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Review Article

The Role of Mesenchymal Stem Cell Exosomes in the Onset and Progression of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease with progressive loss of memory and cognitive function. Because its pathogenesis has not been fully elucidated, there is still a lack of understanding of its pathogenesis and effective treatment. Many studies have shown that Mesenchymal stem cells Exosomes (MSCs-Exo) can promote anti-inflammatory, regulate immune function, enhance amyloid (Aβ) degradation, and promote axon growth of nerve cells. Exosomes can effectively cross the blood-brain barrier, and have better biocompatibility and biosafety than nanomaterials, and more diverse ways to carry drugs. Adipose stem cell exosomes can not only treat AD by their own characteristics, but also regulate AD and other neurological diseases as A drug carrier that can efficiently and freely cross the blood-brain barrier: they can effectively reduce Aβ42 plaques and improve the neuronal microenvironment through microglia. In AD model mice, excessive activation of microglia demonstrated the formation of an inflammatory microenvironment in the brain. The inflammatory microenvironment erodes healthy neurons to a certain extent, forcing them to overactivate inflammatory signaling pathways so that they can't function normally, Adipose stem cell exosomes can effectively clear the expression of inflammatory factors in hypoxia-induced AD neuronal model and promote synaptic repair through microRNA/ phosphatase and tensin homolog (miR-223/PTEN) and phosphatidylinositol kinase (PI3K/Akt) pathways. It can promote the polarization of microglia towards anti-inflammatory phenotype and promote neuronal repair. Adipose stem cell exosomes can also be used to improve memory and cognitive dysfunction by alleviating Tau phosphating or delaying hippocampus volume decay, targeting the core pathological mechanism of AD to achieve therapeutic effects. This article mainly introduces the role of MSC exosomes in the pathogenesis and development of AD.

Keywords

Mesenchymal Stem Cells, Exosomes, Alzheimer’s Disease

1. Introduction

Alzheimer's disease (AD) is a progressive neurological disease mainly caused by neurodegenerative diseases. Patients usually have episodic memory impairment, verbal and verbal memory impairment, executive ability impairment,

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visual-spatial impairment, learning and induction memory impairment and other neuropsychological deficits [1-3]. Its incidence increases with age, with a prevalence of 5%-8% in people over the age of 65 years, and up to 25% to 50% [4] in those over 85 years. The pathophysiological causes of AD mainly include local inflammation in the brain memory and language center, neuronal fiber degeneration, altered blood-brain barrier permeability, and mitochondrial dysfunction caused by oxidative stress [5, 6]. The above factors can cause serious nerve cell damage and cellular autophagy [7].

