

EXOSOMES AS MEDIATORS OF NEUROINFLAMMATION IN PARKINSON'S DISEASE: A REVIEW

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ABSTRACT

Parkinson's Disease (PD), a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons, is closely associated with neuroinflammation mediated by exosomes. This review discusses the role of exosomes in the modulation of neuroinflammatory processes in PD. Small Extracellular Vesicles (EVs) are exosomes that communicate between cells by transporting proteins, lipids, and RNAs that affect neuronal health. We investigated how exosomes propagate misfolded α -synuclein and proinflammatory mediators, leading to microglial activation and neurodegeneration. The key questions addressed include the following: (1) How do exosomes promote the spread of α -synuclein pathology? (2) What molecular pathways drive exosome-mediated neuroinflammation in PD? (3) Can exosomes serve as diagnostic biomarkers or therapeutic vehicles? By analyzing these mechanisms, this review underscores the dual role of exosomes in exacerbating disease progression and their potential for innovative treatments. This finding highlights the challenges in current methodologies and future prospects of exosome-targeted therapy in PD.

Keywords: Exosomes, Neuroinflammation, PD, Dopaminergic neurons, α -Synuclein, Glial cells, Microglia, Astrocytes, Immune response

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INTRODUCTION

Parkinson's Disease (PD) is the second most common neurodegenerative disorder worldwide after Alzheimer's Disease (AD) [1]. PD is the second most prevalent neurodegenerative disorder worldwide, affecting approximately 1% of individuals over 65 y of age, with the prevalence increasing to 1–3% in those aged 80 y or older [2]. Unraveling the complex pathogenesis of PD is urgently needed, as aging populations are expected to increase the incidence of PD by 30% by 2030 [3]. Genetic studies have identified 23 PARK genes associated with PD, and environmental factors also play a role in PD development, highlighting the heterogeneous nature of PD [4]. Glucocerebrosidase Beta 1 (GBA1) mutations are major risk factors for both Gaucher disease and sporadic PD [5]. Environmental factors, including exposure to neurotoxins such as 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), also play a role in PD development. This interplay between genetic predisposition and environmental influences highlights the heterogeneous nature of PD [6].

Research into the role of exosomes in PD is rapidly expanding, reflecting their potential importance in understanding disease mechanisms [7]. Understanding this connection is crucial, as it lays the groundwork for exploring how exosomes mediate neuroinflammatory processes in PD [8]. It focuses on the complex connection between brain inflammation and nerve cell damage [9]. Exosomes, which are nanosized extracellular vesicles important in cell communication, have gained recognition for their contribution to neuroinflammatory processes [10, 11]. In PD, α -synuclein, a characteristic proteinaceous inclusion, aggregates to activate inflammatory pathways, causing neuronal injury [12].

Exosomes have emerged as key mediators of neuroinflammation in PD, a progressive neurodegenerative disorder caused by the deposition of misfolded α -synuclein [13]. Thus, these small extracellular vesicles (which transport signaling molecules) also participate in intercellular signaling in the transit of disease-causing proteins to cause neuronal death and inflammation [14]. Research has shown that inflammatory cytokines and neurotoxic factors can be transferred into exosomes and that they can increase neuroinflammation and exacerbate PD symptoms [15]. The purpose of this review is to integrate existing evidence on the role of exosomes in facilitating these inflammatory processes, with implications for their use as biomarkers and therapeutic targets.

Significant role of exosomes in intercellular communication

Exosomes have emerged as significant mediators of neuroinflammation in PD and play crucial roles in disease

progression. Therefore, it is important to understand what functions and composition exosomes execute as a medium to communicate between cells. These particles, which are usually approximately 30 to 150 nanometers in size, are released by most cells with a nucleus and play a part in many normal and abnormal processes in the body [16, 17]. Exosomes are known to transport an extensive range of various signaling components, such as miRNAs, proteins, lipids and nucleic acids, that can influence the biological behavior and functionality of recipient cells [18].

Functions and composition of exosomes in cell-to-cell communication, neuroinflammation, and disease pathogenesis

Exosomes are recognized as vital intercellular signaling organelles that play a significant role in various physiological processes. To appreciate their contribution to neuroinflammation, examining the fundamental characteristics and functions of exosomes, which are involved in multiple physiological and pathological conditions, is essential. They are defined as nanosized noncellular membrane-bound compartments that encompass diverse loads of proteins, lipids and nucleic acids capable of altering the physiological response of the recipient cell. The synthesis of these multiple cargoes enables exosomes to regulate numerous cellular processes and regulate cellular homeostasis [19]. Owing to the ability of exosomes to transfer a wide variety and large number of biomolecules, they are ideally suited for applications in the treatment of diseases via gene and drug delivery, especially by mesenchymal stem cells [20]. In the area of neuroinflammation, exosomes are necessary for relaying signals between microglia and neurons. The release of exosomes from activated microglia is associated with specific proteins and forms of microRNAs that can shift neuronal function and lead to the beginning of neurodegenerative sickness [21]. This intercellular signaling mechanism not only helps elucidate the pathophysiology of neuroinflammation but also provides insight into the beneficial use of exosomes as biomarkers and therapeutic targets for ailments such as depression and Alzheimer's disease [22].

Exosomes are tiny extracellular vesicles that help intercellular communication and convey biomolecules. These proteins are composed of several proteins and lipids, which increase their structure and improve their functionality [23]. In fig. 1 A, the structure of exosomes is shown with their different proteins, including some Transmembrane Protein (TM) proteins such as tetraspanins [24], antigen-presenting proteins, glycoproteins and adhesion proteins. In the interior of the exosome, proteins include

Heat Shock Proteins (Hsps), proteins of the cytoskeleton, endosomal sorting complex required for transport (ESCRT) proteins, proteins for membrane transport and fusion, and growth factors and cytokines [25]. The lipid membrane of exosomes is composed of cholesterol, ceramides, sphingomyelin, Phosphatidylinositol (PI), Phosphatidylserine (PS), Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), and Gangliosides (GM), as well as RNA, mRNA, miRNA, non-coding RNA and Deoxyribonucleic Acid (DNA) [26, 27]. This ability endows exosomes with the ability to

carry out functions such as mediating cell signaling and immune modulation and to affect the interchange of genetic material in cells. As shown in fig. 1A, exosomes contain a variety of proteins and lipids that contribute to their structural integrity and functional diversity. Exosomes also mediate cell signaling and immune modulation via key transmembrane proteins, such as tetraspanins, along with internal components, including Endosomal Sorting Complex Required for Transport (ESCRT) proteins and nucleic acids (fig. 1B), and are thus released into the extracellular space.

