HIGHLIGHTS

The emerging roles of transplanted radial glial cells in regenerating the central nervous system

Scientists conclude that a combination of treatments involving rehabilitation, drug delivery, surgery and cell transplantation are necessary to achieve significant progress in regenerating the injured central nervous system (CNS). The benefits of pluripotent stem cells in neurodegenerative disorders are well recognised (Thompson and Bjorklund, 2015) and cell culture methods have advanced to condition and enrich cells of therapeutic interest, thereby optimising their assimilation into diseased CNS regions. Radial glial cells are a unique cell type that act as both cell progenitors and scaffolds during development, orchestrating many brain and spinal cord formation events. In light of new developments elucidating their precursor and regenerative capacities, we will place a spot light on the transplantation potentials of embryonic stem (ES) cell or cell line derived radial glia and endogenous radial glial cell populations in re-establishing neural connectivity and restoring cell populations following neurodegeneration.

Radial glial cells mediate neural connectivity during development: The proliferating CNS exists as a population of multipotent neural stem cells and progenitor cells arranged as polarized neuroepithelium which ultimately produces all neurons, glia and oligodendrocytes in the adult CNS. The earliest glial progeny of the neuroepithelium are termed radial glial cells, a secondary class of neural progenitor which gives rise to the majority of brain neurons and astrocytes. Radial glia and their subtypes are found throughout the developing CNS and in neurogenic niches in the adult (Barry et al., 2014). They possess an apical - basal polarity which creates the architectural framework for the laminar patterning of migrating neurons (Rakic, 1972). This morphology also facilitates their interaction with axons along a number of axes providing boundaries, conduits and sorting structures in the brain and spinal cord (Norris and Kalil, 1991; Barry et al., 2013). These proliferative and boundary forming functions are especially significant when understanding the developmental defects affecting motor and sensory systems in vertebrates and present multiple therapeutic opportunities for radial glial cell transplantation into the degenerating or injured CNS. Moreover, the roles of radial glia in regenerative neuroscience in amphibians and fish are becoming more widely studied, where it appears they effectively safeguard the mature brain and spinal cord from permanent injury by restoring entire CNS compartments (Becker and Becker, 2015).

Transplantation of ES cells and cell line derived radial glial cells: A major obstacle to functional recovery after mammalian CNS degeneration is the near inability of damaged or dead neurons and glial cells to regenerate and restore synaptic connectivity. However, in recent decade a clearer understanding of the trophic factors, drug treatments, transplantation vectors and tissue scaffolds that promote the survival of neurons and glial cells have benefitted the outcomes of cell replacement therapies. In particular, cell transplantation strategies aim to compensate for CNS defects using endogenous embryonic neurons, grafts of neural tissue or conditioned immortalized neural precursors that may or may not be genetically modified. Recently, increasing attention has been placed on the benefits of transplanting both differentiated and/or pluripotent ES cells. ES cells proliferate extensively (Thomson et al., 1998; Gage, 2000), yet their allogenic transplantation often results in tumour formation. This limitation has resulted in greater interest being placed on pre-differentiated ES cells that are less tumorigenic (Batista et al., 2014). For example, the transplantation of dopaminergic neurons in Parkinson's disease (Shin et al., 2014; Han et al., 2015) and motor neurons in amyotrophic lateral sclerosis (Coatti et al., 2015) have yielded significant functional recovery in humans.

Generating primary radial glial cell cultures generally requires their co-culture with neurons or other brain extracts (Hunter and Hatten, 1995), making them difficult to study in isolation or to prepare pure populations for transplantation. However, cell line derived collections of radial glia and neurons, termed substrate adherent neural aggregates (SENAs), have proven to be an excellent source of neuronally-fated cells and have been successfully transplanted into mouse models of Huntington's disease (Dihne et al., 2006), Parkinson's disease (Cui et al., 2010) and spinal cord injury (Cui et al., 2011), without tumour formation. The majority of cells in these aggregates initially show similarities to *in vivo* cortical radial glial cells, including nestin expression and a propensity to differentiate to neurons in culture (Dihne et al., 2006). However, their identity as true radial glial cells that recapitulate their *in vivo* counterparts is debatable. Notwithstanding the phenotypic consistency of SENAs, an isolated human neural stem cell line termed SD56, expressing vimentin, nestin and 3CB2 (markers of early appearing radial glia (Prada et al., 1995)) showed extensive migration without tumorigenesis around a striatal ischaemic lesion in the rat, significantly improving the independent use of the stroke impaired forelimb (Daadi et al., 2008).

