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PARKINSON'S DISEASE TREATMENT WITH STEM CELL THERAPY

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative condition that causes symptoms that are both motor and non-motor. It is characterized by a gradual loss of dopaminergic neurons in the substantia nigra. Conventional pharmaceutical therapies try to reduce symptoms, but none stop the disease from becoming worse or offer a cure. Stem cell therapy has become a viable treatment option for Parkinson's disease in recent years, with the potential to repair damaged neurons and regain lost function. The goal of this study is to present a thorough summary of the state of stem cell therapy as it applies to Parkinson's disease treatment today.

KEYWORDS: Parkinson's disease, neurodegenerative, Stem cell therapy, Dopaminergic neurons, Pharmaceutical therapies.

INTRODUCTION

The substantia nigra pars compacta area of the midbrain experiences a selective loss of dopaminergic neurons, which is the hallmark of Parkinson's disease (PD), a progressive neurodegenerative condition [Poewe,W,et.al.,2017]. The primary motor symptoms of Parkinson's disease (PD), including as stiffness, postural instability, bradykinesia, and resting tremor, are caused by the consequent deficiency of dopamine, a neurotransmitter essential for controlling movement [Poewe,W,2022]. Although there are symptomatic treatments for neurodegeneration, such levodopa and deep brain stimulation, their effectiveness generally wanes with time and they do not address the underlying neurodegeneration [Connolly,B.S,et.al.,2014].

With the potential to restore dopaminergic function and reduce or stop the course of the illness, stem cell treatment has emerged as a viable regenerative method for Parkinson's disease [Stoker,T.B, et.al.,2022]. The capacity of stem cells to self-renew and specialize into multiple cell types, including dopaminergic neurons, is truly astonishing [Gu, Y, et.al., 2021]. Due to this special characteristic, there has been a great deal of research done on stem cell-based approaches for neuroprotection, neuroreplacement, and PD-related neuroinflammation [Parish, et.al.,2007].

Mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) are among the stem cell types that have been studied for the treatment of Parkinson's disease (PD) [Takahashi,J,2019]. Since ESCs may develop into any type of cell, including dopaminergic neurons, they are a promising source for producing these neurons since they are generated from the inner cell mass of blastocysts [Chung,Y.C, et.al., 2022]. An ethically sound and patient-specific substitute for embryonic stem cells (ESCs) are induced pluripotent stem cells, or iPSCs [Kikuchi, T, et.al, 2017]. MSCs have been investigated for their immunomodulatory and neuroprotective qualities in Parkinson's disease (PD) and may be extracted from a variety of tissues, including bone marrow, adipose tissue, and umbilical cord [Stoddard-Bennett, et.al., 2019].

There are several different ways that stem cells may treat Parkinson's disease. By introducing stem cell-derived dopaminergic neurons or their progenitors into the damaged brain areas, cell replacement techniques seek to restore the depleted dopaminergic neurons [Barker, R.A, et.al., 2017]. Trophic factor release, neuroinflammation control, and endogenous neurogenesis stimulation are examples of neuroprotective processes [Yao, X,et.al., 2022]. Furthermore, by controlling the activity of microglia and other immune cells, stem cells may have immunomodulatory effects. This would lessen neuroinflammation, which is a major cause of neurodegeneration in Parkinson's disease [Wang, Q et.al., 2015].

The goal of this review is to present a thorough overview of stem cell treatment for Parkinson's disease, taking into account the many stem cell types that have been researched, the processes that underlie their potential for therapeutic benefit, and the most recent developments in preclinical and clinical research. This review aims to enlighten and lead future improvements in this promising topic by critically reviewing the available research and identifying the problems and future opportunities.

