Research Progress of Exosomes in the Treatment of Neurodegenerative Diseases

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Abstract. With the intensification of global population aging, the incidence of neurodegenerative diseases (NDs) is continuously rising. This type of disease is characterized by progressive loss of neuron groups, with cognitive decline and motor dysfunction as typical symptoms. For the time being, drugs for NDs mainly focus on alleviating symptoms and have limited effect on preventing the progression of the diseases. In recent years, exosomes have gradually become a research hotspot in the treatment of NDs. It has been found that exosomes derived from microglial cells and astrocytes have bidirectional regulation on pathology, and exosomes derived from mesenchymal stem cells have therapeutic potential for NDs. This article will systematically review the structure and properties of exosomes, and state the mechanism and therapies in NDs in virtue of the roles of the above three typical exosomes in the central nervous system in order to provide new treatment ideas.

Keywords: Exosomes, neurodegenerative diseases, Parkinson's Disease, Alzheimer Disease.

1. Introduction

Neurodegenerative Diseases (NDs) are a series of disorders characterized by the progressive loss of specific neuronal populations in the central or peripheral nervous system, mainly including Alzheimer's disease (AD), Parkinson's disease (PD), etc, whose pathological features are complex but common points are incorrect folding, aggregation, and accumulation of pathological amyloid proteins around brain cells. Due to the loss of neurons and myelin sheaths, patients display mild neurological damage symptoms in movement, sensation, vision, language, and cognition. As they develop, several functions gradually decline, and eventually, patients will be disable to take care of themselves and even suffer brain death [1].

With the intensification of population aging, there is a yearly growing trend in NDs. According to the report of WHO, over 55 million people have been suffering from NDs worldwide so far. It is estimated that the number will be up to 139 million in 2050 [1]. The early symptoms of NDs are usually nonspecific and easily confused with other disease. Meanwhile, effective biological markers are still not found, which leads to extremely challenging early diagnosis. The pathology of NDs involves complex crosstalk patterns between different cell types, leading to unclear causes, and high selectivity of blood-brain barrier (BBB) in the central nervous system limits the therapeutic effect of drugs [2]. As all the reasons above, there are still no effective therapeutic strategies with good prognosis [3]. Existing drugs such as cholinesterase inhibitors, and physical intervention such as DBS can moderately ameliorate clinical symptoms but cannot reverse damaged neural circuit, as well as prevent the development of the disease. The treatment of NDs remains a long-standing problem. In recent years, exosomes have attracted widespread attention in NDs field and is expected to become an emerging therapy for NDs.

2. Overview of Exosomes

2.1. Concept of Exosomes

Exosomes are lipid bilayer membrane vesicles secreted by cells, with a diameter of approximately 30-200nm [2]. They can be secreted by various cells such as microglia and lymphocytes. Exosomes are produced by inward budding of endosomes in the later stage of cells. They form intracavitary

vesicles in multivesi cular bodies (MVBS) and release finally after fusing with the plasma membrane [1].

2.2. Composition and biochemical characteristics

Exosomes are composed of constitutive molecules and carrier molecules. Their high stability helps avoid factors such as the immune system and hydrolases reflecting on their internal carrier molecules. Exosomes are rich in contents, composed of nucleic acids (RNA, DNA and microRNA), proteins (nonspecific proteins such as Rab, GTPases, HSP70/90 that attend the formation and secretion of vesicles, and specific proteins), lipids (regulate the rigidity of the exosome membrane, attend the biogenesis of exosomes and regulate homeostasis within recipient cells), cytokines, transcription factor receptors, etc [1].

In terms of biochemical characteristics, exosomes with diminutive dimensions can effectively prevent mononuclear macrophages from phagocytosis, thus can enter the central nervous system through the blood-brain barrier (BBB) as a drug carrier. Their half-life period in vivo is only several minutes, and meanwhile under normal circumstances, most of them can be excreted within a few hours. The activation of the content-mediated cascade reaction is capable of extending their half-life, so they can target specific locations after modification or provide personalized treatment, and remain in the target tissue for a long time without causing vascular embolism. Exosomes have the capacity to deliver contents to recipient cells through multiple ways such as endocytosis, ligand-receptor interaction or direct membrane fusion, to achieve intercellular communication. In addition, the stability of exosome RNA is higher than that of cellular RNA, which offers therapies with higher stability and immune tolerance [1].

