Indian J. Surg. (September–October 2008) 70:212–214

REVIEW

The role of stem cells in neural injury – emerging paradigms

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Received: 3 July 2008 / Accepted: 31 July 2008

Abstract Stem cells capable of proliferating along neuronal and glial lines persist in the adult central nervous system (CNS). These cells are found pedominantly in the subventricular zones and in the hippocampus. The therapeutic potential of both endogenous and exogenous stem cells in achieving repair of the injured CNS is being explored. Stem cells from embyonal lines, mescnchymal stromal cells and neural stem cells are being investigated for their potential role in the management of neural loss due to traumatic hypoxic or inflammatory insult.

Keywords Neural stem cells · Neuroregeneration · Stem cell therapy

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Introduction

In the past decade, there have been profound changes in our understanding of the mechanisms of injuries to the CNS. Simultaneously, new insights into the regenerative potential of neural cell lines have provided a glimmer of therapeutic hope. Neuronal loss may not be as irretrievable as we once surmised. Contemporary surgical practice merits a conceptual understanding of the pathophysiological mechanisms of neural injury production and a critical awareness of the status and horizons of stem cell biology.

The pathophysiology of traumatic injury to the neuraxis – a brief overview

Primary injury

Neural injury may be produced by the impact and pressure waves of an injuring agent or by inertial stresses of acceleration and deceleration. Impact injuries result in skull fractures, epidural and subdural hematomas and surface contusions. The spheroidal contour of the cranium focuses the impact wave to the geometric centre of the sphere. This confocal point is in the region of the hippocampus and the basal ganglia. It may be an oversimplification of a complex issue to state that the impact and its pressure waves predominantly and primarily disrupt the soma or cell body of the neurons. Inertial injuries on the other hand result in axonal and microvascular disruptions. Diffuse axonal injuries and spinal cord injuries are situations where the clinical spectrum is predominantly due to axonal rupture.

The injury cascade

There is a glutamatergic exitotoxic surge after injury [1]. The NMDA gated calcium channels open, resulting in a calcium influx. Intracellular calcium triggers off inflammatory cascades. This results in breakdown of the blood-brain barrier. There is damage to the mitochondrial membrane, shutting off the cells power supply. Calpains produce breakdown of the structural proteins like spectrin and tubulin resulting in cytostructural collapse. Caspases are activated culminating in apoptotic cascades. The cascade of injury continues till reparative gliosis sets in, effectively impeding any attempts as axonal regeneration.

Secondary injury

Edema, both vasogenic and cytotoxic and mass producing hematomata which may be extradural, intradural or intracerebral increase the volume of intracranial contents. This results in an increase of intracranial pressure. Although a normal brain can maintain neuronal perfusion at any pressure head between 60 to 140 mm of Hg, a cerebral perfusion pressure (mean arterial pressure – intracranial pressure) of 70 mm Hg is considered optimal for an injured brain. Hypoxic insult results in further neuronal loss and an aggravation of the injury cascade.

Neuronal mechanisms of regeneration and repair

One of the mechanisms of neural restoration is neosynaptogenesis. New connections attempt to compensate for fixed losses with some restoration of function. This is the phenomenon of neuronal plasticity.

The discovery of stem cell niches in the adult brain [2] has revealed the potential for CNS neuroregeneration [3]. This discovery has also posed perplexing questions on the inadequacy of this potential to fulfill clinical restoration. The engram for CNS restoration is in place. Why is neuronal regeneration clinically unapparent? The answer to this enigma may be more Theo- philosophical rather than physiological. Stem cell niches in the CNS have been identified in the subependymal zone of the ventricular system [4], in the dentate gyrus of the hippocampus and in the basal forebrain including the olfactory tract. Neural Stem Cells (NSC) can evolve along neuronal, oligodendroglial and astrocytic lineages [5]. The sonic hedgehog molecular pathway and retinoic acid urge stem cell differentiation along neuronal and oligodendroglial lines while the notch pathway directs the cell towards an astrocytic lineage.

