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Stemming Hope: Exploring the Promise of Stem Cell Therapy in Parkinson's Disease and the Emergence of a Promising New Biomarker

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ABSTRACT

Characterized by the progressive loss of dopaminergic neurons in the brain, Parkinson's disease (PD) is a relatively common neurodegenerative disorder that affects millions worldwide. PD leads to the gradual manifestation of motor symptoms, including tremors, rigidity, and bradykinesia, as well as non-motor symptoms, such as mood disruption and cognitive impairment. These symptoms can significantly reduce an individual's quality of life, yet it is essential to note that the progression of PD is highly variable amongst those affected. There is currently no cure for PD; thus, the need for research surrounding improved symptomatic treatments, disease-modifying therapies, and biomarker identification is crucial. This review addresses the use of stem cell therapy as a promising avenue in combating the challenges posed by PD and provides insight into a recent Parkinson's biomarker study sponsored by The Michael J. Fox Foundation for Parkinson's Research (MJFF).

Keywords

Biomarker, Dopamine, Dopaminergic neurons, Embryonic stem cells, Induced pluripotent stem cells, Mesenchymal stem cells, Parkinson's disease, Targeted treatment.

Abbreviations

αSynSAA: Alpha-Synuclein Seed Amplification Assay, COMT: Catechol-O-Methyltransferase, CSF: Cerebrospinal Fluid, CT: Computed Tomography, DaTscan: Dopamine Transporter Scan, DBS: Deep Brain Stimulation, ESCs: Embryonic Stem Cells, FDA: Food and Drug Administration, fMRI: Functional Magnetic Resonance Imaging, iPSCs: Induced Pluripotent Stem Cells, MAOB: Monoamine Oxidase-B, MSCs: Mesenchymal Stem Cells, MJFF: Michael J. Fox Foundation, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography, PD: Parkinson's Disease, PPMI: Parkinson's Progression Markers Initiative.

Introduction

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that impacts millions of individuals across the globe. Presently, an estimated 500,000 Americans have PD, making it the second-most prevalent neurodegenerative disorder in the United States, ensuing Alzheimer's disease [1]. Although PD is not generally considered to be a direct cause of death, individuals with PD typically live ten to twenty years following initial diagnosis and often reach a normal life expectancy. Nonetheless, PD can severely impact a person's quality of life and may even amplify their susceptibility to other health issues and complications [2].

While the exact cause of PD is not fully understood, researchers suggest that a combination of genetic and environmental factors play a role in its development. With that said, roughly 15% of individuals with PD have a family history of the disease. Genetic mutations in genes, including PARK2, PARK7, PINK 1, SNCA, and LRRK2, have been associated with inherited forms of PD, yet most of these cases are relatively infrequent and lack a distinct genetic link [3]. Additionally, research indicates that age is a significant risk factor in the development of idiopathic PD. Around 1% of individuals over the age of 60 are affected by PD, and the prevalence increases to 5% in those over the age of 85 [4]. As individuals advance in age, they are subject to the accumulation of cellular damage, mitochondrial dysfunction, protein aggregation, and decreased neuroplasticity [5]. These factors can directly contribute to the degeneration of neurons in the brain, as well as

the reduced ability of the brain to compensate for potential neural damage or dysfunction [4]. Furthermore, exposure to environmental toxins, including heavy metals, pesticides, and illicit substances, has been linked to PD-associated neurodegeneration [6].

In terms of disease detection, PD is diagnosed following the observation of both motor and non-motor cardinal manifestations. Distinguishing clinical symptoms are as follows: bradykinesia or loss of movement, resting tremor, muscle rigidity, postural instability, mood disruption, and cognitive decline. Unfortunately, by the time these characteristics become evident, extensive neurological impairment has likely occurred; thus, early detection of PD is of utmost importance [6]. Diagnostic tests, such as magnetic resonance imaging (MRI) or computed tomography (CT) scans, can also be utilized to rule out other potential causes of symptoms. In 2011, the Food and Drug Administration (FDA) approved the use of a dopamine transporter scan (DaTscan) that allows for visualization of the brain's dopamine system and can indicate a reduction in function. However, it is essential to note that a negative DaTscan does not eliminate the odds of having PD, especially within the early stages of the condition, yet a positive DaTscan can aid in confirming it [7]. Other potential biomarkers, including cerebrospinal fluid (CSF) analysis and specific genetic indicators, can also assist in the early detection and diagnosis of PD [8].