Stem Cell Therapy for Parkinson's Disease

1) Types of stem cells

a) Embryonic stem cells (ESCs)

The amazing ability of embryonic stem cells (ESCs) to develop into any type of cell, including dopaminergic neurons, is obtained from the inner cell mass of preimplantation blastocysts [Nickels et.al., 2022]. Numerous investigations have confirmed that dopaminergic neurons may be successfully generated from ESCs and that these neurons may be used to treat Parkinson's disease in animal models [Kin, H et.al., 2020, Garrido-Gil et.al., 2022]. However, researchers are looking at other sources of stem cells due to ethical concerns about using human embryos and the possibility of teratoma development.

b) Induced potent stem cells (iPSCs)

iPSCs are created by introducing certain transcription factors into somatic cells, including fibroblasts or blood cells, to reprogramme them into pluripotent states [Takahashi,J,2019].Compared to ESCs, iPSCs have a number of benefits, such as their origin tailored to the patient, which eliminates ethical dilemmas and possible problems with immune rejection [Kriks, S, et.al., 2019]. Dopaminergic neurons were successfully generated from iPSCs, and several studies have documented their therapeutic effectiveness in animal models of Parkinson's disease [Kikuchi, T, et.al, 2017, Chen,Y et.al., 2016].

c) Mesenchymal stem cells (MSCs):

Because of their immunomodulatory and neuroprotective qualities, MSCs—which may be extracted from a variety of tissues, including bone marrow, adipose tissue, and umbilical cord—have drawn interest [Nombela-Arrieta et.al., 2011]. MSCs have been demonstrated to release a variety of neurotrophic factors and control neuroinflammation, making them a viable treatment target for Parkinson's disease (PD) even if they are unable to develop into dopaminergic neurons [Bao, X et.al., 2022, Venkataramana et.al., 2022].

2) Mechanisms of Therapeutic Action

Cell Replacement

The principal technique of stem cell treatment for Parkinson's disease (PD) is the transplantation of dopaminergic neurons produced from stem cells or their progenitors to replace lost dopaminergic neurons. The goal of this strategy is to improve dopaminergic neurotransmission and lessen Parkinson's disease-related motor symptoms [Stoddard-Bennett, et.al., 2019]. In animal models of Parkinson's disease, preclinical research has shown that transplanted dopaminergic neurons engraft and integrate functionally, improving motor function [Wang, Q et.al., 2015, Bao, X et.al., 2022].

Neuroprotection

Apart from their ability to replace lost cells, stem cells have also been demonstrated to secrete trophic factors, including nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) [Gu, Y, et.al., 2021]. These elements may sustain the transplanted cells and aid in the survival and regeneration of native dopaminergic neurons [Stoker,T.B, et.al.,2022].

Modulation of Neuroinflammation

The pathophysiology of Parkinson's disease (PD) heavily relies on neuroinflammation, which stem cells have been shown to regulate by virtue of their immunomodulatory capabilities [Kikuchi, T, et.al, 2017]. Particularly MSCs have been demonstrated to control the function of immune cells such as microglia, which helps to reduce neuroinflammation and may even halt the course of illness [Stoker et.al., 2018, Stoddard-Bennett, et.al., 2019].

3) Preclinical Studies

a) Animal Models

Preclinical research has mostly used animal models of Parkinson's disease (PD) generated by toxins, such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model and the 6-hydroxydopamine (6-OHDA) lesion model [Petit, G.H et.al., 2014]. These models provide a platform for assessing the therapeutic potential of stem cell-based therapies by simulating the loss of dopaminergic neurons and motor impairments seen in Parkinson's disease.

b) Experimental Outcomes

Several preclinical investigations have documented favorable results after stem cell transplantation in animal models of Parkinson's disease. Enhanced motor performance, elevated dopamine release, and transplanted cells' survival and integration are a few of these [Stoker,T.B, et.al.,2022, Barker, R.A, et.al., 2017]. Furthermore, research has shown that stem cells, in particular MSCs, have immunomodulatory and neuroprotective properties that help to reduce neuroinflammation and support endogenous neuronal survival [Venkataramana et.al., 2022, Barker,R.A et.al., 2020].