Perhaps a more accurate paradigm of radial glial cell transplantation is the C6 glioma derived radial glia-like cell line C6-R. C6-R cells show a bipolar morphology *in vitro* and support neuronal migration, while expressing markers typical of *in vivo* radial glia including vimentin, nestin, glial fibrillary acidic protein (GFAP) and RC1 (Friedlander et al., 1998). These cells integrate well into the developing forebrain and are capable of adopting the typical radial glial apical - basal polarity without forming tumours over time. They also infiltrated into the adult forebrain and spinal cord white matter after implantation, where they supported the migration of co-implanted primary neurons in the healthy and lesioned cortex, corpus callosum and hippocampus (Hormigo et al., 2001a, b). While their potential in brain injury is clear, C6-R cells formed tumours when implanted into the contused spinal cord (Hasegawa and Grumet, 2003), rendering them impractical in spinal cord injury. However, a similar clone RG3.6 produces radial glial cells that express brain lipid binding protein (BLBP), glutamate aspartate transporter and vimentin, which are markers of mature radial glia in the brain and spinal cord, are bipolar and migrate extensively through the spinal cord white matter without forming tumours after transplantation (Hasegawa et al., 2005; Chang et al., 2009). When transplanted into the contused rat spinal cord, RG3.6 cells localized extensively above and below the injury epicentre and decreased the appearance of macrophages and chondroitin sulfate proteoglycans, thus limiting inflammation. Indeed, axon growth across the lesion was enhanced, leading to increased Basso Beattie Bresnahan scores of greater than two points within the first week following the injury (Hasegawa et al., 2005). Moreover, Chang et al. (2009) showed that transplanted RG3.6 cells upregulate various protective factors in the host including anti-apoptotic Hsp70 mRNA as well as the neurogenic and cell lineage factors Foxg1, Top2a, Nkx2.2 and Sox11, a factor critical for neurite growth and survival. Together these studies show

Table 1 Radial glial cell transplantation strategies and outcomes

Endogenous RGCs	Graft site	Outcomes	Reference
NSPCs isolated from mouse cortex	Adult rat cortex and photochemically lesioned cortex *TS	Good integration and differentiation to functional neurons 1 week after transplantation.	Prajerova et al., 2010
Embryonic mouse forebrain	Adult thoracic rat SC	Good survival and migration, differentiation to astrocyte and oligodendrocytes first and later to neurons. No BBB functional recovery.	McMahon et al., 2010
Embryonic SC neural stem cells and Schwann cells from newborn (sciatic nerve)	Adult thoracic rat contused and non-contused SC	Moderate BBB functional recovery.	Li et al., 2007
Retinal stem cells isolated from radial glial cells from postnatal retinas	Adult mouse retina and degenerating retina	Good migration into degenerated retinas. Differentiation into neurons and glial cells. Poor differentiation into photoreceptors.	Canola et al., 2007
Retinal progenitor cells, similar to radial glia	Adult pig subretinal space	Good transplant survival. Expression of photoreceptor rhodopsin.	Klassen et al., 2007
ES cell and cell line RGCs			
SENA	QA lesioned striatum of adult mouse models of Huntington's disease	Enhanced cell survival. Non tumour forming. Increased GABA-ergic phenotype 1 month after transplant.	Dihne et al., 2006
SENA overexpressing L1	Striatum and substantia nigra of MPTP treated adult mouse models of Parkinson's disease	Increased neuronal migration, and DA and TH cell numbers. Non tumour forming after striatal graft. Protected TH neurons in substantia nigra. Significant functional recovery.	Cui et al., 2010
SENA overexpressing L1	Adult mousethoracic compression SC injury	Increased 5-HT and TH axons caudal to graft. Reduced glial scar formation three and six weeks after injury.	Cui et al., 2011
hNSCs SD56	MCA occlusion of rat striatum *TS	Enhanced cell survival, neuronal differentiation and migration decreased immune response. Increased locomotor activity.	Daadi et al., 2008
C6-R	Embryonic rat cerebral ventricles.	Non tumour forming. Large cell migration to ischaemic site Neuronal differentiation GABA-ergic expression. Good (37%) cell survival. Some functional recovery.	Friedlander et al., 1998
C6-R-GH	Adult rat parietal lobe	60% Integrated radially into developing cortex, 30% attached to pial surface.	Hormigo et al., 2001
C6-R	Adult rat contused and non-contused thoracic SC	Suppressed tumour formation due to HPT expression.	Hasegawa and Grumet, 2003
C6-R	Above splenium of corpus callosum and cervical SC IA-lesioned adult rat brain	Tumour formation in contused SC. Cells retained bipolar morphology. Good migration along corpus callosum and in white matter of the SC. Enhanced migration after lesion. Supported migration of co-implanted neurons in the corpus callosum and hippocampus, which was enhanced in the lesioned brain.	Hormigo et al., 2001b
RG3.6	Adult rat contused and non-contused thoracic SC	Extensive white matter migration. Cells retained bipolar morphology and crossed lesion in contused SC, acting as a substrate for axon growth. Reduced macrophage invasion. CSPG reduction. Good functional recovery after 6 weeks.	Hasegawa et al., 2005
RG3.6	Adult rat contused and non-contused thoracic SC	Inhibited microglialactivation and macrophage infiltration. Increases in tissue protection genes Hsp70 and Hsp32 and cell development Foxg1, Top2a, Sox11, Nkx2.2 genes by 12 hours.	Chang et al., 2009