Current Treatment Options

While there is currently no cure for PD, there are several treatment options available to manage associated symptoms. These options typically include a combination of medications and lifestyle changes, yet some patients may even receive surgical treatment. Levodopa, a dopamine precursor, is the most potent drug available in the treatment of symptoms caused by PD [9]. Due to its adverse side effects, levodopa is often paired with carbidopa, a peripheral dopa decarboxylase inhibitor, to enhance its effectiveness and reduce unfavorable side effects. In addition to levodopa, dopamine agonists and nondopaminergic agents, such as monoamine oxidase-B (MAOB) inhibitors and catechol-O-methyltransferase (COMT) inhibitors, represent the diverse scope of medications used to treat PD. Dopamine agonists function to mimic the activity of dopamine in the brain, while MAOB inhibitors function to prevent the breakdown of cerebral dopamine. COMT inhibitors, on the other hand, can extend the therapeutic effects of levodopa by blocking its breakdown in peripheral tissues [10]. Nevertheless, the effectiveness of treatment can vary among those with PD; thus, treatment options are often tailored to meet the needs of each patient individually [9]. In patients with advanced PD, where medication alone is insufficient in moderating symptoms, deep brain stimulation (DBS) may be utilized. DBS involves the implantation of electrodes throughout different regions of the brain and can aid in regulating abnormal brain activity through electrical stimulation [11]. Despite the potential for DBS to decrease the severity of symptoms associated with PD, invasive procedures come with their risks, and not every patient is a suitable candidate for surgical intervention. It is important to consider that current treatment options typically focus on symptom management rather than disease modification. Ongoing research is necessary to develop more effective treatments for those suffering from PD.

Stem Cell-Based Therapy

Considering their self-renewal and differentiation capabilities, the use of stem cells has shown vast promise in the treatment of Parkinson's disease (PD). This form of therapy involves the use of stem cells to replace damaged or degenerated cells within the brain, particularly dopamine-producing neurons that are affected in those with PD [12]. Compared to current treatment methods aimed at symptom management, the use of stem cell-based therapy represents a potential paradigm shift in the treatment of PD and provides hope for more effective and disease-modifying interventions in the future. With that said, researchers have been investigating various stem cell types, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs), for the treatment of PD [12]. While stem cell therapy holds promise in the treatment of PD, there are still several challenges to overcome, such as ensuring long-term survival and proper integration of transplanted cells, reducing potential negative side effects, and addressing associated regulatory and ethical considerations.

Embryonic Stem Cells

ESCs are a form of pluripotent stem cells derived from the inner cell mass of a developing embryo. Pluripotent stem cells are noted for their ability to differentiate into various cell types representing all three germ layers: ectoderm, mesoderm, and endoderm. This attribute makes ESCs a valuable resource in the realm of regenerative medicine [13]. Regarding the treatment of PD, ESCs can be induced to differentiate into dopaminergic neurons. These neurons can produce dopamine–the neurotransmitter deficient in those suffering from PD. Current research aims to gain control of this differentiation process to generate a population of dopaminergic neurons that can be transplanted into regions of the brain impacted by PD. The primary objective of this cell replacement therapy is to replenish the depleted or damaged dopamine-producing neurons, leading to improved neurotransmitter levels and consequently alleviating impaired motor function [13]. In addition to this, ESCs also have the potential to release neurotrophic factors and may even function to modulate the cerebral microenvironment, providing support to existing neurons and delaying the progression of PD. Nevertheless, despite the promise of ESCs in the treatment of PD, there are several challenges and ethical considerations associated with their use in clinical trials. Challenges encompass the risk of immune rejection, tumorigenic potential, and ethical concerns related to the utilization of human embryos [13,14].

Induced Pluripotent Stem Cells

In lieu of ethical concerns surrounding the use of ESCs, researchers are also investigating other potential sources of pluripotent stem cells for treating PD. iPSCs, for example, which share several characteristics of ESCs, are derived from adult stem cells and can differentiate into various cell types, including dopaminergic neurons [15]. One of the primary advantages of iPSCs is their capacity for personalized medicine. More specifically, iPSCs can be obtained from a patient's own cells, decreasing the risk of

immune rejection when transplanted back into the same individual. This personalized approach may enhance the efficacy of treatment for PD [15,16].

Mesenchymal Stem Cells

Found in several tissue forms throughout the body (e.g., bone marrow, adipose tissue, and umbilical cord tissue), MSCs are a type of multipotent stromal cells that also have differentiation capabilities. However, MSCs have recently gained attention regarding their unique therapeutic potential [17]. In addition to neuroprotective properties, MSCs have been shown to modulate the immune system towards an anti-inflammatory phenotype. For instance, MSCs can secrete trophic factors and cytokines that promote tissue repair, angiogenesis, and nutrient exchange, which ultimately aid in cell survival [17]. MSCs can also be derived from a patient's own tissue, reducing the risk of immune rejection in autologous transplants. With that said, clinical trials are underway in the investigation of MSCs for the treatment of PD. These trials aim to identify optimal sources of MSCs, develop effective delivery methods, and understand the overall impact of MSC-based therapy in the treatment of PD [18].

