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Efficacy of stem cell-based therapies for stroke

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Abstract

Stroke remains a prevalent disease with limited treatment options. Available treatments offer little in the way of enhancing neurogenesis and recovery. Because of the limitations of available treatments, new therapies for stroke are needed. Stem cell-based therapies for stroke offer promise because of their potential to provide neurorestorative benefits. Stem cell-based therapies aim to promote neurogenesis and replacement of lost neurons or protect surviving neurons in order to improve neurological recovery. The mechanism through which stem cell treatments mediate their therapeutic effect is largely dependent on the type of stem cell and route of administration. Neural stem cells have been shown in pre-clinical and clinical trials to promote functional recovery when used in intracerebral transplantations. The therapeutic effects of neural stem cells have been attributed to their formation of new neurons and promotion of neuroregeneration. Bone marrow stem cells (BMSC) and mesenchymal stem cells (MSC) have been shown to enhance neurogenesis in pre-clinical models in intracerebral transplantations, but lack clinical evidence to support this therapeutic approach in patients and appear to be less effective than neural stem cells. Intravenous and intra-arterial administration of BMSC and MSC have shown more promise, where their effects are largely mediated through neuroprotective mechanisms. The immune system has been implicated in exacerbating initial damage caused by stroke, and BMSC and MSC have demonstrated immunomodulatory properties capable of dampening post-stroke inflammation and potentially improving recovery. While still in development, stem cell therapies may yield new treatments for stroke which can improve neurological recovery.

Keywords

Stroke; Inflammation; Neuroregeneration; Stem cell; Mesenchymal stem cell; Neural stem cell

1. Introduction

In the 1600's Jacob Wepfer provided the first insights into the cause of strokes, observing evidence of blood flow obstruction in the brains of cadavers that had a history of stroke-like symptoms. Since then advances in medicine have elucidated different types of stroke as well

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as their underlying mechanisms (Paciaroni and Bogousslavsky, 2008). Although our understanding of stroke has come a long way since its description by Wepfer, stroke remains a prevalent disease with a high incidence rate, poor prognosis, and few treatment options. The United States experiences approximately 795,000 S per year, more than a stroke-per-minute, including 165,000 recurring strokes. Of these 795,000S, 28.7% ultimately lead to mortality. The vast majority of strokes are ischemic, accounting for 87% of all strokes, with intracranial and subarachnoid hemorrhages accounting for the remaining 10% and 3% respectively (Benjamin et al., 2017).

Initial treatment of stroke varies based on type. Ischemic strokes, if caught within three hours of stroke symptom onset, may be treated with intravenous injection of tissue plasminogen activator (tPA) which can break down clots and restore blood flow (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). Alternative surgical procedures may be used to remove the clot or enhance delivery of tPA but require dedicated stroke teams. Both tPA administration and surgical intervention have a limited window for efficacy and act to prevent additional damage, contributing little to neurorestoration (Doberstein et al., 2017; Prince et al., 2013). Hemorrhagic strokes are limited to surgical interventions, which are often of necessity. Surgical intervention for hemorrhagic stroke aims to relieve intracranial pressure caused by bleeding and to eliminate aneurysms or defective blood vessels to minimize risk of additional strokes (Morgenstern et al., 2010).

Because current treatments for ischemic and hemorrhagic strokes are restricted by their narrow time window and lack of regenerative benefits, new treatments for stroke are needed to overcome these obstacles (Doberstein et al., 2017; Morgenstern et al., 2010). Stem cell-based therapies for stroke offer a promising avenue because of their potential to address the unmet needs of stroke patients, providing neuroprotective and regenerative benefits (Mahla, 2016), as well as expanding the window and availability of treatment.

The benefits of stem cell therapies for stroke can be broadly defined as neuroregenerative, alleviating the loss of neurons due to stroke or mediating their replacement (Chena et al., 2001; Iihoshi et al., 2004; Ishibashi et al., 2004; Wang et al., 2018), and neuroprotective, acting in the acute phase of stroke to limit the spread of damage (Nan et al., 2016). While neuroregenerative and neuroprotective effects are not mutually exclusive, treatments have typically focused on harnessing one of these effects, with neuroregeneration-based treatments predominating preclinical and clinical trials (Chen et al., 2016; Detante et al., 2017; Lees et al., 2012). Additionally, although stroke is a disease of the vasculature, it induces a significant immune response. The immune response is linked to healing, but also includes a neuroinflammatory component implicated in exacerbating the initial injury through destruction of neuronal tissue (Rayasam et al., 2018). Some stem cell populations have demonstrated the ability to modulate the immune system, and offer the promise of neuroprotective and neuroregenerative effects, enhancing the healing effects while mitigating inflammatory damage (Wislet-Gendebien et al., 2005; Caplan and Correa 2011).

