Mesenchymal Stem Cell-Derived Exosomes and Their Therapeutic Potential on Parkinson's Disease

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Abstract

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra, resulting in dopamine depletion and a spectrum of motor and non-motor symptoms in patients. Mesenchymal stem cells (MSCs) have garnered attention for their therapeutic potential across various diseases. They can differentiate into various cell types, including dopaminergic cells, and secrete neurotrophic and anti-inflammatory factors with robust neuroprotective properties. In PD, midbrain dopaminergic neurons express miR-133b, a crucial regulator of tyrosine hydroxylase and dopamine transporter synthesis. MSCs facilitate interactions with brain parenchymal cells by transferring miR-133b via exosomes, promoting neurite outgrowth and functional recovery. Notably, studies have demonstrated elevated dopamine levels and its metabolites in the striatum of PD rats following treatment with these exosomes. This review examines mesenchymal stem cell-derived exosomes, their unique attributes, and their potential as a promising therapeutic avenue for PD.

Key Terms: Parkinson's disease, substantia nigra, dopamine, stem cells, mesenchymal stem cells, exosomes, MSC-EXOs, nanovesicles, microRNAs

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1 Introduction

Parkinson's disease (PD) is a neurodegenerative disease known for its relentless attack on a specific type of brain cell called dopaminergic neurons in the substantia nigra. This attack leads to a shortage of dopamine in the brain, causing a wide range of motor and non-motor symptoms. PD puts a heavy burden on thousands of patients every year, and there is yet a cure for this disease to be found. [Elb16]. There remains a demand for new and innovative treatments in the field.

Scientists in the field of regenerative medicine are exploring the therapeutic potential of mesenchymal stem cells (MSCs). These cells carry a high potency, being able to differentiate into various types of cells, including dopaminergic neurons lost in PD patients. Furthermore, MSCs release substances that can protect neurons and reduce inflammations caused by a variety of neurological disorders. [Ven17]. This review closely examines the connection between PD and MSCs, focusing on exosomes derived from mesenchymal stem cells (MSC-EXOs).

MSC-EXOs are nanovesicles released by MSCs, containing substances such as microRNAs, growth factors, and anti-inflammatory molecules. [Yu14]. These substances make MSC-EXOs specifically great for protecting nerve cells. Specifically, the microRNA miR-133b plays a crucial role in controlling dopamine production. In PD, MSC therapies have been shown to act as messengers by passing miR-133b using MSC-EXOs, which further encourage the growth of nerve fibers and neurological functions. [Xin12].

This review aims to summarize how MSC-EXOs can be used in treating PD, explaining the connection and science behind the existing successful studies regarding them and laying the groundwork for future research and development in this field.

2 Parkinson's disease and MSC-EXOs

2.1 Parkinson's disease

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease affecting elderly people, with an estimated occurrence of 1 to 2 people in a 1000-person population at any given time. The pervasiveness of PD increases with age, impacting approximately 1 percent of the elderly population

above 60 years. [Tys17]. The disease is initiated by the loss or degeneration of dopaminergic neurons located in the substantia nigra region of the midbrain, alongside the creation of Lewy bodies. These Lewy bodies are associated with abnormal deposits of the alpha-synuclein protein in the brain, causing damage to the brain's cognitive abilities and triggering dementia. [niand]. PD risk factors include aging, family history, pesticide exposure, and environmental chemicals. [Bei14]. PD displays both motor and non-motor symptoms, ranging from tremors and rigidity to depression and anxiety. Patients with PD also face an elevated risk of developing dementia. Although surgical procedures like deep brain stimulation (DBS) and various pharmaceutical therapies have increased in recent decades, there remains a pressing need for the development of effective and accessible disease-modifying medications.

2.1.1 Clinical Presentation

Currently, there is no conclusive diagnostic test to detect PD, necessitating clinical criteria for diagnosis. The four main PD symptoms are rest tremor, bradykinesia, rigidity, and loss of postural reflexes. [Jan08]. These presentations can be used to distinguish PD from other motor and neurodegenerative diseases. The clinical presentation of PD can be categorized into motor and non-motor symptoms. Beyond the motor symptoms, individuals with PD may also manifest a spectrum of non-motor symptoms, such as autonomic dysfunction, neuropsychiatric abnormalities, sleep disturbances, sensory abnormalities, anosmia, and dementia. [Pfe16].

a. Motor Symptoms

A notable slowness of movement in affected patients can describe bradykinesia. The factors involved with bradykinesia are muscle weakness, rigidity, tremor, movement variability, and slowness of thought. Patients find it difficult to control the accuracy and speed of their movements. [Ber01]. Rigidity is another defining characteristic of PD, defined by a significant, velocity-independent increase in muscle activity. Patients experience stiffness and involuntary tightness in their muscles. [Bol20]. Tremor, one of the most prevalent motor symptoms of PD, is described by uncontrolled shaking in the patient's body. In PD, tremors typically occur at rest, a condition known as 'tremor-at-rest.' Though tremor begins asymmetrically throughout the body, both sides of the body can become affected as the disease progresses. [Abu22]. Gait dysfunctions also emerge during the early stages of PD, including symptoms such as a slowing of gait, lack of arm swing, shorter steps, postural instability, and reduced trunk movements. Patients are more likely to be at risk of falls due to increased gait, with studies showing that 70 percent of PD patients fall at least one time a year, while 39 percent suffer from recurring falls. [Kim18].

