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Spinal Cord Injury

Research is a dynamic enterprise that generates a wealth of knowledge. It provides a forum for debating ideas and working them into evidence-based theories. The clinical trial setting puts these theories to the test and may lead to evidence-based medicines that can alleviate symptoms or cure disease. But the process of taking research from bench to bedside is a lengthy one, and demands not only vision but also years of hard work and dedication on the part of scientists, physicians and patients. This document presents basic information about spinal cord injury and frames the context for the discussion that follows about the future application of stem cells to treat this disease. Readers may also wish to peruse additional web resources or speak with their physicians for more information.

About Spinal Cord Injury

The brain and spinal cord together form the central nervous system (CNS) which is responsible for processing all the information coming from our senses, keeping our organs and reflexes functioning, and directing our movements, thoughts and feelings.

The spinal cord is the critical organ that connects the brain to the rest of the body by conveying electrical impulses along the long nerve fibres that are bundled within it.

The nerves that branch out from the spinal cord to the rest of the body comprise the peripheral nervous system (PNS). These peripheral nerves both receive and convey messages creating a feedback loop that allows us to feel sensation and enable movement.

A nerve cell, or neuron, has a long slender projection, called the axon that acts like a transmission line coming from the control centre of the cell. Even though axons are microscopic in diameter, they may be many feet long. Wrapped around the nerve fibres is a fatty substance called myelin that is similar to insulation on a telephone wire. Myelin is a critical component of the nervous system in that it speeds up the electrical signals and protects the nerves. In addition to neurons, the brain is also home to glial cells which play a critical role in stabilizing the environment, making myelin and supporting and protecting the neurons.

Spinal cord injury (SCI) may occur anywhere from the neck to the lower back. During an initial trauma in which the spinal vertebrae fracture or dislocate, the delicate spinal cord is violently struck. While the cord itself typically remains in one piece, many of the tiny nerve fiber bundles within it are severed. After this initial mechanical injury, inflammation, swelling, and other metabolic processes are triggered, causing further damage and disruption of the nerve fibers. The severity of paralysis experienced by the patient is dependent upon the degree of damage done to the spinal cord. However, even in cases of ‘complete paralysis’ where the patient has no feeling or movement below the injury, the spinal cord itself is not severed completely, and in fact, there are some axons that remain intact across the injury site. Some of these are thought to have lost their myelin sheaths (their insulation) and therefore do not conduct electrical signals well.

Causes and Treatment

Spinal cord injury affects mostly young adults, about 80% of whom are males. Car accidents are responsible for about 50% of cases. Sporting accidents, serious falls, wounds, and diseases of the spine, such as spina bifida, can also cause permanent injury to the spinal cord. In North America, it is estimated that more than a million individuals live with a disability resulting from some type of spinal cord injury.

Because spinal cord injuries are often the result of terrible accidents which paralyze otherwise fit and mostly healthy young people, they can cause significant and prolonged suffering. Depending on the severity of the injury, rehabilita-

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tion may help many people to regain some degree of function.

Unlike the skin, blood, muscle and other organs, for many reasons the CNS does not routinely regenerate after damage – hence, the disability caused by spinal cord injury may be permanent and profound. In contrast, the nerves in the PNS tend to regenerate after injury, both because they are intrinsically better programmed to regenerate, and because the cells that myelinate axons in the PNS (called Schwann cells) tend to encourage regeneration.

After spinal cord injuries occur, there is only a small window of opportunity – hours, maybe weeks – in which therapies may reduce the disability. Restoring the electrical transmission between the brain and spinal cord requires repairing the myelin sheath around the damaged neurons and, in severe cases, the regrowth of severed nerve fibres across the site of injury and into the neural network below the lesion. Scarring and other cellular damage that occurs when the body responds to injury often compounds the difficulties in bridging the lesion site in the aftermath of the injury, and in many cases rehabilitation is the only recourse.

Can Stem Cells Help?

Stem cells have incredible regenerative capacity. The rationale for developing stem cell therapies to treat spinal cord injury is to use stem cells as a source of new cells and products that will help prevent further cellular damage, restore axon function by replacing oligodendrocytes, generate new nerve cells, or guide the regrowth of severed nerve fibres.

A number of different types of stem cells (embryonic stem cells, umbilical cord stem cells, adult neural stem cells, mesenchymal/bone marrow stem cells and induced pluripotent stem cells) are currently being studied as potential sources of neurons, glial cells or neurotrophic factors to treat neurological disorders and traumas. Of particular interest are transplantation strategies aimed at using these cells to create oligodendrocytes, which are the glial cells that normally add myelin to nerve fibres in the brain and spinal cord.

