LUPINE PUBLISHERS

Online Journal of Neurology and Brain Disorders

DOI: 10.32474/OJNBD.2024.07.000253

ISSN: 2637-6628

Short Communication

MSC Derived Extracellular Vesicles Therapy: A Promising Frontier in Neuroregeneration

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Received: February 19, 2024 **Published:** February 26, 2024

Introduction

Over the past few years, Extracellular vesicles (EV's) including exosomes have emerged as promising therapeutics in numerous clinical applications. Initially disregarded as mere cellular debris, they are now recognized as powerful mediators of intercellular communication, playing crucial roles in a wide array of physiological and pathological processes. Mesenchymal stem cells (MSCs)-derived EV mimic the effects of MSCs while offering numerous advantages, including non-infusion toxicity, low retention in lungs, easy preservation and handling, the ability to penetrate the blood-brain barrier, and absence of tumorigenic potential. Additionally, these natural nanocarriers offer several advantages over conventional drug delivery systems, including enhanced biocompatibility, prolonged circulation, and intrinsic targeting capabilities. Furthermore, engineered exosomes can be tailored to encapsulate specific cargo molecules or modified to enhance tissue tropism and pharmacokinetics. MSC-derived EV-based therapeutics hold promise across a spectrum of applications, including neuroregenerative medicine. In this review, we highlight the therapeutic benefits of MSC-derived EV therapy in mitigating the pathological symptoms associated with ischemic neural damage and discuss the underlying mechanism behind these favorable effects.

Ischemic Stroke (IS) stands as the second leading cause of death globally [1] and is clinical characterized by a sudden blood vessel occlusion triggered brain ischemic resulting in neuronal damage to brain tissue blood vessel occlusion [2]. Additionally, severe inflammation exacerbates neuronal injury and brain dysfunction. Oxidative stress induced by ischemia and subsequent reperfusion in brain tissue activates macrophages, stimulating the release of proinflammatory cytokines that further escalate detrimental inflammation within the brain microenvironment, prompting immune cells to polarize into an inflammatory phenotype [3]. One potentially effective approach for treating ischemic stroke may involve directing therapy towards neuronal regeneration and improving the inflammatory environment. In this setting, MSC-derived EV emerge as a promising candidate due their inherited ability to potentially induce a shift towards an anti-inflammatory phenotype and their intrinsic properties to direct repair and enhancement of neuronal survival post-injury, impacting microglial and astrocyte polarization.

Extracellular Vesicles (EVs) and exosomes are lipid enclosed particles that are released from cells. Exosomes are a subtype of EV's originated by an endosomal route and are typically 40–160 nm in diameter, principally carrying proteins, lipids, and a high diversity of nucleic acids (DNA, mRNA, microRNAor miR, lncRNA, circRNA) [4]. Exosomes serve as conduits for cell-to-cell communication, shuttling bioactive molecules to neighboring or distant recipient cells. Through the horizontal transfer of proteins, RNAs, and lipids, exosomes modulate diverse cellular processes, including proliferation, differentiation, immune regulation, and tissue repair [5]. Moreover, exosomes due their stability and protective lipid membrane, effectively transport biologically active molecules, crossing barriers like the blood-brain barrier [6]. This highlights their significant potential as a delivery system in the clinic.

Recent studies have demonstrated that MSC-Exos can enhance stroke recovery by modulating the innate and adaptive immune responses activated following the event [7,8]. Using a middle cerebral artery occlusion (MCAO) rat model, Dong et al. demonstrated that exosomes derived from bone marrow MSCs could deactivate BV2 microglia and induce M2 polarization in vitro. Additionally, in vivo experiments showed a reduction in infarct size and improvement in neuronal function through the transfer of miR-23a-3p [9]. Similarly, Deng et al. reported that heightened miR-126 levels in MSC exosomes significantly boosted the expression

of TNFα, IL-1β, and IL-6, while concurrently decreasing neuronal apoptosis in a mouse model of middle cerebral artery occlusion [10]. Additional experimental evidence indicates that miRNA-26b-5p sourced from HUCMSC exosomes targets CH25H to deactivate the TLR pathway, consequently suppressing M1 polarization. Simultaneously, it mitigates autophagy-induced brain injury by promoting M2 microglia polarization [11]. Furthermore, the engineering of MSC exosomes to overexpress mir-145 able to shift microglia polarization toward anti-inflammatory M2 phenotype in a MCAO model [12]. Mechanistically, exosomal miR-145 reduced FOXO1 expression, resulting in the suppression of apoptosis, cell cycle arrest, and oxidative stress in BV2 cells.

Extensive research has been conducted on the potential role of MSC exosomes in inhibiting neural cell death or apoptosis [13-15]. Recently, Huang et al. demonstrated that in an in vitro ischemia model (oxygen-glucose deprivation/reperfusion, OGD/R), miR-124 and the mTOR pathway play a role in regulating GLT-1 expression in astrocytes injured by OGD/R [16]. Notably, miR-124 does not directly target GLT-1. Instead, MSC-Exos upregulate GLT-1 expression through the miR-124/mTOR pathway in astrocytes injured by OGD/R. BMSCs-Exos were found to enhance hippocampal neuronal recovery in mice treated with MCAO and in N2a cells subjected to OGD/R-induced injury [17]. They upregulated miR-455-3p expression, which targeted and regulated PDCD7. Downregulating miR-455-3p reduced the protective effect of BMSCs-Exos on N2a cells, while overexpression increased cell activity and decreased apoptosis. Xiao et al, demonstrated that BMSCs-derived exosomes suppressed OLs apoptosis through exosomal miR-134 by negatively regulating the caspase-8-dependent apoptosis pathway [18]. Wei et al. suggested that Zeb2/Axin2 found in exosomes derived from bone marrow MSCs could potentially enhance post-stroke neurogenesis, neural plasticity, spatial memory, and nerve function [19]. These effects are believed to occur through modulation of the SOX10, Wnt/β-catenin, and endothelin-3/EDNRB pathways.

Similarly, MSCs-Exo attenuated injury in a ischemic mice by inhibiting microglia apoptosis might via exosomal miR-26a-5p mediated suppression of CDK6 [20]. Moreover, Xi et al reported that the overexpression of miR-17-92 on MSC exosomes could enhanced neuro-functional recovery after stroke [21]. This effect is attributed to an increase of axonal extension and myelination, and this enhanced axon-myelin remodeling may be mediated in part via the activation of the PI3K/Akt/mTOR pathway induced by the downregulation of PTEN. In another study, MSC exosomes can inhibit inflammation-induced Astrocyte activation by modulating the Nrf2-NF-κB signaling pathway [22]. In vitro studies revealed that MSC-Exo has the potential to counteract hippocampal astrogliosis by reversing oxidative stress (such as by increasing Nrf2 expression and promoting its nuclear translocation) and dampening inflammation phenotypes (for example, by inhibiting NF-κB activation and translocation) [22]. Together, these studies indicates that MSC-derived exosomes represent a promising therapeutic approach for ischemic stroke, promoting neuroprotection, enhancing neurogenesis, reducing inflammation, and modulating immune responses after event. Their ability to transport diverse bioactive molecules, including miRs, enhances their multifaceted benefits and underscores their significance as novel treatment modalities in stroke therapy. Continued research is essential to fully understand their mechanisms and optimize their clinical application.

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DOI: 10.32474/OJNBD.2024.06.000253