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STEM CELL THERAPY IN SPINE SURGERY, CURRENT STATUS AND ETHICAL CONSIDERATION

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Abstract

The use of stem cells in spine surgery is compelling especially with the increasing age of the general population. Regenerative medicine using stem cell therapy has sparked much interest in this 21st century not only because of the controversies that surround the ethics involving stem cells but their potential for use in the clinic. The ability of stem cells to repair and regenerate new tissues and organs holds tremendous promise for the treatment of many serious diseases and injuries. This review provides a brief summary of the current status of research in stem cells with special emphasis on where we are in terms of the possible clinical application of stem cell therapy in spine surgery and it looks at the available evidence and examines the ethical issues and considerations associated with the clinical use of stem cell.

Introduction

Stem cells are cells having the capacity for self-renewal and the ability to differentiate into various types of tissues under certain conditions as seen in Fig.1.

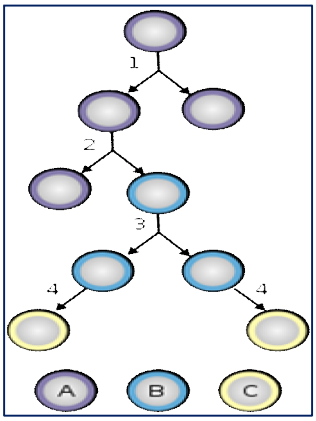

Fig.1: Stem cell division :
A - Stem cells;
B - Progenitor cell;
C - Differentiated cell

Sources of stem cell: Stem cells are derived from three main sources:

1. Embryonic stem cells: These stem cells originate from one of the earliest stages of development of the embryo called blastocyst. More specifically from the inner cell mass of the blastocyst at a stage before it would implant in the uterine wall. These cells can self replicate and are pleuripotent.

2. Adult stem cell: It is an undifferentiated cell that is found in a differentiated tissue. It can renew itself and become specialized to yield all the specialized cell types of the tissue from which it originated. In contrast to the embryonic stem cells, these are not capable of forming all the cells of the body that is they are multipotent but not pleuripotent. Adult stem cells have been found in the bone marrow, blood stream, cornea and retina of the eyes, the dentine, liver, skin, pancreas and gastrointestinal tract.

3. Umbilical cord stem cells: These are cells harvested from the cord blood. Cord blood is rich in the stem cells and after appropriate human leukocyte antigen [HLA] matching

may be used to treat a variety of conditions

Applications of Stem Cell Therapy in Spine Surgery

The challenge in spine surgery is to repair and regenerate damaged or diseased tissues. Another challenge would be to expand stem cells in adequate numbers and ensure that they are able to differentiate into to correct phenotype of tissue that they are intended to repair. The main aspects of stem cell treatment in spine surgery include:

1). Spinal Cord Injury (SCI)

Repair of the spinal cord is a very complex process that includes restoring or enhancing local spinal reflex arcs and reconnecting regenerating axons. Evidence of axonal regeneration and functional recovery has been seen in animal models of spinal cord injury.

Obstacles to regeneration of injured spinal cord: SCI initiates a chain of events that lead to cell death, scarring and the loss of function. The initial trauma injures cells and induces swelling. The damaged cells release toxins that cause necrosis of the cells above and below the injury site. Subsequent events include the formation of a cystic cavity at the injury site, which becomes surrounded by a glial scar, composed mainly of reactive astrocytes. The demyelination that occurs after injury produces several inhibitory molecules that contribute to the lack of regeneration.

Types of cellular therapy: A variety of cell types have been evaluated in the context of SCI.

1. Embryonic stem cells

The ability of embryonic stem cells (ESCs) to differentiate into cells from all three germ layers makes them an attractive source for a variety of applications. Some of the challenges in using ESCs include determining the correct cues to direct differentiation in the specific desired cell types *in vitro* and *in vivo* and preventing tetratoma formation.

