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Therapeutic Potential of Neural Stem Cells for Regenerating Damaged Neural Pathways: Current Evidence and Future Directions

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Abstract

Neural stem cells (NSCs) represent a promising therapeutic strategy for repairing damaged neural circuits in the central nervous system (CNS). The therapeutic promise of NSCs stems from their dual capacity for sustained self-renewal and differentiation into neurons, astrocytes, and oligodendrocytes, which collectively support the regeneration of injured neural tissue and the recovery of neurological function. Beyond direct cell replacement, NSCs exert powerful paracrine effects through the secretion of neurotrophic factors, cytokines, and extracellular vesicles that modulate inflammation, enhance neuronal survival, and promote axonal regeneration. Increasing evidence indicates that NSC-mediated immunomodulation plays a central role in shifting the post-injury microenvironment from a neurotoxic to a regenerative state, primarily through regulation of microglial polarization and suppression of pro-inflammatory signaling pathways.

In addition, NSCs contribute to neural repair by enhancing synaptic plasticity, supporting remyelination, stabilizing the blood–brain barrier, and facilitating angiogenesis. Accumulating preclinical evidence suggests that both NSC transplantation and the therapeutic application of NSC-derived secretomes lead to significant functional improvement in animal models of spinal cord injury, stroke, and traumatic brain injury. However, clinical translation remains limited by challenges such as poor cell survival, immune rejection, tumorigenic risk, and lack of standardized delivery protocols. Emerging strategies, including gene-edited NSCs, biomaterial scaffolds, and exosome-based cell-free therapies, are being developed to overcome these limitations. Overall, NSCs provide a multifaceted regenerative platform with strong potential for future clinical applications in neurological disorders, although further large-scale clinical studies are essential to validate the long-term safety and efficacy of these therapies.

Keywords: Neural stem cells, CNS regeneration, Neuroplasticity, Immunomodulation; Axonal regeneration.

Introduction

Damage to neural pathways resulting from spinal cord injury, traumatic brain injury, stroke, and neurodegenerative disorders remains one of the greatest challenges in modern neuroscience. Unlike the peripheral nervous system, the adult central

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nervous system (CNS) exhibits limited regenerative capacity due to inhibitory microenvironments, glial scar formation, chronic inflammation, and reduced intrinsic neuronal growth potential (1, 2). Consequently, the restoration of functional neural circuits following injury is often incomplete, leading to persistent neurological deficits and disability. Recent advances in regenerative medicine have highlighted neural stem cells (NSCs) as promising therapeutic candidates because of their ability to self-renew, differentiate into neurons and glial cells, modulate immune responses, and secrete neurotrophic factors that support tissue repair (3, 4). Experimental studies have demonstrated that endogenous and transplanted NSCs can promote axonal regeneration, remyelination, synaptic plasticity, and reconstruction of disrupted neural networks after CNS injury (5, 6). Furthermore, emerging biomaterial-based approaches, including hydrogel-supported NSC transplantation, have shown enhanced cell survival and integration within injured tissues, thereby improving functional outcomes in preclinical models (7). These findings have generated significant interest in NSC-based therapies as a potential strategy for restoring damaged neural pathways and improving neurological recovery.

In recent years, substantial progress has been made in understanding the mechanisms through which NSCs contribute to neural regeneration and circuit reconstruction. Beyond direct cell replacement, NSCs exert paracrine effects by releasing extracellular vesicles, cytokines, and growth factors that attenuate neuroinflammation and stimulate endogenous repair processes (8). Advances in stem cell engineering, gene editing technologies, and the manipulation of endogenous neural stem/progenitor cell populations have further expanded the therapeutic potential of NSCs in spinal cord injury and other CNS disorders (5, 9). Preliminary clinical evidence supports the safety and feasibility of neural stem cell transplantation in chronic spinal cord injury and stroke (10, 11). Nevertheless, several challenges remain, including limited cell survival, insufficient functional integration, tumorigenic risk, immune rejection, and ethical considerations associated with stem cell sources (3, 7). Therefore, a comprehensive evaluation of current evidence is essential to determine the translational potential of NSC-based therapies. This review aims to summarize recent advances in neural stem cell biology, explore their role in regenerating damaged neural pathways, and discuss future directions for clinical application.

