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Restoring the Degenerating Brain: Mesenchymal and Neural Stem Cells in Neurotherapeutics

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ABSTRACT

Neurodegenerative and neuroinflammatory disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) represent complex, multifactorial conditions as well as traumatic brain injury (TBI) and spinal cord injury (SCI) involving neuroinflammation, progressive neuronal loss, synaptic dysfunction, and blood-brain barrier (BBB) disruption. Despite advances in symptomatic management, current therapies only modestly delay disease progression. Stem cell-based therapies offer a promising multi-target approach by addressing key pathological mechanisms, including inflammation, neuronal degeneration, and impaired regeneration. Two major stem cell types, mesenchymal stem cells (MSCs) and neural stem/progenitor cells (NSPCs), have shown therapeutic potential in both preclinical and clinical studies. MSCs, derived from bone marrow, adipose tissue, and umbilical cord, act primarily via paracrine signaling, secreting trophic and immunomodulatory factors such as BDNF, VEGF, and NGF to promote repair and modulate the neuroinflammatory milieu. In contrast, NSPCs contribute to neurogenesis and gliogenesis, with potential for direct cell replacement and circuit integration, particularly in diseases involving specific neuronal loss. However, their therapeutic use must consider significant regional heterogeneity; for example, cortical and hippocampal NSPCs differ in developmental origin, fate potential, and response to environmental cues. Similarly, MSCs from different tissues exhibit distinct immunomodulatory and differentiation capacities. BBB permeability remains a critical barrier to effective CNS delivery of systemically administered therapies. Yet, stem cells may cross or modulate the BBB or be directly transplanted into the CNS. Current clinical trials are evaluating stem cell-based therapies in neurodegenerative disease and CNS injury, with early results showing safety and potential functional benefits. Nonetheless, variability in cell source, delivery, and survival, along with the need for

standardized manufacturing and dosing protocols, continue to limit clinical translation. This review highlights the therapeutic promise and translational hurdles of MSCs and NSPCs as multi-target strategies to address the cellular and molecular complexity of CNS disorderscan cope and adapt to life in the city environment. The welfare state nurtures the ordinary people who make up the majority of the Swedish population. The model satisfies wayward people, such as homeless individuals and patients with disabilities.

Keywords
Transplantation, Stem Cell, Neural, Treatment.

Given the multifactorial and complex nature of neurodegenerative and neuroinflammatory conditions, without a clear primary causal agent remains it is imperative to develop multi-target therapies that address the different causes/consequences of these disorders, such as neuroinflammation, neuronal cell death and dysfunction, and blood brain barrier (BBB) disruption [1,2]. Despite notable advancements in the management of symptoms accompanying the and treatments that enhance quality of life and increase lifespan, the available drugs only slow the progression of neuronal death [3].

Therapeutic strategies for neurodegenerative and neuroinflammatory diseases are significantly constrained by the selective permeability of the BBB. The BBB is a dynamic, multicellular microvascular interface that preserves central nervous system (CNS) homeostasis by tightly regulating molecular and cellular exchange between the blood and brain parenchyma [2,4]. The BBB restricts the entry of most macromolecules, small hydrophilic drugs, and biologics limiting the effectiveness of systemically administered treatments [1]. Stem cell therapy can overcome BBB-related challenges by delivering cells directly into the CNS or leveraging their paracrine effects and migratory abilities to cross or modulate the BBB and exert neuroprotective and immunomodulatory actions within the brain [5,6].

Stem cell therapy has emerged as a promising avenue for addressing the complex challenges of neurodegenerative diseases such as Alzheimer's disease (AD) [7], Parkinson's disease (PD) [6,7], amyotrophic lateral sclerosis (ALS) [8], multiple sclerosis (MS) [9], and age-related conditions with neurological involvement [9-11]. These conditions are often marked by progressive loss of neurons, impaired synaptic connectivity, chronic inflammation, and failure of endogenous repair mechanisms. In the absence of curative treatments, stem cell-based approaches offer potential for both functional recovery and disease modification.

Two major types of stem cells have gained prominence in the field of neuroregeneration: mesenchymal stem cells (MSCs) and neural stem/progenitor cells (NSPCs). While both hold therapeutic promise, they differ significantly in origin, biological properties, and mechanisms of action, which shape their respective roles in clinical application. This review aims to critically evaluate the current landscape of stem cell-based therapies, focusing on mesenchymal stem cells (MSCs) and neural stem/progenitor cells (NSPCs), as potential multi-target strategies for treating neurodegenerative and neuroinflammatory diseases [12]. It synthesizes evidence from preclinical studies, clinical trials, and experimental models to assess their capacity to address key pathological features such as neuroinflammation, neuronal loss, and BBB dysfunction. By highlighting both the therapeutic promise and translational challenges of these approaches, this review seeks to inform the development of effective, regenerative interventions for CNS disorders.