b. Non-Motor Symptoms

Although PD is still primarily diagnosed based on motor symptoms, neuropsychiatric signs and symptoms are increasingly recognized to have equal relevance in many patients. As a result, PD can now be conceptualized as a complex neuropsychiatric disorder. The indicators and symptoms fall into three major categories: affect (such as anxiety and depression), perception and thought (such as psychosis), and motivation (such as impulse control disorders and apathy). [Wei22]. Another non-motor manifestation of PD is autonomic dysfunction, which includes gastrointestinal dysfunction, cardiovascular dysregulation, urine disruption, sexual dysfunction, thermoregulatory aberrance, and pupillo-motor and tear abnormalities. [Che20b]. The regulation of sleep and wakefulness depends on the coordinated and highly complex operation of numerous brain regions and neurotransmitters, many of which have been demonstrated to be compromised in people with PD. Given this pathophysiological context, it is not unexpected that sleep and wakefulness problems are virtually always present in PD patients. [Ste20]. A survey study in 1988 revealed that 98 percent of PD patients had disabilities at night or upon waking since the onset of their disease, and disturbed wakefulness regulation was shown to be a prominent feature in up to 30 percent of PD patients. [lee88]. Additionally, sensory symptoms are prevalent in PD, which generally tend to affect the side of the body that was first or more severely disrupted by the motor fluctuations. These symptoms include musculoskeletal pain, dystonic pain, akathisia, CNP, olfactory disturbance, and visual dysfunctions. [Zhu16]. Other underappreciated non-motor aspects of PD are anosmia, the loss of smell, and aguesia, the loss of the sense of taste. [Tar17]. Many PD patients also suffer from cognitive deficits, with a systematic review revealing that 36 percent of newly diagnosed patients suffer from cognitive impairment. [Aar05]. This condition, known as Parkinson's disease dementia (PD-D), is primarily associated with older age at the disease onset or time of evaluation. [Han17]. In addition to cognitive dysfunctions, the clinical features of PD-D include behavioral symptoms, autonomic dysfunctions, sleep disorders, and parkinsonism. [Sez19].

2.1.2 Etiology and Epidemiology

PD stands as the most prevalent neurodegenerative disease after Alzheimer's. It is a multifactorial disease influenced by numerous risk and protective variables, including genetic and environmental factors. While classified as a rare disease, the incidence of PD is predicted to quadruple by the year 2030, primarily driven by the aging demographic of the population. [Elb16].

It has been observed that men are more susceptible to PD compared to women. The meta-analysis results of 7 door-to-door studies show that the ratio

of male-to-female PD cases is 1.49, with a 95 percent confidence interval between 1.24 and 1.95. [Woo04]. Several factors have been proposed as potential explanations for this gender difference, including the protective effects of estrogens, the higher frequency and intensity of occupational toxin exposure, more prevalent minor head trauma in males, and recessive susceptibility genes of the X chromosome. [Wir11a]. Studies also show that the risk of death in PD differs between men and women, estimated at 2 percent for men and 1.3 percent for women. Overall, the mortality risk was estimated at 1.7 percent after age 40, and the gender difference decreased with the increase in age. [Elb02].

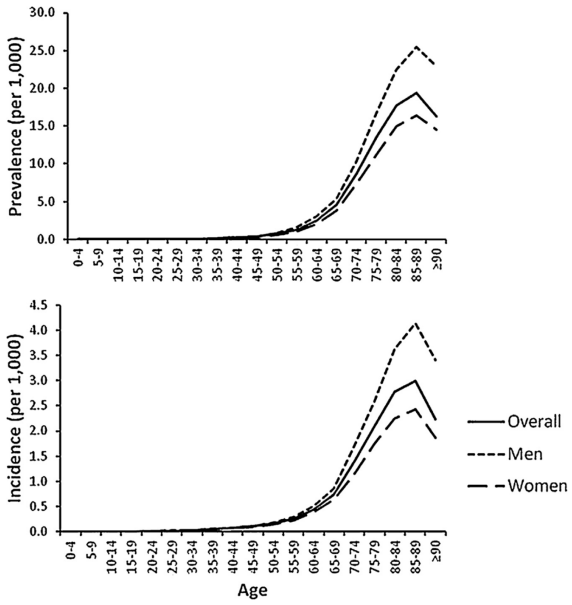

Figure 1: Prevalence and incidence of Parkinson's disease (PD) in France in 2010. The numbers of patients with prevalent and incident PD were estimated from nationwide drug-claims databases based on social security systems. [Elb16].

The incidence of PD dramatically rises with age. Though it is uncommon before the age of 50, both its incidence and prevalence exhibit an upward trajectory in older age groups. According to a meta-analysis of prevalence studies, PD incidence increased from 107 cases per 100,000 individuals between the ages of 50 and 59, to 1087 cases per 100,000 individuals between the ages of 70 and 79. [Pri14]. It has also been found that younger PD patients have a higher mortality risk than older PD patients when compared to age-matched PD-free controls. [Pos11]. Heart disease, pneumonia, and stroke have been recorded as the three primary causes of death in PD. [Pen10].

Curiously, lower cancer risk in PD patients has also been observed in a

significant body of epidemiological data. This intriguing antagonist connection between cancer and PD has undergone scrutiny in a meta-analysis involving 29 studies. [Baj10]. One plausible theory to explain this phenomenon is that genetic factors influencing cell-cycle control may simultaneously guard against cancer and predispose to the development of PD. For example, the Parkin gene, one of the genes responsible for recessive familial PD, is involved in the formation and progression of cancer. [Xu14]. [Elb16].

