Review

Neurobiology

Sources and Mechanisms of Cell-Based Therapeutic Strategies for Neurodegenerative Diseases

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Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, are characterized by progressive loss of neurons and neural function, leading to cognitive and motor impairments. Current pharmacological treatments primarily offer symptomatic relief without addressing the underlying neuronal degeneration. Cell-based therapies have emerged as a promising approach to restore neuronal function, modulate neuroinflammation, and promote tissue repair. Various cell types, including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, and neural stem/progenitor cells, have demonstrated potential in preclinical and early clinical studies. These therapies aim to replace lost neurons, secrete neurotrophic factors, and create a supportive microenvironment for endogenous repair. Despite encouraging results, challenges remain regarding cell survival, differentiation, immune rejection, tumorigenicity, and ethical considerations. This review summarizes recent advances in cell therapies for neurodegenerative diseases, highlights clinical applications, and discusses future perspectives for translating these therapies into effective treatments.

Keywords: Stem Cells; Neurodegeneration; Neuronal Replacement; Neuroprotection; Microenvironment Remodeling

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Introduction

Neurodegenerative diseases (NDs) encompass a group of disorders characterized by progressive loss of neurons, leading to functional decline in motor, cognitive, and behavioral domains (Gadhave et al., 2024). Major NDs include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) (Wareham et al., 2022). The

incidence of these disorders is increasing worldwide, largely due to aging populations, posing significant social, economic, and healthcare challenges. Conventional treatments are largely symptomatic and fail to halt disease progression.

Recent advances in regenerative medicine have introduced cell-based therapies as a novel strategy to address neuronal loss (Deng et al., 2025). These therapies aim not only to replace damaged neurons but also to modulate neuroinflammation, enhance neuroprotection, and stimulate endogenous repair mechanisms. Preclinical and clinical studies have highlighted the potential of various cell types in promoting functional recovery in neurodegenerative conditions (Temple, 2023). This review explores the current landscape of cell therapies for NDs, focusing on cell sources and mechanisms.

Cell Sources for Neurodegenerative Therapy

Embryonic Stem Cells (ESCs)

Embryonic stem cells are pluripotent cells derived from the inner cell mass of the blastocyst during early embryonic development (Nicaise et al., 2021). These cells are distinguished by their ability to self-renew indefinitely and differentiate into all cell types of the body, including neurons, astrocytes, and oligodendrocytes. The pluripotency and proliferative capacity of ESCs make them uniquely suited for addressing the complex cellular deficits observed in neurodegenerative disorders (Dantuma et al., 2010). In addition to their ability to replace lost neurons, ESCs can provide supportive trophic factors and modulate the local microenvironment, offering multiple avenues to restore neural function. Their versatility allows for the generation of specific neuronal subtypes tailored to the affected regions in various neurodegenerative diseases, such as dopaminergic neurons for Parkinson's disease or motor neurons for amyotrophic lateral sclerosis (Limone et al., 2022).

The therapeutic potential of ESCs in neurodegenerative diseases is mediated through several mechanisms. One of the most direct approaches is neuronal replacement. In conditions such as Parkinson's disease, degeneration of dopaminergic neurons in the substantia nigra leads to impaired motor control. Transplantation of ESC-derived dopaminergic neurons into affected brain regions has demonstrated the ability to survive, extend axons, form synapses, and restore dopamine signaling in preclinical models (Alekseenko et al., 2022). Similarly, in Huntington's disease, ESC-derived striatal neurons can replace the degenerated medium spiny neurons, which are critical for motor coordination and cognitive function. Beyond direct cell replacement, ESC-derived cells can secrete neurotrophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and nerve growth factor, which support the survival and function of both transplanted and endogenous neurons (Vassal et al., 2024). These trophic effects can reduce apoptosis, enhance synaptic connectivity, and stimulate neurogenesis, contributing to improved neural network function.

Another important mechanism is the modulation of neuroinflammation. Chronic inflammation is a hallmark of many neurodegenerative diseases and contributes to ongoing neuronal damage (Charlton et al., 2023). ESC-derived cells have been shown to interact with microglia and astrocytes, reducing the release of pro-inflammatory cytokines and promoting an anti-inflammatory, neuroprotective environment. This immunomodulatory effect is critical not only for slowing disease progression but also for enhancing the survival and integration of transplanted cells (Čaprnda et al., 2017). Additionally, ESC-derived cells can influence angiogenesis and extracellular matrix remodeling, improving vascular support and structural integrity in damaged brain regions, which further facilitates neuronal repair.

Preclinical studies have provided compelling evidence supporting the use of ESCs in neurodegenerative therapy (Lindvall & Kokaia, 2010). In animal models of Parkinson's disease, transplantation of ESC-derived dopaminergic neurons has led to sustained improvements in motor function and restoration of dopaminergic signaling (Sonntag et al., 2018). In Alzheimer's disease models, ESC-derived neural progenitors have been shown to reduce amyloid-beta accumulation, enhance synaptic plasticity, and improve learning and memory (Armijo et al., 2021). Huntington's disease models have demonstrated that ESC-derived striatal neurons can ameliorate motor and cognitive deficits, while studies in amyotrophic lateral sclerosis have explored the potential of ESC-derived motor neurons to replace degenerated cells and support neuromuscular function (Reidling et al., 2017). Collectively, these findings highlight the multifaceted capabilities of ESCs, which extend beyond simple cell replacement to encompass trophic support, immunomodulation, and microenvironmental improvement.

Despite their promise, the clinical translation of ESC-based therapies faces several significant challenges. Ethical concerns are a primary limitation, as the derivation of ESCs involves the destruction of human embryos. This has led to extensive debate and regulatory restrictions in many countries, and has prompted the exploration of alternative sources of pluripotent cells, such as induced pluripotent stem cells (Condic & Rao, 2010). Safety issues are also paramount; the pluripotent nature of ESCs carries the risk of tumorigenicity, as residual undifferentiated cells can form teratomas following transplantation. Immune rejection represents another obstacle, particularly for allogeneic ESC-derived cells, which may require immunosuppressive therapy or genetic modification to reduce immunogenicity (Harding et al., 2023). Additionally, the survival and functional integration of transplanted cells remain limited in some contexts, necessitating strategies to enhance engraftment, such as co-administration of growth factors, use of biomaterial scaffolds, or preconditioning of the host environment.