Exosomes are membrane vesicles with a diameter of 40-160nm secreted by the inner membrane system through a complex mechanism (Figure 1), carrying a variety of proteins and RNA [8]. Almost all cells throughout the body can secrete exosomes, which can mediate the exchange of information and material between cells. Exosomes play a very important role in the pathogenesis of AD. Studies have shown that AD patients contain a large number of specific Tau oligomers. With the deposition and phosphorylation of Tau protein, microglia will be promoted to differentiate toward inflammatory characteristics, and secrete a large number of exosomes encased with phosphorylated Tau protein, aggravating AD progression [9]. The exosomes secreted by cholesterol accumulating astrocytes encapsulates with high levels of the amyloid-related peptide [10]. Exosomes can freely cross the blood and brain barrier. Therefore, blood-derived exosomes are tested for use as potential markers of AD pathogenesis. For example, exosomes carrying specific microRNA such as miR-30b-5p, miR-22-3p, miR-378a-3p, and exosomal [11] carrying brain-specific proteins such as neurogranin and synaptophysin 1. Interestingly, in addition to brain-derived exosomes that can spread to the blood, exosomes imported into the blood due to the chronic inflammation of the whole body can also enter the brain, affecting the progression of AD. The siRNA exosomes carrying antagonist Beta amyloid precursor protein-cutting enzyme 1 (BACE1) were injected into mice through the tail vein, and we found that BACEI in the brain downregulated [12] for both mRNA and protein expression. With the development of stem cell therapy technology and the deepening of related research, various stem cell-derived exosomes began to be used to treat various diseases, among which the most widely used are adipose stem cells and bone marrow stem cells. Studies have shown that adipose MSCs-Exo carry a large number of nerve growth factors, which can not only guide neuronal axon and synapse formation to a certain extent, but also upregulate the expression of memory-related factors such as presynaptic cytomatrix protein (PCLO), triggering receptor expressed on myeloid cell-1 (TENM1) and inhibit the [13] expression of apoptosis-related proteins. Exosomes of BMSCs can effectively inhibit the production of Tumor necrosis factor (TNF-α) and Nitric oxide (NO) [14] by BV-2 microglia mimicking AD activation in vitro. Human umbilical cord MSCs can promote cognitive improvement, clear Aβ42 plaque accumulation and reduce neuronal loss [15]. In addition, MSCs-Exo also have extensive immunomodulatory and inflammatory effects, because they can freely cross the blood-brain barrier. Of course, using exosomes as drug delivery vehicles also has the disadvantages such as poor targeting and difficulty to enrich, but some studies have focused on the modification of exosomes in order to avoid some deficiency [16] of exosomes. In summary, the application of MSCs-Exo to treat neurological diseases such as AD is absolutely practical.

This paper aims to explain the effects of MSCs-Exo in treating AD in the following aspects: (a) eliminate inflammatory microenvironment and inhibit the formation of neuronal fiber tangles; (b) promote nerve cell regeneration and inhibit neuronal apoptosis; (c) repair neuropsychological defects such as memory and language.

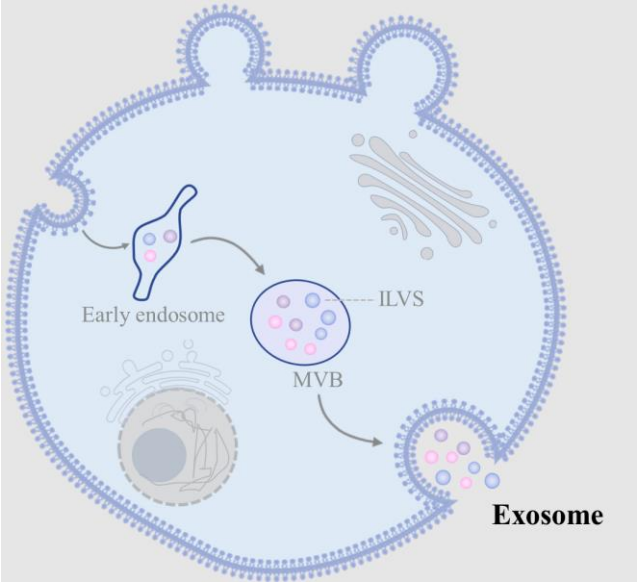

Figure 1. *Secretory pathway of exosomes. Exosomes are membranous vesicles released outside the cells in diameter between 40 and 160 nm. Early endosomes undergo exocytosis and the complex role of the intimal system continuously fuse early luminal vesicles (ILV) to form the polyvesicular body (MVB) releases ILV via exocytosis.*

2. MSCs-Exo Improve the Inflammatory Microenvironment in the Brain of AD Mice

Amyloid precursor protein (amyloid precursor protein, APP) is a single transmembrane protein of about 100-140 KD. It is widely found in biological systemic tissue cells and plays an important role in the transmission of γ -aminobutyric acid (GABA) [17, 18]. Aβ plaques are modified by APP lysis by three secretases (secretases α, β and γ). Secretase-β was first cleaved at the β site in the APP into two β-Nterminal fragment and β-C terminal fragment, and then γ -secretase further modified the β-C terminal fragment into Aβ plaque [19] of 39 – 43 amino acids size. A β plaques in the human body are divided into two kinds, one is A β 40, the other is A β 42, due to the different cutting mode, the latter is easier to form plaque aggregate [20]. With the accumulation of A β 42 plaque and the degree of fibrosis, nerve fibers will release a lot of microglia, such as Interferon induced protein with tetratricopeptid e repeats 3 (IFIT3), Signal transduction and activators

