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Stem Cell-Paved Biobridges Facilitate Stem Transplant and Host Brain Cell Interactions for Stroke Therapy

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Abstract

Distinguished by an infarct core encased within a penumbra, stroke remains a primary source of mortality within the United States. While our scientific knowledge regarding the pathology of stroke continues to improve, clinical treatment options for patients suffering from stroke are extremely limited. Tissue plasminogen activator (tPA) remains the sole FDA-approved drug proven to be helpful following stroke. However, due to the need to administer the drug within 4.5 hours of stroke onset its usefulness is constrained to less than 5% of all patients suffering from ischemic stroke. One experimental therapy for the treatment of stroke involves the utilization of stem cells. Stem cell transplantation has been linked to therapeutic benefit by means of cell replacement and release of growth factors; however the precise means by which this is accomplished has not yet been clearly delineated. Using a traumatic brain injury model, we recently demonstrated the ability of transplanted mesenchymal stromal cells (MSCs) to form a biobridge connecting the area of injury to the neurogenic niche within the brain. We hypothesize that MSCs may also have the capacity to create a similar biobridge following stroke, thereby forming a conduit between the neurogenic niche and the stroke core and peri-infarct area. We propose that this biobridge could assist and promote interaction of host brain cells with transplanted stem cells and offer more opportunities to enhance the effectiveness of stem cell therapy in stroke.

Keywords

ischemia; stem cell therapy; neural repair; mesenchymal stromal cells

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1. Introduction

The therapeutic benefits of stem cells have been demonstrated endogenously [1–4] as well as exogenously within damaged organs [5–11]. Stem cell involvement after organ injury is especially important within regenerative medicine [1–13] as limited clinical trials involving brain disorders have evolved on the basis of laboratory research in this area [14–16]. The predominant opinion regarding the role of stem cells in organ repair suggests that restoration occurs due to either the direct replacement of dying cells with transplanted stem cells or the indirect repair of damaged tissue via the secretion of trophic factors by the stem cells [17, 18]. Our knowledge of the mechanisms behind stem cells' ability to repair the brain remains somewhat lacking despite the evidence of positive effects following transplantation. Recent investigation on TBI in rats revealed an interesting behavior of transplanted stem cells indicating that transplanted MSCs play an integral role in recruiting cells from the neurogenic niche to the injured area within the cortex. This conduit for endogenous cells results in a "biobridge", which has been visualized immunohistochemically and laser captured. This biobridge is located in the region between the neurogenic subventricular zone (SVZ) and the affected cortex, and may play a vital role in the functional benefit of stem cell transplantation by assisting in the directed migration of adequate numbers of endogenous stem cells to the injured cortex [19,20].

The concept of this biobridge demonstrated in TBI can be broadened to other neurodegenerative diseases, including stroke. We explore the prospective benefit of extrapolating biobridge-mediated stem cell therapy into the areas of stroke, Parkinson's disease (PD), and spinal cord injury (SCI).

2. Principles of Stroke

Stroke is the result of the disruption of blood flow to a region within the brain. Its defining pathological characteristic is an area of dead neuronal cells known as the infarct core encased within a zone of injured and dying tissue termed the penumbra. Vessel blockage within the CNS results in cerebral ischemic injury. This cardinal feature of vascular disability associated with ischemic stroke instigates a regional deficiency in glucose and oxygen resulting in the stimulation of intricate pathological pathways and massive neuronal death [21].

In a matter of minutes after infarction, regions with the largest decrease in effective circulation become incurably damaged resulting in necrotic cell death and forming what has been termed as a necrotic core. Cells that are less damaged and still able to maintain their metabolic functions despite suffering functional loss comprise the ischemic penumbra, which surrounds the previously mentioned necrotic core [22].

Sufficient circulation must be re-established in very acute window, preferably less than three hours, in order to prevent the penumbra undergoing necrosis. Evidence suggests that tPA therapy during the initial 4.5 hours following stroke onset may be advantageous, however this particular treatment modality does involve significant risk and is therefore limited in its application [23]. Therapeutic interventions that can be utilized throughout a much larger post-stroke window are necessary and will likely require a more advanced knowledge of the

roles of neurogenesis, angiogenesis, and neuroplasticity in minimizing, reducing, and reversing stroke-related damage.