Despite these challenges, early clinical studies provide cautious optimism. Human ESC-derived retinal pigment epithelial cells have been safely transplanted in patients with macular degeneration, demonstrating some functional improvement and offering proof of concept for the clinical applicability of ESCs (Schwartz et al., 2014). While direct clinical trials in brain-related neurodegenerative disorders are still limited, these studies establish foundational principles for future research and underscore the importance of rigorous cell characterization, controlled differentiation protocols, and careful monitoring of safety and efficacy.

Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells are somatic cells that have been genetically reprogrammed to a pluripotent state through the introduction of key transcription factors, such as OCT4, SOX2, KLF4, and c-MYC (Rivera et al., 2020). This process restores the cells' ability to differentiate into virtually any cell type, including neurons, astrocytes, and oligodendrocytes, while maintaining the capacity for unlimited self-renewal. Unlike embryonic stem cells, iPSCs are derived from adult tissues such as skin fibroblasts, blood cells, or urine, circumventing the ethical concerns associated with embryo-derived stem cells (Swingler et al., 2023). Furthermore, iPSCs can be generated from individual patients, enabling the production of autologous cell lines that are genetically matched to the recipient, thereby minimizing the risk of immune rejection (Nsair & MacLellan, 2011). This patient-specific nature allows for personalized therapy and provides a platform for disease modeling and drug screening.

The therapeutic potential of iPSCs in neurodegenerative diseases lies in several mechanisms. One of the primary strategies is neuronal replacement. In diseases such as Parkinson's disease, the degeneration of dopaminergic neurons in the substantia nigra leads to impaired motor control. iPSC-derived dopaminergic neurons can be transplanted into affected brain regions to replace lost neurons, restore dopamine signaling, and improve motor function (Sonntag et al., 2018). Preclinical studies in rodent and primate models have demonstrated that these cells can survive transplantation, extend axons, form functional synapses, and integrate into existing neural circuits (Xiong et al., 2020). Similarly, in Huntington's disease, iPSC-derived striatal neurons have shown the ability to replace degenerated medium spiny neurons, partially restoring motor coordination and cognitive function (Fox et al., 2014). For amyotrophic lateral sclerosis, iPSC-derived motor neurons offer a potential means of replacing the lost motor neuron population and supporting neuromuscular function, although challenges with long-term survival and integration remain.

Beyond direct neuronal replacement, iPSCs provide therapeutic benefits through the secretion of neurotrophic factors. These cells release molecules such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and nerve growth factor, which support the survival of both transplanted and endogenous neuron (Rhee et al., 2011)s. This paracrine effect can enhance synaptic connectivity, reduce apoptosis, and promote neurogenesis, creating a more supportive microenvironment for neural repair. In Alzheimer's disease models, transplantation of iPSC-derived neural progenitors has been associated with improved cognitive performance, reduction of amyloid beta plaques, and increased synaptic density (Armijo et al., 2021). Similarly, in Parkinson's disease, these cells have been shown to support residual dopaminergic neurons and enhance overall neural circuit function.

Another critical aspect of iPSC therapy is immunomodulation. Neuroinflammation is a common feature of neurodegenerative diseases and contributes to ongoing neuronal damage (Liu et al., 2021). iPSC-derived cells can modulate the activity of microglia and astrocytes, reduce the production of pro-inflammatory cytokines and promote a neuroprotective environment (Guttikonda et al., 2021). This effect not only helps slow disease progression but also enhances the survival and integration of transplanted cells. Additionally, iPSCs can influence angiogenesis and extracellular matrix remodeling, improving vascular support and structural integrity in affected brain regions (Lacalle‐Aurioles et al., 2020). By addressing both cellular replacement and microenvironmental support, iPSCs offer a multifaceted approach to neurodegenerative therapy.

The development of iPSC technology has also facilitated disease modeling and drug discovery. Patient-derived iPSCs can be differentiated into disease-relevant neuronal subtypes, creating in vitro models that recapitulate key pathological features (Trudler et al., 2021). These models allow researchers to study disease mechanisms, screen potential therapeutic compounds, and evaluate the efficacy of interventions in a patient-specific context. This capability is particularly valuable for disorders with complex genetic and phenotypic heterogeneity, such as Alzheimer's disease and amyotrophic lateral sclerosis, where individualized approaches may be necessary (Supakul et al., 2021).

Despite the considerable promise of iPSC-based therapies, several challenges remain. One major concern is tumorigenicity, as residual undifferentiated iPSCs can form teratomas if transplanted into patients. Stringent differentiation protocols, purification techniques, and quality control measures are essential to minimize this risk. Genetic and epigenetic abnormalities can also arise during reprogramming and expansion, potentially affecting the safety and functionality of the cells. In addition, the long-term survival and integration of iPSC-derived neurons remain variable, necessitating strategies to enhance engraftment, such as co-administration of neurotrophic factors or supportive biomaterials. For allogeneic iPSC lines, immune rejection remains a concern, although HLA-matched or gene-edited lines may mitigate this issue.

Recent advances aim to overcome these limitations. The use of CRISPR/Cas9 and other gene-editing technologies enables correction of disease-causing mutations in patient-derived iPSCs prior to differentiation, providing a personalized and genetically precise therapeutic approach (Jang & Ye, 2016). Three-dimensional culture systems and biomaterial scaffolds can support cell survival, guide differentiation, and facilitate functional integration into host neural networks (Mello et al., 2025). Combination therapies, which integrate iPSC transplantation with pharmacological treatments or rehabilitation strategies, may further enhance therapeutic outcomes. Moreover, the establishment of iPSC banks with diverse HLA haplotypes could provide ready-to-use cell lines for patients who require rapid intervention.