Biology and Characteristics of Neural Stem Cells

NSCs are characterized by their self-renewal capacity and multilineage differentiation potential, allowing them to generate the principal neural cell types that support central nervous system development and regeneration (13, 14).The adult mammalian brain contains two principal neurogenic niches that harbor NSCs: the SVZ and the SGZ of the hippocampal dentate gyrus (15, 16). These specialized microenvironments consist of endothelial cells, astrocytes, microglia, and extracellular matrix components that tightly regulate NSC fate decisions (15). Recent single-cell transcriptomic analyses have demonstrated that NSCs are highly heterogeneous, comprising multiple subpopulations with distinct transcriptional signatures and regenerative capacities (16). This heterogeneity enables adaptive neurogenic responses under both physiological and pathological conditions. NSCs maintain a dynamic equilibrium between quiescence and activation, which is essential for preserving long-term regenerative potential (17). Disruption of this balance contributes to impaired neurogenesis and reduced neural repair capacity.

NSC function is tightly regulated by a network of conserved signaling pathways, including Notch, Wnt/β-catenin, Sonic Hedgehog (Shh), and BMP signaling, which collectively coordinate stem cell maintenance and differentiation (13, 17). Notch signaling is primarily responsible for maintaining NSC quiescence, whereas Wnt signaling promotes activation and neuronal differentiation (17, 18). Beyond classical signaling pathways, epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs serve as critical regulators of gene expression that influence NSC fate decisions (18). In addition, metabolic regulation and mitochondrial dynamics significantly influence NSC proliferation and differentiation capacity (19). Age-associated alterations in these molecular pathways result in a progressive decline in neurogenic potential (17). Therefore, targeting these regulatory networks represents a promising strategy for enhancing endogenous neural repair mechanisms.

Beyond intrinsic properties, NSCs actively interact with their microenvironment through paracrine signaling and cell-cell communication (14, 16). They secrete cytokines, neurotrophic factors, and extracellular vesicles that regulate inflammation, support enhance synaptic plasticity and neuronal survival (16). NSCs also respond to neurotransmitters such as GABA and glutamate, which influence their proliferation and differentiation dynamics (13). Bidirectional communication between NSCs, neurons, and immune cells forms a complex regulatory network within neurogenic niches (15). This network is essential for maintaining CNS homeostasis and facilitating repair processes following injury. Collectively, these features highlight NSCs as key

regulators of neural plasticity and regeneration.

Sources and Classification of Neural Stem Cells

The adult CNS contains two principal neurogenic niches that serve as the primary reservoirs of NSCs: the SVZ along the lateral ventricles and the SGZ located in the dentate gyrus of the hippocampus (15, 20). Neurogenesis in the SVZ involves the formation of intermediate progenitor cells from NSCs, followed by the differentiation of these progenitors into neuroblasts that migrate through the rostral migratory stream to the olfactory bulb (20). Conversely, NSCs in the SGZ generate granule neurons that integrate into hippocampal neural circuits, thereby supporting cognitive functions, particularly learning and memory (16). These region-specific neurogenic processes reflect functional specialization within the CNS. Developmentally, adult NSCs originate from embryonic radial glial cells that persist as quiescent stem cells after birth (21). This lineage relationship underlies the lifelong, albeit limited, regenerative capacity of the brain.

In addition to classical neurogenic niches, emerging evidence suggests the presence of NSC-like populations in non-canonical regions such as the hypothalamus, striatum, and spinal cord (20). These cells exhibit restricted neurogenic activity under specific physiological or injury conditions. Moreover, cellular reprogramming studies have demonstrated that astrocytes and pericytes can be converted into induced neural stem cells (iNSCs) using defined transcription factors (19). This finding expands the concept of NSC origin beyond traditional developmental pathways. Furthermore, induced pluripotent stem cell (iPSC)-derived neural progenitors provide an exogenous and scalable source for regenerative applications (18). However, challenges such as incomplete maturation and functional heterogeneity remain.