Efforts using stem cells to treat stroke have been categorized into overarching cell types including neural stem cells, bone marrow stem cells, and mesenchymal stem cells (which overlap with bone marrow stem cells).

2. Neural stem cells

The foundation for neural stem cell therapies was based on the observation that neural progenitor cells (NPC) derived from the neural plate of early mouse embryos contributed to neuronal cell formation when transplanted into adult mouse brains (Uchida et al., 1995). The potential for these NPC to contribute to neuronal cell formation prompted investigation into whether neural progenitor transplants could be used for treating neurodegenerative diseases, including stroke (Fukunaga et al., 1999). Experiments in rats demonstrated that rat NPC, derived from the mesencephalic neural plate, could form electrically active and functioning neurons when transplanted directly into the brain (Auerbach et al., 2000). In rat models of ischemic stroke, NPC transplants improved Morris water maze performance and enhanced angiogenesis at the site of transplantation, suggesting NPC transplants improved cognitive function and recovery following stroke (Fukunaga et al., 1999). Expanding on the work in rats, efforts interrogating human NPC (hNPC) showed that neurospheres derived from human fetus forebrain could be expanded *in vitro* and transplanted into a focal ischemia model of Mongolian gerbils to improve neurological outcomes (Ishibashi et al., 2004).

Experiments using hNPC in rat ischemic models provided further support for the use of hNPC transplants to treat stroke. In a study following the fate of hNPC transplanted into the brains of rat ischemic models, hNPC were found to differentiate into neurons, oligodendrocytes, and astrocytes. Analysis of graft-derived neuronal cells, using immuno-electron microscopy and electrophysiological recording, demonstrated connectivity, showing hNPC could form functioning neurons which contributed to improved recovery from stroke in rats (Daadi et al., 2009). In addition to contributing new neurons, the therapeutic effects of NPC transplants have also been tied to the secretion of angiogenic and neurotrophic factors (Olle and Zaal, 2011). hNPC engineered to overexpress endovascular growth hormone have been shown to enhance angiogenesis and improve engraftment survival, leading to improved functional recovery in a mouse stroke model and implicating hNPC secreted factors in promoting endogenous repair (Lee et al., 2007).

Based on the preclinical success of hNPC transplants for treatment of stroke, Pollock et al. worked to generate a stable cell line under GMP conditions and produced the immortalized hNPC line CTX0E03 (Pollock et al., 2006). In murine models, CTX0E03 demonstrated the ability to survive transplantation into the brains of ischemic rats and induce angiogenesis, neurogenesis, behavioral improvement, and reduce infarct volume (Smith et al., 2012; Stroemer et al., 2009). Following its success in ischemic rat models, the CTX0E03 line progressed to clinical trials. PISCES I (phase 1) first demonstrated the safety of CTX0E03 DP (the CTX0303 drug product) in humans, where intracerebral transplantation of up to 20 million cells was tolerable, without adverse effects. Additionally, following transplantation, patients demonstrated improvements in NIH Stroke Scores, the summed arm and leg Ashworth scale, and Barthel Index scores, suggesting CTX0303 DP transplants improved functional neurological recovery (Kalladka et al., 2016). PISCES II (phase 2) has since been

completed, and PISCES III (phase 3) is now underway investigating the efficacy of CTX0E03 DP. In addition to the PISCES series, a phase 1 clinical trial using transplants of the neural stem cell line NSI-561 to treat ischemic stroke is underway based off the success of a previous clinical trial using NSI-561 transplants to treat amyotrophic lateral sclerosis (Glass et al., 2012).

While embryonic tissue has been the primary source of hNPC, efforts are also under way to use induced pluripotent stem cells to generate hNPC. In rat models of stroke, induced human neural progenitor cells (ihNPC) have been shown to form functional neurons and improve recovery following stroke (Oki et al., 2012). Recently, Tornero et al. demonstrated that neurons derived from hiNPC grafts received direct synaptic inputs from host neurons in patterns similar to corresponding endogenous neurons in the intact brain, suggesting hiNPC contribute to functional recovery from stroke through direct contribution of new neurons (Tornero et al., 2017). The success of hiNPC in preclinical treatments of murine stroke models provides support for the idea of patient-specific NPC therapies for treatment of stroke in the clinic.

