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Review

Stem Cells as a Potential Game Changer in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders (NDDs) are debilitating conditions that progressively affect the central nervous system, causing a gradual decline in motor function, cognitive abilities, and quality of life. The most well-known types of NDDs are Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Despite extensive research, there are currently no known cures for these disorders, making them a significant public health challenge. In recent years, however, stem cell (SC) therapy has emerged as a promising treatment option for NDDs. Stem cells have the ability to regenerate and replace damaged or lost cells in the body, and can be used to stimulate neurogenesis and promote tissue repair. The types of SCs used in NDDs are including embryonic stem cells, adult stem cells, mesenchymal stem cells, and neural stem cells (NSCs). Each type of stem cell has unique properties that can be used as an active therapeutic agent for NDDs and reduce the risk of these disorders in today's world. In this chapter, we both emphasize the feature of SCs and their types used in NDD, we also examine their potential and applications in treating NDD, with a focus on PD, AD, HD, and ALS. Furthermore, we discuss the current state of knowledge and research on their therapeutic strategies and emphasize their promising application to present effective future insights for SCs studies.

Keywords: Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, neurodegenerative disorders, Parkinson's disease, stem cells.

Stem cells (SCs) are unique types of cells present in the body while these features are caused by self-renewing ability and capacity to differentiate into various cell types in the body of these cells. Due to the increasing appeal of SCs, there are many different studies on using SCs in the medical field such as dental applications and regenerative medicine.[1] Besides these fields, the properties of SCs provide advantages that are promising for use in neurodegenerative disorders (NDDs) as well. Therefore, SCs have emerged as a promising avenue in the field of NDDs, holding tremendous potential for both understanding the underlying mechanisms of these conditions and developing innovative therapeutic approaches.[2]

Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are characterized by the progressive loss of specific populations of neurons in the central nervous system (CNS). This loss leads to a range of debilitating symptoms and, currently, there are no effective treatments to halt or reverse the degenerative process. Stem cells, due to their unique ability to self-renew and differentiate into various cell types, including neurons, offer an unprecedented opportunity to address the challenges posed by NDDs. One approach involves the use of embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) to generate functional neurons that can replace the damaged or lost ones in the affected regions of the brain. Researchers have made significant progress in differentiating SCs into specific types of neurons and successfully transplanting them into animal models of NDDs, where they have demonstrated the ability to integrate into existing neural circuits and restore lost functions.[3] Furthermore, SCs can be utilized as a valuable tool in studying the mechanisms underlying neurodegenerative disorders. By

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reprogramming patient-derived cells into iPSCs and differentiating them into neurons, researchers can create *in vitro* disease models that accurately represent the patient's genetic background. This enables the investigation of disease progression, identification of novel therapeutic targets, and testing of potential drugs in a personalized and controlled environment.[4,5] Additionally, stem cells have the potential to provide neuroprotective effects by releasing various trophic factors and cytokines that promote cell survival, reduce inflammation, and stimulate endogenous repair mechanisms. These paracrine effects of stem cells can create a supportive environment for existing neurons, leading to their preservation and improved function. Furthermore, stem cell-based therapies can be combined with other strategies, such as gene therapy or biomaterial scaffolds, to enhance their therapeutic potential and provide a more comprehensive approach toward neuroregeneration.[6]

TYPES OF STEM CELLS USED IN NEURODEGENERATIVE DISORDERS

In the field of NDDs, several types of SCs have been explored for their potential use in research and therapeutic applications. Each type of SCs possesses unique characteristics and advantages, contributing to their suitability for different approaches in addressing these diseases. The types of SCs used in NDDs include ESCs, iPSCs, neural stem cells (NSCs), and mesenchymal stem cells (MSCs). Each type offers distinct advantages and can be utilized for different purposes, such as generating neurons for transplantation, creating disease models, or providing neuroprotective effects.[7] As stem cells differentiate, their ability to renew themselves decreases and they become more specialized as they continue to grow and divide. In addition, each type of stem cell shows its own characteristics. Continued research into these SC types and their application in NDDs holds great promise for future therapeutic advancements.[8]

Embryonic Stem Cells

The inner cell mass of early-stage embryos is the main origin of ESCs. Embryonic stem cells possess remarkable characteristics that make them a valuable tool in regenerative medicine and the study of NDDs. One of the key features of ESCs is their pluripotency, meaning they have the ability to differentiate into any cell type in the body, including neurons. This ability allows researchers to generate a virtually unlimited supply of neurons for transplantation purposes, which is particularly relevant in the context of NDDs where specific populations of neurons are lost.[9]

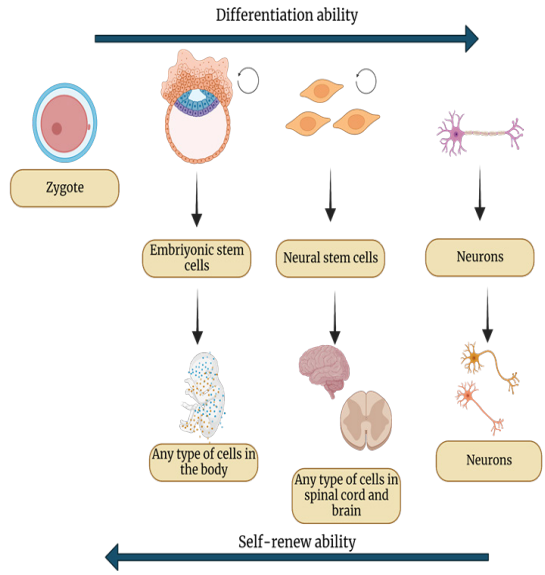

Figure 1. Stem cell differentiation and self-renew abilities.