Ten to fifteen percent of PD patients report that their first-degree relatives have a history of the disease. [Tha08]. Various causative genes have been identified, and their mutations are typically associated with an earlier age of onset. However, only a small percentage of patients have a single mutation linked to Mendelian disease transmission. [Ver15]. Twin studies have discovered poor concordance rates for the illness, except in cases where it manifests early in life. Therefore, a significant portion of the time, primarily when the disease does not display in younger individuals, PD cannot be solely explained by genetic factors. In contrast, epidemiological and toxicological investigations yield significant findings regarding the importance of environmental factors. [Tan99]. [Wir11b].

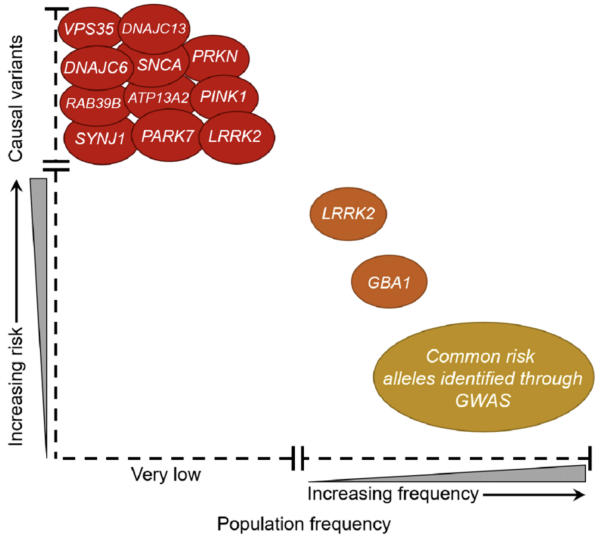

Figure 2: The emerging genetic architecture of Parkinson's disease. [Cha21].

For over three decades, numerous studies have shown an adverse relationship between smoking and PD. A meta-analysis of 44 case-control and four cohort studies has revealed that ever-smokers had a 60 percent lower risk of PD than never-smokers. [Her02]. Similarly, a study of individual data from eight case-control studies and three cohort studies from the US corroborated this relationship. [Rit07]. Remarkably, this inverse relationship has been observed

even among subjects to pesticide exposure. [Gal05]. [Bre16]. According to another cohort study, the duration of smoking appeared to be more significant than the intensity of smoking. This finding is important because it shows that several years of smoking may be necessary before noticing a decreased risk of PD. [Che10a]. However, cohort studies of PD patients indicate that smoking has little impact on the progression of the illness. [Alv04].

According to a meta-analysis of eight case-control studies and four cohort studies, observational studies have also shown that coffee drinkers had a 30 percent lower chance of developing PD than non- drinkers. [Her02]. This association was independent of cigarette smoking, and risk reduction increased with daily coffee consumption. Additionally, a recent cohort study found that individuals who consumed more than three cups daily exhibited a 40 percent lower risk of developing PD. [Sä08].

The idea that PD and pesticide exposure were related first surfaced when many cases of Parkinsonism followed intravenous MPTP injections in the early 1980s. In dopaminergic cells, MPTP is converted into 1-methyl-4-phenylpyridinium (MPP+), a mitochondrial respiratory chain inhibitor with neurotoxic characteristics. The molecule resembles the chemical structure of paraquat, a nonselective herbicide that has been in use since the 1960s and remains extensively employed. Given these observations, numerous research studies have delved into the connection between farming, pesticide exposure, and PD. [Elb16]. According to a meta-analysis of 46 research, people exposed to pesticides have an approximately 1.6 times increased chance of developing PD. Among different types of pesticides, herbicides and insecticides have a stronger connection with PD despite significant study heterogeneity. While fungicides exhibited a weaker correlation, less research has investigated their potential link to the disease. [vdM12].

2.1.3 Pathology

The substantia nigra, pars compacta (SNpc), an essential component of the basal ganglia, is the primary brain region damaged by PD. Dopamine is a necessary brain monoamine that primarily serves as an inhibitory neurotransmitter, and this region is predominantly made up of neurons that secrete it. In a healthy brain, dopamine controls the excitability of striatal neurons, which are essential in regulating the balance of bodily movement. However, in PD, dopamine levels decrease, and SNpc dopamine neurons deteriorate. [Ger89]. Low levels of dopamine result in reduced inhibition of striatal neurons' activity, allowing them to fire excessively. This underlying mechanism elucidates why individuals with PD are unable to control their movements, experiencing tremors, stiffness, and bradykinesia, which are the hallmarks of PD-related motor symptoms.

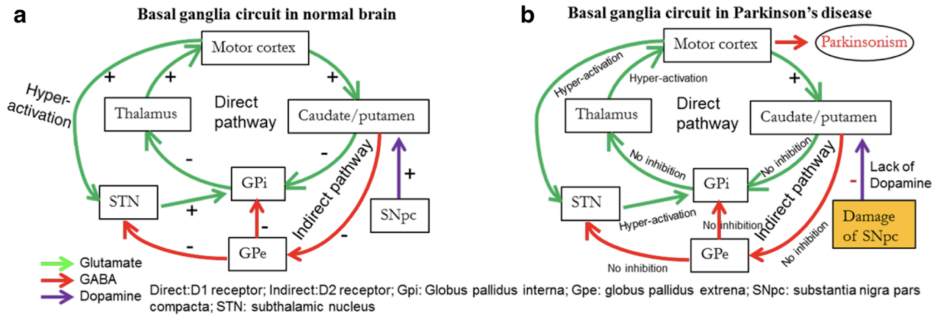

Figure 3: Neuronal circuits and neurotransmission mechanisms of control in the brains of normal individuals and those with Parkinson's disease. a: Neuronal circuit in basal ganglia in normal brain. b: Degeneration of substantia nigra pars compacta (SNpc) impair cortico-striatal circuit in PD brain. [Mai17].