NSCs can also be classified based on their functional states, including quiescent NSCs (qNSCs) and activated NSCs (aNSCs) (17, 21). Quiescent NSCs serve as a long-term reservoir, preserving stem cell pools and preventing depletion (21). Activated NSCs, in contrast, enter the cell cycle in response to injury or physiological demands and contribute to tissue regeneration (17). Recent single-cell sequencing studies suggest that NSC states exist along a dynamic continuum rather than discrete categories (16). This plasticity is regulated by both intrinsic genetic programs and extrinsic niche-derived signals. Understanding these functional states is critical for optimizing therapeutic strategies aimed at enhancing neurodegeneration.

Mechanisms of Neural Pathway Damage in the Central Nervous System

Neural pathway damage in the CNS occurs due to traumatic, ischemic, inflammatory, and neurodegenerative processes, including traumatic brain injury, spinal cord injury, stroke, and diseases such as multiple sclerosis (22, 23). These conditions lead to axonal disruption, neuronal apoptosis, demyelination, and synaptic loss, ultimately impairing neural circuit connectivity. A major barrier to regeneration is forming of a glial scar composed of reactive astrocytes and extracellular matrix molecules (22). This scar physically and chemically inhibits axonal regrowth. Additionally, inhibitory molecules such as Nogo-A, MAG, and chondroitin sulfate proteoglycans further restrict neural regeneration (23). Together, these factors create a non-permissive environment for repair.

Neuroinflammation is recognized as a major driver of secondary injury progression after CNS damage. Following CNS injury, inflammatory cytokines released by activated microglia and infiltrating immune cells, including TNF-α, IL-1β, and IL-6, contribute to neuronal degeneration. This process is further intensified by oxidative stress and mitochondrial dysfunction, which impair cellular energy production and increase tissue damage (22). Glutamate-induced excitotoxicity promotes excessive intracellular calcium accumulation, thereby triggering neuronal degeneration and cell death (23). Chronic inflammation also suppresses endogenous NSC activation and migration, limiting intrinsic repair capacity. Therefore, modulation of inflammatory pathways is a critical therapeutic target in CNS injury.

At the network level, disruption of long-range axonal connections leads to severe functional deficits, including motor impairment, cognitive dysfunction, and sensory loss (22). Although compensatory plasticity mechanisms exist, they are often insufficient for full functional recovery (23). Aging further worsens outcomes by reducing NSC activity and regenerative responsiveness (21). The severity of functional impairment is influenced not only by primary injury but also by failure of endogenous repair signaling (20). Enhancing intrinsic regenerative capacity, particularly through NSC-based strategies, represents a promising therapeutic approach for restoring damaged neural pathways.

Molecular Mechanisms of Neural Stem Cell–Mediated Neural Regeneration

Neural stem cells (NSCs) promote regeneration of damaged neural pathways through highly coordinated molecular signaling networks that regulate proliferation, differentiation, and neuronal integration (24, 25, 26). Among these, the Wnt/β-catenin pathway plays a central role in promoting neuronal lineage commitment and enhancing neurogenic activity following CNS injury (24). The

Notch signaling pathway, in contrast, maintains NSC quiescence under physiological conditions but becomes dynamically regulated after injury to balance self-renewal and differentiation (25). Sonic Hedgehog (Shh) signaling also contributes significantly by enhancing NSC proliferation and guiding neural patterning during regeneration (26). These pathways interact in a tightly regulated manner, ensuring controlled neurogenesis without depletion of the stem cell pool. Dysregulation of these mechanisms leads to impaired regenerative responses and incomplete neural repair (Table 1).

Epigenetic regulation is another fundamental mechanism underlying NSC-mediated neural repair. Histone modification, DNA methylation, and chromatin remodeling collectively regulate transcriptional programs involved in NSC activation and lineage specification (27, 28). MicroRNAs (miRNAs) and long non-coding RNAs further refine gene expression by post-transcriptional regulation of key regenerative genes (27). These epigenetic mechanisms enable NSCs to respond dynamically to injury-induced environmental cues such as inflammation and hypoxia. Additionally, metabolic reprogramming from glycolysis toward oxidative phosphorylation is essential for NSC differentiation and maturation (29). Mitochondrial dynamics also influence NSC fate decisions and regenerative capacity (28). Together, these processes establish the molecular basis of NSC plasticity in CNS repair.

