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Research Progress of Exosomes in Parkinson's Disease

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Abstract: *Exosomes are nano-vesicles secreted by cells, which can carry the transfer of intracellular protein and other substances. Parkinson's disease (PD) is one of the neurodegenerative diseases, characterized by the progressive loss of neurons, and the production of α -synuclein is its pathological marker. Studies have shown that during the onset of Parkinson's disease, exosomes mediate the toxic transmission of α -synuclein, which leads to the aggravation of the disease. At the same time, it can also be used as a potential biomarker for PD prodromal diagnosis and a potential drug carrier to help the early diagnosis and treatment of PD. This article will review the research progress of exosomes in the pathogenesis, diagnosis and treatment of PD, with a view to clinical application.*

Keywords: *Exosomes; Parkinson's disease; Review*

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive degeneration of neurons in the substantia nigra densa. The survey showed that the prevalence rate of PD over 60 years old was 1.37%. Therefore, it is estimated that the total number of people suffering from Parkinson's disease in China may be as high as 3.62 million [1]. Globally, the incidence of Parkinson's disease ranges from 5 to more than 35 new cases per 100, 000 people [2]. Another characteristic of PD is the formation of lewy bodies, which are mainly composed of α-synaptic nucleoproteins (ASN). Oligomers and fibril of alpha-synaptic nucleoproteins are cytotoxic and mediate neuronal degeneration. With progressive degeneration of neurons, motor symptoms such as tremors, myotonia, slow movements, postural balance disorders, and non-motor symptoms such as sleep disorders, olfaction disorders, autonomic nervous dysfunction, and cognitive and psychiatric disorders may occur. This puts a huge burden on patients and society. At present, PD is faced with problems such as difficulties in early diagnosis and unsatisfactory treatment effect. Early diagnosis is difficult mainly because symptoms and signs do not appear until the basal ganglia (caudate and putamen) and pars compactus nigra have reached 80% dopamine deficiency. The treatment of PD is limited by the blood-brain barrier, so drugs cannot play a full role, resulting in unsatisfactory therapeutic effect. Exosomes are vesicles secreted by cells. Studies have shown that exosomes have the potential to diagnose PD in the early stage and serve as drug carriers. At the same time, exosomes can load and transfer ASN, so as to affect the whole course of PD.

2. Exosomes

In 1967, Wolf discovered a tiny particle of material that could be detected in the blood, which he called "platelet dust." Platelet dust is the earliest prototype of exosomes. Twenty years later, Rose Johnstone discovered that sheep reticulocytes cultured in vitro secreted bioactive vesicles, which he first named exosomes. Exosomes are spheroidal or ellipsoid membranous extracellular vesicles secreted by cells with a diameter of 40~100nm. Extracellular vesicles originate from the plasma membrane and bud inward to form early endosomes. Part of the membrane invaginates and buds into the surrounding lumen containing cytoplasmic contents to form intracavitary vesicles (ILVs). Late endosomal structures containing dozens of ILVs are called polycystis (MVB), which are eventually transported to the Golgi apparatus network (TGN) for endosomal recirculation, and then delivered to lysosomes to degrade all the carried substances, or fused with the plasma membrane and released into the extracellular space [3,4].

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The portion of the vesicle that is released into the extracellular space is the extracellular vesicle. Exosomes are a type of extracellular vesicle that can carry specific proteins, lipids, functional mRNAs, and a large number of non-coding Rnas (mirnas, lncRNAs, and circRNAs).

The most direct function of exosomes is to remove excess organelles as antigen presenting cells. Exosomes also have the function of transporting specific proteins, lipids, micrornas and other substances in the source cells, and can transmit intercellular signals to regulate the proliferation, differentiation and apoptosis of the recipient cells. Studies have shown that exosomes are closely related to the pathogenesis, diagnosis and treatment of Parkinson's disease. Firstly, exosomes can participate in the pathogenesis of PD by transferring alpha-synaptic nucleoprotein, increasing neuroinflammation and regulating PD-related gene expression. Secondly, exosomes have different expression in body fluids of PD patients and healthy people, which can be used for PD diagnosis. Finally, exosomes can be used as drug carriers to carry drugs smoothly through the blood-brain barrier. It is not recognized by the immune system, which can improve the bioavailability of drugs and is beneficial to the treatment of PD.

