

Potential of adult neural stem cells for cellular therapy

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Abstract: Cellular therapy is the replacement of unhealthy or damaged cells or tissues by new ones. Because neurodegenerative diseases, cerebral strokes, and traumatic injuries to the central nervous system (CNS) produce neurological deficits that result from neuronal loss, cell therapy is a prominent area of investigation for the treatment of neurological diseases and injuries. Neural progenitor and stem cells generate the main phenotypes of the nervous system, and offer a model of choice for cellular therapy in the CNS. With the confirmation that neurogenesis occurs in the adult brain, and the recent isolation and characterization in vitro of neural progenitor and stem cells from the adult CNS, new strategies are being devised and have the potential to treat a broad range of CNS diseases and injuries.

Keywords: neurogenesis, central nervous system, neurodegenerative diseases, trophic factors, regeneration, transplantation

Introduction

Neural stem cells (NSCs) are self-renewing multipotent cells that generate the main phenotype of the nervous system, neurons, astrocytes, and oligodendrocytes. Neural progenitor cells are more mature multipotent cells with limited proliferative capacity; they are generated through transient amplification of NSCs. Contrary to a long held dogma, neurogenesis occurs throughout adulthood in the mammalian brain and NSCs reside in the adult CNS (Gage 2000; Gross 2000), including human (Eriksson et al 1998; Curtis et al 2007). Neurogenesis occurs primarily in two areas of the adult mammalian brain, the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ). In the DG, newly generated neuronal cells in the subgranular zone migrate to the granular layer, where they differentiate into mature neuronal cells, and extend axonal projections to the CA3 area. In the SVZ, cells are generated in the anterior part of the SVZ, and migrate to the olfactory bulb (OB), through the rostro-migratory stream (RMS), where they differentiate into interneurons of the OB. In human, the RMS is organized, differently than in other species, around a lateral ventricular extension reaching the OB (Curtis et al 2007).

It is hypothesized that neurogenesis originates from residual stem cells in the adult brain. Self-renewing multipotent NSCs have been isolated and characterized in vitro from various areas of the adult CNS, suggesting that NSCs reside throughout the CNS and providing valuable sources of material for cellular therapy (Taupin and Gage 2002). Cell therapeutic interventions may involve both in vivo stimulation and transplantation of neural progenitor and stem cells of the adult brain.

Stimulation of endogenous neural progenitor and stem cells

The adult CNS is seeded with neural progenitor and stem cells. The stimulation of these cells would represent a strategy to promote regeneration in the diseased and injured

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CNS. This has been particularly studied in animal models of Parkinson's disease (PD). In a recent study that report the generation of new dopaminergic neuronal cells in the adult rat substantia nigra (SN), the authors have investigated the generation of new dopaminergic neuronal cells following lesion of the SN (Zhao et al 2003). The rate of neurogenesis, as measured by BrdU labeling, was reported to be increased by 2-fold, 3 weeks following lesion induced by a systemic dose of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a model of PD. In contrast, a more recent study found no evidence of new dopaminergic neurons in the SN of 6-hydroxydopamine-lesioned hemi-Parkinsonian rodents (Frielingsdorf et al 2004). Furthermore, the generation of new dopaminergic neurons in the adult SN remains source of controversy (Lie et al 2002; Frielingsdorf et al 2004). Though the generation of new dopaminergic neuronal cells in the adult SN remains to be confirmed, hypothetically, regeneration could be promoted locally by stimulating neural progenitor and stem cells at sites of degeneration. It is the premise of cellular therapy that the environment would contribute to the development and integration of the cells in the tissue (Watt and Hogan 2000).

Investigators are aiming to identify factors promoting adult neurogenesis and the integration of new neuronal cells after lesion. Factors like platelet-derived growth factor (PDGF-BB) and brain-derived neurotrophic factor (BDNF) induce striatal neurogenesis in adult rats with 6-hydroxydopamine lesions, with no indications of any newly born cells differentiating into dopaminergic neurons following growth factor treatment (Mohapel et al 2005). Such factors may prove to be beneficial for recovery in PD. The stimulation of endogenous neural progenitor and stem cells has also been reported in other models of CNS injuries. The implantation of dendritic cells, antigen-presenting cells of the immune system, in the spinal cord after injury in adult mice stimulates neurogenesis *de novo*, and locomotor recovery. Histological analysis suggests that the dendritic cells, by releasing trophic factors, may have induced regeneration of the corticospinal tract axons (Mikami et al 2004).