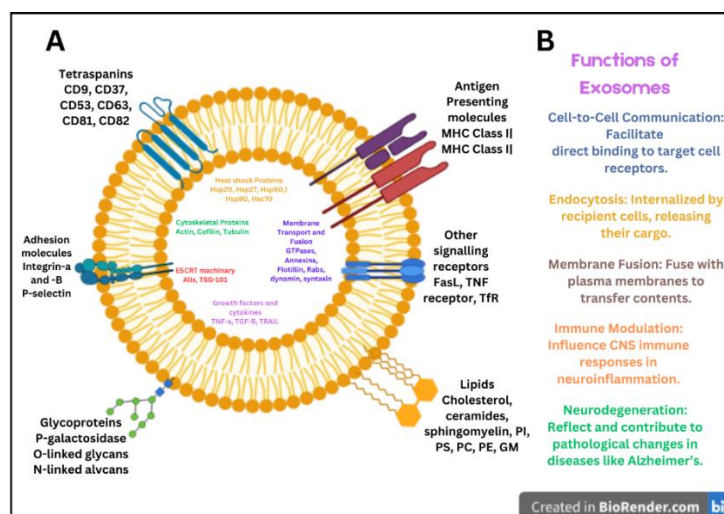


Fig. 1: Schematic representation of exosome composition and functions. (A) Illustration of the key components of exosomes, including transmembrane proteins (e. g., tetraspanins), antigen-presenting proteins, glycoproteins, adhesion proteins, Heat Shock Proteins (Hsps), ESCRT proteins, membrane transport and fusion proteins, growth factors, cytokines, cholesterol, ceramides, sphingomyelin, Phosphatidylinositol (PI), Phosphatidylserine (PS), Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), Gangliosides (GM), RNA, mRNA, miRNA, noncoding RNA, and DNA. (B) The diverse functions of exosomes in health and disease, including cell signaling, immune modulation, and genetic material exchange, are highlighted. Created in BioRender

Table 1 lists the versatile functions of exosomes involved in different biological activities, including cell signaling, neuroinflammation, and disease progression. These are isolated nanoscale vesicles known as exosomes, which act as shuttles by transporting protein and microRNA between neurons and glial cells. Cytokines such as Interleukin-1 Beta (IL-1 β) and Tumor Necrosis Factor Alpha (TNF- α) exist in exosomes and can trigger inflammation, resulting in destruction of the neural environment [28]. In addition, exosome cargo, such as Amyloid-Beta (A β) and tau proteins, has been

implicated in the development of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [29]. Consequently, Mesenchymal Stem Cell (MSC)-derived exosomes have therapeutic utility in the context of inflammation since they can modulate and enhance neuroprotection. They are also used in diagnostic tests for prodromal indicators of neurological disorders and in immunosuppression through the suppression of T-cell activation [30]. In summary, exosomes play critical roles in the molecular interactions between cells and the molecular etiology of different diseases.

Table 1: Functions of exosomes in various biological activities relevant to Parkinson's disease. The roles of exosomes in cell-to-cell communication, neuroinflammation disease pathogenesis, their potential as therapeutics, biomarkers, immune modulators, and repair mechanisms of neurons are summarized in the table

Category	Examples	Role	Ref
Cell-to-cell communication	Exosomal proteins, microRNAs	Facilitate intercellular signaling and information exchange between neurons and glial cells.	[31–33]
Neuroinflammation	Cytokines (e. g., IL-1 β , TNF- α), α -synuclein	Induce inflammatory responses, promote neurotoxic environments, and mediate immune responses	[34, 35]
Disease pathogenesis	A β , tau proteins, toxic cargo	Contribute to the progression of neurodegenerative diseases like Alzheimer's and Parkinson's	[36]
Therapeutic potential	MSC-derived exosomes	Regulate inflammation and promote neuroprotection through signaling pathways	[37]
Biomarkers	Exosomal miRNAs (e. g., miR-21, miR-146a)	Serve as potential biomarkers for early diagnosis of neurodegenerative diseases	[38, 39]
Immune Modulation	Exosomal PD-L1	Inhibit T-cell activation and promote immune evasion in tumors	[40, 41]
Neuronal Repair	Neurotrophic factors (e. g., Brain-Derived Neurotrophic Factor (BDNF))	Support neuronal survival, growth, and repair following injury or disease	[42, 43]

Review

Search methodology

The review plan is structured to analyze aspects of exosome communication in cell-to-cell interactions, neuroinflammation, and disease manifestation adequately. The research objective is to provide an

overview of the current literature concerning the biochemical content of exosomes and their roles, particularly in neuroinflammation. To identify relevant studies, a comprehensive search was conducted across several databases, including PubMed, Scopus, and Web of Science, prioritizing PubMed for its extensive coverage of biomedical literature. Sample characteristics will involve only those studies addressing topics such as

'Differential Expression of Exosome-Associated MicroRNAs in Cancer', 'Molecular Mechanisms of Exosome-Mediated Intercellular Communication', 'Role of Exosome-Associated MicroRNAs in Glioblastoma Multiforme', 'Nontumor Cell-Derived Exosomes', 'Drug Resistance in Cancer', 'Prostate Cancer Exosomes', etc. Keywords searched will include "exosomes," "neuroinflammation," and "Parkinson's Disease". Boolean operators (AND, OR) will be applied to refine the search results and limit publication dates to within the last 15 y; studies must be written in either American or British English. The study selection process will involve a two-step screening approach: first, assessing titles/abstracts electronically on the basis of inclusion/exclusion criteria, followed by full-text evaluations where necessary. To ensure the quality and validity of the included studies, the Mixed Methods Appraisal Tool (MMAT) will be used to assess the methodological rigor of each study. Variables related to exosome functions will be included on the basis of established methods ensuring sufficient data extraction accuracy. Study quality will be assessed via quality assessment checklists suitable for mixed-method studies alongside systematic quality assessments via the PICO criteria.

Neuroinflammation in Parkinson's disease

The pathophysiology of Parkinson's Disease (PD) involves the loss of dopaminergic neurons, which is primarily mediated by neuroinflammation [44]. Recent studies have revealed significantly greater levels of brain inflammation in individuals with PD than in healthy individuals; this inflammation is most pronounced in regions relevant to motor control and cognition [45].

Inflammatory response in the brain

The resident immune cells of the Central Nervous System (CNS), microglia, are key for maintaining brain homeostasis and orchestrating immune responses. However, in purified populations, they act as immune sentinels that can detect disturbances and mount inflammatory responses. Aging induces amplification and prolongation of microglial activation, which is a state of primed activation that is prolonged upon aging, suggesting a role in neurodegenerative processes. In addition to initial simplification, posttraumatic inflammation involves the activation of other glial cells, such as astrocytes, monocytes and macrophages, due to the inflammation they infiltrate from the first layer of complexity [46, 47].