Despite the tremendous promise of using stem cells for treating spinal cord injury, there are also limitations of an ethical and practical nature. For example, the source (embryonic versus adult), the risk of tumour formation, cell availability, the need for immunusuppression, and the potential to differentiate into the wrong tissues are all important considerations. Ongoing research is attempting to address these and other challenges while taking stock of the wishes of patients living with the devastation of spinal cord injuries.

Research Directions

Until 15 years ago, it was believed that the brain could not repair itself by generating new neurons. However, we now know that patients who have partial lesions to the spinal cord do experience a degree of spontaneous functional recovery arising from the ability of the brain to reorganize itself to produce new connections. This observation prompted scientists to wonder about the role of stem cells in the recovery process. The exciting discovery of neural stem cells (NSCs) in 1992 added to the stem cell arsenal and provided hope that such cells might someday be used to regenerate cells lost through CNS injury and disease. Numerous transplantation studies in animals have since provided the “proof of principle” that stem cells could potentially improve function after spinal cord injury.

In recent years, neural stem cells, derived from adults or embryos, and embryonic stem cells have shown great promise as potential sources of neural cells for regenerative therapies. Now scientists can grow these stem cells into neurons and glial cells, either in the laboratory before transplanting them, or directly implanting progenitor cells (partially-differentiated stem cells). For the laboratory approach, scientists first optimize cell culture conditions and experiment with the neurotrophic factors that stimulate stem cells to grow into the desired cell types prior to transplantation. For the direct transplantation approach, signals from the brain are expected to stimulate the progenitor cells to differentiate into the right kind of cells. These two strategies are generally known as exogenous repair (transplanting the required cell that is developed in the laboratory, or in vitro) and endogenous repair (relying on internal cues to differentiate neural stem cells in an animal, or in vivo). In the case of spinal cord injury, both approaches have merit and are being actively pursued by research teams around the world.

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Looking to the future

Scientists continue to experiment in animal models of spinal cord injury by developing culture systems and drugs that can direct stem cell differentiation. The goal is to be able to transplant cells or their products that will ultimately replace or repair the damaged spinal cord tissue. As new discoveries are made, scientists are able to choose the most advantageous stem cells for transplantation studies.

Human embryonic stem cells are currently being tested as a source of oligodendrocytes or neural progenitor cells that repair spinal cord injury in animals. Oligodendrocytes made from human embryonic stem cells have successfully restored neural function in animal models of spinal cord injury, but it is often tricky to differentiate oligodendrocytes in the laboratory without also differentiating other unwanted cells types or forming tumours. In an effort to streamline the differentiation protocols so that only the desired cell types are being made for transplantation, researchers have found that if they first coax human embryonic stem cells to become neural progenitors and transplant only the progenitors that the chances of tumour formation are decreased. They have also showed that transplanting the neural progenitors on a biodegradable scaffold is advantageous because the scaffold provides a surface for the neural progenitors to cling to and helps with the release of beneficial growth factors.

Much work is also being focussed on recruiting the body's own neural stem cells or transplanting adult neural stem cells. These cells have the capacity to make a range of cells types, including oligodendrocytes, astrocytes, and neurons. Studies in rats have shown that first differentiating neural stem cells into either oligodendrocyte or astrocyte precursors and transplanting these cells can lead to the remyelination of damaged axons and decrease motor neuron loss.

Researchers in Colorado and New York are particularly interested in astrocytes as a therapy for spinal cord injury. Astrocytes are extremely important in generating nerve fibre growth in early development of the nervous system, but they complicate spinal cord injury by creating scar tissue that prevents transmission of nerve impulses. Building on their discovery in 2008 identifying two distinct sub-types of astrocytes, the scientists have now shown that by manipulating different growth factors they can differentiate two different kinds of astrocytes from the same human fetal glial precursor stem cell population, and that only one population can promote behavioural recovery and protection in spinal cord injury in rats. This finding lends weight to the idea that differentiating a specific astrocyte pool is more successful than transplanting precursor cells, and this approach is being optimized in preparation for clinical trials.

Another approach that is being investigated involves exploiting the characteristics of olfactory ensheathing cell, a unique stem cell-like population of glial cells found in the nasal cavity. These cells secrete many different neurotrophic factors, have properties similar to Schwann cells and astrocytes, and are able to continually stimulate the regrowth of peripheral and central nervous system axons. Transplanting olfactory ensheathing cells in animals with spinal cord injury has shown promise and the addition of bioscaffolds to the mix is helping to direct axon cell growth and remodelling.

