NEURAL REGENERATION RESEARCH
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Review

Enhanced neurogenesis after ischemic stroke: The interplay between endogenous and exogenous stem cells

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https://doi.org/10.4103/NRR.NRR-D-24-00879

Date of submission: August 28, 2024

Date of decision: September 2, 2024

Date of acceptance: November 26, 2024

Date of web publication: January 13, 2025

From the Contents

Abstract

Ischemic stroke is a significant global health crisis, frequently resulting in disability or death, with limited therapeutic interventions available. Although various intrinsic reparative processes are initiated within the ischemic brain, these mechanisms are often insufficient to restore neuronal functionality. This has led to intensive investigation into the use of exogenous stem cells as a potential therapeutic option. This comprehensive review outlines the ontogeny and mechanisms of activation of endogenous neural stem cells within the adult brain following ischemic events, with focus on the impact of stem cell-based therapies on neural stem cells. Exogenous stem cells have been shown to enhance the proliferation of endogenous neural stem cells via direct cell-to-cell contact and through the secretion of growth factors and exosomes. Additionally, implanted stem cells may recruit host stem cells from their niches to the infarct area by establishing so-called "biobridges." Furthermore, xenogeneic and allogeneic stem cells can modify the microenvironment of the infarcted brain tissue through immunomodulatory and angiogenic effects, thereby supporting endogenous neuroregeneration. Given the convergence of regulatory pathways between exogenous and endogenous stem cells and the necessity for a supportive microenvironment, we discuss three strategies to simultaneously enhance the therapeutic efficacy of both cell types. These approaches include: (1) co-administration of various growth factors and pharmacological agents alongside stem cell transplantation to reduce stem cell apoptosis; (2) synergistic administration of stem cells and their exosomes to amplify paracrine effects; and (3) integration of stem cells within hydrogels, which provide a protective scaffold for the implanted cells while facilitating the regeneration of neural tissue and the reconstitution of neural circuits. This comprehensive review highlights the interactions and shared regulatory mechanisms between endogenous neural stem cells and exogenously implanted stem cells and may offer new insights for improving the efficacy of stem cell-based therapies in the treatment of ischemic stroke.

Key Words: brain-derived neurotrophic factor; endogenous neuroregeneration; exosomes; hydrogels; ischemic stroke; mesenchymal stem cells; neural stem cells; neurogenesis; stem cell transplantation

Introduction

Stroke is a significant global health issue that frequently leads to disability or death (Lian et al., 2024; Zhao et al., 2024). It includes both hemorrhagic and ischemic types, with the latter accounting for approximately 75% of all cases (Virani et al., 2021). Despite growing scientific understanding of stroke pathology, medical intervention options for stroke patients remain extremely limited (Huo et al., 2024; Wang et al., 2024). The primary therapeutic approach during the acute phase of ischemic stroke (IS) is to restore cerebral perfusion as quickly as possible, either through intravenous thrombolysis, endovascular thrombectomy, or a combination of both (Virani et al., 2021). Tissue plasminogen activator (tPA) is the only pharmaceutical intervention approved by the Food and Drug Administration (FDA) to treat acute IS; however, it must be administered within a narrow window of 4.5 hours following stroke onset. This time constraint means that only a small fraction of patients receive timely and effective therapy (Patil et al., 2022). Although the time window for thrombectomy can be extended to 24 hours, many primary hospitals lack the capability to perform this procedure, resulting in a significant number of IS patients not being timely treated (Berkhemer et al., 2015). After an IS, the brain initiates an innate restorative process; however, this is often insufficient for complete recovery (Berlet et al., 2021).

The transplantation of exogenous stem cells is regarded as a promising therapeutic strategy to address this issue (Huo et al., 2024). Numerous studies have demonstrated that the engrafted stem cells can engage in complex interactions with various cellular constituents of the post-stroke brain, including neurons, microglia, and endogenous neural stem cells (NSCs), thereby influencing the trajectory of intrinsic repair mechanisms (Bao et al., 2011; Hicks et al., 2013; Mousavi et al., 2022). Pilot studies provided evidence that stem cell transplantation can promote neurological recovery following IS (Zhang et al., 2019, 2020b). Building upon earlier experimental evidence (Stroemer et al., 2009), in 2016 a British team reported modest neurological and functional improvements in some patients in the Phase I PISCES trial evaluating stereotactic injection of allogeneic NSCs (CTX0E03 cells) in patients with chronic stable IS. A two-year follow-up study (PISCES-2) evaluating improvement of arm motor function during the earlier stages of stroke recovery confirmed the safety and feasibility of the CTX0E03 transplantation protocol (Muir et al., 2020). Likewise, the fetal spinal cord-derived NSC cell line NSI-566 has also been used in clinical trials for the treatment of IS. In a single-arm, dose-escalation trial, the maximum safe dose for stereotactic injection of NSI-566 was established

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Funding: *This work was supported by the National Key Research and Development Program of China, No. 2018YFA0108602; the CAMS Initiative for Innovative Medicine, No. 2021-1-I2M-019; National High-Level Hospital Clinical Research Funding, No. 2022-PUMCH-C-042 (all to XB).*
How to cite this article: *Geng R, Wang Y, Wang R, Wu J, Bao X (2026) Enhanced neurogenesis after ischemic stroke: The interplay between endogenous and exogenous stem cells. Neural Regen Res 21(1):212-223.*

at 7.2 × 10^7 cells, with 1-year follow-up results revealing improvements in motor function in patients (Zhang et al., 2019).

Although stem cell therapy (SCT) has shown great potential in preclinical studies, further research is necessary to enhance its efficacy in patients. Endogenous NSCs are present in the adult mammalian brain, and numerous studies have demonstrated that implanted exogenous stem cells can promote their activation, proliferation, and differentiation. Therefore, in this review, we aim to systematically summarize the complex interactions between endogenous and exogenous stem cells and discuss therapeutic strategies to further enhance the effectiveness of SCT.

Search Strategy and Selection Criteria

We searched WOS (Web of Science Core Collection) using the search terms TS (topic) = ((neural stem cell OR stem cell OR neural progenitor cell) AND (stroke OR ischemic stroke)). For specific sections, additional search terms included "transplantation," "neurogenesis," "neurorestoration," "heterogeneity," "single-cell," "stem cell therapy," Subventricular Zone," "Subgranular Zone," "stem cell product," OR "clinical trials." We also searched the references within the selected papers for relevant articles. We reviewed papers in English and Chinese. We did not apply date restrictions to the search. The last search was done on July 1, 2024. Results from 2015 and older papers were included only if deemed necessary to understand the subject under discussion. The final reference list was generated on the basis of relevance to the topics covered in this review.

Endogenous Neural Stem Cells in the Adult Mammalian Brain

NSC is a term that typically refers to a collection of neural progenitor populations rather than a homogeneous group of cells with equal plasticity (**Figure 1**). NSCs are characterized as multipotential cells that have the ability to self-renew, proliferate, and differentiate into various cell types within the central nervous system (CNS) (Andreotti et al., 2019). Several molecular markers have been identified to characterize NSCs, including glial fibrillary acidic protein (GFAP), epidermal growth factor receptor (EGFR), CD133, Nestin, CD9, CD81, and CD24 (Llorens-Bobadilla et al., 2015; Luo et al., 2015). NSCs exhibit regional diversity that reflects their embryonic origin and the patterning of their niches during brain development and maturation (Birbrair, 2019). This heterogeneity is also maintained when radial glial cells become quiescent NSCs (qNSCs) in the subventricular zone (SVZ) and the hippocampal subgranular zone (SGZ) of adult mammals (Andreotti et al., 2019).