Azevedo *et al.* (2018) offered an important perspective on the mechanisms of damage caused by cell death linked with fatal cases of microcephaly resulting from Zika virus infection. These findings emphasize the central role of immune cells in driving neuroinflammation and thus establish a mechanistic context for how pathogens can exacerbate or initiate inflammatory responses in the

brain [48]. Hong *et al.* (2016) reported that the immune complement system contributes significantly to synaptic loss and correlated deficits in cognition in AD patients. They reported that microglial activation and complement involvement are not just late events but also part of the pathology right in the early stages of the disease [49]. This finding agrees with that of Leng and Edison (2020), who discussed the persistent activation of microglia and their influence on AD progression and proposed that neuroinflammation is a marker and probably a pusher of neurodegeneration [50].

Peripheral immune contributions

Chronic neuroinflammation caused by both central and peripheral immune mechanisms is the pathophysiology of PD. Studies suggest that a dysfunctional Blood–Brain barrier (BBB) in PD allows peripheral immune cells to infiltrate the brain, potentially initiating or exacerbating neuroinflammation and perpetuating the degenerative process [51]. Postmortem studies of PD brains have revealed increased infiltration of peripheral immune cells, including CD4+ and CD8+ T lymphocytes, into the substantia nigra and striatum [52]. These cells may recognize misfolded α -synuclein as an antigen, perpetuating autoimmune responses. For example, Brochard *et al.* (2008) demonstrated that T-cell infiltration is correlated with dopaminergic neuron loss in PD patients, suggesting a direct link between peripheral immunity and CNS pathology [53]. Clinical studies have revealed elevated levels of proinflammatory cytokines (e. g., IL-6 and TNF- α) in the serum and Cerebrospinal Fluid (CSF) of PD patients, which are correlated with disease severity and progression. A study conducted by Qin *et al.* (2016) demonstrated that PD patients with elevated serum IL-6 levels experienced rapid deterioration of motor symptoms, which indicates that systemic inflammation affects disease progression [54].

Clinical studies have validated these findings, demonstrating alterations in the peripheral immune profiles of PD patients. These alterations include changes in the proportions and serum immunoglobulin levels of T-cell subsets, indicating the active participation of peripheral immunity in disease progression and neuronal health. Furthermore, enhanced immune activation in the peripheral system of PD patients is correlated with disease characteristics, highlighting the potential of peripheral immune responses as therapeutic targets. To provide a comprehensive therapeutic approach and modulate the immune microenvironment of PD, engineered nanoformulations bridging neuroinflammation and peripheral immune cell infiltration have been developed [55, 56]. The activation of inflammatory signaling pathways, such as the NF- κ B/NLRP3 pathway, in type 2 diabetes mellitus may increase the risk of PD, suggesting a link between peripheral inflammatory disorders and PD neuropathology [57].

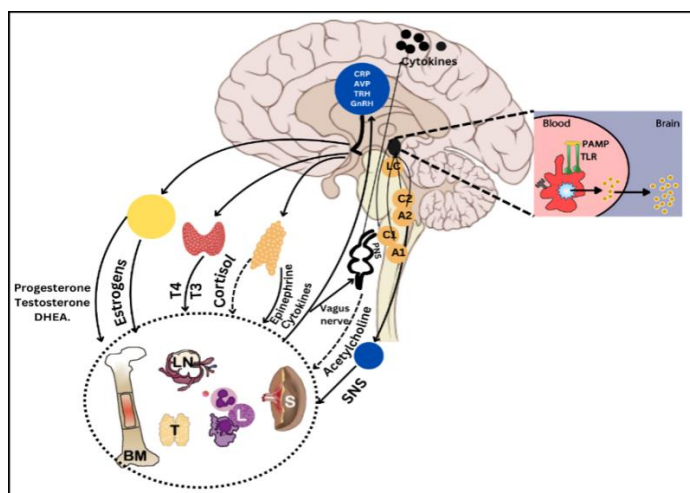


Fig. 2 illustrates the intricate network of brain-immune system pathways and feedback loops that demonstrate how physical and emotional stress interact in maintaining health. It highlights the activation of the Sympathetic Nervous System (SNS), which stimulates immune cell responses, whereas the Parasympathetic Nervous System (PNS) and the Hypothalamic Pituitary Adrenal (HPA) axis typically inhibit these immune activities. The role of cortisol is emphasized, as it provides negative feedback to the HPA axis, ensuring a well-regulated system. However, chronic activation of stress response systems arises from reduced cholinergic anti-inflammatory pathways and glucocorticoid insensitivity, leading to heightened systemic inflammation and excessive immune cell activity [58]. Cytokines play dual roles, regulating autonomic nervous system functions and inducing sickness behaviors, thus contributing to a feedback loop that affects overall health. Additionally, the afferent vagal nerve conveys information about systemic inflammation levels to the brain, particularly through a compromised blood-brain barrier. The solid lines indicate peripheral activation pathways, the dotted lines represent inhibition, and the dashed lines illustrate feedback mechanisms to the brain, collectively depicting the dynamic interplay between stress and immune responses [59].

Peripheral or neural inflammation strongly influences the overall functioning of the body. This crucial mechanism involves the activation of the immune system to eliminate injury or infection. In this process, inflammatory mediators, such as cytokines and hormones, are released, leading to healing by stimulating blood flow as well as drawing immune cells to the affected areas [60]. However, chronic or excessive inflammation can cause harm to the body, affecting different bodily systems. Systemic inflammation has been associated with atherosclerosis, a cardiovascular disease featuring inflammatory processes that contribute to plaque formation and vascular damage [61]. Neuroinflammation can also damage the BBB, allowing potent poisons to pass through and wreak havoc inside the central nervous system, leading to cognitive decline, nerve damage and mood disorders. Neurodegenerative diseases associated with inflammatory diseases include chronic diseases and Alzheimer's disease and Parkinson's disease, where inflammation exacerbates neuronal damage and accelerates disease progression. For health, then, one must maintain a balanced inflammatory response—a damaging overdoing of either acute or chronic inflammation can have a powerful influence on physical and mental well-being [62].

Immune cell activation

Resident immune cells of the CNS, microglia are central to maintaining brain homeostasis and coordinating immune responses. These cells act as immune sentinels; they can detect disturbances and initiate an inflammatory response. In aging, microglial activation not only is amplified but also persists longer than it does in young adults, suggesting a primed activated state that could be associated with neurodegenerative processes. In fact, posttraumatic inflammation also involves the activation of other glial cells, such as astrocytes, as well as multiple types of peripheral immune cells, adding additional layers of regulation and response [46, 47]. In addition, microglia orchestrate neuronal death and new generations of cells, suggesting that their opposing protective and detrimental effects contribute to outcomes after injury or disease [63]. In addition to being integral parts of the inflammatory cascade, microglia can play a critical role in neurobiological processes, meaning that, as a group in which they are activated, their activation state may define how brain health develops [64].