Early clinical studies have begun to explore the safety and feasibility of iPSC-based therapies (Escribá et al., 2024). While most human trials remain limited, pioneering work in macular degeneration has demonstrated the ability to transplant iPSC-derived retinal pigment epithelial cells safely, providing proof of concept for future applications in neurodegenerative disorders (Palomo et al., 2015). These studies underscore the importance of rigorous preclinical evaluation, standardized protocols, and careful monitoring to ensure both efficacy and patient safety.

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells are multipotent stromal cells found in various tissues, including bone marrow, adipose tissue, umbilical cord, dental pulp, and placenta (Volarević et al., 2017). Unlike embryonic stem cells or induced pluripotent stem cells, MSCs are not pluripotent but retain the capacity to differentiate into multiple mesodermal lineages such as osteoblasts, adipocytes, and chondrocytes. Importantly, under specific conditions, MSCs can also acquire neuronal-like properties and express neural markers, suggesting potential for neural differentiation (Wislet‐Gendebien et al., 2005). However, their therapeutic potential extends beyond cell replacement, as MSCs exhibit potent paracrine, neuroprotective, and immunomodulatory effects that are particularly relevant for treating neurodegenerative disorders. These properties enable MSCs to modulate the disease environment, promote endogenous repair, and support surviving neurons, even without full differentiation into functional neurons.

One of the central mechanisms by which MSCs exert therapeutic effects is through the secretion of neurotrophic and growth factors. MSCs release molecules such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and vascular endothelial growth factor (Fričová et al., 2020). These factors enhance neuronal survival, stimulate synaptic plasticity, promote axonal growth, and reduce apoptotic cell death in the diseased brain. For example, in models of Parkinson's disease, MSC-derived trophic factors support residual dopaminergic neurons and contribute to improved motor function (Seo & Cho, 2012). Similarly, in Alzheimer's disease models, MSC secretions can reduce amyloid-beta accumulation, enhance synaptic density, and improve cognitive performance (Moghadasi et al., 2021). This paracrine effect is considered a primary mechanism underlying the functional benefits of MSC transplantation.

MSCs also exert immunomodulatory effects, which are particularly relevant in neurodegenerative diseases where chronic inflammation contributes to disease progression. Activated microglia and astrocytes release pro-inflammatory cytokines, reactive oxygen species, and other cytotoxic molecules that exacerbate neuronal injury (Subhramanyam et al., 2019). MSCs can interact with these glial cells to reduce the production of inflammatory mediators, promote anti-inflammatory cytokines, and shift the microglial phenotype from a pro-inflammatory to a neuroprotective state (Ohtaki et al., 2008). This immunomodulatory capability not only slows disease progression but also creates a more favorable environment for neuronal repair and regeneration, enhancing the efficacy of other therapeutic interventions.

Preclinical studies have provided robust evidence supporting the efficacy of MSCs in various neurodegenerative models. In Parkinson's disease animal models, transplantation of MSCs has been shown to improve motor function, restore dopamine levels, and protect remaining dopaminergic neurons (Bouchez et al., 2008). In Alzheimer's disease models, MSCs have been demonstrated to reduce amyloid deposition, enhance cognitive performance, and promote synaptic connectivity (Regmi et al., 2022). In Huntington's disease, MSCs can support striatal neurons, reduce inflammation, and ameliorate motor deficits (Shariati et al., 2020). Similarly, in amyotrophic lateral sclerosis, MSC transplantation has been associated with slowed disease progression, increased survival of motor neurons, and improved neuromuscular function (Xu et al., 2021). These studies highlight the versatility of MSCs and their ability to target multiple pathological mechanisms simultaneously, including neuronal survival, inflammation, and tissue repair.

Beyond their therapeutic mechanisms, MSCs offer practical advantages for clinical application. They can be readily isolated from autologous or allogeneic sources, expanded in culture, and delivered through various routes, including intravenous, intrathecal, or direct intracerebral injection (Li et al., 2022). Their immunoprivileged nature allows for allogeneic transplantation with minimal risk of rejection, reducing the need for immunosuppressive therapy. MSCs also exhibit a favorable safety profile, with most clinical studies reporting minimal adverse effects (Fričová et al., 2020). These characteristics make MSCs a highly translational option for neurodegenerative therapy, capable of bridging the gap between preclinical promise and clinical implementation.

Clinical trials have begun to explore MSC therapy in patients with neurodegenerative diseases, primarily focusing on safety, feasibility, and preliminary efficacy. In Alzheimer's disease, early-phase trials have demonstrated that intravenous or intrathecal MSC transplantation is well tolerated, with some studies reporting cognitive stabilization or modest improvements in memory and executive function (Hernández & García, 2021). Parkinson's disease trials have shown improvements in motor symptoms and quality of life, although larger, controlled studies are needed to confirm efficacy (Wang et al., 2023). In amyotrophic lateral sclerosis, MSC therapy has been associated with delayed disease progression and improved muscle function, highlighting its potential as a disease-modifying intervention (Duranti & Villa, 2023). These trials underscore the feasibility of MSC therapy while emphasizing the need for standardized protocols, optimized dosing, and long-term follow-up to fully assess therapeutic outcomes.

Despite their promise, MSC-based therapies face several challenges. The survival and engraftment of transplanted cells in the hostile environment of the diseased brain remain limited. Strategies such as co-administration of growth factors, preconditioning of cells, or the use of biomaterial scaffolds are being investigated to enhance cell survival and integration. The variability of MSC preparations, influenced by tissue source, donor age, and culture conditions, can affect therapeutic efficacy and reproducibility, highlighting the need for standardized manufacturing and quality control. Additionally, while MSCs have shown the ability to differentiate into neuronal-like cells in vitro, their capacity to functionally replace complex neuronal circuits in vivo remains limited. Therefore, the primary benefits of MSC therapy currently stem from their paracrine and immunomodulatory actions rather than direct neuronal replacement.