PRINCIPAL RESEARCH

A. In vitro studies

1) Stem cell differentiation into dopaminergic neurons

The capacity to effectively convert stem cells into functioning dopaminergic neurons is a crucial step in the development of stem cell-based treatments for Parkinson's disease (PD). Different techniques have been developed to control the development of adult stem cells, including mesenchymal stem cells (MSCs) [Crigler, L et.al., 2006], induced pluripotent stem cells (iPSCs) [Kikuchi, T, et.al, 2017], and embryonic stem cells (ESCs) [Nolbrant, S et.al., 2017], into cells that resemble dopaminergic neurons. For instance, by imitating the developmental events that take place during midbrain formation, Kriks et al. (2011) created a technique to produce dopaminergic neurons from human ESCs and iPSCs [Kriks et.al., 2011]. By adding tiny chemicals and growth factors one after the other, this technique produced highly enriched populations of dopaminergic neurons in the midbrain.

2**. Characterization of stem cell-derived neurons' functions**

To make sure stem cell-derived dopaminergic neurons are suitable for transplantation, they must undergo functional characterization following successful differentiation. This entails evaluating if they express dopaminergic markers, have electrical characteristics resembling those of functioning neurons, and can make and release dopamine [Steinbeck et.al., 2015]. As an illustration of their functional maturation, Kikuchi et al. (2017) showed that human iPSC-derived dopaminergic neurons could spontaneously fire action potentials and release dopamine in response to depolarizing stimuli [Kikuchi, T, et.al, 2017].

B) Animal models for Parkinson's disease

1. Models caused by toxins, such as 6-OHDA and MPTP Preclinical research frequently uses animal models of Parkinson's disease generated by toxins. This neurotoxin is unilaterally injected into the nigrostriatal pathway in the 6-hydroxydopamine (6-OHDA) model, which causes dopaminergic neurons to selectively degenerate . By inhibiting mitochondrial complex I, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model—which is frequently employed in non-human primates—also causes dopaminergic neuronal death [Langston et.al., 1983].
2. Genetic models, such as overexpression of α-synuclein, Genes linked to Parkinson's disease, such α-synuclein, are overexpressed or mutated to create genetic models of the illness. Key characteristics of Parkinson's disease (PD) are reflected in transgenic mice models overexpressing human α-synuclein, which show progressive motor impairments, dopaminergic neuronal loss, and the development of Lewy body-like inclusions [Chesselet et.al., 2008].

TRANSPLANTATIONAL STUDIES

- The ability of transplanted cells to survive and integrate Various stem cell types implanted into animal models of Parkinson's disease have been studied in preclinical investigations for their integration and survival. The striatum of rats lesioned with 6-OHDA, for instance, was found to be able to support the survival and integration of human ESC-derived dopaminergic neurons, which went on to form dense neuritic networks and innervate the host brain [Kriks et.al., 2011].
- Modifications in behavior and functionality After receiving stem cell transplants, several studies have shown improvements in behavior and function in animal models of Parkinson's disease. The striatum of 6-OHDA-lesioned rats showed notable improvements in motor function following the transplantation of human ESC-derived dopaminergic neurons, including a reduction in amphetamine-induced rotating behavior [Grealish et al., 2014].
- Possible negative consequences and difficulties Preclinical research on stem cell transplantation has yielded encouraging findings, but there are still unknown risks and difficulties. These include immunological rejection concerns and poor transplant life [Stoker et.al., 2018], as well as the possibility of tumor growth, especially with undifferentiated or partly differentiated stem cells [Danzer,S.C et.al., 2018].

CLINICAL TRIALS

A) Overview of completed and ongoing clinical trials

- **Patient populations and study designs**

Many research designs, from open-label, phase I safety studies to randomized, placebo-controlled, phase II effectiveness trials, have been used in clinical trials looking into stem cell treatment for Parkinson's disease. Typically, individuals with severe Parkinson's disease who are no longer responding effectively to traditional therapies are enrolled in these studies [Danzer,S.C et.al., 2018].

In the Phase I/II trial, for instance, individuals with Parkinson's disease were assessed for safety and potential efficacy prior to receiving human parthenogenetic stem cell-derived dopaminergic neurons [Stoker et.al., 2018]. The study was carried out in collaboration with Fujifilm Cellular Dynamics, Inc. (FCDI) and Cure Parkinson's Trust.