Neural regeneration mediated by NSCs extends beyond cell replacement, as these cells actively modulate the injured microenvironment through paracrine signaling. This effect is largely attributed to the secretion of neurotrophic factors, including BDNF, GDNF, and VEGF (30). These molecules enhance neuronal survival, promote angiogenesis, and reduce apoptotic signaling in injured tissue (30, 31). NSC-derived extracellular vesicles (EVs) carry proteins, lipids, and regulatory RNAs that modulate gene expression in recipient cells (31). These EVs also suppress neuroinflammation and enhance endogenous repair mechanisms (32). Furthermore, NSCs interact with immune cells, particularly microglia, to regulate inflammatory responses and promote a regenerative microenvironment (33). This dual role of NSCs as both cellular replacements and secretory regulators highlights their therapeutic potential.

Neural Stem Cells and Axonal Regrowth After Neural Injury

Axonal regeneration in the central nervous system (CNS) is severely limited due to both intrinsic neuronal constraints and inhibitory extracellular environments (34, 35). Neural stem cells (NSCs) contribute to axonal regrowth by creating a permissive environment that supports axonal elongation, synaptic reconnection, and circuit remodeling (34). Experimental models of spinal cord injury and stroke have demonstrated that NSC transplantation significantly enhances axonal sprouting and functional recovery (35). This regenerative effect is mediated in part by secretion of neurotrophic factors such as BDNF, NGF, and NT-3 (30). These factors promote neuronal survival and stimulate axonal extension in damaged neural networks. Additionally, NSCs differentiate into oligodendrocyte lineage cells, contributing to remyelination and improved signal conduction (6, 35).

A major barrier to axonal regeneration is the presence of inhibitory molecules in the injured CNS environment, including Nogo-A, MAG, OMgp, and chondroitin sulfate proteoglycans (CSPGs) (34, 36). NSCs counteract these inhibitory signals by modulating extracellular matrix composition and

Table 1. Major Molecular Mechanisms and Regenerative Functions of Neural Stem Cells in CNS Repair

Molecular Mechanism/Pathway	Biological Function in NSCs	Regenerative Outcome in CNS Injury	References
Wnt/β-catenin signaling	Promotes neuronals differentiation and NSC activation	Enhanced neurogenesis and neural repair	(24,25)
Notch signaling	Maintains NSC quiescence and self-renewal	Preservation of stem cell pool balance	(25)
Sonic Hedgehog (Shh) pathway	Stimulates NSC proliferation and neural patterning	Improved of stem cell pool balance	(26)
Epigenetic regulation (DNA methylation, histone modification, miRNAs)	Controls gene expression and lineage specification	Adaptive response to injury microenviroment	(27,28)
Neurotrophic factor secretion (BDNF, GDNF, VEGF)	Supports neuronal survival and angiogenesis	Axonal regeneration and reduced apoptosis	(30,31)
Extracellular vehicles (EVs)/exosomes	Transfer regulatory RNAs and proteins	Suppression of neuroinflammation and promotion of endogenous repair	(31,32)
Immunomodulation of microglia	Shifts microglia from M1 to M2 phenotype	Reduced inflammatory damage and improved tissue repair	(33,41)
Remyelination support	Differentiation into oligodendrocyte lineage cells	Restoration of neural signal conduction	(6,35)

reducing glial scar formation (36). They suppress reactive astrocyte activation and decrease deposition of inhibitory CSPGs, thereby improving axonal growth conditions (36). NSCs also promote synaptic plasticity, facilitating the formation of new functional connections between surviving neurons (35). Moreover, NSC-derived exosomes have been shown to enhance axonal regeneration by transferring regenerative microRNAs to host neurons (31). These combined mechanisms significantly enhance structural and functional recovery after CNS injury.

