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A possible new focus for stroke treatment – migrating stem cells

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Abstract

Introduction—Stroke is a leading cause of mortality in the US. More so, its infliction often leaves patients with lasting morbidity and deficits. Ischemic stroke comprises nearly 90% of incidents and the majority of medical treatment aims at reestablishing perfusion and preventing recurrence.

Areas covered—Long-term options for neurorestoration are limited by the infancy of their innovative approach. Accumulating evidence suggests the therapeutic potential of stem cells in neurorestoration, however, proper stem cell migration remains a challenge in translating stem cell therapy from the laboratory to the clinic. In this paper, we propose the role that exogenous stem cell transplantation may serve in facilitating the migration of endogenous stem cells to the site of injury, an idea termed 'biobridge'.

Expert opinion—Recent research in the field of traumatic brain injury has provided a foundational understanding that, through the use of exogenous stem cells, native tissue architecture may be manipulated by proteinases to allow better communication between the endogenous sites of neural stem cells and the regions of injury. There is still much to be learned about these mechanisms, though it is the devastating nature of stroke that necessitates continued research into the prospective therapeutic potential of this novel approach.

Keywords

Biobridge; neural repair; neural stem cells; stem cell migration; stem cells; stroke

1. Introduction to the etiology of stroke

On average, an American dies every 4 min from a stroke, equating to nearly 130,000 persons annually [1]. More staggering, nearly six times as many people will suffer from a

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stroke each year, with three-fourths being their first incident [1]. This totals almost 40 billion dollars in cost including health care, medications, and missed work. Stroke is currently the fourth leading cause of death, with two-thirds of hospitalizations being individuals older than 65 years of age [2]. Despite the progression in our understanding of etiology, risk factors, and current treatments, these statistics remain astonishing, unacceptable even. Still, with advancements in preventative medicine, neuroimaging, and medical intervention, we must continue our search for better management. In this paper we will begin by defining strokes, discuss conventional treatment, and then describe the current stem cell literature while exposing the gaps in our knowledge that necessitate further research.

Stroke is classified into two categories: hemorrhagic and ischemic. Hemorrhagic stroke is due to the rupture of vasculature that leads to bleeding. This bleeding can be divided into two main subtypes, an intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH). ICH occurs directly into the brain parenchyma and can continue to expand, causing a hematoma [3]. Symptoms of ICH are subsequent to the region of brain matter afflicted. SAH arises from the rupture of vascular malformations, including aneurysms. Patients often present with severe headache, often described as the worst headache of their life [4,5]. Even with aggressive treatment subsequent complications, such as vasospasm, can threaten a patient's recovery [6–8].

Ischemic stroke accounts for 87% of all strokes [1] and is secondary to hypoperfusion, embolism, or thrombus formation. When one of these preceding events occurs, brain tissue distal to the site of occlusion is deprived of blood and oxygen, leading to injury. Hypoperfusion is often a systemic issue resulting from reduced cardiac output [9,10]. These ischemic strokes are seen in the watershed areas of the brain, regions in which blood supply is provided by the distal ends of two arteries, causing the tissue to be exceptionally susceptible to decreases in blood perfusion. Embolisms occur when dislodged particles of debris travel to occlude vasculature. These events are often secondary to blood clots that are cardiac in origin [11]. Thrombus is similar to an embolism in that a clot obstructs the vessel, however, this clot forms at the site in injury [12]. There are many small vessel pathologies that predispose patients to such an event [13].

2. Conventional treatment of stroke

The toolbox for the treatment of stroke is expansive, with many options often predicated on patient variables. Management can be medical, surgical, or both. The American Heart Association and American Stroke Association frequently release guidelines for ICH and SAH that give consideration to the most current literature [14,15]. These guidelines universally emphasize the urgency and critical nature of hemorrhagic strokes with continuous monitoring in a critical care unit translating to improved patient outcomes [16].