3. The Mechanism and Therapies of Exosomes in Neurodegenerative Diseases

In the central nervous system, exosomes can interact with target cells through endocytosis, receptor-ligand binding, attachment and other means, exerting various biological functions, including intercellular communication, maintaining myelination, antigen presentation and providing nutritional support for neurons. The composition and function of exosomes vary from different cell sources and microenvironments [2].

Exosomes secreted by microglia (MG-exos), the immune detection cell in the central nervous system, have various functions. M1-type microglia can activate the inflammatory response through inflammatory cytokines (IL-17). M2-type microglia help restrain inflammation in the nervous system through anti-inflammatory cytokines (IL-10) so as to promote reconstruction of damaged tissues. The regulation of MG-exos on neuroinflammation varies in the different stages of AD. With the development of AD pathology, M2-type will gradually transform into M1-type, which leads to aggravated neuronal damage. This bidirectional regulatory mechanism gives rise to complex functions of microglia in neuroinflammation [2, 4].

MG-exos can also mark synapses by delivering complement factors (such as C3) to facilitate synaptic pruning [3]. This process can induce the upregulation of complement factors in target cells in a way independent of mRNA, and strengthen the phagocytic activity of microglia on degenerated neural synapses, and thus may mediate synaptic loss in NDs [3]. Besides, MG-exos can facilitate communication between cells through miRNA. For instance, they are able to inhibit p53/p21/CDK1 signaling pathway by delivering miR-151-3p to neurons in order to reduce neuronal apoptosis, promote axon regeneration and improve neurological function [5].

Exosomes secreted by mesenchymal stem cells (MSC-exos) also play an important part on the central nervous system. MSC-exos can make use of miRNA accelerate the reconstruction and regeneration of damaged nerves through a triple mechanism. They can not only deliver information between cells, maintain the dynamic and static balance among local microenvironments, stimulate axon growth and cerebral angiogenesis to alleviate local inflammatory responses caused by nerve damage, but also promote the differentiation and maturation of neurons and axon remodeling,

maintain the number of neurons, and still activate AKT, ERK1/2, and STAT3 signaling pathways, induce the expression of various growth factors such as hepatocyte growth factor, IGF-1, NGF, and SDF-1, to promote the regeneration and functional recovery of injured neural tissues [5]. In addition, MSC-exos can improve neuronal apoptosis by activating AMP-dependent protein kinase phosphorylation and downregulating JAK2/STAT3/NF-κB signaling pathway [2]. MSC-exos can reduce neuroinflammation by restraining activations of microglia and astrocytes and inflammatory responses meditated by release of cytokines [4]. For example, their inner miR-146a can reduce the generation of M1-type microglia and restore the function of astrocytes [4]. MSC-exos can also regulate vascular integrity, communication between neurons and macrophages, and inflammatory responses by upregulating the level of miR-21 so that they further restore the function of synapses and improve the capabilities of learning and memorizing [2].

Exosomes secreted by astrocytes (ADEs) function as assisting in neuronal metabolism, regulating extracellular ion concentration, and providing nutrients, etc in nerve injury [5]. By transforming miR - 34 to repair these damaged brain nerves and promote their regeneration, they regulate TLR7, NF - κB, mitogen-activated protein kinase (MAPK) and other pathways. Also, exosomes control NF-κB signaling pathway by secreting miR-873a-5p to activate microglia, promote the release of anti-inflammatory cytokine, and reduce the area of brain defects and neurological deficits, thus play a positive role in improvement and reconstruction [5].