The majority of NSCs in the adult human brain exist in a dormant state, ensuring the conservation of the stem cell reservoir for the duration of an individual's lifespan. qNSCs can convert into activated NSCs (aNSCs) and undergo a series of proliferation and differentiation processes, ultimately giving rise to neural progenitor cells (NPCs) as they progress along their lineage

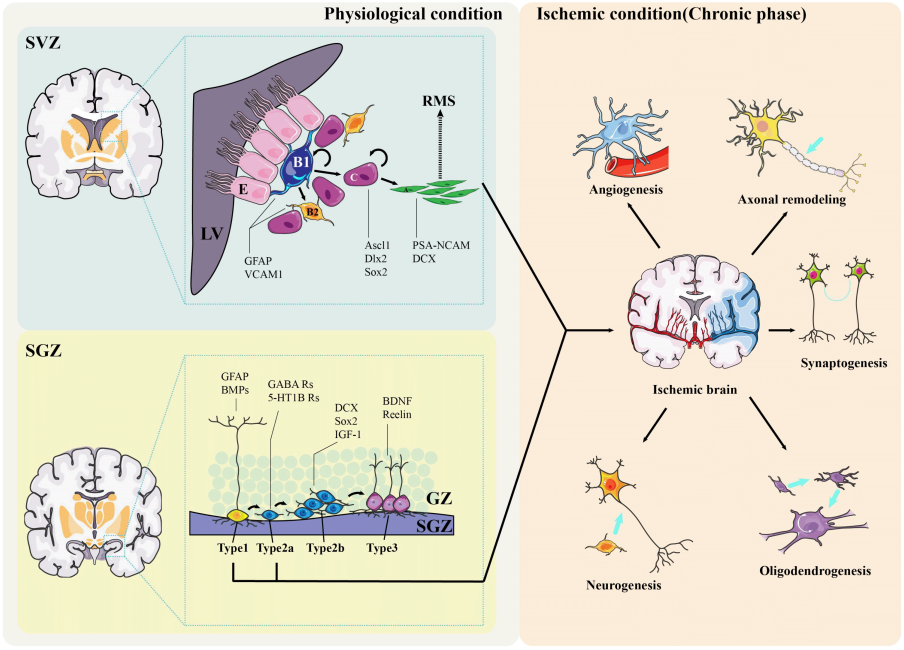

Figure 1 | **The endogenous heterogeneity of NSCs and stroke recovery.**
Diagram showing two major NSC niches SVZ/SGZ and the features of different subpopulations of NSCs. Under physiological conditions, NSCs in these two regions continuously generate new cells to maintain normal functions in the olfactory bulb and hippocampus. After an ischemic stroke, NSCs from these areas also contribute to neurorestoration (Lim and Alvarez-Buylla, 2016; Abbott and Nigussie, 2020). The materials were sourced from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Generic License (https://creativecommons.org/licenses/by/3.0/). Ascl1: Achaete-scute complex-Like 1; BDNF: brain-derived neurotrophic factor; BMPs: bone morphogenetic proteins; DCX: doublecortin; GABARs: gamma-aminobutyric acid receptors; GFAP: glial fibrillary acidic protein; IGF-1: insulin-like growth factor-1; NSC: neural stem cell; RMS: rostral migration stream; SGZ: subgranular zone; Sox2: sex-determining region Y-box-2; VCAM1: vascular cell adhesion protein 1.

(Kriegstein and Alvarez-Buylla, 2009). Single-cell transcriptome profiling reveals that the transition from qNSCs to aNSCs involves a continuum of cell types, each characterized by a specific combination of transcripts associated with cell cycle progression, DNA repair, protein synthesis, lysosome activation, and cellular metabolism (Leeman et al., 2018).

Neural stem cells during brain development

The intricate structural organization of the emerging cerebral cortex arises from the differentiation of billions of diverse cells originating from a consistent neuroepithelial layer. Neuroepithelial cells, which function as the principal neural stem/progenitor cells, undergo both symmetrical and asymmetrical cell division throughout development. Initially, they engage in symmetrical division before neurogenesis, transitioning to asymmetrical division afterward. This process produces distinct secondary neural stem and progenitor cells, such as radial glial cells and basal progenitors, as well as neurons. These secondary cells also undergo both symmetrical and asymmetrical divisions (Farkas and Huttner, 2008).

Radial glia function as NSCs that self-renew and produce more restricted progenitors, leading to three main neural lineages: neurons, oligodendrocytes, and astrocytes (Liu et al., 2023). Liu et al. (2016) elucidated that radial glial cells characterized by the expression profile $CD24^{-}THY1^{-/lo}$ are the progenitors responsible for generating all three principal neural lineages in the murine cerebral cortex. In contrast, cells expressing high levels of THY1 (THY1hi) were identified as oligodendrocyte precursors committed to oligodendroglial differentiation, while $CD24^{+}THY1^{-/lo}$ cells were recognized as dedicated precursors for both excitatory and inhibitory neuronal lineages (Liu et al., 2023).

During embryogenesis, two proliferative zones – the ventricular zone (VZ) and the SVZ – generate neurons and glial cells (Pevny and Rao, 2003). In mouse models, VZ progenitors express Emx2, Pax6, Sox6, and Couptf1, while SVZ progenitors express Tbr2 (Zhang and Jiao, 2015).

Before the initiation of embryonic neurogenesis, NPCs within the VZ undergo symmetric divisions to expand the pool of progenitors. Cell lineage tracing experiments in mice showed that around embryonic day 11.5 (E11.5), NPCs transition to asymmetric divisions to promote self-renewal and generate neurons that migrate to the mantle zone (MZ) under the guidance of radial glial cells. Some daughter cells of NPCs differentiate into intermediate progenitor cells (IPCs), which then migrate to the SVZ and give rise to neurons that populate the upper cortical layers. As neurogenesis concludes around E17.5, NPCs shift their fate toward gliogenesis, producing astrocytes in both the cortical and subependymal zones, as well as ependymal cells (Kwan et al., 2012).

Neural stem cells in the subventricular zone

The predominant NSCs in the adult SVZ exist primarily in a quiescent state, and their renewal

and differentiation processes are regulated by a complex interplay of various signaling pathways (Ahn and Joyner, 2005). The SVZ is home to four principal cell types: type A, type B, type C, and ependymal cells. Type C cells are the most proliferative, generating a substantial supply of type A cells, which are essential for maintaining the functionality of the olfactory bulb through their continuous division. Type A cells, characterized as neuroblasts, migrate through the rostral migratory stream (RMS) and differentiate into neurons. Type B cells, classified as astroglial cells, can be further divided into two distinct subpopulations: type B1 and type B2 cells (Ihrie and Alvarez-Buylla, 2011). These cells possess numerous motile cilia that facilitate the circulation of CSF (Yamashita et al., 2006). Type B cells also regulate NSC behaviors through direct contact and the secretion of factors such as Noggin (Lim et al., 2000). Molecular biomarkers in SVZ NSCs can help define these subpopulations. GFAP specifically marks type B cells but not type C cells, while polysialic acid-neural cell adhesion molecule (PSA-NCAM) marks type A cells. Sox2 serves as a marker for both active astrocytes and progenitor cells within the SVZ (Yamashita et al., 2006).

Using *in vivo* labeling strategies, Merkle et al. (2014) demonstrated that the types of cells produced by NSCs in the SVZ vary depending on their specific position within the niche. They also identified several new interneuron types from distinct progenitor microdomains in the anterior ventral ventricular-subventricular zone (V-SVZ) (Merkle et al., 2014). Further single-cell analysis in mice revealed 14 transcriptional subgroups of SVZ cells, 7 of those being stem or progenitor cells (Xie et al., 2020b). In turn, single-cell RNA sequencing (scRNA-seq) analysis of over 56,000 cells from the V-SVZ and the olfactory bulb delineated the neuronal lineage progression from astrocytes to olfactory bulb neurons, identifying Notum —a secreted inhibitor of WNT signaling— as a predominant marker of the intermediate cell population during this transformation (Mizrak et al., 2020). The scRNA-seq analysis also confirmed the similarity between NSCs and astrocytes, as both cell types shared an expression profile characterized by high levels of Slc1a3 and low levels of S100b. Notably, the stem cell marker Prom1, which is frequently used in research, is rarely detected in NSCs; instead, it is predominantly found in endothelial cells (Zywitza et al., 2018).

