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Review Article

The Advances in Stem Cell Therapy for Ischemic Stroke

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Abstract

Ischemic stroke is a leading cause of death and long-term disability worldwide, resulting from the interruption of cerebral blood flow and subsequent neuronal injury. Current treatment strategies, including recanalization strategies, endovascular techniques, and neuroprotective agents, are limited by narrow therapeutic windows and the inability to promote neural regeneration. Stem cell therapy has emerged as a promising approach to restoring neurological function by replacing damaged tissues, decreasing inflammation, inhibiting apoptosis and enhancing endogenous repair mechanisms. Neural stem cells (NSCs) facilitate recovery through differentiation into neurons, astrocytes and oligodendrocytes, as well as the secretion of neurotrophic factors and modulation of the post-stroke environment. Both preclinical and early clinical studies have demonstrated improvements in motor function, gray and white matter recovery and functional brain improvements. Mesenchymal Stem Cells (MSCs) primarily exert paracrine and immunomodulatory effects, preserving the blood-brain barrier, reducing neuroinflammation and supporting neurovascular remodeling with intra-arterial, intravenous and intranasal delivery, showing safety and functional benefits in preclinical and limited clinical trials. Despite these promising findings, challenges such as limited NSC expandability, variable MSC sources and the influence of post-stroke microenvironment hinder clinical translation. This review will evaluate NSC and MSC based therapeutic strategies, highlight current limitations and explore emerging approaches to these fields. Overall, stem cell-based therapies hold significant potential for ischemic stroke recovery, permitting further investigation in both preclinical and clinical settings.

Keywords: Ischemic stroke; Neural Stem Cells; Mesenchymal Stem Cells, Transforming Growth Factor-β

Abbreviations

ASIC1a: Acid-Sensing Ion Channel 1a; fMRI: functional Magnetic Resonance Imaging; MSCs: Mesenchymal Stem Cells; MCAO: Middle Cerebral Artery Occlusion; MCP-1: Monocyte Chemoattractant Protein-1; NSCs: Neural Stem Cells; NIHSS: National Institute of Health Stroke Scale; PISCES: Pilot Investigation of Human Neural Stem Cells in Chronic Ischemic Stroke Patients; CTX: ReNeuron's CTX0E03 cell line; TGF-β: Transforming Growth Factor-β

Introduction to Ischemic Stroke

Stroke is the second largest cause of death worldwide, with 62.4% of stroke patients experiencing ischemic strokes [1-10]. Ischemic stroke is defined as a syndrome that is characterized by the disruption of the function of the central nervous system through an interruption of cerebral blood flow [11-14]. Ischemic strokes can occur as either a thrombotic or embolic event. In a thrombotic event, a blood clot obstructs an affected vessel, which can cause atherosclerotic diseases, arterial dissection, fibromuscular dysplasia or inflammatory conditions. In an embolic event, material from elsewhere in the body enters the bloodstream, travels to the brain and blocks a cerebral vessel, thus cutting off blood flow [8]. As the global population continues

to increase, the incidence of ischemic stroke will continue to increase, which has resulted in increased pressure for a safe and effective treatment.

The overall goal in treating ischemic stroke is to save the brain tissue in regions where blood flow is diminished but still adequate to avoid permanent damage [8]. Traditional treatment options have included recanalization strategies, endovascular techniques and neuroprotective agents. However, these approaches are limited in their ability to repair or regenerate damaged neural tissue. Meanwhile, stem cell therapy is beginning to show promising outcomes for repairing and regenerating damaged tissues. Stem cells aid in replacing damaged host tissue, providing neuroprotection through the reduction of inflammation, inhibition of apoptosis and enhancement of endogenous repair by regulating the control mechanisms of these processes [4]. Two of the most widely studied stem cell therapies are Neural Stem Cells (NSCs) and Mesenchymal Stem Cells (MSCs). Once transplanted, both NSCs and MSCs utilize their specific homing characteristics and facilitate migration towards the injury site. Once positioned, they exhibit survival, growth and differentiation into glial and neuronal cells [17]. Despite extensive preclinical research, the clinical translation of stem cell therapies remains challenging due to biological variability, delivery limitations and inconsistent efficacy outcomes.

