Mini-Review • DOI: 10.1515/tnsci-2015-0016 • Translational Neuroscience • 6 • 2015 • 162-167

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Translational Neuroscience

TARGETING THE VASCULATURE TO IMPROVE NEURAL PROGENITOR TRANSPLANT SURVIVAL

Justin Hill[1,2,3], John Cave[1,3*]

[1]Burke Medical Research Institute, 785 Mamaroneck Ave, White Plains, NY 10605, USA

[2]Burke Rehabilitation Hospital, 785 Mamaroneck Ave, White Plains, NY 10605, USA

[3]Brain and Mind Research Institute, Weill Cornell Medical College, 1300 York Ave, New York, NY 10605, USA

Received 01 June 2015
accepted 05 August 2015

Abstract

Neural progenitor transplantation is a promising therapeutic option for several neurological diseases and injuries. In nearly all human clinical trials and animal models that have tested this strategy, the low survival rate of progenitors after engraftment remains a significant challenge to overcome. Developing methods to improve the survival rate will reduce the number of cells required for transplant and will likely enhance functional improvements produced by the procedure. Here we briefly review the close relationship between the blood vasculature and neural progenitors in both the embryo and adult nervous system. We also discuss previous studies that have explored the role of the vasculature and hypoxic pre-conditioning in neural transplants. From these studies, we suggest that hypoxic pre-conditioning of a progenitor pool containing both neural and endothelial cells will improve engrafted transplanted neuronal survival rates.

Keywords

• Neural progenitors • Neural stem cells • Transplant vasculature pre-conditioning

Introduction

Neural progenitor transplantation is a promising therapeutic option to improve impaired neurological function resulting from disease or injury. Transplants of progenitors derived from a variety of sources have provided functional improvement in several animal models of neurological diseases and injury, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, traumatic brain injury, stroke and spinal cord injury (for reviews, see [1-7]). Human clinical trials have shown that neural progenitor transplants both are feasible and can provide functional improvement for patients with Parkinson's disease, Huntington's disease or stroke (reviewed in [8-10]).

Implementing neural progenitor transplant strategies into widespread clinical practice, however, requires improvement of several practical issues. Each disease and injury has its own specific concerns, but there are some issues that affect nearly all translational applications of progenitor transplants. One such general problem is the low survival rate of progenitors (regardless of their origins) after engraftment. This is an important issue because many applications require a minimum number of engrafted cells to survive in order to see therapeutic benefit. In Parkinson's disease, for example, significant clinical benefit is estimated to require the survival of at least 100,000 dopaminergic neurons in each hemisphere [11]. Increasing the number of cells transplanted is one solution, but keeping injection volumes minimal is optimal. Thus, improving viability post-transplantation is a more pragmatic approach.

Several issues are thought to underlie the low survival rate of transplanted neural progenitors, including the extracellular matrix into which the transplant is placed, immune-related responses, lack of appropriate trophic factors, oxidative stress, and insufficient integration into the host circuitry [12-15]. A potential factor that has been underexplored is the role of the blood vasculature in the recipient brain. In this paper, we review the close relationship between the blood vasculature and neural progenitors in both the embryo and adult. We also review previous studies that have explored the role of the vascularization and hypoxic pre-conditioning in neural transplants. From these studies, we suggest that hypoxic pre-conditioning of a progenitor pool containing both neural and endothelial cells will improve engrafted transplanted neuron survival rates.

Vasculature and neural progenitor interactions in development and adult neurogenic niches

Angiogenesis and neurogenesis are coordinated during embryonic development. In early brain development (between E8-E10 in the mouse), a perineural vascular plexus envelops the neural tube. In the hindbrain, sprouts from this plexus extend into the neural parenchyma towards the ventricular surface. Upon reaching the subventricular zone (SVZ), these vessels branch at right angles, spread parallel to the ventricular surface and anastomose to form a subventricular vascular plexus (reviewed in [16]). By contrast, the developing telencephalon has two distinct origins of blood vessels (reviewed in [17, 18]). Like the hindbrain, the perineural vascular plexus contributes to the vasculature in the telencephalon by generating sprouts that grow in towards the ventricular surface. Extension of these pial vessels appears to be guided and stabilized by radial glia in the developing cortex [19]. Unique to the developing telencephalon, however, is a set of periventricular vessels