Harnessing stem cells

Stem cell therapy may be achieved by manipulation of the endogenous stem cell [6] population or by the administration of exogenous pluripotent cells after purification and in vitro culture. Resident stem cells can be urged to proliferate along desired lines by manipulating the intercellular messengers and the chemical milieu. However, an incomplete understanding of control influences precludes the therapeutic utility of this approach today [7].

The second modality is to administer exogenous stem cells. Instillation of these cells can be either at the injury sites or at a point distally. In the latter scenario we depend on chemotactic influences to guide the cells to the injury site. Stem cells, which have been used clinically and in an animal experimental setting include embryonic stem cells (ESC). Neural stem cells and bone marrow derived mesenchymal stromal cells (MSC) [8].

Embryonic stem cells can be urged to differentiate fairly easily along neural lines. In Parkinson's disease which is caused by neuronal dropout of dopaminergic neurons, implanted ESC's have shown functional integration [9]. The use of ESC's however is confounded by ethical issues.

Autologous neural stem cells are not easy to harvest except from the olfactory tract. Olfactory ensheathing glial cells can be harvested through the nose. There have been largely unsubstantiated claims of the therapeutic application of olfactory derived stem cells in spinal cord injuries.

Mesenchymal stromal cells obtained by autologous bone marrow harvest act by two potential mechanisms. Firstly these cells act as immunomodulaters, aborting the secondary injury producing cascades [10]. Secondly these cells may promote remyelination. MSC's can be urged along an oligodendroglial lineage by in vitro culture with FGF-2 (Fibroblast growth factor) and retinoic acid. This results in the production of 'Oligospheres' which may be implanted into the injured spinal cord.

The affinity of stem cells to home on to areas of inflammation has resulted in their being used as vectors for the delivery of oncolytic viruses in glioblastoma multiforme.

Rationale and clinical use of stem cells in neurosurgery

Stem cells for neuronal replenishment

ESC's have been used in the treatment of Parkinson's disease. The dopaminergic neurons generated by these stem cells display electrophysiological and behavioral properties of midbrain neurons. There are phase two trials on the use of stem cells in other neurodegenerative disorders like Huntington's chorea. In the stroke model [11], implanted stem cells have been shown to establish synaptic connections. There are ongoing trials on stem cell use to replace neuronal loss following traumatic brain injury [12]. ESC's and NSC's are more likely to undergo neuronal differentiation and integration.

Stem cells as immune modulators

In the spinal cord, stem cells have been tried in multiple sclerosis, amyotrophic lateral sclerosis and in spinal cord injury. In multiple sclerosis, stem cells provide immunomodulation. They alleviate the recurrent insults to the cord in the relapsing remitting variety of the disease.

Stem cells to promote remyelination [13]

In spinal cord injuries, stem cells may help in the early phase by acting as debris scavengers. This is therapeutically beneficial in incomplete injuries. Some amount of functional ambulation can be achieved in Spinal cord injury cases if even ten percent of the long tracts are conserved.

The disability in spinal cord injury is predominantly due to impairment of the long tracts. The aim of stem cell therapy is to provide oligodendrocyte precursors. These cells take up residence at the injury zone and provide for long tract remyelination.

Amyotrophic lateral sclerosis is one of the few conditions where a significant quantum of the deficit is due to neuronal loss rather than to axonal ruptures. Neurogenesis is therefore a target in this condition.

Conclusion

In the coming years Stem cells will have a role to play in all conditions involving neuronal loss or axonal disruption. A clear understanding of the pathophysiology is imperative to clearly define targets in stem cell therapy. The field of stem cell research is still evolving. The absence of class 1 evidence makes it difficult to justify the use of stem cells in clinical practice other than in the setting of a clinical trial. There is an ongoing clinical trial at the Hadassah hospital in Israel on the use of stem cells in multiple sclerosis, amyotrophic lateral sclerosis and spinal cord injuries. As the result of this and other scientifically structured trials come in, the role of stem cells will be better defined. Hype will then give way to hope and neurogenesis will take precedence over news genesis.

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