Serotonin (5-HT), in addition to dopamine, is a critical substance in the development of PD. This neurotransmitter is particularly implicated in several motor and non-motor symptoms, such as tremors, cognitive deterioration, depression, and psychosis, as well as L-DOP A-induced dyskinesia. [Huo17].

Another neurotransmitter, acetylcholine (ACh), essential for cognitive function, experiences dysregulation in a number of neurological disorders like PD and AD. The nucleus basalis of Meybert (nbM), a wide band of cell clusters that are primarily cholinergic in nature, is located in the basal forebrain subventricular region. The nbM of individuals with PD, AD, or other kinds of dementia has shown various patterns of neuronal death, which strongly supports the concept that the cholinergic system is involved in PD. [Liu15].

Gamma amino butyric acid (GABA) is an inhibitory neurotransmitter that, directly through GABAergic receptors and indirectly through the astrocyte network, regulates calcium (Ca++) influx. The Ca++-excitotoxicity and neuronal death stabilizes both cellular and systemic levels of neuronal activity in the SNpc. [Hur13]. In contrast, the Ca++-buffering system is regulated by GABA activity. Approximately 80 percent of patients recently diagnosed with PD exhibit impaired olfaction caused by dopamine neuron loss in the olfactory bulbs. [Ste12]. Glial cell-derived neurotrophic factor (GDNF), likewise controlled by the Ca++/GABA system, regulates the activity of dopamine neurons in the midbrain and the olfactory system. Additionally, GDNF serves as a potent chemo-attractant for dopaminergic axons and GABAergic cells. When GDNF was delivered to GABAergic neurons in the striatum rather than the SNpc, neuroprotective benefits in PD animal models were seen, indicating that collapse of the GABA/Ca++ pathway is involved in dopamine-neuronal death in PD. [Iba17]

The intracellular buildup of Lewy bodies in dopamine neurons of the SNpc, which contain misfolded aggregates of alpha-synuclein (SNCA) and other related proteins, is one of the defining diseases of PD. [Car14]. Several molecular, genetic, and biochemical studies have shown that post-mortem human brains from patients with mixed dementia with Lewy bodies (DLB) and PD with dementia (PDD) who were diagnosed neuropathologically are frequently found to contain a variety of misfolded protein aggregates, including p-tau, A-beta, and SNCA. (Stefanis, 2012). According to research, amyloid deposition in some PD patients' brains has been associated with cognitive reductions without dementia, indicating that amyloid contributes to cognitive but not motor decline over time. [Iba17]. It has also been discovered that the load and amount of A-beta pathology influences cognitive deficits in PDD and LDB. [Bla16]. Alpha-synuclein or other misfolded amyloid proteins can kill neurons by creating a pore in the membrane and inducing neuroinflammation, excitotoxicity, oxidative stress, and energy failure. [Mar12]. Oxidative stress has been associated with various general mitochondrial abnormalities, including variations in the dynamics and shape of the mitochondria, mutations in the mitochondrial DNA, and abnormalities in calcium homeostasis. Dysfunctional mitochondria can result in decreased energy production, the creation of reactive oxygen species, and the activation of stress-induced apoptosis. [Sub13].

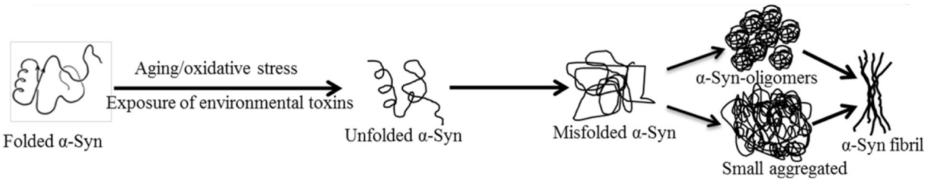

Figure 4: Schematic diagram showing the steps that cause an accumulation of SNCA. Natural SNCA becomes misfolded under stress and is deposited as oligomers, small aggregates, or fibrils, which play a significant role in DA-neuronal loss in PD. [Mai17].

Neuro fibrillary tangles, a hallmark of the pathology of numerous neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia with parkinsonism (FTDP), and progressive supranuclear palsy (PSP), can be produced by the tau hyper-phosphorylation (p-tau) protein. [SM08]. The FTDP is associated with chromosome 17 (FTDP-17), and the cortex and SNpc region exhibit p-tau accumulation. The development of sporadic PD is frequently linked to the colocalization of the p-tau with Lewy bodies. Similar to FTDP, an increase in the accumulation of p-tau is brought on by a mutation in the gene encoding for a microtubule- associated protein (MAPT). [Ari99]. This accumulation leads to the formation of neurofibrillary tangles, which play a significant role in the disruption of dopamine-neuronal architecture, ultimately resulting in fast degeneration and death of dopaminergic neurons, even though they are most closely connected with Alzheimer's and can co-localize with alpha-synuclein in

Lewy bodies. [Hep16].

2.1.4 Existing Treatments

Drug medication is the most common treatment for PD patients, with patients receiving different doses of several generic drugs. Although there still is no definitive cure for PD altogether, some drugs can help slow the course of the disease or alleviate some of the symptoms. PD drugs are generally categorized as dopaminergic and non-dopaminergic drugs.

