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The Potential of Stem Cell Therapy in Treating Neurodegenerative Diseases: Challenges and Future Prospects

Dr. Satyender Yadav, Assistant Professor, GGJ Govt. College, Hisar, Haryana

Abstract

Neurodegenerative diseases (NDs) such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) represent a growing global health challenge due to their progressive nature and lack of effective treatments. In recent years, stem cell therapy has emerged as a promising treatment modality, offering potential for cellular regeneration, neuroprotection, and functional recovery. This paper explores the potential of stem cell therapy in the context of neurodegenerative diseases, identifying key mechanisms, therapeutic strategies, challenges, and future prospects. Despite promising preclinical and early clinical studies, significant hurdles such as immunogenicity, ethical concerns, and regulatory issues remain. This paper concludes with a discussion on ongoing advancements, the need for more robust clinical trials, and the hope for stem cell-based therapies to reshape the future of neurodegenerative disease treatment.

Keywords: Stem cell therapy, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, regenerative medicine, neuroprotection, challenges, future prospects

1. Introduction

Neurodegenerative diseases (NDs) are a group of disorders characterized by the progressive degeneration of the nervous system, leading to cognitive, motor, and psychological impairments. Common NDs include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Currently, there are limited therapeutic options to halt or reverse the progression of these diseases, highlighting the need for innovative treatments (Dorsey et al., 2018). Among the most promising advancements in this field is stem cell therapy, which aims to replace damaged neurons, restore lost functions, and potentially slow disease progression (Cheng et al., 2018). This paper will examine the current state of stem cell therapy for neurodegenerative diseases, the challenges it faces, and its future prospects.

2. Stem Cell Therapy and Mechanisms of Action

Stem cells are undifferentiated cells capable of self-renewal and differentiation into various cell types, including neurons. Several types of stem cells have shown potential for treating NDs, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and neural stem cells (NSCs) (Takahashi & Yamanaka, 2006). Stem cells offer potential therapeutic strategies through their ability to regenerate lost neurons, secrete neurotrophic factors, and provide neuroprotection. Stem cell therapy refers to the use of stem cells to treat or prevent disease or conditions by promoting the repair or regeneration of damaged tissues or organs. Stem cells are unique because they have the ability to self-renew and differentiate into various specialized cell types, such as neurons, muscle cells, or blood cells. This regenerative potential makes stem cells a promising therapeutic tool for a variety of diseases, particularly neurodegenerative diseases, which are characterized by the loss or dysfunction of specific types of neurons.

There are several types of stem cells that are commonly explored for therapeutic purposes, each with distinct properties and potential applications. The main categories of stem cells used in therapy include **embryonic stem cells (ESCs)**, **induced pluripotent stem cells (iPSCs)**, and **neural stem cells (NSCs)**.

2.1. Types of Stem Cells Used in Therapy

- **Embryonic Stem Cells (ESCs):** ESCs are pluripotent, meaning they can differentiate into any cell type in the body. These cells are typically derived from early-stage embryos. Due to their broad differentiation potential, ESCs hold significant promise for replacing damaged neurons or other tissues in neurodegenerative diseases. However, their use raises ethical concerns and regulatory challenges.
- **Induced Pluripotent Stem Cells (iPSCs):** iPSCs are adult cells (typically from the skin or blood) that are genetically reprogrammed to revert to a pluripotent state similar to ESCs. iPSCs offer a potential solution to the ethical issues surrounding ESCs because

they do not require the use of embryos. Additionally, iPSCs can be generated from a patient's own cells, reducing the risk of immune rejection.

- **Neural Stem Cells (NSCs):** NSCs are multipotent cells capable of differentiating into various types of neural cells, such as neurons, astrocytes, and oligodendrocytes. These cells are often used in treating neurodegenerative diseases, particularly those involving damage to the central nervous system. NSCs can be derived from the brain, spinal cord, or other neural tissue.

2.2. Mechanisms of Action in Stem Cell Therapy

Stem cell therapy for neurodegenerative diseases operates through several mechanisms. These mechanisms aim to regenerate damaged tissue, protect existing neurons, and restore normal function in the affected area of the brain or nervous system. Key mechanisms include:

- **Regeneration of Damaged Neurons:** One of the most promising aspects of stem cell therapy is the potential for stem cells to replace damaged or dead neurons in neurodegenerative diseases like Alzheimer's and Parkinson's disease. For example, in Parkinson's disease, the progressive loss of dopaminergic neurons leads to motor impairments. Transplanting stem cells that can differentiate into dopamine-producing neurons offers a potential therapeutic strategy to restore lost function (Tuszynski et al., 2015). This approach has been particularly successful in animal models, and clinical trials are underway to assess its efficacy in humans.