Neural Stem/Progenitor Cells (NSPCs)

Neural stem cells are multipotent cells found in specific regions of the developing and adult central nervous system, including the subventricular zone and the hippocampal dentate gyrus (Almeida et al., 2023). These cells have the capacity to self-renew

and differentiate into neurons, astrocytes, and oligodendrocytes, making them particularly well-suited for replacing lost or damaged neural populations. Progenitor cells, which are more lineage-restricted than stem cells, can give rise to specific neural subtypes and provide targeted cellular replacement in disease contexts (Fischer et al., 2020). NSPCs can be harvested from fetal or adult brain tissue or derived from pluripotent stem cells, including embryonic stem cells or induced pluripotent stem cells, offering flexibility in sourcing and expansion for therapeutic purposes. Their capacity to respond to local cues and differentiate in a context-dependent manner enables them to adapt to the specific requirements of the diseased brain.

One of the principal therapeutic strategies of NSPCs is direct neuronal replacement. In Parkinson's disease, the degeneration of dopaminergic neurons in the substantia nigra leads to impaired motor function. NSPCs can be differentiated into dopaminergic neurons and transplanted into affected brain regions, where they have demonstrated the ability to survive, extend axons, form synapses, and restore dopaminergic signaling in preclinical models (Hargus et al., 2010). In Huntington's disease, NSPC-derived striatal neurons can replace medium spiny neurons that are selectively lost, potentially restoring motor coordination and cognitive function (Schellino et al., 2023). For amyotrophic lateral sclerosis, NSPC-derived motor neurons offer a potential means of replenishing lost motor neuron populations, providing functional support to neuromuscular systems, and slowing disease progression (Xu et al., 2021). Beyond neuronal replacement, NSPCs contribute to neuroregeneration by generating supportive glial cells, including astrocytes and oligodendrocytes, which are essential for maintaining synaptic function, myelination, and metabolic support in the central nervous system.

In addition to direct cellular replacement, NSPCs exert therapeutic effects through the secretion of neurotrophic factors. These cells release molecules such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and vascular endothelial growth factor, which promote the survival and function of both transplanted and endogenous neurons. The paracrine effects of NSPCs enhance synaptic connectivity, reduce apoptosis, stimulate neurogenesis, and support angiogenesis, collectively contributing to improved structural and functional outcomes (Al-Mayyahi, 2021). In Alzheimer's disease models, transplantation of NSPCs has been shown to enhance cognitive performance, reduce amyloid-beta deposition, and increase synaptic density, suggesting that NSPCs can modify disease pathology while providing functional benefits (Hayashi et al., 2020). Similarly, in Parkinson's disease, NSPC transplantation can support residual dopaminergic neurons and improve overall motor function (Santos et al., 2025).

NSPCs also modulate neuroinflammation, which is a key contributor to disease progression in neurodegenerative disorders. Chronic activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines and reactive oxygen species that exacerbate neuronal damage (Zhang et al., 2023). NSPCs interact with glial cells to attenuate the inflammatory response, promote anti-inflammatory cytokine production, and encourage a neuroprotective microenvironment (Ni et al., 2023). This immunomodulatory capacity not only slows disease progression but also enhances the survival and integration of transplanted cells, creating conditions conducive to long-term repair. Additionally, NSPCs influence extracellular matrix remodeling and vascular support, facilitating structural stability and improving the local milieu for neuronal regeneration.

Preclinical studies have provided substantial evidence for the efficacy of NSPCs in various models of neurodegenerative diseases. In Parkinson's disease animal models, transplantation of NSPCs differentiated into dopaminergic neurons has led to improvements in motor coordination, restoration of dopamine levels, and enhanced synaptic connectivity (Nguyen et al., 2018). In Alzheimer's disease models, NSPCs have improved learning and memory, enhanced neurogenesis, and reduced amyloid plaque burden (Yue et al., 2022). Huntington's disease studies have shown that NSPC-derived striatal neurons can ameliorate motor and cognitive deficits, while in amyotrophic lateral sclerosis models, NSPC transplantation has been associated with delayed disease progression, improved motor function, and prolonged survival (Gharaibeh et al., 2017; Yoon et al., 2020). These findings demonstrate the multifaceted potential of NSPCs to address both the cellular and microenvironmental deficits characteristic of neurodegenerative disorders.

Clinical translation of NSPC therapy faces several challenges. Ethical concerns arise primarily when cells are derived from fetal brain tissue, limiting accessibility and prompting the exploration of pluripotent stem cell-derived NSPCs as an alternative. Safety concerns, including the risk of tumorigenicity and uncontrolled differentiation, necessitate rigorous characterization and quality control prior to transplantation. Immune rejection is another consideration, particularly for allogeneic NSPCs, although autologous or HLA-matched cells can mitigate this risk. Additionally, the survival, migration, and functional integration of NSPCs in the diseased brain are often limited, and optimizing delivery methods and microenvironmental support remains an active area of research.

To overcome these limitations, several strategies are under investigation. Genetic modification of NSPCs can enhance survival, promote targeted differentiation, and increase secretion of neurotrophic factors. Biomaterial scaffolds, including hydrogels and three-dimensional matrices, provide structural support, guide migration, and improve integration of transplanted cells. Combination therapies, integrating NSPC transplantation with pharmacological agents, neurorehabilitation, or other stem cell types, may produce synergistic benefits by addressing multiple aspects of disease pathology. Additionally, advances in induced pluripotent stem cell technology allow the derivation of patient-specific NSPCs, reducing immune rejection and facilitating personalized therapy.

Early-phase clinical studies have begun to assess the feasibility and safety of NSPC transplantation in humans. These studies generally report favorable safety profiles, with minimal adverse effects, and provide preliminary evidence of functional improvements in motor and cognitive domains. While large-scale, randomized trials are still needed to confirm efficacy, these investigations establish the foundation for translating NSPC-based therapies into clinical practice. They also underscore the importance of standardized protocols, long-term monitoring, and careful assessment of functional integration and

disease-modifying effects.