While previous reviews have examined the treatment of NSC and MSC, fewer studies have compared their treatment impacts, delivery strategies and challenges in ischemic stroke treatment. This review aims to evaluate both approaches to understand the benefits and implications of each strain in the treatment of ischemic stroke.

Neural Stem Cells in Ischemic Stroke Treatment

NSCs can be collected from various sources throughout the body. They can be obtained directly from brain tissue, generated by reprogramming somatic cells or derived from embryonic stem cells and induced pluripotent stem cells. NSCs can mature into specific neural lineages, including neurons, oligodendrocytes and astrocytes [15]. The ability of NSCs to differentiate into these lineages enables them to generate numerous new nerve cells in the brain, thereby facilitating neural regeneration and repair.

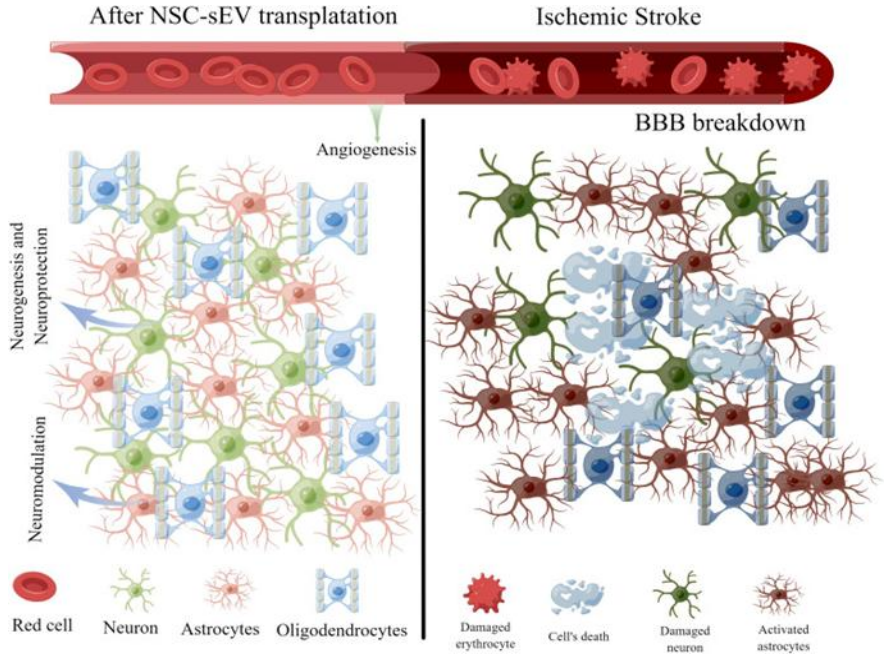

Figure 1: Comparison of the blood-brain barrier before and after NSC treatment [17].

Preclinical studies using rodent models of Middle Cerebral Artery Occlusion (MCAO) have demonstrated that NSC transplantation improves sensorimotor function, reduces motor asymmetry and enhances recovery of both gray and white matter [9]. In Figure. 1, the neuroprotective, inflammatory response suppression, nerve regeneration facilitation and vascular regeneration caused by treating ischemic stroke with NSC therapy is shown. NSC transplantation not only facilitates structural repair but also modulates the post-stroke environment by reducing inflammation in the brain and promoting endogenous neurogenesis [13].