Treatment of ischemic stroke may also include medical and/or surgical intervention. Many of the medical treatments aim at the prevention of causation or reoccurrence of factors leading to an ischemic event, namely attempting to prohibit clot formation. Antithrombotic therapy such as aspirin and anticoagulation, lipid lowering agents such as statins, blood

pressure control, blood sugar control, and smoking cessation are many of the methods utilized to decrease incidence rates [17–21]. However, once an ischemic stroke occurs, the goal changes from prevention to reperfusion. To this end, the medical mainstay is thrombolysis, typically with tissue plasminogen activator. The literature continues to further evaluate the potential for its use outside of the traditional 3-h window (extended to 4.5 h in the last few years), but the consensus remains that the use of thrombolytic therapy improves patient outcomes [22–24]. The use of IV thrombolysis, however, is limited to a narrow spectrum of patients due to the brief window in which symptomatic patients must present for intervention as well as the numerous contraindications to its use which include uncontrolled hypertension, previous intracranial hemorrhage, head trauma, or previous MI or stroke 3 months prior, to name a few.

Although thrombolysis demonstrates reconstitution of blood flow, ischemic injury may persist, contributing to substantial patient morbidity. This is where major gaps remain in the medical management for patients. After a stroke, we offer patients risk factor reduction, largely because our ability to facilitate endogenous brain repair remains limited. It is here, in this gap, where stem cell research provides encouraging intervention. As research continues, the literature substantiates the role that stem cells, endogenous and exogenous, autologous and allogeneic, may have in neural repair, which can extend beyond the acute stages of stroke. In this paper will continue with our discussion of stem cell sources, their benefits in cerebrovascular injury, and then shed light on the current limitations with particular interest in the targeting of endogenous stem cells to the site of injury.

3. Translational potential for stem cells in stroke

The potential for stem cell therapy in cerebral vascular disease has gained traction within neuroscience research. Whether endogenous, recruited from neurogenic niches, or recruited from the peripheral circulation, stem cells ameliorate the consequences of cerebrovascular events, especially ischemia. These ideas have prompted investigations into the role of many stem cell niches including, but not limited to, endogenous neural stem cells (NSCs) and the potential use of bone marrow (BM) as a source for transplantation. Here, we focus heavily on the BM-derived stem cells because of the long safety record supporting their use in treating hematological diseases, and with the extensive literature extending their use in neurological diseases. In particular, their ability to mobilize in response to neurological injury, and the availability and ease by which they may be harvested are a few of their appealing transplantable stem cell features. However, it should be noted that these sources, and stem cells, are not without limitations. Concerns include immunogenicity of allogeneic transplantation, stem cell migration, cell survival, and tumorigenesis.

BM constituents are a heterogeneous population of cells, some of which include: hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and very small embryonic-like stem cells (VSELs). Following a cerebrovascular injury, these cells mobilize to the blood and respond with the secretion of growth factors [25] and possible further cell line differentiation [26].

3.1 Hematopoietic stem cells

HSCs are a mesoderm-derived cell line that can differentiate into both myeloid and lymphoid lineages. These cells can be isolated from umbilical blood, peripheral blood (PB), and BM. HSCs, in response to the chemoattractant stromal cell-derived factor 1 (SDF-1) via the CXCR4 receptor, transverse the BM into the PB [27,28] where they may serve an integral role in early host repair mechanisms. The SDF-1/CXCR4 is expressed in the brain endothelium. Thus, with regards to stroke, it has been evidenced that functional recovery correlates with the extent of PB immature hematopoietic CD34+ mobilization [29]. Furthermore, HSCs serve as a favorable source for stem cell therapy due to their safety and efficacy profile [30].

3.2 Mesenchymal stem cells

MSCs are also a mesoderm-derived cell line that can further differentiate into adipocytes, chondrocytes, osteocytes, and muscle. These cells can be isolated from additional tissues such as umbilical cord (Wharton's jelly), umbilical cord blood, and placenta. MSCs have also demonstrated functional recovery in ischemic stroke. Similar to HSCs, the SDF-1/CXCR4 pathway serves as a homing signal for MSCs. Hypoxia-responsive transcription factor hypoxia inducible factor 1 regulates the expression of SDF-1, thus a hypoxia gradient provides a signal for MSC attraction [31]. Mechanisms of mesenchymal transplantation currently favor the idea of a microenvironment furnished by trophic factors such as: hepatocyte growth factor, VEGF, nerve growth factor, brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor, and insulin growth factor 1. It is the influence of these factors on the site of injury that is thought to elicit endogenous repair [32]. Because transplanted MSCs do not differentiate into neurons, it is postulated that their role may include the recruitment of endogenous NSCs [32], as will be discussed in a later section. Furthermore, MSCs are noted to influence native immunomodulatory function, in which the microenvironment may suppress local inflammatory response [33].