Recent advances in biomaterials and tissue engineering have further improved NSC-based axonal regeneration strategies. Hydrogels, nanofiber scaffolds, and 3D-printed matrices provide structural support for NSC survival and axonal guidance (7, 37). These biomaterials enhance cell retention, improve spatial organization, and facilitate directed axonal growth across lesion sites (37). Genetically modified NSCs expressing enhanced growth-promoting or anti-inhibitory molecules have shown superior regenerative outcomes in preclinical models (38). In addition, combining NSC therapy with electrical stimulation and rehabilitative training further enhances axonal plasticity and functional recovery (35). These multimodal approaches represent a promising direction for improving outcomes in CNS injury repair.

Immunomodulatory and Neuroprotective Effects of Neural Stem Cells

Following injury to the central nervous system (CNS), neural stem cells (NSCs) serve as key regulators of the immune response. After CNS damage, microglial activation, together with the recruitment of immune cells from the periphery, contributes to excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which amplify secondary neuronal damage (39, 40). NSCs counteract this inflammatory cascade by secreting anti-inflammatory cytokines including IL-10 and TGF-β, thereby promoting a shift from M1 to M2 microglial polarization (41). This shift creates a regenerative microenvironment that supports tissue repair and limits neurodegeneration. In addition, NSCs interact directly with resident immune cells, regulating both innate and adaptive immune responses in the CNS (42). NSC-derived extracellular vesicles further enhance immunomodulation by transferring microRNAs that suppress inflammatory signaling pathways (43).

Beyond immune regulation, NSCs provide strong neuroprotective effects in injured neural tissue. They secrete neurotrophic factors such as GDNF, BDNF, NGF, and VEGF, which promote neuronal survival and synaptic stabilization (44). These factors reduce apoptosis, enhance axonal integrity, and improve resistance to oxidative stress (45). NSCs also contribute to blood–brain barrier (BBB) stabilization, thereby reducing infiltration of toxic molecules and immune cells into neural tissue (46). Furthermore, NSCs regulate glutamate excitotoxicity and calcium imbalance, which are key drivers of neuronal death after injury (47). These combined effects significantly improve structural preservation and functional recovery in CNS disorders.

Importantly, the therapeutic impact of NSCs is largely mediated through paracrine signaling rather than direct neuronal replacement. Their secretome includes cytokines, growth factors, and extracellular vesicles that modulate multiple signaling pathways in host cells (43, 48). NSC-derived exosomes can reproduce many of the regenerative effects observed in cell transplantation models (43). This has shifted current therapeutic strategies toward cell-free regenerative medicine. Overall, NSCs function as both immune regulators and neuroprotective mediators in CNS repair.

Clinical Applications of Neural Stem Cells in Neurological Disorders

Therapeutic approaches utilizing neural stem cells (NSCs) have gained considerable attention as potential treatments for various neurological conditions, such as spinal cord injury (SCI), stroke, traumatic brain injury (TBI), and neurodegenerative diseases (49, 50). Preclinical studies consistently demonstrate that NSC transplantation enhances neurogenesis, axonal regeneration, and remyelination, leading to improved functional outcomes (51). In SCI models, NSCs integrate into host neural circuits and contribute to reconstruction of disrupted pathways (52). In ischemic stroke models, they promote angiogenesis and neuronal survival, improving both motor and cognitive recovery (53). These findings strongly support the translational potential of NSC-based therapies (Table 2).

Early-phase clinical trials have evaluated the safety and feasibility of NSC transplantation in CNS injury patients. Overall, these studies report acceptable safety profiles with no significant tumor formation or severe immune rejection (54, 55). Some patients show modest improvements in motor and sensory functions, although outcomes remain variable (55). Differences in cell source, delivery route, timing of intervention, and injury heterogeneity contribute to inconsistent results (54). Common delivery methods include intrathecal, intracerebral, and intravenous administration (56). However, lack of standardized clinical protocols remains a major limitation in translating NSC therapies.

