REVIEW ARTICLE

Neural Transplantation in Spinal Cord Injury

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ABSTRACT: Although medical advancements have significantly increased the survival of spinal cord injury patients, restoration of function has not yet been achieved. Neural transplantation has been studied over the past decade in animal models as a repair strategy for spinal cord injury. Although spinal cord neural transplantation has yet to reach the point of clinical application and much work remains to be done, reconstructive strategies offer the greatest hope for the treatment of spinal cord injury in the future. This article presents the scientific basis of neural transplantation as a repair strategy and reviews the current status of neural transplantation in spinal cord injury.

RÉSUMÉ: Transplantation neurale dans le traumatisme de la moelle épinière. Bien que les progrès de la médecine aient augmenté significativement la survie des patients ayant subi un traumatisme de la moelle épinière, la restauration de la fonction n'a pas encore été réalisée. La transplantation neurale a été étudiée pendant la dernière décennie chez des modèles animaux comme stratégie de réparation de la lésion de la moelle. Même si la transplantation neurale n'a pas atteint le stade de l'application clinique et qu'il reste beaucoup de travail à faire, ce sont les stratégies de reconstruction qui offrent le plus d'espoir dans le traitement des traumatismes de la moelle épinière. Cet article présente les bases scientifiques de la transplantation neurale comme stratégie de réparation et revoit l'état actuel de la transplantation dans les traumatismes de la moelle épinière.

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Spinal cord injury (SCI) has a permanent and devastating effect on the lives of affected individuals. Deficits in sensation, motor function and bowel/bladder control drastically diminishes the quality of life of SCI patients. The degree to which individual patients are affected depends on the level and the extent of the spinal cord lesion. Spinal cord injury also exerts a high cost to society as SCI patients are often young with a peak incidence in the second and third decades of life. In Canada alone, the incidence of SCI approaches 900 new cases each year. It has been estimated that lifetime costs of caring for an SCI patient can easily exceed one million dollars, depending upon the level and severity of the injury.[1-3]

Although significant advancements have been made in the survival of SCI sufferers, primarily through improved bladder care,[4,5] attempts at restoration of function have remained largely unproductive. Current treatment for the acute injury is primarily medical, with the use of high dose steroids,[6,7] and supportive, through aggressive nursing care, and rigorous rehabilitation. Surgical interventions are primarily aimed at spinal column stabilization.[8] Recently, there has been an effort to examine the role of aggressive decompressive surgery in SCI.[9,10] However, to date, there is no therapeutic intervention to significantly restore function after SCI.

Over the past two decades the notion of spinal cord repair has been investigated. Development of animal models for SCI have been crucial for this effort. These models (Figure 1) include simulated contusions,[11-16] transections[11,17-21] and hemisections.[11,21-24] Neural transplantation has been employed as a repair strategy in the majority of these models.[25-29] Tissue sources for transplantation have involved peripheral nerve grafts,[30-33] dorsal root ganglia,[34] Schwann cells,[35,36] adrenal tissue,[37] and fetal spinal cord tissue, derived from both rat[11,38-40] and human[41,42] sources. The present review focuses on the current status of neural transplantation for SCI.

Role of transplants on axonal recovery

Traumatic injury to the spinal cord results in neuronal cell death and disruption of ascending and descending axonal pathways in the region of the injury. The concepts of primary and secondary injury are widely used in describing the sequence of events leading to neuronal dysfunction.[43,44] Primary injury results from the direct mechanical forces applied to the spinal

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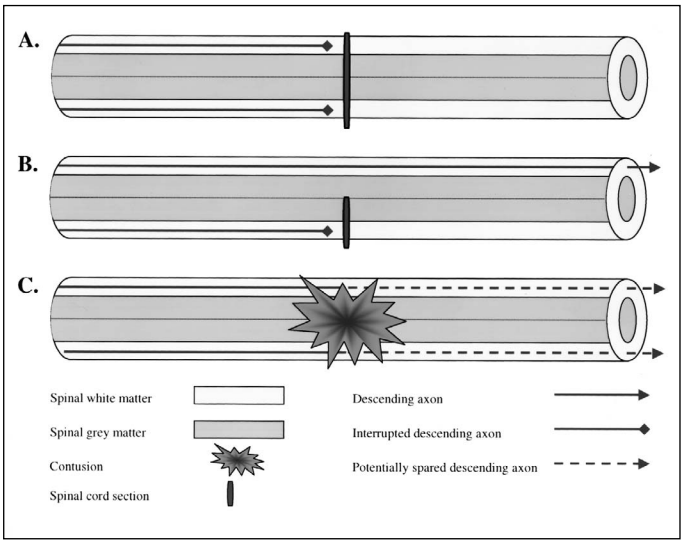

