减轻炎症反应、调节小胶质细胞极化、促进血管生成和神经发生等生物学功能,在调节中枢神经系统疾病病理生理过程中具有多方面的作用。此外,中枢神经系统的血脑屏障(Blood-brain barrier, BBB)是一种高度选择性的半通透性屏障,限制了许多治疗药物以有效浓度到达中枢神经系统^[3]。多项研究发现,外泌体具有高递送效率、低免疫原性、良好的生物相容性和血脑屏障穿透特性^[4-5]。因此,干细胞来源的外泌体可能被引入作为 IS、AD 和 PD 等中枢神经系统疾病的有效治疗策略。本研究基于对中枢神经系统疾病体内、体外实验模型的分子病理机制进行阐述,进一步讨论了干细胞来源的外泌体作为细胞旁分泌因子对中枢神经系统疾病的治疗潜力。

1 外泌体简介

干细胞具有自我复制和多向分化能力,包括胚胎干细胞(Embryonic stem cells, ESCs)、间充质干细胞(Mesenchymal stem cells, MSCs)和诱导多能干细胞(Induced pluripotent stem cells, iPSCs)等^[6]。干细胞还可以产生旁分泌因子^[7]。最近的研究发现,干细胞的旁分泌作用部分是由外泌体(Exosomes)介导的^[8]。外泌体是具有脂质双层膜结构的细胞外囊泡,直径为 30~150 nm,其生物发生始于细胞膜内陷,后逐渐成熟为具有腔内囊泡(Intraluminal vesicles, ILVs)的多泡体(Multivesicular bodies, MVBs)。当 MVBs 与质膜融合时将 ILVs 释放到细胞外,即外泌体^[9-10]。外泌体内含来自其起源细胞的多种生物活性分子如蛋白质、脂质、mRNA 和 microRNA(miRNA)等^[11]。外泌体携带这些生物活性分子通过内吞作用、配体-受体相互作用或直接膜融合的内化作用于靶细胞,从而介导细胞间通讯^[12-13]。越来越多的研究发现,利用外泌体自身特性包括运输内容物的能力、循环稳定性及跨血脑屏障特性,实现了从外周循环到中枢神经系统的

信号交流^[14-15]。因此,外泌体可能是治疗中枢神经系统疾病的潜在选择。

2 外泌体治疗中枢神经系统疾病

2.1 缺血性脑卒中

IS 发生后的内源性大脑修复涉及一组高度交互的过程如血管生成、神经发生、突触生成和轴突生长,它们共同协调神经功能恢复^[16]。干细胞来源的外泌体及其携带的内容物通过调节细胞信号通路在改善 IS 预后方面发挥着重要作用。

2.1.1 体内模型 通过模拟病因和病理生理机制。大鼠和小鼠的大脑中动脉闭塞(Middle cerebral artery occlusion, MCAO)模型常被用来模拟 IS 的体内实验。有研究发现,间充质干细胞来源的外泌体(Mesenchymal stem cell-Exosomes, MSC-Exos)可促进大脑皮质和纹状体缺血边界区域的血管生成和神经发生,这将有利益于大脑组织进行重塑^[17-18]。此过程也可以由 MSC-Exos 携带的 microRNA-17-92 通过靶向下调磷酸酶张力蛋白同源物(Phosphatase and tensin homolog, PTEN),激活磷脂酰肌醇-3-激酶/蛋白激酶 B/雷帕霉素/糖原合酶激酶 3 β (Phosphatidylinositol 3-phosphate kinase/Protein kinase B/Rapamycin/Glycogen synthase kinase 3 β , PI3K/Akt/mTOR/GSK-3 β)信号通路来实现^[19-20]。Xu 等^[21]发现, MSC-Exos 被静脉注射后可有效迁移到小鼠 MCAO 模型缺血病变区域,并进一步与神经元融合,然后通过促进血管生成和神经发生来发挥保护作用。最近的一项研究表明, MSC-Exos 可有效促进老年大鼠 MCAO 模型皮层缺血区域的血管生成和神经发生,进而促进 IS 的神经功能恢复和梗死周围脑组织重塑^[22]。这些数据表明 MSC-Exos 是促进 IS 后血管生成、神经发生,进而增强脑组织重塑的有效治疗策略。MSC-Exos 还可以激活 AMP 依赖的蛋白激酶(AMP-activated protein kinase, AMPK)磷酸化和下调蛋白酪氨酸激酶 2/信号转导和转录激活因子 3/核因子- κ B (Janus kinase 2/Signal transducer and activator of transcription 3/Nuclear factor- κ B, JAK2/STAT3/NF- κ B)信号通路,改善 MCAO 模型的神经元凋亡进程^[23]。此外,牙髓干细胞(Dental pulp stem cells, DPSCs)来源的外泌体(DPSC-Exos)通过抑制高迁移率族蛋白 B1/Toll 样受体 4/髓样分化因子 88/核因子- κ B(High mobility group Box-1/Toll-Like receptor 4/Myeloid differentiation primary response 88/Nuclear factor- κ B, HMGB1/TLR4/MyD88/NF- κ B)信号通路来减轻 MCAO 小鼠的神经炎症^[24],进而减轻