3. Bone marrow stem cells

Similar to NPC, bone marrow stem cells (BMSC) were investigated for use in stroke therapies because of the discovery that BMSC could differentiate into neural and glial cells *in vitro* (Brazelton et al., 2000). Later *in vivo* studies demonstrated that BMSC, following intracerebral transplantation in rat stroke models, could migrate to the site of ischemic brain injury and differentiate into neural cells which was linked to improved recovery (Chena et al., 2001). Additional in vivo studies explored the migratory capabilities of BMSC and showed that BMSC administered intra-arterially (IA) and intravenously (IV) could migrate to the brain as well (Iihoshi et al., 2004; Li et al., 2001a,b). In rat stroke models both IA and IV administration of BMSC led to greater functional recovery, attributed to the accumulation of BMSC at the site of ischemic (Iihoshi et al. 2004; Li et al., 2001a,b). While initially investigated for their potential to contribute new neurons, additional work has largely shown BMSC do not contribute therapeutic benefits through neuronal replacement. Instead, BMSC have been shown to secrete factors which promote neurogenesis and suppress inflammation, enhancing endogenous recovery. In mouse models of stroke, BMSC have been shown to migrate to ischemic conditions where they in turn upregulate production of neurotrophins and growth factors which are associated with neurorestoration and the observed therapeutic benefits (Qu et al., 2007). BMSC engineered to overexpress neurotrophic factors have also been shown to enhance recovery, supporting the role of BMSC-derived factors as the primary mechanism of therapeutic benefit (Horita et al., 2006).

Building on the success of preclinical models, over a dozen clinical trials using BMSC for treatment of stroke are now underway or have been completed. BMSC therapies using IA or IV administration predominate the clinical trials, which is likely a reflection of their safety and less rigorous technical requirements when compared to intracerebral transplantations. Three published phase I clinical trials have investigated the safety of BMSC administered to treat stroke IA. In one study two out of ten patients suffered isolated partial seizures at the three month follow up and were put on antiepileptics. No seizures were reported following

the initial event, however patients were only followed six months after treatment (Francisco et al., 2012). The other two studies did not report any major adverse events (Friedrich et al., 2012; Battistella et al., 2010), and IA administration of BMSC across the published phase I studies was not shown to induce additional strokes, tumor formation, or death (Francisco et al., 2012; Friedrich et al., 2012; Battistella et al., 2010). A phase II study found similar results, demonstrating the safety of IA administration of BMSC (Savitz et al., 2019). While phase I and II trials have demonstrated reasonable safety of IA administration of BMSC, significant improvements to neurological recovery have not been observed (Francisco et al., 2012; Friedrich et al., 2012; Battistella et al., 2010; Savitz et al., 2019).

The safety and feasibility of IV BMSC administration for treatment of stroke has been evaluated in two phase I and one phase II published studies. Similar to IA administration, IV administration was safe. Studies of IV administration yielded no treatment-related adverse events, however, similar to the results of IA studies, improvements to neurological outcomes were not observed or lacked significance (Savitz et al., 2011; Prasad et al., 2012; Kameshwar et al., 2014). Although animal stroke models showed improvements following IA or IV administration of BMSC, the same results have yet to be seen in human patients.

The differences between animal models and patient outcomes may be due to differences in timing of BMSC administration. Pre-clinical studies which demonstrated improved neurological outcomes with BMSC treatment often administered BMSC IA or IV within three days of stroke (Iihoshi et al., 2004; Li et al., 2001a,b; Brenneman et al., 2010). A time-course study of BMSC administration in rats with ischemic strokes showed that neurological improvement did not occur when treatment was started after seven days (De Vasconcelos et al., 2009). In clinical trials, time of collection and reinfusion of autologous BMSC varied between trials. While no trials reached significant neurological improvement across their patient groups, trials which noted some improvements among patients started treatment within seven days (Friedrich et al., 2012; Savitz et al., 2011; Prasad et al., 2012).