3. Correlation between exosomes and PD

3.1. Exosomes and early diagnosis of PD

Lewy bodies are the signature pathological products of PD, and α-synucleoprotein (α-syn) is its main component. Alpha-syn is a vesicle protein rich in presynaptic nerve endings. Under pathological conditions, alpha-syn transforms its conformation and assembles into oligomers and fibrils. These metastable oligomeric structures are the most virulent and can spread like a virus from damaged healthy neurons to neighboring healthy neurons, thereby spreading alpha-synaptic nucleoprotein aggregation throughout the brain and triggering widespread neuronal degeneration. The release of exosomes is one of the ways of its metastasis [5]. Meanwhile, exosomes secreted into body fluids can also be used to diagnose PD.

Exosomes, as early diagnostic markers for PD, have the following characteristics: (1) Specificity: Differences in exosome size and contents reflect the state and type of source cells. Studies have shown that alpha-SYN can be secreted through exosomes in a calcium-dependent manner, which can accelerate the progression of PD [6]. Exosomes containing a wide range of oligomers and fibrous alpha-syn can be isolated from the plasma of early PD patients [7,8]. Moreover, the diagnosis of neurodegenerative diseases, such as PD and multisystem atrophy (MSA), can be distinguished by quantitative and qualitative analysis of the contents carried by neuronal exosomes. Compared with the control group ($p<0.01$) and MSA ($p<0.05$), the plasma level of neuron-derived exosomes in PD patients is significantly increased [9]. (2) Stability: Exosomes exist stably in body fluids, including blood, saliva, urine, and cerebrospinal fluid [10-12]. Exosomes' bilayer membrane and nanoscale size protect their contents from elimination or damage by immune cells. Previous studies have shown that exosomes containing alphaSYN can be detected in plasma and are significantly associated with disease severity ($r=0.176$, $p=0.004$) [13]. Cao Zhentang et al. [14] detected exosomes in saliva of PD patients by electrochemiluminescence. (3) Plurality: Exosomes contain many molecular substances, including proteins, lipids, metabolites, mRNA, mitochondrial DNA, micrornas, and many other non-coding Rnas [15]. In addition to exosomes, micrornas carried by them have also become a hot topic in the study of biomarkers for Parkinson's disease in recent years. Studies have shown that compared with healthy control group, hsa-miR-30c-2-3p level in plasma exosomes of PD patients is significantly higher than that of control group. The levels of hsa-miR-15b-5p, hsa-miR-138-5p, hsa-miR-338-3p, hsa-miR-106b-3p and hsa-miR-431-5p were lower than those of the control group. Therefore, hsa-miR-15b-5p, hsa-miR-30c-2-3p, hsa-miR-138-5p, hsa-miR-106b-3p, hsa-miR-338-3p and hsa-miR-431-5p can be used as potential biomarkers for the diagnosis of PD [16]. Similarly, proteins carried in exosomes also have the potential to diagnose PD. Japanese researchers used two-dimensional differential gel electrophoresis to analyze the protein profiles of exosomes extracted from the plasma of healthy people and patients with stage II and III Parkinson's disease. The results showed that the three exosome proteins (clusterin, complement C1r subcomponent and apolipoprotein A1) and the fibrinogen γ chain in plasma may be biomarker candidates for the diagnosis of PD. In particular, the expression level of apolipoprotein A1 in exosomes can be used to track the progression of PD [17].