缺血性脑损伤。因此,干细胞来源的外泌体是一种改善神经系统功能恢复有前景的治疗策略。

缺血后炎症反应是 IS 进展的关键环节,而小胶质细胞是脑中促炎细胞因子水平升高的主要细胞来源。干细胞来源的外泌体可通过调节小胶质细胞极化以抑制神经炎症来促进 IS 恢复。Zhao 等^[25-26]发现, MSC-Exos 通过逆转半胱氨酰白三烯 II 型受体-细胞外信号调节激酶 1/2 (Type 2 receptor for cysteinyl leukotrienes-extracellular regulated kinase 1/2, CysLT2R-ERK1/2) 介导的小胶质细胞 M1 极化,促进了小胶质细胞向抗炎 M2 表型转化;进一步的研究发现外泌体 miR-223-3p 显著降低了 CysLT2R 的 mRNA 和蛋白表达水平。该研究表明,外泌体携带的 miR-223-3p 可通过抑制 CysLT2R 表达来介导小胶质细胞极化过程。Li 等^[27]研究发现, MSC-Exos 携带的 miR-26b-5p 通过靶向胆固醇-25-羟化酶 (Cholesterol-25-hydroxylase, CH25H) 抑制 Toll 样受体 (Toll-like receptor, TLR) 信号通路来减弱缺血诱导的小胶质细胞 M1 极化和炎症反应,进而减轻脑缺血后的神经损伤。外泌体还通过将小胶质细胞从促炎 M1 表型转化为抗炎 M2 表型来抑制 NLRP3 炎症小体介导的细胞焦亡和炎症,从而改善缺血性脑损伤^[28]。因此,通过外泌体途径干预小胶质细胞活化是治疗 IS 的重要策略。基于抑制小胶质细胞 M1 极化或将小胶质细胞从 M1 表型转变为 M2 表型的新疗法开发将可能是缓解 IS 炎症反应有希望的治疗策略。

2.1.2 体外模型 氧和葡萄糖剥夺 (Oxygen and glucose deprivation, OGD) 是一种广泛用于研究 IS 的体外实验模型^[29]。有研究发现, MSC-Exos 能减轻 OGD 诱导的原代大鼠脑内皮细胞损伤^[30]。Kang 等^[31]发现,外泌体通过抑制 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 炎症小体介导的细胞焦亡,进而减轻 OGD 诱导的原代皮层神经元和神经母细胞瘤 N2a 细胞损伤。此外, MSC-Exos 通过促进 AMPK 依赖性自噬通量来抑制 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 炎症小体介导的细胞焦亡,从而减轻 OGD 诱导的 PC12 细胞损伤^[32]。Hu 等^[33]发现, MSC-Exos 通过上调叉头转录因子 O 亚家族成员 3a (Forkhead box protein O3a, FOXO3a) 表达以增强线粒体自噬,从而抑制 OGD 诱导的小胶质细胞焦亡,并减轻随后的神经元损伤。因此,通过激活线粒体自噬以抑制细胞焦亡可能是治疗 IS 的重要策略。