of transcription1/2 (STAT 1 / 2), antibody reactive protein, which will raise a lot of microglia accumulation, but can damage the phagocytic capacity of microglia, so that these microglia can only secrete inflammatory factors but difficult to remove Aβ42 plaque [21, 22]. Moreover, Aβ42 plaques can also weaken the blood-brain barrier permeability by damaging the cholinergic system, further affecting the neuronal microenvironment [23]. Mijung Lee The team found that Aβ42 plaques and Aβ40 plaques in the hippocampus and cortical areas of AD model mice treated with MSCs-Exo [24]. The role of microglia in shaping the inflammatory microenvironment is beyond doubt, but we can improve it by inhibiting its persistent secretion of inflammatory factors or inhibiting its inflammatory activation. Gierin Thomi et al found that WJ MSCs-Exo (Wharton gum mesenchymal stem cell derived exosome) could effectively inhibit [25] of LPS-induced TNF-αsecretion by BV-2 microglia model in vitro; Maud Gratuzel et al found that inducing microglial activation that could stably express trinucleotide repeat expansion mutations (TREM 2) factor could effectively reduce the [26] induced by Aβ1-42 plaques. In conclusion, MSCs-Exo can effectively reduce Aβ42 plaques and improve the neuronal microenvironment through microglia.

3. MSCs-Exo Inhibit Neuronal Senescence and Promote Neuronal Repair in AD Mice

Cell senescence is not equal to individual senescence, but senescent cells can indeed have severe effects on the organism [27] to some extent. Senescent cells secrete a large number of inflammatory factors such as interleukin-1 (IL-1) family and TNF family through the paracrine pathway. In addition, mitochondrial dysfunction will also lead to excessive reactive oxygen species (ROS) in the cellular and surrounding microenvironment, resulting in an inflammatory and oxidative stress microenvironment around them, thus forming a harsh negative feedback chain [28]. Therefore, clearing the inflammatory microenvironment and inhibiting the senescence of functional cells became the first problems to be solved to some extent. The formation of an inflammatory microenvironment in the brain is demonstrated by excessive activation of microglia in AD model mice. Inflammatory microenvironment can erode healthy neurons to some extent, forcing them to overactivate inflammatory signaling pathways so that neurons cannot exercise normal functional [29]. Hong Wei The team found that MSCs-Exo could effectively remove the expression of inflammatory factors in hypoxia-induced AD neuronal model through miR-223 / PTEN and PI3K / Akt pathway and could promote the repair [30] of neuronal synapses. Guofeng Cai et al found that Mesenchymal stem cells Exosomes inhibited The Toll-like receptor-4 (TLR4) expression in microglia by transporting miR-542-3p, which in turn reduced the activated [31] of the nuclear factor κB (NF- κB) inflammatory pathway. Liang Wen et al found that MSCs-Exo could promote microglia polarization toward anti-inflammatory phenotype and could promote neuronal repair of [32]. Moreover, Yinpeng Jin et al found that AD-SCs-derived Exo treatment significantly reconstructed the metabolic balance of glutamate / glutamine in their hepatocytesG [33]. lutamate can trigger neuronal depolarization by acting on N-methyl-D-aspartate. If glutamate / glutamine metabolism is unbalanced, it can trigger persistent neuronal excitation, cause serious damage to the synapse, and aggravate the progression of AD [34, 35]. Although it has not been found whether MSCs-Exo can also exert such efficacy in the brain, it is undeniable that MSCs-Exo can indeed reduce the toxic effect of glutamate on neurons in vitro [36].