In conclusion, exosomes have the potential to diagnose PD. Exosomes derived from the plasma of PD patients are specific, and we can diagnose the disease by identifying exosomes in PD patients. Moreover, exosomes are also different in different neurodegenerative diseases. At the same time, exosomes can exist relatively stably in body fluids, which provides a material basis for their detection. Finally, exosome contents are different in different patient populations, such as micrornas and proteins, which can be used as potential biomarker candidates for the diagnosis of PD.

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3.2. Exosomes and the incidence of PD

Exosomes are mainly involved in the pathogenesis of PD from the following three aspects: (1) Transfer of α-syn: Exosomes are important carriers of α-syn. Danzer et al. found that exosomes mediate the transfer of alpha-syn oligomers between cells. Alpha-syn oligomers can be transferred between cells by the way that neurons secrete exosomes. Not only are alpha-syn oligomers excreted by host cells through exosomes, but alpha-syn oligomers in exosomes are more easily absorbed by endocytosis than alpha-syn fibulles [18], which accelerates the onset of PD. By injecting lewy body extracts from PD patients into the intestines of non-human primates, scholars have also demonstrated that toxic alpha-syn can be transmitted from the intestines to the brain through exosomal delivery [19]. The spread of this toxic alpha-SYN is pathogenic. Studies have shown that lewy bodies extracted from the brains of PD patients and transplanted into mice and monkeys lead to progressive neurodegeneration of the substantia nigrostriatum starting from the dopaminergic endings of the striatum in monkeys and mice [20]. It was further confirmed that exosomes cause neuronal death by transmitting the toxic form of alphasyn, thereby accelerating the onset of PD. (2) Aggravating cellular inflammation: Inflammation is a key process in the progression of PD, and appropriate inflammatory response is essential for tissue repair, but excessive and delayed inflammatory response may cause neuronal damage. Yin Zhenyu et al. [21] showed that exosomes containing miR-21-5p released by neurons were phagocytosed by microglia and induced microglia to become M1-type polarized, thus exacerbating neuroinflammation and causing neuronal damage. Microglia cells are the main immune cells in neuroinflammation, which can lead to the loss of DA neurons through abnormal activation of the complement-phagocytosis pathway [22,23]. M1 microglia express pro-inflammatory cytokines, which can cause secondary neuron damage, aggravate cellular inflammation, and further accelerate the onset of PD. (3) Regulation of PD-related gene expression: Although most cases of Parkinson's disease are sporadic, familial cases are also associated with different gene mutations, including the nucleoprotein gene, leucine-rich repeat kinase 2 (LRRK2), and deglycation enzyme (DJ-1). Studies have shown that some miRNAs carried by exosomes can target PD-related genes and regulate the expression of PD-related genes to affect the progression of PD disease. Chen Yimeng et al. found that the increased expression of HSA-Mir-4699-5p would lead to dose-dependent reduction of DJ-1 protein level, which would lead to severe oxidative stress and neuronal death [24]. Kirsty et al. also confirmed that miR-7 in exosomes can bind to mouse nuclear protein gene site 3'UTR, thereby inhibiting the expression of mouse nuclear protein gene [25]. Similarly, ELena also confirmed that miR-34b/c also targeted nucleoprotein genes and was associated with DJ-1 and decreased expression [26]. In addition, exosomes can transport alpha-SYN to lysosomes for degradation. Disruption of this clearance pathway leads to accumulation of alpha-SYN in neurons, which further causes neuronal degeneration. LRRK2 is a protein kinase whose overexpression induces abnormal MVBs formation, reduces exosome secretion, and further disrupts α-syn clearance pathways. Studies have shown that the expression of exosomal protein 14-3-3 can regulate the release of LRRK2 in exosomes, and 14-3-3 inhibitors to disrupt the interaction between 14-3-3 and LRRK2 can effectively block the release of LRRK2 in exosomes and delay the onset of PD [27].