Dopaminergic drugs are typically prescribed by doctors to PD patients in an effort to raise dopamine levels. Levodopa, or L-DOPA, is a popular dopamine precursor since dopamine cannot penetrate the blood-brain barrier alone. Levodopa is particularly effective in lowering "resting tremors" and other main symptoms, but it cannot restore or replace dopaminergic neurons that have deteriorated or halt the progression of PD. Common side effects of levodopa include nausea, vomiting, hypotension, restlessness, drowsiness, or a quick beginning of sleep. [Bar69]. [Mai17]. Other popular and well-tolerated dopaminergic drugs include selegiline and rasagiline, also known as MAO-B inhibitors. The catalytic enzyme monoamine oxidase-B (MAO- B), whose level is elevated in the brain of PD patients, may be the cause of the decreased dopamine levels in PD. When used with levodopa, MAO-B inhibitors have been observed to prolong levodopa's effects for a year or more. [Rie04]. Similarly, COMT inhibitors, which inhibit the catechol-O-methyl transferase (COMR) enzyme that is indirectly responsible for the breakdown of dopamine, can also prolong levodopa's effectiveness. Widespread COMT inhibitors, entacapone and tolcapone, also prolong the viability of levodopa. [Ant08]. Another type of dopaminergic drug is dopamine agonists. These medications are most helpful in the early stages of PD and can raise dopamine levels in the brain. They can also be used in the late stages of PD to extend levodopa's effectiveness. Pramipexole and ropinirole are two of the most frequent dopamine agonists used to treat PD patients. However, they are typically less effective than levodopa in decreasing symptoms and may have a high list of side effects. [Bro00].

Non-dopaminergic drugs are typically antidepressants used for managing non-motor symptoms in PD, including depression and anxiety. One of the most popular medications for treating anxiety in PD patients is benzodiazepine, although it has some associated side effects. [Che14]. Similarly, clozapine is given to treat dyskinesia in PD; however, this drug also has many side effects, including agranulocytosis. [Dur04].

The majority of drug treatments as mentioned have significant side effects and provide only momentarily relief, particularly for particular patient types.

They are also powerless to halt additional dopaminergic neuron loss. Therefore, some clinicians turn to surgical procedures to lessen the motor symptoms when drug medication is deemed ineffective, especially in the late stages of the disease.

In PD, a number of basal ganglia nuclei become dormant or dysfunctional. Deep brain stimulation (DBS), the surgical placement of very small electrodes in these regions, can be employed to maintain their functional activity. Target areas for DBS include the thalamus, globus pallidus interna, or subthalamic nucleus, where the electrodes are placed in one or both hemispheres. These batteries, which can be appropriately programmed in accordance with the particular requirements of the PD patient, are what produce the electrical pulses. The implanted batteries can be checked, changed, or recharged as necessary every three to five years. Many of the primary motor symptoms of PD can be alleviated by DBS, which reduces the reliance on levodopa to treat dyskinesias. However, it's important to note that DBS must be surgically implanted, which carries risks of infection, speech or balance issues, stroke or bleeding, and other potential complications. DBS is also ineffective for addressing psychological, cognitive, or other non-motor problems. [Her16].

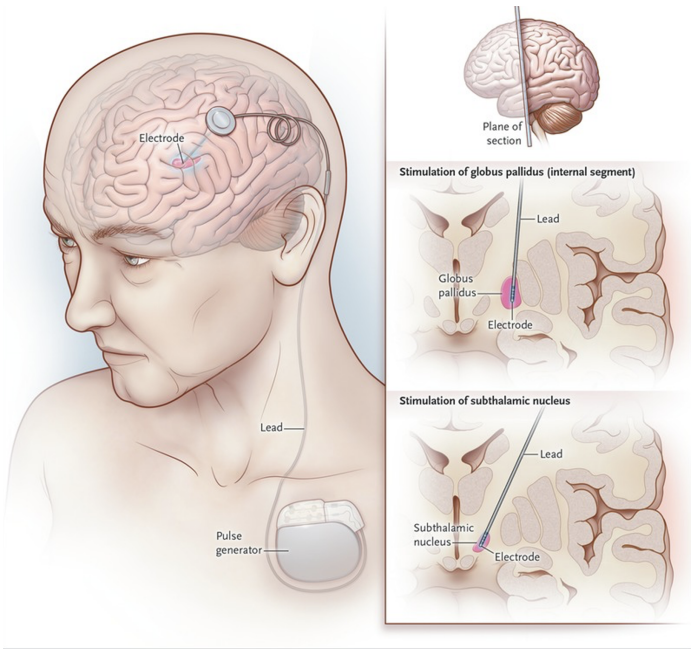

Figure 5: Electrode implantation for Deep Brain Stimulation. [Oku12].

As some PD incidences have shown to be caused by multiple genes associated with the disease, despite most PD cases being sporadic in origin, researchers have been investigating gene therapy strategies as a potentially viable treatment

option. [Cou12]. Despite efforts, further research and trials are needed in this field to show the viability of this type of treatment.

A promising method for treating PD involves the transplantation of neural stem cells into the patient's brain. Researchers have developed a technique to produce dopaminergic neurons from mouse embryonic stem cells and transplant them into the striata of animals with PD. This method involves modulating several growth factors. Intriguingly, these transplanted neurons in the animal model of PD survive, integrate into the existing brain circuitry, and reverse the behavioral abnormalities. [Kim11]. Researchers can produce even more dopaminergic neurons to transplant into the brains of mice with PD by overexpressing Nurr1, a transcription factor for developing dopaminergic neurons, in embryonic stem cells. [Roy04]. A rise in dopamine levels has also been seen after the grafting of human fetal-derived dopaminergic tissues into the striatum of PD patients, indicating that the implanted stem cells can survive and develop into dopaminergic neurons. [Lin11]. Similarly, allogeneic human fetal ventral mesencephalic (FVM) tissue transplantation in PD patients has shown remarkable therapeutic advantages. [Hau99].