Mechanisms of Action in Cell Therapy

Neuronal Replacement

The primary mechanism of neuronal replacement involves the differentiation of stem or progenitor cells into functional neurons. Stem cells, as mentioned above, are capable of generating neuronal populations under specific differentiation conditions. Once transplanted into the diseased brain, these cells respond to local molecular cues that guide their maturation into neuronal subtypes relevant to the pathology. For instance, in Parkinson's disease, transplanted cells are directed to differentiate into dopaminergic neurons to replace those lost in the substantia nigra, whereas in Huntington's disease, medium spiny neurons of the striatum are generated (Limone et al., 2022). Differentiation is regulated by a combination of intrinsic transcription factors, extracellular signaling molecules, and interactions with the surrounding microenvironment, which together ensure that the developing neurons acquire the appropriate neurotransmitter profile, electrophysiological properties, and connectivity patterns (Borodinsky et al., 2004).

Following differentiation, the integration of new neurons into existing neural circuits is a critical step for functional restoration. This process requires the extension of axons and dendrites, the formation of synapses, and the establishment of functional connectivity with host neurons (Götz & Bocchi, 2021). Neuronal integration is guided by both chemical and physical cues present in the brain, including gradients of neurotrophic factors, adhesion molecules, extracellular matrix components, and electrical activity patterns (Falkner & Scheiffele, 2019). Transplanted neurons must form excitatory and inhibitory synapses with the appropriate partners to restore neural network function without disrupting existing circuitry. Preclinical studies have demonstrated that transplanted neurons can establish synaptic contacts, generate action potentials, and participate in neurotransmission, highlighting the potential for meaningful functional recovery (Quezada et al., 2023; Strell et al., 2023).

A complementary mechanism in neuronal replacement involves the modulation of the local microenvironment to support both transplanted and endogenous neurons. Neurodegenerative diseases often create hostile environments characterized by inflammation, oxidative stress, and glial dysfunction, which impair neuronal survival and integration (Gioia et al., 2020). Stem and progenitor cells contribute to a more favorable milieu through the secretion of neurotrophic factors, cytokines, and extracellular vesicles containing microRNAs and proteins. These secreted molecules promote neuronal survival, enhance synaptic plasticity, reduce apoptosis, and stimulate endogenous neurogenesis (Oyarce et al., 2022). In Alzheimer's disease models, transplanted neural progenitors have been shown to increase the survival of existing neurons, reduce amyloid plaque burden, and enhance cognitive performance, illustrating how environmental modulation complements direct neuronal replacement.

Immunomodulation is another important mechanism associated with neuronal replacement. Chronic neuroinflammation, mediated by activated microglia and astrocytes, contributes to ongoing neuronal loss in many neurodegenerative disorders. Transplanted stem cells can attenuate this inflammatory response by promoting the release of anti-inflammatory cytokines, reducing the production of reactive oxygen species, and shifting glial cells toward a neuroprotective phenotype (Kamila et al., 2025). By mitigating inflammation, transplanted cells not only enhance the survival and integration of replacement neurons but also protect existing neurons, thereby amplifying therapeutic efficacy.

Axonal guidance and synaptogenesis are critical processes within neuronal replacement mechanisms. Newly differentiated neurons must navigate complex three-dimensional brain structures to establish connections with distant targets (Tornero, 2022). Axonal guidance is directed by gradients of signaling molecules, including netrins, semaphorins, ephrins, and neurotrophins, which provide spatial cues for proper pathfinding (Yuasa‐Kawada et al., 2022). Synaptogenesis is regulated by adhesion molecules such as neuroligins and neurexins, ensuring that pre- and postsynaptic components align correctly (Shen & Cowan, 2010). These processes are essential for restoring communication within affected circuits and for enabling transplanted neurons to participate in meaningful neural network activity.

Electrical activity also plays a role in the functional maturation of replacement neurons. Activity-dependent mechanisms influence synaptic strength, dendritic arborization, and neurotransmitter release (Yamaguchi & Mori, 2005). Exposure to physiological patterns of neural activity promotes functional integration and the refinement of synaptic connections. In experimental models, transplanted neurons that receive appropriate electrical stimulation exhibit enhanced survival, improved dendritic complexity, and increased synaptic efficacy, underscoring the importance of activity-dependent maturation in neuronal replacement therapy (Flavell & Greenberg, 2008).

In addition to cell-autonomous mechanisms, host factors contribute significantly to the success of neuronal replacement. The age, disease stage, and microenvironment of the recipient brain influence the survival, differentiation, and integration of transplanted neurons (Harary et al., 2023). Younger brains with more plasticity generally allow for better integration, whereas chronic neurodegeneration, gliosis, and scar formation can hinder engraftment and functional connectivity. Strategies to optimize the host environment, such as reducing inflammation, delivering supportive growth factors, or employing biomaterial scaffolds, have been explored to enhance the efficacy of neuronal replacement therapies.

Finally, ongoing advances in bioengineering and genetic modification have the potential to enhance neuronal replacement mechanisms (Purvis et al., 2020). Gene-editing technologies, such as CRISPR/Cas9, allow for the correction of disease-causing mutations in stem or progenitor cells before transplantation, ensuring that replacement neurons are healthy and functional. Biomaterial scaffolds can provide structural support, guide migration, and facilitate connectivity in transplanted neurons. Three-dimensional culture systems and organoid models allow pre-transplantation maturation and network formation, improving the likelihood of successful integration and functional recovery.

Neuroprotection and Paracrine Effects

Neuroprotection in stem cell therapy involves multiple complementary mechanisms that safeguard existing neurons from apoptosis, oxidative stress, excitotoxicity, and inflammatory damage (Raza et al., 2018). Stem cells secrete a wide array of neurotrophic factors, including brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and vascular endothelial growth factor. These molecules promote neuronal survival, enhance synaptic plasticity, stimulate axonal growth, and protect neurons from apoptotic pathways. In models of Parkinson's disease, stem cell transplantation has been shown to preserve dopaminergic neurons and improve motor function through these neurotrophic effects (Zeng & Qin, 2022). Similarly, in Alzheimer's disease models, stem cell-derived neurotrophic factors enhance synaptic connectivity, reduce amyloid-beta toxicity, and promote cognitive recovery, demonstrating the broad protective influence of stem cell paracrine signaling (Wu et al., 2016).

