Review Article

Towards a Cure for Traumatic Paraplegia - Is there cause for hope?

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Abstract

In the past decade, great strides have been made in the field of CNS tissue repair and expectations have been raised that a cure of spinal paralysis is at hand. The two broad categories of investigational approaches to spinal regeneration are: (1) Enhancing the Regenerative Milieu of the Cord and (2) Cellular and Tissue Transplantation. Amongst the latter approaches, the early use of foetal cord tissue has given way to the more sophisticated studies on stem cell therapy and the implants of olfactory ensheating cells. These have engendered considerable public interest and are being offered as commercially available therapies in clinics round the world to desperate patients. The internet by allowing the dissemination of non-peer reviewed information of experimental interventions catalyses this process. Physicians must be informed of developments in this area to offer appropriate advice and counsel to their patients.

Introduction

The standard of care in spinal cord injury with neurological deficits has been prevention of secondary neural injury followed by rehabilitation. The missing link between these is an efficacious therapeutic intervention that would promote neural regeneration and restoration of function. Advances in molecular biology have extended to the study of neural restoration and in the past decade great strides have occurred in this area particularly spinal cord injury research.[1] However, the internet has allowed much unsubstantiated and unverified information to be available to potential patients[2] and it is imperative that physicians who may be called upon to counsel such patients be familiar with the relevant scientific and clinical information.

Approaches to Regeneration: Conventional wisdom holds that the functional specialization of the central nervous system (CNS) is established at the expense of its reparative potential and in the adult spinal cord (SC) a complete injury precludes any possibility of recovery of function. However, observations of SC regeneration in amphibians and neonatal mammals give hope to investigators of replicating this in adult mammals if the intricacies of the biology of neurorestoration could be unraveled. In the past decade, great strides have been made in the field of CNS tissue repair and expectations have been raised that a cure of SC paralysis is at hand. Indeed, a number of the lines of investigation being perrsued in the laboratory have, in response to the demands from eager patients, engendered a host of novel clinical interventions. The two broad categories of investigational approaches to SC regeneration are enhancing the regenerative milieu of the cord and.cellular and tissue transplantation.

Inhibition at Glial Scar: Following a traumatic insult to the SC, disrupted axons undergo Wallerian degeneration and neurons may die in a process of necrosis and a more delayed apoptosis. Surviving neurons initiate neurite regrowth, but this regenerative activity is abortive and of no functional significance after a complete injury. In a classical experiment David and Aguayo in 1981 demonstrated that when grafted with peripheral nerves, CNS axons in a

sectioned SC would grow the full length of the graft but failed to extend back into the distal stump of the cord.[3] It has since been established that CNS axons do have regenerative capabilities but are inhibited physically by the glial scar that forms at the site of injury[4] and biochemically by inhibitory molecules upregulated by the injury.[5] Enhancing the regenerative milieu of the cord focuses on experimental strategies that would attenuate the glial scar and block the activity of growth inhibitory molecules and the receptors that they bind to. Thus, the recruitment of reactive astrocytes and oligodendrocytes to the injury site has been inhibited by x-irradiation[6] and a direct injection of the cytoxic ethidium bromide into the cord[7] with enhanced axonal regeneration in both experiments

Inhibition in Extracellular Matrix: During neural development, a variety of neurite-promoting and guidance molecules exist in the extracellular matrix that are subsequently downregulated in the adult CNS, permitting stable and complex circuitry. Thus, in the adult CNS, the balance of factors that support neurite growth and factors that inhibit neurite growth shifts toward enhanced expression of growth-inhibiting molecules. After SCI, many of the neurite guidance factors are reexpressed and may provide strategies for neurite growth if better understood.[8] The extracellular matrix proteins, particularly chondroitin sulfate proteoglycans, have received considerable attention in the search for factors contributing to the failure of CNS regeneration and have been associated with inhibion of neurite outgrowth and collapse of the growth cone. Reports of functional recovery in rats with dorsal column lesions treated with intrathecal infusion of chondroitinase ABC suggests that removal of the chondroitin sulfate will be useful in regeneration.[9] Although it is early in the field of SCI research for this area to have made a contribution, the extracellular matrix proteins will be an important consideration in a combinatorial approach for successful regeneration of axons after injury.[10]