4. MSCs-Exo Can Improve Memory and Cognitive Dysfunction

Patients with AD usually develop memory and cognitive dysfunction, and currently, there are relevant detection indicators [4] at the clinical level. The causes of memory and cognitive dysfunction are relatively complex, which include decreased synaptic plasticity and downregulation of postsynaptic protein expression in [38]. The Kidney / Brain (KIBRA) protein is a postsynaptic protein encoded by the WWC 1 gene, which regulates memory and synaptic shaping processes by interacting with other postsynaptic proteins such as synapsin. Studies have shown that the KIBRA protein content in the brain of patients with severe AD significantly downregulates [39]. Tau is a microtubule-associated protein involved in the dynamic assembly of neuronal microtubules and maintaining the neuronal cytoskeleton to stabilize [40]. A β 42 plaques can affect Tau in hyperphosphorylation by affecting the activity of cyclin-dependent kinase-5 (CDK 5). Tau protein not only fails to exercise normal function after phosphorylation or acetylation, but also leads to the formation of pathological fibrillary tangles of neuronal fibers, resulting in [41, 42] formation of neuronal synapses, loss of signaling function, and reduced synaptic plasticity. Tracy TE shows that the decrease in KIBRA protein expression is closely related to the hyperacetylation and hyperphosphorylation of Tau [43]. Sen Liu et al studies showed that lateral ventricle injection of BMSCs-Exo (BMSC stem cell-derived exosomes) can significantly downregulate the level of phosphorylated Tau protein and upregulate brain-derived neurotrophic factor (BDNF) [44] in AD model mice. This suggests that BMSCs-Exo can be used to ameliorate memory and cognitive dysfunction triggered by reduced synaptic plasticity. Hippocampal atrophy is seen in many disorders associated with memory and cognitive impairment, suggesting that the latter volume is inextricably linked to memory and cognitive function [45]. Wang gang The recent phase I / clinical trial of the team delayed the attenuation of the hippocampus volume of the patients and alleviated the pain caused by abnormal neu-

rological symptoms. Most excitedly, one of the subjects had a significant [46] decrease in A β 1-42 plaques in the brain. This suggests that MSCs-Exo can be used to improve memory and cognitive dysfunction by alleviating Tau phosphoor delaying hippocampus volume decay.

5. MSCs-Exo Can Be Used as an RNA Delivery Vehicle to Treat AD

Exosomes contain multiple nucleic acid components that can transfer mRNA, miRNA, lncRNA, siRNA, and DNA to adjacent cells. Among them, miRNA is the most widely studied class of non-coding short-chain RNA, which participates in many biological processes and phenotypic development [47-49] by regulating gene expression. Bioinformatics analysis revealed that MSCs exosomes were abundant in miRNA. Baglio et al found that adipose and bone marrow mesenchymal stem cell-derived exossome contained miR-486, miR-143 with immunoregulatory capacity, and miR-191, miR-222, miR-21 and let-7a [50], which are involved in cell proliferation and angiogenesis. In chronic inflammation and apoptotic states, miR-21 levels are significantly reduced; however, MSCs-EXO contains high levels of miR-21, which helps to reduce inflammation and apoptosis. A large number of studies have shown that miR-21 (miR-21-5p) is closely related to almost all major CNS diseases, and its concentration change in plasma is a potential biomarker of cognitive impairment in AS patients [51-53]. In vitro, miR-21 could attenuate A β -triggered apoptotic [54] by modulating the Programmed cell death protein 4 -phosphatidylinositol 3-kinase (PI3K)/AKT/GSK-3β pathway (PDCD 4 / PI3K / AKT / GSK-3 β). The occurrence and progression of AD disease course is often accompanied by differentiation of specific miRNA expression, with downregulation of miRNA expression favorable for neuronal survival, but elevated miRNA expression promoting the development of pathology. As a latest ideal RNA carrier, MSCs-Exo can freely pass through various biological barriers, including the blood-brain barrier, which can effectively target miRNA mimics or miRNA antagonists to target cells, reverse the differential expression of miRNA and then regulate the progression of AD and other neurological diseases. Nowadays, strategies to use MSCs exosomes as miRNA carriers for the treatment of neurodegenerative diseases such as AD have been widely recognized by [55-57].

