

·综述·

骨髓间充质干细胞来源外泌体对创伤性颅脑损伤的影响研究进展[☆]

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【摘要】创伤性颅脑损伤(trumatic brain injury, TBI)是一种发病机制复杂的疾病,目前仍缺乏行之有效的治疗方法。研究证明,骨髓间充质干细胞来源的外泌体(bone marrow mesenchymal stem cell-derived extracellular vesicles, BMSC-EVs)通过减轻病灶处的神经炎症反应、促进神经血管再生,发挥其对TBI的治疗作用,但具体作用机制未完全明确。本文旨在探究BMSC-EVs治疗TBI的作用机制和研究进展,并初步探讨BMSC-EVs未来的研究方向及临床应用前景。

【关键词】创伤性颅脑损伤 神经炎症 神经修复 骨髓间充质干细胞 外泌体 微小RNA

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The research progress on the impact of bone marrow mesenchymal stem cell-derived extracellular vesicles on traumatic brain injury. LIU Haodong, WU Zejun, ZHAO Junshuang, HU Juntao. Taihe Hospital Affiliated to Hubei University of Medicine, Shiyan 442000, China. Tel: 0719-8801938.

【Abstract】Traumatic brain injury (TBI) is a multifaceted disease with a complex pathogenesis for which there are currently no effective therapeutic interventions. Research has shown that bone marrow mesenchymal stem cell-derived extracellular vesicles (BMSC-EVs) may play a therapeutic role in TBI. They attenuate neuroinflammatory responses at the site of the lesion and promote neurovascular regeneration. However, the exact mechanisms underlying their actions are not fully understood. This article aims to review the current state of research on the therapeutic mechanisms of BMSC-EVs in TBI. It also aims to discuss possible future research directions and potential clinical applications of BMSC-EVs.

【Key words】Traumatic brain injury Neuroinflammation Neural regeneration Bone marrow mesenchymal stem cells Extracellular vesicles MicroRNA

创伤性颅脑损伤(trumatic brain injury, TBI)是世界范围内致死、致残的重要原因。目前TBI的主要治疗措施包括外科手术、细胞疗法、神经保护剂、低温疗法以及神经电刺激等。TBI的病因、临床表现、严重程度各不相同,目前的治疗方式难以达到理想的治疗效果。因此,仍然需要寻找新

的治疗方案以提高TBI的疗效。骨髓间充质干细胞(bone marrow mesenchymal stem cell, BMSC)具有强大的自我更新能力和多向分化潜能,在神经系统疾病的治疗中有很好的临床应用前景^[1-2]。研究^[3-4]证明, BMSC移植后可以定植到损伤区域并分化为神经细胞和胶质细胞,促进损伤区域的修复和再生,但细胞移植的安全性仍不明确,需要进一步的临床验证。研究发现骨髓间充质干细胞来源的外泌体(bone marrow mesenchymal stem cell derived extracellular vesicles, BMSC-EVs)可抑制TBI后的神经炎症、促进神经再生和血管生成发挥神经保护作用,并能有效避免细胞移植引起的不良反应^[5]。本文以TBI的病理生理机制和治疗现状为切入点,讨论BMSC-EVs在TBI治疗中的研究进展,包括治疗效果、分子机制及临床应用的前景,以期明确作用机制和临床应用提供指导。

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1 创伤性颅脑损伤的病理生理机制及治疗现状

TBI依据损伤发生的时间相关性可分为弥漫性轴索损伤、脑挫裂伤和颅内出血等原发性颅脑损伤,神经炎症反应、神经退行性疾病和延迟性神经元死亡等继发性颅脑损伤^[6]。继发性损伤在TBI非急性期可破坏脑部结构和功能,导致严重的运动障碍、认知功能障碍以及不可逆的神经功能损伤。研究^[7]表明,继发性颅脑损伤中神经炎症反应在其发生发展中扮演着重要角色。TBI发生后可引起小胶质细胞(microglia, MG)、星形胶质细胞激活,并上调肿瘤坏死因子(tumor necrosis factor, TNF)、白介素(interleukin, IL)家族成员等多种炎症相关因子释放。因此,抑制神经炎症反应的亢进、上调神经保护因子的表达,可能是一种有效的TBI治疗方法。

