Stem Cell Therapies and Neuroregeneration in Alzheimer's and Parkinson's Disease

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Abstract

Alzheimer's Disease (AD) and Parkinson's Disease (PD) are two of the most common neurodegenerative disorders, characterized by progressive neuronal loss and a lack of curative treatments. Stem cell therapies offer regenerative potential by replacing lost neurons, promoting neuroprotection, and managing neuroinflammation. Induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs) can differentiate into neurons and glial cells, a process crucial for neural repair and functional recovery. Studies highlight the various roles of stem cells in cell replacement, neurotrophic support, and the control of inflammation. Early clinical trials yielded results consistent with improvements in motor and cognitive function, reduced inflammation, and decreased pathological markers. However, some challenges remain: long-term survival, integration, and immune response. Continued investigation and progress in biomaterials and targeted delivery are necessary to realize the full potential of stem cell therapy in treating AD and PD.

Introduction

Neurodegenerative diseases (NDDs) are conditions that gradually damage the central and peripheral nervous systems, leading to the progressive loss of nerve cells. Over time, this degeneration severely affects brain function, causing declines in nearly every function that was previously intact. While these diseases affect a significant portion of the global population, a cure has yet to be found. Alzheimer's disease and Parkinson's Disease are the most notable NDDs, though they affect the body in distinct ways. Alzheimer's disease is characterized by the buildup of amyloid plaques and neurofibrillary tangles in the brain, which then leads to the death of brain cells. This causes brain shrinkage, then cognitive decline, and eventually death. In the U.S., 6.9 million people aged 65 and older are currently living with the disease—a number expected to double to 13.8 million by 2060. Parkinson's disease, also known as paralysis agitans, impairs movement. Since the disease is so complex to detect early on, a diagnosis typically occurs only after symptoms like tremors, slow movement, rigidity, and balance issues appear. Parkinson's disease involves Lewy bodies—abnormal protein deposits in the brain. Both Alzheimer's and Parkinson's fall under the umbrella of dementia, which slowly deteriorates cognitive function, causing memory loss, loss of motor skills, and hindrance of everyday activities. Because there is no cure for either, the only therapeutic relief offered is treatments that temporarily ease symptoms, such as memory loss and confusion, through medications that can temporarily boost brain chemicals or manage movement. However, stem cell research has the potential to change this reality.

Background and Objectives

Current therapies geared towards Alzheimer's disease (AD) and Parkinson's disease (PD) solely manage symptoms and don't stop or target neuronal loss. In AD, beta-amyloid plaques and tangles are primarily the leading cause of cognitive decline in an individual because they block cell communication and kill brain cells, leading to cognitive decline. Alzheimer's disease disrupts this communication, causing widespread loss of brain function as many neurons stop working properly and eventually die. Drugs like Lecanemab, Donanemab, and Aducanumab were made to slow the progressive nature of the decline by clearing sticky protein buildup (like amyloid) that harms cells and slows down memory loss. Still, their relief is limited and has numerous risks and side effects. Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra. The biochemical imbalance manifests with typical clinical symptoms, including resting tremor, rigidity, bradykinesia (i.e., a gradual slowness of spontaneous movement), loss of postural reflexes, or poor balance and motor coordination. Studies have shown that most people with PD have lost 60 to 80% or more of the dopamine-producing cells in the substantia nigra by the time symptoms appear. Stem cells are unique because they have the remarkable potential to renew themselves. They can develop into many different cell types in the body, including neurons and glial cells. Stem cells can restore neurons, reduce inflammation, and support brain function in AD and PD. Embryonic Stem Cells (ESCs), iPSCs, MSCs, and NSCs each offer promising forms of therapy, though risks remain, especially tumor formation and immune rejection.

Nevertheless, some preclinical models have demonstrated promising progress. The transplantation of these cells into rodent models of PD robustly restores motor function and reinnervates the host brain, with no evidence of tumor formation or redistribution of the implanted cells. It's proposed that this platform is suitable for successfully implementing human personalized autologous cell therapy for PD.