3. Endogenous Response to Stroke

Neurogenesis in adult mammals is typically thought to be limited to the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) in the dentate gyrus of the hippocampus [24, 25]. Neural stem cells located within these areas do not divide often and yield a range of rapidly dividing neural precursor cells (NPCs) [21]. The characteristics and distinguishing attributes of neural precursor subtypes, their ambient environments, and the synaptic integration of newborn neurons persist as areas of in-depth exploration and study [24]. Neurogenesis within other areas of the CNS is thought to be fairly restricted, though possible in the case of injury [24, 26].

Many forms of brain injury, including ischemic stroke, result in various molecular responses. These molecular-level reactions stimulate neurogenic niches in adults and regulate NPC division, propagation, differentiation, relocation, and survival [21]. NPCs have demonstrated the ability to travel from the SVZ to the post-ischemic striatum in MCAO rat models [27, 28]. The CA1 region of the hippocampus and the cerebral cortex are both areas in which post-ischemic neurogenesis has been detected. Unfortunately, post-mortem analysis of stroke patients has offered no evidence to support the creation of new cortical neurons during the time period of 3 days to 13 years subsequent to stroke onset [29]. Additionally, the highest possible rate of unobserved neurogenesis secondary to ischemia would not be greater than 0.1%, or 1 out of every 1,000 neurons [29]. It is very possible that difficulty relocating the newly developed endogenous cells from their origin within the neurogenic niche all the way to the injured area could severely restrict the extent of endogenous repair and ischemia-related neurogenesis.

4. Formation of a Biobridge

The concept that stem cell transplantation delivers therapeutic benefit by means of direct cell replacement as well as modification of the microenvironment via secretion of trophic factors which act on injured tissue (including the brain) has been demonstrated and largely accepted for some time [17, 18]. Detection of biobridges was first accomplished in experimental TBI models using modified mesenchymal stromal cells (MSCs). Following experimental TBI in adult rats, the MSCs exhibited the ability to construct a biobridge to direct host cells from the neurogenic niche to the injured area [19]. Immunohistochemistry and laser capture assay have made it possible to observe this biobridge, which stretches between the SVZ and the damaged cortex. Elevated levels of extracellular matrix metalloproteinases (MMPs) can be found within the biobridge and are aligned with the trail of grafted MSCs between the SVZ and injured site. MMP-9 in particular is present at high levels within the biobridge, strongly suggesting that this proteinase plays an important role in biobridge formation. This is supported by the known role of MMP-9 in neural progenitor cell migration in response to injury-induced chemokines [30], however experiments to determine the functional effects of varying MMPs (e.g., levels and types) on biobridge formation are warranted.

In this TBI study, the grafted MSCs do not survive long and are eventually substituted by newly generated host cells originating from the biobridge [19]. The transplanted MSCs assist in the biobridge formation by way of MMP-dense signals until the biobridge is complete, at which time the MSCs yield their role to endogenous neurogenic cells [19]. Such biobridge formation appears to facilitate that sufficient quantities of host stem cells successfully hone from the SVZ to the TBI-impacted cortex, and likely to the surrounding peri-impact areas as well. This unique mode of action by grafted stem cells observed in TBI may hold great potential for the treatment of other neurodegenerative conditions. More specifically, the ability to promote cell migration by means of a biobridge to a damaged site across tissues that would normally obstruct cell migration has considerable implications for stem cell therapy for the treatment of stroke [19].

