Review Article

Indian Journal of Neurotrauma (IJNT)
2008, Vol. 5, No. 1, pp. 7-10

Stem cell therapy for spinal cord injury

A plea for rationality

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Abstract: The discovery of neural stem cells has offered a glimmer of hope to those afflicted by neurodegenerative diseases or those bearing the brunt of neurological insult. Spinal cord injuries affect young adult males predominantly and there is often pressure on the medical community to 'do something'. The hype in the lay press on this modality has fostered in many, the hope that these cells can nurture neurological recovery. Presented below, is an overview of the current state of stem cell research and the impact of this and other newer modalities on the paradigms of spinal cord injury management.

Keywords: neural stem cells, spinal cord injury

INTRODUCTION

The discovery of the potential utility of stem cells in neurological repair and regeneration is an exciting development in neuroscience. If Guttman gave the paraplegics dignity and the capability to cope with their disability, stem cells today offer them the hope that their disability may one day be alleviated. Stem cells are also big bucks and news genesis is always a step ahead of neurogenesis. Reality however should provide a damper to this unbridled enthusiasm. There is limited evidence from the animal model that stem cells improve the functional outcomes in spinal cord injured rats, but the mode by which functional improvement is achieved is far from clear. Translational trials have not been sanctioned and the evidence from uncontrolled and poorly conceptuated human trials is far from convincing.

The Location of Stem Cells in the CNS

Stem cell niches in the CNS are in discrete anatomic zones. They have been identified in the dentate gyrus of the hippocampus and in the subventricular zone along the lateral ventricles[1,2,3]. Stem cells have also been found around the ependyma of the central canal[4] and around the fourth ventricle. Other CNS niches include the hypothalamus, the optic nerves and the substantia nigra[5].

Factors controlling stem cell differentiation and multiplication

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Neural stem cells found in the CNS niches can proliferate along neuronal or glial lineages. Stem cell based natural repair occurs through the phases of multiplication, differentiation, migration and neo-synaptogenesis.

Cell proliferation is triggered by growth factors like FGF-2 (fibroblast growth factor) and EGF-1(epidermal growth factor)[6,7]. Differentiation along neuronal lines occurs under the influence of Shh (Sonic hedgehog), while the notch pathway guides proliferation towards a glial lineage [8]. Shh, a secreted glycoprotein is involved in anterior motor neuron induction in the spinal cord[9]. In adult rats too, Shh increases the proliferation of neural progenitors[10].

So, in the CNS we have stem cells which have a potential to proliferate and we have factors which can induce their proliferation and guide the multiplying cells along various lineages.

Stem cell response to Neuroinjury

Stem cells, in the niches around the ependymal layer proliferate after neuronal loss. This proliferation is triggered off by the various messenger cascades provoked by the injury. The proliferation however is predominantly astroglial[11]. One of the mechanisms by which steroids and immune modulating drugs aid the functional recovery after spinal cord injury is by suppressing the messenger cascades, thus limiting gliosis. Gliosis in most situations impairs attempts of axons to regrow and reestablish communications.

The degree and direction of stem cell multiplication that occurs endogenously is thus insufficient (along neural

lineages) or inappropriate (along glial lines)[12]. Functional restoration is hence rarely achieved.

One of the major deterrents to neuronal differentiation is an upgradation of the notch pathway[13]. The limiting factor in endogenous stem cell proliferation is not therefore the quantum of stem cells which are available. It is the direction of multiplication of these cell lines. This is controlled by the intercellular messengers. This merits modulation.

Manipulating neural stem cells. The current directions of research

There is ongoing research on endogenous stem cell manipulation in basal ganglionic disorders like Huntington's chorea[14] and Parkinson's disease[15]. Stem cell mediated recovery of function has been achieved in animal models of ischemic injury[16].

Transplantation of exogenous neural stem cells in animal models of TBI has shown promise in promoting motor and behavioral recovery[17]. This recover is attributable to remyelination. Oligodendrocyte lineage cells are primarily involved in this process.

Exogenous stem cell transplantation has produced functional improvement in animal models of spinal cord injury[18]. Mesenchymal stromal cells have been shown to support axonal growth[19]. The addition of sonic hedgehog to the injury site in a spinal cord injury model has again shown a firm functional benefit[20].

Applicability of stem cell therapies in spinal cord injury

The structures injured in a spinal cord injury model are:

- the long tracts including the corticospinal may be functionally or anatomically disrupted
- the neurons at the level of injury, mostly the motor neurons would be injured
- vascular disruptions

Promoting Remyelination

Conventional treatment regimes involving immuno-modulatory drugs have been shown to benefit the restoration of the long tracts preferentially. In the NASCIS study for example, an improvement in functional status, rather than in the neurological levels was the index of documented benefit.