Mechanisms of Stem Cell Therapy in Alzheimer's and Parkinson's Diseases

While many types of stem cells can be used in various ways for different illnesses, certain ones are recommended explicitly for neurodegenerative diseases, as they appear to have a higher potential for providing increased neuroprotective and regenerative benefits for Alzheimer's disease (AD) and Parkinson's disease (PD). iPSCs can become neural cells that secrete brain-derived neurotrophic factor (BDNF), which supports the survival and recovery of existing neurons in damaged areas. Mesenchymal stem cells (MSCs) enhance this effect by influencing iPSC-derived neurons' metabolic function. MSC-secreted proteins then enhance glycolytic pathways in iPSC-derived neurons, boosting cellular energy production and significantly reducing neuroinflammation, a primary driver of neurodegeneration in AD and PD. Neural stem cells (NSCs) also play a key role. These multipotent cells generate neurons and glial cells, which are critical to healthy brain networks. The common factor that all these stem cells share is that they create new neural pathways, which is what AD and PD work to reverse and deteriorate**.** In PD, NSCs also help maintain dopaminergic pathways needed for motor control by replacing damaged cells and supporting neuron repair. Inflammation, a key feature of both AD and PD,

worsens brain damage, so this is another factor that needs to be managed when considering creating a cure and/or treatment for NDDs using stem cells. While iPSCs offer long-term potential, MSCs add immunomodulatory benefits. MSCs can respond to excessive proinflammatory signals by releasing a burst of anti-inflammatory cytokines, chemokines, and high levels of immunosuppressive factors. By interacting with microglia, MSCs promote a more neuroprotective state, which benefits the brain in slowing disease progression. Combining iPSCs, MSCs, and NSCs offers a multifaceted approach with numerous benefits, rather than just one. Still, a more complicated treatment and approach further increase the possible risks.

Clinical Trials and Research Findings on AD and PD

Alzheimer's (AD) and Parkinson's Disease (PD) are so complex that despite early-stage trials of stem cell therapies seeming promising, the sizable long-term scale data is limited, and the struggle in transforming lab data to patient care remains. A 2022 study found that MSCs and their secreted exosomes improved memory, reduced amyloid plaque accumulation — a hallmark of AD — and decreased neuroinflammation. PD research has progressed as well. In 2018, Kyoto University attempted to use patient-derived iPSCs to create dopamine-producing neurons. Initial results showed cell survival, safety, and symptom relief**.** However, transplanted cells often struggle to survive or fully integrate. The most considerable risk is immune rejection, particularly with donor cells, which would cause your body to attack cells or tissue that it sees as "not yours". Scaling up production for widespread clinical use also poses challenges. Obstacles such as immune rejection and tumorigenicity must be addressed before iPSC-based cell therapies can be widely used. iPSCs have ethical considerations that need to be considered, many of which are

linked to those surrounding embryonic stem cells, such as proper differentiation and function post-transplant. Poor differentiation can lead to tumors or unsuccessful treatments, raising safety concerns and consent issues. There are further various concerns, such as genetic information being misused, consent, and genetic cloning or enhancement. Advances are being made in biomaterials, which are essential as stem cell research progresses, and solutions must be actively developed to address these risks. Exosome-based therapies are helping to support cell survival and integration, which allows stem cell therapies for AD and PD to come closer to clinical integration.

Conclusion

Stem cell therapies are the future, reshaping the treatment of neurodegenerative diseases by replacing neurons, reducing inflammation, and rebuilding neural connections before clinical use. Induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs) have shown the most promising data, as they are highly adaptable and secrete large amounts of neurotrophic factors that support brain recovery. However, clinical success depends on overcoming challenges related to cell survival, integration, immune response, and safety. This is why research needs to be continued, given the breakthroughs already being made. Just consider the remarkable achievements that lie ahead with the continuation of trials and research.

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