Human embryonic stem cells: Development of methods and strategies for using human ESCs for treatment of SCI allows for translation to clinical studies. Testing the ability of human ESCs to promote recovery of injury models requires immuno-supression. Many of the human ESC lines that currently exist have been cultured in the presence of mouse feeder cell layers, making them undesirable for use in clinical trials.

A study has investigated differentiating human ESCs into neurons for use as a therapy for SCI[1]. This study determined a protocol for producing large numbers of motor neurons from human ESCs. These cells were able to maintain their phenotype after *in vivo* transplantation into the adult rat spinal cord. This study demonstrate the potential to create human ESC derived neurons, but these cells still need to be further characterized to determine how they will integrate and contribute to functional recovery after SCI.

On January 23, 2009, clinical trials for transplantation of a human-ES-derived cell population into spinal cord-injured individuals received approval from the U.S. Food and Drug Administration (FDA). Geron Corp. will test its oligodendrocytes precursor cells (OPC1) cells in 10 patients completely paralyzed by recent spinal cord injuries. It's the first FDA-approved study of an embryonic stem cell product in human patients. It's hoped that the OPC1 cells will restore nerve function not only by replacing lost myelin but by giving off chemical signals that promote new nerve growth[2].

2. Bone marrow stromal stem cells (BMSCs)

Eight people with spinal cord injury received surgeries that included removing scar tissue, untethering the spinal cord and receiving infusions of cells collected from their own bone marrow. Patients received the procedures within 40 days-6 years of their injuries; Patients were assessed for quality of life six months, one year and two years after the study, according to measures of bladder function, mobility and sensation. Almost all the patients reported some level of improvement on the measures assessed[3].

Autologous bone marrow derived stem cells have been transplanted in the injured spinal cords of 25 patients in Guayaquil, Ecuador, Encouraging results have been reported such as improved walking and sensory perception[4].

In a study by Jos G Jasper et al.; six patients with Dorsal Spinal Cord Injury, 100 ml of Bone marrow harvested from the posterior iliac crest .Bone Marrow Mono Nuclear cells were isolated. The isolated cells were injected through lumbar puncture. One of the six patients received two sittings of Stem Cell Therapy (SCT), while all others have undergone only one sitting. The patients were followed on a monthly basis . The one patient who was given two sittings of SCT made very good improvement and is now ambulant with the aid of an Orthosis. Two other patients who received one sitting of SCT had objective sensory and mild motor improvement; Three other patients had no improvement. There were no adverse reactions in any of them[5].

3. Olfactory ensheathing cells (OECs)

These cells are already part of our nervous systems and function in our sense of smell. The olfactory cells include neurons, progenitor stem cells that can differentiate into neurons, and olfactory ensheathing cells. OECs normally surround and protect neurons that are part of the olfactory system and assist those neurons in first developing and then repairing themselves if needed. They can secrete “growth factors” that stimulate neuronal growth. OEC cells also provide a track or framework on which the neuron grows. The fact that olfactory neurons, unlike neurons in the central nervous system, can repair themselves is one reason researchers are studying them. OECs can be obtained for autologous trans-plantation through nasal biopsies and grown in cell culture until needed.

Human studies of olfactory ensheathing cell transplantation following spinal cord injury have been performed in China, Portugal, and Australia. In 2008, the outcomes of the Australian Phase I/IIa feasibility and safety study were reported. In the six patients who were enrolled in the study, there were no adverse findings three years after autologous transplantation of olfactory ensheathing cells. The investigators concluded that transplantation of olfactory ensheathing cells into the injured spinal cord is feasible and safe for up to three years after implantation[6].

A team headed by Dr. Carlos Lima in Lisbon, Portugal, has surgically transplanted olfactory cells into over 7 individuals with spinal cord injuries which had occurred anywhere from six months to six years prior to the surgery. The physicians have indicated that while there have been no dramatic cures; there has been improvement with many, but not all, patients. Improvement ranges from increased sensation or decreased pain to improved motor abilities or bowel and bladder function[7].