Cytokine release

This release of various cytokines profoundly influences neuronal behavior and brain function in general. The typical upregulation of proinflammatory cytokines such as IL-1, TNF, and IL-6 in response to stressors recruits immune cells into the brain [64]. However, anti-inflammatory cytokines such as interleukin 10 (IL-10) and transforming growth factor have the potential to control the immune response and ameliorate neuroinflammation. The balance between these cytokine types is important, with dysregulation of these types potentially leading to maladaptive responses that contribute to depression, anxiety, and neurodegeneration [47].

These studies highlight the recent interest in the involvement of microglia not only in the immune response but also in synaptic interactions and neurogenesis, with the latter two contributing to the many roles played by microglia in brain pathology [63]. Among the various cell types, their relationships with cytokines create a complex network of interactions that can initiate pathological cascades, including those featuring oxidative stress, which can add to the complex puzzle of inflammation [64].

Reactive oxygen species production

Reactive Oxygen Species (ROS) are key mediators of oxidative stress, and their production can be traced to several different cellular behaviors, such as inflammation. Thus, their production depends on the activation of immune cells and the release of cytokines, establishing an autoregulatory loop that may enhance neuroinflammatory responses [47]. The pathological consequences of the interaction of ROS with other signaling pathways, including excitotoxic neurotransmitter signaling and calcium homeostasis, constitute a nexus of pathologies that may result in neuronal damage and/or dysfunction. Oxidative stress is a result of a prolonged state of microglial activation, especially in aged brains, where this balance between neuroprotective and neurotoxic factors is disrupted, as has been shown by research [65]. On the other hand, if oxidative stress and modulated microglial activation are used as therapeutic targets, then possible treatments for neurodegenerative diseases and other diseases with chronic inflammation can result.

Mechanisms of neuroinflammation in Parkinson's disease

α -syn aggregation

The microscopic analysis of aggregated proteins has been linked with neurodegenerative diseases such as Parkinson's disease through a protein called α -synuclein (α -syn) [66]. It is hypothesized that inflammation may serve as a prerequisite for the development of α -syn pathology since activated microglia release several neurotoxic factors, including reactive oxygen species and the proinflammatory cytokines IL-1 β and TNF- α [67]. These inflammatory responses not only mediate neuronal damage but also promote the misfolding and aggregation of α -syn. The pathological forms of α -syn can be internalized by neurons and induce the misfolding of endogenous α -syn and, thus the formation of neurotoxic aggregates. The continuing controversy about the source of α -syn triggering, the gut or the brain, shows that its pathology is multifaceted and may involve both systems in the development of synucleinopathies [68, 69]. Awareness of these mechanisms is important for designing possible remedial approaches directed at regulating inflammation and its impact on neurons.

Microglial activation

Microglia, which are the main immune cells of the central nervous system, can be activated by several factors, including misfolded proteins such as α -synuclein and products from proinflammatory bacteria. Mature α -synuclein is positive for the proteins TLR2 and TLR4, indicating that oligomeric α -synuclein acts as an agonist of TLRs. Stimulation of these receptors causes neuroinflammation and neurodegeneration. Specifically, the administration of an anti-TLR2 antibody that prevents α -synuclein binding significantly ameliorated α -synuclein-induced aggregation and consequent behavioral dysfunction in animal models of PD [70]. However, Lipopolysaccharides (LPSs), components of the bacterial cell wall that can activate microglia, are also able to affect microglial activation. Thus, the findings of the present study support previous findings that LPS treatment augments microglial activation and that hesperidin's ability to dampen this effect highlights avenues through which neuroinflammation might be manipulated [71]. Furthermore, α -synuclein accumulation in the human brain is associated with the activation of microglia, which underscores the relationship between protein misfolding and inflammation [72]. Major Histocompatibility Complex Class II (MHCII) and Poly (ADP-ribose) Polymerase (PARP) have been examined in the process of microglial activation. Research has demonstrated that the suppression of microglial activation by α -synuclein when MHCII and PARP are blocked is therefore, an essential component of the inflammatory cascade involving misfolded proteins [73]. In addition, crosslinking/interlinking, Janus

kinase/signal transducer and activator of transcription (JAK/STAT) signaling has also been associated with neuroinflammation, and it

has been proposed that the inhibition of this signaling pathway can prevent microglial activation [74].