Preceding clinical trials for stroke, BMSC were used in clinical trials to treat ischemic heart disease, whose success has influenced the design of clinical trials targeting stroke (Savitz et al., 2011). However, pre-clinical and clinical results from BMSC treatments for myocardial infarction suggest a window for intervention that may not mirror stroke. A meta-analysis examining clinical trials of BMSC treatment following myocardial infarction showed significant improvements to cardiac function with a median intervention time of ten days post-infarction (Abdel-Latif et al., 2007). Pre-clinical models of ischemic heart disease treated with BMSC have also demonstrated improvements to cardiac function with intervention occurring at fourteen days post-myocardial infarction (Jiang et al., 2008; Ji et al., 2013). BMSC treatment for stroke, when administered IA or IV, may be effective in an acute setting, shorter than that found in treating ischemic heart disease. The results from pre-clinical and clinical trials suggest a window for intervention to treat stroke with IV or IA BMSC administration, while potentially longer than available treatments, may be limited to only a few days post-stroke. While time restrictive, rapid collection and administration of BMSC has been proven feasible, with a phase I study using IV administration of BMSC to treat patients within 24–72 h of stroke onset (Friedrich et al., 2012).

While preclinical and clinical studies have shed light on the importance of BMSC administration timing, fewer studies have explored the state of bone marrow during collection and whether this affects therapeutic outcomes. Denes et al. 2011 first showed that ischemic stroke in mice induces activation of bone marrow leukocytes (Denes et al., 2011). Building upon this, Yang et al. (2012) investigated whether changes to the bone marrow induced by stroke affected the properties of BMSC, including their therapeutic effect when used as treatment for stroke. BMSC administered IA that were harvested one day post-stroke demonstrated greater improvements to recovery and reduced lesion size compared to BMSC harvested one day pre-stroke. This benefit was attributed to increased levels of cytokines with anti-apoptotic, pro-angiogenic, pro-neurogenic, and immunomodulatory factors found in BMSC harvested post-stroke (Yang et al., 2012). More recent work has shown that stroke induces proliferation and differentiation in the bone marrow of rats, skewed towards the myeloid lineage, with a peak at 4 days following stroke. The skew towards the myeloid lineage includes increased production of inflammatory monocytes, neutrophils, and their progenitors (Courties et al., 2015). Although it was shown in rats that BMSC harvested 1 day post-stroke were more therapeutically effective than those from 1 day pre-stroke (Yang et al., 2012), it is unclear if BMSC harvested at a later time following stroke would be more or less efficacious. The transient shift in the bone marrow towards an inflammatory profile may alter the therapeutic effects of BMSC. While demonstrating that post-stroke BMSC are more effective than pre-stroke BMSC bodes well for clinical application, the transient nature of changes to the bone marrow following stroke may necessitate harvesting within a short time frame if BMSC are to be captured which recapitulate for human patients the neurorestorative properties observed in preclinical studies.

While IV and IA administration have garnered more clinical trials, additional routes for BMSC transplantation have been explored. Similar to trials using NSC, BMSC have been transplanted directly into the brain. A phase I study collected and transplanted BMSC into the perilesional region of patients who had a stroke between one and ten years prior to admission for therapy. Patients tolerated doses of BMSC up to 55 million cells, displaying no major adverse events, and demonstrated improved neurological outcomes albeit in a small sample size (n = 5) (Suárez-Monteagudo et al., 2009). Another route studied for administering BMSC is intrathecal transplantation. In a phase I trial, 24 patients with chronic stroke (between 4 and 144 months since diagnosis) received intrathecal injections of BMSC into the L4-L5 lumbar space. Improvements for several patients were seen in ambulation, hand control, and balance, without any reported adverse events (Sharma et al., 2014). While results from studies using IA and IV administration of BMSC suggest there may be a restricted time window for therapeutic benefits, intracerebral and intrathecal transplantations appear to have a broader window for applicable clinical benefit.

Other stem cells derived from bone marrow include multipotent adult progenitor cells (MAPCs). MAPC exhibit properties similar to pluripotent stem cells (Jiang et al., 2002). Direct injection of MAPCs into the peri-infarct regions of the rat brain following ischemic brain injury resulted in restoration of limb movement (Zhao et al., 2002). Intravenous injections of MAPCs administered during the acute period following ischemic brain injury also resulted in improved motor and neurological function (Yasuhara et al., 2008). In a Phase 2 study MAPCs have been evaluated for treatment of ischemic stroke (Hess et al., 2017). In

this trial MAPCs were administered intravenously at two doses (400 million or 1200 million) between 24 and 48 h after symptom onset, and compared with placebo controls. No dose-limiting toxicities were observed, however, no significant improvement in neurological outcomes were observed at 90 days post therapy.