3.1. The Mechanism and Therapies of Exosomes in Alzheimer's Disease

Alzheimer's Disease (AD) is a kind of degenerative diseases of the central nervous system characterized by progressive cognitive dysfunction and behavioral impairment. Although the cause of this disease remains unclear, the deposition of β-amyloid protein (Aβ) to form plaques and the abnormal aggregation of hyperphosphorylated Tau protein to form neural nodules prove to be the main pathological hypothesis [6]. Over time, patients will experience aggravated cognitive impairment, memory decay, and eventually develop into physical functional disorders.

Exosomes promote the generation, secretion, aggregation and dissemination of Aβ. They can not only facilitate the cleavage of amyloid precursor protein (APP) to form Aβ by providing an acidic environment. Exosomes which are rich in glycolipids and lipid rafts can especially offer a favorable environment with the formation of Aβ fibers. Aβ can also spread outside the cells through the secretion of exosomes, proving the ability of exosomes to spread toxic Aβ between cells [2].

Microglia itself can take up and eliminate neuronal exosomes that contain low-phosphorylated Tau protein or Aβ to restrain the proliferation of Tau protein [1]. MG-exos play a protective role in the pathogenesis of AD. They can combine with Aβ in a way that rely on TREM2(an important protein that express on the membrane of MG-exos, which can control the secretion of exosomes without influencing the size of exosomes) to change the inflammatory environment around Aβ, and thus protect the vitality of microglia in order to prompt microglia to phagocytose Aβ [1, 4]. The miR-146a-5p from MG-exos may restrain nucleotide from combining with oligomerized NLRP3 inflammasome by targeting HIF1α/mtROS pathway to reduce the subsequent release of pro-inflammatory factors induced by intermittent hypoxia, and thus reduce neuroinflammation and neuronal damage, which proves that miR-146a-5p from MG-exos is expected to become a good therapy [4]. In the early stage of AD, microglia can phagocytose Aβ through releasing exosomes to reduce the deposition of Aβ so as to avoid microglial dysfunction caused by excessive deposition of Aβ. Persistent dysfunction may cause MG-exos to release a series of disease-related molecules such as pro-IL-1β, caspase-1 and toxic Aβ by microglial exosomes, which further intensify neuroinflammation and nerve injury [2]. This makes MG-exos' therapeutic function for AD shift from positive to negative. Similarly, ADEs have the function of maintaining the survival of neurons and restraining neuroinflammation in normal circumstances [2]. With the development of AD, astrocytes have gone through many pathological changes, such as activization and dysfunction. Therefore, the activation of astrocytes by Aβ may cause cells to secrete pro-apoptotic exosomes and thus intensify the damage to neurons [2]. Furthermore, ADEs can target neurons related to AD and then transfer

therapeutic molecules, such as brain derived neurotrophic factor (BDNF), and thus promote the survival and functional recovery of nerve cells. BDNF genes from AD patients are negatively regulated by miR-206-3p. ADEs can inhibit the activation of δ -secretase through miR-206-3p/BDNF axle to reduce the load of Aβ in AD patients' brains [7].

MSC-exos can reduce the level of Aβ and pathological deposits in the development of AD [4]. Research shows that the reduction of Aβ plaques can be achieved by the degradation of protease such as neprilysin (NEP) and insulin-degrading enzyme (IDE) in MSC-Exos [4]. MSC-Exos can significantly increase the expression and activity of NEP, promote the degradation of various extracellular substrates including Aβ, and thus reduce the deposition of Aβ in the hippocampus and cortex [4]. MSC-exos derived from adipose tissues also contain huge amounts of NEP that can significantly reduce the level of Aβ40 and Aβ42, so they can be used as drug delivery system for NEP to improve spatial memory ability, reduce hippocampal neuron damage and accumulation of age spots, and relieve cerebral inflammation [1]. IDE can degrade peptides such as insulin and glucagon, and can also degrade Aβ so as to reduce the risk of AD, but so far, there are no relevant reports on the involvement of MSC-Exos in Aβ clearance mediated by IDE [4].