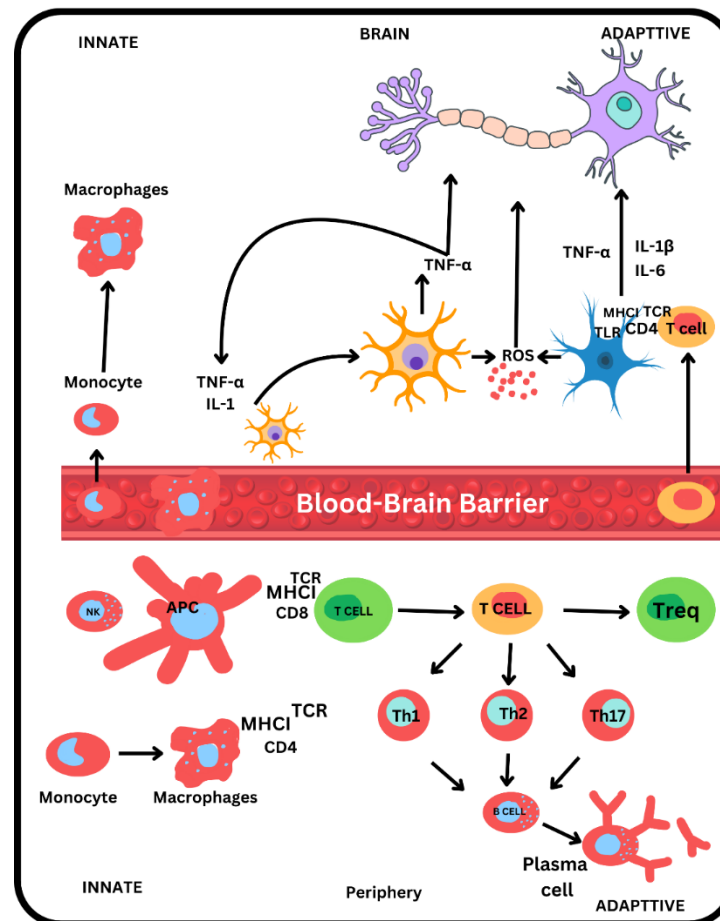


Fig. 3: Simplified reviews of the dynamic immune system. In the innate system, mast cells, neutrophils, Natural Killer (NK) cells and monocytes can transform into macrophages. There are Toll-like Receptors (TLRs) on these cells for pathogen recognition. Macrophages and dendritic cells are critical essential links in the activation of adaptive immunity. Inflammasomes (e. g., NOD-, LRR-and Pyrin Domain Containing Protein 3 [NLRP3]), which are expressed in monocytes, macrophages, granulocytes, dendritic cells, and microglia, secrete proinflammatory cytokines. The differentiation of naïve T cells in the periphery is determined by cytokine conditions. Naïve CD8+T cells further develop into cytotoxic lymphocytes; Th1 and Th17 cells are helper cells of the proinflammatory state, whereas Th2 and Treg cells are in the inflammatory state. A greater concern is that each T-cell type produces different cytokines. Specific T cells help with the help of B cells, which in turn become effector or plasma cells that secrete antibodies. There is evidence that B and T lymphocytes and other immunocytes can penetrate the CNS. Macrophages play the same role in the brain as microglia do. These naked cells, which are more abundant than microglia, have homeostatic functions and pathogen/injury responses but can produce noxious free reactive oxygen species (ROS). Created in Canva

T-cell activation and dysregulation

T-cell-mediated dysfunction also actively contributes to neuronal cell death, which occurs through MHC II on microglia to present antigens to T cells. A lack of MHCII provides resistance to α -syn-related toxicity. Mice depleted of functional T cells or with SCID (T and B-cell deficiency) are resistant to parkinsonism caused by MPTP-mediated neurodegeneration. Higher numbers of T cells that react to α -syn peptides in humans with PD than in cord-blood donors, for example, have been described [75]. The blood from 1 person with PD indicated that α -syn-specific T cells are present a decade prior to sign manifestation and diagnosis; cohort analyses revealed that subjects with increased α -syn T-cell reactivity are more recently diagnosed with PD [76]. Although we are studying the relationship between α -syn and autoimmunity, the precise function of α -syn-specific T cells remains unclear. Other researchers have reported reduced Tregs in patients diagnosed with PD as well [76]. Tregs control the aberrant helper T-cell hierarchy, which results in proinflammatory conditions; thus, Tregs are crucial for immune modulation. Another subtype of T-helper has been implicated in autoimmunity; Th17 cells and Th17 cells

have been implicated in the pathogenesis of PD. Th17 cells express the indicator cytokine IL17A, and this cytokine has many effects, including the induction of the differentiation of B cells into plasma cells that produce antibodies [77].

Exosome release in Parkinson's disease

PD is a major neurodegenerative disorder in which misfolded α -synuclein is deposited in neurons, Lewy bodies initiate the loss of neurons, and several motor and nonmotor symptoms occur. Recent studies have focused on exosomes, which are small, membrane-bound particles involved in the exchange of cellular products and are potentially essential for PD development. Exosomes contain proteins, lipids, mRNAs and microRNAs, which play a role in disease development [78, 79]. The extracellular release of exosomes from neurons, astrocytes and microglia into the brain fluid implies that they play a critical role in the spread of pathological α -synuclein across the brain. This transmission takes place when the exosomes transport α -synuclein aggregates to adjacent cells and may induce neuroinflammation and enhance neurodegeneration [80].

Exosomes are intracellular signaling organelles that are regarded as the official transporters of cellular waste products such as misfolded proteins in the human body. Research on the mechanisms of exosome release in the context of PD and their roles has focused on disease progression and potential for treatment planning. Taken together, one of the main findings is that microglial exosomes promote the development of α -synuclein pathology in PD. These exosomes can promote protein misfolding in neurons and are involved in inflammation, suggesting the possibility of organizing treatments aimed at microglial exosomes [81]. The toxic gain of function due to oligomer accumulation at presynaptic terminals, which results in synaptic impairment and possibly neurodegeneration, underlines the function of α -synuclein in neurotransmission [82]. This raises a significant concern as to whether exosomes may facilitate the transmission of α -synuclein aggregates through synthetic neural circuits and thereby enhance disease pathogenesis.

Furthermore, the participation of exosomes in extracellular release underlies their usefulness in cellular catabolism and signaling. This phenomenon is relevant where diseases are characterized by neurodegeneration, and maintaining cellular homeostasis is important [83]. The modulation of autophagy-lysosome pathways affects the secretion of α -synuclein through extracellular vesicles; therefore, these pathways are integral in controlling the incorporation of exosomes and synucleinopathies [84]. This link between autophagy and exosome release raises the idea of intervention for the intensity arising from α -synuclein in PD.

Role of exosomes in Parkinson's disease

There are two main mechanisms underlying the contribution of exosomes to the pathogenesis of PD. First, they facilitate the intercellular transfer of α -synuclein (α -syn), which is essential for the development of PD. This occurs since exosomes, which are tiny vesicles produced within cells, can transport misfolded α -syn from one neuron to another, leading to the progression of disease-related processes. It is, therefore clear that exosomes play a crucial role in the transfer of neurotoxic signals.

Second, exosomes transport miRNAs that are known to be involved in PD [85]. These small noncoding RNAs, which functionally regulate the expression of individual genes at the level of translation, can be encapsulated in exosomes and transferred to other cells to affect their function and possibly assist in the pathogenesis of PD [86]. The sorting and loading of miRNAs into exosomes are very well-controlled mechanisms that enable cells to selectively communicate with one another and thus participate in numerous biological processes related to PD [87].

α -Synuclein, autophagy and exosomes

The interplay among α -synuclein, autophagy, and exosomes has garnered increasing interest in neurodegenerative research, especially in relation to Parkinson's disease (PD) and related disorders [88]. α -Synuclein is a presynaptic protein implicated in the pathogenesis of PD due to its aggregation propensity with subsequent cellular dysfunction [89]. Recent findings have revealed the roles of both the autophagic pathway and the exosome pathway in mediating the effects of α -synuclein on neuronal health and disease propagation. One of the major discoveries in this context was the fact that α -synuclein is resistant to degradation, leading to a significant blockade of autophagic processes due to the inhibition of autophagosome maturation (Choi *et al.*, 2019) [90]. Furthermore, microglia can eliminate neuron-released α -synuclein via selective autophagy as an important protective mechanism against neurodegeneration, indicating that the activation of autophagic clearance could be used as a therapeutic approach against α -synuclein aggregate-mediated toxicity in PD. However, under pathological conditions, increasing evidence has also demonstrated that α -synuclein accumulation impairs normal autophagic function, suggesting the existence of a pathogenic feedforward loop that exacerbates neurodegeneration.

