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Mesenchymal Stem Cells (MSC)-Derived Exosomes Could Alleviate Neuronal Damage and Neuroinflammation in Alzheimer's Disease (AD) as Potential Therapy-Carrier Dual Roles

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Abstract : Alzheimer's disease (AD) is an age-related neurodegenerative disease that is a leading cause of dementia syndromes and has become a huge burden on society and families. The main pathological features of AD involve excessive deposition of β-amyloid (Aβ) and Tau proteins in the brain, resulting in loss of neurons, expansion of neuroinflammation, and cognitive dysfunction in patients. Researchers have found effective drugs to clear the brain of error-accumulating proteins or to slow the loss of neurons, but their direct administration has key bottlenecks such as single-drug limitation, rapid blood clearance rate, impenetrable blood-brain barrier (BBB), and poor ability to target tissues and cells. Therefore, we are committed to seeking a suitable and efficient delivery system. Inspired by the possibility that exosomes may be involved in the secretion and transport mechanism of many signaling molecules or proteins in the brain, exosomes have attracted extensive attention as natural nanoscale drug carriers. We selected exosomes derived from bone marrow mesenchymal stem cells (MSC-EXO) with low immunogenicity and exosomes derived from hippocampal neurons (HT22-EXO) that may have excellent homing ability to overcome the deficiencies of oral or injectable pathways and bypass the BBB through nasal administration and evaluated their delivery ability and effect on AD. First, MSC-EXO and HT22 cells were isolated and cultured, and MSCs were identified by microimaging and flow cytometry. Then MSC-EXO and HT22-EXO were obtained by gradient centrifugation and qEV SEC separation column, and a series of physicochemical characterization were performed by transmission electron microscope, western blot, nanoparticle tracking analysis and dynamic light scattering. Next, exosomes labeled with lipophilic fluorescent dye were administered to WT mice and APP/PS1 mice to obtain fluorescence images of various organs at different times. Finally, APP/PS1 mice were administered intranasally with two exosomes 20 times over 40 days and 20 μL each time. Behavioral analysis and pathological section analysis of the hippocampus were performed after the experiment. The results showed that MSC-EXO and HT22-EXO were successfully isolated and characterized, and they had good biocompatibility. MSC-EXO showed excellent brain enrichment in APP/PS1 mice after intranasal administration, could improve the neuronal damage and reduce inflammation levels in the hippocampus of APP/PS1 mice, and the improvement effect was significantly better than HT22-EXO. However, intranasal administration of the two exosomes did not cause depression and anxious-like phenotypes in APP/PS1 mice, nor significantly improved the short-term or spatial learning and memory ability of APP/PS1 mice, and had no significant effect on the content of Aβ plaques in the hippocampus, which also meant that MSC-EXO could use their own advantages in combination with other drugs to clear Aβ plaques. The possibility of realizing highly effective non-invasive synergistic treatment for AD provides new strategies and ideas for clinical research.

Keywords : Alzheimer's disease, exosomes derived from mesenchymal stem cell, intranasal administration, therapy-carrier dual roles
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