5. Biobridge: Novel Stem Cell Repair Mechanism

A novel stem cell repair mechanism exists in the formation of the biobridge. The formation of a permissive environment for cell migration and axon growth characterizes the biobridge. Enhanced cellular proliferation and neural differentiation in the peri-injured cortical areas along with a solid stream of neuronally-labeled cells (nestin and DCX) migrating across the corpus callosum from the SVZ to the impacted cortex was observed three months post-MSC transplantation [19]. In comparison, TBI rats which only received vehicle infusion, did not display any noteworthy migration of newly formed cells. A 9-fold upregulation of MMP-9 activity and expression [19] directly corresponds to the migration. Similarly, we hypothesize that the transplantation of stem cells following stroke may augment the migration of endogenous cells from the neurogenic niche to the stroke core and damaged tissue. The active role of MMPs and ECMs in stroke pathology [1, 13] and their increasing importance as therapeutic targets further distinguishes this biobridge. A variety of stem cells such as those derived from umbilical cord blood, peripheral blood, and the adult brain, have demonstrated the ability to alter levels and functions of MMPs and ECMs [30–32]. The potential of stem cells to produce similar biobridges in stroke merits additional studies. Studies that inhibited MMPs subsequently halted neurogenic migration from the SVZ to damaged tissues elucidate the importance of MMP in chronic brain injury recovery [33]. A noticeable hindrance in neurovascular remodeling results from this specific inhibition, which supports the notion of a biobridge, characterized by elevated levels of MMP, that reinforces the neurovascular unit and assists in the transplant-mediated host cell migration toward the site of injury. Furthermore, a physiochemical balance between cell deformation and physical tissue constraints, and migration rates governed by the capacity to degrade ECM by proteolytic enzymes, especially MMPs, and integrin- and actomyosin-mediated mechanocoupling dictate cell migration [34].

As a result of a biobridge formation in a TBI model [19], we advance the concept that following intracerebral stem cell transplantation, a similar biobridge formation will occur between the neurogenic niche and site of stroke injury. The function of this biobridge is to allow endogenous stem cells to populate the ischemic stroke brain, contributing to the functional recovery. In order to accomplish that, the biobridge in stroke must lead cells by paving the way towards the damaged tissue resulting in significant benefits [35]. Keeping this in mind, endogenous stem cells from the neurogenic niches of the SVZ and the

subgranular zone of hippocampal dentate gyrus (DG) make great candidates of sources for these host cells.

An enhanced recovery of brain functions following ischemic injury follows the transplantation of MSCs. While the underlying mechanisms are not yet fully understood, immune modulation has been suggested as the mechanism of action [36]. The secretion of transforming growth factor-beta (TGF- β) following transplantation of MSCs has been reported to suppress the propagation of MCP-1, which may attenuate the stroke-induced breakdown in the blood brain barrier [36]. The biobridge may also serve to contribute beneficial effects, as well as secrete a broad repertoire of trophic and immunomodulatory cytokines, referred to as MSC secretome, following MSC transplantation in stroke models [37]. In animal models of stroke via middle cerebral artery occlusion (MCAo), increased level of insulin-like growth factor (IGF)-1 were observed in the brains of transplanted rats, as compared to controls [38]. Intracerebral transplantation of stem cells provided a biological vehicle in increasing the brain supply of exogenous stromal cell derived factor (SDF-1 α), brain derived neurotrophic factor (BDNF), and glial cell-line derived neurotrophic factor (GDNF) [38]. Altogether, these findings suggest an overlap between biobridge formation and secretory function of stem cells in affording therapeutic benefits against stroke.

6. Limitations of the Biobridge Concept

Multiple limitations accompany the biobridge concept in TBI and stroke. There is still a gap in knowledge as to whether this biobridge concept actually facilitates endogenous stem cell migration in stroke. If successful, the much less invasive transplantation approach may be more practical for both TBI and stroke in the clinic as both TBI and stroke occur from debilitating brain insults. Nonetheless, studies confirming whether peripherally transplanted stem cells will form a biobridge are warranted in both TBI and stroke models.

Another drawback to the biobridge formation stems from the severity of brain insult. Since the progression of the disease pathology in TBI and stroke vary, there will be a need for different treatment strategies. Adjusting the timing of therapeutic intervention in order to afford beneficial outcomes is just one of the many factors to consider. Similarly, the non-conductive nature of the brain microenvironment may influence biobridge formation. In the case of severe brain insults or the chronic stage of the disease, it is presumable to expect that a larger extent of dead and dying brain tissue pose as a limiting factor against biobridge formation. In order to evade such non-hospitable environments in severe and chronic disease states of TBI and stroke, transplanting stem cells in a much acute stage to limit the extent of the evolving secondary cell death during the disease progression must be taken into consideration.