Small interfering RNA (Small interfering RNA; siRNA) is a double-stranded RNA [58] of 20 to 24 bp that can mediate RNA interference. SiRNA delivery is necessary and sufficient for cells to undergo RNA interference, so therapies using exogenous siRNA to directly mediate cellular autologous RNA interference are increasingly emerging [59]. Especially with the increasing enrichment of human genome database data and the development and improvement of computer gene editing software, the research related to siRNA has flourishing [60]. Yutong Zhou et al. Targeted inhibiting BACE 1 gene expression [61] in the APP / PS1 transgenic AD mouse model by constructing a stable polymer siRNA nanodrug (Gal-NP @ siRNA) that can cross the blood-brain barrier. Xiaotong Yang et al. constructed nanocarrier (Rapa @ DAK) to carry siRNA, and effectively delivered BACE1 siRNA and rapamycin to the brain by nasal administration, which significantly reduced the [62] deposition of A β 1-42 plaques in the brain of AD mice. It is not difficult to see that due to the existence of the blood-brain barrier, an easy and efficient administration method has become the premise for the treatment of brain diseases. At present, various types of nanomedicine have been developed for disease treatment, such as gold nanoparticles (AuNPs), magnetic nanoparticles (MNPs), and silicon-based nanoparticles (SiN Ps) [63]. Because of the appropriate volume, the above materials can freely enter and exit the blood-brain barrier, and it is difficult to stably synthesize and prepare. The biological metabolism after crossing the blood-brain barrier, and the complex structure of the brain limit the development of nanomaterials in the treatment of neurological diseases [64]. In contrast, MSCs-Exo should have a higher priority. Exsomes It can effectively cross the blood-brain barrier, and has better biological compatibility and biosafety than nanomaterials, and more diverse ways to carrying drugs. In conclusion, MSCs-Exo can not only treat AD based on its own properties, but also serve as a drug carrier that can efficiently and freely cross the blood-brain barrier to regulate neurological diseases such as AD.

Table 1. *Exosomes derived from mesenchymal cells and the effects of RNA on AD and their mechanism.*

Type	Function and mechanism	References
ADMSCs-Exo	caused some reduction in Aβ42 plaques and Aβ40 plaques in both hippocampal and cortical regions of AD model mice	[24]
	Treatment of a mouse model of liver fibrosis significantly reestablishes the metabolic balance of glutamate/glutamine in its hepatocytes	[33]
WJMSCs-Exo	Lipopolysaccharide-induced secretion of inflammatory factors such as TNF-α can be effectively inhibited in vitro in a BV-2 microglia model	[25]
MSCs-Exo	The miR-223/PTEN and PI3K/Akt pathways effectively scavenge the expression of inflammatory factors	[30]

Type	Function and mechanism	References
	in a neuronal model of hypoxia-induced AD and promote neuronal synaptic repair	
	Delivery of miR-542-3p inhibits microglial TLR4 expression and thus reduces NF-κB inflammatory pathway activation	[31]
	In vitro attenuates the toxic effects of glutamate on neurons	[36]
	Improvement of memory and cognitive dysfunction by attenuating Tau protein phosphorylation or delaying hippocampal volume decay	[46]
	Improves memory and cognitive dysfunction caused by reduced synaptic plasticity	[44]
BMSCs-Exo	Promotes polarization of microglia towards an anti-inflammatory phenotype and can facilitate neuronal repair	[32]
miR-486	Inhibition of cellular senescence	[50]
miR-143	Immunomodulatory capacity	[50]
miR-191, miR-222, let-7a	Associated with cell proliferation and angiogenesis	[50]
miR-21	Attenuating Aβ-triggered apoptosis by modulating the PDCD4/PI3K/AKT/GSK-3β pathway	[55, 57]
siRNA	Double-stranded RNA of 20-24 bp mediating RNA interference	[58]