Mesenchymal stem cell (MSC) transplantation has also been proven in investigations to ameliorate PD-related motor dysfunctions. In studies conducted with PD rat models, the systemic infusion of human MSCs resulted in a significant reduction in the uncoordinated limb movement as observed in behavioral tests. It was connected to increased dopaminergic neurons and raised dopamine levels in the striatum of MSC recipients, pointing to a restorative function of MSCs. [Bou08]. Similarly, direct striatal injection of MSCs led to increased locomotor activity, boosted neurogenesis, and stimulated neuroblast migration in mouse models of PD. [Off07]. Furthermore, alpha-synuclein transmission has also been shown to be inhibited by MSC therapy in a PD model. [Oh16].

Before stem cell therapy can be authorized as a viable treatment for people with PD, additional research must assess its safety and effectiveness. One concern lies in the self-replicating ability of stem cells, which carries the risk of tumor formation after clinical transplantation. [Zha23]. In this regard, stem cell exosomes could be used as an alternative option, as explained in the upcoming sections of this review.

2.2 Mesenchymal Stem Cell-Derived Exosomes

2.2.1 Stem cells

Stem cells are a classification of cells that carry long-term self-renewal abilities and can differentiate into other cell types that are more specialized within their functions. Through this differentiation progress, these cells maintain their DNA structure while exhibiting distinct gene expression patterns in their technical roles. [Kol13]. Stem cells are distributed throughout nearly every adult organ, where they are responsible for replacing the cells lost within these organs and responding to any injury or disease in the tissue. In their differentiation pathways, there are intermediate or progenitor states. These progenitor cell states can influence the behavior of the cells surrounding them. Additionally, stem cells can be engineered and modified in vitro to be differentiated into desired cells. Leveraging these unique properties, stem cells have been widely researched in tissue engineering and cell therapy fields. [Bac18].

The potential of stem cells differentiating into specialized cell types is known as stem cell potency. Potency defines the ability of stem cells to adopt a different phenotype. Stem cells can be categorized by their potencies as totipotent, pluripotent, and multipotent. [Kol13]. Totipotent stem cells are relatively rare and initially present in low amounts in the zygote. These stem cells can differentiate into every cell type in the body and the placenta. Pluripotent stem cells are found in the blastocyst and can differentiate into all body cell types other than the placenta. Multipotent stem cells are more specialized and are found in three germ layers: the ectoderm, endoderm, and mesoderm. They differentiate into different cell types according to the germ layer that they originate from. In contrast, unipotent stem cells exhibit long-term self-renewal and can reproduce in large amounts. However, these cells are committed to differentiating into one specific cell type. [Arb23].

Mesenchymal Stem Cells

MSCs are stromal cells that exhibit multilineage differentiation and have the ability of self- renewal, akin to other types of stem cells. MSCs can be extracted from various tissues, including adipose tissue, bone marrow, menstrual blood, endometrial polyps, and the umbilical cord. [Din07]. This is because these sources are most useful for experimental and potential clinical applications because of the ease of extraction and yield. Thus, MSCs also carry fewer ethical issues compared to other stem cells, such as induced pluripotent stem cells and embryonic stem cells, due to this ease in harvest. [Din11].

Under particular in vitro circumstances, MSCs can develop into diverse lin-

eages of mesodermal, ectodermal, and endodermal cells, including bone, fat, chondrocyte, muscle, neuron, islet cells, and liver cells. [Ois09]. Additionally, genetic processes involving transcription factors control differentiation. Some regulatory genes that cause progenitor cells to differentiate into a particular lineage can govern differentiation to a specific phenotypic route. [Bac18]. A microenvironment created with biomaterial scaffolds can offer MSCs the ideal circumstances for proliferation and differentiation in addition to growth factors and induction chemicals. [Ser04]. Research has also found that adult human MSCs can easily and directly be developed into dopaminergic neurons. [Kha19]. [Ven17].

2.2.2 Exosomes

Exosomes, tiny organelles surrounded by a single membrane, harbor a distinct array of proteins, lipids, nucleic acids, and glycoconjugates. In the cell, they are available in the nucleus and cytoplasm and take part in RNA processing. Exosomes can be secreted by B and T cells, dendritic cells, mesenchymal stem cells, epithelial and endothelial cells, and cancer cells. [Kal20]. Exosomes are capable of remodeling the extracellular matrix and transmitting signals and molecules between cells once they are released from the host cell.

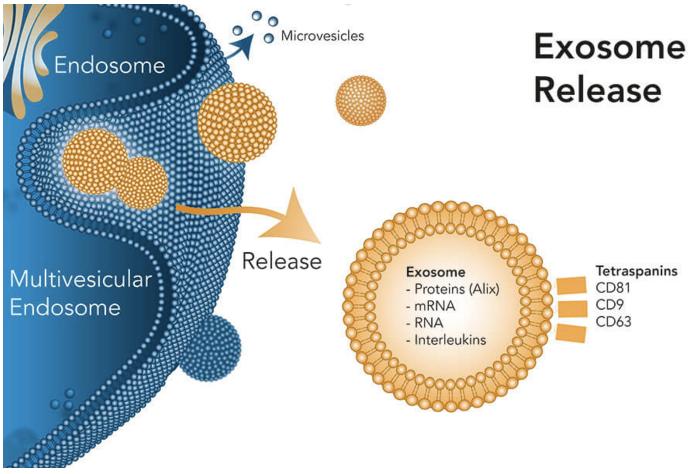

Figure 6: Virtually all cells release exosomes, most commonly identified by the tetraspanins CD9, CD81, and CD63 on their surface. Exosomes carry molecules such as proteins, RNA, or DNA and mediate cell-to-cell communication. [Neund].