In summary, exosomes are involved in the pathogenesis of PD by delivering alpha-SYN, causing excessive or delayed inflammatory responses, and regulating the expression of PD-related genes through contents. In addition, exosomes also have neuroprotective effects. Human bone marrow mesenchymal stem cells secrete a large number of growth factors, cytokines, and chemokines, which have various implications in the regulation of key biological processes, such as neuroprotection [28]. Chen et al. demonstrated that exosomes secreted from mesenchymal stem cells can promote the proliferation of SH-SY5Y cells stimulated by 6-hydroxydopamine (6-OHDA) and inhibit apoptosis by inducing autophagy [29]. This demonstrates the therapeutic potential of exosomes in Parkinson's disease.

3.3. Treatment of exosomes and PD

Currently, drugs such as levodopa, anticholinergics, and dopamine receptor agonists can relieve motor symptoms caused by PD. However, due to the blood-brain barrier (BBB), these drugs are not efficient at reaching the site of neuronal damage. Exosomes are widely found in the human body and are thought to have low immunogenicity and long cycle half-life [30]. On the one hand, exosomes can easily pass the blood-brain barrier without being recognized by the immune system. On the other hand, the long half-life of exosomes gives them a stable biological structure. As long as they do not bind to the recipient cells, the half-life of exosomes can be as long as several hours. This makes exosomes have the structural basis as drug carriers: ① As drug carriers: Exosomes are one of the most important aspects of PD treatment. Substances such as dopamine, siRNAs and antisense oligonucleotides (ASOs) are modified on exosomes to overcome shortcomings such as short efficacy and poor bioavailability. The study of Mengke et al. [31] found that in PD mouse models, dopamine loading with exosomes could increase the brain distribution by more than 15 times, and dopamine-loaded exosomes showed better therapeutic

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effect and lower systemic toxicity than free dopamine after intravenous administration. Izco et al. [32] used exosomes to deliver siRNAs interfering with alpha-SYN formation to a PD mouse model and found that they reduced synaptic nucleoprotein aggregation, reduced dopaminergic neuronal death, and improved clinical symptoms of PD in the PD mouse model. Antisense oligonucleotides (ASOs) can reduce α-syn expression. Yang et al. [33] injected exosomes loaded with ASOs into PD mouse models from lateral ventricles and found that exogenous ASO4 could significantly reduce the expression and aggregation of alpha-SYN. These results suggest that exosomes can be used as promising drug delivery mediators for targeted treatment of PD and other central nervous system diseases. ② Play neuroprotective and regenerative roles. Exosomes can transport alpha-SYN to lysosomes for degradation, which is itself a neuroprotective effect. Sun et al. [34] found that exosomes extracted from the blood of healthy volunteers had neuroprotective effects on PD mouse models. These protective effects were reflected by improving impaired motor symptoms in mice, reducing the loss of dopaminergic neurons, alleviating oxidative stress damage and neuroinflammation, and reducing cell apoptosis. Mesenchymal stem cells (MSCs) are adult stem cells that are found in the brain. MSCs isolated from dental pulp (DP-MSCs) and brain (B-MSCs) can differentiate into functional neuron cells, and produce immune regulatory factors to induce the generation of new blood vessels and provide nutritional support for injured neurons, thus enhancing the repair and regeneration of neural tissue [35-37]. Stem cell therapy is the only basic principle and feasible tool for nerve tissue regeneration, and its secretion of exosomes has been proven to play a neuroprotective role. Jar and colleagues investigated the parasecretory nerve regeneration properties of human dopaminergic neurons by microvesicles and exosomes secreted from dental pulp stem cells of human SHEDs. They revealed that SHEDs derived exosomes were able to inhibit 6-OHDA induction in more people. In addition, the secretion of MSCs contains important neuroregulatory molecules, including BDNF, IGF-1, vascular endothelial growth factor, pigment epithelium-derived factor (PEDF), DJ-1, and cystatin C (Cys-C), which can improve the motor phenotype and neuronal structure in PD mouse models. This supports the potential role of MSCs secretion in anti-PD [38].