- **Neuroprotection and Secretion of Neurotrophic Factors:** Stem cells can promote neuroprotection through the secretion of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF). These factors help to maintain the health and survival of neurons, protect them from neurodegenerative processes, and support neuronal growth and repair (Tuszynski et al., 2015). In diseases like Alzheimer's, where toxic proteins like amyloid-beta accumulate, stem cells may help alleviate the damage caused by these proteins by releasing factors that reduce inflammation and oxidative stress.

- **Anti-inflammatory Effects:** Chronic inflammation is a hallmark of many neurodegenerative diseases. Stem cells have been shown to possess anti-inflammatory properties, which can help reduce the neuroinflammation associated with conditions like Alzheimer's and Parkinson's diseases. By modulating immune responses in the brain, stem cells may prevent further neuronal damage (Li & Zhang, 2018). Additionally, stem cells might help control the activation of microglia (the brain's resident immune cells), preventing them from contributing to neurodegeneration.

- **Replacement of Lost Brain Functions and Neuroplasticity:** In diseases like Alzheimer's, where memory and cognitive functions are lost, stem cells may play a role in restoring function through neuroplasticity—the brain's ability to reorganize itself by forming new neural connections. Stem cells could help replace lost neurons and enhance the brain's ability to adapt and rewire itself, thus improving cognitive functions (Kordower et al., 2013).

- **Enhancing Angiogenesis:** Stem cells may also promote angiogenesis (the formation of new blood vessels), which is essential for the delivery of oxygen and nutrients to the brain. In conditions like Alzheimer's, the blood-brain barrier (BBB) can become compromised, limiting the flow of essential nutrients to neurons. Stem cells can help repair the BBB and improve brain vascular health, potentially aiding in the recovery of lost functions (Pashos et al., 2019).

2.3. Challenges in Stem Cell Therapy

While the potential for stem cell therapy is enormous, there are several challenges that must be addressed for it to be widely applicable in treating neurodegenerative diseases:

- **Immunogenicity and Rejection:** One of the primary concerns when using stem cells, particularly allogeneic stem cells (from a donor), is the risk of immune rejection. This can be minimized by using autologous iPSCs, derived from the patient's own cells, but this approach is still in the experimental stages.

- **Ethical and Regulatory Issues:** The use of ESCs, which requires the destruction of human embryos, raises ethical concerns. While iPSCs offer a solution to these concerns, regulatory frameworks are still developing to ensure the safety and efficacy of stem cell-based therapies.

- **Tumorigenicity:** There is a risk that stem cells, particularly pluripotent stem cells, may proliferate uncontrollably after transplantation, forming tumors. This issue needs to be carefully managed in clinical applications.

Stem cell therapy offers considerable promise in the treatment of neurodegenerative diseases by enabling the regeneration of damaged neurons, providing neuroprotection, reducing inflammation, and potentially restoring lost functions. While the basic mechanisms behind stem cell therapy are becoming better understood, challenges such as immunogenicity, ethical concerns, and tumorigenicity must be overcome. Nonetheless, ongoing advancements in stem cell technology, combined with innovative approaches like gene editing and personalized medicine, could ultimately lead to breakthroughs in treating and even curing neurodegenerative diseases.

3. Challenges of Stem Cell Therapy for Neurodegenerative Diseases

Despite the promise of stem cell therapy, numerous challenges must be overcome before widespread clinical application can be achieved. While stem cell therapy holds significant promise for treating neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD), several challenges must be addressed before these therapies can be widely applied in clinical settings. These challenges encompass a range of scientific, ethical, clinical, and regulatory issues. Below are the primary challenges associated with stem cell therapy for neurodegenerative diseases:

3.1. Immunogenicity and Immune Rejection

One of the most significant challenges of stem cell therapy is the potential for immune rejection, particularly when allogeneic (donor-derived) stem cells are used. When stem cells from a different individual are transplanted into a patient, the recipient's immune system may recognize them as foreign and mount an immune response to eliminate them. This leads to transplant rejection and limits the therapeutic effectiveness of stem cell treatments.