目前TBI的治疗方式主要是手术、神经电刺激、药物、细胞治疗^[8]。成熟的开颅减压术和长期的亚低温治疗能有效控制TBI后颅内高压,但对于受损神经的修复难以达到理想效果。促红细胞生成素、黄体酮等药物^[9-10],在体外试验中被证明有神经保护作用,但由于药物具有难以透过血脑屏障等局限性,在TBI的临床药物实验中未表现出显著疗效。研究表明,BMSC的移植治疗有效减少了动物模型的神经炎症反应和继发性神经变性,促进了神经发生和血管生成,最终改善了神经功能^[11-12]。但BMSC移植治疗可能引起免疫排斥反应、肿瘤形成、微血管栓塞、癫痫发作以及细胞凝血等不良后果,其安全性仍需大量的临床试验来验证^[13]。

2 骨髓间充质干细胞来源的外泌体与创伤性颅脑损伤

最初的研究认为,移植的BMSC能被募集到损伤部位,并自主分化替代受损细胞,发挥自我更新作用。近年有学者提出,这种治疗有益效果可能与BMSC分泌的外泌体相关^[14]。外泌体是一种由细胞释放的纳米级小囊泡,由多泡内体成熟过程中向内出芽形成,多泡内体与细胞表面结合后将其分泌出胞。外泌体富含蛋白质、核酸和小分子代谢产物等生物活性分子,其中小分子蛋白质和核酸类是细胞间通讯的重要介质^[15]。外泌体可来源于脂肪、脐带、骨髓等多种组织,其中BMSC-EVs在治疗神经系统疾病中表现出巨大潜力,临床前研究^[16]表明,经眶后途径将BMSC-EVs应用于TBI小鼠模型可有效抑制早期神经炎症反应并改善神经功能及预后。此外,多项试验^[17]证实BMSC-EVs除能够减轻TBI后神经炎症反应外,还可通过促进神经血管的修复

发挥神经保护作用。与BMSC相比,其外泌体具有易保存、稳定、安全、易透过血脑屏障和有效转运生物分子等优势。对于BMSC-EVs治疗TBI的作用机制尚未完全阐明,但目前的研究发现BMSC-EVs可通过调节炎症细胞表型、下调神经凋亡因子和促进神经血管生成等途径发挥作用。

3 BMSC-EVs对TBI后炎症调节作用

3.1 BMSC-EVs对炎症细胞的调节作用 MG是TBI的神经炎症反应过程中的主要炎症细胞,根据其作用不同,将其分为M1和M2两种细胞表型。M1型MG在炎症过程中分泌IL-1 β 、IL-6、TNF- α 等促炎细胞因子,并释放氧自由基和氮氧化物导致细胞损伤或凋亡;M2型MG可分泌IL-10、TGF- β 等抑炎细胞因子,抑制过度免疫反应^[18-19]。TBI发生后促发MG激活并向M1型极化,导致严重的神经炎症。因此,对TBI后MG表型的调控可能是治疗TBI后神经炎症的有效方法。研究^[20-21]表明,BMSC-EVs可释放包裹在其内部的生物活性分子,减少TBI后炎症细胞浸润或促进MG向抗炎表型极化,并抑制炎症介质释放,进而抑制炎症反应、减少细胞凋亡。BMSC-EVs对炎症细胞表型的调节机制并未完全阐明,研究认为外泌体中的微小RNA(miRNA, miRNA)可能在其中发挥重要作用。miRNA是一类单链非编码小RNA,长度在20~25个碱基之间,可调节靶细胞中的基因表达,介导蛋白质翻译和整体细胞功能^[22-23]。研究^[24-26]表明,BMSC-EVs携带的miR-124-3p、miR-140-5p可通过不同的信号通路和调控基因表达,调节TBI后M1和M2型MG之间的平衡,从而发挥神经保护作用。值得注意的是,目前BMSC-EVs中已被发现数百种不同的miRNA,不同种类miRNA的作用机制不同,对外泌体中miRNA的探索有望进一步明确BMSC-EVs治疗TBI的作用机制并揭示更多的治疗靶点。

星形胶质细胞可分化为A1和A2两种不同的细胞表型,对促炎刺激和损伤产生与MG类似的免疫反应^[27]。BMSC-EVs可通过调节Nrf2-NF- κ B信号通路抑制A1型星形胶质细胞的激活并抑制下游炎症因子的释放^[28]。上述研究结果表明BMSC-EVs对于炎症细胞的调控具有重要意义,BMSC-EVs可调整神经炎症细胞促炎、抗炎表型的比例,下调病灶处炎症因子的表达,抑制亢进的炎症反应。

3.2 BMSC-EVs减少神经元凋亡 除对炎症细胞表型的调控作用外,BMSC-EVs中携带的miR-138通过抑制TNF- α 、IL-6、IL-1 β 、Bcl-2相关X蛋白(Bcl-2-associated X protein, Bax)和Caspase3等炎症因子和促凋亡因子的表达,上调星