4. Mesenchymal stem cells

Mesenchymal stem cells (MSC) were investigated for therapeutic application towards stroke because of their multilineage differentiation potential, including neuronal-like cells (Wislet-Gendebien et al., 2005), and their ability to induce immunomodulatory and trophic effects (Caplan and Correa 2011). *In vivo* studies showed that MSC injected into the periphery preferentially migrated towards areas of damage (Li et al., 2001a,b), which in ischemic injury models correlated with improved recovery (Li et al., 2001a,b; Sarmah et al., 2018). In studies of murine stroke models, MSC treatments demonstrated the ability to increase axonal density around the ischemic lesion, contributing to axonal remodeling and correlating with improved functional recovery (Li et al., 2005; Shen et al., 2006; Liu et al., 2007). The therapeutic effects of MSC treatment were attributed to the secretion of factors which reduce levels of axonal growth inhibitors and promoted growth and neurogenesis (Shen et al., 2006, 2008).

MSC while first found in bone marrow have now been identified from multiple different tissue sources including adipose tissue and umbilical cord blood (Wang et al., 2018). Classification of MSC remains a challenge because of their heterogeneous nature and variance attributed to their tissue source method of isolation and culture technique (when expanded *ex vivo*) (Galipeau and Sensebe 2018). These discrepancies may be responsible for differences amongst preclinical and clinical trials and must be overcome if MSC therapeutic application is to be scaled up to meet clinical demands To date multiple phase III trials have been completed using MSC for various diseases, although not for stroke, and have demonstrated a robust safety profile with transient febrile reactions as the only MSC-infusion associated event (Lalu et al., 2012). Phase I studies for treatment of stroke have similarly demonstrated the safety of ex vivo expanded MSC when administered IV (Bang et al., 2005; Honmou et al., 2011). Efforts to evaluate the efficacy of MSC treatment for stroke have shown modest or absent therapeutic effects. A clinical trial in South Korea tested IV administration of two separate doses of *ex vivo* expanded autologous MSC with a median intervention time of 40 and 54 days (dose one and two) following the onset of stroke symptoms. Recipients of MSC demonstrated neurological improvements immediately following IV MSC administration, but improvements declined overtime indicating MCS may elicit a transient effect. Patients who received MSC did however have greater overall survival when compared to the control group of stroke patients who received only the standard of care, suggesting there may be separate short and long-term therapeutic effects. The researchers noted however that their results were limited by the small sample size, 16 MSC beneficiaries and 36 controls, and the lack of patient blinding (Lee et al., 2010). In another phase II trial 67 patients received allogeneic MSC 24–48 h post-stroke symptom onset and were followed and compared to 62 placebo patients over the course of a year. Treatment with MSC was shown to be well tolerated and associated with a short-term

decrease in circulating T-cells and inflammatory cytokines. However, no improvements to neurological outcomes were noted when compared to the placebo group (Hess et al., 2017).

MSC and BMSC-based cell therapies administered peripherally as treatment for stroke have demonstrated very limited success in ameliorating ischemic brain injury when compared to preclinical models (Chen et al., 2016; Detante et al., 2017; Lees et al., 2012). The predominant challenges to MSC and BMSC-based therapies appear to be timing of therapy administration and in the case of autologous therapies when to harvest patient cells. Collecting and administering autologous cells with the desired phenotype for each stroke patient is difficult to scale in order to address the large number of stroke patients and variety of resources available to different health care teams (Hourd et al., 2014). An allogeneic “off the shelf” cell-based therapy would better meet the timing demands of intervention for stroke. Allogeneic MSC therapies have proven safe but have shown limited efficacy decreasing measurable inflammatory markers but failing to induce improvements patients could notice (Hess et al., 2017). MSC are relatively heterogeneous as noted earlier and different MSC derivatives may prove more effective