Various delivery strategies have been explored for NSCs. Intracerebral implantation, such as in the Pilot Investigation of Human Neural Stem Cells in Chronic Ischemic Stroke Patients (PISCES) trials, has demonstrated that the stereotactic injection of neural-derived ReNeuron's CTX0E03 cell line (CTX) cells into the ipsilateral putamen of patients with chronic ischemic stroke is safe and well-tolerated. Patients receiving these cells three months post-stroke demonstrated improvements in National Institute of Health Stroke Scale (NIHSS) scores and increased functional activation on functional Magnetic Resonance Imaging (fMRI) over a 12-month follow-up, without any cell-related adverse events [9,13]. Intranasal delivery offers a less invasive alternative, with early administration in rodent models resulting in improved neurological outcomes by facilitating targeted migration of NSCs to ischemic regions and supporting recovery of motor, sensory and hypothalamic functions [7].

Beyond cell replacement, NSCs secrete neurotrophic factors and extracellular vesicles that enhance angiogenesis, synaptic plasticity and white matter repair. Meta-analyses of preclinical and early clinical studies indicate that NSC transplantation consistently improves neurological impairments and motor function, supporting its potential as a viable therapy even in the chronic phase of stroke [17]. Advances in conditionally immortalized NSC lines, such as CTX, have addressed previous challenges related to limited expandability and phenotypic instability, providing a reliable source for translational applications [9].

Mesenchymal Stem Cells in Ischemic Stroke Treatment

MSCs are multipotent, fibroblast-like cells that can be found in numerous adult tissues, including fat, periosteum, liver, spleen, muscle connective tissue, placenta, umbilical cord blood, dental pulp and fetal tissues from abortion [11]. Unlike NSCs, MSCs primarily exert therapeutic effects through paracrine signaling rather than direct neuronal replacement. Studies have shown that transplanted MSCs have helped preserve the integrity of the blood-brain barrier and limit the infiltration of inflammatory cells into the brain [5].

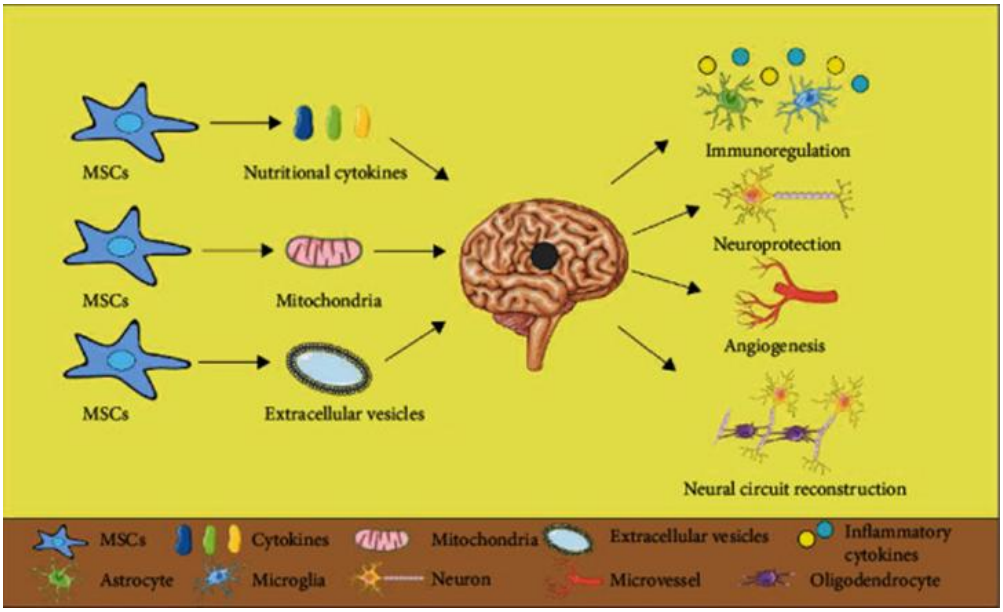

Figure 2: The Mechanisms of MSCs in the treatment of ischemic stroke [5].