While on the subject of secondary cell death processes intrinsic to TBI and stroke, the inflammatory reaction poses as another limitation to stem cell-paved biobridge formation. Contrary to belief, inflammation in the acute stage may actually support the biobridge in the recruitment of endogenous stem cells by providing chemoattractant cues towards the site of injury. Unfortunately, the pro-death inflammatory response persists during the chronic stage,

which may reduce the survival and migration of transplanted and host cells. This thereby negates biobridge formation and the recruitment of stem cells to the site of injury. As previously mentioned, transplanting at an earlier period post-insult may aid in the biobridge formation and may enhance the pro-survival over the pro-death properties of inflammation. Evidently, studies are needed to understand and maximize the therapeutic potential of stem cell biobridges.

7. Conclusion

Every year, about 795,000 Americans experience stroke, as reported by the American Heart Association. From those 795,000 victims, roughly 17% die from the stroke, suggesting that about 1 in every 18 deaths in the US is a result of stroke [39]. Survivors of stroke typically exhibit moderate to severe disability and result in an estimated \$18.8 billion in healthcare costs. This number can be augmented to 34.3 billion if \$15.5 billion is included for lost productivity and premature mortality [40]. Although the stroke mortality rate fell 33.5% from 1996–2006, the cost of healthcare expenses continues to increase dramatically [39].

As a result of the high costs of treatment and significant unmet clinical needs for the treatment of many neurological disorders including TBI, stroke, PD, and SCI, investigations for the discovery of safe and effective therapies are increasingly warranted. Having a multi-pronged regenerative mechanisms including cell replacement and bystander effects [41–44], stem cell-based interventions stand out as the leading potential treatment for CNS diseases. Our recent data [19] indicate that stem cell transplantation promotes the creation of a biobridge that links exogenous and endogenous repair mechanisms towards rescuing the brain against injury and neurodegeneration. If the mechanism of a biobridge for brain repair in the TBI model translates to similar efficacious outcomes in stroke, PD and SCI, new venues in improving the functional effects of cell therapy for brain repair open up.

In conclusion, overlapping regenerative processes involving cell replacement, bystander effects, and the formation of a biobridge may be working cooperatively to provide the therapeutic benefits of stem cell therapy [19]. The functional recovery produced by the creation of a biobridge following transplantation of stem cells highlights an intimate interaction between exogenous and endogenous repair mechanisms. These accompany the regenerative potential of stem cell therapy for treatment of neurological disorders.

References

1. Borlongan CV. Bone marrow stem cell mobilization in stroke: a ‘bonehead’ may be good after all! *Leukemia*. 2011; 25:1674–1686. [PubMed: 21727900]
2. Barha CK, Ishrat T, Epp JR, et al. Progesterone treatment normalizes the levels of cell proliferation and cell death in the dentate gyrus of the hippocampus after traumatic brain injury. *Exp Neurol*. 2011; 231:72–81. [PubMed: 21684276]
3. Jackesliff M, Muller FL, Paik JH, et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature*. 2011; 469:102–106. [PubMed: 21113150]
4. Wang L, Chopp M, Teng H, et al. Tumor necrosis factor α primes cerebral endothelial cells for erythropoietin-induced angiogenesis. *J Cereb Blood Flow Metab*. 2011; 31:640–647. [PubMed: 20700128]