Figure 1: *Schematic horizontal longitudinal sections of the rat spinal cord. Demonstrating: A. the transection model representing bilateral disruption of descending axons, B. the hemisection model illustrating ipsilateral disruption of descending axons and C. the contusion model depicting the potential sparing of descending axons in an incomplete injury.*

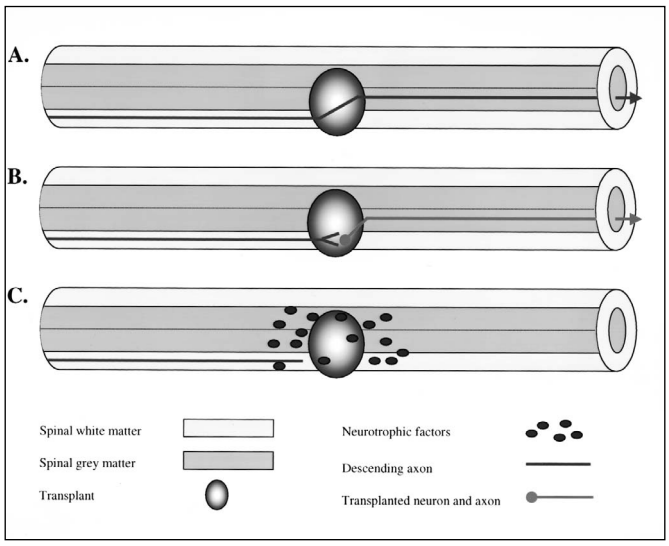

Figure 2: *Schematic horizontal longitudinal sections of the rat spinal cord. A. Demonstration of graft acting as a bridge for regenerating axons. B. Graft functioning as a synaptic relay for descending axons. C. Transplant secreting neurotrophic factors to support the severed axon and reduce axonal retraction.*

cord at the time of the trauma. These include compression, contusion, shearing and laceration.[44,45] Secondary injury has been attributed to local inflammation, edema, decreased blood flow, loss of autoregulation and microhemorrhage as well as electrolyte changes, particularly related to potassium and calcium.[44,45] These biochemical changes result in lipid peroxidation and free-radical production, which promotes further neuronal and axonal damage.[44,46] All these events culminate in the formation of a cavity at the injury site and the development of a glial scar,[45,47] which prevents axonal reconnections across the injury site.[38,48,49]

Transplantation of various types of tissue into and around the site of SCI in animal models have shown promise for functional recovery. However, the mechanism by which these grafts may induce beneficial functional effects is still not known.[11,25] One potential mechanism is that the graft serves as a bridge through which host axons can regrow to find their targets caudal to the lesion (Figure 2A). Various studies have shown that the bridge mechanism occurs in experimental injury models utilizing newborn rats undergoing fetal tissue transplantation.[17,22,50] Similar observations have been repeated in adult rats using either peripheral nerve graft[18,51] or Schwann cell conduits.[52] Another proposed mechanism is that grafts provide neurons, which can serve as synaptic relays for descending axons. Several studies have shown that host descending axons can penetrate into the graft and form synapses with the grafted neurons (Figure 2B). There is also evidence that grafted neurons themselves can send axons into the host spinal cord.[53-57] The third proposed mechanism is that the transplant may provide neurotrophic factors which may limit the degree of axonal retraction and may even promote survival and regeneration of host neurons (Figure 2C). The ability of fetal transplanted tissue to reduce host retrograde induced cell death in axotomized neurons in neonatal and adult models of SCI has been well-documented.[58-63] Fetal transplantation has also been shown to upregulate the expression c-Jun, an inducible transcription factor associated with regrowth of axotomized neurons.[64] This observation suggests a novel mechanism by which transplants can promote survival and regeneration at the cellular level. There is also evidence that fetal grafts can influence GABAergic interneurons in the region of the transplant, suggesting that appropriate grafts may reestablish, at least to some degree, local spinal circuitry.[65] However, it is likely that the mechanism by which neural transplants facilitate functional recovery is multifactorial and may involve all or some of the proposed mechanisms and may also be dependant upon the source of tissue transplanted.