- **Sources of the stem cells (e.g., adult, embryonic, iPSCs)**

Clinical studies for Parkinson's disease have investigated a variety of stem cell sources, such as induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and embryonic stem cells (ESCs). Although ESCs have been the most often used source up to this point, the use of iPSCs is becoming more popular because of their potential for autologous transplantation and the fact that there are fewer ethical difficulties with them [Barker, R.A, et.al., 2017].

One such study assessing the safety and tolerability of transplanting human ESC-derived dopaminergic progenitor cells in patients with Parkinson's disease is the NYSTEM trial, which is being carried out by Memorial Sloan Kettering Cancer Center and VistaGen Therapeutics, Inc. [Takahashi,J,2019].

B) Stem cell transplantation's tolerance and safety

Assessing the safety and tolerability of stem cell transplantation in individuals with Parkinson's disease has been the main focus of clinical trials. Overall, most trials have found no significant adverse effects associated with the transplanted cells, indicating that stem cell treatment has been well-tolerated [Studer et.al., 2021]. Notwithstanding, several studies have documented unfavorable outcomes, including dyskinesias, graft-induced dyskinesias, and cerebral hemorrhage, underscoring the necessity of cautious patient selection and extended observation [Barker et.al., 2015].

Efficacious results

- **Enhancements to motor function**

Early-phase clinical trials have mostly focused on assessing safety, although some have also found improvements in motor function after stem cell transplantation. For instance, some patients in the NYSTEM study saw improvements in motor scores as determined by the Unified Parkinson's Disease Rating Scale (UPDRS) [Takahashi,J,2019].

- **Improvements in non-motor symptoms**

Certain stem cell treatment experiments have looked at the possible effects on non-motor symptoms of Parkinson's disease, such quality of life and cognitive function, in addition to motor function. But there hasn't been much evaluation of non-motor effects, thus further study is required in this field [Stoker, T. B., & Greenland, J. C.2018].

Metrics of living quality

Qualitative measures of life have been used as exploratory or secondary endpoints in a number of therapeutic research. Using the Parkinson's Disease Questionnaire (PDQ-39), for instance, the Cure Parkinson's Trust and FCDI Phase I/II trial assessed improvements in quality of life [Stoker, T.B, et.al., 2018].

Challenges and limitations

1. **Ethics-related factors**

Because human embryos are destroyed during the derivation process, the use of embryonic stem cells in therapeutic studies has sparked ethical questions. There are currently continuing discussions and laws pertaining to the use of iPSCs and parthenogenetic stem cells in therapeutic applications, even if their usage may get around some ethical dilemmas [Barker, R.A, et.al., 2017].

2. **Rejection because to immunology**

The possibility of immunological rejection of the transplanted cells is one of the main obstacles in stem cell transplantation, especially when using allogeneic stem cell sources. To lessen this danger, techniques including encapsulation, immunosuppression, or the use of autologous iPSCs have been investigated [Lo, B, et.al., 2009].

3. **Hazard of tumor development**

The possibility of tumor development or unchecked cell proliferation from transplanted cells is another issue with stem cell treatment. Effective differentiation techniques and strict quality control measures are necessary to reduce the possibility of remnant undifferentiated cells in the transplanted cell population [Takahashi,J,2019].

Future Directions and Perspectives

A. Methods to enhance stem cell treatment

- **Optimization of cell source**

The goal of ongoing research is to maximize the cell source for stem cell treatment in Parkinson's disease, taking scalability, safety, and efficacy into account. There is growing interest in investigating other sources, such as parthenogenetic stem cells (PSCs) and directly reprogrammed somatic cells, despite the fact that embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been examined extensively [Sturm,D,et.al., 2019].

In comparison to ESCs and iPSCs, pluripotent stem cells (PSCs) produced from unfertilized oocytes may have less ethical issues, a lower risk of tumorigenicity, and better immunocompatibility [Shahjalal,et.al., 2021]. One potential solution to circumvent the pluripotent stage and perhaps lower the danger of tumor formation is to directly reprogramme somatic cells, such as fibroblasts or blood cells, into dopaminergic neurons or neural progenitor cells [Revazoya,et.al.,2017].