In addition to cell transplantation, NSC-derived extracellular vesicles and secretome-based therapies have gained increasing attention (43, 57). These

Table 1. Major Molecular Mechanisms and Regenerative Functions of Neural Stem Cells in CNS Repair

Neurological Disorder	Therapeutic Effects of NSCs	Major Benefits	Current Limitations	Key References
Spinal cord injury (SCI)	Axonal regeneration, remyelination, neural circuit reconstruction	Improved motor recovery and neural connectivity	Poor cell survival, inhibitory microenvironment	(50,52)
Ischemic stroke	Promotion angiogenesis and neuronal survival	Recovery of motor and cognitive function	Variable clinical outcomes	(49,53)
Traumatic brain injury (TBI)	Neuroprotection and anti-inflammatory effects	Reduced neuronal apoptosis and enhanced repair	Limited long-term integration	(40,45)
Multiple sclerosis (MS)	Immunomodulation and remyelination	Reduction of inflammatory damag	Immune rejection risk	(39,41)
Neurodegeneratve disorders	Neurotrophic support and synaptic stabilization	Potential slowing of neurodegeneration	Tumorigenic risk and delivery challenges	(44,55)
Exosome-based therapies	Cell-free regenerative signaling	Lower tumorigenic and immunogenic risk	Standardization regulatory concerns	(43,57)
Gene-edited NSCs	Enhanced regenerative capacity	Improved therapeutic precision	Ethical and regulatory concerns	(59,65)

approaches reduce risks associated with live cell transplantation while maintaining regenerative effects (57). Biomaterial-assisted delivery systems such as hydrogels and nanoscaffolds improve NSC survival, localization, and integration (58). Gene-edited NSCs with enhanced regenerative properties are also under investigation (59). Despite these advances, long-term safety, optimal dosing, and functional integration remain unresolved challenges (54). Large-scale randomized clinical trials are essential for clinical validation.

Challenges, Limitations, and Future Perspectives

Despite promising progress, several biological and technical challenges limit the clinical translation of NSC-based therapies. One major limitation is poor survival of transplanted NSCs in the hostile post-injury microenvironment categorized by inflammation, oxidative stress, and inhibitory extracellular matrix molecules (60, 61). These factors significantly reduce cell viability and functional integration. Another concern is the risk of uncontrolled proliferation and tumorigenesis, particularly with pluripotent stem cell-derived NSCs (62). Immune rejection in allogeneic transplantation also remains a critical barrier (63). These limitations collectively reduce therapeutic consistency.

Technical challenges include the absence of standardized protocols for NSC derivation, expansion, and transplantation (64). Variability in manufacturing methods leads to inconsistent biological and functional outcomes. Additionally, precise control of NSC differentiation and incorporation into existing neural circuits remains difficult (60). The complexity of CNS architecture further complicates reconstruction of functional connectivity. Ethical concerns regarding embryonic stem cell sources also influence clinical translation pathways (62). Therefore, regulatory standardization is essential for clinical advancement.

Future directions focus on overcoming these limitations through advanced biomedical strategies. Gene-editing technologies such as CRISPR/Cas9 allocate precise enhancement of NSC safety and regenerative capacity (59, 65). Biomaterial scaffolds, nanotechnology, and 3D bioprinting provide structural guidance for axonal growth and neural network reconstruction (58, 66). Exosomes derived from neural stem cells (NSC-derived exosomes) have emerged as a promising cell-free therapeutic approach, offering the potential for enhanced safety compared with cell-based therapies (43, 57). Combination therapies integrating NSCs with pharmacological agents, rehabilitation, and electrical stimulation further enhance functional recovery (67). Ultimately, multidisciplinary approaches will be essential for successful clinical translation.

Controversies and Limitations (Critical View of NSC-Based Therapies)

Despite substantial progress in neural stem cell (NSC)-based therapies, several important controversies and limitations remain that restrict their full clinical translation. One of the most significant challenges is the limited survival and poor functional integration of transplanted NSCs within the injured central nervous system (CNS). Following injury, the local microenvironment becomes strongly detrimental to tissue repair, largely as a result of sustained inflammation, oxidative damage, excitotoxic processes, and inhibitory extracellular matrix molecules, including chondroitin sulfate proteoglycans (68, 69). These factors severely impair NSC survival, differentiation, and synaptic integration, leading to inconsistent and often transient functional recovery in experimental models (69).