Moreover, exosomes have recently been shown to function as mediators of intercellular α -synuclein transmission. Danzer and

colleagues (2012) demonstrated that exosomal cell-to-cell transmission of α -synuclein oligomers is possible, suggesting a mechanism for the intercellular propagation of toxic species within the CNS. This discovery raises questions regarding the potential role of exosomes not only in the spread of pathology but also in the potential clearance of toxic proteins. The fact that exosomes are vehicles for both pathological forms of α -synuclein and candidates for their removal underscores a complicated relationship that is poorly understood at present [91].

Another important aspect of this interplay is the relationship between lysosomal dysfunction and impaired autophagy and α -synuclein pathology. Mazzulli *et al.* (2016) reported that the loss of ATP13A2 results in a defect in lysosomal degradation in human fibroblasts and primary neurons, thereby establishing the role of lysosomes in α -synuclein turnover. This finding concurs with earlier theories that the genetic factors and the cellular pathways known to be involved in the accumulation of α -synuclein may be directly related to lysosomal dysfunction in the case of synucleinopathies [92].

Moreover, Shi *et al.* (2014) established that autophagy and exosomes are closely associated since plasma exosomal α -synuclein is upregulated in Parkinson's disease and possibly originates in the CNS. This highlights the possibility of using exosomal α -synuclein as a biomarker for disease progression, demonstrating that exosomes may be involved in the clearance or spread of misfolded proteins [93].

However, several gaps in knowledge still exist. For example, the detailed molecular, cellular and physiological roles of α -synuclein in the regulation of autophagy and lysosomal degradation processes have not been elucidated. Furthermore, these findings indicate the need to further elucidate the anti-neuroinflammatory effects of exosomes related to α -synuclein pathology. More investigations into these mechanisms should be conducted in the future, as well as further studies to define potential treatments that might interfere with autophagy and exosomes and how genetics and the environment influence α -synuclein-dependent neurodegeneration.

Exosomes and miRNAs

Exosomes are small membrane spheroids measuring between 30–150 nm and are seen within signal cell entities most likely engaged in intercellular communication by transmitting microRNAs (miRNAs). Small secretory vesicles are secreted from different types of cells and are known to pack a wide range of biomolecules, such as proteins, mRNAs and miRNAs, which can strongly affect the physiological and pathophysiological response of recipient cells. This is because recent research has suggested that exosome-mediated miRNA transfer is indeed a basic mechanism of intercellular communication, and as such, exosomal miRNAs in biofluids could be useful minimally invasive biomarkers for many human diseases, as supported by Gurunathan *et al.*, 2019 [94].

Nonetheless, a reformulation of the current understanding of the time course of exosome-associated miRNAs is necessary. For example, one study revealed that standard preparations of exosomes yield low amounts of only a few specific miRNAs and questioned current models of a high and universal payload of miRNAs in exosomes [95]. These results support the need for quantitative studies of miRNA copy number within exosomes and other EVs to fully understand intercellular communication. Specific examples of the functional consequences of exosomal miRNAs in diverse biological systems are demonstrated. For example, ESC-derived exosomes transferred miR-294 to CPCs, which improved their viability, proliferation and overall CPC regenerative potential after myocardial infarction [96]. Furthermore, the let-7 miRNA family is selectively secreted in the extracellular environment embedded in exosomes, and such exosomal miRNAs might serve as new biomarkers of metastatic gastric cancer [97].

In addition, exosomes are involved in epigenetic regulation and cell signaling since they transport essential genetic factors such as miRNAs, which can alter resident mRNAs in target cells [98]. Exosomes enable the transfer of miRNAs that can modulate several cellular activities, such as angiogenesis and senescence [99]. This aspect is important specifically with respect to cancer, in which

exosomal miRNAs have been deemed diagnostic and treatment indicators [100]. However, several areas remain unidentified, even though the roles of exosomal miRNAs in cell signaling and pathological conditions have been extensively examined. For example, how miRNAs are sorted into exosomes is still a mystery. Moreover, the difference in miRNA signal intensity within different exosome populations requires further study to determine the best method for exosome sample preparation and identification [101].

In future studies, it may be important to evaluate whether certain profiles of miRNAs are biologically relevant for exosomes released from different cell types in health and disease. There is also a future direction that can be explored; the relationship between exosomal miRNAs and their target mRNAs in recipient cells may also provide additional functions. Moreover, the ability to create novel therapeutic approaches using miRNA inhibitor-delivered exosomes could have potential for eradicating drug resistance in cancer treatment [102].

Therapeutic potential of exosomes in Parkinson's disease

PD is a chronic degenerative neurological disease characterized by motor and nonmotor symptoms due to the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Current research has drastically targeted exosomes as carriers of drugs, especially siRNAs, to reduce α -Syn aggregation, which is characteristic of PD. Zheng *et al.* (2010) demonstrated that vehicles formed through RVGs embedded in exosomes can effectively target brain tissue and delay and reverse α -Synuclein-induced neurodegeneration [103]. This new strategy highlights the importance of the use of exosomes to induce gene therapy procedures, which might change the dynamics of illnesses. In addition to exosomal delivery systems, neurotrophic factors, including brain-derived neurotrophic factors, may be used for

PD treatment. According to the evidence reviewed by Jiang *et al.* (2016), high BDNF levels due to gene modulation or exercise promote neuroprotective effects. These data indicate that enhancing Brain-Derived Neurotrophic Factor (BDNF) signaling could be used to extend exosomal therapies in a bidirectional manner to promote neuronal protection against oxidative stress and degeneration in PD [104].

There are several possible therapeutic strategies based on exosome-derived factors for the treatment of Parkinson's disease. The relative advantages and disadvantages of several approaches, including hucMSC-derived exosomes, SHED-derived exosomes, DPSC-derived exosomes, stem cell therapy and the use of genetically modified macrophage-derived exosomes, can be compared. Both strategies yield similar results, but SHED-derived exosomes and genetically modified macrophage-derived exosomes had the highest percentages. To date, these findings shed light on the future application of exosome-based therapy for enhancing neuroprotection, encouraging neuronal differentiation and crossing the blood-brain barrier, as well as more advanced treatments for Parkinsonism diseases.

The comparative effectiveness of various therapeutic methods shows how effective the different approaches that utilize exosome-derived therapeutic approaches in Parkinson's disease are in the article titled "Effectiveness of various exosome-derived therapeutic approaches in Parkinson's disease". The effectiveness of hucMSC-derived exosomes is 70% [105], that of SHED-derived exosomes and DPSC-derived exosomes is 80% [106], that of stem cell therapy is 60% [107], and that of genetically modified macrophage-derived exosomes is the highest, at 85% [108]. This comparison suggests that an exosome-based therapeutic paradigm shift has a bright future for treating PD, particularly in the context of genetically modified macrophage-derived exosomes.