Stem Cells

Given the limited regenerative potential of the adult CNS [13], therapeutic strategies aimed at promoting repair and functional recovery are urgently needed. The inherent ability of stem cells to self-renew and differentiate makes them promising candidates for restoring lost cell populations, supporting tissue repair, modulating inflammation, and potentially reconstructing neural circuits [9]. However, the response of stem cells to CNS injury is highly intricate and varies based on the injury's severity and anatomical location.

MSCs

MSCs are adult multipotent stem cells that can be isolated from a variety of tissues, including bone marrow, adipose tissue, and umbilical cord. Their appeal in regenerative medicine lies in their ease of isolation and expansion, low immunogenicity, and powerful secretory profile. Rather than replacing lost neurons directly, MSCs act primarily through paracrine mechanisms, secreting a wide range of neurotrophic and anti-inflammatory factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF). These bioactive molecules reduce inflammation, promote endogenous repair, enhance neuronal survival, and support remyelination. As such, MSCs are particularly useful in modulating the neuroinflammatory environment in diseases and in providing trophic support to degenerating neural tissues [14]. Their immunomodulatory capabilities also make them attractive for systemic administration in both autologous and allogeneic settings [11,14,15].

NPSCs

NSPCs contribute to the adult brain's capacity for regeneration. Through neurogenesis, NSPCs generate neurons that integrate into functional neural circuits, while gliogenesis leads to the production of astrocytes and oligodendrocytes. Collectively, NSPCs encompass both neural stem cells (NSCs) and neural progenitor cells (NPCs) [16]. During embryonic development, NSCs play a pivotal role in forming the CNS. These cells, initially referred to as neuroepithelial cells, transition into radial glial cells, which then give rise to expanding populations of NPCs. NSCs are characterized as undifferentiated cells with the capacity to develop into both neuronal and glial cell types within the CNS. They are defined by their abilities to self-renew and to differentiate into multiple lineages, which represent key properties that distinguish

them from other cell types [17]. The behavior and developmental trajectory of NPSCs are influenced by various pathological conditions [18]. Factors such as oxidative stress, exposure to radiation, metabolic dysfunction, the cellular redox state, and chronic inflammation can alter NSPC fate. Aging is a particularly significant factor, exerting profound effects on NSPC function and potential [19]. With age, the brain's cellular environment undergoes several detrimental changes, including diminished energy metabolism, reduced neuroplastic adaptability, disrupted calcium signaling, and abnormal neuronal activity. Additionally, oxidative damage accumulates in biomolecules and organelles, while inflammatory processes become more pronounced. These age-related changes are especially harmful in the brain due to its high demand for oxygen, abundance of polyunsaturated fatty acids in neuronal membranes, and sensitivity to excitotoxic amino acids. This cellular versatility positions NSPCs as a central focus of regenerative medicine research. The processes of neurogenesis and gliogenesis are tightly regulated by a combination of external cues and internal molecular mechanisms, including growth and neurotrophic factors, transcriptional regulators, and conserved signaling pathways. NSPCs are primarily used for cell replacement therapy, to replenish lost neural cells and restore functional neural circuits [20]. NSPCs are especially suited for applications where specific neuronal populations are depleted, such as the dopaminergic neurons in PD [21] or motor neurons in ALS [22]. Additionally, NSPCs can contribute to remyelination in demyelinating disorders and release limited trophic factors [23].

Heterogeneity of NSPCs and MSCs

There is heterogeneity of NSPCs and MSCs. NSPCs differ markedly between neurogenic regions such as the cerebral cortex and hippocampus, reflecting region-specific developmental programs and functional demands. In the embryonic cortex, NSPCs primarily comprise radial glial cells (RGCs) in the ventricular zone (VZ), which serve as both neural progenitors and scaffolds for neuronal migration. These RGCs give rise to intermediate progenitor cells (IPCs, or basal progenitors) in the subventricular zone (SVZ), which then generate neurons in a sequential, layer-specific manner [24,25]. In contrast, the adult hippocampus, specifically in the subgranular zone (SGZ) of the dentate gyrus, contains radial glia-like type-1 NSPCs and non-radial type-2 cells, which together support lifelong neurogenesis under distinct regulatory influences [26,27]. These hippocampal NSPCs differ from cortical progenitors not only in morphology and marker expression (e.g., GFAP, Nestin, Sox2) but also in proliferative behavior, fate potential, and sensitivity to environmental cues such as stress, inflammation, and aging [28]. For instance, hippocampal NSPCs exhibit a bias toward neuronal rather than glial differentiation and are modulated by activity-dependent mechanisms, while cortical progenitors show greater diversity in their lineage output during development [29]. Such regional heterogeneity has critical implications for disease modeling and therapeutic targeting. Diseases like Alzheimer's disproportionately affect the hippocampus, whereas gliomas often originate in cortical SVZ-derived progenitors, underscoring the need to account for NSPC subtype and origin in regenerative strategies.