Alternatively, new neuronal cells are generated at sites of degeneration in the diseased brain and after CNS injuries, and originate from the SVZ. Curtis and colleagues (2003) and Tattersfield and colleagues (2004) reported an increase in SVZ neurogenesis, leading to the migration of neural progenitor cells and the formation of new neuronal cells to damaged areas of the striatum in Huntington's disease (HD) patients and in animal model of HD (quinolinic acid lesion). After experimental strokes (middle cerebral artery

occlusion), new neuronal cells are detected at the major sites of degeneration, like the striatum and cortex distal to the infarction (Jiang et al 2001; Zhang et al 2001; Li et al 2002; Parent et al 2002). Cell tracking studies revealed that newly generated neuronal cells migrate partially through the RMS to the sites of degeneration, where they differentiate into the phenotypes of the degenerated nerve cells. It is estimated that 0.2% of the degenerated nerve cells in the striatum after focal ischemia are replaced (Arvidsson et al 2002; Jin et al 2003).

Hence, neurogenesis is stimulated in the adult CNS after injury, and new neuronal cells are generated at the sites of degeneration. The identification of the SVZ as the source of neural progenitor and stem cells with regenerative potential after injury suggests that strategies to promote regeneration and repair may focus on stimulating SVZ neurogenesis after injury. Both environmental enrichment and administration of various factors and molecules have been reported to promote SVZ neurogenesis. The rate of cell proliferation in the SVZ increases following exposure to an environment enriched in odors (Rocheffort et al 2002). Trophic factors, like epidermal growth factor (EGF) and basic fibroblast growth factor (FGF-2) (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999), and other factors, like Ginkgo biloba extract (Didier et al 2002), have also been reported to stimulate SVZ neurogenesis in rodents. Transforming growth factor- α (TGF- α) infusion into the adult rat striatum leads to migration of neuronal progenitor cells from the SVZ to the infusion site (Fallon et al 2000). These molecules and factors are potential candidates to recruit new neuronal cells from the SVZ for cellular therapy in the CNS. Future investigations will aim at identifying factors promoting neurogenesis in the degenerated areas.

The identification of the SVZ as a source of newly generated neuronal cells at the sites of degeneration after injuries presents several features that can benefit cellular therapy in the CNS. First, in the intact CNS and after injury, a significant proportion of newly generated neuronal progenitor cells in the SVZ undergo programmed cell death rather than achieving maturity, eg, 80% of the new striatal neuronal cells that are generated from the SVZ after stroke in rats die within the first weeks after the insult (Morshead et al 1992; Arvidsson et al 2001; Cameron and McKay 2001). This transient increase in newly generated neural progenitor cells provides a window of opportunity when newly generated neural progenitor cells could be salvaged, and directed to participate to the regeneration of the damaged tissue. Factors preventing cell death, like caspases (Namura et al 1998; Pompeiano et al 2000; Ekdahl et al 2001), would thus also be

potentially beneficial for cellular therapy, alone or in combination with the administration of trophic factors, and environmental enrichment that promote SVZ neurogenesis (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999; Didier et al 2002; Rochefort et al 2002). Second, the identification of the SVZ, along the ventricles, as the source of neural progenitor and stem cells with regenerative potential after injury also suggests that molecules and factors could be administered either by systemic injection, intracerebroventricular, subcutaneous injection, or through the cerebrospinal fluid (CSF) to promote neurogenesis in the brain (Craig et al 1996; Kuhn et al 1997; Wagner et al 1999), but also the spinal cord (Martens et al 2002), as the central canal is a presumed location of putative NSCs (Horner et al 2000). Procedures that are less invasive would be beneficial for the treatment of the injured patients. In support to this contention, intravenous administration of brain-derived neurotrophic factor stimulates neurogenesis in the DG and enhances migration of subventricular zone progenitor cells to the nearby damaged striatum after ischemic stroke (Schabitz et al 2007).

Transplantation of adult-derived neural progenitor and stem cells

Neural progenitor and stem cells have been isolated and cultured *in vitro* from various areas of the adult CNS, including the spinal cord, and from various species (Taupin and Gage 2002), including from human biopsies and post-mortem tissues (Palmer et al 2001; Roisen et al 2001; Schwartz et al 2003), potentially allowing the generation of neural progenitor and stem cells from multiple sources for cellular therapy. Adult neural progenitor and stem cells could also be isolated from the an undamaged area of the patient's brain, expanded *in vitro*, and grafted back to the degenerated area(s), allowing autologous transplantation. This would obviate the need to find a matching donor and to administer drugs that suppress the immune system, like cyclosporine, to prevent tissue rejection. However, risk associated with invasive surgical procedure that would probably involves the destruction of healthy brain tissue, limits the clinical application of such strategy.

In all this shows that adult derived-NSCs represent a potent model for cellular therapy. Recent studies have confirmed the engraftment potential of adult derived neural progenitor and stem cells in animal studies (Gage et al 1995; Suhonen et al 1996; Shihabuddin et al 2000; Akiyama et al 2001; Wu et al 2001; Zhang et al 2003), confirming their potential for cellular therapy.