3.3 Endothelial progenitor cells

EPCs are in peripheral circulation and serve to differentiate into endothelium, cells that constitute the inner layer of blood vessels. These cells are responsible for vasculogenesis and the repair of damaged blood vessels. EPCs have been isolated from regions of neovascularization in ischemic brain tissue following transplantation after stroke, thus making them great candidates to repair endothelium [34]. Because of their role in vascular stability, EPCs have been proposed as a biomarker for clinical outcome, suggesting the number of EPCs in PB following a stroke may inversely correlate with the degree of functional impairment. This research is being carried a step further to assess the role of endogenous EPCs in risk factors for stroke.

3.4 Very small embryonic-like stem cells

VSELs are epiblast-derived stem cells [35] and therefore have been considered great candidates for tissue rejuvenation and regeneration. VSELs are found in BM and can give rise to HSCs, thus, these cells are thought to be deposited in organs and tissues during early gastrulation and may serve to keep other stem cell sources replete [36]. In ischemic stroke,

VSELs are mobilized into PB and express increased levels of pluripotent stem cell markers as well as early cardiac (GATA-4, Nkx2.5/Csx), neural (GFAP, nestin, β-III-tubulin, Olig1, Olig2, Sox2, and Musashi), and endothelial lineage markers (VE-cadherin, von Willebrand factor) [37]. Much like the aforementioned stem cells, VSELs are also present in the PB. Because of their availability and ability to influence other stem cells, they could be harvested, proliferated, and then transplanted for therapeutic purposes.

3.5 Neural stem cells

Up to this point the stem cells that we have discussed are present outside of the brain and circulate within the blood, gaining access to the site of injury. This is where we diverge to discuss a seemingly obvious option for stroke therapy, endogenous NSCs. Endogenous stem cells are located in the subgranular zone (SGZ) of the dentate gyrus (DG) and the subventricular zone (SVZ). These NSCs are close in proximity, but still must be recruited to the ischemic site of injury. Chemokine signals such as SDF-1 (discussed above), VEGF, and angiopoietin are released from the ischemic tissue to influence the course of NSCs along blood vessels to reach the site of injury [38–41]. Once localized to the peri-infarct, endogenous stem cell survival is minimal [42–44], supporting the hypothesis that these cells influence repair rather than differentiating for neuronal replacement. The potential role of NSCs in stroke rehabilitation is paramount and the remainder of this paper will explore the limitations associated with cell migration, with respect to all of the cell lines discussed, as described by the ability to ‘bridge the gap’ between stem cell location and the site of injury.

4. Gaps in knowledge: Proper stem cell migration

Although some degree of spontaneous functional recovery may occur in certain stroke patients, the majority often suffer from significant disability and reduced quality of life. Restoration of blood flow through the delivery of thrombolytic medications has produced notable benefits, however, its clinical utility remains limited to a narrow spectrum of stroke patients. As a result of this lack of definitive treatments, cell-based therapies are gaining momentum as a possible modality to enhance brain reorganization and repair following ischemic injury. A distinct advantage of cell-based therapies is their unique ability to respond dynamically to complex and highly variable environments within the stroked brain. Furthermore, the efficacy of cell-based therapies is no longer based solely on a tissue replacement paradigm; potential benefits now extend to include effects on inflammation, immunomodulation, and enhancement of endogenous repair mechanisms. Currently, cell-based therapies for the treatment of stroke are stratified into two general categories, either endogenous stem cell induction or exogenous stem cell transplantation.

One approach to the use of cell-based therapies focuses on recruitment of endogenous neural stem/precursor cells (NSPCs) from within the neurogenic niche to the site of ischemic injury. In the adult brain, NSPCs are located primarily in two specific locations: the SVZ of the lateral ventricles and the SGZ located in the DG of the hippocampus. Under normal physiologic conditions, adult NSPCs predominantly produce neurons, interneurons of the olfactory bulb for SVZ-derived cells, and dentate granule cell neurons for SGZ-derived cells. It has been shown that these endogenous neural progenitor cells in the rat brain normally participate in long distance migration of 3–8 mm from the SVZ along the rostral

medial stream into the olfactory bulb [45]. Following ischemic neural injury, these same progenitor cells have been observed *in vivo* to migrate up to 4 mm into the peri-infarct cortex, which may correlate with a distance of several centimeters in the adult human brain [46–48]. However, for many cells, the long journey from the neurogenic niche in the SVZ across the white matter tracts of the corpus callosum into the gray matter of the injured neocortex is a perilous process ultimately resulting in their demise. Persistent limitations in the form of the transient nature of the migratory response, low cell survival, and poor functional integration into damaged circuitry continue to curb the success of these endogenous stem cell responses.