In NDDs, ESCs have been utilized to generate functional neurons that can replace the damaged or lost ones in the affected areas of the brain. By guiding the differentiation of ESCs into specific neuronal subtypes, such as dopaminergic neurons for PD or cholinergic neurons for AD, researchers aim to restore neural circuitry and improve functional outcomes.[10]

Animal studies using ESC-derived neurons have shown promising results, with transplanted cells successfully integrating into existing neural networks and restoring lost functions. For instance, the study conducted by Grealish et al.[11] aimed to evaluate the therapeutic potential of dopamine neurons derived from human embryonic stem cells (hESCs) in a rat model of PD. In the study, the researchers generated dopamine neurons from hESCs and compared their efficacy and potency to that of fetal dopamine neurons, which have previously shown promising results in preclinical studies. The researchers transplanted the hESC-derived dopamine neurons into the brains of rats with induced Parkinson's-like symptoms. The results demonstrated that the hESC-derived dopamine neurons successfully integrated into the rat brain and showed similar functional effects as the fetal dopamine neurons. The transplanted cells survived, developed mature characteristics, and released dopamine in the rat brain, leading to improvements in motor function. The study also found that the transplanted hESC-derived dopamine neurons showed similar potency to the fetal neurons in terms of their ability to restore motor function.

Furthermore, ESCs have been instrumental in creating disease models for NDDs.[12] By generating ESCs lines from patients with specific genetic mutations associated with these conditions, researchers can recapitulate disease processes in the laboratory. This allows for the study of disease progression, identification of novel therapeutic targets, and screening of potential drugs in a more relevant and personalized manner. ESC-derived models have contributed to a better understanding of disease mechanisms and the development of innovative treatment strategies. Within the scope of this, the study by Sabogal-Guáqueta et al.[13], focused on the alterations in microglia, the resident immune cells of the CNS, in NDDs. The researchers aimed to explore the role of microglia in neurodegeneration and investigate the utility of human-induced pluripotent stem cells (hiPSCs) and other platforms for modeling microglial dysfunction in these diseases. The findings of this study highlighted the heterogeneity of microglia in NDDs, as well as the potential mechanisms underlying their dysfunction. The researchers discussed various factors that contribute to microglial alterations, including genetic predisposition, aging, and the interaction with other cells in the brain.

On the other hand, the usage of ESCs raises ethical considerations due to the destruction of embryos during their derivation. To overcome this limitation, iPSCs have been developed. iPSCs are generated by reprogramming adult cells, such as skin cells, to an embryonic-like state, mimicking the properties of ESCs. iPSCs offer an ethically acceptable alternative and can be derived from patients with NDDs, allowing for the creation of disease-specific models and personalized medicine approaches.[14]

Table 1. Embryonic and induced pluripotent stem cells in neurodegenerative disorders

Types of Stem cells	Their origin	Function	Advantages	Disadvantages
ESCs	-Blastocyst inner cell mass	-Differentiation ability into neural stem cells	-Proliferation capacity -Ability to induce different specialized cells	-Ethical considerations -Possible immune rejection -Carcinogenesis
iPSCs	-Adult somatic tissue that are reprogrammed	-Alternative cells to ESCs	-Non-immune rejection -Easy isolation techniques -No ethical considerations	-Lack of efficiency of reprogramming from ESCs

Examples of the application of ESCs in NDDs include the generation of dopaminergic neurons for transplantation in PD, where several clinical trials are underway. Additionally, ESC-derived neurons have been used to model and study AD, HD, and ALS among others. These disease-specific models have provided insights into disease pathology and facilitated the development of potential therapeutic interventions.[12-14]

Adult Stem Cells

Adult stem cells, also known as somatic or tissue-specific stem cells, are present in various adult tissues and organs throughout the body. Unlike ESCs, adult stem cells are more limited in their differentiation potential, typically giving rise to cell types within the tissue from which they originate. While they may not possess the same degree of pluripotency as ESCs, adult stem cells still hold significant potential for the treatment of NDDs. One key advantage of adult stem cells is their relative accessibility. They can be sourced from tissues such as bone marrow, adipose tissue, and neural tissue itself. Neural stem cells, a type of adult stem cell found in specific regions of the adult brain, have the capacity to self-renew and differentiate into neural cell types. Neural stem cells have been explored for their potential in NDDs by using them to generate new neurons that can replace those lost due to disease progression. Additionally, NSCs can be expanded *in vitro* and transplanted into targeted regions of the brain to promote tissue repair and functional recovery[15].