Peripheral nerve grafts

Peripheral nerve grafts have been utilized since the time of Tello (1911) to stimulate CNS axonal repair.[66,67] Tello[67] was the first to demonstrate that CNS axons can penetrate a grafted peripheral nerve. Attempts to repair the spinal cord by using peripheral nervous system (PNS) tissue grafted into spinal cord lesions were carried out in the mid-twentieth century.[68-71] The initial report by Sugar and Gerard[68] suggested that new fibres could grow into a grafted segment of sciatic nerve. Further studies utilizing electron microscopy demonstrated that axons originating in the host, entered and crossed a sciatic nerve graft in a transected dog spinal cord.[72] During the 1980s, increased effort was directed towards using peripheral nerve grafts to facilitate CNS axonal recovery.[73-76] These studies repeatedly showed that PNS grafts promoted regeneration. However, they were unable to demonstrate that host axons could re-enter the

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CNS environment after traversing the peripheral nerve graft.[73,75,76] Using retrograde and anterograde tracing techniques, it was observed that regrowing axons penetrating the peripheral nerve graft originated from neurons in the CNS as well as from PNS neurons located in the dorsal root ganglia. These studies also demonstrated the significant role the distance of the injury from the cell body plays in the ability to regenerate axons. Injured bulbospinal axons were found to penetrate a peripheral nerve graft only if it was transplanted into the cervical region but not if it was transplanted into the thoracic region.[76]

A recent study in the complete spinal cord section model in the rodent attempted to connect spinal grey matter to white matter tracts by placing multiple intercostal nerve grafts between proximal white matter to distal grey matter, for descending motor tracts, and distal white matter to proximal grey matter, for ascending sensory tracts.[51] The grafts were held in place with a fibrin glue containing a neurotrophic factor (acidic fibroblast growth factor). Behavioural testing showed improved hind limb function and histological analysis showed evidence of cortico- and bulbospinal tracts passing through the graft and into the lumbar enlargement.

In an effort to facilitate axonal growth at the graft-host interface, attempts to modify the local environment by pretreating the host spinal cord with X-rays[49] or by genetically modifying the graft to overexpress outgrowth-promoting proteins have recently been conducted.[77] Unfortunately, despite the ability to identify the transduced gene product post-implantation, the axon ingrowth noted in sciatic nerve transplants was not greater than in a saline-injected control group.[77] However, irradiation of the spinal cord tissue prior to transplantation appears to decrease glial scar formation and may be useful in axonal growth through the graft-host interface.[49]

Grafts of myelin producing cells

It is generally accepted that Schwann cells play a significant role in the ability of the PNS to regenerate damaged axons. There is evidence that Schwann cells secrete various neurotrophic factors, such as nerve growth factor (NGF),[78] brain-derived neurotrophic factor (BDNF)[79] and ciliary neurotrophic factor,[80] as well as extracellular matrix molecules[81] which may play a significant role in axonal regeneration. Cultured Schwann cells from rat sciatic nerves have been seeded into channels and transplanted into a thoracic transection model of SCI.[82] These studies showed evidence of regeneration of propriospinal and sensory axons into the graft; however, there was no evidence of supraspinal axonal regeneration based on immunohistochemistry.[82] Further tracing studies of this model demonstrated not only extensive projection of spinal axons into the cervical and sacral regions but also limited growth of supraspinal axons into the rostral end of the graft.[83] This observation has been confirmed by other studies that have shown survival and integration of Schwann cell grafts into the host spinal cord.[84] Although the presence of regenerated spinal axons into the grafts has been observed, penetration of the graft by supraspinal axons continues to be elusive.[85]

The addition of neurotrophic factors via a mini-pump in Schwann cell grafts increased the number of myelinated fibres found in the transplanted region. Furthermore, tracing studies demonstrated labelling of brain stem nuclei.[86] To enhance the intrinsic ability of Schwann cells to secrete these neurotrophs, genetically modified Schwann cells have been used in grafting experiments.[87-90] Considerably more brain stem and hypothalamic labelling was observed in the modified Schwann cell grafts compared to the nonmodified Schwann cell grafts.[87] Furthermore, modified Schwann cell grafts were spontaneously arranged into regular arrays within the cord and showed evidence of enhanced axonal growth and remyelination when compared to untreated grafts.[90] Human Schwann cell grafts have also been studied.[91] When transplanted into the transected rat spinal cord these human Schwann cells showed evidence of axonal regeneration and induced some functional recovery.[91]