Biochemical Inhibition: A number of inhibitory factors derived from the disrupted myelin have been isolated and chemical antagonists to them encourage recovery from experimental spinal injury. The best known inhibitory molecule is the high molecular weight NoGo.[11] The IN-1 monoclonal antibody, and NEP 1-40, a receptor blocker, which neutralise the inhibitory protein activity of NoGo, have been shown to encourage long tract regeneration[12] and these promising therapies will soon be in phase I clinical trials. Another myelin-derived growth-inhibitory protein, myelin-associated glycoprotein (MAG), was identified and has been characterized both in vitro and in vivo. One family of the intracellular signaling molecules that regulate the inhibition of neurite outgrowth that is drawing attention is the Rho pathway,[13] blockade of which has been shown to allow axons to overcome the inhibitory milieu in vitro by reversing the inhibitory signaling, not only by NoGo but also the inhibitory proteoglycans present in the glial scar and to regenerate after optic nerve and SC sections. Clinical trials of a C3 Rho inhibitor (Cethrin) which gives sustained reversal of Rho activation are underway.

Nerve Growth Factors: Another approach to stimulating axonal growth is to use local delivery of neurotropins eg. Nerve Growth Factor (NGF) which stimulates the sprouting of fine, primary afferent fiber systems and Neurotrophin 3 (NT-3) which has been demonstrated to potentiate corticospinal growth. It is obvious that subsets of nerve cells will respond differently to each growth factor, so that a combinatorial approach will be needed to encourage robust regeneration of several systems.[14] Recently, treatment with intrathecal infusion of NGF, NT-3, Gial Derived Neurotrophic Factor (GDNF) and Brain Derived Neurotrophic Factor (BDNF) demonstrated some success in regeneration of cut dorsal roots into the dorsal root entry zone.

Promoting Neurite Growth: Approaches that act through direct intracellular mechanisms by targeting the downstream signalling molecules in the nerve cell body that promote axonal outgrowth, for example cAMP, should prove useful. Recent findings with inosine, a purine nucleoside and cAMP that have demonstrated neurite outgrowth promotion in vitro and in the rodent spinal cord are encouraging.[15] Currently in clinical trials for SCI is the compound AIT-082 (Neotrofin),[16] a synthetic hypoxanthine derivative containing a para-aminobenzoic acid moiety which had been shown to promote both axonal sprouting and the production of NGF, NT-3, and bFGF in astrocytes in culture systems and in vivo.

Encouraging scavenging by macrophages could clear the inhibitory factors engendered by the disrupted myelin of the traumatized SC and this rationale underlies one of the multicentre clinical trial that has entered Phase II (Proneuron) in a number of countries. The macrophages from the patient's own blood (autologous macrophages) are activated by exposure to skin and implanted at the site of the spinal injury in an attempt to encourage regenerative growth without eliciting an immune response.[17] A number of other cellular and tissue transplantation strategies have been applied in animals and increasingly in humans to bridge the physical gap resulting from the cord injury and the challenge has been to find the bridging graft that would be permissive to axonal growth and integrate efficiently to permit function without any tissue or immune response.[18] Early results of foetal tissue grafting in rodents and primates were encouraging and subsequently there are several clinical trials in Sweden, Florida, Russia, and China in which foetal tissue en bloc has been used in patients with SC injury with

good graft survival and even integration but disappointing return of function. However, foetal grafts have been useful in treating posttraumatic syringomyelia.[19]

Schwann Cell Implants: Implants into the injury gap composed of Schwann cells,[20] which form the myelin in the peripheral nervous system where regeneration does occur, or multiple grafting of intercostal nerves[3] in rodent models of spinal injury are both approaches in which some regenerating nerve cell axons have been able to grow across the gap, but penetration into the host tissue has not been impressive. Some functional recovery was demonstrated in both approaches. The Schwann cells can be cultured and purified with relative ease and the experimental literature attests to their facilitatory role in neural regeneration but they do not cohabit well with astrocytes. When grafted into the spinal cord, they evoke astroglial scarring and the grafts soon get walled off, restricting access of regeneration fibres to the implant. No human trial of schwann cell implants have been reported.