* E-mail: joc2042@med.cornell.edu

that branch off from a vessel within the basal ganglia primordium. These vessels expand in a lattice pattern as they grow in a ventral-to-dorsal direction. The spatial migratory pattern of endothelial cells responsible for this growth parallels migration pattern of cortical interneuron progenitors, although the endothelial cell the migration pattern preceeds that of the interneuron progenitors by about a day [17]. This coordination of angiogenic and neurogenic programs is regulated by the shared expression of transcription factors (including Nkx2.1, Dlx1/2 and Pax6) in both endothelial and interneuron progenitor cells. As the periventricular vessel network expands, capillaries from this network anastomose with pial vessels descending from the cortical plate. This nascent cortical vasculature network makes frequent contact, and is stabilized by interactions, with radial glia [20, 21].

The close association of the blood vasculature and neural progenitors is maintained in the neurogenic niches of the adult brain. In the hippocampus, neural stem cells within the subgranular zone are adjacent to a bed of endothelial cells that is active with angiogenesis and vascular remodeling (reviewed in [22]). Neural stem cell processes directly contact the blood vessels within this endothelial layer and growth factors secreted by this vasculature, including vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF1), are associated with increased neural progenitor proliferation rates [23-26].

In the neurogenic niche of the adult SVZ within the walls of lateral ventricles, both neural stem cells and transit-amplifying cells have processes that contact the surrounding blood vasculature plexus [27]. These cells contact the vasculature at sites lacking pericytes, enabling exposure to small molecules circulating in the blood as well as factors secreted by endothelial cells that alter progenitor proliferation rates [18, 28]. In addition, adenosine triphosphate (ATP) released by neural stem cells regulates capillary blood flow in the SVZ [29]. Neuronal progenitors generated in the adult SVZ tangentially migrate to the olfactory bulb in the rostral migratory stream in glial tubes that use blood vessels running parallel to the rostral-caudal axis stream as a scaffold [30, 31]. Formation of this vascular scaffolding develops postnatally and is directed by VEGF-expressing astrocytes [32]. Once in the main olfactory bulb, neuroblasts radially migrate without the assistance of glial tubes along blood vessels to their final position where they differentiate [33].

Interactions between endogenous neural progenitors and the vasculature in the pathological adult brain

With the exception of some specialized regions (such as the pineal gland and area postrema), mature neurons in the adult brain are only indirectly connected to the blood vasculature through interactions with astrocytes. Nutrients and metabolic byproducts are transported through astrocytes and exchanged with the blood supply by perivascular endfeet of astrocytes that contact the vasculature. This metabolic support mediated by astrocytes is also essential for oligodendrocytes. In addition, the interaction between astrocytes and the vasculature can regulate blood flow in response to neuronal activity (reviewed in [34]).

Many pathological conditions are associated with significant changes to the interactions between the mature neural circuits and the vasculature in the adult brain. For stroke and traumatic brain injury, there is physical damage and cell death associated with both the neural and vascular components that induces several vascular and neural repair programs [35, 36]. Animal models of Parkinson's and Huntington's disease also indicate that alterations in the brain vasculature accompany neurodegeneration [37, 38].

One of the most dramatic responses to injury from stroke in the adult brain is an increase in neural progenitor proliferation within the SVZ neurogenic niche and the re-routing of neuroblasts away from the olfactory bulb and towards the site of injury. The brain vasculature is instrumental in directing this neurogenic response (reviewed in [28, 39]). The induction of angiogenesis as well as the release of growth factors, chemokines and other signaling molecules at the injury site both stimulate progenitor proliferation and attract migrating neuroblasts. Blood vessels serve as the scaffold that migrating neural progenitors follow to the injury site. The SVZ produces progenitors that migrate towards the injury site for many weeks following the stroke, but very few of these progenitors successfully differentiate, integrate and survive at the injury site [40-42].