One of the most exciting landmarks in recent years occurred in 2006 with the discovery of induced pluripotent stem cells. iPS cells are made by reprogramming adult fibroblasts into embryonic-like stem cells that are capable of making different types of neurons, oligodendrocytes and astrocytes. Because induced pluripotent stem cells are patient-specific, they are being considered revolutionary in that they could provide a source of cells directly matching the genetic profile of a recipient. iPS cells also have advantages over other stem cells in that they are a more accessible source of cells and lack the inherent ethical consideration of embryonic stem cells. However, the same pitfalls that apply to iPS cells as to other stem cells, namely tumour formation. Although scientists have much work to do before they can use iPS cells in transplantation studies in humans, the work done towards optimizing cell culture conditions and reprogramming techniques are rekindling the possibility of transplanting patient-specific cells that will circumvent the problems of graft rejection and the need for risky immunosuppressant drugs.

Canadian Stem Cell Studies

A milestone in spinal cord injury research using adult stem cells was achieved in 2007 with the work of Dr Freda Miller and her colleagues in Toronto and British Columbia. Dr Miller discovered that stem cells derived from the patient's own skin (skin-derived dermal precursors – SKPs) share characteristics with embryonic neural stem cells and can produce Schwann cells -- cells that create a good growth environment to repair injured nerve fibres including the ability to

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make myelin, which is crucial for impulse conduction.

In pre-clinical experiments, Dr. Miller in collaboration with Dr. Wolfram Tetzlaff at UBC was able to prove that Schwann cells created from SKPs produced myelin along the damaged spinal cord of rats. They then tested whether this approach would result in functional improvement by directly transplanting Schwann cells created from skin into rats with spinal cord injury. Mobility and coordination improved after 12 weeks and there was evidence that new nerves were growing in the cavity of the spinal cord. The Schwann cells had created a sort of bridge that spanned the cavity allowing nerves to grow through the bridge. In addition, many spared nerve fibres near the lesion site that had lost their myelin were remyelinated by the Schwann cells.

Looking to the Future with Clinical Trials

There are few clinical trials at present examining the usefulness of stem cells to treat spinal cord injuries. Although the trials underway at a very early stage, they should yield much needed information about the safety and feasibility of transplanting stem cells into the injured spinal cord. Further clinical trials will be required to answer whether these early trials have actually helped to improve function, and those answers are still many years away.

In 2010, the Wroclaw Medical University in Poland began a phase I trial assessing the feasibility of transplanting olfactory ensheathing precursor cells into patients with complete spinal cord injury. The primary goal of the study is to assess the safety of the transplant in 10 patients. The long-term view is to test if the transplanted olfactory ensheathing precursor cells will be able to provide growth factors to support and enhance the survival of neurons. The trial also includes intense neurorehabilitation as an integral part of the therapy.

A recent trial sponsored by the California-based biotechnology company Stem Cells Inc. at Balgrist University Hospital In Switzerland began March 2011. Stem Cells Inc. has developed a technique for harvesting human central nervous system stem cells, known as HuCNS-SC, from brain tissue. The phase I/II trial aims to test the safety of transplanting HuCNS-SCs into the spine of 12 patients with chronic spinal cord injury. The study is due to be completed in 2016.

Another trial that began in 2011 is a phase I trial sponsored by the Memorial Hermann Healthcare System. The study participants are children under 15 years of age with spinal cord injury and as the primary goal the study plans to test the safety of transplanting a patient's own bone marrow progenitor cells. As a secondary goal the study will assess whether outcome measures relating to function, physiology and anatomy are improved. The trial is expected to end in 2014.

Further Reading

- The Christopher and Dana Reeve Foundation: http://www.christopherreeve.org/
- Spinal Cord Injury Information Network: http://www.uab.edu/medicine/sci/
- Rick Hansen Foundation: http://www.rickhansen.com/
- EuroStemCell: http://www.eurostemcell.org/factsheet/spinal-cord-injuries-how-could-stem-cells-help
- National Institute of Neurological Disorders and Stroke: http://www.ninds.nih.gov/disorders/sci/detail_sci.htm
- R Vawda, J Wilcox, and MG Fehlings. "Current stem cell treatments for spinal cord injury." Indian J Orthop. 2012 Jan-Feb; 46(1): 10–18. doi: 10.4103/0019-5413.91629. Online: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3270592/?tool=pubmed