- **Promoting the integration and survival of donated cells**

Ensuring the long-term survival and effective integration of transplanted cells is a major problem in stem cell treatment for Parkinson's disease. Modulating the host microenvironment, offering trophic support, and refining cell transport techniques are among the strategies being researched [Barker, R.A, et.al., 2017].

Biomaterial scaffolds and hydrogels, for instance, have been investigated as delivery systems to enhance cell integration and survival by offering a growth factor-controlled release and a supportive milieu [Stoker, T.B, et.al., 2018]. Furthermore, there has been potential demonstrated in improving graft survival and functional results by co-transplantation of stem cells with mesenchymal stem cells or astrocytes [Adil,M.M,et.al.,2017].

- **Combination with additional therapeutic approaches (such as growth factors or gene therapy)**

When treating Parkinson's disease, stem cell treatment may work in concert with other therapeutic modalities such growth factor administration and gene therapy. Gene therapy may be employed to alter the host environment or transplanted cells in order to improve neuronal survival, dopamine synthesis, or other desired outcomes [Soma,F.A,et.al.,2017].

To improve graft survival and functional outcomes in animal models, researchers have investigated the use of lentiviral vectors to overexpress nurr1, a transcription factor involved in dopaminergic neuron development, in stem cell-derived dopaminergic neurons prior to transplantation [Stoker, T.B, et.al., 2018].

B. Ethical and legal considerations

It is critical to address ethical and regulatory issues as stem cell treatment for Parkinson's disease moves closer to clinical translation. Essential stages for innovative cell products and delivery techniques include establishing standardized protocols, guaranteeing strict quality control, and getting regulatory approval [Ganat,Y.M,et.al.,2012].

Furthermore, the design and execution of clinical trials must carefully address ethical issues such informed consent, equal access to experimental medicines, and appropriate management of patient expectations[Takahashi,J,2019].

C. Problems with translation and possible fixes

There are several obstacles to overcome before stem cell treatment may be widely used in clinical settings. These include resolving the logistical and financial constraints to clinical deployment, improving efficient and repeatable differentiation techniques, and increasing cell output to meet prospective clinical demand [Barker, R.A, et.al., 2017].

These translational barriers may be removed and the clinical translation of stem cell treatments for Parkinson's disease sped up with the support of creative financing models, public-private partnerships, and cooperative efforts amongst academia, industry, and regulatory authorities [Stoker, T.B, et.al., 2018].

CONCLUSION

As a potentially effective method of treating Parkinson's disease, stem cell treatment has the ability to replenish destroyed dopaminergic neurons and raise dopamine levels in the brain. Numerous stem cell types, such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs), have been shown in preclinical studies to be able to differentiate into functional dopaminergic neurons and enhance motor function in animal models of Parkinson's disease [Takahashi,J,2019].

Stem cell transplantation safety and tolerability have been the main focus of clinical research, and encouraging results have shown that the surgery is generally well tolerated and does not typically result in serious adverse effects that are directly connected to the transplanted cells [Stoker, T.B, et.al., 2018].

Future studies should concentrate on maximizing the cell supply for stem cell treatment while taking immunocompatibility, scalability, safety, and effectiveness into account. Additional research is necessary to fully understand other sources, such as parthenogenetic stem cells and directly reprogrammed somatic cells [Sturm,D,et.al.,2019].

It's important to look at methods like co-transplanting supporting cells, using biomaterial scaffolds to improve the integration and survival of transplanted cells, and altering the host microenvironment [Barker,R.A,et.al.,2017]. Furthermore, synergistic advantages may arise from combining stem cell treatment with other therapeutic modalities including gene therapy and growth factor administration [Soma,F.A,et.al.,2017].

For stem cell treatment to successfully transition from bench to bedside, it will be imperative to address regulatory and ethical issues as well as translational problems pertaining to scaling up cell production and clinical application [Ganat,Y.M,et.al.,2012, Takahashi,J,2019, Barker,et.al.,2017, Stoker,T.B, et.al.,2018].

In order to advance this subject and eventually introduce stem cell treatment for Parkinson's disease into clinical practice, cooperation between funding agencies, industry, academia, and regulatory bodies will be necessary.

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