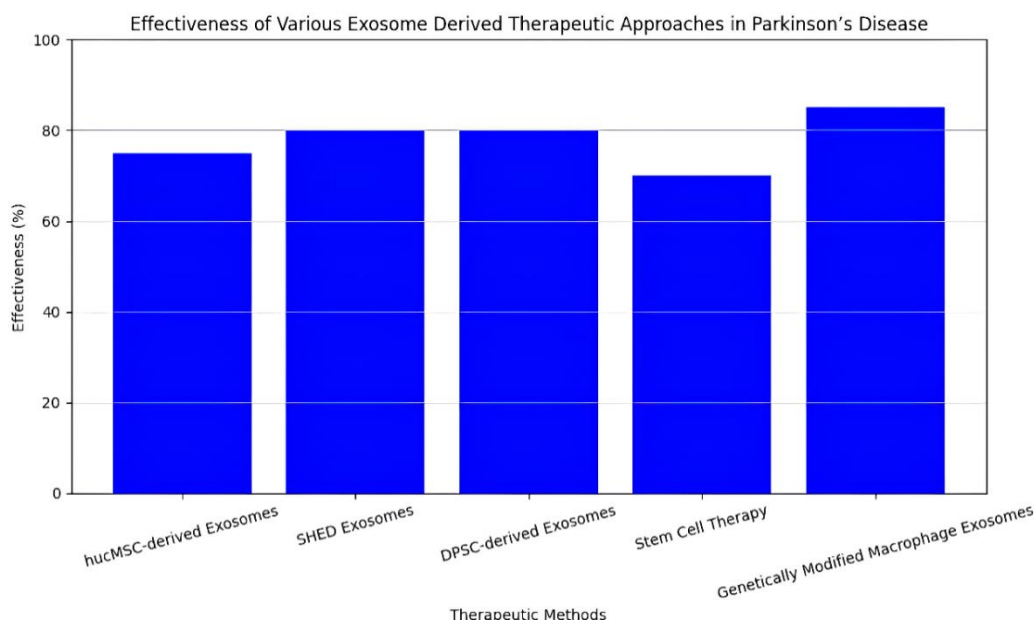


Fig. 4: Effectiveness of various exosome-derived therapeutic approaches for Parkinson's disease [105–108]

Exosome-based drug delivery

Targeting inflammatory pathways

In one study, inflammation continued to play a role in the development of Parkinson's disease. Microglia and astrocytes become activated and begin secreting proinflammatory cytokines, resulting in enhanced neurodegeneration. Mesenchymal Stem Cells (MSCs), the exosomes of MSCs, have been shown to potentially modulate these inflammatory signaling pathways. MSCs possess significant anti-inflammatory properties that can effectively intervene in the immune response within the CNS. Moreover, MSC-

derived exosomes may be used to decrease the levels of inflammatory cytokines, including TNF- α and IL-1 β , in PD models. In this case, the exosome transport of anti-inflammatory molecules will reach neurons that have been exposed to chronically toxic inflammation. This approach also downregulates inflammation and safeguards dopaminergic neurons from apoptosis to enhance motor and general neurological function [109].

Neuroprotective approaches

Exosomes can target inflammation and provide neuroprotective effects as a result of the various mechanisms by which they can. A

one promising strategy involves loading exosomes with neuro-protectant agents such as antioxidants or neurotrophic factors, for example, investigators have demonstrated that administering exosomes containing catalase, an antioxidant that destroys hydrogen peroxide can decrease oxidative stress in neuronal cells [110]. Lipid peroxidation is one of the major conditions that causes neuronal loss in PD, resulting in mitochondrial disorders and apoptosis [111]. Researchers believe that antioxidants can help counteract oxidative damage and therefore improve cell survival if delivered to the neurons in question via exosomes. Previous *in vitro* experiments have also shown that DOX-loaded exosomes strongly increase neuronal survival under oxidative stress [112]. Another method involves the use of exosomes to carry neurotrophic factors such as GDNF or BDNF. All these factors play significant roles in neuron survival and proper functioning [113]. Preclinical understanding of the ability of GDNF delivered in exosomes to increase the survival of dopaminergic neurons, as well as improve motor skills, has been successful in experimental models of PD. In addition, exosomes can enhance the clearance of toxic proteins involved in PD, such as alpha-synuclein proteins [114]. By promoting the clearance of such aggregates from the extracellular space, exosomes can potentially decrease neurotoxicity and increase the viability of neurons.

Modulating exosome release and cargo

While exosome-based drug delivery holds great promise for treating PD, optimizing their release and cargo is crucial for maximizing therapeutic efficacy [115].

Manipulating exosome biogenesis

Exosome biogenesis is a well-orchestrated process in which the multivesicular body from the endosome is formed by inward budding rather than fusing with the plasma membrane for the release of exosomes into the extracellular milieu [116]. This process can be manipulated to increase the production, as well as the therapeutic efficiency, of exosomes. The first concerns the regulation of proteins that are involved in the formation of exosomes, including tetraspanins or Rab GTPases [117]. For example, enhancement of certain tetraspanins, such as CD63 or CD81, enhances the release of functional exosomes from different types of cells. This improvement could result in increased payload density of the therapeutic cargo in the liberated exosomes [118]. Moreover, for the development of new therapeutic approaches, researchers are searching for substances that promote pharmacological agents or genetic modifications, creating preconditions for MVB formation and exosome release [119]. Substances that stimulate signaling pathways involved in endosomal transport may increase exosome shedding and extend their application in the healing process [120].

Exosome content engineering

The third component of the process of using exosomes in PD therapy is engineering their content [121]. Owing to the nature of exosomes, in which specific molecules are loaded selectively for form and function, the latter potentially holds keys to several therapeutic strategies. One method is to use an electroporation technique or ship Small Interfering RNAs (siRNAs) or miRNAs into exosomes for gene regulation processes [122]. For example, the utilization of miRNA-incorporated exosomes directed toward genes involved in alpha-synuclein production could be utilized to decrease the levels of toxic proteins in PD patients [123]. However, efforts are being made by researchers to improve the loading stability and control the release profile of therapeutic cargo encapsulated in exosomes. Lipid formulations that shield molecules from degradation during circulation may increase molecule bioavailability once they reach target cells [124]. Furthermore, the engineering of surface markers on these exosomes can improve their targeting functionality. Thus, linking surface proteins or lipids with ligands to target receptors on dopaminergic neurons or activated microglia enables researchers to increase target binding and reduce side effects [125].