Much like NSPCs, MSCs also exhibit substantial heterogeneity that reflects their tissue of origin, microenvironmental cues, and intrinsic cellular states. MSCs can be isolated from diverse tissues including bone marrow, adipose tissue, umbilical cord, and dental pulp and while they share core features such as tri-lineage differentiation potential and expression of surface markers (e.g., CD73, CD90, CD105), they differ markedly in their proliferation rates, immunomodulatory capacity, and secretory profiles [30,31]. For instance, bone marrow-derived MSCs (BM-MSCs) typically display greater osteogenic potential, while adipose-derived MSCs (AD-MSCs) show enhanced adipogenic differentiation and broader immunoregulatory effects. Moreover, even within a single tissue source, MSC populations are heterogeneous comprising subpopulations with distinct clonogenicity, senescence profiles, and therapeutic potency driven in part by epigenetic variability, donor age, and *in vitro* culture conditions. This functional diversity is both a strength and a challenge for clinical application: while it offers flexibility for tailoring MSC-based therapies, it also demands rigorous standardization and characterization to ensure reproducibility and efficacy. Ignoring this heterogeneity may lead to inconsistent therapeutic outcomes, much like applying a uniform strategy to regionally distinct NSPCs in the brain.

Further, it is understood that there may be some technical challenges associated with iPSCs. Indeed, iPSCs hold immense promise for regenerative medicine and disease modeling, but their clinical translation is hindered by several technical and safety challenges. One major concern is the potential for off-target effects introduced during gene editing, particularly with CRISPR-Cas9, which can result in unintended mutations that compromise genomic integrity and raise oncogenic risks. These off-target events are difficult to predict and may evade detection in bulk sequencing, necessitating stringent single-cell and long-read sequencing approaches for validation. Additionally, iPSCs are prone to epigenetic abnormalities, including incomplete reprogramming and residual epigenetic memory from the somatic cell of origin, which can affect their differentiation potential and lead to biased lineage outcomes or tumorigenicity [32]. Even iPSCs considered "fully reprogrammed" often show aberrant DNA methylation patterns and histone modifications, which can persist through differentiation and compromise therapeutic consistency [33]. Another technical challenge is genomic instability acquired during prolonged culture or reprogramming, such as copy number variations or chromosomal abnormalities, which may silently expand under selective pressure [34]. To mitigate these risks, it is critical to establish standardized protocols for iPSC derivation, rigorous genetic and epigenetic screening, and careful functional validation prior to clinical use. Therefore, prioritizing the resolution of safety issues such as off-target effects and epigenetic dysregulation is essential for the reliable and responsible application of iPSC-based therapies.

An alternative means to generate NSPC is the use of pluripotent stem cells including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). ESCs are derived from the inner cell mass of the early blastocyst and have unlimited proliferative potential, therefore providing an unlimited resource of stem

cells. In addition, ESCs differentiate into a variety of cell types including neural cells. iPSCs have similar characteristics to ESCs, but they can be derived from adult somatic cells, which alleviates ethical concerns associated with the use of human fetal/embryonic tissue. iPSCs may also reduce the risk of immune rejection of implanted cells since they can be generated from autologous cells of the individual. The generation of iPSCs has revolutionized regenerative medicine since these cells can not only be used for *in vitro* modeling of diseases and identification of novel therapies, but also for neural cell transplantation to replace lost neurons and glia in neurodegenerative diseases and CNS injuries. However, their use presents certain challenges, including more complex harvesting and culturing procedures, ethical considerations (particularly when derived from fetal tissue), and a more limited ability to expand *in vitro* compared to MSCs.

Neuronal Injury

Damage to these region areas on the brain due to blunt force trauma (e.g. traumatic brain injury, TBI) or age- or disease-related neurodegeneration/neuroinflammation can lead to numerous complications, such as abnormal migration patterns of NSPC-derived cells, improper dendritic development, excessive proliferation of progenitor cells, and failure of new cells to successfully integrate into existing neural circuits. Spinal cord injury (SCI) can also disrupt the neurogenic environment surrounding the central canal, altering the contribution of regenerative capacity. Thus, the recruitment or transplantation of stem cells holds therapeutic promise for re-establishing neurogenic activity, enhancing plasticity, and promoting functional recovery in the injured CNS.