Another group of myelin-forming cells with similar potential for use in spinal cord transplantation are the olfactory ensheathing cells. These cells support the growth of axons from the olfactory bulbs and possess qualities of both Schwann cells and astrocytes.[92] However, they differ in their ability to traverse the boundary between the PNS and the CNS. It has been shown that these cells are able to myelinate axons in culture.[93] Li and co-workers[94] transplanted a suspension of ensheathing cells cultured from the adult rat olfactory bulb into the transected corticospinal tract in the cervical region. The graft was found to induce unbranched growth of the severed corticospinal tract into and through the transplant, re-entering the host spinal cord distal to the graft. The graft cells were seen to myelinate individual axons and surround groups of axons, thereby forming fascicles. Functional testing, using a directed forelimb reaching test, showed that animals receiving the grafts exhibited improvement in reaching of the affected limb, whereas, animals not receiving a graft did not improve. The enhanced regeneration induced by transplants of olfactory ensheathing cells has been confirmed in other studies,[95,96] and include evidence that the electrical conduction block of a demyelinating lesion can be overcome.[97] These promising results have promoted the use of olfactory ensheathing cells from human olfactory nerves. A recent report by Kato and colleagues[98] showed considerable spinal cord remyelination after human olfactory ensheathing cells were grafted into the demyelinated spinal cord of adult rats.

Grafts of fetal tissue

Over the past decade, there has been extensive experience in grafting fetal tissue for spinal cord repair and to promote functional recovery in animal models of SCI. Grafts of fetal cortical and spinal cord tissue have been implanted into neonatal and adult rats with spinal cord lesions. There is evidence of rescue of host spinal cord neurons by fetal grafts within seven days of lesioning. However, grafts implanted after this time had decreased effectiveness in preventing cell death, suggesting an optimal window for fetal grafting postinjury.[23]

Rat embryonic neocortical tissue has been shown to survive and differentiate into normal appearing neurons in the injured rat spinal cord.[99] Fetal grafts (E11-E17) have been used in both adult and neonatal rats.[99-102] Differentiated neurons and neuroglia have been identified as early as seven days postimplantation in these animals.[101] These implants appear to express cortical biochemical and morphological features despite their heterotopic location in the spinal cord.[103] There is evidence of glial migration; astrocytes derived from these grafts have been identified up to 3.5 cm away from their thoracic site of

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implantation, reaching both the cervical and lumbar regions.[104] Homotopic fetal spinal cord grafts appear to enhance neural reconnectivity as suggested by the formation of plexuses showing arborizations within motoneuron pools.[105] Homotopic spinal cord grafts seem to promote greater functional recovery when compared to heterotopic cortical grafts.[106] Furthermore, descending axons in the neonatal rat failed to grow into a cortical heterotopic graft but traversed a homotopic spinal cord graft.[18,21]

Fetal spinal cord tissue transplanted at the time of injury initially undergoes a period of cell death but once integrated into the host tissue, the cells rebound and proliferate to fill the lesion cavity.[107] There appears to be a need for immunosuppression, at least initially after grafting and cellular rejection is based on host and graft MHC expression.[107] This observation suggests that the region of injury and transplantation does not retain the immunological privilege presumed in the brain. Furthermore, it has been shown that the blood-spinal cord barrier is altered following SCI.[108] A study using the alpha-aminoisobutyric acid technique showed that although grafting with fetal tissue did not alter blood-tissue transfer rates initially, a significant decrease in permeability in graft areas was observed caudal to the injury site 14 and 28 days after implantation.[109] These results indicate a decreased need for immunosuppression following transplantation as the graft matures and the injury site regains its normal physiologic barriers.

Although there is clear evidence for graft survival and functional recovery following fetal tissue transplantation,[11,26,48,110] it has been difficult to demonstrate that regenerated axons project through the graft for more than 1-2 mm into the distal adult spinal cord.[54,60,111,112] In contrast, the results of fetal tissue grafting in neonatal pups following SCI has showed that descending axons penetrate the graft and extend for substantial distances distal to the transplant site.[20,40,50] There is also evidence that transplanted spinalized neonatal rats show improved functional recovery and near normal development in comparison to controls.[20,40,113] These studies suggest that the immature environment of the developing spinal cord is more conducive to graft survival and functional recovery.