Mesenchymal stem cells, on the other hand, another type of adult stem cell, have shown promise in the context of NDDs. Mesenchymal stem cells can be obtained from sources such as bone marrow (BM), umbilical cord blood (UCB), and adipose tissue (AT). Although MSCs do not naturally differentiate into neurons, they possess immunomodulatory and trophic properties that can have a positive impact on neurodegenerative conditions.[16] When transplanted, MSCs can secrete factors that promote cell survival, reduce inflammation, and enhance tissue repair mechanisms, thereby providing a neuroprotective environment for existing neurons. Several examples demonstrate the potential of adult stem cells in neurodegenerative disorders. Within this scope in PD, clinical trials have explored the transplantation of MSCs or NSCs into the brain, aiming to replace lost dopaminergic neurons and improve motor symptoms.[17] Similarly, MSCs have been investigated as a potential therapeutic option for AD, where their immunomodulatory effects may help reduce neuroinflammation and promote neural regeneration. For instance, the study conducted by Farahzadi et al.[18], explores the potential of MSCs as

a candidate for cell-based therapy in AD by targeting signaling pathways. The study discusses the signaling pathways implicated in AD pathogenesis, such as the Wnt/β-catenin pathway. Moreover, researchers study expression levels of genes and proteins of mTOR, p-mTOR, p-AMPK, GSK-3β, p-GSK-3β, Wnt3 ve β-katenin. The researchers highlight the potential of MSCs to modulate these pathways and restore cellular functions. They found that MSCs could enhance the clearance of amyloid-beta plaques, reduce neuroinflammation, promote neurogenesis, and improve cognitive function in animal models of AD. These effects were attributed to the secretion of various factors by MSCs, including neurotrophic factors, anti-inflammatory cytokines, and extracellular vesicles.

While adult stem cells offer advantages such as ethical sourcing and reduced risk of immune rejection, there are still challenges to overcome. Adult stem cells are often present in limited quantities and exhibit restricted differentiation potential compared to ESCs. Researchers are working to optimize methods for expanding and directing the differentiation of adult stem cells to enhance their therapeutic efficacy. Additionally, ensuring their survival and integration within the host tissue remains a critical consideration for successful transplantation.[17-19]

Mesenchymal Stem Cells

One of the significant types of adult stem cells are MSCs that can be sourced from various tissues, including BM, AT, and UCB. Mesenchymal stem cells possess unique characteristics that make them attractive for therapeutic applications in NDDs. Although they do not have the same degree of pluripotency as ESCs, MSCs exhibit immunomodulatory properties and secrete various bioactive molecules that can have profound effects on neuroregeneration and neuroprotection.[20] One of the key mechanisms by which MSCs exert their therapeutic effects is through the secretion of cytokines, growth factors, and other biomolecules. MSCs can produce factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and vascular endothelial growth factor (VEGF), among others. These factors promote cell survival, reduce inflammation, stimulate endogenous repair mechanisms, and enhance angiogenesis. Mesenchymal stem cells can also modulate the immune response by suppressing inflammatory cells and promoting an anti-inflammatory environment, which is beneficial in NDDs where inflammation plays a significant role in disease progression.[21]

In neurodegenerative disorders, MSCs have demonstrated therapeutic potential in preclinical and clinical studies. In PD, MSC transplantation has shown promising results in animal models by promoting the survival and differentiation of dopaminergic neurons and improving motor function. In AD, MSCs have been shown to reduce amyloid-beta accumulation and neuroinflammation, as well as promote synaptic plasticity and cognitive improvement. On the other hand, in ALS, MSCs have displayed neuroprotective effects, reducing motor neuron loss and improving motor function. The study on ALS disease by Barczewska et al.[22], presents an original study focused on investigating the potential of UC-MSCs in the treatment of ALS. In the study, 67 patients were treated with Wharton jelly mesenchymal stem cells (WJ-MSC). The patients received three intrathecal injections of WJ-MSC 30×106 cells every two months, and the survival times of the patients were followed. According to the observed results, the risk-benefit ratios were positive in all groups. With no adverse effects observed, the researchers noted that WJ-MSCs are safe in some ALS patients, regardless of clinical characteristics and demographic effects other than gender. A good therapeutic response for the first application and female sex has been indicated as an important indicator for further applications.

Furthermore, MSCs have the advantage of being easily accessible and expandable in culture, allowing for large-scale production. They can be obtained from various tissue sources, including the patient's own tissue known as autologous transplantation or from donors known as allogeneic transplantation, reducing the risk of immune rejection. Mesenchymal stem cells can be administered through different routes, such as intravenous infusion, intrathecal injection, or local transplantation, depending on the target disease and desired therapeutic effects.[23] While the exact mechanisms of MSC-mediated effects on NDDs are still being elucidated, ongoing research aims to optimize MSC transplantation strategies, including the timing, dosage, and route of administration. Additionally, efforts are being made to enhance MSC properties through genetic modifications or priming with specific factors to maximize their therapeutic potential.[24]