Animal experiments in which peripheral nerves are used as bridges have shown that these grafts induce and support axonal outgrowth over long distances in the spinal cord. Clinical trials are in progress in Ecuador and at the University of Sao Paulo, where more than 100 patients have received nerve bridges.[2] Reports of results in peer reviewed literature are sparse though some patients offer effusive endorsements over the internet.

Olfactory Ensheathing Cells (OEG): These are very unusual cell type that normally reside with the olfactory nerve in the nasal mucosa and in the olfactory bulb and are a promising regenerative therapy for spinal cord injury.[21] The olfactory nerve is the only cranial nerve that continuously regenerates in adult mammals and this ability has been credited to the presence of these cells.[22] OEG cells appear to be specialized for enhancing axonal regeneration. First, they are migratory cells that seem to be attracted to growing axons. Second, they can form multipolar cells with long processes that express a variety of axon-stimulating cell adhesion molecules and seemingly serve a guidance function. Third, they can myelinate axons, hence the word "ensheathing" in their name. At least half a dozen laboratories have now reported that these cells will facilitate functional neural regeneration when transplanted to the brain or spinal cord in rodents [21] and these findings, being striking is some reports,[23] have driven patient interventions. Implants of OEG are clinically available in Beijing[24] where over 600 patients from round the world have been grafted and Lisbon[25] where the experience extends to some 20 patients but from neither centre have the results been reported adequately. Workers in Brisbane have initiated human trials after extensive animal experimentation and the preliminary results demonstrating the safety of the procedure have recently been published.[26]

More recent studies on the biology of OEGs have tempered the earlier enthusiasm and caution is being advised by authorities in the clinical application of implantation.

Stem Cells: Human neural progenitor cells and embryonic stem cells have been used in rodent spinal injury models[27] and having demonstrated functional recovery have engendered much anticipation in the lay public as heralding the cure to spinal paralysis.[28] Although considerable work in the field of stem cell biology remains, there are some clinical trials in Russia in which foetal stem cells are used as transplant sources for chronic SCI or in combination with olfactory ensheathing glial cells. Stem cell therapies have been given greater impetus by the isolation and culturing of pluripotential neural cell lines from bone marrow,[29] blood and umbilical cord blood.[30] However, despite extensive efforts in spinal injured patients, no verified case of substantive recovery has been reported in the peer-reviewed literature. Results in SC injured patients infused with retrodifferentiated stem cells derived from the patients blood in the method of Dr Ilham Abuljadayel working in Karachi,[31] have been similarly disappointing.[32] Other transplant sources include transposition of the omentum and transplantation of embryonic shark cells in Mexico. These latter two approaches are generally viewed as lacking serious scientific merit.[33]

Bridging the Gap: Advances in the field of biomatrix material have provided opportunities to bridge the gap with artificial material, such as biodegradable hydrogels or combinations of hydrogels and cells that may promote regeneration.[34] Desired properties of a synthetic bridge are to provide simultaneously a physical substrate for axonal attachment and growth without triggering antigenic host reactions. Although this approach is in its infancy, great strides are possible with polymer chemistry.

Conclusion

Scientific work of the past decade has demonstrated a number of approaches to enhancing SC regeneration to be promising in rodent models and the challenge is to translate these into treatments for human patients.[35] Premature translation of animal work to humans who are often desperate and feel they have nothing to lose, harms them by precluding them from future trials of developing therapies and detracts from the promise that such research holds for future generations.

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