Besides, MSC-exos can prevent synaptic damage, protect neurons, reduce apoptosis and promote regeneration [8]. MSC-exos can reduce the excessive activity of inducible nitric oxide synthase (iNOS) in the diseased neurons, and thus alleviate neuronal oxidative damage induced by Aβ protein [8]. MSC-exos can also maintain a stable number of synapses in the hippocampus neurons and promotes synaptic growth by inhibiting the reduction of synaptic protein PSD-95 caused by Aβ protein, and thus improve AD patients' cognitive deficits [8]. In addition, MSC-exos reduce high expression of pro-apoptotic factors like p53, Bax and caspase-3, and increase the expression of anti-apoptotic factors like Bcl-2 in order to inhibit the apoptosis of neurons and promote the synaptic regeneration of diseased and damaged neurons [8].

3.2. The Mechanism and Therapies of Exosomes in Parkinson's Disease

Parkinson's Disease (PD) is the second largest category of NDs after AD. Although the cause of this disease remains unclear, the loss of dopaminergic neurons in the substantia nigra pars compactus prove to be its main pathology [2], and meanwhile the misfolding and abnormal aggregation of insoluble α-synuclein (α-syn) are its key events [1, 2, 6, 9]. They can intensify the development of disease by neuroinflammation, oxidative stress, autophagy and other ways, which results in many symptoms such as bradykinesia, sleep disorders and poor ability in balance and coordination [2]. Exosomes act as a double-edged sword. They may not only provide suitable environment for abnormal aggregation of α -syn and intensify the occurrence and development of diseases [9] but also inhibit the pathology in a way of reducing oxidative stress and inflammatory responses and degrading α -syn.

On the one hand, exosomes can negatively regulate the pathology of PD. Hereditary PD is related to the mutation of leucine-rich repetitive kinase 2 (LRRK2) gene. LRRK2 can combine with Ras family members to regulate the fusion of MVBs with the plasma membrane and the release of exosomes. Among them all, LRRK2 interact with Rab5b to regulate the transportation of endocytic vesicles; Under pathological conditions, the mutation of R1441C on LRRK2 can induce the formation of filamentous abnormal MVBs, promote the fusion of MVBs and plasma membrane, and thus prompt damaged neurons to release a large number of exosomes that contain α -syn. Those exosomes will send α-syn to target cells and release it. There are a large number of misfolded oligomerized α -syn in cerebrospinal fluid exosomes and they are transmitted between neurons. It is more neurotoxic than free oligomerized α -syn and is more easily taken up by cells. It can induce the aggregation of α -syn in healthy neurons, which may cause neuronal injury and apoptosis, and thus accelerate the development of neuropathy [2]. Although cells like microglia and reactive astrocytes plays a certain protective role in the body in a resting stage, they can produce neurotoxicity under the long-term activation of chronic inflammation, and thus cause neural degeneration. At the same time, MG-exos can transfer α-syn oligomer through microglia – neurons pathway, and α-syn also induce the secretion

and increase of MG-exos, which creates a vicious circle and aggravate the pathological spread of α-syn mediated by MG-exos [1]. In addition, impaired formation of autophagosomes in midbrain dopamine neurons will lead to an increase in α-syn in exosomes. NLRP3 inflammasome can activate TLR4/MyD88 pathway to facilitate the diffusion and deposition of α-syn [6]. Although microglia can even phagocytose and eliminate misfolded α-syn in theory, exosomes derived from plasma can reduce the expression of microglia's V1G1 protein, responsible for the acidification of the intracellular environment, damage the acidification function of lysosomes, cause a decrease in the activity of lysosomal enzymes, and thus inhibit the degradation function of lysosomal proteins and then lead to further aggregation and inflammatory activation of α -syn in microglia [2].

Some miRNA belongs to inflammatory mediators related to neurodegeneration [9]. For example, miR-146a and miR-155 can inhibit the upgrowth of T follicular helper cells, and thus regulate the occurrence of chronic inflammation in the body [9]; miR-7 can bind to the 3' -untranslated region of the α-syn gene in order to inhibit the transcription [9, 10], so the deficiency of miR-7 can lead to the upregulation of α-syn synthesis and the increase in the loss of dopaminergic neurons in PD patients' brains [10]; has-miR-4639-5p can negatively regulate the protein DJ-1 after transcription, which leads to severe oxidative stress (OS) and neuronal death in PD patients since its expression level is significantly upregulated in PD patients [10].