Strategies to overcome the limitations of post-stroke endogenous neurogenesis have sought the use of extrinsic growth factors, like erythropoietin, G-CSF, BDNF, glial cell-derived neurotrophic factor, and delivery of specific molecules, such as statins and fluoxetine [49–54]. Although these factors and specific molecules proved to be effective in increasing the proliferation of endogenous stem cells, the overall number and survival rates of neurons produced from these proliferative cells were extremely low [42,55]. Specific features of the disease pathology may contribute to the reduced ability of these newly formed cells from the neurogenic niche to reach the site of injury. Loss of structural integrity of brain tissue through enzymatic degradation as well as breakdown of the blood–brain barrier (BBB) with ensuing cerebral edema contribute to disruption of normal anatomic connections within the brain, posing significant navigational challenges for migrating endogenous cells [56–58]. They should be able to overcome these obstacles and successfully migrate to the ischemic site, newly arrived cells are often met with a hostile hypoxic environment deficient in necessary trophic factors and rife with radical oxygen species which make survival and integration doubtful [59,60]. Reduced neuronal plasticity in the aged brain, the setting in which the majority of strokes occur, may be an additional hurdle limiting the success of endogenous neurogenic responses [61]. As it stands, the main gap in knowledge for endogenous cell therapy for stroke is how to safely bridge the neurogenic site (SVZ) to the remote ischemic brain area in order to direct successful migration, survival, and integration of large numbers of endogenous cells. Indeed, finding ways to ‘bridge the gap’ may help amplify and sustain the endogenous post-stroke neurogenic response and ultimately lead to improved overall functional gains for stroke victims.

In an effort to bridge the gap between the neurogenic and the ischemic site, while enhancing endogenous neurogenic responses to stroke, research attention has focused toward the facilitative role of exogenous stem cell transplantation. As stated earlier, the original concept of direct cell replacement has given way to a more contemporary view of stem cells as sources of neurotrophic factors and modulators of inflammatory responses contributing to an overall environment conducive to restoration and repair. It has been shown that local delivery of stem cells in the CNS allows for large numbers of cells to be administered, which facilitates secretion of high concentrations of growth factors that ultimately promote the endogenous neurogenic response [62]. Once transplanted, several types of exogenous stem cells have been observed to successfully migrate and persist at the site of ischemic injury [63–66]. The mechanisms that govern migration of transplanted stem cells to the ischemic boundary are very similar to those that regulate migration of endogenous cells

from within the neurogenic niche. Migration of exogenous cells is modulated by the interaction of CXCR4 and CCR2 chemokine receptors on stem cells with SDF-1 and CCL2 chemokines secreted by activated neuronal and glial cells within the ischemic lesion [67,68]. Furthermore, once localized to the ischemic cortex exogenous stem cells have been shown to increase endogenous neurogenesis and recruit newly formed cells to the site of injury [69–72].

A key feature supporting the efficacy of exogenous stem cell transplantation may be the ability of exogenous cells to alter the expression of MMPs and extracellular matrix metalloproteinases (ECMs) to create a biobridge between the neurogenic and ischemic sites. Recent work in the setting of traumatic brain injury (TBI) has shown that transplanted exogenous MSCs are able to guide the migration of endogenous cells from the neurogenic site to the area of injury in the cortex via a biobridge paved with MMPs and ECMs [73]. Considering the similarities between the inflammatory and neurogenic responses following both types of brain insults, we advance the notion that transplanted exogenous stem cells may be able to prime endogenous cells toward directed homing over long distances within the stroke brain. As these exogenous cells do not display stroke pathology and may even possess the migratory cues of MMPs and ECMs, they possess great potential in navigating both white and gray matters, scar tissues, and regions of hypoxia/ischemia rampant in stroke brain tissues to pave the way for successful migration of large numbers of endogenous cells.