Dr. Hongyun Huang transplants OEC cells obtained from the brains of aborted fetuses into patients at Xishan Hospital near Beijng, China. While the OEC cells Dr. Hwang uses are not obtained from the patient, he reports that there have not been problems with rejection. Dr. Huang has performed the procedure on hundreds of patients and claims there has been some improvement in 70% of the individuals operated on. The length of time from the date of spinal cord injury to surgery has ranged from six months to 18 years[8].

A different approach to the use of olfactory cells has been taken by a team headed by Drs. Tim Gerahty and Alan McKay-Sims at Princess Alexandria Hospital in Brisbane, Australia. They remove olfactory tissue from the patient and then culture it to grow additional cells. The cells (around 12,000,000) are then injected into the area of the injury. The injections do not require surgery. Some researchers question whether cells injected into the spinal cord will remain in the area of injury, given that cerebrospinal fluid bathes the cord and can wash the cells to other parts of the central nervous system, including the brain. The Brisbane team limited the patients in their small study (8 patients) to individuals with complete spinal cord injuries in the thoracic area that are six months to three years old. Results of their study, which began in 2001 and was scheduled to end in 2004, have not been published[8].

In conclusion Olfactory ensheathing cells from olfactory lamina propria in the nose are among the best transplants for "bridging" descending and ascending pathways in damaged spinal cord.

Delivery methods for cellular therapy: Once a decision has been made regarding what type of cells to use, the next consideration is how to deliver the cells to the injury site. Most of the studies discussed previously involved directly implanting the cells into and around the injury site. Other minimally invasive injection methods have been studied, such as intravenous injection, and infusion into CSF by lumbar puncture. An alternative method of delivery involves seeding cells into scaffolds and then implanting the scaffolds into the injury site.

2). Intervertebral Disc Degeneration

Intervertebral disc degeneration, which is manifested by gradual loss of water and proteoglycans result in instability of the associated spinal motion segment, which largely accounts for low back pain, secondary spinal deformity, and neural compressive manifestations. Treated conservatively approximately 90% of patients show improvement. After failure of conservative treatment, surgical options can be considered. Cell-based tissue engineering offers considerable promise for a biological alternative.

Potential Cell Sources

1. **Autologous or allogeneic nucleus pulposus(NP) cells**

A novel method to obtain activation of NP cells was reported by Yamamoto et al. using a direct cell-to-cell contact co-culture system with mesenchymal stem cells (MSCs). Besides differentiating into multiple cell types of mesenchymal origin, MSCs serve as feeder or nursing cells for other cells. The ability of MSCs to enhance the biological and metabolic viability of NP cells was evaluated using rabbit cell cultures. The results showed significantly better NP cell proliferation, DNA synthesis,

proteoglycan synthesis, and cytokine and/or growth factor production in a co-culture system with direct cell-to-cell contact with MSCs, compared to a conventional co-culture system or using monolayer cultures of NP cells. Furthermore, concentrations of transforming growth factor (TGF)-β, insulin-like growth factor 1 (IGF-1), epidermal growth factor, and platelet-derived growth factor were significantly increased in the direct cell-to-cell contact co-culture group, which presumably led to enhanced NP cell proliferation[9].

2. Stem cells

If a suitable cell source is unavailable, obvious candidates would be progenitor cells or stem cells. Sakai et al. studied the potential of MSCs as an alternative cell source. They transplanted autologous MSCs tagged with the gene for green fluorescent protein (GFP) in rabbit disc degeneration model created by nucleus aspiration, and followed for a period of 48 weeks. MSCs transplanted into degenerating discs in vivo can survive, proliferate, and differentiate into cells expressing the phenotype of NP cells[10]. although autogenic MSC implantation could not fully regenerate the disc, it could indeed overcome and counter the degeneration process to some extent. To enhance the full potential of MSC therapy, perhaps other factors such as mechanical stimulus, efficient removal of degeneration by-products, or inactivation of the degeneration precipitating factors need to be considered.