Neural Stem Cells

Neural stem cells are a type of adult stem cell found in specific regions of the adult brain, including the subventricular zone and the hippocampus. Neural stem cells possess the ability to self-renew as well as other SCs and differentiate into neural cell types,

including neurons, astrocytes, and oligodendrocytes. This unique property makes NSCs attractive for their potential use in the treatment of NDDs. Neural stem cells hold significant promise for NDDs due to their ability to generate new neurons that can replace those lost or damaged in the disease process. In conditions such as PD, where dopaminergic neurons are progressively lost, NSCs can be harnessed to differentiate into dopaminergic neurons and restore the neuronal population.[25] Similarly, in diseases such as AD, where there is widespread neuronal loss, NSCs can differentiate into the appropriate neuronal subtypes and integrate into the existing neural networks, potentially restoring cognitive function. For example, the study by McGinley et al.[26], investigates the therapeutic potential of human neural stem cell transplantation in a murine model of AD. In this study, human neural stem cells (hNSCs) were transplanted into the fimbria fornix, a region of the brain critical for memory and learning, of the APP/PS1 rodent model. The researchers aimed to assess the effects of hNSC transplantation on cognitive function and the underlying mechanisms involved. Targeted transplantation of hNSCs to the fimbria fornix in two hippocampal-dependent memory tasks 4-16 weeks after transplantation was observed to significantly improve memory cognition. After stem cell transplantation, mice showed a reduction in amyloid plaque load, while the levels of cholinergic neurons and Synapse-related proteins were unaffected. It can be said that NSCs have an immunomodulatory capacity by inducing microglial activation and amyloid phagocytosis *in vitro*. Nevertheless, the study provides valuable insights into the potential of hNSC transplantation for AD and paves the way for future investigations and potential clinical applications in human patients.

In addition to their capacity for neuronal replacement, NSCs also possess paracrine effects mediated through the secretion of various biomolecules, including cytokines, growth factors, and extracellular vesicles. These factors can modulate the microenvironment and exert neuroprotective effects by promoting cell survival, reducing inflammation, enhancing neuronal plasticity, and stimulating endogenous repair mechanisms. The specific cocktail of biomolecules secreted by NSCs can vary depending on the conditions present in the surrounding environment.[27] Preclinical studies using NSCs have demonstrated their therapeutic potential in various neurodegenerative disorders. The usage of NSCs in clinical settings is still in the early stages of development. Challenges such as the limited availability of NSCs from adult brain tissue and the need for robust and scalable protocols for their expansion and differentiation remain. However, ongoing research aims to address these challenges and optimize the therapeutic potential of NSCs.[25,26]

Table 2. Mesenchymal and neural stem cells in neurodegenerative disorders

Types of Stem cells	Their origin	Function	Advantages	Disadvantages
MSCs	-Adipose tissue -Umbilical cord and peripheral blood -Bone marrow	-Differentiation ability into neural lineages	-Cell sources variety -Showing immuno-regulatory effect	-Lack of efficiency -Tumor formation
NSCs	-Neural lineages	-Differentiation ability into glial cells and neurons	-Low risk of tumor formation	-Limited origin -Restricted cells related to limited origin

CONCEPT OF NEUROGENESIS

Neurogenesis refers to the process of generating new neurons in the brain throughout an individual's life. It was long believed that the adult brain had a limited capacity for neurogenesis, but research has shown that neurogenesis occurs in specific regions of the brain, such as the hippocampus and the subventricular zone. This process plays a crucial role in brain development, learning, memory, and overall brain plasticity. One of the prominent features of neurogenesis is the generation of new neurons from NSCs or neural progenitor cells. Neural stem cells are present in certain regions of the adult brain and have the ability to self-renew and differentiate into various neural cell types, including neurons. This process provides a continuous supply of new neurons that can integrate into existing neural circuits and contribute to brain functions. Neurogenesis has important implications for NDDs.[28]

In conditions like AD and PD neurogenesis is often impaired. The loss of neurons and synaptic connections in these diseases can lead to cognitive decline, motor dysfunction, and mood disorders. Restoring neurogenesis may offer potential therapeutic strategies for these conditions. Within this aim the study by Walgrave et al.[29], focuses on the role of microRNA-132 (miR-132) in adult hippocampal neurogenesis (AHN) and memory deficits in AD. The researchers aimed to investigate the impact of miR-132 on AHN, which is the process of generating new neurons in the hippocampus, a brain region important for learning and memory. They also aimed

to determine whether restoring miR-132 expression could rescue memory deficits in an AD mouse model. The study demonstrated that miR-132 expression was significantly decreased in the hippocampus of AD mice compared to healthy controls. Moreover, the reduced expression of miR-132 correlated with impaired neurogenesis and memory deficits in the AD mice. To further investigate the functional role of miR-132, the researchers performed experiments to restore its expression in the hippocampus of AD mice. They found that restoring miR-132 expression not only rescued AHN but also improved memory performance in AD mice.

