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Review

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 h 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.

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Contents

1. Introduction

The therapeutic benefits of stem cells have been demonstrated endogenously (Borlongan, 2011; Barha et al., 2011; Jackeslioff et al., 2011; Wang et al., 2011) as well as exogenously within damaged organs (Andres et al., 2011; Liu et al., 2011; Mazzocchi-Jones et al., 2009; Lee et al., 2010; Hargus et al., 2010; Yasuda et al., 2011; Mezey, 2011). Stem cell involvement after organ injury is especially important within regenerative medicine (Borlongan, 2011; Barha et al., 2011; Jackeslioff et al., 2011; Wang et al., 2011; Andres et al., 2011; Liu et al., 2011; Mazzocchi-Jones et al., 2009; Lee et al., 2010; Hargus et al., 2010; Yasuda et al., 2011; Mezey, 2011; Yasuhara et al., 2006, 2008) as limited clinical trials involving brain disorders have evolved on the basis of laboratory research in this area (Seol et al., 2011; Yasuhara et al., 2009; Pollock et al., 2006). 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 (Redmond et al., 2007; Lee et al., 2007). 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 (Tajiri et al., 2013; Sanai et al., 2011).

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 (Merson and Bourne, 2014).

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 (Broughton and David, 2009).

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 h following stroke onset may be advantageous; however this particular treatment modality does involve significant risk and is therefore limited in its application (Graham, 2003). 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 subventriclular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) in the dentate gyrus of the hippocampus (Ming and Song, 2011; Gage, 2000). Neural stem cells located within these areas do not divide often and yield a range of rapidly dividing neural precursor cells (NPCs) (Merson and Bourne, 2014). 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 (Ming and Song. 2011). Neurogenesis within other areas of the CNS is thought to be fairly restricted, though possible in the case of injury (Ming and Song, 2011; Gould, 2007).

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 (Merson