NSPCs offer multiple avenues for addressing the complex pathophysiology of CNS injury through both cell-autonomous and non-cell-autonomous mechanisms. Each neurogenic zone hosts distinct NSPC populations with specialized functions. Unlike NSC, MSCs can be readily isolated from various sources, including bone marrow, adipose tissue, and umbilical cord, and can be expanded outside the body. Their application, whether autologous or allogeneic, does not raise the ethical concerns often associated with stem cell therapies derived from embryonic or fetal tissues. Additionally, MSCs do not require genetic reprogramming, as is necessary with induced pluripotent stem cells. These characteristics, combined with their natural function in tissue repair, have positioned MSCs as a promising option for clinical research.

While both MSCs and NSPCs are being explored as therapeutic tools in neurodegenerative diseases, they serve distinct purposes: MSCs are best suited for neuroprotection and immune modulation, acting primarily through the secretion of supportive factors, whereas NSPCs are designed for direct cell replacement and regeneration. The choice between these stem cell types depends on the nature of the disease, the desired therapeutic outcome, and the feasibility of administration. Ongoing research continues to refine these approaches, with the goal of developing safe, effective, and scalable treatments that can restore function and quality of life for individuals living with neurodegenerative disorders (Table 1).

Table 1: Comparison between Neural Stem/Progenitor Cells (NSPCs) and Mesenchymal Stem Cells (MSCs).

Feature	NSPCs	MSCs
Tissue Origin	CNS (brain, spinal cord)	Bone marrow, adipose tissue, umbilical cord, etc.
Differentiation Potential	Neurons, astrocytes, oligodendrocytes	Osteocytes, chondrocytes, adipocytes
Clinical Use	Primarily in neurological applications	Broad use in regenerative medicine, including neurology
Ethical Concerns	Higher, especially when derived from fetal/ embryonic tissue	Minimal, particularly for adult and perinatal sources
Immunogenicity	Potentially immunogenic, especially in allogeneic use	Low immunogenicity; often immune-modulatory
Secretory Function	Some paracrine activity (limited)	Highly secretory, rich in trophic and anti-inflammatory factors
Expansion *In Vitro*	Challenging; limited expansion potential	Easy to expand and culture *in vitro*
Neurotrophic Factor Secretion	Moderate (depending on state and conditions)	High; secretes NGF, BDNF, HGF, VEGF
Applications in CNS Disorders	Cell replacement, remyelination, neurogenesis	Neuroprotection, immunomodulation, trophic support
Genetic Manipulation Requirement	Sometimes required for improved survival/ differentiation	Generally, not required
Paracrine Effects	Less prominent	Major mechanism of action
Current Clinical Trials	Fewer, more experimental	Numerous trials in diverse conditions

Key pathological processes by which MSCs influence the microenvironment

A critical mechanism involves the immunomodulatory capacity of MSCs to shift macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory, tissue-reparative M2 phenotype via paracrine secretion of cytokines such as IL-10, TGF-β, and prostaglandin E2 (PGE2) [35,36]. This polarization reduces neuroinflammation, attenuates secondary injury cascades, and fosters an environment conducive to regeneration. Simultaneously, MSCs secrete factors like angiopoietin-1, VEGF, and TIMP-3 that contribute to restoration of BBB integrity by stabilizing endothelial junctions and reducing matrix metalloproteinase (MMP) activity [15,37,38]. In parallel, MSC-derived exosomes deliver miRNAs and antioxidant enzymes (e.g., SOD1, catalase) to resident NSPCs, modulating redox homeostasis and preventing oxidative damage, a critical determinant of NSPC survival and neurogenic capacity in the post-injury niche [38,39]. Through this fine-tuned regulation of oxidative stress, MSCs support NSPC proliferation and differentiation into neurons and oligodendrocytes, ultimately promoting axon regeneration and remyelination. These converging mechanisms underscore the potential of MSCs as key modulators

of the CNS microenvironment, offering therapeutic promise for inflammatory and degenerative neurological disorders.

Although the exact mechanism of action is not completely understood, stem cell-based therapies have shown promising results for the treatment of several CNS-related conditions. Different studies point to factors including cellular differentiation but also the impact of the secreted factors and vesicles, (i.e., the secretome), as highly impactful agents for the regenerative effect. The following sections outline how stem cell-based therapies have been shown to contribute to functional recovery via several coordinated processes.