Neural stem cells in the subgranular zone

The process of neurogenesis within the SGZ also involves astroglial cells. NSCs residing in both the SVZ and SGZ exhibit similarities, as both populations express astroglial markers and display ultrastructural features characteristic of astroglial cells, including elongated endfeet that terminate on blood vessels (Fuentealba et al., 2012).

The SGZ contains six types of cells, distinguished by molecular and morphological features: type 1, type 2a, type 2b, type 3, immature, and mature cells (Kempermann et al., 2004). Type 1 cells exhibit low proliferation activity and possess an astroglial morphology and high multipotency. They express GFAP and Nestin and are negative for the immature neuronal marker doublecortin (DCX). Type 1 cells extend long radial processes that penetrate the granular layer and produce two groups of transient amplifying cells: type 2 and type 3 cells (Filippov et al., 2003). Type 2 cells, which express Nestin and are associated with the neuronal lineage, are characterized by short processes and compact nuclei, exhibiting robust migratory and proliferative capabilities. Depending on the expression level of DCX, type 2 cells can be subdivided into two subtypes: DCX^- type 2a cells and DCX^+ type 2b cells (Kronenberg et al., 2003). Type 3 cells are in turn $DCX^+/Nestin^-$ (Seri et al., 2001).

Artegiani et al. (2017) used scRNA-seq to delineate the composition and dynamics of the cellular constituents within the SGZ. NSCs were identified by the expression of genes such as Aldoc, Apoe, Id4, Hopx, Sox9, GFAP, Scl1a3, and Sox2. Astroglial cells exhibited a molecular signature similar to that of NSCs. In an additional scRNA-seq analysis, the ontogenetic trajectory of the SGZ was reconstructed, revealing the molecular identifiers of qNSCs in the adult brain. The results demonstrated that genes associated with Notch signaling, GABAergic and glutamatergic synapses, BMP signaling pathways, the MAPK cascade, calcium dynamics, and cell adhesion mechanisms were downregulated as qNSCs transitioned out of their dormant state (Shin et al., 2015).

Berg et al. (2019) identified a conserved population of Hopx-positive quiescent radial glial-like neural progenitors that persisted from the embryonic stage into adulthood. This population exhibited stable molecular and epigenetic profiles, along with consistent ontogenetic dynamics. Additionally, direct evidence of cellular heterogeneity was revealed through the integration of recombination-based genetic targeting, two-photon microscopy, and scRNA-seq techniques. Results demonstrated that NSCs expressing the regulatory elements of the stem cell-expressed genes Gli1 and Ascl1 exhibited highly similar yet distinguishable transcriptional profiles (Bottes et al., 2021).

Neurogenesis After Ischemic Stroke

Liu et al. (1998) documented that stroke-induced neurogenesis serves as an early indicator of spontaneous neurological recovery, highlighting the therapeutic potential of cellular and pharmacological interventions to alleviate neurological deficits in patients with stroke. Following an IS event, endogenous NSCs are activated and migrate to the site of injury, where they give rise to neurons and glial cells. However, evidence indicates that the extent of neural regeneration and repair resulting from this process is at best modest.

NSCs derived from the SVZ and the SGZ of the dentate gyrus are believed to be the source of novel neurons, a phenomenon that is essential for the recovery and restoration of injured brain regions following a stroke (Rahman et al., 2021). In rodent models, IS has been shown to promote the migration of NPCs from the SVZ to the striatum, the hippocampal CA1 region, or the cerebral cortex, where they differentiate into neurons or neuroglia (Bendel et al., 2005; Hou et al., 2008; Ohira et al., 2010). Further research indicates that neurogenesis is not achieved through enhanced proliferation of radial glia-like type 1 cells, but rather by a specific increase in the population of rapidly proliferating type 2a cells and their subsequent differentiation into immature neurons (Keiner et al., 2010). Additionally, in brain tissue of patients with stroke, an increased proliferation of NPCs in the SVZ has been observed, along with the presence of cells expressing markers indicative of immature neurons in the ischemic penumbra of the cerebral cortex and striatum (Martí-Fàbregas et al., 2010; Nakayama et al., 2010).

The topic of ischemia-induced neurogenesis has been extensively addressed in rodent models. Seong et. al (2018) reported that after induction of photothrombotic cerebral ischemia in mice, activation of Toll-like receptor 2 (TLR2) promoted neurogenesis in the dentate gyrus SGZ (Seong et al., 2018). Previous studies in rats had indicated that unlike NPCs in the SVZ, which migrate laterally from the RMS to the injured area, NPCs from the SGZ do not seem to target the damaged zone following IS (Parent et al., 1997; Ernst and Christie, 2006). In turn, other reports in rodent models concluded that peaks of neurogenesis occur in the SVZ and SGZ during the third and fourth weeks, respectively, after ischemic injury (Kuge et al., 2009; Zhu et al., 2018).

Preclinical studies demonstrated also that the Wnt/β-catenin signaling pathway in adult NSC niches plays a critical role in promoting neurogenesis and restoring neurological function after cerebral ischemia. In a study by Lei et al. (2008), β-catenin was deactivated by intracerebroventricular administration of β-catenin-targeted small interfering RNA (siRNA) to mice that had undergone transient middle cerebral artery occlusion (MCAO). This intervention resulted in an increased infarct volume and a decrease in neurogenesis within the SVZ (Lei et al., 2008).

Conversely, intranasal administration of Wnt3a protein following focal IS in mice led to a reduction in infarct volume, improvements in sensorimotor functions, and an increase in neurogenesis in both the SVZ and the SGZ. Wnt3a enhanced also the migration of DCX^+/bromodeoxyuridine ($BrdU^+$) cells from the SVZ towards the peri-infarct area, resulting in a higher number of newly formed neurons ($BrdU^+/NeuN^+$ cells) in the peri-infarct zone (Wei et al., 2018). Indeed, mounting evidence indicates that therapeutic activation of the Wnt/β-catenin pathway is a plausible strategy to promote neurogenesis and aid the recovery of neurological function following cerebral ischemia (Yang et al., 2021; Xu et al., 2024). Nevertheless, the ischemic cascade of oxidative stress, hypoxia, and inflammation that occurs after a stroke triggers programmed cell death in endogenous NSCs and promotes transformation into astrocytes, rather than neurons, in surviving NSCs. This shift serves as a limiting factor in the self-repair mechanisms that are activated following a stroke (Gan et al., 2022; Zhu et al., 2024).

Animal studies showed that after a stroke, the vast majority of NPCs that migrated to the injury site undergo apoptosis within ~4 weeks, with just a few of them giving rise to functional neurons

(Malone et al., 2012). In turn, approximately 5%–10% of post-stroke newborn dentate granule cells exhibit significant morphological abnormalities, including supernumerary basal dendrites, ectopic localization, and increased generation of mushroom-shaped spines (Niv et al., 2012). Furthermore, in both mice and humans, the neurons generated in the SVZ are predominantly GABAergic interneurons, which can insufficiently replace the diverse neuronal types lost due to the stroke. Consequently, endogenous neurogenesis is typically insufficient to compensate for the cellular loss that follows ischemic injury (Inta and Gass, 2015).