Most of today's regimes therefore are aimed at the facilitation of axonal re-growth. Oligodendrocytes restore myelination and are vital for axonal repair. Astrocyte proliferation would result in gliosis which in all likelihood impedes axonal regrowth. This chapter is far from closed as a trophic supportive role of astrocytes has been postulated. The neurons for the corticospinal tract for example, are situated in the motor cortex and are not targets for stem cell replenishment.

In the setting of spinal cord injury therefore, stem cell therapy could potentially be in the following forms.

1. Stimulating the endogenous stem cell population to proliferate along neuronal lines. These differentiated cells would migrate from around the central canal along tracts similar to the one provided by the radial glia in the cortex. They would serve to replenish the anterior horn cells injured at the level of injury.
2. Controlling the switches or messengers, for example using sonic hedge hog to push neural stem cells along neuronal lines would augment the process. However, replenishing anterior horn cells at injury levels would only produce a small quantum of clinical benefit.
3. If the endogenous cell population proves to be inadequate, we could administer stem cells provoked into neural differentiation in vivo. These cells would need to be delivered to appropriate locations i.e., either to the area of neuronal loss or along the direction of normal neuronal migration. In the second case augmentation of the chemotactic stimuli for migration would be desirable.
4. A more appropriate target for therapy in spinal cord injury is the long tracts. It is the disruption of these tracts that produce motor, sensory and autonomic loss below the level of injury. The neurons involved are either in the brain or in the case of sensory tracts at the root entry levels. Lush glial proliferation at the injury level is detrimental to axonal regeneration. Rational treatment aims at curtailing glial proliferation. Oligodendrocyte precursors have been shown to promote myelination of tracts after cord injury.
5. Mesenchymal stromal cells have been shown to facilitate axonal regeneration in the rat model. This can occur due to the genesis of oligodendrocyte precursors. It can also be explained by the scavenger and immunomodulatory effect of these multipotential cells. Conventional methods of therapy using methylprednisolone or newer trials

including Rho inhibitors also act by the second mode.

Cell based therapy for tract preservation/restoration would be by the use of cells of mononuclear or lymphocytic lineage to act as immunomodulators and scavengers. These could provide a window for axonal regrowth. Stem cells may be urged in vivo to differentiate along oligodendrocytic lines before delivery to the injury sites.

Management paradigms in spinal cord injury

The aims of spinal cord injury management today are-

1. To immobilize the injured segment by external devices to minimize the risk of further injury.
2. To optimize blood pressure to maintain cord perfusion in the face of hypotension that occurs as a result of the loss of vasomotor tone. This may necessitate the use of vasopressors.
3. To surgically decompress the compressed cord, followed by stabilization. The timing of surgical intervention was addressed in the recently concluded STASCIS (Surgical treatment of acute spinal cord injury study), the results of which were presented at the annual conference of the American Association of Neurological Surgeons-Apr 2008. This study has shown an unequivocal benefit for surgical decompression performed within 24 hours of injury, both in neurological outcomes and in the reduction of complications.
4. To initiate treatment for aborting secondary cascades and for facilitating axonal regeneration. The NASCIS 2 and NASCIS 3 studies have shown some functional benefit of methylprednisolone when administered within the early hours after spinal cord injury. GM-Ganglioside and Tirilazad have also been used to abort these inflammatory cascades.

Future therapies

a) Manipulating the endogenous stem cell population. The modulation of gliosis would permit axonal regeneration and long tract restoration. Inhibition of the notch pathway has been shown to inhibit gliosis. Stimulation of the sonic hedgehog pathway would promote cell differentiation along neural lines and may help replenish damaged anterior horn cells.

b) The use of exogenous stem cells. Exogenous stem cells which have been used include mesenchymal stromal cells (purified from a bone marrow aspirate) and olfactory ensheathing glial cells, harvested transnasally from the olfactory tracts.

The routes through which these cells can be instilled include direct injection to the injury site at the time of surgery, delivery through the vascular route by highly selective angiography, delivery through the central canal by instillation into the fourth ventricle and by intrathecal instillation, Of these routes, the intrathecal route is technically the simplex and the least likely to provoke iatrogenic damage to regenerative potential. These cells possibly perform a macrophagic role by removing the inflammatory debris which would aggravate the local inflammation.

CONCLUSION

The primary aim of management in spinal cord injury is to restore the long tracts. This can be achieved by providing a milieu for axonal regeneration to occur. Suppressing glial proliferation and aborting the cascades of secondary injury are hence primary aims.

The role of mesenchymal stromal cells or activated lymphocytes which act as immuno-modulators merits evaluation in a controlled trial setting before being used in patients. The potential for mesenchymal stromal cells to differentiate along oligodendrocytic lineage needs further research.

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