RGC: radial glial cell; BBB: Basso, Beattie, and Bresnahan; QA: quinolinic acid; SENA: substrate adherent neural aggregates; SC: spinal cord; GABA: gamma-aminobutyric acid; DA: dopamine; TH: tyrosine hydroxylase; hNSCs: human neural stem cells; HPT: hygromycin phosphotransferase; *TS: model of thrombotic stroke; MCA: middle cerebral artery. IA: ibotenic acid; CSPG: chondroitin sulphate proteoglycan.

that both stem cell derived radial glia and aggregates of radial glia and neurons repopulate and offer neurotrophic support at various CNS lesion sites (**Table 1**).

The transplantation and manipulation of radial glia-like cells such as pre-differentiated astrocytes is also effective in improving outcomes following spinal cord injury by dorsolateral funiculus transection of the adult rat cervical spinal cord (Davies et al., 2011). In this study, human glial precursor cells were differentiated into GFAP-expressing astrocytes using either bone morphogenic protein (BMP) or ciliary neurotropic factor (CNTF). Interestingly, cells differentiated with BMP expressed brain-derived neurotrophic factor, connexin-43 and glutamate transporter-1, which are proteins expressed *in vivo* in astrocytes. Furthermore, rats transplanted with astrocytes differentiated

with BMP, but not undifferentiated precursors or CNDF-derived astrocytes, exhibited elevated numbers of neurons at the injury site and significantly improved functional recovery via the grid walk test. Moreover, the recent rapid progression in our understanding of cell reprogramming technologies has placed induced pluripotent stem (iPS) cells as a viable alternative to ES cells as the future of human cell therapy, thereby bypassing ethical and transplantation rejection issues (Thompson and Bjorklund, 2015). Indeed, a recent report described the production of human radial glial cells from human pluripotent stem cells that performed similar lineage and patterning roles as *in vivo* after ventricular transplantation (Duan et al., 2015). This represents an exciting advance, yet at the time of writing the regenerative potentials of iPS-derived radial glial cells in trauma conditions such as spinal cord injury or stroke had not been reported.

Transplantation of endogenous radial glial cells: The most widely understood use of endogenous radial glia in a clinical context is in spinal cord injury, which likely underlies their *in vivo* axon guidance capacities. Simply stated, as upper motor neuron cell bodies are located in the motor cortex it is more plausible to regenerate axons at the lesion site before they die. Radial glial cells have been demonstrated to reappear in response to injury, at least in the spinal cord. Shibuya et al. (2003) reported 3CB2-expressing radial glial cells in both grey and white matter regions near an adult thoracic spinal cord compression lesion site 1 week after injury. Their processes became radialized after 4 weeks, resembling their embryonic morphology. In addition, Nomura et al. (2010) showed that endogenous radial glial cells have the potential to differentiate and migrate across the loci of a complete adult spinal cord transection site promoting the movement of axons through a chitosan channel, acting as a neural bridge. Likewise, White et al. (2010) demonstrated that at 3 days post mid-thoracic contusion injury cells expressing BLBP, but not GFAP, were present at the injury epicentre, some of which also expressed nestin. As these cells were no longer found at 7 days post injury, it is possible that the endogenous BLBP-expressing population differentiated into mature astrocytes between 3 and 7 days after contusion, and may be manipulated in order to facilitate repair. While transplantation of neurotrophic cells remains perhaps the most viable strategy for many neurodegenerative diseases, improving the local microenvironment by introducing neurotrophic factors to the lesioned areas also promotes synaptogenesis and native cell proliferation. Interestingly, treatment of the contused spinal cord with transforming growth factor-α (TGF-α) resulted in a shift in astrocyte phenotype from hypertrophied and interdigitated to an elongated shape reminiscent of radial glia (White et al., 2011). Furthermore, *in vitro* experiments showed that dorsal root ganglion cells co-cultured with TGF-α treated astrocytes exhibited neurite outgrowth capabilities similar to those cultured on laminin, while fetal bovine serum-treated astrocytes had significantly shorter neurites than those grown on laminin. In addition, fibroblast growth factor (FGF) has demonstrated much therapeutic promise after injury in a variety of CNS regions. Goldshmit et al. (2014) showed that FGF2 mediated a reduction in reactive astrocyte invasion to the glial scar and an up-regulation of pro-regenerative glial precursor cells, likely radial glia, in the grey and white matter, which accompanied significant motor recovery in the mouse. FGF2 is currently being trialled in humans with cervical spinal cord injury.