Targeting the vasculature to improve transplanted progenitor survival

The poor survival of endogenously generated progenitors is similar to the fate of transplanted exogenous progenitors. In both situations, the poor survival of progenitors may result, at least in part, from the inability of the host vasculature in the target region to sustain the sudden and large influx of cells. Animal studies with solid tissue allographs have shown that donor tissue vessels will anastomose with the host brain vasculature, but this process requires several days [43]. These studies also showed that transplants of combined neuronal and glial cell suspensions are vascularized by the host more rapidly than the solid tissue allographs, but this process still requires at least a day. As many studies of stroke have shown, however, an inadequate supply of oxygen and nutrients for minutes can be sufficient to induce neural cell death. Thus, the delay between engraftment of progenitors and vascularization is likely to be lethal for many progenitor cells.

These observations strongly suggest that increasing the rate of vascularization in the target area will improve survival of transplanted neural progenitors. Several studies have shown that some neural progenitors have the capacity to transdifferentiate into cells with vascular phenotypes [44-46]. This differentiation occurs independently of cell fusion and facilitates concurrent angiogenesis and neurogenesis in the pathological region. Interestingly, recent studies indicate that this transdifferentiation may work both ways. These studies showed that following ischemia, brain vascular pericytes differentiate into both neural and vascular lineage cells [47, 48]. Together, these studies suggest that neural and vascular components have some capacity to facilitate regeneration of each other. This endogenous capacity, however, is modest and not sufficient to either provide significant repair following catastrophic injury or support an influx of neural progenitors introduced by transplantation.

One strategy to accelerate the rate of vascularization in the target area is to co-transplant endothelial cells. Co-transplantation of cortically derived injury-induced progenitors and endothelial cells into the cortex of post-stroke mice showed a significant improvement in progenitor survival and neuronal differentiation when compared to transplants without endothelial cells [49]. Similarly, studies using a rat model of transient cerebral artery occlusion showed that co-transplantation of fetal neural progenitor cells and embryonic vascular progenitor cells provided more efficient improvements in neurobehavioral deficits and attenuated the infarct volume [50]. The findings in both studies indicate that reconstruction of the neurovascular unit by integrating endothelial lineage cells with neural progenitors can provide superior functional recovery, particularly in treating stroke.

An alternative strategy is to administer factors that stimulate angiogenesis. Addition of growth factors, such as VEGF, to the transplant media only provides a short, temporary angiogenic stimulus. To achieve sustained elevation in angiogenic signals, genetically modified neural progenitor cells constitutively expressing VEGF have been tested [51, 52]. These studies showed enhancement of both vascularization and long-term survival of the engrafted cells. Studies with a rat model of transient focal cerebral ischemia showed a significant functional recovery of motor function when compared to control animals receiving unmodified neural progenitors [53]. The improvement in both progenitor survival and functional recovery is not limited to VEGF. Co-transplantation of neural progenitors with cells constitutively expressing either basic fibroblast growth factor (bFGF) or glial cell-derived neurotrophic factor (GDNF) increased both survival of progenitor and functional recovery in rodent models of Parkinson's disease [54, 55]. Whether bFGF or GDNF improved the vasculature within the transplant, however, was not addressed. An alternative cell-based approach is to use non-neural cell types, such as mesenchymal stem cells or mononuclear cells derived from bone marrow, which can stimulate angiogenesis when transplanted into the nervous system under pathological conditions [56-59]. Although the mechanisms of action are not clearly established, these cell types can significantly increase levels of several growth factors, such as VEGF, GDNF and BDNF, both in and around the injured area. These increased growth factor levels are associated with improved functional outcomes and increased neural progenitor proliferation as well as new capillary formation.

Pre-conditioning improves survival of progenitor transplants

A previously recognized challenge for the survival of transplanted neural progenitors is that they are typically cultured in media at atmospheric oxygen levels (20%), but oxygen levels in the brain range from 0.1-5% [60, 61]. This drastic change in oxygen tension leads to substantial metabolic stress, and *in vitro* modeling with neural progenitor cultures has demonstrated that this stress results in a substantial level of cell death [62]. Hypoxic pre-conditioning prior to transplantation, however, improves survival following transplantation [63, 64]. This improved survival with transient hypoxia results from the activation of several pro-survival pathways, such as the hypoxia-inducible factor-1 (HIF-1) neuroprotection pathway [65]. Alternatively, pre-conditioning cells with either interleukin-6 (IL-6) or minocycline also enhances neural progenitor survival following transplantation by improving their tolerance to oxidative stress [66, 67]. IL-6 exposure activates the signal transducer and activator of transcription 3/superoxide dismutase 2 (STAT3/SOD2) pathway, whereas minocycline upregulates expression of nuclear factor (erythroid derived-2)-like factor 2 (Nrf2) and its downstream target genes. Together, these studies indicate that pre-conditioning is an effective strategy for improving progenitor survival for time between transplantation and their integration into the host vasculature.