5. Andres RH, Horie N, Slikker W, et al. Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. *Brain*. 2011; 134:1777–1789. [PubMed: 21616972]
6. Liu Z, Li Y, Zhang RL, et al. Bone marrow stromal cells promote skilled motor recovery and enhance contralesional axonal connections after ischemic stroke in adult mice. *Stroke*. 2011; 42:740–744. [PubMed: 21307396]
7. Mazzocchi-Jones D, Döbrössy M, Dunnet SB. Embryonic striatal grafts restore bi-directional synaptic plasticity in a rodent model of Huntington's disease. *Eur J Neurosci*. 2009; 30:2134–2142. [PubMed: 20128850]
8. Lee HS, Bae EJ, Yi SH, et al. Foxa2 and Nurr1 synergistically yield A9 nigral dopamine neurons exhibiting improved differentiation, function, and cell survival. *Stem Cells*. 2010; 28:501–512. [PubMed: 20049900]
9. Hargus G, Cooper O, Deleidi M, et al. Differentiated Parkinson patient-derived induced pluripotent stem cells grow in the adult rodent brain and reduce motor asymmetry in Parkinsonian rats. *Proc Natl Acad Sci U S A*. 2010; 107:15921–15926. [PubMed: 20798034]
10. Yasuda A, Tsuji O, Shibata S, et al. Significance of remyelination by neural stem/progenitor cells transplanted into the injured spinal cord. *Stem Cell*. 2011; 29:1983–1994.
11. Mezey E. The therapeutic potential of bone marrow-derived stem cells. *J Cell Biochem*. 2011; 112:2683–2687. [PubMed: 21678464]
12. Yasuhara T, Matsukawa N, Hara K, et al. Transplantation of human neural stem cells exerts neuroprotection in a rat model of Parkinson's disease. *J Neurosci*. 2006; 26:12497–12511. [PubMed: 17135412]
13. Yasuhara T, Hara K, Maki M, et al. Intravenous grafts recapitulate the neurorestoration afforded by intracerebrally delivered multipotent adult progenitor cells in neonatal hypoxic-ischemic rats. *J Cereb Blood Flow Metab*. 2008; 28:1804–1810. [PubMed: 18594556]
14. Seol HJ, Jin J, Seong DH, et al. Genetically engineered human neural stem cells with rabbit carboxyl esterase can target brain metastasis from breast cancer. *Cancer Lett*. 2011; 311:152–159. [PubMed: 21868150]
15. Yasuhara T, Matsukawa N, Hara K, et al. Notch induced rat and human bone marrow stromal cell grafts reduce ischemic cell loss and ameliorate behavioral deficits in chronic stroke animals. *Stem Cells Dev*. 2009; 18:1501–1514. [PubMed: 19301956]
16. Pollock K, Stroemer P, Patel S, et al. A conditionally immortal clonal stem cell line form human cortical neuroepithelium for the treatment of ischemic stroke. *Exp Neurol*. 2006; 199:143–155. [PubMed: 16464451]
17. Redmond DE, Bjugstad KB, Teng YD, et al. Behavioral improvement in a primate Parkinson's model is associated with multiple homeostatic effects of human neural stem cells. *Proc Natl Acad Sci U S A*. 2007; 104:12175–12180. [PubMed: 17586681]
18. Lee JP, Jeyakumar M, Gonzalez R, et al. Stem cells act through multiple mechanisms to benefit mice with neurodegenerative metabolic disease. *Nat Med*. 2007; 13:439–447. [PubMed: 17351625]
19. Tajiri N, Kaneko Y, Shinozuka K, et al. Stem cell recruitment of newly formed host cells via a successful seduction? Filling the gap between neurogenic niche and injured brain site. *PLoS One*. 2013; 8:e74857. [PubMed: 24023965]
20. Sanai N, Nguyen T, Ihrie RA, et al. Corridors of migrating neurons in the human brain and their decline during infancy. *Nature*. 2011; 478:382–386. [PubMed: 21964341]
21. Merson T, Bourne J. Endogenous neurogenesis following ischaemic brain injury: insights for therapeutic strategies. *Int J Biochem Cell Biol*. 2014; 56:4–19. [PubMed: 25128862]
22. Broughton B, David C. Apoptotic mechanisms after cerebral ischemia. *J Am Heart Assoc*. 2009; 40:e331–e339.
23. Graham G. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003; 34:2847–2850. [PubMed: 14605319]
24. Ming G, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron*. 2011; 70:687–702. [PubMed: 21609825]
25. Gage FH. Mammalian neural stem cells. *Science*. 2000; 287:1433–1438. [PubMed: 10688783]