While difficult to purify and maintain in culture, endogenous populations of early appearing neuronal stem/progenitor cells (NSPCs) can be preserved in the short term and have been homotopically transplanted into the neocortex, hippocampus, olfactory bulb and striatum, where they preserve their lineage fates (Carletti et al., 2004). Furthermore, when heterotopically transplanted they respond to their local microenvironment by showing site specific integration and differentiation (Gaillard et al., 2003; Kallur et al., 2006). However, transplanted progenitors become more fate restricted as development proceeds (Brock et al., 1998; Pinaudeau et al., 2000). These temporal, lineage-restriction characteristics of neural progenitors have been exploited as rat cortical NSPCs were grown as neurospheres, expressing markers typical of radial glia including BLBP and GFAP, and then transplanted to the lesioned adult cortex in a model of thrombotic stroke, where they primarily differentiated to functional neurons 1 week after implantation and replaced lost cells (Prajerova et al., 2010). Furthermore, multipotent radial glial cells have been transplanted in the contused spinal cord of adult rats following isolation and co-culture with Schwann cells from the developing spinal cord (Li et al., 2007) and forebrain (McMahon et al., 2010) (**Table 1**). Both migration and integration was observed in these cases and transplanted radial glia differentiated into neurons, oligodendrocytes and astrocytes (McMahon et al., 2010).

A further application for radial glial cells lies in retinal degeneration as cell transplantation is rapidly becoming a viable strategy for treating neuro-retinal diseases including retinitis pigmentosa and age-related macular degeneration. A subtype of radial glial cell, the Müller glial cell, has been assigned some limited regenerative capacities in the mammalian retina following neurotoxic insult (Ooto et al., 2004; Jayaram et al., 2014), an attribute greatly magnified in fish (Yurco and Cameron, 2005). Moreover, the survival and integration of transplanted retinal stem cells into normal and diseased retinas in mice and pigs has been reported and these cells expressed markers typical of radial glial cells including RC2, Pax6 and Mash1 (Canola et al., 2007) and nestin, vimentin and LewisX (Klassen et al., 2007). Many of these cells migrated and differentiated into layer-specific retinal cells, while Klassen et al. (2007) demonstrated their potential to become subretinal photoreceptors cells. Moreover, purified Müller glia express protein similarities with dopaminergic (DA) neurons, including tyrosine hydrolase, L-DOPA decarboxlyase, the nuclear receptor-related factor 1 and DA associated transporter expression (Stutz et al., 2014). Their subsequent transplantation into the striatum of hemi-Parkinson's disease mice resulted in increased DA and 3,4-dihydroxyphenylacetic acid expression when compared to the contralateral brain, which significantly enhanced motor functions (Stutz et al., 2014).

In a rapidly advancing field, biomaterial-based transplantation platforms such as hydrogels and nanofibre scaffolds are enhancing engraftment by allowing multiple cell matrixes to be implanted, thereby replacing both the cells lost due to injury and the neurotrophic populations necessary to enrich them and modulate immune responses at the injury site (Tam et al., 2014). For example, we are currently growing radial glial cell-rich cultures isolated from the embryonic spinal cord on specialised biopolymers and aim to apply these to spinal cord injury loci to recreate the supportive embryonic CNS microenvironment (unpublished).

Closing remarks: It is clear that intricate networks of radial glial cells or their progeny form scaffolds that segregate/guide growing axons, while contributing to both gliogenesis and neurogenesis during development. Although significant strides have been made to elucidate their roles and regenerative potentials in some injury paradigms, they seem as yet to be an untapped resource to promote recovery in multiple neurological conditions. Recent reports describing the ability of radial glial cells to re-differentiate at injury loci, and offer neurotrophic support to surviving cells in both amphibians and mammals, will ensure that attention will continually be placed on radial glia and their

derivatives. By combining this research with technological developments in neural tissue engineering to support the growth and transplantation of CNS progenitors, we are confident that radial glial cells and in particular ES cell derivatives such as RG3.6 cells will play significant roles in advancing cell replacement and regeneration therapies.

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