When contemplating the clinical viability of cell-based therapies for treatment of stroke, especially in the application of exogenous stem cells, a major concern is the safety profile of introducing foreign material into the host brain. The possibility that exogenous cells may differentiate into lineages other than the one that is desired and give rise to ectopic or malignant tissue is of concern as this would pose significant risk to the transplanted patient. Therefore, the mobilization of a patient's own endogenous stem cells for repair of damaged tissue would appear to have a superior safety profile. The unique interplay of exogenous and endogenous stem cells in the novel mechanism outlined above further addresses this safety issue by advancing the concept that exogenous cells do not need to persist over prolonged periods, but merely serve the purpose of migratory cues and temporary conduits to ferry endogenous stem cells from the neurogenic niche to the injured sites. In stroke, once the exogenous stem cells have fulfilled their role as shepherds guiding the host brain cells between the SVZ and the cortex, they are able to give way to the endogenous cells which then persist and integrate into local circuitry at the site of injury. This transient, though meaningful, existence of exogenous cells in the brain may actually be a natural answer to resolving the potential toxic effects associated with graft persistence.

5. Directed cell migration via stem cell biobridges

Based on recent TBI research in rat models, it is likely that mesenchymal stromal cell transplantation may assist in the migration of host cells from the neurogenic niche to the damaged region of the cortex. The MSCs create a channel or 'biobridge' for endogenous cells, which can be seen using immunohistochemistry and laser captured. This biobridge stretches from the neurogenic SVZ to the injured cortex and may be fundamental to the functional benefit observed following transplantation by promoting the relocation of

endogenous stem cells [73,74]. It has been widely accepted that stem cell transplantation confers therapeutic benefit via a combination of direct cell replacement and changes to the microenvironment by means of trophic factor secretion which act on damaged tissue such as that found in the brain following cerebral insult [75,76]. A novel mechanism has been observed in the form of the biobridge, which was initially recognized following modified mesenchymal stromal cell transplantation in adult rat experimental TBI models.

Interestingly, significantly increased concentrations of extracellular MMPs can be identified within the biobridge along the conduit of MSCs. It is thought that the grafted cells aid in the creation of the biobridge using MMP-dense signals. Importantly, upon completion of the biobridge, the MSCs defer the repair process to endogenous neurogenic cells [73]. As the newly generated host cells substitute the grafted cells, the MSCs die, leaving only endogenous cells to maintain the bridge between the SVC and the injured site. This is of great clinical importance due to the risk of unregulated cell proliferation associated with prolonged persistence of exogenous cells in the brain.

This unique mechanism of stem cell repair is distinguished by the development of a permissive environment conducive to axon growth and cell migration. Three months after MSC grafting, the area surrounding the injured cortex displayed improved neural differentiation and cellular proliferation. A steady flow of nestin- and DCX-labeled cells was also observed traversing the corpus callosum from the SVC to the damaged area [73]. In contrast, no significant movement of newly formed endogenous cells was seen in TBI rats that were given the vehicle infusion only.

Notably, this migration observed in the transplanted rats corresponded to a ninefold increase in MMP-9 expression and activity [73]. Experiments that reduced MMP levels resulted in the termination of neurogenic cell migration from the SVZ to the injured cortex [77]. This strongly suggests that MMPs may play an important role in the brain’s recovery following various types of insults. The significant impediment to neurovascular remodeling caused by MMP inhibition endorses the concept of a biobridge, distinguished by high numbers of MMPs and capable of promoting transplant-mediated endogenous cell transfer to the area of damage in addition to supporting the neurovascular unit. However, the precise role of MMPs in biobridge formation merits additional study.

6. Potential application of biobridges in stroke

Following the discovery of the biobridge in a TBI model, we purport that intracerebral stem cell transplantation within a stroke model will result in an analogous conduit from the neurogenic niche to the stroke core, thereby facilitating functional recovery by promoting host cell migration to the area of insult. To this end, the biobridge has the potential to forge a path to the injured tissue and confer notable benefits [78]. Promising sources of appropriate endogenous stem cells include the neurogenic niche of the SVZ and the SGZ of hippocampal DG.

The capacity of the biobridge to encourage cell movement across typically obstructive tissues to an injured area offers great possibility in the area of ischemic injury. A biobridge in this context would be further characterized by the importance of ECMs and MMPs in

stroke pathology and therapeutics [65,79]. Many types of stem cells have displayed the capacity to modify the functions and concentrations of ECMs and MMPs, including those found in PB, umbilical cord blood, and the adult brain [38,80,81]. Immune modulation has been proposed as a possible mechanism of action for the improved functional recovery post-MSC transplantation in stroke [82]. However, the biobridge may provide further assistance in addition to releasing a variety of immunomodulatory and trophic cytokines following transplantation [83]. Future experimental studies will be needed to confirm whether this biobridge does indeed assist in relocation of endogenous stem cells in the stroke setting.

