

The Role of Exosomes in The Pathogenesis of Parkinson's Disease and Potential Therapeutic Strategies

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Abstract: The pathogenesis of Parkinson's disease (PD), the second most prevalent neurodegenerative disorder after Alzheimer's disease, continues to be a focal point of research within the medical community. In recent years, advancements in exosome research have revealed a significant role of exosomes in the pathogenesis of Parkinson's disease. Exosomes, distinguished by their lipid bilayer membrane, are small vesicles actively secreted by cells. Exosomes play a crucial role not only in modulating the immune response and serving as transporters in inflammatory pathways but also have a substantial impact on tumor initiation, progression, and therapeutic strategies in the field of medicine. In PD, disturbances in exosome functionality can directly influence neuronal health. Research suggests that exosomes in PD patients may experience changes in quantity, composition, and function. These alterations have the potential to cause neuronal damage and death, thus exacerbating the disease progression. This study delves into the role of exosomes in the pathogenesis of PD and explores potential therapeutic approaches.

Keywords: Exosomes; Pathogenesis of Parkinson's Disease; Potential Therapeutic Strategies.

1. Introduction

Parkinson's disease (PD), a common neurodegenerative condition, has had a profound effect on the well-being of many individuals, given its typical clinical symptoms including bradykinesia, resting tremors, and muscle rigidity [1]. However, diagnosing PD presents difficulties primarily due to the subjective assessment of clinical indicators, leading to a delay in diagnosis relative to disease onset and subsequently delaying the initiation of timely and effective treatment [2, 3]. Therefore, the identification of biological markers capable of early prediction and diagnosis of PD plays a critical role in improving treatment outcomes and enhancing patient quality of life [4]. In recent years, the advancement of biotechnology has sparked increasing research interest in exosomes as a novel mode of intercellular communication [5]. Exosomes, being vesicles external to cells, contain various bioactive substances like proteins, nucleic acids, and other elements. They function as messengers in cell-to-cell signaling, contributing to a variety of both normal and abnormal biological processes [6].

Exosomes play a crucial role in immune-related disorders such as multiple sclerosis [7], optic neuritis [8], and myasthenia gravis [9], as well as neurodegenerative conditions like Alzheimer's disease and PD within the realm of neurology [10]. PD primarily impacts individuals in the middle-aged and elderly population. As individuals age, the incidence of PD increases [11]. Epidemiological data indicates a sharp increase in the incidence of PD among individuals aged 65 and above. By 2040, it is projected that the global number of individuals diagnosed with PD will surpass 12 million [12]. Despite the substantial number of individuals affected by PD, a thorough comprehension of its etiology and pathogenesis remains incomplete. Currently, it is widely acknowledged that a multifactorial interplay involving genetic, environmental, and age-related factors is believed to play a role in the initiation and advancement of PD [13].

Investigating the role of exosomes in PD pathogenesis provides an avenue to deepen understanding and potentially reveal innovative therapeutic strategies. Exosomes, pivotal for intercellular communication, may contribute to the propagation and exacerbation of neuronal damage in PD. Furthermore, the varied bioactive molecules encapsulated within exosomes hold potential as therapeutic targets for PD management [14]. One perspective entails the modulation of exosome quantity and functionality to attenuate the progression of neuronal degeneration and mortality [15], while an alternative standpoint proposes the utilization of exosomes as delivery vehicles for conveying therapeutic compounds directly to impacted neurons in PD, thereby augmenting treatment efficacy and mitigating adverse events [16]. Notwithstanding, the current investigation into the role of exosomes in PD is in its early stages, underscoring the imperative for further scrutiny and validation. Forecasts envision exosomes emerging as an innovative therapeutic modality for PD as understanding advances regarding their functions and precise mechanisms of action in the disorder.

Furthermore, considering the cellular communication role of exosomes, they hold promise as biomarkers for early PD detection. Surveillance of changes in exosome quantity, composition, and cargo in the patient's biofluids may allow for timely identification of PD biomarkers, aiding in early intervention and therapeutic strategies. The main objective of this study is to explore the role of exosomes in the pathogenesis of PD and assess potential therapeutic strategies involving exosomes. As a burgeoning field within PD research, exosomes present vast opportunities for application and hold substantial research value. A more comprehensive understanding of exosome functionality in PD is anticipated to drive the development of more accurate diagnostic tools and personalized treatment approaches, thereby enhancing treatment effectiveness and the quality of life for individuals with PD.