On the other hand, exosomes can positively regulate the pathology of PD. Exosomes derived from pulp stem cells of human deciduous teeth can inhibit OS damage and dopaminergic neuronal apoptosis induced by 6-hydroxydopa (6-OHDA), and meanwhile, those mesenchymal stem cells with miR-181a-2-3p have the same effect [6, 10]. MSC-exos can alleviate cognitive impairment in PD patients, which is related to changes in cholesterol metabolism in neurons [1]. In addition, MSC-exos prove to be a kind of effective biological antioxidant. They may inhibit the expression of the target gene NADPH oxidase 4 through delivering miR-100-5p, and thus reduce the generation of reactive oxygen species (ROS), reduce oxidative stress, and significantly increase the levels of dopamine and its metabolites in the striatum [1]. Further research reveals that there is a peak expression level of the pro-inflammatory factor IL-1β 6-12 hours after brain trauma, which can arouse secondary damage to fragile damaged neurons in the early stage caused by intense acute inflammation. MSC-exos can significantly inhibit the overexpression of this factor to form lesion microenvironment conductive to repairing damaged neurons, and also reduce the levels of oxidoreductase, catalase, superoxide dismutase and other antioxidants in brain tissue [8]. Exosomes can promote neural differentiation by regulating the transfer of endogenous and exogenous miRNA. They transfer miR-133b (one of the down-regulated miRNAs in PD. Proteins such as ERK1/2, STAT3 and cyclic adenosine monophosphate effector element-binding protein (CREB) activated by exosomes with miR-133b are signaling pathway proteins involved in neuronal survival and axon regeneration) to promote the growth of axons in in vitro and in vivo experimental models of PD [1]. Moreover, there are important neuroregulatory molecules existing in MSC-exos, including BDNF, insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), pigment epithelium-derived factor, DJ-1 gene, serum cystatin C, and matrix metalloproteinase (MMP), which can degrade α -syn aggregates, thus improving PD symptoms [11].

Meanwhile, it is easy for MSC-exos to penetrate BBB, then reach dopaminergic neurons in BBB substantia nigra, and reduce the asymmetric rotation of apomorphine in order to inhibit the apoptosis of dopaminergic neurons and upregulate the dopamine level in the striatum [1, 2]. It proves that MSC-exos can act as a drug carrier for targeted therapy of PD [6].

4. Limitation of Exosomes Therapy

Currently, exosomes still face multiple challenges in clinical applications. The separation and purification of exosomes from body fluids is an important technical step in the research of NDs [2]. However, the separation and purification of exosomes are still technical bottlenecks that restrict application [2]. Due to the small volume and complex composition of clinical samples, and the low

content of exosomes especially in the cerebrospinal fluid samples, the separation of exosomes becomes even more difficult [2].

Common methods include differential centrifugation (the most used extracting method for separating exosomes at present [12], simple and practicable without pretreatment, and has a wide range of applications, but can deposit exosomes, microvesicles, proteins, liposomes and other substances of the same mass, density and size together, which limits the extracting purity. Meanwhile, high centrifugal force can cause damage to the biological structure of exosomes, leading to low reclamation [12], density gradient centrifugation (further enhance the purity based on the different densities of extracellular components, but it is hard to separate extracellular substances of the same density but different sizes. On this basis, moving-zone density-gradient centrifugation is achieved, which can further purify exosomes in the two-dimensional directions of density and size, but the samples it can accommodate are limited, the equipment is expensive, and it requires highly qualified technicians [12], Ultrafiltration is a technique relying on filter membrane screening, fast and efficient without special equipment. Due to the easy clogging of ultrafiltration membranes, the separation efficiency may be affected [12], Coprecipitation is simpler and more practicable, and can be used for large-scale extraction of exosomes and rapid diagnosis of diseases. The hydrophilic polymers used in this technology may simultaneously cause the deposition of exosomes and hydrophilic substances such as nucleic acids, lipoproteins, and some viruses, which results in a large number of impurities and highly toxic exosomes obtained [12]. Polymer immune affinity can obtain exosomes of higher purity but is costly. Moreover, the pH and salt concentration of the buffer solution will affect the activity of exosomes, and then, exosomes bound to antibodies are only suitable for disease diagnosis and not for functional research [12], microfluidic separation technology (precise and efficient, suitable for small samples but its equipment is complex, and it can also obtain only specific subsets of exosomes and it is difficult to maintain the biological structure of exosomes [12]. According to the experimental requirements, a single or combined method can be selected to enhance the separation efficiency and purity [2].