Because this limited endogenous regeneration determines restricted neurological recovery after a stroke, numerous approaches targeting this phenomenon have been explored. Emerging therapeutic strategies for IS include immune modulation, growth factor administration, exosome transfusion, and injection of biomaterials. Immune modulation with drugs such as interleukin (IL)-1 receptor antagonists and fingolimod, an immunosuppressant that targets the sphingosine-1-phosphate (S1P) receptor, has been shown to reduce neurodegeneration and infarct volume in stroke patients (Emsley et al., 2005, Bai et al., 2022). Growth factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) promote neurogenesis and angiogenesis, with VEGF also facilitating macrophage migration and the reconstruction of cerebral blood vessels (Lessmann and Brigadski, 2009). Exosomes are small extracellular vesicles produced by virtually all cells, including stem cells. Exosomes can enhance angioneurogenesis and modulate immune responses, with potential for nasal delivery to improve targeting to the brain (Wang et al., 2020). Biomaterial scaffolds made of biocompatible polymers provide structural support and can be combined with drugs or cells to enhance their function; conjugation with nanoparticles, in particular, enables efficient penetration of the blood–brain barrier (Jiang et al., 2023). However, further preclinical studies and clinical trials are needed to optimize these therapies and address potential risks. Compared to cell-free approaches, and eventually complementing them, stem cell injection is considered a promising therapeutic option due to the ability of stem cells to differentiate into neurons and become functionally integrated into neural circuits. Additionally, stem cells have the capacity to secrete various trophic and growth factors, as well as exosomes, which may enhance the potential for neurological recovery after a stroke (Boese et al., 2018). There are primarily three methods for delivering stem cells into the brain: stereotactic injection, intranasal mucosal injection, and intravenous/intra-arterial injection (Rust and Tackenberg, 2024). A recent study tended to favor stereotactic injection over other methods because it allows bypassing the blood-brain barrier, thus maximizing their utilization (Liu et al., 2024). While stem cells injected through the circulatory system can migrate to the infarct area via chemotaxis, this method also carries the risk of embolism (Rust and Tackenberg, 2024). In turn, the intranasal mucosal route causes less damage, and stem cells can migrate into the CNS over a shorter distance. Accordingly, intranasal delivery of stem cells emerged as a topic of significant interest in recent years. However, this route still faces challenges, including a substantial loss of stem cells during the delivery process (Jiang et al., 2024).

Viable choices for post-stroke stem cell implantation include NSCs/NPCs and mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) that have been induced to specifically differentiate toward a neural lineage (Wang et al., 2018a; Huang and Zhang, 2019; Rahimi Darehbagh et al., 2024). The implantation of these cells is believed to promote functional recovery through two major mechanisms: via direct replacement and indirectly, through a "bystander" effect (Boese et al., 2018). Direct replacement and functional integration involve migrating to the peri-infarct region, differentiating into functional neurons, and establishing connections within neural circuits. The bystander effect refers to the ability of implanted stem cells to regulate post-stroke neurogenesis, angiogenesis, and inflammatory responses through the secretion of cytokines, exosomes, and other factors (Liska et al., 2017; Boese et al., 2018).

Stem Cell Transplantation Therapy in Stroke

Since the first attempts at brain tissue implantation in the 1990s, SCT for stroke has shown great promise (Kondziolka et al., 2000). There are generally two approaches: one is to activate endogenous neural stem cells to promote neural protection and restoration, and the other is to inject exogenous stem cells for tissue replacement and induction of paracrine neuroprotective effects (Yang et al., 2020). Reflecting on the past 30 years, our understanding of NSCs in the context of stroke can be divided into three stages. The first stage primarily focuses on addressing the question: "Can stroke recovery occur?"

Since 1995, thrombolytic therapy with tissue plasminogen activator (t-PA), applied as soon as possible (up to 4.5 hours) after stroke onset remains the standard treatment for acute IS ((Röther et al., 2013). At that time, whether neurogenesis occurred in the adult brain was still unknown, and the mechanisms of functional recovery after stroke remained unclear (Ances and D'Esposito, 2000; Gladstone and Black, 2000).

Efforts to understand functional recovery after stroke have involved BrdU labeling and the isolation of progenitor cells. An *in vitro* clonal study performed to observe individual neural cells and reveal their differences lead to the discovery of NSCs (Cattaneo and McKay, 1990). Subsequently, stereological analysis of BrdU-labeled cells enabled researchers to trace proliferating neuronal precursors *in vivo*, confirming the presence of newborn neurons in the adult dentate gyrus and in the SVZ (Lois and Alvarez-Buylla, 1994; Kempermann et al., 1997).

Initial evidence that SVZ neurogenesis is enhanced after global ischemia was provided by Liu et al. (1998), a finding that paved the way for cellular and pharmacological therapies aimed at promoting brain repair and improving neurological function in stroke patients. Two decades ago, Ishibashi et al. (2004) confirmed for the first time enhanced recovery in Mongolian gerbils with IS transplanted with human NSCs.

A second stage in our knowledge of the role of NSCs in stroke came from advancements related to the development of gene modification techniques and differentiation induction methods to produce sufficient quantities of cells for clinical purposes. Stem cells can be induced *in vitro* into NSCs or NPCs, and the introduction of exogenous genes allowed the creation of stable cell lines. In 2006, Pollock et al. created a cell line, termed CTX0E03, by retrovirally inserting into embryonic NSCs the myc-ERTAM transgene, which confers phenotypic and genotypic stability. In what represented one of the closest approaches to success in the field of NCS therapy for stroke, clinical studies employing stereotactic injection of CTX0E03 cells in chronic stroke patients reported improved neurological or motor function in some patients, and no immunological or cell-related adverse effects (Kalladka et al., 2016, Muir et al., 2020).

In 2007, Takahashi et al. achieved a research breakthrough by successfully generating from fibroblasts iPSCs with the same properties and genetic profile as ESCs. This discovery enabled the generation of NSCs from a patient's own cells and facilitated the large-scale production of clinical-grade cells. Although iPSCs thus present promising potential for transplantation, challenges remain, including potential tumorigenicity and possible unwanted effects resulting from genomic and epigenetic alterations introduced during differentiation (Aly, 2020).

The third, current stage of research on NSCs involves a deeper investigation into the detailed mechanisms and optimization of SCT. Since 2015, single-cell analysis has emerged as a valuable tool for classifying NSC subpopulations. By dissecting NSCs based on their transcriptomic, proteomic, and even epigenomic features, researchers can now uncover their inherent heterogeneity. Insights into the function and potential of NSCs should enhance the therapeutic effects of NSC therapy for stroke while also limiting tumorigenicity (Johnson et al., 2015; Rennert et al., 2016; Sun et al., 2021a).

While deciphering the mechanisms of SCT, the efficacy of stem cells may be further enhanced through gene modification, targeted pretreatment, and synergistic administration with various drugs and biomaterials. Wichterle and Lim (1960) successfully synthesized the first artificial hydrogel, marking the beginning of significant interest in materials that can work in conjunction with stem cell transplantation. In 2014, the development of CRISPR/Cas9-based genome editing technology allowed researchers to alter the expression levels of specific genes and track the fate of fluorescently-tagged target proteins (Wang et al., 2018b). In recent years, stem cell-derived exosomes have also garnered considerable attention. In 2010, it was first demonstrated in a mouse model of myocardial ischemia/reperfusion injury that exosomes in the culture medium of MSCs were responsible for its cardioprotective effect (Lai et al., 2010). This discovery sparked significant interest among researchers in MSC-

derived exosomes. By transfecting BDNF into exosomes derived from NSCs, an engineered exosome known as BDNF-hNSC-Exo was constructed. This exosome significantly inhibited the activation of microglia in animal models of IS and promoted also the differentiation of endogenous NSCs into neurons *in vivo* (Zhu et al., 2023). **Figure 2** shows a timeline of stem cell transplantation therapy in stroke.

Figure 2 | **Timeline of stem cell transplantation therapy in stroke.**
The materials were sourced from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Generic License (https://creativecommons.org/licenses/by/3.0/). NSC: Neural stem cell; SGZ: subgranular zone; SVZ: subventricular zone.

Exogenous Stem Cells Enhance the Proliferation of Endogenous Neural Stem Cells

In the realm of neurogenesis, which is the focal point of our research, the modulation of endogenous NSCs by implanted stem cells can be distilled into three principal mechanisms: the augmentation of NSC proliferation, the facilitation of their migration, and the manipulation of the microenvironment to foster their growth and differentiation (**Figure 3**).