The functional benefit conferred by stem cell transplantation via the biobridge evidences the strong connection between endogenous and exogenous repair mechanisms. The efficacy of the biobridge mechanism of repair in TBI warrants further investigation in other neurological disorders including stroke. If successful, it could open new areas of potential improvement in the regenerative potential and functional effects of stem cell therapy within the brain.

7. Conclusion

Stroke is one of the leading causes of death within the US. Given the current limitations to stroke management, alternative treatment modalities are desperately needed. A novel mechanism in the form of the biobridge has been effectively demonstrated in the TBI model, and may offer great possibility within the area of stroke. Regenerative medicine utilizing cell-based therapies has typically focused on cell replacement and neurotrophic factor secretion. However, the biobridge model would provide a third mechanism of action which is unique in that it does not require exogenous cells to survive for a prolonged period of time. This is beneficial because it circumvents the major issue of graft persistence which is associated with tumorigenicity. Due to the debilitating nature of stroke, the prospect of delivering efficacious cell-based therapy intravenously or intra-arterially is both promising and appealing. Translational studies are necessary to demonstrate the biobridge method in stroke and address the possibility of minimally invasive means for administration. Ultimately, the extension of biobridge application to stroke models has the potential to advance our basic science understanding of cell therapy while offering a safe and effective regenerative medicine approach that combines and maximizes both exogenous and endogenous stem cell therapeutic potential.

8. Expert opinion: From proof-of-concept to translational research on biobridges

Due to the debilitating nature of neurological disorders such as stroke, more feasible routes of transplantation are needed. Current proof-of-concept for the biobridge model involves intracerebral transplantation, however, intra-arterial and intravenous modalities to facilitate biobridge formation should be investigated. The first roadblock to this method is the ability of exogenous cells to cross the BBB. Multiple studies have demonstrated that transplanted MSCs are indeed capable of migrating across the BBB in the presence of injury and inflammation [84–86]. MSCs express several leukocyte homing molecules including cell adhesion molecules (CD44, CD99, integrins $\alpha 4$ and $\beta 1$) and chemokine receptors (CXCR4

and CCR2) which allow them to successfully interact with and traverse the BBB to migrate toward areas of injury within the CNS [87].

A second caveat to the use of peripherally administered stem cells is their capability to migrate to the neurogenic niches and sites of stroke injury within the brain. Recent investigations have shown that grafted cells delivered both intravenously and intra-arterially have the capacity to localize to the site of infarcted tissue [88,89]. Despite significant sequestration in peripheral organs such as liver, lung, and spleen associated with intravenous delivery of cells, a recent meta-analysis of preclinical results suggests robust benefits [90]. Intra-arterial transplantation seems to largely bypass the problem of peripheral sequestration resulting in larger numbers of cells migrating to the area of infarct, and refined techniques have reduced the risk of microembolic infarct due to adherent cell clusters previously associated with this modality [91,92]. The debate continues as to which mode of transplantation is superior but it remains clear that both have shown benefits in reducing infarct size and promoting functional recovery in experimental models of stroke.

Another important aspect of stem cells transplanted outside the brain is their demonstrated capacity for co-localization with endogenous cells. In one study which used a rat model of hypoxic-ischemic brain damage in neonates, stem cells from human umbilical cord blood were transplanted into the peritoneal cavity of the affected rats. This resulted in considerable functional improvement following incorporation of the grafted cells into the lesioned area of the brain [93]. A related study by Chen *et al*. administered umbilical cord blood cells to adult rats intravenously and effectively demonstrated the cells' ability to migrate to areas of the brain affected by stroke [94]. These studies support the co-localization and previously mentioned homing abilities of exogenous cells in the context of peripheral injection and lend further credence to the biobridge model and its potential application as a therapy in the setting of stroke.

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Article highlights

- Gaps in knowledge in stroke pathology and treatment
- Therapeutic potential of stem cell therapy in stroke
- Endogenous neurogenic niches in the brain
- Strategies to overcome the limitations of post-stroke endogenous neurogenesis
- Directed cell migration via exogenous stem cell ‘biobridges’ in the setting of stroke

This box summarizes key points contained in the article.