26. Gould E. How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci.* 2007; 8:481–488. [PubMed: 17514200]
27. Zhang RL, Chopp M, Gregg SR, et al. Patterns and dynamics of subventricular zone neuroblast migration in the ischemic striatum of the adult mouse. *J Cereb Blood Flow Metab.* 2009; 29:1240–1250. [PubMed: 19436318]
28. Yamashita T, Ninomiya M, Hernandez P, et al. Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. *J Neurosci.* 2006; 26:6627–6636. [PubMed: 16775151]
29. Huttner HB, Bergmann O, Salehpour M, et al. The age and genomic integrity of neurons after cortical stroke in humans. *Nat Neurosci.* 2014; 17:801–803. [PubMed: 24747576]
30. Barkho BZ, Munoz AE, Li X, et al. Endogenous matrix metalloproteinase (MMP)-3 and MMP-9 promote the differentiation and migration of adult neural progenitor cells in response to chemokines. *Stem Cells.* 2008; 26:3139–3149. [PubMed: 18818437]
31. Sobrino T, Pérez-Mato M, Brea D, et al. Temporal profile of molecular signatures associated with circulating endothelial progenitor cells in human ischemic stroke. *J Neurosci Res.* 2012; 90:1788–1793. [PubMed: 22513751]
32. Lin CH, Lee HT, Lee SD, et al. Role of HIF-1 α -activated Epac1 on HSC-mediated neuroplasticity in stroke model. *Neurobiol Dis.* 2013; 58C:76–91.
33. Zhao BQ, Wang S, Kim HY, et al. Role of matrix metalloproteinases in delayed cortical responses after stroke. *Nat Med.* 2006; 12:441–445. [PubMed: 16565723]
34. Wolf K, Te Lindert M, Krause M, et al. Physical limits of cell migration: control by ECM space and nuclear deformation and tuning by proteolysis and traction force. *J Cell Biol.* 2013; 201:1069–1084. [PubMed: 23798731]
35. Stone L, Grande A, Low W, et al. Neural Repair and Neuroprotection with Stem Cells in Ischemic Stroke. *Brain Sciences.* 2013; 25:322–333.
36. Yoo SW, Chang DY, Lee HS, et al. Immune following suppression mesenchymal stem cell transplantation in the ischemic brain is mediated by TGF- β . *Neurobiol Dis.* 2013; 58:249–257. [PubMed: 23759293]
37. Jul-Yu H, Hsei-Wei W, Shing-Jyh C, et al. Mesenchymal stem cells from human umbilical cord express preferentially secreted factors related to neuroprotection, neurogenesis, and angiogenesis. *PLoS One.* 2013; 22:8.
38. Drago D, Cossetti C, Iraci N, et al. The stem cell secretome and its role in brain repair. *Biochimie.* 2013; 95:2271–2285. [PubMed: 23827856]
39. Lloyd-Jones D, Adams R, Brown T, et al. Heart Disease and Stroke Statistics 2010 Update: a report from the American Heart Association. *J Am Heart Assoc.* 2010; 2010:e99–e110.
40. Fang J, Shaw K, George M, et al. Prevalence of stroke-United States. *J Am Heart Assoc.* 2012; 2012:228–230.
41. Chiang Y, Morales M, Zhou FC, et al. Fetal intra-nigral ventral mesencephalon and kidney tissue bridge transplantation restores the nigrostriatal dopamine pathway in hemi-parkinsonian rats. *Brain Res.* 2001; 889:200–207. [PubMed: 11166704]
42. Snyder EY, Yoon C, Flax JD. Multipotent neural precursors can differentiate toward replacement of neurons undergoing targeted apoptotic degeneration in adult mouse neocortex. *Proc Natl Acad Sci USA.* 1997; 94:11663–11668.
43. Pastori C, Librizzi L, Breschi GL, et al. Arterially perfused neurosphere-derived cells distribute outside the ischemicore in a model of transient focal ischemia and reperfusion in vitro. *PLoS One.* 3:e2754. [PubMed: 18648648]
44. Acosta SA, Tajiri N, Shinozuka K, et al. Combination therapy of human umbilical cord blood cells and granulocyte colony stimulating factor reduces histopathological and motor impairments in an experimental model of chronic traumatic brain injury. *PLoS One.* 2014; 9:e90953. [PubMed: 24621603]

Highlights

- Therapeutic options for stroke is limited
- Stem cell therapy is an experimental treatment for stroke
- Transplanted stem cells form biobridge in traumatically injured brain
- Biobridge formation may similarly mediate cell therapy in ischemic brain

Figure 1. Stem Cell-Paved Biobridges in Stroke

Panel A: Stem cells that are transplanted into the injured brain forms extracellular matrix between neurogenic site and stroke core and pre-infarct area. **Panel B:** Transplanted stem cells may also secrete extracellular matrix mettaloproteinases which contribute to the formation of biobridge. **Panel C:** Endogenous stem cells from the neurogenic niche migrate towards the stroke lesion site via the stem cell-paved biobridge, and eventually become the major component of this bridge.