2. The Pathogenesis of Parkinson's Diseases

PD is a chronic neurodegenerative disorder marked by the predominant degeneration of dopaminergic neurons situated in the substantia nigra [17]. Dopaminergic neurons play a crucial role in the synthesis and release of dopamine, which is an essential key neurotransmitter for brain function. Damage to dopaminergic neurons can lead to a decrease in dopamine levels, affecting the brain's motor control regions, and consequently causing symptoms characteristic of PD. Genetic factors play a crucial role in the onset of PD, with research revealing that mutations or variations in certain

genes can increase susceptibility to the condition [18]. These genes may contribute to multiple processes, including dopamine metabolism, oxidative stress, and mitochondrial function, collectively impacting the health and functioning of neurons (Figure 1). Environmental factors are acknowledged as important contributors to the onset of PD. Prolonged exposure to specific heavy metals, pesticides, toxic substances, or certain medications may increase the risk of developing PD [19, 20]. These compounds can potentially damage dopaminergic neurons in the substantia nigra by interfering with neuronal function, inducing oxidative stress, or triggering cellular apoptosis.

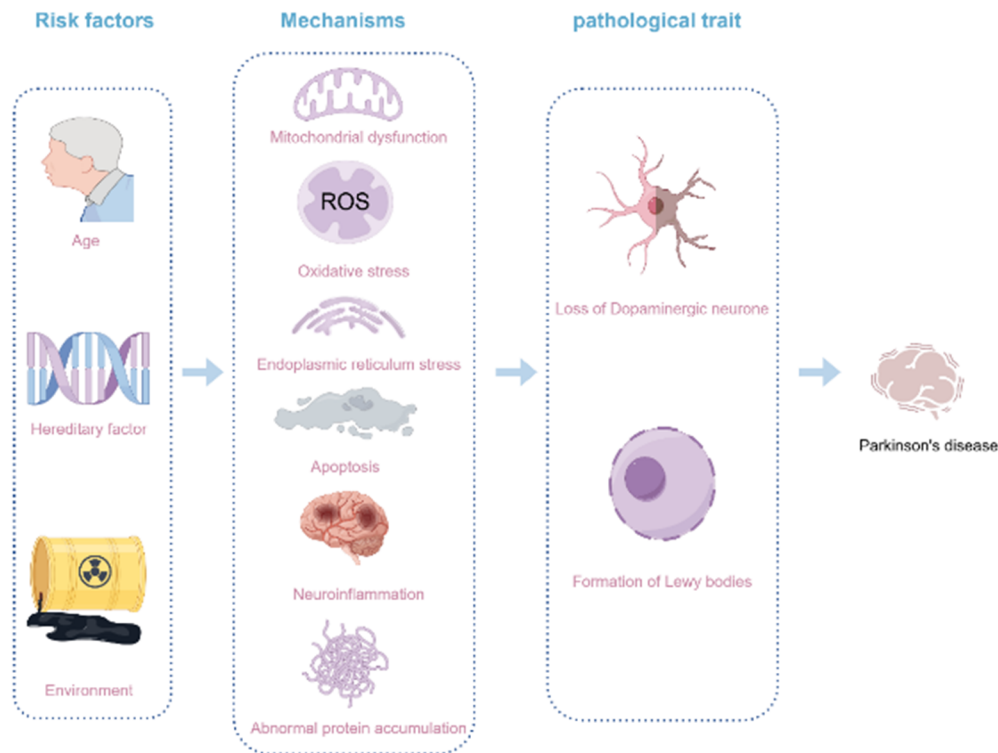


Figure 1. Schematic gram of risk factors and potential mechanisms with Parkinson's disease

Age plays a significant role in the pathogenesis of PD. PD primarily afflicts individuals in middle and old age, possibly attributable to the increased susceptibility of aging neurons to various internal and external stressors. The aging process can lead to a range of changes, including genomic instability, disrupted protein homeostasis, mitochondrial dysfunction, oxidative stress, inflammation [21], which are all closely linked to the susceptibility to PD. Oxidative stress emerges as a crucial factor in the pathophysiological mechanisms underlying PD. Oxidative stress refers to the disturbance of intracellular redox homeostasis, leading to the excessive formation of reactive oxygen species (ROS). ROS can directly harm neurons, resulting in cell apoptosis and dysfunction. Higher levels of oxidative stress are commonly detected in PD patients, possibly linked to mitochondrial dysfunction, genetic alterations, or environmental factors. Additionally, the immune inflammatory response is acknowledged as a crucial element in the development of PD. Research has shown a close relationship between PD and the activation of microglia and the release of inflammatory mediators [22]. These immune responses possess the capability to exacerbate neuronal degeneration and