Cell transplantation aims mainly at delivering cells at specific sites. This is particularly suitable for the treatment

of diseases, and injuries where the degeneration is limited to mainly one area, like for neurodegenerative diseases as PD and after traumatic injury to the CNS (Armstrong et al 2003; Lepore et al 2005). When the degeneration is widespread, as in neurodegenerative diseases like Alzheimer's disease, HD and multiple sclerosis, such strategy is not applicable. Neural progenitor and stem cells migrate to tumor (Aboody et al 2000; Brown et al 2003; Glass et al 2005), injured (Macklis et al 1993; Veizovic et al 2001; MODO et al 2004; Boockvar et al 2005), diseased sites (Pluchino et al 2003), when transplanted in the CNS, or administered either by systemic injection, or through the cerebrospinal fluid (CSF) by injecting cells into the 4th ventricle in the rat. The injected cells conveyed to the damaged areas, where they integrate the host tissue. A recent study has reported that the systemic injection of neural progenitors and stem cells may provide significant clinical benefits in an animal model of multiple sclerosis (Pluchino et al 2003). Thus, NSC therapy may provide a therapeutic tool for the treatment of a broad range of neurological diseases and injuries. Such migratory properties of NSCs can be used as a general mode for administering neural progenitor and stem cells for cellular therapy, avoiding surgical procedures, and their associated risks and secondary effects. Hence, systemic injection and injection through CSF are regarded as promising ways to administer NSCs for cellular therapy, particularly for the treatment of spinal cord injuries (Wu et al 2002; Fujiwara et al 2004).

Adult neural progenitor and stem cells can be genetically modified by retroviral-mediated infection, rendering them a vehicle for gene therapy. Mouse and human neural progenitor and stem cells genetically modified to express acid sphingomyelinase reverse lysosomal storage pathology when transplanted into animal models of Niemann-Pick's disease (Shihabuddin et al 2004; Sidman et al 2007). This highlights the potential of genetically modified NSCs for the treatment of lysosomal storage diseases and other genetic diseases of the CNS. The potential of genetically modified NSCs is further highlighted by their potential for the treatment of brain tumors. Grafted neural progenitor and stem cells migrate to tumors. The properties of NSCs to be genetically modified and to migrate to tumor sites have been proposed for the treatment of brain tumors. It is proposed to genetically modified NSCs with "suicide genes", like genes coding for cytolytic activities or anti-tumor cytokines, to attack and destroy brain tumor cells. Intravascular administration of neural progenitor and stem cells genetically engineered to express interferon- β lead to tumor regression in mice (Kim et al 2006; Dickson et al 2007). This strategy further extends the use of cell engineering of NSCs for cancer therapy in the CNS.

Altogether these data show that cell transplantation of adult NSCs provide a model of choice for cellular therapy in the CNS, and has the potential to treat a broad range of CNS diseases and injuries, ranging from neurodegenerative diseases, strokes, spinal cord injuries, genetic diseases of the CNS, to brain tumors.

In a study where human fetal neural progenitor and stem cells were injected after spinal cord injury in mice, the improvements in walking disappeared following treatment with diphtheria toxin, which kills only human cells and not mouse cells (Cummings et al 2005). This suggests that the grafted neural progenitor and stem cells themselves are responsible for recovery. Beside the replacement of the degenerated cells by the grafted cells, grafted NSCs may also promote functional recovery by promoting the survival of injured neuronal cells through the secretion of neurotrophic factors (Ourednik et al 2002; Lu et al 2003; Llado et al 2004; Pfeifer et al 2004; Yan et al 2004), and its interaction with the injured brain and immune system (Park et al 2002; Pluchino et al 2005), further underlining the relevance of NSCs for cellular therapy in the CNS.

Conclusion

Because of their potential to generate the different cell types of the CNS, NSCs represent a model of choice for cellular therapy in the CNS. The recent confirmation that neurogenesis occurs in the adult brain and NSCs reside in the adult CNS opens new opportunities for cellular therapy. On the one hand, new neuronal cells are generated at the sites of degeneration in the diseased and injured brain. Though the CNS has limited capacity to recover after injury, the data shows that the CNS has the ability to repair itself after injury. On the other hand, the grafting of adult neural progenitor and stem cells offers an alternative for cellular therapy in the CNS. Hence, adult NSCs offer a potent and promising model for cellular therapy. Futures studies will aim at identifying the factors and mechanisms underlying adult neurogenesis, to promote and enhance the regenerative potential of endogenous NSCs. Isolated adult neural progenitor and stem cell populations are heterogeneous, likely a factor limiting their potential for recovery. Future studies will aim at identifying the NSCs, enriched them, as a source of homogeneous populations of NSCs for cellular therapy. Futures directions will aim at addressing the challenges and limitations of adult NSC therapy. Particularly, to what extent newly formed or transplanted neural progenitor and stem cells integrate and become functional? What are the potential and risk that newly formed or transplanted neural progenitor and stem

cells establish the wrong connections or transplanted neural progenitor and stem cells develop into tumors upon grafting? These questions will need to be answered before the adult NSCs could be brought to therapy.

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