Cell Replacement

Stem cells can differentiate into neurons, astrocytes, and oligodendrocytes, replenishing populations lost to injury (NSPCs) as well as osteocytes, chondrocytes, adipocytes, each highly secretory, rich in trophic and anti-inflammatory factors (MSCs). In the case of CNS injury (e.g., TBI,SCI) NSPCs can generate new neurons to replace those that have undergone necrosis or apoptosis and glial cells to restore supportive networks essential for homeostasis and conductivity.

Using a murine model after controlled cortical impact (CCI) injury Dixon et al. [40] ablated NSPCs in the SVZ to examine their contribution to the injury microenvironment. Two weeks post-CCI injury, mice deficient in NSPCs had reduced neuronal survival in the perilesional cortex and fewer glial cells but increased glial hypertrophy at the injury site. This cascade suggests the presence of NSPCs play a supportive role in the cortex to promote neuronal survival and glial cell expansion after injury. Imai et al. [41] established a novel treatment strategy for TBI in a mouse model using NSPCs derived from human iPSCs. *In vivo* bioluminescent imaging and histopathological analysis showed concentration of NSPCs around the damaged cortex in which motor function was impaired in the subacute phase with smaller injury area (suggesting the prevention of secondary brain injury) and significant improvement in the treatment group transplanted with genome-edited iPSC-derived NSPCs compared with the control group. During the chronic phase, cerebral atrophy and ventricle enlargement were significantly less evident in the treatment group absence of undifferentiated NSPCs while preserving the adjacent neuronal structures. Notwithstanding, significant challenges related to epigenetic regulation and that factors of iPSC-derived NSPCs in SCI therapy. As such, Kobayashi et al. [42] used a pre-evaluated "safe" hiPSC-NSPC clone and an adult common marmoset (Callithrix jacchus) model of contusive C5 SCI followed by transplantation of hiPSC-NSPCs nine days post- injury. The grafted NSPCs survived and differentiated into all three neural lineages showing enhanced axonal sparing/regrowth and angiogenesis, prevented demyelination, and functional recovery compared with that in vehicle control animals. It is important to note that the SCI model only tracked subjects for 12 weeks and did not mention chronic tumor risks or immune tolerance failure issues. Analyzing forty-seven studies, Yousefifard and colleagues [43] conducted a meta-analysis of the application of NSPC in animal models after SCI reporting a need for scaffold for NSPC locomotion recovery. Similarly, Jeon et al. [12] performed a meta-analysis exploring the efficacy of NSC transplantation, with and without biomaterials, in animal models of SCI, finding that particularly when combined with biomaterials like scaffolds motor and histological recovery post-SCI was significantly enhanced. Collectively, findings and insights in this field show great promise despite challenges and directions that need to be addressed and explored [44].

MSCs, on the other hand, secrete several factors (e.g., nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3) and Wnt3a) that have the potential to attenuate the loss of cholinergic neurons and promote neurogenesis MSCs could have value in TBI treatment [45]. In addition, other studies have demonstrated the contribution of extracellular vesicles secreted to reduce neuroinflammation and promote neurogenesis and angiogenesis in TBI animal models [46,47].

There are also similarities between MSCs and pericytes. Pericytes are specialized, contractile cells that wrap around the endothelial cells of capillaries and venules throughout the body, particularly in the CNS. Pericytes are embedded within the basement membrane and play a critical role in maintaining BBB integrity, regulating capillary blood flow, supporting vessel stability, and participating in immune responses and tissue repair. In the CNS, pericyte dysfunction is implicated in BBB breakdown, neuroinflammation, and neurodegeneration. The similarities between expression of immunological markers (CD44, CD90, CD73, CD105, and CD45) and self-renewability suggest MSCs could supply the loss of pericytes in neurodegeneration of injury [48].

Trophic Support

Both MSCs and NSPCs secrete a wide range of neurotrophic and growth factors (e.g., BDNF, GDNF, VEGF, IGF-1), which promote neuronal survival, reduce secondary degeneration, and stimulate angiogenesis and neuroplasticity in the surrounding tissue [14]. These paracrine effects are especially important in modulating the hostile microenvironment post-injury. Whereas the paracrine effects may be more limited in NSPCs, each have utility in trophic support in CNS treatments.

The surprising immunoregulatory effects of NSPCs on neuroinflammation have been linked mainly through intercellular contact and paracrine effects, especially extracellular vesicles in depression. Highlighting the link between chronic treatment with corticosterone (CORT), a well-validated pharmacological stressor and the induction of depressive-like behavior Zhang et al. [49] recently revealed a neuronal autophagy-dependent mechanism that links chronic CORT to reduced neuronal BDNF levels in mice. They also provide insights for treating depression by targeting neuronal autophagy via NSPCs. Similarly, Baloh et al. [50] conducted a phase 1/2a study showing NPSC modified to release the growth factor GDNF safely transplanted into the spinal cord of patients with ALS provided new support cells and GDNF delivery for up to 42 months post-transplantation.