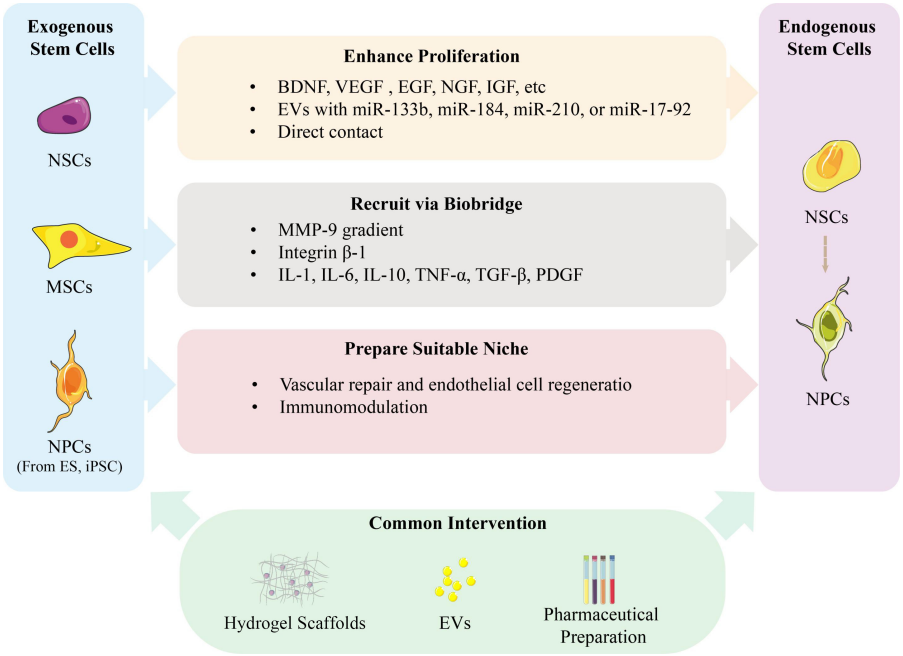

Figure 3 | **Modulation of exogenous stem cells on endogenous NSCs.**
The schematic illustrates the three primary actions of exogenous stem cells on endogenous NSCs. Exogenous stem cells can promote the proliferation of endogenous NSCs through cytokines (such as BDNF, EGF, and IGF), exosomes, and direct contact. They can also recruit endogenous NSCs to migrate to the damaged area by establishing a "biobridge." Additionally, exogenous stem cells can indirectly improve the microenvironment following ischemia, enhancing the survival and differentiation of endogenous NSCs. By targeting common pathways in both endogenous NSCs and exogenous stem cells, certain drugs, hydrogels, and exosomes can synergize with stem cell transplantation to improve neurological function recovery more effectively. The materials were sourced from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Commons Attribution 3.0 Generic License. (https://creativecommons.org/licenses/by/3.0/). BDNF: Brain-derived neurotrophic factor; EGF: epidermal growth factor; ES: embryonic stem cells; EVs: extracellular vesicles; IGF: insulin-like growth factor; IL: interleukin; iPSC: induced pluripotent stem cells; MMP-9: matrix metalloproteinase 9; MSCs: mesenchymal stem cells; NGF: nerve growth factor; NPCs: neural progenitor cells; NSCs: neural stem cells; PDGF: platelet-derived growth factor; TNF-α: tumor necrosis factor-alpha; TNF-β: tumor necrosis factor-beta; VEGF: vascular endothelial growth factor.

As illustrated, implanted stem cells can stimulate the regeneration of endogenous NSCs through three distinct pathways, thereby enhancing post-stroke neurological recovery. A wide variety of stem cell types have been used in preclinical and clinical studies for transplantation into the CNS. MSCs, ESCs, and NSCs are among the most commonly used stem cell types in stroke therapy (Mosconi and Paciaroni, 2022). Cells of different origins come with distinct sets of advantages and disadvantages. MSCs can be readily isolated and cultured from bone marrow, adipose tissue, umbilical cord blood, and other tissues, and possess immunomodulatory properties that reduce the risk of rejection and transplantation complications. However, due to their origin, MSCs often require specific induction to differentiate for the treatment of CNS disorders (Cha et al., 2024). NSCs have a natural advantage in CNS transplantation, as they can more readily differentiate and integrate into neural circuits and have a greater ability to migrate to the lesion site. However, the sourcing of NSCs from human fetal brain tissue, which contains them in abundance, raises ethical concerns (Boese et al., 2018). ESCs are generally not injected directly due to their high tumorigenic potential; therefore, they need to be differentiated into NPCs *in vitro* before injection, in a process similar to that of iPSCs (Varzideh et al., 2023).

In the following section, we will explore how exogenous stem cells regulate endogenous NSCs through the release of growth factors, the secretion of exosomes, and direct cell-to-cell contact.

Growth factors

Insulin-like growth factor 1 (IGF-1), BDNF, and VEGF have been shown to directly influence the proliferation of NSCs (Ruan et al., 2015).

BDNF is an essential peptide for the development and function of the nervous system. Belonging to the family of neurotrophic factors, BDNF is crucial for the sustenance, maturation, and synaptic plasticity of neurons, processes that are central to the acquisition and consolidation of learning and memory. Following ischemia, BDNF plays a vital role in enhancing the viability of neural cells, augmenting synaptic plasticity, and facilitating neurogenesis (Azman and Zakaria, 2022; Rao et al., 2024). In a rat model of cortical photothrombotic ischemia, intravenous applications of BDNF after stroke induction resulted in significantly improved sensorimotor scores, increased hippocampal neurogenesis, and enhanced migration of SVZ progenitor cells to the striatum ipsilateral to the stroke site (Schäbitz et al., 2007). Bone marrow–derived stem cells (BMSCs) produce a range of cytokines, including BDNF. In a mouse model of IS, BMSC transplantation promoted the migration of greater numbers of DCX^+ neuroblasts from the ipsilateral SVZ to the peri-infarct area, compared to vehicle-treated control mice. Moreover, increased expression of stromal cell–derived factor 1 (SDF-1), VEGF, and BDNF was further

observed in the injured brain (Song et al., 2013). Another study using a rat MCAO model reported that transplantation of human BMSCs promoted neurological function recovery, with increased expression of BDNF and nerve growth factor (NGF) in the stroke region (Li et al., 2002).

IGF-1 plays a pivotal role in the development, maturation, and neuroplasticity of the CNS. IGF-1 profoundly influences cellular neuroplasticity through its glycoprotein receptor (IGF-1R) and classical signaling pathways, including the PI3K-Akt and Ras-Raf-MAP kinase cascades (Dyer et al., 2016). Following brain ischemia, IGF-1 acts to prevent intracellular calcium overload, inhibit the upregulation of neuronal nitric oxide synthase, activate hypoxia-inducible factor 1-alpha, regulate Bcl-2 to resist apoptosis, and enhance endothelial function (Li et al., 2021). Furthermore, IGF-1 is associated with neurogenesis stimulated by MSC transplantation, with a significant increase in the number of cells expressing IGF-1 and DCX noticed following MSC implantation (Zhang et al., 2004; Ruan et al., 2015).

VEGF is an important pleiotropic growth factor that plays a crucial role in stimulating cell proliferation in the SVZ and facilitating the migration of immature neurons to ischemic tissues, thereby promoting neural regeneration and repair (Quittet et al., 2015). Since VEGF characteristically exhibits also potent pro-angiogenic and neuroprotective actions, its therapeutic use has attracted considerable interest in stroke research. Evidence shows that VEGF administration in the early, acute phase of stroke may actually exacerbate brain damage through disintegration of endothelial barriers. However, the detrimental effects of VEGF on vascular cohesion are transient, and optimal selection of administration route and timing might be key to maximize the ability of VEGF to support neurogenesis and neurovascular remodeling, promote neurogenesis, and curtail cerebral edema (Hu et al., 2022). VEGF is instrumental in the restorative processes of the neurovascular unit following IS by binding to VEGF receptor 2 and activating numerous signaling cascades within endothelial cells. Stem cells and volatile gases (including nitric oxide and carbon monoxide) may provide therapeutic benefits by reducing VEGF-induced vascular permeability and enhancing the regenerative capacity mediated by VEGF (Moon et al., 2021). Ipsilateral engraftment of human BMSCs into the cerebral parenchyma of ischemic rats has been shown to increase the expression of BDNF, neurotrophin-3 (NT-3), and VEGF within the ischemic brain tissue. This engraftment reduces the volume of infarction and alleviates neurological deficits. The underlying mechanisms for these beneficial outcomes may include increased proliferation of NPCs in the SVZ and SGZ, accelerated migration of nascent neuroblasts to the ischemic boundary zone, inhibition of neuronal apoptosis, and enhanced differentiation of neuronal precursors into mature neurons (Bao et al., 2011).