Yang^[34]等发现,外泌体促进了脑微血管内皮细胞的血管生成,进一步的研究发现 M 型瞬时受体电位通道 7 (Melastatin transient receptor potential channel 7, TRPM7) 是 miR-181b-5p 的直接靶基因,外泌体携带的 miR-181b-5p 通过靶向下调 TRPM7 的 mRNA 和蛋白表达水平,从而上调血管内皮生长因子 (Vascular endothelial growth factor, VEGF) 的蛋白表达。Zhang 等^[35]发现, MSC-Exos 与 BV2 小胶质细胞共培养后显著降低了白细胞介素-6 (Interleukin-6, IL-6)、TNF- α 和白介素 1 β (Interleukin-1 β , IL-1 β) 的 mRNA 和蛋白表达水平;进一步的实验结果表明外泌体包裹的

miR-146a-5p 通过抑制白细胞介素-1 受体相关激酶/TNF 受体相关因子 6 (IL-1 receptor associated kinase/TNF receptor associated factor 6, IRAK1/TRAF6) 信号通路来减轻小胶质细胞介导的神经炎症。Deng 等^[36]发现, MSC-Exos 通过递送 miR-138-5p 下调脂质运载蛋白 2 (Lipocalin-2, LCN2) 来促进星形胶质细胞增殖,并抑制细胞凋亡和炎症反应;双荧光素酶报告实验结果表明, miR-138-5p 可以特异性结合 LCN2 的 3' 非翻译区 (3'-Untranslated region, 3' UTR) 并下调 LCN2 的基因表达,表明 LCN2 是 miR-138-5p 的直接靶基因。此外,人尿源性干细胞 (Urine-derived stem cells, UDSCs) 来源的外泌体携带的 miR-26a 可通过靶向抑制组蛋白去乙酰化酶 6 (Histone deacetylase 6, HDAC6) 来改善神经干细胞的增殖和神经元分化^[37]。综上所述,外泌体通过递送不同的 miRNA 与相应的靶基因结合来调控炎症、凋亡和血管生成相关基因的表达,进而改善 IS。因此,外泌体作为干细胞的旁分泌因子,包裹的 miRNA 可能是其发挥神经保护作用的潜在机制 (表 1)。

表 1 外泌体中 miRNA 在 IS 治疗中的研究

外泌体来源	miRNA	靶基因	保护作用	参考文献
BMSCs	miR-17-92	PTEN	促进血管生成、神经发生	[20]
BMSCs	miR-223-3p	CysLT2R	促进 M2 小胶质细胞极化	[26]
MSCs	miR-26b-5p	CH25H	抑制 M1 小胶质细胞极化和炎症	[27]
ADSCs	miR-181b-5p	TRPM7	促进血管生成	[34]
BMSCs	miR-138-5p	LCN2	抑制星形胶质细胞凋亡和炎症	[36]
UDSCs	miR-26a	HDAC6	促进神经干细胞的增殖和神经元分化	[37]

2.2 阿尔兹海默病

AD 是最常见的神经退行性疾病,主要以痴呆的形式出现,其特征是认知能力、精神状态和日常生活活动能力严重受损^[38]。 β 淀粉样蛋白 (A β , A β) 蛋白的积聚和磷酸化 Tau 蛋白的逐步积累是阿尔兹海默病的标志性病理特征。此外,神经胶质细胞的激活也是 AD 的重要特征^[39]。多项研究表明,干细胞来源的外泌体可以通过抑制神经胶质细胞激活和减轻 A β 蛋白沉积带来的负面影响,从而发挥对 AD 保护作用。

2.2.1 体内模型 小胶质细胞活化可介导 A β 蛋白沉积引起的炎症,促进 AD 的发展^[40]。干细胞来源的外泌体可以抑制 AD 模型中神经胶质细胞活化,继而减轻 A β 蛋白积聚带来的负面影响。MSC-Exos 可以有效减少星形胶质细胞的活化和抑制炎症因子 TNF- α 、IL- β 和 IL-6 的 mRNA 表达^[41],从而减轻 AD 模型的神经炎症。Losurdo 等^[42]发现,外泌体也可有效抑制小胶质细胞活化及小胶质细胞标志物离子化钙结合衔接分子 1 (Ionized calcium binding adapter molecule-1, Iba-1) 和 CD68 的表达,这在一定程度上改善了 AD 小鼠脑中小胶质细胞介导的神经免疫炎症。此外,缺氧预处理 MSCs 衍生的外泌体通过上调 AD 小鼠脑中 miR-21