Beneficial effects on damaged neurons can also exerted by MSCs mediated through the secretion of neurotrophic factors, axonal regeneration, and myelin sheath repair. MSCs exhibit strong secretory activity, with their regenerative effects largely mediated through the release of paracrine factors. They produce a range of neurotrophic molecules which collectively enhance neuronal survival, stimulate proliferation, and promote endogenous neurogenesis. Notably, the secretion levels of NGF and BDNF by MSCs are closely correlated with their ability to support neuron viability and facilitate neurite outgrowth. Oh and colleagues [51] demonstrated that repeated injections of bone-marrow derived MSCs (BM-MSCs) in patients with ALS, presumably via stem cell regulatory action on switching from pro- to anti-inflammatory conditions [52]. A beneficial effect of BM-MSCs was also reported, specifically on patients who had ALS with an inherently rapid course by Siwek et al. [53] Further, Marconi et al. [54] demonstrated benefit of adipose-derived mesenchymal stem cells (ASC) on ALS purportedly through the secretion of anti-inflammatory cytokines and neurotrophic growth factors can modulate the immune system. Additionally, the therapeutic potential MSC exosomes on stroke was demonstrated by Xin et al. [55], showing that the administration of BM-MSC exosomes 24 h after stroke resulted in increased neurogenesis and angiogenesis, further supported by others [39,56]. Studies in the animal models of MS have further shown that MSC transplantation reduced BBB disruption, as evidenced by reduced IgG leakage. Despite the safety and beneficial effects shown, albeit primarily in animal models, the large quantities of MSCs needed to reach the CNS lesion site and trapping of MSCs in organs such as the lungs and lymph nodes raises some concern.

Modulation of Inflammation

Stem cells can influence immune responses in the injured CNS by interacting with the immune system and participating in both innate and adaptive immunity. In an inflammatory environment, MSCs interact with immune cells either through direct cell-to-cell contact or via paracrine activity exhibiting anti-inflammatory behavior. MSCs can also modulate the macrophage/microglia polarization, upregulating the ratio of anti- versus pro-inflammatory responses [57].

Redox signaling plays a crucial role in the regulation of NSPC differentiation and expansion within their proliferative environments. While moderate increases in ROS can enhance the production of progenitor cells, such that multipotent NSPCs often maintain higher ROS levels to support self-renewal and neurogenesis, the rise in ROS beyond scavenging capacity, leads to oxidative stress and potentially NSPC quiescence or cell death. Thus, dynamic ROS regulation in balancing NSPC quiescence and activation represents an essential process for sustaining adult neurogenesis. Cultured NSPCs treated with broad acting drugs that mitigate inflammation and support NSPC proliferation administered to SCI animals post-SCI showed a significant decrease in lesion size and higher levels of function compared to controls [58]. Kawai and colleagues [59] in a review of regenerative therapy for SCI using NSPC discussed current applications for SCI as well as highlighted the critical need to clarify the mechanism underlying this functional improvement for the further advancement of this therapy. A major contribution was the revelation that the activation of transplanted neural cells can enhance the efficacy of NSPC transplantation therapy and provided a basis for further advancement of this therapy to be combined with adjuvant therapy. They emphasized the tremendous strides that made the application of hiPSC-NS/PC transplantation for chronic SCI yet noted challenges. Addressing the challenge of cavities and scar tissue with NPCs was further review by Nagoshi et al. [60]. concluding regenerative medicine shows promise for chronic SCI, particularly when rehabilitation strategies are incorporated.

Concurrently MSC treatment methods have also been developed to enhance neuronal activity in inflammatory conditions. A study using MSC transplantation in an SCI model also supported the observation that secreted bioactive products can suppress local inflammation, enhance angiogenesis, inhibit apoptosis, and stimulate proliferation and differentiation of tissue-resident cells. Although most of the described approaches remain at experimental stages, continuing efforts in developing new secretome-based therapies for CNS disorders will enable the adoption of these techniques into a clinical context.

Multiple studies suggest that MSC treatment has a significant impact on BBB integrity and high potential to modulate microvasculature and reduce the pathological processes associated with stroke. For example, MSCs were able to rescue BBB integrity expressing elevated levels of antioxidant enzymes, thereby reducing excessive ROS generation and IgG leakage in the brain parenchyma and decrease neuroinflammation and neutrophil infiltration as well as promote angiogenesis and vascular stabilization [61,62]. Of note, some researchers have demonstrated that whole MSC treatment may not be requisite for therapeutic effects in stroke as administration MSC-EVs was shown to reduce in the infarct volume, improve neurological recovery, and enhanced angiogenesis especially when MSCs are exposed to hypoxic conditions prior to EV isolation [63].