Due to their extremely small proportions, they can easily pass compartments and membranes. This cell-to-cell interaction mediation of exosomes plays a significant role in human metabolism and health, including the development of

immunity and the maintenance of homeostasis, the onset of malignancy, and the development of numerous diseases. Viruses and other evading particles can use these vesicle pathways to spread their infections. One remarkable attribute of exosomes lies in their ability to be harnessed for targeted interventions and drug delivery. Furthermore, their capability to traverse the blood-brain barrier positions them as an excellent drug delivery pathway. [Zho23].

Exosomes also play a crucial role in paracrine signaling and are the primary determinant of stem cell efficacy. Cell-free exosome therapy can overcome numerous drawbacks of stem cells, such as their stability and storage convenience. Exosomes exhibit high biocompatibility, eliminating the risk of host rejection and enabling precise dose-control. [Gur21]. One significant feature of exosomes lies in their ability to transfer RNA to recipient cells and affect their proteome, functions, and RNA expression. These processes are essential for controlling immunological responses or various other pathological reactions through intercellular communication. [Har13]. These RNA molecules include messenger RNA (mRNA) and microRNA (miRNA), which affect the protein synthesis of the recipient cells in the process of cell-to-cell communication. [Xin12].

MSC-EXOs

MSCs have been found to carry the ability to differentiate into neural cells and secrete several neurotrophic and anti-inflammatory substances after transplantation, showing strong neuroprotective capabilities for diseases such as amyotrophic lateral sclerosis, multiple sclerosis, PD, and glaucoma. [Joh10].

It is currently widely accepted that MSCs primarily use secreted trophic factors in order to exert their therapeutic benefits. Exosomes are thought by many researchers to be the paracrine effectors of MSCs with their involvement in cell-to-cell communication. They have been tested in various illness models, and the results have shown that they perform similar tasks to MSCs, including reducing the size of myocardial infractions, enabling kidney injury repair, modifying immunological responses, and encouraging tumor growth. [Yu14].

MSC-EXOs were initially studied in a mouse model of cardiac ischemia injury in 2010, [Che10b]. and they have been subsequently examined in a number of disease models. MSCs have been shown to produce more exosomes than other cell lines. [Reo13]. Exosomes generated from MSCs and other sources are identical in terms of morphological characteristics, isolation, and storage conditions. MSC-EXOs can be identified by several adhesion molecules, such as CD29, CD44, and CD73 expressed on the membrane of MSCs, in addition to the general exosome surface markers CD9 and CD81. [Lai15].

MSC-EXOs have also been investigated with regard to their miRNAs. It

has been discovered that most of the miRNAs included in MSC-EXOs are in their precursor form. [Che10b]. MSCs influence other cells biologically by secreting miRNAs through these exosomes. Exosomes from MSCs administered to neurons and astrocytes cause target cells to produce miR-133b, which aids the functional recovery process in spinal cord injury and PD. This discovery indicates that MCSs control neurite outgrowth by delivering miR-133b to neurons and astrocytes via exosome release. [Xin12].

3 MSC-EXOs as a treatment for Parkinson's disease

As explained in previous chapters, MSCs have the potential to become a valuable therapeutic tool in the treatment of neurological disorders. To aid functional recovery, they interact with brain parenchymal cells. It has been proposed that MSCs and parenchymal cells communicate via miRNA found in exosomes. [Yu14]. MiRNAs are evolutionarily conserved, nonprotein coding transcripts of 18-25 nucleotides that post-transcriptionally regulate gene expression by inhibiting translation and degrading mRNA. MiRNAs are a significant regulatory gene family in eukaryotic cells. [Fio08]. They act as critical factors in various regulatory systems, including host-pathogen interactions, developmental timing, stem cell differentiation, proliferation, apoptosis, and tumorigenesis in animals. [Lim10]. MicroRNA 133b (miR- 133b) is expressed in midbrain dopaminergic neurons. It controls the synthesis of tyrosine, hydroxylase, and dopamine transporter in people with PD. [Dre10]. Furthermore, a study has used morpholino antisense oligonucleotides to inhibit the expression of miR-133b following spinal cord injury in adult zebrafish and has discovered that locomotor recovery was significantly hampered and that the decrease in miR-133b expression inhibited the regeneration of axons from neurons. [Yu11]. It has thus been concluded that in cases of PD and spinal cord injury, miR-133b has aided functional recovery, although its efficacy in cases of cerebral ischemia has yet to be investigated. [Xin12]. [Li21].

A study has found that MSC treatment dramatically increased the levels of miR-133b in the ipsilateral hemisphere of rats who had undergone middle cerebral artery occlusion (MCAo). Exosomes from MSCs that had been exposed to ipsilateral ischemia tissue extracts from rats that had undergone MCAo in vitro, showed a substantial increase in miR-133b levels, significantly in primary cultured neurons and astrocytes. However, treatment of the astrocytes with exosome- enriched fractions from MSCs transfected with a miR-133b inhibitor dramatically reduced miR- 133b levels. This study stands as the first evidence that MSCs interact with brain parenchymal cells via exosome-mediated miR-133b transfer, controlling the expression of particular genes in order to promote

neurite outgrowth and functional treatment. [Xin12]. The research team later showed that intravenous injection of MSC-EXOs can increase axonal density and synaptophysin-positive areas along the ischemic boundary zone of the cortex and striatum and hasten functional recovery in the same model as above, confirming that MSC-EXOs could significantly improve neurologic outcome and contribute to neurovascular remodeling. [Xin13].