Another critical aspect of stem cell-mediated neuroprotection involves the modulation of oxidative stress, which is a key contributor to neuronal damage in neurodegenerative diseases. Reactive oxygen species generated during neurodegeneration cause lipid peroxidation, protein misfolding, and DNA damage, ultimately leading to cell death (Pardillo-Díaz et al., 2022). Stem cells release antioxidant molecules, such as superoxide dismutase, catalase, and glutathione, which neutralize reactive oxygen species and mitigate oxidative injury. This antioxidant capacity supports neuronal survival and preserves the structural integrity of neural networks, complementing the direct trophic effects of stem cells (Guan et al., 2019). Moreover, stem cells can stimulate endogenous antioxidant defenses in host neurons, further enhancing resistance to oxidative stress.

Stem cells also exert potent immunomodulatory effects, which are essential for neuroprotection. Chronic neuroinflammation, mediated by activated microglia and astrocytes, contributes significantly to neuronal injury and disease progression in neurodegenerative disorders (Pekdemir et al., 2024). Stem cells can reduce the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1 beta, and interferon-gamma, while promoting the release of anti-inflammatory cytokines, including interleukin-10 and transforming growth factor-beta (Chen et al., 2022). This immunomodulatory activity shifts the microenvironment toward a neuroprotective state, reducing glial-mediated toxicity and facilitating the survival and integration of both transplanted and endogenous neurons. In amyotrophic lateral sclerosis models, stem cell transplantation has been shown to modulate microglial activation, delay motor neuron degeneration, and improve neuromuscular function through these immunomodulatory mechanisms (Zhang et al., 2021).

The paracrine effects of stem cells extend beyond neurotrophic and immunomodulatory signaling to include the secretion of extracellular vesicles, exosomes, and microRNAs. These nanoscale vesicles carry proteins, lipids, and regulatory RNAs that influence gene expression, synaptic function, and cell survival in recipient neurons (Wilson et al., 2021). Exosomes derived from stem cells can cross the blood-brain barrier, deliver bioactive molecules to target neurons, and modulate signaling pathways involved in apoptosis, inflammation, and oxidative stress (Xiong et al., 2022). In preclinical studies, administration of stem cell-derived exosomes has replicated many of the neuroprotective effects of cell transplantation, suggesting that paracrine signaling alone may be sufficient to confer therapeutic benefits (Harrell et al., 2021). This cell-free approach also mitigates concerns related to tumorigenicity, immune rejection, and engraftment, providing a promising avenue for clinical translation.

Angiogenesis and vascular support are additional components of stem cell-mediated neuroprotection. Neurodegenerative diseases often compromise cerebral blood flow and vascular integrity, exacerbating neuronal injury (Saft et al., 2020). Stem cells secrete angiogenic factors, such as vascular endothelial growth factor and angiopoietin-1, which stimulate the formation of new blood vessels, improve perfusion, and enhance nutrient and oxygen delivery to affected brain regions. Improved vascularization not only supports neuronal survival but also facilitates the engraftment and integration of transplanted cells, creating a synergistic effect between vascular remodeling and neural repair (O'Donnell et al., 2021). In animal models of stroke and Parkinson's disease, stem cell-induced angiogenesis has been associated with improved functional outcomes and enhanced neuroprotection, highlighting the multifaceted benefits of paracrine signaling (Horie et al., 2011).

The microenvironmental modulation provided by stem cells is also crucial for promoting endogenous repair mechanisms. Paracrine signaling can stimulate the proliferation and differentiation of resident neural stem and progenitor cells, enhancing neurogenesis and glial support within affected brain regions (Dause et al., 2022; Shimada & Spees, 2010). By activating these intrinsic repair pathways, stem cells amplify the regenerative potential of the host tissue and contribute to long-term functional recovery. In Alzheimer's disease models, stem cell transplantation has been shown to enhance hippocampal neurogenesis and improve spatial memory, illustrating the ability of paracrine factors to recruit endogenous repair mechanisms (Qin et al., 2022; Yue et al., 2022).

Despite the therapeutic promise of stem cell-mediated neuroprotection, challenges remain in optimizing efficacy and clinical translation. Variability in stem cell sources, culture conditions, and differentiation states can influence the profile and potency of secreted factors. Standardization of protocols, rigorous quality control, and identification of optimal dosing regimens are essential to ensure reproducible therapeutic outcomes (Mohammadipoor et al., 2018). Additionally, the long-term survival, distribution, and sustained activity of transplanted cells must be addressed to maintain neuroprotective effects over extended periods. Emerging strategies, such as preconditioning stem cells with hypoxia, genetic modification to enhance secretion of neurotrophic factors, and the use of biomaterial scaffolds, are being investigated to overcome these limitations and maximize therapeutic efficacy (Nguyen et al., 2018).

Clinical studies of stem cell therapy in neurodegenerative diseases have demonstrated feasibility and safety, with some evidence of functional improvements attributable to neuroprotective and paracrine mechanisms. For instance, in

Parkinson's disease and amyotrophic lateral sclerosis, early-phase trials have reported stabilization of motor symptoms, enhanced quality of life, and evidence of neural repair without significant adverse effects (Lombardi et al., 2025; Zalfa et al., 2019). While large-scale randomized controlled trials are needed to confirm efficacy, these studies provide proof of concept for the translational potential of stem cell-mediated neuroprotection.