Several mechanisms contribute to the effect of neurogenesis in NDDs. First of all, the integration of newly generated neurons into existing neural networks can compensate for the loss of function caused by neuronal death. These new neurons can form connections, contribute to circuitry, and potentially restore impaired functions. Secondly, neurogenesis promotes neuroplasticity and synaptic plasticity, which are vital for learning and memory processes. The formation of new neurons enhances the brain's capacity for adaptation and cognitive flexibility, which can be beneficial in combating the cognitive deficits associated with neurodegenerative disorders.[30] Furthermore, neurogenesis has been associated with neuroprotective effects. Newly generated neurons release growth factors like insulin-like growth factor 1 (IGF-1) and fibroblast growth factors (FGFs), and other neurotrophic factors such as BDNF, nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF) that support the survival of existing neurons and promote their resilience to injury and disease-related processes.[30,31]

Additionally, neurogenesis can contribute to the reduction of neuroinflammation, which is a common feature of many NDDs. Examples of neurogenesis modulation in the context of NDDs include studies on neurotrophic factors, exercise, and environmental enrichment. Neurotrophic factors such as BDNF have been shown to promote neurogenesis and enhance neuronal survival in various disease models. Physical exercise and environmental enrichment have also been found to stimulate neurogenesis and improve cognitive function in animal models and human studies. The study conducted by Choi et al.[31], investigates the combined effects of AHN and BDNF on cognition in an AD mouse model. The researchers aimed to examine whether promoting AHN, the process of generating new neurons in the adult brain and enhancing BDNF levels could have beneficial effects on cognitive function in an AD mouse model. The study employed a combination of genetic and pharmacological approaches to enhance neurogenesis and BDNF levels in the hippocampus, a brain region crucial for learning and memory. According to the evaluation results, stimulation of AHN alone had little benefit in improving cognition in 5×FAD mice, whereas stimulation of AHN with exercise was associated with reduced Aβ load and increased BDNF, interleukin-6, fibronectin type III domain-containing protein-5 (FNDC5) and synaptic markers appeared to improve cognition. However, no such effect was observed in non-transgenic wild-type mice as a result of AHN ablation, suggesting that AHN has a specific role in AD.

NEURODEGENERATIVE DISORDERS AND RECENT APPLICATIONS OF STEM CELLS

Recent advancements in SCs research have opened up new possibilities for the treatment of these challenging conditions.[33] Stem cell-based therapies offer the potential to replace lost or damaged neurons, promote tissue repair, and provide neuroprotective effects. Embryonic stem cells, iPSCs, and adult stem cells, such as NSCs and MSCs have shown promise in preclinical and clinical studies.

ESCs and iPSCs, with their ability to differentiate into any cell type in the body, including neurons, hold great potential for regenerating damaged neural tissue. These PSCs can be guided to differentiate into the desired neuronal subtypes and then transplanted into the affected areas of the brain or spinal cord. On the other hand, NSCs derived from adult brain tissue or generated from iPSCs can also be used to replace lost neurons and restore functional neural networks. Neural stem cells can differentiate into various neural cell types and integrate into existing circuits, providing the potential for functional recovery. Mesenchymal stem cells possess immunomodulatory and trophic properties that can benefit NDDs.[34]

Mesenchymal stem cells secrete factors that promote cell survival, reduce inflammation, and enhance tissue repair mechanisms, creating a supportive environment for existing neurons and potentially slowing disease progression.

While challenges remain, such as optimizing cell survival, ensuring appropriate differentiation, and addressing potential immune responses, stem cell-based therapies hold immense potential for the treatment of NDDs.[35] Continued research and clinical trials are crucial to further refine and establish the

safety and efficacy of these innovative approaches for patients suffering from these devastating conditions.

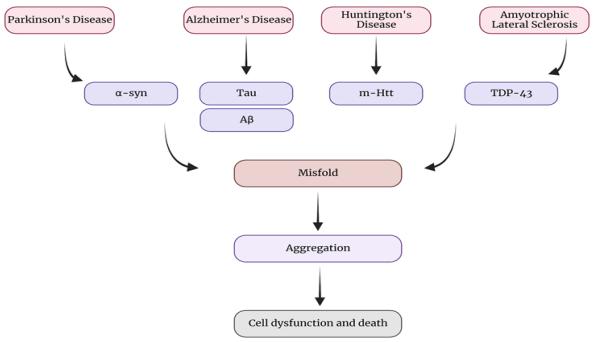

Figure 2. Neurodegenerative disorders and their mechanisms.

Parkinson's Disease

Parkinson's disease is a chronic and progressive neurodegenerative disorder that primarily affects the motor system. It is characterized by a gradual loss of dopamine-producing cells in a region of the brain called the substantia nigra. Dopamine is a neurotransmitter that plays a crucial role in coordinating movement and regulating emotions. The primary symptoms of PD include tremors, rigidity (stiffness), bradykinesia (slowness of movement), and postural instability. These motor symptoms often start on one side of the body and progressively affect both sides as the disease advances. Individuals with PD may also experience non-motor symptoms such as depression, anxiety, cognitive changes, sleep disturbances, and autonomic dysfunction.[36]

The exact cause of PD is not fully understood, but a combination of genetic and environmental factors is believed to contribute to its development. The majority of cases are considered sporadic, occurring without a clear genetic link, while a small percentage of cases are classified as familial, with specific genetic mutations associated with the disease.