Another concern associated with NSC-based therapy is the potential for tumor formation and aberrant cell proliferation, especially when neural stem cells are generated from embryonic stem cells

(ESCs) or induced pluripotent stem cells (iPSCs) (70). Even small populations of undifferentiated cells can form teratomas or aberrant tissue structures, raising serious safety concerns for clinical application. In addition, immune rejection remains a critical barrier, especially in allogeneic transplantation, where host immune responses can eliminate grafted cells or reduce their therapeutic efficacy (71). Although immunosuppressive strategies may mitigate rejection, they introduce risks such as systemic immunosuppression and increased susceptibility to infection (71).

A further controversy concerns the mechanism of action of NSCs. While early studies emphasized direct cell replacement, more recent evidence indicates that the majority of therapeutic benefits are mediated across paracrine signaling and extracellular vesicle (EV)-based mechanisms rather than long-term neuronal integration (43, 72). This shift has raised important questions regarding whether NSCs should be used primarily as regenerative grafts or as biological sources for secretome- and exosome-based therapies. However, the optimal balance between these mechanisms remains unclear and likely depends on injury type and disease context.

Finally, the lack of standardized protocols for NSC derivation, expansion, differentiation, and transplantation remains a major translational barrier (73). Variability in cell preparation methods, delivery routes, timing of transplantation, and injury models leads to inconsistent outcomes across studies. Ethical concerns related to the use of embryonic stem cells further complicate regulatory approval and clinical implementation (70). Together, these issues highlight the need for improved standardization, safety optimization, and mechanistic clarity in future NSC research.

Conclusion

Neural stem cells (NSCs) have emerged as a versatile therapeutic approach with considerable potential for promoting repair and recovery following injuries to the central nervous system (CNS). Their regenerative potential extends beyond simple cell replacement, encompassing neuroprotection, immunomodulation, and the secretion of bioactive molecules that reshape the injured neural microenvironment. Through the regulation of inflammatory responses, enhancement of neuronal survival, promotion of axonal regeneration, and support of remyelination, NSCs contribute to both structural and functional recovery in diverse neurological conditions.

Findings from preclinical studies provide substantial evidence for the therapeutic effectiveness of NSC-based strategies in experimental models of stroke, spinal cord injury, and traumatic brain injury. However, clinical translation remains limited due to challenges such as poor cell survival, variability in transplantation outcomes, immune rejection, and safety concerns including tumorigenicity. Despite these challenges, recent progress in biomaterials, gene-editing technologies, and cell-free strategies, particularly exosome-based therapies, is opening new avenues for enhancing the therapeutic potential of NSC-based approaches. Collectively, NSCs hold substantial promise as a next-generation regenerative therapy for CNS disorders, although further optimization and validation are essential for routine clinical application.

Future Directions

Future research should address improving the survival, integration, and functional maturation of transplanted NSCs within the hostile post-injury CNS environment. Advanced biomaterial scaffolds, 3D bioprinting technologies, and hydrogel-based delivery systems are expected to enhance cell retention and guide axonal growth. In parallel, gene-editing approaches such as CRISPR/Cas9 may be used to engineer NSCs with enhanced regenerative capacity, reduced immunogenicity, and improved safety profiles. Another major direction is the development of standardized, clinically scalable NSC production protocols to ensure reproducibility across studies and clinical trials.

In addition, increasing attention is being directed toward NSC-derived extracellular vesicles and secretome-based therapies as safer, cell-free alternatives. Such strategies could help mitigate several of the potential risks inherent to the transplantation of living cells while retaining therapeutic efficacy. Combination therapies integrating NSCs with pharmacological agents, electrical stimulation, and rehabilitation strategies may further enhance functional recovery. Ultimately, interdisciplinary approaches combining stem cell biology, bioengineering, and clinical neuroscience will be essential to accelerate translation from bench to bedside.

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