Xenotransplantation using human fetal spinal cord tissue has also been studied in the rat model of SCI.[114-116] Following transplantation into a contusion model of SCI, human fetal spinal cord tissue could be identified immunohistochemically at 2-3 months postgrafting.[115] Solid grafts of fetal tissue placed acutely into a lesion site had an 83% survival rate compared to 92% survival rate when transplanted into a chronic contusion (14-40 days after injury).[116] When a cell suspension was used in the chronic model the survival was 85%. These experiments suggest that although human fetal spinal cord grafts can survive in rat models of SCI, graft viability, differentiation and integration is dependent upon the timing of the transplant and the type of graft (solid versus cell suspension).

In neural transplantation studies from our laboratory, we have been able to confirm the survival of human fetal spinal cord grafts in the hemisected rat model. Utilizing a double grafting technique, which has been shown to increase functional recovery and neural reconstruction in the rat Parkinson's disease model,[117] we were able to demonstrate improved functional recovery in rats transplanted with human fetal spinal tissue compared to hemisected only controls.[118]

Despite the promising results of fetal spinal cord transplantation, fetal tissue is not an ideal source of tissue because of ethical and availability concerns. A good deal of research is currently being conducted on developing alternatives to fetal tissue which could be used in neural transplantation for SCI repair.[119,120]

Grafts of neuronal stem cells and other neural cell lines

Recently there has been great interest in developing stem cell cultures and investigating their potential role in CNS disease.[121-124] In models of SCI, stem cells have been shown to survive, migrate over considerable distances and differentiate into both neuronal and glial phenotypes.[125,126] This degree of integration has coincided with behavioural recovery in transplanted animals.[126] Stem cells have also been shown to be capable of secreting neurotrophins after transfection with retroviral vectors.[125] The pluripotent qualities of stem cells hold conceivable promise as an alternative tissue source for transplantation in SCI.

A cell line derived from a human teratocarcinoma (NT2N; commercially available as hNT cells from Layton Bioscience Inc,) has yielded a homogeneous population of neural progenitor cells.[127] Following *in vitro* treatment with retinoic acid, the progeny of this cell line is restricted to a neuronal lineage yielding postmitotic neuronal cells. These cells retain their neuro-chemical, -physiological and -morphological properties.[128-135] The NT2N cells have been successfully transplanted into brains of immunodeficient mice with good survival and no evidence of tumour formation, graft rejection, significant apoptosis or necrosis after one year.[136-138] Furthermore, the NT2N transplanted cells integrated well into the surrounding host neural tissue by extending dendritic and axonal processes.[139] These results led to the implantation of NT2N cells into experimental animal models of neurological conditions such as: stroke,[140-142] Huntington's disease,[143] Parkinson's disease[144] and a traumatic brain injury.[145] Recently, it has been shown that hNT grafts integrate into the mouse spinal cord and project axons at lengths greater than 2 cm.[146] Recent experience from our laboratory indicates that hNT grafts survive and proliferate in a rat spinal cord hemisection model.[147]

Another neural progenitor cell line that has been developed is the RN33B cell line. These cells are derived from embryonic rat raphe nuclei that have been infected with a retrovirus encoding the temperature sensitive mutant of SV40 large T-antigen.[148] When transplanted into neonatal rat models of SCI these cells survive and differentiate to resemble bipolar neurons.[149] By altering the host environment, it appears that these cells respond to cues from the local microenvironment and have the plasticity to differentiate accordingly.[149,150] Unfortunately similar attempts to immortalize human neurons has been unsuccessful to date due to the development of chromosomal aberrations.[150]

Role of neurotrophic factors

There is abundant evidence of the role of neurotrophic factors in supporting growth and development of axons.[151-154] Although these proteins do not readily cross the blood-brain barrier, a variety of techniques have been devised to deliver them to the injury site, including: local injection,[155] embedding into a

collagen matrix,[156] use of mini-pumps,[157] or through transplantation of genetically modified cells.[158] Several neurotrophic factors have been shown to enhance recovery of damaged spinal axons *in vitro* and *in vivo*. These factors include glial cell line derived neurotrophic factor,[159,160] BDNF,[24] NGF,[157,161] ciliary neurotrophic factor,[24] neurotrophin-3 (NT-3)[155] and neurotrophin-4/5 (NT-4/5).[162] Neurotrophic factors appear to exert their effects via different subgroups of receptors such as the tyrosine kinase neurotrophin receptors (Trk). It is now known that specific Trk receptors have high affinity for specific neurotrophins, for example TrkA binds NGF, TrkB binds both BDNF and NT-4/5 and TrkC binds NT-3.[163,164] Furthermore, neurotrophins can be used to enhance recovery in specific axonal tracts depending upon the predominant subgroup of Trk receptors expressed in the neuronal population. It has been shown that dorsal root ganglion cells contain a high degree of TrkA positive neurons[165] and treatment with NGF yields significant regrowth of sensory axons[157,158] but no regrowth of corticospinal axons.[161] Similarly, TrkB is known to be expressed by rubrospinal neurons[166] and it has been shown that BDNF reduces axotomy induced rubrospinal cell death in newborn[167] and adult rats.[168] Corticospinal tract axons contain both TrkB and TrkC receptors and respond to both BDNF and NT-3.[166,169]