Challenges and limitations of exosome-based therapies

Exosome-based therapies represent a promising frontier in regenerative medicine and targeted drug delivery, yet they are beset by significant

challenges and limitations that hinder their clinical application. However, one of the leading problems is that exosome production is characterized by low yield and efficiency. Harvesting less than 1 µg of exosomal protein from 1 ml of culture medium is a substantial barrier to scale-up for therapeutic use [126]. Furthermore, the inherent heterogeneity of exosomes in terms of size, content and surface markers makes this complex problem of both isolating and purifying them. Despite popular current methods, such as ultracentrifugation, which is considered the gold standard, these methods are time-consuming, costly and prone to lipoprotein contamination [127]. Furthermore, no single isolation technique is universally applicable; each method has its own advantages and disadvantages that can affect the purity and physicochemical properties of the exosomes [128].

Another critical limitation is the rapid clearance of exosomes from circulation, primarily due to their uptake by macrophages in the mononuclear phagocytic system. Exosomes typically have a half-life ranging from 2-30 min in circulation, which significantly restricts their therapeutic efficacy. Therefore, engineering strategies must be applied to provide stability to prolong the circulation time. For example, exosome surfaces overexpressing CD47 have been shown to increase their half-life threefold by escaping phagocytosis. However, these modifications can also lead to increased aggregation and potential immunogenicity, complicating their therapeutic application [129].

The other major hurdle is targeting specificity. However, the natural targeting capabilities of exosomes from their cellular origin are usually insufficient for specific tissue or tumor site delivery. Owing to the lack of precise targeting, off-target effects and poor therapeutic outcomes can occur [130]. To address this, researchers are exploring various engineering techniques to modify exosome surfaces for enhanced targeting; however, achieving optimal specificity while maintaining biocompatibility remains a challenge [131].

Moreover, the scalability of production methods poses significant practical challenges. Most current methods for manufacturing clinical-grade exosomes do not meet the required standards for scale-up production. Batch-to-batch variability can cause inconsistency and reliability of therapeutic products because of the lack of a reproducible protocol [126, 131]. Additionally, the choice of cell source for exosome production can influence their biological activity and therapeutic efficacy; thus, careful consideration must be given to selecting appropriate donor cells [128, 132].

Future directions for research

Exosomes are associated with the propagation of pathological alterations and are potential therapeutic targets in PD. These routes of membrane-bound nanovesicles involve the transfer of proteins, lipids, mRNAs and microRNAs across cells, which can profoundly change the inflammatory milieu of the CNS [133]. In PD, misfolded α -synuclein, one of the major hallmarks of the disease, is conveyed through exosomes. This transmission provokes neuroinflammation in glial cells, which possibly contributes to worsening neuronal injury and the course of the disease. However, several questions emerged from the present study concerning exosomes and PD. Although the findings of the present study corroborate the claims of prior studies suggesting that exosomes are involved in the progression of the disease, there are still certain factual issues that remain unexplained [78]. These gaps are as follows: first, the precise molecular processes through which exosomes participate in neuroinflammation; second, the exploration of the potential therapeutic exploitation of exosomes is needed. For example, exosomes deliver proinflammatory signals, and while they are implicated in almost every stage of PD pathology, much work is still needed to determine their specific contributions [134]. Future directions may include investigating exosomes as diagnostic tools for early detection of the disease and for tracking disease progression in response to treatment, as well as the therapeutic application of exosomes for delivering anti-inflammatory agents to neuroinflammation sites. Taken together, further investigations of exosome functions may provide novel approaches for the treatment and treatment of demyelinating diseases, including Parkinson's disease [15].

CONCLUSION

Parkinson's disease (PD) is driven by a complex interplay of neuroinflammatory mechanisms, with exosomes emerging as

central players in propagating pathology and amplifying neurodegeneration. These extracellular vesicles facilitate the spread of misfolded α -synuclein aggregates and proinflammatory mediators, activating microglia, perpetuating oxidative stress, and accelerating dopaminergic neuron loss. Beyond PD, exosomes may underpin shared pathogenic pathways in neurodegenerative disorders such as Alzheimer's and Huntington's diseases, highlighting their universal role in protein misfolding and immune dysregulation. Clinically, exosomes hold dual promise: as noninvasive biomarkers for early diagnosis and as engineered carriers for brain-targeted therapies. Innovations in exosome isolation, cargo modification, and delivery systems are paving the way for interventions that disrupt disease progression. Short-term priorities include standardizing isolation protocols and validating biomarkers in longitudinal cohorts, whereas mid-term goals focus on preclinical optimization of exosome-based therapies. Long-term translation hinges on clinical trials evaluating safety and efficacy alongside personalized approaches tailored to individual patient profiles. Challenges persist, including improving exosome specificity, quantifying cargo, and understanding their crosstalk with mitochondrial dysfunction and oxidative stress. Addressing these gaps will unlock the full potential of exosomes as diagnostic and therapeutic tools. By bridging mechanistic insights with clinical innovation, exosome research offers transformative strategies to mitigate neuroinflammation, halt neurodegeneration and redefine treatment paradigms for PD and related disorders.

ABBREVIATIONS

Alzheimer's Disease (AD), Amyloid-Beta ($A\beta$), Blood-Brain Barrier (BBB), Brain-Derived Neurotrophic Factor (BDNF), Central Nervous System (CNS), Deoxyribonucleic Acid (DNA), Endosomal Sorting Complex Required for Transport (ESCRT), Small Extracellular Vesicles (EVs), Glucocerebrosidase Beta 1 (GBA1), Ganglioside GM1 (GM1), Heat Shock Proteins (Hsps), Interleukin-1 Beta (IL-1 β), microRNA (miRNA), Mixed Methods Appraisal Tool (MMAT), Messenger Ribonucleic Acid (mRNA), 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), Mesenchymal Stem Cells (MSC), Phosphatidylcholine (PC), Parkinson's Disease (PD), Programmed Death-Ligand 1 (PD-L1), Phosphatidylethanolamine (PE), Phosphatidylinositol (PI), Population, Intervention, Comparison, Outcome (PICO), Phosphatidylserine (PS), Ribonucleic Acid (RNA), Transmembrane Protein (TM), Tumor Necrosis Factor Alpha (TNF- α), Mesenchymal Stem Cell (MSC)

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AUTHORS CONTRIBUTIONS

Mujibullah Sheikh conceptualized and finalized the review, supervised the literature analysis and acted as the corresponding author. Arshiya Saiyyad conducted literature searches, analyzed the data, and drafted key sections of the manuscript. Pranita S. Jirvankar contributed to the methodology, validated the data, and drafted the technical sections, ensuring scientific accuracy.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest, financial or otherwise.

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