的水平来恢复突触功能障碍,并且抑制神经胶质细胞活化、神经胶质细胞信号转导和转录激活因子3(Signal transducer and activator of transcription 3, STAT3)的磷酸化以及 NF- κ B p65 的核易位^[43],最终改善 AD 小鼠的学习和记忆能力。

大脑中 A β 蛋白沉积的减少可缓解 AD 小鼠的症状^[44],此过程可以由干细胞来源的外泌体来介导改善。Wang 等^[45]发现,外泌体可通过抑制外源性 A β 诱导的诱导型一氧化氮合酶(Inducible nitric oxide synthase, iNOS) mRNA 和蛋白表达,减少 A β 蛋白聚集产生的不良反应,从而改善 AD 小鼠的神经功能障碍。注射外泌体到脑室后还可以有效减少 A β 蛋白沉积和促进脑室下区神经发生^[46]。值得注意的是, MSC-Exos 也可能通过增加模型体内胰岛素降解酶(Integrated development environment, IDE)和脑啡肽酶(Nepilysin, NEP)两种 A β 降解酶的水平,进而减轻大脑皮层和海马 A β 蛋白积聚引发的炎症反应^[47],最终改善 AD 模型小鼠的认知能力。

2.2.2 体外模型 MSC-Exos 可以减少 AD 模型细胞过表达具有黄素腺嘌呤二核苷酸(Flavin adenine dinucleotide, FAD)突变的神经母细胞瘤细胞系中 A β 蛋白的表达并促进神经元记忆/突触可塑性相关基因的表达^[48]。Wei 等^[49]使用人神经母细胞瘤细胞(SH-SY5Y)与 A β 蛋白共培养构建了体外 AD 模型,进一步的研究发现 MSC-Exos 携带的 miR-223 通过靶向磷酸酶张力蛋白同源物/磷脂酰肌醇-3-激酶(Phosphatase and tensin homolog/Phosphatidylinositol 3-phosphate kinase, PTEN/PI3K)信号通路来减少 AD 模型中的细胞凋亡。此外, MSC-Exos 通过携带的蛋白也可对 AD 产生神经保护作用。外泌体携带的生长分化因子-15(Growth differentiation factor-15, GDF-15)通过激活蛋白激酶 B/糖原合酶激酶-3 β / β -连环蛋白(Pkb/Akt/Glycogen synthase kinase-3 β / β -catenin, AKT/GSK-3 β / β -catenin)通路来上调 NEP 和 IDE 蛋白表达,从而降解 A β 蛋白以减轻 SH-SY5Y 细胞损伤^[50]。Bodart-Santos 等^[51]发现, MSC-Exos 中含有的活性过氧化氢酶(Catalase)介导了淀粉样蛋白 β 寡聚体(A β O)诱导的海马神经元氧化应激和突触损伤的保护作用。综上所述,干细胞来源的外泌体作为一种无细胞治疗策略,为 AD 的未来治疗研究提供了新思路。

2.3 帕金森病

PD 是第二常见的神经系统退行性疾病^[52]。主要的神经病理学改变是含 α -突触核蛋白(α -synuclein, α -syn)的路易体形成和黑质中多巴胺能神经元的丢失^[53-54]。多项研究表明,外泌体可以穿过血脑屏障,尤其是在 PD 和其他神经退行性疾病等病理状态下实现了从外周循环到中枢神经系统的细胞间通讯。

2.3.1 体内模型 PD 是一种神经退行性疾病,除少数遗传病例外,其病因在很大程度上仍是未知的。因此,动物模型有助于阐明 PD 的病因和发病机制。有研究发现,酪氨酸羟化酶表达减少可导致 PD 的发生^[55],而 DPSCs 来源的细胞外囊泡通过鼻内给药后使 6-羟基多巴胺(6-Hydroxydopamine, 6-OHDA)处理的大鼠黑质和纹状体中酪氨酸羟化酶表达正常化,从而改善 PD 大鼠的症状^[56]。Li 等^[57]发现,外泌