Biological molecules that inhibit axonal growth have also been described in association with oligodendrocytes in the CNS and are considered an impediment to regeneration.[170,171] In particular, myelin-associated glycoprotein (MAG),[172-174] neurite growth inhibiting proteins NI-35/NI-250[175,176] and bovine neurite growth inhibitor (bNI-220)[177] have been of interest. It has been felt that by inhibiting the effects of these proteins an environment more suitable for neural regeneration could be achieved. However, when MAG-deficient mice are used to assess the role of MAG in axonal regeneration, there was no significant difference found between the deficient mice and the wild type.[172,174] Therefore, it has been postulated that the inhibitory effects of MAG do not occur in isolation but rather act in conjunction with other inhibitory factors.[174] In addition to NI-35/250 and bNI-220, the chondroitin sulfate proteoglycans are a family of molecules which have been implicated in the formation of a glial scar and the inability of neurons to regenerate their axons.[178,179] The upregulation of chondroitin sulfate proteoglycans has been shown to correspond closely to regions of inflammation with activated macrophages, and a disrupted blood-brain barrier following SCI in rats.[179] These results are consistent with the concept that the factors inhibiting neural regeneration are likely multifactorial and may be derived from both sides of the blood-brain barrier.

It appears that our ability to promote axonal regeneration in the spinal cord may improve by activating growth promoting factors and decreasing inhibitory factors. Development of an antibody, IN-1, directed towards these inhibitory proteins has been shown to negate their effects in culture.[175,180] *In vivo* studies using SCI in rats have shown improved regeneration when IN-1 was present in the cerebrospinal fluid. Although the density of regenerating corticospinal tract fibres was low, animals treated with IN-1 were found to extend axons distal to the graft up to 18 mm, whereas in control animals, axons barely re-entered the distal host spinal cord.[181] A further improvement in axonal regeneration was observed histologically when IN-1 and NT-3 were used in conjunction.[155] However, when examining ascending sensory tracts in the dorsal funiculus a similar beneficial effect of IN-1 antibodies was not elicited.[176] This suggests a possible tract selectivity for these inhibitory proteins.

Human trials and the future

Neural transplantation for SCI is at its very early stages and considerable research using animal models is still needed before it can be considered a reconstructive strategy in humans. However, clinical trials have been reported. A trial of transplanting fetal neocortex into 41 patients with chronic SCI was performed in Russia about a decade ago.[182] No long-term follow-up or evidence of graft survival is available but the authors reported an improvement in sensory function over a number of dermatomes in some patients. More recently, a team in Denver, Colorado reported the use of human embryonic spinal cord tissue to obliterate a post-traumatic syrinx.[183] The authors reported a seven-month follow-up with persistent obliteration of a 6-cm cystic cavity and good visualization of the graft on MR imaging.

Although research in neural transplantation in animal models of SCI has showed some promising results, clinical trials of neural transplantation in SCI patients are premature. A greater understanding of the molecular mechanisms involved in SCI is necessary to achieve spinal cord repair by neural transplantation strategies. It is likely that genetic modification of cells to secrete neurotrophic factors or block the effects of inhibitory factors may be crucial in repair mechanisms. Undoubtedly, neuronal cell replacement will remain an essential part of any repair paradigm. With further advancement and development of novel cell lines, such as human stem cells, and a greater understanding of their versatility to differentiate into multiple phenotypes, a reliable source of cells for transplantation may be developed. The ability to re-establish local neural circuitry and reconnect neural pathways proximal and distal to the lesion, while limiting the extent of primary and secondary injury, will play an important role in attaining the ultimate goal of functional recovery. Although we have yet to reach the point of clinical application and much work is still left to be done, reconstructive strategies offer the greatest hope for the repair of SCI.

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