Immunomodulation

Stem cells exert immunomodulatory effects through multiple complementary mechanisms. One of the primary actions is the suppression of pro-inflammatory cytokine production. In neurodegenerative diseases, microglia and astrocytes often adopt a pro-inflammatory phenotype characterized by the release of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, and interferon-gamma (Lively & Schlichter, 2018; Smith et al., 2011). These cytokines contribute to oxidative stress, excitotoxicity, and apoptosis, accelerating neuronal degeneration. Stem cells release anti-inflammatory molecules, such as interleukin-10, transforming growth factor-beta, and prostaglandin E2, which inhibit the production of pro-inflammatory cytokines and shift glial cells toward a neuroprotective phenotype (Dabrowska et al., 2019). This reprogramming of the immune environment mitigates neuronal injury and provides a supportive milieu for regeneration and repair.

Another key mechanism involves the modulation of microglial and astrocytic activation. Microglia are the resident immune cells of the central nervous system and are highly responsive to signals from damaged or stressed neurons (Hermann & Gunzer, 2021). Chronic microglial activation is a hallmark of many neurodegenerative diseases, resulting in sustained neurotoxicity. Stem cells interact with microglia through both direct cell-to-cell contact and the secretion of soluble factors, promoting a transition from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype (Regmi et al., 2022). This phenotypic shift reduces the release of cytotoxic mediators and enhances the production of neurotrophic factors, thereby supporting neuronal survival and synaptic maintenance. Astrocytes, which play crucial roles in synaptic homeostasis, blood-brain barrier integrity, and metabolic support, are also modulated by stem cells (Neal & Richardson, 2017). Stem cell-mediated signals can attenuate astrogliosis, reduce inflammatory signaling, and promote astrocytic support functions, further contributing to a neuroprotective microenvironment.

Paracrine signaling plays a central role in the immunomodulatory actions of stem cells. Stem cells secrete a diverse array of soluble molecules, including cytokines, chemokines, growth factors, and extracellular vesicles, that collectively modulate immune cell activity (Dabrowska et al., 2021). These factors influence not only microglia and astrocytes but also peripheral immune cells that infiltrate the central nervous system under pathological conditions. For instance, stem cells can inhibit T-cell activation and proliferation, reduce the infiltration of pro-inflammatory immune cells, and enhance the activity of regulatory T cells (Raza et al., 2018). By orchestrating both local and systemic immune responses, stem cells attenuate chronic neuroinflammation and create conditions conducive to neuronal survival and repair.

Extracellular vesicles, including exosomes and microvesicles, are emerging as important mediators of stem cell immunomodulation. These vesicles contain bioactive molecules, such as microRNAs, proteins, and lipids, which can influence gene expression and signaling pathways in target cells. Stem cell-derived exosomes have been shown to suppress microglial activation, reduce cytokine production, and enhance the expression of anti-inflammatory mediators in experimental models of neurodegeneration (Gotoh et al., 2023). Importantly, exosomes can cross the blood-brain barrier, allowing systemic administration to exert effects on central nervous system immune cells. This cell-free approach offers a promising alternative to direct stem cell transplantation, mitigating concerns related to tumorigenicity, immune rejection, and engraftment while retaining potent immunomodulatory capacity.

Stem cells also enhance neuroprotection indirectly by modulating the balance between pro-inflammatory and anti-inflammatory signaling pathways. For example, they can upregulate the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and other antioxidant response pathways, reducing oxidative stress-induced immune activation (Saha et al., 2020). They also influence signaling pathways such as phosphoinositide 3-kinase/Akt and Janus kinase/signal transducer and activator of transcription, which regulate cell survival, cytokine production, and inflammatory responses (Michalak & Michalak, 2025). By fine-tuning these pathways, stem cells reduce the detrimental effects of chronic inflammation while promoting regenerative processes.

In addition to regulating immune cell activity, stem cells contribute to the preservation of blood-brain barrier integrity, which is often compromised in neurodegenerative diseases. Disruption of the blood-brain barrier allows peripheral immune cells, toxins, and inflammatory mediators to infiltrate the central nervous system, exacerbating neuronal injury (Kim et al., 2025). Stem cells release angiogenic and barrier-stabilizing factors, such as vascular endothelial growth factor, angiopoietin-1, and tight junction proteins, which reinforce vascular integrity and limit harmful immune cell infiltration. Maintaining the blood-brain barrier supports a controlled and protective environment that enhances the efficacy of neuronal repair and functional recovery (Qi et al., 2024).

Preclinical studies have demonstrated the therapeutic potential of stem cell immunomodulation in various neurodegenerative models. In Parkinson's disease animal models, mesenchymal stem cell transplantation reduces microglial activation, decreases pro-inflammatory cytokines, and protects dopaminergic neurons, resulting in improved motor function (Kim et al., 2008). In Alzheimer's disease models, stem cells attenuate neuroinflammation, reduce amyloid-beta-associated immune activation, and enhance cognitive performance (Chan et al., 2021). In amyotrophic lateral sclerosis and Huntington's disease, stem cells modulate glial activation, suppress neurotoxic signaling, and improve neuronal survival, highlighting the broad applicability of stem cell immunomodulatory mechanisms across different neurodegenerative contexts.

Despite the promise of stem cell-based immunomodulation, several challenges remain. Variability in cell sources, donor characteristics, and culture conditions can influence the

immunoregulatory capacity of stem cells. Standardization of cell preparation, characterization, and quality control is essential to ensure consistent therapeutic efficacy. Long-term safety, including the risk of unintended immune suppression or aberrant immune activation, must also be carefully monitored in clinical applications. Advances in genetic engineering, preconditioning, and exosome-based therapies are being explored to enhance immunomodulatory potency while minimizing potential risks.

Angiogenesis and Microenvironment Remodeling

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, plays a central role in supporting neuronal survival and function in neurodegenerative disorders. Neurons rely on a continuous supply of oxygen, glucose, and trophic support delivered through the vascular network. Impaired vascularization in diseased brain regions contributes to hypoxia, oxidative stress, and nutrient deprivation, all of which exacerbate neuronal loss (Watanabe et al., 2020). Stem cells, including mesenchymal stem cells, neural stem/progenitor cells, and induced pluripotent stem cell-derived progenitors, secrete angiogenic factors such as vascular endothelial growth factor, angiopoietin-1, fibroblast growth factor, and platelet-derived growth factor (Cha et al., 2024). These factors stimulate endothelial cell proliferation, migration, and tube formation, promoting the establishment of functional vascular networks within damaged tissue. Enhanced vascularization improves oxygen and nutrient delivery, facilitates waste removal, and provides structural support for neuronal and glial cells, creating a favorable environment for repair.