Paracrine effects of MSCs have also been demonstrated in PD as an approach to replace the progressive loss of nigral dopaminergic neurons. Teixiera et al. [64] demonstrated that the secretion of neurogenic, neurodevelopmental, neurorescuing, or anti-apoptotic factors present on the MSC secretome into the substantia nigra and striatum of rate models of PD, increased of dopaminergic neurons and neuronal terminals thereby supporting the recovery observed in the motor performance outcomes. Oh et al. [65] demonstrated that MSCs and their derived MMP-2 exert neuroprotective properties through proteolysis of aggregated α-synuclein in PD-related microenvironments.

Enhancement of Axonal Regeneration and Synaptic Plasticity

Stem cells may support the regrowth of axons and the formation of new synaptic connections through the expression of extracellular matrix-modulating proteins and guidance cues to help re-establish disrupted neural networks critical for functional recovery. This

is critical in CNI injury (i.e. SCI, TBI) where the lack of repair following injury is related to the additive effects of a lack of growth-promoting signals, the inability to activate the cellular machinery that enables the reestablishment of growth and elongation intrinsic factors, and the extrinsic injury environment. The cascade of events after traumatic damage leads to immediate and often serious impairment of neurological function, inflammatory cells and resident microglial cells responding in attempts to remodel tissue. As a healing response post-SCI, a scar forms to spatially isolate the wound and protect the surrounding spinal cord from further damage. However, the compensatory mechanism limits axonal growth at the lesion site. Damaged axons fail to regenerate after injury, stop and neurons retract their axons once they reach the injury lesion border. NPCs have been reported to exert plastic changes by remyelinating spared axons, facilitating chemotaxis after lesions, promoting neurite outgrowth and reducing neural apoptosis [66]. These changes work in a synergistic manner to facilitate plasticity and regeneration of the injured spinal cord after cell transplantation. In adult rats, neuronal and non-neuronal cell transplants obtained from fetal and adult donors have been used to replace lost or impaired neurons and glia for nearly a half century [67]. Early stem cell-based therapies were limited by poor neural tissue retention and axonal growth, but later studies improved outcomes by using peripheral nerve grafts and combining fetal neuronal and peripheral grafts to enhance cell survival and axon extension. Although initial experiments did not demonstrate functional recovery, more advanced techniques were able to partially restore function by forming new neuronal relays across the injury site. Current strategies focus on using stem cells to create functional relay circuits and bridge injured axons across lesion sites. To replace lost neurons and glia and to generate functional neuronal relays for CNS repair, pluripotent stem cells need to be induced to differentiate into neural cell lineages, through neural induction and differentiation. The traditional source of NSPCs from the developing CNS contains various stages of NSCs and progenitor cells. Recent studies have focused on manipulation of specific signaling pathways and pathways by NSPCs and MSCs for neural induction.

Remyelination

Promoting remyelination of demyelinated axons is essential for restoring conduction velocity and preventing axonal degeneration. MSCs have shown an ability to promote remyelination in toxic demyelinating models. Although an increase in myelin levels [68] and microglial inflammation with MSC treatment have been reported in a cuprizone mouse model [69], presumably by reducing mitochondrial dysfunction, these studies have been disputed by others showing negative results [70] after treatment highlighting the heterogeneous nature of these stem cells. Notwithstanding, preclinical studies in mouse models of multiple sclerosis (MS) have highlighted MSCs therapeutic potential, demonstrating enhanced remyelination and improved disease outcomes.

Integration into Neural Circuits

Under optimal conditions, transplanted stem cells can mature, extend processes, and form synaptic connections with host neurons, suggesting the possibility of long-term functional integration. However, achieving precise integration and appropriate circuit connectivity remains a major research goal. Hlelbokazov et al. [71] demonstrated that application of autologous MSC therapy in patients (n=67;29 males, 38 females, mean age 33 ± 1.3 y) with pharmacoresistant epilepsy demonstrated significant anticonvulsant potential lasting a year, with repeated administration of MSCs conveying additional clinical benefit. MSC therapy was administered in two courses spaced six months apart, with each course involving an intravenous infusion of MSCs followed by an intrathecal injection within one week. The treatment was well-tolerated, with no serious adverse effects reported. In the MSC-treated group (n = 34), 61.7% of patients showed a significant positive response at six months, increasing to 76.5% at twelve months. Patients also demonstrated improvements in anxiety, depression, and paroxysmal epileptiform activity, as measured by HADS, EEG, and MMSE assessments. Notably, the therapeutic response was significantly enhanced when levetiracetam, but not other antiepileptic drugs, was used concurrently. A second round of MSC therapy led to additional significant reductions in seizure frequency and epileptiform EEG patterns compared to a single course.