体携带的 miR-188-3p 通过靶向 NLRP3 和细胞周期蛋白依赖性蛋白激酶 5(Cyclin-dependent kinase 5, CDK5)的 3'UTR 来抑制炎症小体和自噬体的表达,从而减轻 1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导的 PD 小鼠模型中的黑质损伤。Chen 等^[58]研究发现, MSC-Exos 可穿过 BBB 到达黑质,进而抑制黑质多巴胺能神经元的凋亡,并上调纹状体中的多巴胺水平。这些实验结果表明,干细胞来源的外泌体具有治疗 PD 的潜力,并且可以穿过 BBB。

2.3.2 体外模型 在多巴胺能神经元中 6-OHDA 通过多巴胺转运蛋白被多巴胺能神经元的突触前末端特异性摄取,可被氧化产生自由基,最终导致线粒体功能障碍和氧化应激并诱导神经元死亡^[59]。6-OHDA 是一种常用于构建 PD 模型药物。外泌体通过降低多巴胺能神经元对 6-OHDA 诱导的氧化应激的敏感性,从而减少多巴胺能神经元的凋亡^[60]。MSC-Exos 还可以通过促进自噬来改善 6-OHDA 诱导的 SH-SY5Y 细胞凋亡水平^[58]。此外,外泌体携带的 miR-188-3p 通过靶向 NLRP3 和 CDK5 的 3'UTR 来抑制炎症小体和自噬体的表达,从而发挥对 1-甲基-4-苯基吡啶(1-Methyl-4-phenylpyridine, MPP+)诱导体外 PD 模型的保护作用^[57]。在 PD 中 miRNA 的表达被认为是用于诊断和治疗目的的有效工具^[61]。富含 miRNA 的外泌体可能成为治疗 PD 的有效策略。

2.4 其他神经系统疾病

实验性自身免疫脑脊髓炎(Experimental autoimmune encephalomyelitis, EAE)动物模型是在多发性硬化(Multiple sclerosis, MS)研究中最常用的模型之一,小胶质细胞 M1/M2 表型的失衡会促进 MS 发展^[62]。MSC-Exos 可促进小胶质细胞 M1 表型转化为 M2 表型,通过调节小胶质细胞极化,从而减轻 EAE 大鼠中枢神经系统的脱髓鞘和炎症细胞浸润^[63]。此外, Soundara 等^[64]发现来自 MS 患者的牙周膜干细胞(Periodontal ligament stem cells, PDLSCs)细胞外囊泡可抑制 EAE 模型中的 NALP3 炎症小体激活。最近的一项研究发现, MSC-Exos 可诱导调节性 T 细胞(Tregs)的形成并改善 EAE 小鼠模型的功能结果^[65]。因此,干细胞来源的外泌体可能在 MS 治疗中具有巨大潜力。慢性轻度应激(Chronic mild stress, CMS)小鼠模型是常用的抑郁症模型。Guo^[66]等发现, MSC-Exos 通过上调 miR-26a 的表达,减轻大鼠海马神经元的凋亡,进而改善抑郁症大鼠模型的症状。这些结果显示了干细胞来源的外泌体在治疗多发性硬化和抑郁症中的积极作用。

3 结束语

综上所述,这些体内和体外研究的结果表明干细胞衍生的外泌体是治疗中枢神经系统疾病的一种无细胞策略。外泌体是能够穿过血脑屏障的细胞外囊泡,具有抑制细胞凋亡、减轻炎症反应和调节小胶质细胞极化等重要生物学功能,是细胞间信息交流的重要载体。外泌体的应用可能会最大限度地减少直接使用干细胞的潜在不利影响包括致癌性、免疫抑制、肺栓塞等。外泌体可通过调节靶细胞中的基因、

蛋白质和 miRNA 表达来诱导神经保护作用,在治疗中枢神经系统疾病方面具有巨大潜力。虽然在多项研究中外泌体表现出良好的神经保护特性,但外泌体转化为神经系统疾病的临床治疗应用还存在诸多问题。外泌体的大规模安全生产和产品质量控制仍然是其应用于临床患者的巨大挑战,然而随着对中枢神经系统疾病及外泌体研究的不断深入,干细胞来源的外泌体在中枢神经系统疾病中的应用前景将更加广阔。

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