5. Umbilical cord blood

Human umbilical cord blood (hUCB) contain MSC and has been shown to exhibit strong immunomodulatory factors. hUCB was first shown to partially rescue behavioral deficits in ischemic rat models (Jieli et al., 2001). Following the induction of ischemic stroke in rats, intravenously administered hUCB preferentially migrated to the site of ischemic injury and treatment with hUCB was associated with reduced lesion volume (Vendrame et al., 2004). Although neuronal-like human cells were found in ischemic rat models treated with hUCB, they were few in number, suggesting hUCB mediated therapeutic effects through trophic factors and cytokines, rather than cell replacement (Jieli et al., 2001; Vendrame et al., 2004).

hUCB contains multiple different cell types, and work investigating the restorative properties of the different cells comprising hUCB led to the isolation of a unique MSC population implicated in the observed therapeutic benefits. This MSC population exhibited properties of self-renewal, but lacked cell surface markers characteristic of hematopoietic stem cells and were classified as non-hematopoietic umbilical cord blood stem cells (nh-UCBSC). In rat stroke models nh-UCBSC demonstrated the ability to reduce lesion volume and ameliorate behavioral deficits, similar to the effects seen with hUCB, but with the additional capacity for in *vitro* expansion (Xiao et al., 2005).

Investigation into the therapeutic properties of nh-UCBSC revealed that there were significant changes to the immune system following treatment with nh-UCBSC. Following stroke, there is an increase in migration of inflammatory macrophages to the brain. Elevated levels of T cells, NK cells, and neutrophils are also observed in the brain following ischemic injury, and microglia populations are skewed towards an activated, inflammatory phenotype. While the initial immune response is implicated in the healing process, the prolonged inflammatory state induced by stroke is associated with worse outcomes. In rats with ischemic stroke, treatment with nh-UCBSC led to a reduction in the number of inflammatory macrophages and microglia in the brain and returned elevated levels of T-cells,

NK cells, and neutrophils to pre-stroke levels. Reduction in levels of inflammatory immune cells was associated with improved neurological function in rats, which suggests that by dampening post-stroke inflammation nh-UCBSC may alleviate exacerbation of the initial injury and promote recovery (Nan et al., 2016; Shiao et al., 2019). In addition to its anti-inflammatory properties and capacity for *in vitro* expansion, UCBSC and hUCB have been shown to be immunologically tolerant, making them readily applicable as an allogeneic cell therapy (Kim and Broxmeyer, 2011).

To date a single phase I trial has investigated hUCB for treatment of stroke. hUCB was infused IV in 10 male patients three to nine days post-onset of stroke symptoms. Patients were followed for 12 months and showed no adverse events related to treatment, and by three months all patients had demonstrated improvements to neurological recovery (Laskowitz et al., 2018). While the sample size remains small, hUCB-derived cell therapies for stroke may offer the most applicable neuro-protective benefits because they have the potential to be readily available to meet the critical window for intervention, are immune tolerant, and demonstrate robust immunomodulatory properties (Nan et al., 2016; Kim and Broxmeyer, 2011; Laskowitz et al., 2018; Shiao et al., 2019).

6. Conclusions

Better treatments for stroke remain a pressing, unmet need. Evolving evidence highlights the potential for stem cell therapies to treat stroke, but also demonstrate the challenges that must be overcome to achieve a consistent, efficacious treatment for patients. NSC transplanted intracerebrally have demonstrated a robust safety profile. Pending the results of the phase three clinical trial, PISCES III, intracerebral NSC transplants may offer an avenue for neuroregeneration through direct replacement of lost neurons, and when compared to other stem cell therapies, may provide the longest window for therapeutic intervention (Kalladka et al., 2016). BMSC treatment of stroke has proven safe, but otherwise ineffective in clinical trials. MSC have similarly proven safe but demonstrated limited improvements for patients. MSC, however, are a heterogenous population, and more recently identified types, such as UCBSC, may prove to be more effective (Nan et al., 2016; Shiao et al., 2019). Additionally, because MSC can be expanded in culture, they may be modified to enhance therapeutic efficacy and prepared in advance as an allogenic therapy, more readily meeting the window for efficacious therapeutic intervention (Hess et al., 2017). Although still in need of exploration, stem cell treatments for stroke may offer ways to protect an replace neurons in order to improve outcomes for stroke patients.

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HIGHLIGHTS

- Stem cell-based therapies promote neurogenesis and protect surviving neurons.
- Neural stem cells promote functional recovery after intracerebral transplantations.
- BMSC and MSC exhibit immunomodulatory properties.
- BMSC and MSC can reduce post-stroke neuroinflammation.