Exosomes derived from exogenous stem cells

Administration of exosomes derived from stem cells has been shown to enhance synaptic plasticity, promote angiogenesis, increase axonal and myelin densities, and facilitate the migration of neuroblasts to ischemic areas (Shiota et al., 2018; Venkat et al., 2018). A study by Zhang et al. (2020a) demonstrated that exosomes derived from NSCs and modified to carry IFN-γ (IFN-γ-NSC-sEVs) have an enhanced ability to guide the conversion of endogenous NSCs into neurons in a rodent model of stroke. Xia et al. (2021) reported that exosomes originating from ESCs reduce inflammation by enhancing regulatory T cell activity, mitigate neuronal death, and improve long-term recovery following MCAO/reperfusion (MCAO/R). Yuan et al. (2021) showed that NSC-derived exosomal microRNA-9 (miR-9) facilitates the differentiation of NSCs and the maturation of neurons and glial cells *in vitro* (Yuan et al., 2021). Likewise, several miRs, such as miR-133b, miR-184, miR-210, and miR-17-92, released from MSC-derived extracellular vesicles (MSC-EVs) were shown to promote neurogenesis and oligogenesis (Moon et al., 2019). A comparative investigation of the implantation of MSCs and MSC-EVs revealed that both therapies similarly increased the abundance of immature (DCX^+) and mature ($NeuN^+$) BrdU-labeled neuronal cell populations. This finding suggests the enticing possibility of using MSC-EVs instead of MSCs for promoting neurovascular regeneration following ischemia (Doeppner et al., 2015).

Interactions between exogenous and endogenous stem cells

Exogenous stem cells can protect and activate endogenous NSCs and NPCs through direct contact. A study by Walker et al. (2010) demonstrated that when NSCs are in contact with MSCs, there is an increase in IL-6 secretion and a reduction in apoptosis among NSCs. Implanted MSCs can activate the NFκB pathway in endogenous NSCs independently of the PI3K/AKT pathway, thereby increasing IL-6 secretion and promoting endogenous neuroregeneration. Notably, this change in NFκB activity is contingent upon direct cell-to-cell contact. Parallel phenomena have also been documented in NSC-NSC interactions. Co-culturing with human bone marrow-derived NCS-01 cells confers protection against oxygen-glucose deprivation (OGD) to primary rat cortical cells and human NPCs. This protective mechanism was attributed to the secretion of IL-6 and basic fibroblast growth factor (bFGF) by NCS-01 cells, coupled to formation of filopodia extending from NCS-01 cells toward OGD-challenged cells (Kaneko et al., 2019). Additionally, it was reported that implanted stem cells can facilitate mitochondrial transfer through direct contact, a process believed to enhance the survival of neurons and neural precursor cells following IS (Liao et al., 2024).

In summary, current evidence suggests that exogenous stem cells can enhance the proliferation, migration, neuronal differentiation, and survival of endogenous NSCs through the secretion of growth factors, exosomes, and direct cell-to-cell contact. However, it is important to note that depending on their origin and administration route and timing, exogenous stem cells may interact with endogenous stem cells in different ways (Panos et al., 2024). For instance, a study in mice reported that stereotactic injection of human iPSC-derived NPCs 7 days post-stroke was associated with significant survival and differentiation of these cells into functional neurons 1 month later (Rust et al., 2022). In turn, intravenous administration of autologous mouse NPCs 3 days after MCAO-induced stroke conferred therapeutic effects primarily associated with the upregulation of glial glutamate transporter 1 expression in astrocytes and reduced peri-ischemic extracellular glutamate levels (Bacigaluppi et al., 206). In contrast, a clinical study evaluating the safety, feasibility, and efficacy of intravenous infusion of autologous bone marrow-derived mononuclear stem cell (BM-MNC) in patients with chronic IS (first diagnosed 3 months to 1.5 years before recruitment) reported modest, non-significant elevation of serum BDNF and VEGF and no clinical benefit compared to placebo-infused patients (Bhasin et al., 2016). Since immune rejection poses a significant challenge in stem cell therapies, the use of autologous/allogeneic stem cell systems is favored in both preclinical and clinical research. Still, in the CNS, the implanted allogeneic stem cells show a greatly limited survival rate, which restricts their interaction with endogenous cells. Given this consideration, autologous iPSCs may offer a more promising avenue to circumvent immune rejection (Yamanaka, 2020).

Exogenous Stem Cells Recruit Endogenous Neural Stem Cells to the Ischemic Region

In addition to stimulating neurogenesis, transplanted stem cells can also assist endogenous stem cells in reaching the ischemic site. To guide NSCs and NPCs to the damaged area, transplanted stem cells establish a “biobridge” from the neurovascular niche to the infarction zone. This phenomenon has been investigated in various types of stem cell transplantation therapies (Liska et al., 2017; Gójska-Grymajło et al., 2018; Jiao et al., 2020; Berlet et al., 2021) and is primarily associated with the upregulation of matrix metalloproteinases (MMPs) following a stroke. MMPs, particularly MMP-9, facilitate extracellular matrix (ECM) remodeling, and serve as chemical cues for exogenous stem cells to direct the migration of endogenous stem cells from the SVZ to the site of damage (Petit et al., 2007; Tajiri et al., 2013; Haque et al., 2020). The migrating NSCs and NPCs themselves can further extend the biobridge through integrin β-1 (Tajiri et al., 2014; Crowley and Tajiri, 2017; Gójska-Grymajło et al., 2018). Eventually, the transplanted cells in the infarcted area will be supplanted by the migrating endogenous NSCs and NPCs, which continue to exert anti-inflammatory effects and differentiate into neurons, astrocytes, and oligodendrocytes (Corey et al., 2019; Zhang et al., 2020c). Additionally, cytokines such as IL-1, IL-6, IL-10, tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), and platelet-derived growth factor (PDGF) also play a role in recruiting endogenous stem cells (Bao et al., 2011; Wang et al., 2018a).

In a study by Park et al. (2002) the implantation of polymer scaffolds containing exogenous NSCs into the brains of rats subjected to ischemia led to significantly increased neurite outgrowth from both host- and exogenous NSC-derived neurons, with occasional evidence of functional reconstitution being observed. In this process, the interaction between engrafted NSCs and host cells was proposed to be facilitated by formation of a biobridge. These findings suggest that seeding of exogenous stem cells onto biocompatible scaffolds can enhance the differentiation of host NPCs and coordinate axonal growth directed towards specific areas (Park et al., 2002).

It is noteworthy that the concept of biobridge is not limited to the interaction between exogenous and endogenous stem cells. Hassani et al. (2012) showed that transplantation of CTX0E03 NSCs sustained neuroblast proliferation in the striatum and promoted the recovery of sensory and motor functions in rats subjected to MCAO. Interestingly, neuroblast proliferation was preceded and accompanied by the recruitment of by high numbers of anti-inflammatory, proliferating microglia (Hassani et al., 2012). In neonatal hypoxic-ischemic mice, the transplantation of oligodendrocyte progenitor cells has been shown to improve neurological function. Since the implanted cells did not undergo significant differentiation, the functional improvements observed post-implantation were attributed to the secretion of paracrine molecules and possible establishment of biobridges among oligodendrocytes (Rumajogee et al., 2018).

Exogenous Stem Cells Create an Optimal Niche for Endogenous Neural Stem Cells

Besides forming natural scaffolds (biobridges) and secreting neuron-supporting cytokines, chemokines, and growth factors, exogenous stem cells may also stimulate the survival, proliferation, migration, and differentiation of endogenous NSCs by modifying the environment in the ischemic area. This protective mechanism is primarily linked to the regulation of angiogenesis and local microglial activity.