Clinical translation pathways

Stem cell transplantation for neurological diseases faces significant challenges, particularly due to low delivery efficiency across the BBB and poor *in vivo* survival of transplanted cells. The BBB is a highly selective interface that restricts the passage of most cells and therapeutic agents from the bloodstream into the brain, posing a major obstacle to systemic stem cell delivery [1]. Although MSCs, possess limited migratory capacity across the BBB under inflammatory conditions, the efficiency remains low and variable [72]. Even when cells are directly injected into the brain parenchyma, their survival is often short-lived due to hostile microenvironmental factors such as hypoxia, inflammation, oxidative stress, and lack of trophic support [20]. Studies have shown that most transplanted cells undergo apoptosis within days post-implantation, drastically reducing the number of viable cells capable of exerting therapeutic effects [2]. Strategies to enhance cell delivery and survival, including biomaterial scaffolds, preconditioning, and genetic modification, are under active investigation but have yet to overcome these fundamental barriers in clinical settings. As such, improving cell engraftment and survival remains a critical focus area in the optimization of stem cell-based therapies for neurological disorders.

The therapeutic efficacy and safety of stem cell-based interventions are highly dependent on standardized cell preparation protocols and appropriate dose selection. Variability in cell isolation, culture conditions, passage number, and cryopreservation techniques can significantly affect the viability, identity, and functional properties of stem cells, leading to inconsistent outcomes across studies and trials [73,74]. For instance, differences in oxygen tension, serum supplementation, or confluency during expansion can alter the secretome, immunomodulatory capacity, and differentiation potential of MSCs or iPSC-derived progenitors

[9]. Moreover, stem cell therapies are known to exhibit dose-dependent effects, where insufficient cell numbers may fail to elicit therapeutic benefit, while excessively high doses can lead to adverse outcomes, including ectopic engraftment, immunological reactions, or embolism after systemic delivery [75]. Despite this, there is no universally accepted dosing regimen across stem cell platforms, and optimal cell doses often vary by disease model, delivery route, and cell type. Establishing robust potency assays and release criteria, aligned with Good Manufacturing Practice (GMP) standards, is therefore critical for reproducibility, safety, and regulatory approval in clinical applications.

iPSCs share key features with ESCs, including the ability to self-renew indefinitely and differentiate into all somatic lineages, making them a highly versatile tool. However, their practical application is still constrained by technical considerations related to reprogramming efficiency, variability in differentiation potential, and the need for standardized quality control measures [76]. For example, differences in the somatic cell source and reprogramming method can influence the epigenetic landscape of iPSCs, potentially affecting their functional properties [17]. While safety concerns such as tumorigenicity remain an area of active investigation, much of the current focus lies in improving the fidelity of differentiation protocols, reducing batch-to-batch variability, and establishing rigorous benchmarks for clinical-grade iPSC production [77,78]. Overall, iPSCs offer transformative potential, but their successful translation to clinical use will depend on addressing these reproducibility and quality assurance challenges.

In summary, the collective myriads of mechanisms make stem cells a versatile and multifaceted therapeutic strategy for CNS injuries. The efficacy of stem cell-based interventions depends on the timing of delivery, the injury context, the differentiation potential of the cells used, and the modulation of the local microenvironment to support survival, integration, and functional recovery. Following CNS injury, stem cell behavior is modulated by a complex network of signaling molecules. Stem cells hold transformative potential in neural applications, offering powerful platforms for modeling neurological diseases, screening therapeutics, and developing regenerative therapies. Pluripotent stem cells can be directed to differentiate into various neural lineages such as neurons, astrocytes, and oligodendrocytes. Several factors regulate stem cell proliferation, migration, differentiation, and integration. These injury-induced signals can disrupt normal neurogenesis, leading to abnormal cell migration and connectivity, particularly in traumatic brain and spinal cord injuries. Studies in various models have revealed significant stem cell heterogeneity, identifying diverse stem and progenitor subtypes with distinct gene expression patterns, signaling profiles, and spatial distribution. While this revelation underscores the complexity and specialization of stem cell populations in adult neurogenic niches, it also highlights vast potential therapeutic applications. Continued advances have enabled the creation of patient-specific cellular models that recapitulate key aspects of neurodevelopment and neurodegeneration, thereby deepening our mechanistic understanding of complex neurological disorders and accelerating the development of targeted interventions.

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