malfunction, thus intensifying the symptomatic expression of PD. Essentially, the pathogenesis of PD involves a complex and diverse trajectory influenced by genetic predisposition, environmental factors, aging, oxidative stress, and immune-mediated inflammatory processes. The interactions between these factors can collectively lead to damage to dopaminergic neurons in the substantia nigra and the initiation of PD. Although there is some understanding of the pathogenesis of PD, there are several unexplored areas that require further investigation. Future research should focus on genetic, environmental, metabolic, and other factors, examining their interactions and regulatory mechanisms. Additionally, the development of innovative therapeutic strategies and methods is crucial to improve the management and alleviation of PD symptoms, ultimately enhancing the quality of life for patients.

3. The Mechanism of Action of Exosomes

(1) Participate in Immune Response

PD is a persistent neurodegenerative condition distinguished by the deterioration and depletion of

dopaminergic neurons in the substantia nigra of the midbrain and the development of Lewy bodies [17]. The main component of Lewy bodies is α -synuclein (α -syn) nucleoprotein, and the abnormal aggregation and propagation of this protein are considered key mechanisms in the pathogenesis of PD. Exosomes, essential mediators of intercellular communication, play a pivotal role in the etiology and advancement of PD, especially through the transfer of α -syn nucleoproteins and the regulation of immune responses. With their phospholipid bilayer structure, exosomes have the ability to transport and discharge a wide range of biological molecules, such as proteins and nucleic acids. Noteworthy is the conspicuous presence of abnormal expression and aggregation of α -syn nucleoprotein in individuals affected by PD. Research has shown that overexpression of α -syn nucleoprotein in SH-SY5Y cells leads to the secretion of exosomes containing α -syn nucleoprotein. These exosomes have the ability to transfer α -syn to normal SH-SY5Y cells, thereby promoting the aberrant propagation of α -syn nucleoprotein among neurons. The exosome-mediated transmission of α -syn nucleoprotein plays a crucial role in the pathogenesis of PD. On one hand, it may trigger the neurotoxic effects of α -syn on healthy neurons, contributing to their degeneration and death, thus exacerbating the disease progression. On the other hand, exosomes may also modulate the immune response in PD by influencing the activity and function of immune cells.

In the realm of immune modulation, exosomes exhibit the capacity to engage with a variety of immune cells, such as macrophages, dendritic cells, and T cells, affecting their activation and function. Specifically, exosomes can convey antigenic information and initiate immune responses by activating dendritic cells. Moreover, exosomes can inhibit T cell activation, reduce inflammation, and thereby display immunosuppressive characteristics. This bidirectional regulatory mechanism enables exosomes to play a crucial role in immune modulation in PD. Moreover, exosomes may influence the progression of PD by regulating neuroinflammation [23]. Neuroinflammation is a pivotal factor in the pathogenesis of PD, and exosomes can modulate the level of neuroinflammation by transmitting either anti-inflammatory or pro-inflammatory signals [23]. For example, specific exosomes may carry anti-inflammatory mediators, dampening neuronal inflammatory responses and safeguarding them from damage. Conversely, other exosomes could disseminate pro-inflammatory stimuli, exacerbating neuroinflammation and accelerating disease advancement. Although the importance of exosomes in immune regulation in PD is recognized, there are still many areas that remain unexplored regarding their specific mechanisms and pathways. Exosomes, as crucial mediators of intercellular communication, play a central role in immune regulation in PD. Further research into the detailed mechanisms of exosome action is expected to provide new insights and therapeutic strategies for managing PD. This research will also offer new perspectives and clues for a better understanding of the pathogenesis and progression of PD.

(2) As a Transportation Carrier

Exosomes represent specialized vesicles that serve as carriers for transferring essential biomolecules across cell membranes. Owing to their inherent phospholipid bilayer composition, exosomes demonstrate high efficacy in transporting a diverse array of bioactive components, including proteins and nucleic acids, thereby safeguarding

them from external perturbations. Upon fusion with or internalization by target cells, exosomes facilitate the intracellular delivery of these biomolecules, exerting a profound influence on the functional responses of the recipient cells. The unique capability of exosomes to traverse cellular membranes enables them to surmount biological barriers, mediate cellular communication, and facilitate intercellular signaling. Furthermore, exosomes play a pivotal role in orchestrating substance exchange among cells, thereby modulating cellular functions through the secretion of internal metabolites, signaling molecules, and other bioactive compounds into the extracellular milieu or their transfer to neighboring cells. This intricate exchange mechanism plays a critical role in preserving cellular homeostasis and coordination, which are essential for maintaining tissue stability.