Vascular repair and endothelial cell regeneration

Vascular remodeling in ischemic brain tissue promotes neurogenic differentiation of endogenous NSCs. The implantation of exogenous stem cells can enhance the growth of endogenous NSCs by inducing angiogenesis (Moon et al., 2019). Following an IS, the reconstitution of the vascular architecture is closely linked to the activation of endogenous stem cells. Furthermore, endogenous NPCs have been identified within the viable and newly formed vessels that emerge after an stroke event (Kojima et al., 2010). These NPCs migrate from the boundary of the SVZ to the target area at a rate of 28.67 ± 1.04 μm/h. The migrating CDX^+ progenitor cells move along the vascular system and aggregate, with ~35% of them localizing within a 5-μm range of the vessels (Zhang et al., 2009; Boese et al., 2018). Following the implantation of exogenous MSCs, the expression of SDF-1, glial cell–derived neurotrophic factor (GDNF), VEGF, and BDNF increases significantly, promoting vascular regeneration in the infarcted area (Ding et al., 2007; Chen et al., 2014). Consequently, implanted stem cells can indirectly support endogenous stem cells by fostering vascular regeneration in the damaged brain.

Pericytes and endothelial cells represent key endogenous players in the reconstitution of neuronal connectivity in the infarcted brain. Pericytes play a crucial role in regulating neurogenesis by adjusting capillary blood flow and influencing the balance of endogenous stem cells in the post-stroke environment (Armulik et al., 2011; Xie et al., 2020a). Ohab et al. (2006) highlighted the close relationship between NPCs and the vasculature, noting that capillary endothelial cells in the infarcted area secrete SDF-1 and angiopoietin-1 (Ang-1), which are essential for reconstituting the neurovascular niche at the site of ischemic damage (Ohab et al., 2006). SDF-1 creates a concentration gradient around the infarct site, effectively recruiting endogenous NSCs and NPCs (Li et al., 2008). VEGF, secreted by endothelial cells and pericytes, acts as a key neurotrophic factor that promotes the proliferation of cells within the SVZ. Additionally, soluble angiocrine factors secreted by capillary endothelial cells, including betacellulin (BTC, an EGFR ligand), placental growth factor-2 (PlGF-2), and Jagged1 (JAG1, a Notch ligand), have shown to enhance the proliferation and differentiation of both quiescent and activated NSCs into transit amplifying cells and neuroblasts (Rafii et al., 2016).

Immunomodulation

The engraftment of exogenous stem cells has the potential to reduce the systemic inflammatory burden within the CNS, counteract the potentially cytotoxic environment, enhance the secretion of neurotrophic factors, and allow endogenous NSCs to persist and function optimally (Tobin et al., 2020). Exogenous NSCs were shown to alter the levels of cytokines that influence neurogenesis, such as TNF-α, monocyte chemoattractant protein-1 (MCP-1), IL-1β, and IL-6, by modulating the immune response (De Feo et al., 2012). In turn, intra-arterial infusion of MSCs significantly reduced cortical expression of acid-sensing ion channel 1a (ASIC1a) and inflammasome-related proteins in rats exposed to MCAO (Vats et al., 2021).

Post-stroke, endogenous neurogenesis is markedly influenced by microglial cells. A seminal investigation by Lalancette-Hébert et al. (2007) provided initial evidence for the pro-neurogenic role of proliferating microglia after ischemic brain injury (Lalancette-Hébert et al., 2007). Quiescent microglia within the neural niche secrete neurotrophic factors, including IGF-1, which are essential for the proliferation and viability of nascent neurons (Zhu et al., 2018). Activated microglia can also modulate neurogenesis through a process known as bipolar polarization (Kim et al., 2015). It was reported that injecting mouse NPCs into MCAO mice increases the density of $CD11b^+$ microglia in the striatum (Capone et al., 2007). Meanwhile, intracerebral injection of induced NSCs directly reprogrammed from murine fibroblasts into areas affected by traumatic brain injury decreased the density of inflammatory (M1-like; $TNF\text{-}\alpha^+/IBA1^+$) microglia while increasing the density of microglia involved in trophic neuroprotection ($IGF1^+/IBA1^+$) in mice (Gao et al., 2017). Therefore, the implantation of exogenous stem cells can indirectly influence the proliferation and survival of endogenous stem cells by modulating microglial activity.

Common Targets for Endogenous and Exogenous Stem Cells

Endogenous and exogenous stem cells share similarities in various regulatory mechanisms; thus, certain drugs and treatments can stimulate both types of cells. In this section, we will discuss research progress related to the injection of stem cells in combination with various drugs, exosomes, and hydrogels. When drugs or exosomes are transplanted alongside stem cells into the brain, they can simultaneously promote both endogenous neuroregeneration and regulate the proliferation and differentiation of the implanted stem cells. In turn, hydrogels not only serve as scaffolds for stem cell engraftment, but provide also mechanical support for the differentiation of endogenous stem cells and the establishment of functional neural circuits.

Co-administration of pharmaceuticals and stem cells

As mentioned, the recruitment of NPCs to the site of ischemic injury is facilitated by BDNF. Atorvastatin, an HMG-CoA reductase inhibitor, promotes BDNF expression and intensifies the migration of cells in the SVZ (Chen et al., 2005). The concomitant administration of BMSCs with sodium ferulate and n-butylidenephthalate, two plant-derived compounds, markedly enhanced neurogenesis in a post-stroke setting by increasing the expression of VEGF and BDNF, as well as by activating the AKT/mTOR signaling pathway (Zhang et al., 2016). Intravenous administration of salvianolic acid, the most abundant and bioactive water-soluble compound in *Salvia miltiorrhiza*, facilitates the proliferation of endogenous stem cells, elevates the population of viable newborn neurons within the SVZ, and enhances neurological functional recovery in MCAO mice. The proposed mechanism was the activation of the Sonic hedgehog-Patched-Gli (Shh-Ptch-Gli) signaling cascade in the infarct region, leading to robust synthesis of BDNF and NGF (Zhang et al., 2017). The administration of cystamine, an organic disulfide derived from oxidative dimerization of cysteamine, has been observed to significantly amplify the proliferative capacity and plasticity of NPCs in the post-stroke environment, an effect mediated through the BDNF/TrkB signaling axis (Li et al., 2015). The above organic compounds target common pathways in both endogenous and exogenous stem cells, suggesting their potential advantages when combined with stem cell therapies. An intriguing study has elucidated that p53-mediated apoptosis is a primary pathway for the demise of dopaminergic neurons characteristic of Parkinson's disease, with the TNF-α/NF-κB signaling pathway acting as a proximal trigger in this process. Administration of the TNF-α inhibitor adalimumab enhanced the survival rate of transplanted dopaminergic neurons in mouse models of Parkinson's disease,

resulting in extensive neural reinnervation and functional recovery. Although this research was not conducted in a stroke model, the approach of pharmacologically inhibiting apoptosis in grafts is novel and suggests that adalimumab could potentially inhibit the death of endogenous NSCs through a similar mechanism (Kim et al., 2024).

Co-administration of exosomes and stem cells

Exosomes serve as a means of non-contact communication among cells. These membrane-bound vesicles, ranging from 40 nm to 160 nm in diameter, are released from cells through the endosomal pathway. Exosomes contain a diverse array of components, including nucleic acids, proteins, lipids, and metabolites. The unique composition and proportions of these constituents reflect the characteristics of the cells from which the exosomes originate. For example, exosomes derived from stem cells are believed to possess therapeutic potential similar to that of directly transplanted stem cells (Andreotti et al., 2019). Due to their simple structure, inability to self-replicate within the body, and ease of sterilization and long-term storage, exosomes are particularly well-suited for clinical applications. Currently, ultracentrifugation is the most commonly used method for isolating exosomes in laboratories. However, research is ongoing to explore exosome extraction techniques based on larger-scale stem cell culture and membrane separation technologies (Sun et al., 2021b).