MSCs use a variety of mechanisms in the treatment of various consequences caused by an ischemic stroke as shown in Figure. 2. Preclinical studies have shown that intra-arterial infusion of MSCs after MCAO reduces infarct volume, improves neurological and functional scores, normalizes oxidative stress markers and downregulates inflammasome and Acid-Sensing Ion Channel 1a (ASIC1a) expression [12]. MSCs also inhibit immune cell infiltration by reducing Monocyte Chemoattractant Protein-1 (MCP-1) production via Transforming Growth Factor-β (TGF-β) secretion, limiting post-stroke neuroinflammation [11]. Human MSCs delivered intra-arterially further promote recovery of gray and white matter, reduce tissue swelling, restore diffusion tensor imaging metrics and improve behavioral outcomes, likely through modulation of glial responses and the neurovascular environment [1].

Clinical studies and systematic reviews indicate that MSC therapy is safe and well-tolerated, with functional improvements observed even in subacute and chronic stages of ischemic stroke [3,6]. Delivery routes, including intracerebral, intra-arterial, intravenous and intranasal, have been investigated to optimize efficacy. Early administration appears to maximize neuroprotective effects, while later intervention contributes to recovery through tropic and immunomodulatory mechanisms [5,16].

Preclinical Animal Model Studies

Preclinical animal models, most commonly rodent MCAO, have been essential for evaluating the safety, efficacy and mechanisms of stem cell therapy prior to clinical translation. These studies allow controlled investigation of infarct size, behavioral recovery and cellular integration that cannot be performed in humans [9,12,15].

Numerous systematic reviews and meta-analyses of animal studies have reported that both NSCs and MSCs significantly improve neurological scores, motor function and tissue preservation following ischemic stroke compared to control groups [14,17]. NSC transplantation in rodent MCAO models has been associated with reduced lesion volume, enhanced axonal sprouting, increased angiogenesis and improved white matter integrity, particularly when administered during the subacute or chronic phases of stroke [9,15]. These benefits are attributed to both neuronal replacement and secretion of neurotrophic factors that promote endogenous repair.

Similarly, MSC-based therapies consistently demonstrate neuroprotective effects in animal models. Intra-arterial and intravenous MSC delivery following MCAO has been shown to reduce infarct volume, preserve blood-brain barrier integrity, normalize oxidative stress markers and downregulate inflammasome signaling pathways, including ASIC1a expression [12]. Immunomodulatory effects, such as reduced microglial activation and decreased infiltration of peripheral immune cells, further contribute to improving functional outcomes [11].

However, negative and inconsistent findings have also been reported. Some studies have indicated that the limited long-term survival and engraftment of transplanted cells, particularly in hostile post-stroke microenvironments characterized by inflammation, hypoxia and excitotoxicity, reduce therapeutic efficacy [2,17]. Variability in animal species, stroke induction methods, cell dosage, timing of administration and outcome measures has led to heterogeneity in reported results, complicating direct comparison across studies [14]. These limitations underscore the need for standardized preclinical protocols to improve reproducibility and translational relevance.

Human Clinical Trials

Clinical trials investigating stem cell therapy for ischemic stroke have primarily focused on safety and feasibility, with efficacy as a secondary outcome. Early-phase trials evaluating both NSC and MSC therapies have generally demonstrated favorable safety profiles, with no significant increase in mortality, tumor formation or immune-mediated adverse events [3,4,6].

Clinical investigations using NSCs, such as the PISCES trials, have examined stereotactic intracerebral implantation of conditionally immortalized NSCs in patients with chronic ischemic stroke. These studies reported improvements in neurological function, including enhanced NIHSS scores. They increased task-related cortical activation on fMRI, without cell-related adverse effects [9,13]. However, the small sample sizes and lack of randomized control groups limit the ability to draw definitive conclusions regarding efficacy.