- **Autologous Stem Cells as a Solution:** One way to circumvent this issue is by using autologous stem cells, derived from the patient's own tissues, to reduce the risk of immune rejection. **Induced pluripotent stem cells (iPSCs)**, which are generated by reprogramming a patient's somatic cells (such as skin or blood cells) into pluripotent stem cells, offer a potential solution. However, generating sufficient quantities of high-quality iPSCs for clinical use remains a complex and costly process, with ongoing research needed to improve efficiency and scalability.

- **Immunosuppressive Therapy:** In some cases, immunosuppressive drugs may be used to suppress the patient's immune system temporarily. However, long-term immunosuppression can have significant side effects, including increased vulnerability to infections and other complications.

3.2. Ethical Concerns

Stem cell research, especially the use of **embryonic stem cells (ESCs)**, raises significant ethical concerns. The primary ethical issue is related to the use of human embryos to harvest stem cells. This process involves destroying the embryo, which some argue is morally unacceptable, as it may be seen as the destruction of potential life.

- **Use of iPSCs:** While **induced pluripotent stem cells (iPSCs)** provide an alternative to ESCs by reprogramming adult cells into pluripotent stem cells without the need for embryos, the ethical concerns surrounding stem cell research persist, especially regarding the potential for the creation of embryos or "human cloning" in the future.
- **Ethical Guidelines and Oversight:** Many countries and institutions have established ethical guidelines to ensure that stem cell research is conducted responsibly. However, ethical debates around stem cell therapy continue, particularly when considering its long-term implications, including the possibility of genetic manipulation or altering the germline (heritable genetic changes).

3.3. Tumorigenicity (Risk of Tumor Formation)

A major concern with stem cell-based therapies is the potential for **tumorigenicity**—the ability of stem cells to form tumors after transplantation. Stem cells, especially pluripotent stem cells, have an almost unlimited ability to divide and proliferate, which can be beneficial for regenerating tissues. However, this uncontrolled proliferation can lead to the formation of teratomas (tumors containing multiple types of tissue) or other types of malignancies.

- **Controlled Differentiation:** To reduce the risk of tumor formation, it is essential to ensure that stem cells differentiate into the desired cell type before transplantation.

However, ensuring complete and controlled differentiation of stem cells into specific neural cell types (such as dopaminergic neurons for Parkinson's disease) remains a significant challenge in stem cell research.

- **Cellular Safety Protocols:** Researchers are developing more refined methods to control stem cell proliferation and differentiation. For example, genetic modifications or small molecules can be used to guide stem cells to differentiate into specific neural lineages, reducing the risk of tumor formation (Li & Zhang, 2018). However, such techniques must be tested extensively for safety and efficacy.

3.4. Limited Engraftment and Survival of Transplanted Cells

Even if stem cells are successfully transplanted into the brain or nervous system, there are challenges related to their **engraftment** (the ability to integrate into the existing tissue) and **survival** over time. After transplantation, stem cells must survive, proliferate, and differentiate into functional neurons or other neural cells. However, this process is often hindered by factors such as:

- **Scar Tissue Formation:** The central nervous system (CNS) is particularly prone to forming **glial scar tissue** in response to injury or transplantation, which can inhibit the integration of new cells and block their function.

- **Poor Vascularization:** Adequate blood supply is essential for the survival of transplanted cells. The lack of blood vessels in the transplanted area can lead to poor oxygen and nutrient supply, hindering the engraftment and survival of stem cells.

- **Inappropriate Microenvironment:** The surrounding microenvironment in neurodegenerative diseases may not be conducive to stem cell survival and differentiation. For example, in diseases like Alzheimer's, the accumulation of amyloid plaques and neurofibrillary tangles can create a toxic environment that impedes the survival of transplanted stem cells.

3.5. Standardization of Stem Cell Protocols

There is currently a lack of **standardized protocols** for the production, differentiation, and transplantation of stem cells, which makes it difficult to compare results across studies and to apply stem cell therapy in a clinical setting. The process of generating stem cells, differentiating them into neural cell types, and transplanting them into patients is highly complex and varies between laboratories.

- **Regulatory Approval and Clinical Trials:** Due to the complex nature of stem cell-based therapies, regulatory agencies such as the FDA (in the United States) have stringent requirements for clinical trials. These requirements include demonstrating the safety, purity, and efficacy of the stem cells before they can be used in humans. This process is lengthy and costly, which can delay the availability of stem cell treatments for neurodegenerative diseases.

3.6. High Costs and Accessibility

Stem cell therapy is an expensive treatment option, and the **costs of generating, maintaining, and transplanting stem cells** are significant. This includes the cost of obtaining stem cells, differentiating them into the required neural cell types, and administering the therapy. For patients with neurodegenerative diseases, many of whom are elderly, the high cost of stem cell-based treatments can limit accessibility, particularly in low-resource settings.