Regarding the therapeutic mechanism of MSC-exos, MSCs themselves are identified as a potential therapeutic media due to their wide sources, easy acquisition from various tissues such as adipose tissue, umbilical cord, liver, amniotic fluid and placenta, as well as dental pulp, easy isolation and special biological functions [8]. Moreover, the therapies that MSC-exos attend may also have obvious advantages. However, before those therapies can be widely implemented, the loading capacity of exosomes and the half-life of their inclusions need to be determined in order to develop engineered synthetic inclusions for therapeutic purposes; and the dosage of exosomes needs to be subject to pharmacological considerations, and their biodistribution during system use should be evaluated to meet the requirements of current good manufacture practices (CGMP). Besides, it is also necessary to determine the kinetics of exosome uptake in target cells whether the therapeutic delivery of exosome drugs requires bioengineered ligands on the vesicle surface to increase the success rate of delivery to selected targets [8].

In addition, how to enhance the effectiveness and safety of drug carriers, optimize the extraction efficiency and economy of exosomes, and ensure their stability in vivo still remain a crucial research direction. The intercellular transmission mechanism of exosomes, as well as the specific mechanisms and efficiency of their entry into the brain and delivery of contents to the central nervous system, still need further exploration [2]. Meanwhile, current researches are still lack of comparison of the effects of different administration methods, detailed analysis of exosome components, research on the improvement of learning and memory in the final disease model through relevant animal experiments and clinical trial. Further investigation of these issues is critical for making substantive contributions to managing clinical cognitive impairment, including its diagnosis, treatment, and prognosis [4].

5. Conclusion

This study found that exosomes play a key role in NDs. They are able to affect the gene expression of recipient cells and the protein activity in pathways and participate in the spread of pathological proteins through components such as proteins, mRNAs or miRNAs. They can also participate in the occurrence and development of diseases by regulating neuroinflammation, pathological protein deposition and other pathways. They can cross BBB, and their highly stable bilayer lipid membrane can protect the inclusions from degradation, making them ideal drug delivery carriers for the treatment of central nervous system diseases. In addition, the regulation of MG-exos and ADEs on diseases varies in different pathological stages. In the early stage, they have the ability to swallow misfolded proteins or suppress neuroinflammation by releasing anti-inflammatory factors and other ways, thereby improving the condition. As the disease develops, they will aggravate the condition by releasing pro-inflammatory factors or pro-apoptotic factors, etc. MSC-exos can eliminate abnormal protein deposits through secreting proteases or phagocytosis, exert anti-inflammatory and antioxidant effects, and improve pathology through mechanisms such as drug delivery, which can achieve good therapeutic effects. The main contribution of this article lies in systematically clarifying the dual role of exosomes in NDs, which not only participate in pathological transmission but also have therapeutic potential. It fills the research gap of the functional transformation mechanism of exosomes at different pathological stages and provides a new perspective for understanding the dynamic regulation of disease progression. This research is beneficial for researchers in the fields of neuroscience, biotherapy and biomaterials to clarify the role of exosomes and provides potential engineering modification strategies, and meanwhile, it provides brand-new ideas and theoretical basis for clinical experiments. For example, in the early stage of the disease, the clearance functions of MG-exos and ADEs can be utilized to delay the progression, while in the middle and late stages, the appropriate MSC-exos can be infused to regulate the lesion.

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