Exosomes play pivotal roles in the pathogenesis of diseases. In tumor progression, exosomes have the capacity to shape a microenvironment conducive to tumor development by modulating the characteristics and functions of diverse immune cells [24]. They transport tumor-specific antigens, growth factors, and other molecules that facilitate tumor cell proliferation and invasion. Furthermore, exosomes can convey misfolded proteins and pathogenic agents, contributing to the spread and worsening of diseases through intercellular signaling. In conditions like PD, exosomes demonstrate a dual functionality, contributing to neuroprotection through facilitation of toxic protein clearance or their conveyance to neurotrophic factors. Conversely, exosomes may exert neurotoxicity by transporting potentially deleterious molecules to neighboring neuronal cells, resulting in neuronal dysfunction or demise, thereby aggravating the pathogenesis of PD [25]. As research progresses and technologies advance, a more thorough understanding of exosome mechanisms is anticipated, providing enhanced opportunities for their application in disease diagnosis and treatment.

4. Potential Treatment Strategies

Exosomes exhibit substantial potential in the treatment of various diseases, particularly in oncology and neurodegenerative disorders like PD [26, 27]. In the field of oncology, a cutting-edge strategy involves the use of genetically engineered exosomal nanovesicles (GEPN). Through the application of genetic engineering methodologies, exosomes can be customized to transport specific therapeutic molecules or nanomaterials, facilitating precise targeting of tumor cells and promoting a synergistic interplay between chemotherapy and immunotherapy. GEPN surpasses traditional therapeutic modalities with its adjustable structure, versatile function, enhanced targeting specificity, and improved drug delivery capacity, offering potential enhancements in treatment efficacy and reduction of adverse effects. Concerning the management of neurodegenerative conditions such as PD, exosomes hold promise for their ability to modulate the communication barriers between PD-affected neurons, which are associated with the aggregation of misfolded proteins. By regulating exosome release and functionality, there is a potential to restore normal neuronal communication, decrease protein aggregation, and alleviate disease manifestations. Moreover, exosomes can act as carriers for drug transportation, facilitating direct administration of PD medications to damaged neurons, thereby enhancing therapeutic outcomes [16].

In addition to their direct therapeutic applications, exosomes may serve as valuable diagnostic biomarkers for various diseases [28]. Changes in the presence and quantity of exosomes in body fluids, characterized by specific surface markers, have the potential to provide insights into disease progression and prognosis. Detection of relevant exosomal markers could enhance early disease identification and monitoring. However, despite the significant therapeutic potential of exosomes, their practical use faces challenges. These challenges include the need for further refinement of exosome isolation and purification techniques, the impact of in vivo conditions on exosome biological activity and stability, and the necessity for comprehensive evaluation of exosome safety and long-term effects. Advances in research and technology are expected to deepen our understanding of exosome mechanisms of action, expanding possibilities for their application in disease management. It is crucial to address and surmount the obstacles and limitations associated with exosome use to ensure their effectiveness and safety.

5. Conclusion

PD, a prevalent neurodegenerative disorder, is characterized by a multifaceted and incompletely understood etiology. In the quest to unravel the pathogenesis and therapeutic options for PD, exosomes have emerged as a promising entity owing to their unique targeting abilities, low immunogenicity, and efficient transportation of bioactive molecules. Regarded as a highly anticipated "emerging star" in both basic research and clinical practice, exosomes serve as crucial mediators of intercellular communication, playing a pivotal role in the progression of PD. Exploring the specific roles of exosomes in the pathogenesis of PD can deepen our understanding of the disease's fundamental nature and lay the groundwork for innovative therapeutic strategies. In clinical settings, exosomes hold significant promise for diverse applications, especially in their precise targeting of impaired neurons for personalized treatment interventions. This review scrutinizes the participation of exosomes in the pathogenesis of PD and foresees novel therapeutic approaches. By conducting in-depth investigations into the functions of exosomes in PD advancement and the formulation of potential therapeutic modalities, new avenues for enhancing PD management and elevating patient outcomes and quality of life are envisaged. Simultaneously, addressing the challenges and constraints related to exosome utilization is imperative to ensure their safety and efficacy.

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