6. Future Outlook

Cellular senescence leads to dysregulation of cell homeostasis as well as loss of regenerative capacity. Many diseases have been confirmed to be related to cellular aging, such as osteoarthritis, weak chondrocyte regeneration ability and excessive degradation of cartilage extracellular matrix are one of the main factors in the pathogenesis. For such diseases, clearing of factors leading to cellular senescence is clearly an effective treatment, but it is worth thinking about whether we can interfere with disease progression by promoting cellular regeneration. The harm of inflammatory microenvironment to neurons caused by abnormal TAU protein phosphorylation, imbalance of glutamate / glutamine metabolism, and inflammatory phenotype activation of microglia have been described above. Each of these factors leads to neuronal death, and as mammals grow, the ability of neurogenesis is increasingly limited. Although stem and neuronal cells persist, this does not timely remedy the series of negative effects of neuronal death. MSCs-Exo can serve as a carrier to freely enter the blood-brain barrier, which allows it to carry many nanodrugs or miRNA. If it can activate the differentiation of neural stem cells, it will help repair cognitive and memory dysfunction caused by abnormal neuronal function or death. In the future, MSCs-Exo can extend the research direction to the following aspects (1): inhibition of pathological A β 1-42 plaque deposition and production of neuronal fibrous tangles; (2): inhibition of neuronal apoptosis, and (3): inhibition of overactivation of the immune system and reduction of the inflammatory microenvironment. With the development of stem cell therapy technology and the deepening of the research on exosomes, MSCs-Exo gradually gets rid of the difficulty of acquisition, immune rejection and other problems. At the same time, with the development of clinical trials, the application of stem cells to treat related diseases has gradually proved the safety. Application of MSCs-Exo can effectively improve the inflammatory microenvironment and inhibit the aging of neurons; significantly reduce tau phosphorylation, up-regulate BDNF expression and delay hippocampus volume to restore memory and cognitive dysfunction; and regulate AD progression by delivering miRNA or miRNA antagonists. These results suggest that adipose stem cell exosomes are not only a good "therapeutic agent", but also a good vehicle, and that more MSCs-Exo-based drugs will certainly be developed for the treatment of AD in the future. In studies exploring RNA interference relying on siRNA, Exsomes clearly has a brighter future.

Abbreviations

AD: Alzheimer's Disease

MSC: Mesenchymal Stem Cells

PTEN: Phosphatase and Tensin Homolog

PI3K: Phosphatidylinositol Kinase

BACE1: Beta Amyloid Precursor Protein-Cutting Enzyme 1

IFIT3: Interferon Induced Protein with Tetratricopeptid e Repeats 3

PCLO: Presynaptic Cytomatrix Protein

TENM1: Triggering Receptor Expressed on Myeloid Cell-1

TNF: Tumor Necrosis Factor

NO: Nitric Oxide

ILV: Luminal Vesicles

MVB: Polyvesicular Body
GABA: γ -aminobutyric Acid
IFIT3: Interferon Induced Protein with Tetratricopeptid e repeats 3
STAT1/2: Signal Transduction and Activators of Transcription1/2
TREM 2: Inucleotide Repeat Expansion Mutations
IL-1: Interleukin-1
ROS: Reactive Oxygen Species
TLR4: Toll-Like Receptor-4
NF- κB: Nuclear Factor κB
KIBRA: The Kidney / Brain
CDK 5: Cyclin-Dependent Kinase-5
BDNF: Brain-Derived Neurotrophic Factor
AuNPs: Gold Nanoparticles
MNPs: Magnetic Nanoparticles
SiNPs: Silicon-Based Nanoparticles

Conflicts of Interest

The authors declare that they have no conficts of interest.

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