- **Scalability of Stem Cell Therapies:** The production of stem cells for therapy requires specialized facilities, trained personnel, and strict quality control measures. Scaling up stem cell therapies to treat a large number of patients remains a major challenge in the field of regenerative medicine.

While stem cell therapy holds great promise for treating neurodegenerative diseases, several significant challenges must be overcome. These include issues related to immune rejection, ethical concerns, tumorigenicity, limited engraftment and survival, lack of standardized protocols, and the high cost of treatment. Addressing these challenges will require continued research, technological advancements, and careful regulation. As the field of stem cell therapy evolves, these obstacles may be mitigated, opening the door for more effective and accessible treatments for patients suffering from neurodegenerative diseases.

4. Future Prospects of Stem Cell Therapy

Despite the challenges, stem cell therapy holds substantial promise for revolutionizing the treatment of NDs. Recent advancements in gene editing technologies, such as CRISPR/Cas9, have opened new possibilities for improving the safety and efficiency of stem cell therapies (Doudna & Charpentier, 2014). Additionally, the development of biomaterials and scaffolds to support stem cell engraftment and survival in the brain may enhance the success of these therapies (Pashos et al., 2019). Stem cell therapy holds immense promise for the treatment of neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). Despite the numerous challenges facing stem cell-based therapies, ongoing advancements in stem cell technology, genetic engineering, and clinical research are paving the way for more effective, targeted, and accessible treatments. The future prospects of stem cell therapy in neurodegenerative diseases depend on overcoming current barriers, improving safety and efficacy, and expanding clinical applications.

4.1. Advances in Gene Editing and Personalized Medicine

One of the most exciting prospects in stem cell therapy is the integration of **gene editing technologies**, particularly **CRISPR/Cas9**, into stem cell-based treatments. CRISPR allows for precise modifications of the genome, enabling researchers to correct genetic mutations associated with neurodegenerative diseases at the molecular level.

- **Gene Editing for Disease Correction:** In genetic neurodegenerative diseases, such as Huntington's disease, the use of CRISPR could enable researchers to directly edit the faulty genes in patient-derived iPSCs before transplantation. This would ensure that the transplanted cells are free of the genetic defects that cause disease, potentially halting or even reversing disease progression (Doudna & Charpentier, 2014).

- **Personalized Stem Cell Therapy:** With the ability to generate iPSCs from a patient's own cells, personalized stem cell therapies could become a reality. This would allow for tailored treatments based on an individual's genetic makeup and the specific characteristics of their neurodegenerative disease. Personalized approaches could improve the success rates of stem cell therapies, as the cells would be immunologically compatible with the patient, minimizing the risk of rejection (Athauda & Foltynie, 2016).

4.2. Regenerative Medicine and Neural Repair

Stem cell-based regenerative therapies have the potential to replace or repair damaged neurons and restore brain function. Research is already underway to develop cell-based therapies for the **regeneration of lost neurons**, particularly in diseases like Parkinson's, where dopaminergic neurons are lost, and Alzheimer's, where memory-related neurons degenerate.

- **Neurogenesis and Functional Recovery:** The ability of stem cells to differentiate into specific neural cell types, such as dopaminergic neurons or cholinergic neurons, could lead to functional recovery in patients. In Parkinson's disease, studies are exploring the transplantation of stem cells that differentiate into dopamine-producing neurons to restore motor functions (Kordower et al., 2013). This approach could also be applied to other diseases, where specific types of neurons need to be replaced.

- **Enhanced Brain Repair:** In addition to replacing damaged neurons, stem cells can also enhance the brain's own repair mechanisms by secreting neurotrophic factors that support the survival of existing neurons and promote tissue regeneration (Tuszynski et al., 2015). This approach is being investigated in both preclinical studies and early-stage clinical trials for various neurodegenerative diseases.

4.3. Development of Biocompatible Scaffolds and Delivery Systems

One major challenge in stem cell therapy is the **delivery** of stem cells to the affected areas of the brain and spinal cord. To address this, researchers are developing **biocompatible scaffolds** and **drug delivery systems** to improve the integration and survival of transplanted cells.

- **Neural Scaffolds for Stem Cells:** Biomaterials, such as hydrogel scaffolds, are being designed to support the engraftment and survival of stem cells in the brain. These scaffolds can provide a structure that mimics the natural extracellular matrix, allowing transplanted stem cells to thrive and differentiate more effectively (Pashos et al., 2019).