Diagnosis of PD is primarily based on clinical symptoms and neurological examination, as there are no specific diagnostic tests available. Medical professionals may use imaging techniques, such as brain MRI or dopamine transporter (DAT) scans, to support the diagnosis and rule out other conditions. Although there is currently no cure for PD, treatment focuses on managing symptoms and improving quality of life. Medications, such as dopamine replacement therapies and other drugs that enhance dopamine function, are commonly prescribed. In advanced cases, surgical interventions like deep brain stimulation may be considered to alleviate symptoms. Research into PD continues to explore new therapeutic strategies, including stem cell-based therapies, gene therapies, and targeted drug development.[37-39] These advancements aim to develop disease-modifying treatments that can slow or halt the progression of PD and ultimately provide better outcomes for individuals living with this condition. Recent applications of stem cells in PD have shown promising results in preclinical and clinical studies. Stem cell-based therapies offer the potential to replace lost or damaged dopaminergic neurons, which are characteristic of PD. Studies have reported improvements in motor symptoms, increased dopamine production, and enhanced neuronal survival and integration following stem cell transplantation. Furthermore, SCs have been explored for their ability to modulate the inflammatory response and provide neuroprotective effects in PD.[40]

For example, the study by Cai et al.[41] explores the potential therapeutic effects of exosomes derived from BM-MSCs in PD. The researchers aimed to investigate the mechanism by which BM-MSC-derived exosomes exert their protective effects on microglial activation and neuronal apoptosis, both of which contribute to the progression of PD. They focused on the role of the glioma-associated oncogene homolog 1 (Gli1) protein and its interaction with the Sp1 transcription factor promoter signaling pathway. In their *in vitro* experiments, the authors first demonstrated that BM-MSC-derived exosomes could effectively reduce the activation of microglial cells and prevent neuronal apoptosis. They further identified Gli1 as a key factor in mediating these effects. The exosomes were found to deliver Gli1 protein to microglial cells, leading to the inhibition of Sp1 signaling, which plays a role in the inflammatory response and neuronal apoptosis.

Some studies, on the other hand, have investigated the phenotypic effect of PD and possible therapeutic treatments that can be developed within the scope of these studies. One of the studies regarding this aim by Yamaguchi et al.[42] explores potential therapeutic approaches for addressing mitochondrial clearance disorders in neurons associated with familial PD. The researchers aimed to identify compounds that could enhance the removal of damaged mitochondria, a process known as mitophagy, in neurons affected by familial PD. They focused on PTEN-induced kinase (PINK1), a protein involved in regulating mitophagy, and its interaction with mitochondrial clearance. To

investigate potential therapeutic agents, the authors utilized patient-derived iPSCs from individuals with familial PD carrying PINK1 mutations. They screened a library of compounds for their ability to restore mitophagy and improve mitochondrial clearance in these iPSC-derived neurons. Overall, this study highlights the potential of stem cell-based models and screening approaches to identify therapeutic agents for addressing mitochondrial clearance disorders in familial PD. The findings contribute to the development of targeted treatments that aim to restore proper mitophagy and mitochondrial function, offering hope for individuals with familial PD and potentially shedding light on therapeutic avenues for other forms of PD as well.

Moreover, in the case of treatment approaches, the study conducted by Stoddard-Bennett and Reijo Pera[43] explores the potential of personalized medicine and iPSCs for the treatment of PD. The study emphasizes the importance of personalized medicine in PD treatment, as each patient's disease manifestation and response to treatment can vary. iPSCs offer a unique platform for disease modeling, allowing researchers to generate patient-specific neurons to study the disease mechanisms and develop personalized treatment strategies. They discuss various approaches using iPSCs for PD treatment, including transplantation of iPSC-derived dopaminergic neurons, drug screening on patient-specific iPSC-derived neurons, and genetic editing techniques to correct disease-causing mutations in iPSCs. They also highlight the challenges and considerations in iPSC-based therapies, such as ensuring the safety and efficacy of iPSC-derived cells, optimizing differentiation protocols, and addressing immune rejection. While some challenges such as optimizing cell survival, immune responses, and long-term efficacy remain, the recent applications of stem cells in PD offer hope for developing novel therapeutic strategies to improve the quality of life for PD patients. Continued research and clinical trials are necessary to further validate and refine these approaches.[44]

Alzheimer's Disease

Alzheimer's disease is a progressive NDDs and the most common cause of dementia. It affects memory, thinking, and behavior, and gradually impairs an individual's ability to carry out daily activities. Alzheimer's disease is characterized by the accumulation of abnormal protein deposits in the brain, including Aβ plaques and tau tangles, which lead to the destruction and death of brain cells. The exact cause of AD is not fully understood like PD, but it is believed to involve a combination of genetic, environmental, and lifestyle factors. While age is the most significant risk factor, with the majority of cases occurring in individuals over the age of 65, early-onset AD can also occur in individuals in their 30-50s, although it is relatively rare. The symptoms of AD progress gradually over time. Initially, individuals may experience mild memory loss and difficulty with tasks that require cognitive abilities. As the disease progresses, memory loss becomes more severe, and individuals may have trouble with language, decision-making, spatial orientation, and personality changes.[45]

There is currently no cure for AD, but treatment aims to manage symptoms, improve quality of life, and slow disease progression. Medications such as cholinesterase inhibitors and memantine may be prescribed to help manage cognitive symptoms. Research is ongoing to better understand the underlying mechanisms of AD and develop new treatments. This includes investigating the role of genetics, inflammation, and other factors in disease progression. Additionally, efforts are being made to develop disease-modifying therapies and early detection methods to intervene in the disease process and improve outcomes for individuals with AD.[46,47]