Evidence has been accumulating regarding the use of exosomes to enhance neurological recovery following IS. Liu and colleagues reported that administration of BMSC-derived exosomes reduced infarct volume and improved neurological function in MCAO mice through activation of the IL-33/suppressor of tumorigenicity 2 (ST2) axis (Liu et al., 2023). Enticingly, through specific modifications exosomes can be transformed into vehicles for drug delivery. For instance, Tian and colleagues utilized biochemical methods to conjugate exosomes with cyclo Arg-Gly-Asp-D-Tyr-Lys ([c(RGDyK)]), a peptide with high affinity to integrin αvβ3, and loaded them with the natural polyphenol curcumin. In a MCAO mouse model, the exosomes thus modified specifically targeted the ischemic area, resulting in the attenuation of both the inflammatory response and cellular apoptosis (Tian et al., 2018).

Since stem cell–derived exosomes carry molecular components which favor, through autocrine signaling, the growth and survival of stem cells. Hence, co-injection of exogenous stem cells along with their exosomes can further enhance the efficacy of stem cell transplantation. Zhang et al. (2023) reported that intracerebral co-injection of iPSC-derived NSCs along with their exosomes facilitated the repair and functional rehabilitation of infarcted brain tissue, enhanced the differentiation of engrafted NSCs within the infarct zone, reduced oxidative stress and inflammation, and mitigated the formation of glial scar tissue in mice subjected to MCAO/R (Zhang et al., 2023).

Hydrogels for stem cell delivery

Direct injection of stem cells in suspension into brain tissue often results in low cell survival rates. This may be due to cell leakage along the needle track or significant post-implantation cell death caused by mechanical stimulation or the local inflammatory environment. Therefore, providing a more stable mechanical and physiological environment for the implanted stem cells is crucial to enhance their survival following implantation.

In recent years, injectable hydrogel scaffolds have shown great potential to stimulate endogenous tissue regeneration. Hydrogels are a class of biomaterials composed of water-soluble polymer networks, which include natural components such as fibrin and alginate as well as synthetic substances like poly(ethylene glycol). These materials are highly hydrated and can be engineered to incorporate a variety of biophysical and biochemical features. Moreover, they can be designed for minimally invasive injection using syringes and catheters (Burdick et al., 2016). Additionally, hydrogels can serve as carriers for stem cells and exosomes and as sources of growth factors and nanomaterials, thereby exerting synergistic effects (Jiang et al., 2023).

In vitro three-dimensional stem cell culture systems based on hydrogels have demonstrated the capability to produce large quantities of clinical-grade stem cells and to direct stem cells to differentiate into complex neural networks, indicating a favorable compatibility between hydrogels and stem cells (Moxon et al., 2019; Poorna et al., 2021; Yin and Cao, 2021). Thus, the injection of a mixture of stem cells and hydrogels into brain tissue is also considered to have significant therapeutic potential.

When combined with therapeutic agents, hydrogels can provide a more favorable survival environment for stem cells, extending beyond merely providing mechanical support. Studies have shown that incorporating growth factors such as BDNF and GDNF into peptide-based scaffolds can promote the differentiation and integration of neurons *in vivo* (Somaa et al., 2017; Nisbet et al., 2018; Rodriguez et al., 2018). Injectable hydrogels that combine hyaluronic acid and methylcellulose have been utilized to deliver mouse NSCs to the brains of mice with endothelin-1 (Et-1) induced stroke. The NSCs interact with hyaluronic acid and methylcellulose via surface CD44, leading to a more widespread distribution throughout the injection site, improved cell survival, and significant motor recovery (Ballios et al., 2015). In stroke-affected mice, the deployment of exogenous adipose-derived stem cells in conjunction with hyaluronic acid-based biomaterial scaffolds resulted in a marked enhancement of neuroblast, glial, and endothelial cell proliferation within the SVZ. Furthermore, this therapeutic approach facilitated the migration of proliferating cells to the site of damage (Sanchez-Rojas et al., 2019).

The incorporation of myoglobin into hydrogels can provide an oxygen-rich environment for stem cells until endogenous angiogenesis occurs. This modification was shown to enhance the survival and differentiation of NSCs into mature neurons, with extensive innervation from endogenous cells observed within the hydrogel after implantation in mice. This indicates that sustained oxygen release promotes the long-term survival and integration of transplanted stem cells and assists in the regeneration of endogenous nerves (Wang et al., 2023). In turn, notable advancements have been made in the design of conductive polymer hydrogels for biosensor applications, tissue engineering and regeneration, and drug delivery. The application of electrical stimulation to human iPSC-derived NPCs immobilized within polypyrrole hydrogels results in the modulation of genes implicated in metabolic pathways and NPC proliferation, leading also to the upregulation of neurotrophic factors that are crucial for neuroregeneration, synaptic rearrangement, and cellular viability (Song et al., 2019).

By providing mechanical and trophic support to stem cells, hydrogel formulations pose great promise for stem cell-based therapies for stroke and many other conditions.

Limitations

This review shows some limitations. Most of the information reviewed corresponds to preclinical research, which demonstrated the plausibility of using SCT to stimulate neuroregeneration after stroke. In contrast, safety and at best, limited efficacy, with no conclusive evidence of neuroregeneration, were reported in the few clinical trials that evaluated SCT for stroke patients (Kalladka et al., 2016; Boese et al., 2018; Berlet et al., 2021; Cha et al., 2024; Panos et al., 2024). Consequently, caution must be practiced when drawing inferences about the translatability of basic research on SCT for stroke to the clinical setting. In addition, there is currently no consensus on the source, route of administration, dosage, and timing of intervention for SCT applied to stroke. Because these factors arguably contribute to differences in the impact of exogenous stem cells on endogenous neuroregeneration processes across different models, research conclusions should be interpreted within the context of the corresponding experimental design. Lastly, due to space constraints, we have focused our attention on research dealing with post-stroke neuroregeneration, and did not discuss in detail the complex effects of exogenous stem cells on processes such as post-stroke angiogenesis, immune infiltration, and axonal reconstruction, which need to be further dissected to optimize their clinical application.

Conclusions

Exogenous stem cells may directly enhance the proliferation of endogenous NSCs through the secretion of growth factors and exosomes and via intercellular contact. They can also recruit stem cells from neurogenic niches to the infarct area by establishing biobridges. Furthermore, SCT can promote neuroregeneration by modifying the microenvironment through immunomodulatory and angiogenic effects. Given the convergence of regulatory pathways and the necessity for a supportive microenvironment for exogenous and endogenous stem cells, we propose three strategies for synergistic stem cell transplantation therapies aimed at enhancing the therapeutic efficacy of both cell types. First, co-administering various growth factors and pharmacological agents alongside stem cell transplantation may help mitigate stem cell apoptosis. Second, the simultaneous injection of exosomes and stem cells can potentiate beneficial paracrine effects. Lastly,

combining stem cells with hydrogels can provide a protective scaffold for the exogenous cells while promoting the regeneration of neural tissue and the reconstitution of neural circuits. Hydrogels, as excellent biocompatible carriers, can also aid the delivery of oxygen and drugs, and promote NSC differentiation and survival through electrical stimulation. Therefore, it is conceivable that in the future, engineered hydrogels that have been pre-loaded with stem cells and combinations of drugs and exosomes may emerge as a clinically significant solution. The unique ability of hydrogels to simultaneously enhance endogenous repair and facilitate the integration of exogenous stem cells into neural circuits holds great promise for advancing therapeutic strategies.

Author contributions: *Manuscript conceptualization: RG, RW, XB; original draft: RG, YW; manuscript review and editing: XB, JW; funding acquisition: XB, RW; supervision: XB, RW; visualization: RG, YW; approval of final manuscript: all authors.*
Conflicts of interest: *The authors declare no completing interests.*
Data availability statement: *Not applicable.*

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C-Editor: Zhao M; S-Editors: Wang J, Li CH; L-Editor: Song LP; T-Editor: Jia Y