MSC trials have explored multiple delivery routes, including intravenous, intra-arterial and intracerebral administration. Systematic reviews of MSC clinical trials indicate modest improvements in functional outcomes, such as motor recovery and activities of daily living, particularly when treatment is administered during the subacute or chronic phases of stroke [3,6]. Importantly, MSC therapy is well-tolerated across different delivery routes, supporting its continued investigation in larger trials. Despite encouraging safety data, clinical outcomes remain variable. Differences in cell source, dosage, timing of administration and patient selection contribute to inconsistent results across studies [2,10]. Additionally, many trials lack long-term follow-up and statistically powered outcome measures, making it difficult to assess sustained functional recovery. These challenges highlight the need for large-scale, randomized, controlled trials with standardized protocols to establish the accurate therapeutic potential of stem cell-based intervention for ischemic stroke.

Results *(Table 1)*

Feature	Neural Stem Cells (NSCs)	Mesenchymal Stem Cells (MSCs)
Cell Source	Brain tissue, embryonic stem cells, induced pluripotent stem cells and conditionally immortalized lines,	Bone marrow, adipose tissue, umbilical cord blood, placenta, dental pulp
Delivery Routes	Intracerebral, intranasal	Intravenous, intra-arterial, intracerebral, intranasal
Preclinical Outcomes	Improved motor function; gray and white matter recovery; angiogenesis	Reduced infarct volume; preserved blood-brain barrier; reduced inflammation
Clinical Evidence	Early-phase trials (e.g. PISCES); improved NIHSS and fMRI activation	Multiple small trials; modest functional improvements; strong safety profile
Advantages	Direct neural repair; targeted regeneration	Easier sourcing; strong immunomodulatory effects; less invasive delivery
Limitations	Limited expandability; invasive delivery; microenvironment sensitivity	Viable cell sources; inconsistent efficacy; limited engraftment

Table 1: Comparison of results between NSCs and MSCs.

Discussion

The complementary mechanisms of NSCs and MSCs suggest that combined therapy may provide synergistic benefits. NSCs primarily contribute to functional recovery through neuronal replacement and neurotrophic support, while MSCs mediate repair indirectly through paracrine signaling, immunomodulation and protection of the ischemic microenvironment [2,12]. The route and timing of stem cell administration are critical. Intracerebral delivery allows targeted placement but is invasive, whereas intra-arterial and intranasal routes offer less invasive alternatives with effective migration and functional integration [7,9]. Early administration maximizes neuroprotective effects, but delayed integrations can still promote recovery through trophic and immunomodulatory mechanisms [6,7]. Despite these promising findings, challenges remain. Previously conducted preclinical studies often use small sample sizes and clinical trials are limited, primarily focusing on the safety of stem cell therapy rather than the efficacy. NSC therapies face issues of limited expandability and potential phenotypic instability and both NSC and MSC therapies are influenced by the post-stroke microenvironment, which can impact cell survival, integration and therapeutic outcomes [2,17]. Collectively, these limitations contribute to uncertainty regarding the magnitude, consistency and durability of functional recovery observed in current clinical studies.

Future research should investigate combined NSC-MSC therapies, explore extracellular vesicle-based interventions and refine non-invasive delivery methods, such as intranasal infusion, to maximize neuroregenerative and neuroprotective effects [2,17]. Larger, randomized clinical trials with standardized protocols are necessary to establish the efficacy and safety of this approach fully. Meanwhile, mechanistic studies of cell-host interactions will facilitate the translation of laboratory findings to the bedside. Addressing these challenges is essential for advancing stem cell-based therapies from experimental strategies toward standardized, clinically effective treatment for ischemic stroke.

Conclusion

Ischemic stroke remains one of the leading causes of death worldwide, but further exploration of treatment options leaves hope. Stem cell applications for ischemic stroke recovery have shown promise in recent years; however, further research is still needed. Recent studies have shown the safety of stem cell therapy implementation in various animal models and a few small clinical trials.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement
Not applicable.

Ethical Statement
The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement
Informed consent was taken for this study.

Authors' Contributions
All authors contributed equally to this paper.

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