The paracrine secretion of angiogenic factors by stem cells is complemented by their ability to interact with endothelial cells and pericytes in the host tissue. Stem cells can recruit endogenous vascular progenitor cells, promote endothelial cell survival, and enhance pericyte coverage, which stabilizes newly formed vessels (Yang et al., 2009). This coordinated response not only promotes the formation of robust and functional vasculature but also prevents vascular regression, ensuring long-term support for neurons and glial cells. In preclinical models of Parkinson's disease and stroke, stem cell transplantation has been shown to enhance cerebral perfusion, reduce hypoxic stress, and improve motor and cognitive outcomes, highlighting the significance of angiogenesis in functional recovery (Horie et al., 2011).

In addition to promoting angiogenesis, stem cells remodel the neural microenvironment to support regeneration and repair. The microenvironment of the neurodegenerative brain is often hostile, characterized by chronic inflammation, glial scarring, extracellular matrix deposition, and oxidative stress (Lindvall & Kokaia, 2010). These factors inhibit neuronal survival, synaptic plasticity, and endogenous repair mechanisms. Stem cells secrete a diverse array of trophic factors, cytokines, chemokines, and extracellular vesicles that modulate the behavior of resident glial cells, stimulate endogenous progenitors, and reduce inhibitory components of the extracellular matrix (Hart, 2023). For example, matrix metalloproteinases released by stem cells degrade aberrant extracellular deposits and facilitate axonal growth and synaptic connectivity. This remodeling enhances the structural and biochemical landscape of the tissue, allowing both transplanted and host neurons to survive, integrate, and function effectively.

Microenvironment remodeling also involves modulation of glial activity. Astrocytes and microglia play dual roles in neurodegenerative diseases: while they provide essential support under normal conditions, chronic activation contributes to inflammation, oxidative stress, and synaptic dysfunction (Bouvier et al., 2022). Stem cells interact with these glial cells through both direct cells contact and paracrine signaling, promoting a shift from a reactive, pro-inflammatory state to a supportive, neuroprotective phenotype. In addition to suppressing the release of harmful cytokines, stem cells stimulate astrocytes to produce neurotrophic factors and metabolic support molecules, further enhancing neuronal resilience (Tsai, 2017). Microglia are similarly modulated, adopting a reparative phenotype that clears debris, promotes angiogenesis, and supports synaptic remodeling.

Extracellular vesicles and exosomes derived from stem cells are central mediators of microenvironment remodeling (Moretti et al., 2025). These vesicles contain proteins, lipids, microRNAs, and other signaling molecules that influence gene expression and cellular behavior in recipient cells. Stem cell-derived exosomes can promote endothelial cell proliferation, enhance neuronal survival, modulate glial activity, and remodel the extracellular matrix (Hade et al., 2021). Importantly, exosomes can cross the blood-brain barrier, enabling systemic administration to exert effects within the central nervous system. In animal models of Alzheimer's disease, administration of stem cell-derived exosomes has been shown to improve vascular density, reduce amyloid deposition, and enhance cognitive performance, demonstrating that paracrine-mediated microenvironment remodeling can be highly effective (Zhou et al., 2024).

The benefits of angiogenesis and microenvironment remodeling extend beyond immediate neuronal survival to include long-term functional recovery and network repair. Enhanced vascularization ensures sustained delivery of nutrients and oxygen, which supports synaptic plasticity, axonal regeneration, and circuit reorganization (Williamson et al., 2020). Remodeling of the extracellular matrix and modulation of glial activity create permissive conditions for the migration, integration, and connectivity of transplanted neurons. In Huntington's disease models, stem cell transplantation has been shown to increase vascular density, reduce glial scarring, and promote striatal neuron survival, resulting in improved motor coordination and cognitive function (Yoon et al., 2020). These studies underscore the synergistic relationship between angiogenesis and microenvironmental modulation in facilitating effective neuroregeneration.

Clinical translation of these mechanisms has begun in early-phase trials for neurodegenerative diseases. Studies using mesenchymal stem cells, neural stem/progenitor cells, and iPSC-derived progenitors have demonstrated safety and feasibility, with preliminary evidence of improved perfusion, reduced inflammation, and enhanced functional outcomes (Luciani et al., 2024). Although long-term studies are needed to establish efficacy, these trials provide proof-of-concept that angiogenesis and microenvironment remodeling are achievable and therapeutical-

ly meaningful in human patients. Optimization of delivery methods, cell sources, dosing, and supportive interventions remains a key focus to maximize these effects.

Challenges in leveraging angiogenesis and microenvironment remodeling include variability in stem cell preparations, limited survival and engraftment of transplanted cells, and the complex interplay between transplanted cells and the host tissue (Zhao et al., 2021). Strategies such as genetic modification to enhance angiogenic factor secretion, preconditioning cells under hypoxic conditions, or embedding cells in biomaterial scaffolds are being explored to overcome these limitations. These approaches aim to enhance cell survival, guide vascular growth, and sustain a supportive microenvironment, thereby increasing therapeutic efficacy and reliability.

Conclusion

Cell-based therapies represent a transformative approach for neurodegenerative diseases, offering potential for neuronal replacement, neuroprotection, and modulation of neuroinflammation. ESCs, iPSCs, MSCs, and NSPCs each present unique advantages and challenges, and ongoing preclinical and clinical studies continue to refine their safety, efficacy, and delivery strategies. Despite significant hurdles—immune rejection, tumorigenicity, and ethical concerns—emerging technologies, including gene editing, biomaterials, and personalized medicine, hold promise for translating these therapies into effective clinical treatments. Continued interdisciplinary research is essential to harness the full potential of cell therapies for patients suffering from debilitating neurodegenerative disorders. ■

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