Additional benefits to enhancing vascularization of transplant target areas

Functional improvement resulting from progenitor cell transplants requires the successful integration of progenitors into the host neural network, and the vasculature is likely to be influential for both the formation and maintenance of these connections. Stroke studies have shown that proximity to functioning vasculature strongly influences dendritic spine density and the ability to generate new spines [68-70]. The dependence on the distance to vasculature for dendritic spine density following hypoxic insults is also strongly modified by neurological activity levels during postnatal development [71]. Furthermore, since synapses account for the major proportion of energy expenditures in all neurons [72], enhancing vascularization within transplant target regions should promote integration of progenitors into the host neural network by providing metabolic support for synapse formation and maintenance.

For most cell transplant strategies, migration away from the delivery needle track enables the engrafted cells to innervate a larger volume of the host target region and is expected to provide more positive functional outcomes. As noted previously, migrating endogenous neural progenitors in both the embryo and adult rely on the vasculature to guide their migration. Thus, enhancing vasculature formation within transplant target areas may also facilitate dispersal of exogenous progenitors away from the needle track and enhance innervation of the target area.

For some pathological conditions, such as traumatic brain injury and spinal cord injury, the formation of a glial scar presents a challenge for transplanted progenitors to provide functional improvement by impeding axonal growth and progenitor migration [73, 74]. Glial scars, however, also affect the surrounding vasculature. Analyses of the rat vascular architecture of spinal cord lesions have shown that the number of vessels at the lesion margin decreases immediately following injury, but returns to normal in the subsequent weeks [75]. By contrast, the number of vessels at the lesion center increases immediately following injury, but the number of vessels declines substantially over the next several weeks as a cavity is formed. A surprising finding in these studies was that the vessels in the lesion zone were devoid of astrocytes. The reasons for this absence of astrocytes have not been established, but they are likely

to contribute to the inability to restore the neural cytoarchitectonics following injury. Interestingly, studies in the rat cortex have shown that transplanted immature type-1 cortical astrocytes, but not mature astrocytes, associate with the host blood vessels and prevent glial scar formation [76]. These findings suggest that co-transplantation with astrocyte progenitors may be an essential component of cell transplant strategies in order to rebuild the neuro-vascular architecture in and around glial scars.

Conclusions

Both development and homeostasis of the nervous system are tightly linked with the vascular system. This close association, however, has not been routinely exploited in the development of transplant strategies for neurological disease and injury. Based on the studies discussed above, we propose that combining hypoxic pre-conditioning with co-transplantation with both endothelial and astroglial progenitors can improve neuronal progenitor survival. The addition of endothelial progenitors should provide an adequate reserve of cells for initiating and sustaining angiogenesis, which is particularly important for brains of older adults where angiogenic plasticity is greatly reduced [77]. The inclusion of astroglial progenitors will facilitate the reestablishment of a functional blood brain barrier to support the survival and synaptic integration of the neuronal progenitors. Hypoxic pre-conditioning of the neural and endothelial progenitor pool prior to transplantation will activate pro-survival pathways that promote survival in the time between engraftment and neovascularization. Alternative pre-conditioning paradigms that activate pro-survival pathways, such as minocycline treatment, may also be sufficient for enhancing survival post-transplantation. The duration of pre-conditioning as well as the relative proportions of neuronal, astroglial and endothelial progenitors will require optimization for each pathological condition. Optimal neuronal progenitor survival for some conditions may also require additional progenitors, such as oligodendrocyte progenitors. Together, we expect that the combination of hypoxic-preconditioning with progenitor pools containing both endothelial and neural progenitors will improve the survival of transplanted neurons, which is likely to be matched by improvements in functional outcome.

Acknowledgements

The authors thank Weill Cornell Medical College Clinical and Translational Science Center, National Institutes of Health (DC008955) and Burke Medical Research Institute for their support.

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