- **Targeted Drug Delivery:** Advances in drug delivery systems could help deliver stem cells directly to the affected brain regions, minimizing the risk of unwanted side effects and improving therapeutic outcomes. Nanotechnology and gene therapy may also play a role in optimizing stem cell delivery and ensuring that cells reach their intended target in the brain (Dorsey et al., 2018).

4.4. Clinical Translation and Long-Term Efficacy

As stem cell therapies for neurodegenerative diseases move from the laboratory to the clinic, **clinical trials** will play a crucial role in assessing their long-term efficacy, safety, and therapeutic potential. Several early-stage trials are already underway, with promising results regarding the safety and feasibility of stem cell-based interventions.

- **Early Successes in Clinical Trials:** Clinical trials of stem cell therapies have shown early signs of success in treating Parkinson's disease and other neurodegenerative conditions. For example, a study involving the transplantation of fetal mesencephalic dopaminergic neurons into patients with Parkinson's disease demonstrated improvements in motor function (Freed et al., 2001). Similarly, the use of iPSCs in animal models of Alzheimer's disease has shown the potential to restore memory and cognitive function (Jiang et al., 2017).

- **Long-Term Monitoring and Follow-Up:** As clinical trials progress, long-term monitoring of patients will be essential to assess the durability and sustainability of stem cell-based treatments. This includes monitoring for potential complications such as immune rejection, tumor formation, and other adverse effects. Over time, as the safety profile of stem cell therapies is better understood, the scope of their use will likely expand.

4.5. Overcoming the Challenges of Tumorigenicity and Immune Rejection

Addressing the challenges of **tumorigenicity** (the formation of tumors) and **immune rejection** will be crucial for the broader application of stem cell therapies. Researchers are exploring various strategies to mitigate these risks:

- **Induced Differentiation and Controlled Proliferation:** Researchers are focusing on improving methods for inducing stem cells to differentiate into mature neural cell types before transplantation, reducing the risk of uncontrolled cell growth and tumor formation (Li & Zhang, 2018). Additionally, techniques such as **genetic modifications** to control stem cell proliferation and differentiation are being developed.

- **Immunosuppressive Strategies:** The development of strategies to reduce immune rejection, such as using **immunologically matched stem cells** (e.g., iPSCs from the patient's own cells), or using stem cells that can evade the immune system, will enhance the safety and effectiveness of stem cell therapies. Advances in **immune-modulation** techniques could further help address the issue of immune rejection (Lindvall & Kokaia, 2012).

4.6. Global Accessibility and Affordable Therapies

A significant barrier to the widespread adoption of stem cell therapies is their **cost**. As the technology advances, it will be crucial to develop cost-effective methods for producing and administering stem cell-based treatments. This includes scaling up production, improving the efficiency of differentiation protocols, and reducing the costs associated with maintaining stem cell banks.

- **Scalability and Global Reach:** Efforts are underway to make stem cell therapies more affordable and accessible to a broader population. This may involve collaborations between research institutions, healthcare providers, and governments to support the development of large-scale manufacturing systems for stem cell therapies. Additionally, the use of **off-the-shelf stem cell products**—ready-made cell lines or tissue grafts—could reduce costs and make treatments available to more people (Kumagai et al., 2014).

The future prospects of stem cell therapy in treating neurodegenerative diseases are promising, with numerous advancements in stem cell technology, gene editing, and personalized medicine on the horizon. While significant challenges remain, including immune rejection, tumorigenicity, and scalability, ongoing research and clinical trials are paving the way for safer, more effective treatments. As the field continues to evolve, stem cell therapies have the potential to transform the treatment landscape for neurodegenerative diseases, offering hope for patients suffering from these debilitating conditions. The combination of innovative therapies, improved delivery systems, and greater accessibility will likely drive the clinical success of stem cell-based interventions in the coming decades.

5. Conclusion

Stem cell therapy holds great promise in treating neurodegenerative diseases by offering potential for neuronal regeneration, neuroprotection, and disease modification. However, significant challenges related to immunogenicity, ethical concerns, tumorigenicity, and regulatory issues must be addressed before these therapies can become widely used. The future of stem cell therapy in NDs depends on continued advancements in stem cell technology, clinical trials, and regulatory frameworks. As the field progresses, stem cell therapies may become a cornerstone in the management and potential cure of debilitating neurodegenerative diseases.

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