Stem cells, on the other hand, have emerged as a promising avenue of research for the treatment of AD. The unique properties of SCs, such as their self-renewal and differentiation capabilities, make them a potential therapeutic tool for regenerating damaged brain tissue and promoting cognitive function in AD patients. Transplanted SCs can potentially replace damaged or lost neurons in the brain, restore neuronal connectivity, and improve cognitive function in AD. For instance, the study by Huang et al.[48], presents a novel approach for the treatment of AD using nanoformulation-mediated multifunctional stem cell therapy. The genetically engineered NSCs in the study were developed to stably and consistently express Neprilysin (NEP) in the brain to increase Aβ degradation and NSC survival. The PBAE-PLGA-Ag2S-RA-siSOX9 (PPAR-siSOX9) nanoformulation was synthesized to support neuronal differentiation of NSCs expressing NEP with high gene/drug delivery and to overcome the adverse effects associated with the AD microenvironment. It has been observed that the synthesized nanoformulations provide an effect for six months in a single application. The study demonstrated that the engineered nanoformulation successfully

targeted the beta-amyloid plaques in the brains of AD mice and promoted the clearance of beta-amyloid deposits. Additionally, the stem cells within the nanoformulation displayed neuroprotective and regenerative effects by enhancing synaptic plasticity and promoting the survival of existing neurons. This study provides valuable insights into the development of innovative therapeutic strategies for AD using stem cells and nanotechnology.

On the other hand, another innovative study by Han et al.[49] investigated the role of let-7f-5p, a microRNA that enhances the survival and neuroprotective effect of bone marrow-derived mesenchymal stem cells (MSCs) in an Alzheimer's disease model. Researchers have shown that let-7f-5p expression is reduced in mice in the Alzheimer's disease model, which reduces the ability of MSCs to survive and repair brain damage. MSCs showed early apoptosis, with increased expression of caspase-3 and decreased levels of let-7f-5p observed with *in vitro* exposure to Aβ25–35. To examine the effect of let-7f-5p on MSCs, a plasmid vector was used to increase the expression of let-7f-5p. This plasmid vector enhanced the survival and neuroprotective effect of MSCs. In conclusion, let-7f-5p has been shown to contribute to the survival and neuroprotective effect of MSCs.

Huntington's Disease

Huntington's disease is a hereditary and progressive NDDs that affects the brain. It is caused by a mutation in the huntingtin gene (HTT) on chromosome 4, leading to the production of an abnormal form of the huntingtin protein. This mutated protein gradually damages and destroys certain cells in the brain, particularly in the basal ganglia and cerebral cortex. The symptoms of HD usually manifest in adulthood, typically between the ages of 30 and 50, although it can develop at any age. The disease is characterized by a triad of symptoms that progressively worsen over time: movement abnormalities, cognitive decline, and psychiatric disturbances.[50]

Movement abnormalities include involuntary jerking or writhing movements called chorea, which is one of the hallmark features of HD. Other motor symptoms may include impaired coordination, difficulty with balance and gait, and dystonia (muscle rigidity or abnormal posturing). Cognitive decline affects various aspects of cognition, including memory, attention, reasoning, and problem-solving abilities. Individuals with HD may experience difficulties in planning and organizing, as well as changes in judgment and insight. Psychiatric symptoms can include depression, anxiety, irritability, mood swings, apathy, and social withdrawal. As HD progresses, individuals may experience worsening motor and cognitive symptoms, leading to increased dependence on others for daily activities. Complications can arise, including difficulty swallowing, weight loss, and increased vulnerability to infections.[51]

Stem cell therapies, gene therapies, and other innovative approaches are being explored to target the root cause of the disease and potentially slow its progression in the future. For instance, a study by Choompoo et al.[52], explores the developing striatum-derived iPSCs as a potential source of cell replacement therapy for HD. The fetal putative striatum or the entire ganglionic eminence (WGE) may be the source for authentic stratified (STR) progenitors. In the study, four iPSC arrays were generated from human WGE (hWGE), and observed that they have a similar capacity to hESCs in their ability to differentiate towards a STR phenotype. Experiments in mice showed that iPSCs transformed into STR progenitor cells and that these cells could differentiate into mature striatal neurons. In addition, it has been observed that these iPSCs are transplanted in the HD model, which improves motor functions and reduces disease symptoms. In addition, it has been found that iPSCs have the capacity to repair damage to STR neurons and can slow the progression of the disease.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, is a progressive and degenerative neurological disorder that primarily affects the nerve cells responsible for controlling voluntary muscle movement. Amyotrophic lateral sclerosis belongs to a group of disorders known as motor neuron diseases. In ALS, motor neurons, which are located in the brain and spinal cord, gradually degenerate and die. This results in a loss of muscle control and eventual paralysis as the disease progresses.[53]

The exact cause of ALS is not fully understood, but a combination of genetic and environmental factors is believed to play a role in its development. The symptoms of ALS can vary among individuals but commonly include muscle weakness, muscle twitching (fasciculations), cramps, and difficulty speaking, swallowing, and breathing. As the disease progresses, individuals may experience increased muscle atrophy, spasticity, and loss of motor function. Cognitive changes and respiratory difficulties can also occur in some cases. Although there is currently

no cure for ALS, medications such as riluzole and edaravone may be prescribed to slow the progression of the disease and alleviate symptoms.[54]