In conclusion, exosomes participate in the treatment of PD mainly by acting as drug carriers and playing a neuroprotective role. Exosomes act on PD as drug carriers mainly to overcome low BBB permeability, poor neuronal targeting, inefficient endocytosis to cytoplasm and uncontrolled drug release. For this purpose, we need to modify exosomes. Previous studies have shown that exosomes can achieve endogenous and site-specific cargo loading during exosomal biogenesis [39]. However, the low targeting of exosomes is a challenge in the treatment of PD by exosomes. Currently, most targeting approaches aim to promote the coupling of foreign objects to target cells using specific ligand/receptor binding strategies. It is intended to modify neuron-affinity specific ligands onto exosomes through direct expression (biochemical engineering and physical engineering) and indirect expression (genetic engineering), so as to increase their targeting for PD treatment [40]. However, there are some problems in controlling exosome dose, measurement standard, administration route, side effects and so on.

4. Discussion

PD is a common neurodegenerative disease, early diagnosis depends on mdopa test, but there are still some patients who are not sensitive to mdopa test. For these patients, it is of great significance to find available biological markers to confirm the diagnosis of PD. Currently, exosomes are being studied as biomarkers for PD. Its specificity, stability and content diversity all make exosomes have strong potential as early diagnosis of PD. In clinical observation, it has been found that the expression of plasma-derived exosomes is different between PD patients and healthy controls or PD patients and patients with other neurodegenerative diseases. The number of exosomes, micrornas carried in exosomes (e.g. hsa-miR-30c-2-3p described above), proteins (e.g. , complement C1r subcomponent and apolipoprotein A1 described above), and fibrinogen γ in plasma), We can screen exosomes from PD patients through proteomic analysis, molecular quantitation, nucleic acid recognition and other technologies of exosome contents, which will provide help for the development of potential biomarkers of Parkinson's disease and the early diagnosis of Parkinson's disease clinically. In addition, exosomes can be used to treat PD. At present, the main treatment of PD is to supplement exogenous dopamine. Levodopa is a commonly used drug in clinic. In the laboratory, levodopa was modified onto exosomes and injected into PD patients, which can increase the bioavailability of dopamine and reduce systemic toxicity. This is because exosomes can easily cross the blood-brain barrier without being recognized by the immune system. Exosomes act as "messengers" that transmit signals between cells to regulate the proliferation, differentiation and apoptosis of recipient cells. In the laboratory, the exosomes derived from PD mice were modified with siRNAs and antisense oligonucleotides (ASOs) that interfere with alpha-SYN formation, and the modified exosomes were injected into mice. It was found to reduce synaptic nucleoprotein aggregation, reduce dopaminergic neuronal death, and improve clinical symptoms of PD in a mouse model of PD. Stem cell therapy is the only basic principle and feasible tool for nerve tissue regeneration, and its

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secretion of exosomes has been proven to play a neuroprotective role. We can also modify neuroinflammatory drugs on exosomes to reach the disease site and play a role in improving neuroinflammation and reducing neuronal damage.

However, it is challenging for most existing technologies to efficiently isolate exosomes of central nervous system origin from complex body fluids, and to accurately detect and quantify brain-derived or disease-specific proteins and nucleic acids with very low abundance in exosomes. So far, there are five main exosome separation technologies, namely differential centrifugation based technology, size based technology, immunoaffinity capture based technology, exosome precipitation based technology and microfluid-based technology. Among them, immunoaffinity capture technique is more suitable for the isolation of specific exosomes. However, immunoaffinity capture based separation techniques also have drawbacks, such as the possibility that fully functional exosomes may not elute completely from the surface of the magnetic bead once they are captured by the bead. In addition, this method is time-consuming and cumbersome, which makes it easy to make mistakes in the process of separating exosomes. Therefore, the specific isolation of exosomes from central nervous system is still a challenge to be overcome in basic research. Although the technology of exosomes in the treatment and isolation of diseases is still immature, it still has important significance for the future clinical use of exosomes in the treatment of Parkinson's disease and other diseases.

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