Clinical research reports claim that 98 percent of medications that could be used to treat illnesses of the central nervous system failed in clinical trials because of their inability to cross the blood-brain barrier (BBB). [Par12]. Exosomes typically have a diameter between 30 and 150 nm, which is significantly small, allowing them to effortlessly pass across the BBB and reach the central nervous system. [Kal20]. This is another beneficial characteristic of exosomes, allowing them to be used as therapeutic signals or drug delivery vehicles due to their small diameters, minimal immunogenicity's, and extended circulation half-lives. [Kal14]. A study proved this, as MSC-EXOs successfully penetrated the BBB and reached dopaminergic neurons in the substantia nigra in an experiment on rats. MSC-EXOs reduced the apoptotic cell death of dopaminergic neurons and the asymmetric rotation caused by apomorphine. Additionally, in the substantia nigra of MSC-EXOs-treated rats, degenerative and necrotic alterations in the form of profoundly eosinophilic cytoplasms, along with pyknosis and karyolysis, were not seen. The existence of multipolar neurons with nucleoli and basophilic granular cytoplasms in brain tissue samples of MSC-EXOs-treated animals indicated considerable improvement during histological inspection. Importantly, MSC-EXOs elevated dopamine and its metabolites in the striatum, further indicating that MSC-EXO-based therapy enhances dopaminergic neurons' functionality in animals with PD. [Che20a]. Exosomes' ability to interact with cells under various standard and pathological circumstances further suggests their crucial potential in the treatment of PD. [Sma07]. Exosomes also play a role in synaptic plasticity, nerve regeneration, and neuronal development. Exosomes deliver control elements to nerve damage sites, promoting the production of new tissue and proteins. [dRV16]. According to a study, the autophagy triggered by exosomes causes the motor symptoms and dopamine neurons in the substantia nigra striatum to be increased in PD mice after exosome treatment. [Che20a]. [Liu22].

4 Discussion

Despite being preliminary in terms of clinical application, stem cells have shown significant therapeutic potential in a variety of diseases. The biggest shortcoming of stem cells is their high instability. Suffering from their high potency, they carry the risk of tumor formation in clinical applications. Due to this character-

istic, there has been a shift of focus to utilizing their exosomes in regenerative medicine. Exosomes derived from stem cells have been proven to carry therapeutic abilities on par with those of stem cells. As they do not have the ability to multiply on their own and show highly adaptive characteristics, being able to survive in a variety of environments, they are a much stabler option than stem cells regarding clinical application and have a high potential to be optimized in drug usage. These nanoparticles can easily pass membranes throughout tissues thanks to their small sizes. As mentioned, exosomes have an essential responsibility in cell-to-cell communication and have been accepted by many studies to be behind the therapeutic effects of stem cells by enabling their miRNA transmission. For these reasons, there has been a spur of recent research on these microvesicles as potential treatments for many diseases. Similarly, many scientists have been researching the effect of exosomes on neurodegenerative diseases, particularly AD and PD.

Compared to other exosomes, there has been a focus on MSC-EXOs in papers regarding Parkinson's disease. MSCs are a particularly fit choice of stem cells due to their easy harvest and high potential of acting as a cell-based therapeutic agent for tissue regeneration. They do not carry many ethical sourcing issues that other stem cells carry, such as iPSCs. Another factor is the therapeutic effects that MSCs carry on PD. Specifically, their ability to differentiate into dopaminergic neurons and secrete neurotrophic substances has made them an exciting topic in PD research.

The combination of the relatively newfound focus on exosomes and the advantages that MSCs have clearly shown over other stem cells has caused an increase in research on the therapeutic effects of MSC-EXOs on PD. Even though studies on this topic have proved the positive effects that MSC-EXOs carry on PD, there remains a need for more research and attention. MSC-EXOs have been proven highly effective and accessible for treating PD in several rat models. However, there is a lack of and need for follow-up studies that include humans and large animal models. Furthermore, randomized controlled studies need to be carried out to verify the therapeutic benefits of exosomes in this regard. However, some shortcomings of exosome therapy should be discussed as well.

The practical use of exosome-based therapy is currently difficult and constrained by a number of problems. First, the length of time needed to create a large batch of exosomes restricts their effectiveness and clinical use potential. Second, because exosomes include diverse bioactive components, the target tissue may experience unexpected side effects. Third, depending on the characteristics of the donor cells, these components may reveal the potential danger of tumor growth and the impacts of immunogenicity. Finally, the therapeutic implications of exosome formation under intervention during disease are uncertain because of their intricate structure. Exosome-derived stem cells are currently the subject of preliminary research, however; their pharmaceutical use

is hampered by the varied composition and functional activity of spontaneously produced exosomes. It has been revealed that exosomes derived in different conditions have carried other functional factors. Exosomes' precise function is likewise primarily unknown. [Yua18]. There remains a critical need for research on the precise role and components of exosomes for progress in studies regarding the therapeutic delivery of different diseases.

5 Conclusion

Due to their ease in harvest and high potential in tissue regeneration and remodeling, MSCs have become highly anticipated stem cells, being studied in a variety of cell therapies. They carry the potential of differentiating into several different cell lines, including dopaminergic cells, whose deterioration is a prominent issue in PD patients. MSCs have also been proven to secrete neurotrophic and anti-inflammatory substances after transplantation, carrying strong neuroprotective abilities.

Midbrain dopaminergic neurons express miR-133b, which regulates the production of tyrosine hydroxylase and the dopamine transporter in patients with PD. A study has shown that MSCs interact with brain parenchymal cells via exosome-mediated miR-133b transfer in order to promote neurite outgrowth and functional treatment. MSC-EXOs are also able to successfully cross the BBB, a shortcoming of many drugs targeting PD, and reach dopaminergic neurons in the substantia nigra with ease. MSC-EXO therapy on rats with PD has shown increased dopamine and its metabolites in their striatum.

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