形胶质细胞中的细胞周期依赖性激酶4(cyclin-dependent kinase 4, CDK4)、B细胞淋巴瘤2(B-cell lymphoma 2, Bcl-2)、cyclinE和cyclinD1等抗凋亡相关分子表达来发挥抗炎及神经保护作用^[29]。BMSC-EVs中的miR-21、miR-29b-3p可通过调节蛋白磷酸酶和紧张素同源物(phosphatase and tensin homolog, PTEN)与蛋白激酶B(protein kinase B, Akt)信号通路使下游蛋白Bcl-2显著升高进而抑制神经元凋亡^[30]。这些研究结果指出BMSC-EVs改善缺血缺氧中枢神经系统损伤性疾病预后的能力^[31]。

4 BMSC-EVs的血管生成和神经修复作用

4.1 BMSC-EVs对血管生成的作用 TBI发生后分泌的生长因子可激活内源性神经血管的可塑性,从而促进TBI后的功能恢复。但这种自发的恢复是有限的,BMSC-EVs可促进损伤部位的血管修复和发生^[32-34]。研究^[35]证明,BMSC-EVs在TBI动物模型中应用后,显著增加损伤部位、海马体区内皮细胞和神经元的数量,并有效改善神经功能恢复。此外,BMSC-EVs可以上调血管内皮生长因子(vascular endothelial growth factor, VEGF)等多种细胞因子的表达,促进血管生成。这些因子可刺激内皮细胞和外膜细胞的增殖、迁移和分化,从而增加血管密度和改善血流灌注。新生血管可以提供充足的氧气和营养物质,促进受损区域的再生和修复^[36]。研究^[31]证实,BMSC-EVs中富含的miR-29b-3p除发挥抗凋亡能力外,还能诱导VEGF受体2和31号簇抗原(cluster of differentiation 31, CD31)等血管生成刺激因子的表达,从而促进损伤区域的血管生成。

4.2 BMSC-EVs的神经修复作用 TBI导致的神经细胞损伤和轴突断裂可引起感觉、运动、认知和其他神经功能障碍,这些损伤难以依靠机体自身完成修复。BMSC-EVs可促进神经细胞再生和轴突的生长、改善受损区域的微环境。在TBI动物模型中^[37],早期应用BMSC-EVs可上调谷氨酸能系统、GABA能系统、神经转录因子6以及脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)等关键神经修复因子的表达,发挥其促进神经发生、改善神经可塑性的作用。BMSC-EVs将miR-124-3p转移至神经元细胞内,可提高谷氨酸转运体1的表达水平,进而减轻TBI后神经元细胞的死亡并促进神经突生长^[38]。此外,BMSC-EVs中的miR-29b-3p、miR-17-92可显著降低大鼠脑组织PTEN蛋白的表达,导致Akt信号通路及下游蛋白表达增加,进而促进轴突再生^[39-40]。

5 总结与展望

综上所述,BMSC-EVs具有诸多优势,如体积小、无需移植、低免疫原性等,并且可通过抑制神经炎症、增加血管生成、促进神经发生、调节神经修复因子、提供支持神经细胞轴突再生所需的基质环境、减少细胞凋亡等多种机制发挥其神经保护作用。这些特征使BMSC-EVs有望成为一种新型的TBI临床治疗方案。

有研究^[41]证实了BMSC-EVs应用于临床治疗的安全性和有效性。近期的研究^[42-43]发现,外泌体与水凝胶结合运用可以增强外泌体的稳定性,有效延长外泌体在特定区域的滞留时间,促进外泌体对损伤部位的神经修复和血管生成作用。但关于BMSC-EVs治疗TBI仍存在一些局限。由于循环系统的快速清除能力,BMSC-EVs难以在损伤区域蓄积并持续的靶向治疗;临床前研究通过鼻内给药、脑内注射、腹腔注射、静脉注射等多种给药途径和不同浓度证明BMSC-EVs的疗效和安全性,但BMSC-EVs用于TBI治疗的最佳浓度和最佳给药方式仍然未知;BMSC-EVs在作为一种新型的药物或基因输送载体方面具有很大潜力,但目前外泌体的提取技术难以达到大规模生产,关于外泌体的储存、运输和经济成本也鲜有说明;对于外泌体治疗TBI的作用靶点和特异性程度的了解仍然有限,未来需要进一步的研究,更好的了解BMSC-EVs的靶向机制,以揭示更多药物、基因治疗靶点。

总之,BMSC-EVs具有积极的临床应用前景,有望成为新的TBI临床治疗手段,但在建立完善的BMSC-EVs治疗策略前仍有许多问题亟待解决。

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