Biomarker Identification

As mentioned, early detection of Parkinson's disease (PD) allows for prompt interventions and treatment strategies that could not only provide immediate symptom management but could potentially delay the progression of the disease [19]. Biomarkers are measurable indicators that can contribute information regarding both the presence and progression of a disease. Current research is investigating various potential biomarkers in the early detection and treatment of PD, including dopamine transporter scans (DaTscan), cerebrospinal fluid (CSF) analysis, blood-based biomarkers, and hereditary indicators [8]. Moreover, continuous advancements in neuroimaging technologies, for example, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), contribute to the recognition of specific PD-associated patterns [20,21].

Biomarker Breakthrough

The Michael J. Fox Foundation for Parkinson's Research (MJFF) is a non-profit organization dedicated to the establishment of more effective treatments, and ultimately a cure, for PD. With that said, the MJFF plays a significant role in advancing PD research through several contributions, including funding, clinical trial support, data and biospecimen sharing, patient engagement, advocacy, awareness, and the foundation's collaborative research consortia [22].

In April 2023, the MJFF announced a significant breakthrough in the quest for a PD biomarker. A groundbreaking study published in *The Lancet Neurology* by leaders of the Parkinson's Progression Markers Initiative (PPMI), a key PD biomarker study sponsored by the MJFF, revealed a major advancement in this search for a promising new PD biomarker [23]. Researchers found that the alpha-synuclein seed amplification assay (αSynSAA), a newly developed biological test, demonstrated remarkable diagnostic accuracy, distinguished molecular subtypes, and detected Parkinson's disease in individuals before the onset of cardinal motor symptoms. This finding represents a revolutionary advancement in the fight against PD and provides a crucial tool for clinical trial design, treatment assessment, and early disease detection [23,24].

More specifically, the αSynSAA test can detect synuclein pathology, a biological hallmark of PD. This mechanism allows researchers and clinicians to identify and monitor the disorder based on cellular pathology rather than relying solely on clinical assessments [25]. The validation of this biomarker signifies a new era in PD research, offering a biological foundation for drug development, targeted therapies, and potential preventive agents. With a robust sensitivity of 88% and specificity of 96%, the αSynSAA test significantly reduces the risk for industry investment, accelerates therapy development, and reshapes clinical trial design [24]. Furthermore, this groundbreaking development has the potential to attract increased pharmaceutical and biotech investment, fostering a more comprehensive approach to benefit individuals at all stages of PD [23].

Future Direction

While stem cell therapy and biomarker identification hold promise for the future of Parkinson's disease (PD) research and treatment, ongoing clinical trials and rigorous scientific investigation are necessary to establish their safety and efficacy [26,27]. The future of PD research will likely home in on the establishment of personalized or precision medicine approaches, considering a patient's genetic profile for more targeted treatments [15]. The use of stem cell-based therapy is associated with its own set of challenges and limitations; thus, researchers must continue conducting long-term clinical trials and performing follow-up studies to fully assess the sustained therapeutic benefits of stem cell treatment and identify potential adverse effects. In terms of biomarker identification, continuous advances in biomedical technology will aid in the search for reliable biomarkers that play a pivotal role in both the early diagnosis and monitoring of PD [27]. Nonetheless, collaborations between researchers, clinicians, and industry partners are vital for furthering our understanding of PD and translating research findings into practical and productive treatments.

Summary

Current treatments for Parkinson's disease (PD) primarily focus on symptom management rather than addressing the underlying progression of the disease, leading to motor fluctuations, long-term side effects, and challenges in finding optimal medication balances. Non-motor symptoms, such as cognitive impairment and mood disruption, may not be adequately addressed, and several treatment options are often limited in their duration of efficacy. Surgical interventions, including deep brain stimulation (DBS), can be effective but carry risks, and the high cost of medications poses a profound burden for many patients. Furthermore, access to specialized care is limited in certain regions, contributing to disparities in patient outcomes. In addition, it is also essential to consider the heterogeneity of PD, as individual responses to treatment can differ substantially.

No approved disease-modifying therapies are currently available for treating PD. Researchers are actively exploring stem cell therapy and conducting clinical trials to assess its safety and effectiveness. On the contrary, stem cell-based therapy has several associated challenges, such as ensuring the survival and integration of transplanted cells and addressing both regulatory and ethical considerations. Additionally, the identification of reliable biomarkers for Parkinson's is critical for early diagnosis and prompt treatment assessment. All things considered, ongoing research aims to develop new therapies, understand disease mechanisms, and personalize treatment plans, emphasizing the importance of collaboration between individuals with PD and healthcare providers. The goal is to improve the quality of care, advance disease-modifying treatments, and enhance the overall management of PD.

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