Stem cell-based therapies, on the other hand, including the transplantation of NSCs or MSCs, are being investigated as a potential approach to replace damaged motor neurons and promote functional recovery. For instance, the study by Petrou et al.[55], reviews a Phase II clinical trial investigating the use of autologous MSCs by repeated intrathecal injections in ALS patients. This study aims to evaluate the safety and efficacy of intrathecal injections of autologous MSCs in ALS patients. The results show that MSC injections are safe and no side effects to treatment have been reported. In addition, a tendency to slow the progression of the disease and mild improvements in motor functions were observed in patients receiving treatment. This study shows that autologous MSC injections can be a potential treatment modality in the treatment of ALS. The immunomodulatory and regenerative properties of MSCs suggest that they may have the potential to slow disease progression and improve motor functions. However, larger-scale randomized controlled trials are needed and the long-term efficacy and safety profile of this treatment strategy should be further investigated.[56]

There are also various studies that are conducted for understanding disease mechanisms. For instance, the study by Scarian et al.[57], examines the differentiation of patients' SCs in a 3D environment as a promising experimental tool in ALS studies. The study begins with the reprogramming of dermal fibroblasts from skin biopsies of ALS patients into iPSC. These iPSCs are then allowed to transform into motor neurons and organize in a 3D environment. This 3D environment provides a suitable *in vitro* model that mimics the microenvironment of ALS disease. The results show that SCs of ALS patients can differentiate into motor neurons in a 3D environment and can be used to study the pathophysiological mechanisms of the disease. This method offers a new approach in terms of understanding the molecular basis of the disease and developing treatment strategies by using stem cells obtained from the patients themselves.

FUTURE DIRECTION AND PROMISING PERSPECTIVES

The future direction of SCs research in the field of NDDs holds great promise and potential for groundbreaking advancements. There are various areas of application of SCs on NNDs that present promising perspectives. These areas of focus include precision medicine, gene editing techniques, engineering biomimetic microenvironments, non-invasive delivery methods, and combination therapies.[58]

Advancements in stem cell research are moving towards personalized approaches. The use of patient-specific iPSCs allows for disease modeling, drug screening, and personalized therapeutic strategies. By generating iPSCs from individual patients, researchers can study the disease mechanisms specific to each patient's condition and develop tailored treatments. Furthermore, emerging gene editing technologies, such as CRISPR-Cas9, offer the potential to precisely modify the genome of stem cells.[59] This allows for the correction of disease-causing mutations in patient-derived stem cells before transplantation, enhancing the safety and efficacy of stem cell therapies. On the other hand, mimicking the natural tissue microenvironment is a focus of research to improve stem cell survival and differentiation. Biomaterials, scaffolds, and 3D printing techniques are being explored to create artificial niches that provide appropriate physical and biochemical cues to guide stem cell behavior, promoting their integration and functionality within the damaged tissue.[60] Developing non-invasive methods, on the other hand, for SCs delivery to the CNS is a key area of research. Strategies such as intranasal delivery, exosome-based therapies, or utilizing microbubble-mediated ultrasound techniques offer minimally invasive approaches that enhance the targeted delivery and distribution of stem cells.[61]

Stem cell-based therapies can be combined with other approaches to maximize their benefits. Combinations with neuroprotective drugs, growth factors, or biomaterials provide synergistic effects and optimize the survival, integration, and functionality of transplanted cells. These combination therapies can enhance the regenerative potential and improve patient outcomes. By addressing these directions, SCs research holds the potential to revolutionize the treatment of NDDs. The combination of precision medicine, gene editing, synergistic therapies, biomimetic environments, and non-invasive delivery methods will contribute to safer, more effective, and personalized treatments for patients, ultimately improving their quality of life and prognosis. Continued research efforts and clinical trials are essential to translate these promising perspectives into clinically viable therapies for NDDs.[62]

In conclusion, stem cell-based therapies hold immense promise for the treatment of NDDs. The unique features of different types of SCs, such as ESCs, adult stem cells, and NSCs, provide opportunities for neuronal replacement, neuroprotection, and restoration of neural function. These therapies offer a paradigm shift in the field of NDDs, where traditional treatments have focused on managing symptoms rather than addressing the underlying causes. The use of SCs, whether derived from embryonic sources or generated through reprogramming techniques like iPSCs, enables the production of specific cell types needed to replace damaged or lost neurons. Additionally, SCs release various growth factors, neurotrophic factors, and other biomolecules that support the survival of existing neurons, promote tissue repair, and modulate the inflammatory microenvironment. These mechanisms contribute to the potential therapeutic effects of stem cell-based treatments. While significant progress has been made, challenges remain, including optimizing cell survival, integration, and differentiation, as well as addressing immune responses and ethical considerations. Continued research and clinical trials are necessary to refine the techniques, improve safety profiles, and establish long-term efficacy. With ongoing research and advancements, we are moving closer to realizing the full potential of stem cells in combating these devastating disorders and bringing hope to those affected by NDDs.

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