Extending the concept of stem cell therapy further, investigators have exploited the use of allogenic stem cells. Leung et al. reported multiple advantages of allogenic MSC transplantation for disc disease. This has the added advantage of off-the-shelf availability. Moreover, as the cause of disc degeneration is thought to be multifactorial, the use of allogenic stem cells could eliminate potential autogenic precipitating factors such as genetic predisposition, or the diminished potency of stem cells due to natural aging. In fact, IVD is suggested to be immune-privileged due to its avascular nature. A study, showing allogenic nucleus pulposus cell transplantation did not elicit lymphocyte infiltration, is consistent with this notion. The problem of immune rejection is likely to be even less for allogenic MSCs, since MSCs are capable of escaping alloantigen recognition.

3. Spine Fusion

Eleven patients affected by serious forms of congenital infantile scoliosis, idiopathic scoliosis and grade I spondylolisthesis received surgical treatment and delivery of stem cells taken from the iliac bone. The results were evaluated by X-rays and CT at intervals of 1, 2, 4, 6 and 12 months. In the fusion areas the added use of autologous stem cells seems to improve the physiological processes of fusion. It will be necessary to monitor the long-term results of these procedures[11].

A 14-year-old boy has scoliosis undergo spinal fusion surgery using his own bone marrow stem cells and donated bone from bone bank. Three months later the patient stand on his feet with progress[12].

Ethical consideration

On August 9th 2001, President Bush announced that federal funds may be awarded for research using human embryonic stem cell lines that meet certain criteria. These stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed,

informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements.

There is wide variability amongst different countries regarding the ethical guidelines and regulation of stem cell research and therapy. Recognising that these differences are inevitable, the International Stem Cell Forum (ISCF) was initiated in 2002 by Sir George Radda. The ISCF consists of delegates representing the funding agencies of countries involved in stem cell research. The aims of the ISCF are primarily designed to forge international collaborations in stem cell research by working to establish the standardization of techniques, the sharing of cell lines, training, conferences and information. Various subcommittees have been organised to discuss scientific issues, ethics and intellectual property.

The International Society for Stem Cell Research (ISSCR) is a society for scientists involved in stem cell research. In addition to the publication of the Guidelines for the Conduct of Human Embryonic Stem Cell Research in December 2006, the ISSCR recently published its Guidelines for the Clinical Translation of Stem Cells[13]. These guidelines were developed by a multidisciplinary group of stem cell researchers, clinicians, ethicists, and regulatory officials from 13 countries. They highlight the scientific clinical, regulatory, ethical, and social issues that should be addressed so that basic stem cell research is responsibly translated into appropriate clinical applications for treating patients. The ISSCR also provides information for patients and their doctors evaluating stem cell therapy in its Patient Handbook on Stem Cell Therapies[14]. These publications are very important guides and are highly recommended as reading material for those interested in using stem cells for therapeutic purposes.

Conclusion and current status of stem cell therapy

The use of stem cell in spine surgery has provided a new arena for managing complex conditions. Its use holds promise of wide spread applications particularly in areas of spinal cord injury, degenerative disc disorders and spine fusion. and It is the responsibility of every doctor to ensure that he has enough knowledge of the current status of stem cell therapies so that he can correctly advise his patient.

In general the use of adult stem cells is closer to the clinic as these cells are less potent than ESCs and more directed, so there is little or no likelihood of teratoma formation. There are now many pre-clinical studies in animals as well as a few clinical studies stem cells to treat spine problems.

Finally, it is important to note that as a doctor, the patient's safety and well-being must always come first.

Up to date, stem cell therapy is not yet approved by Christianity.

Refrences

1. Lee H, Al Shamy G, Elkabetz Y, Schoefield CM, Harrsion NL, Panagiotakos G, et al. Directed Differentiation And Transplantation of Human Embryonic Stem Cell Derived Motoneurons. Stem cells. Dayton, Ohio: 2007.
2. Daniel J. DeNoon /1st Human Embryonic Stem Cell Study Set 10 Paralyzed Patients to Get Stem Cells in Spine /WebMD Health News/Jan. 23, 2009.
3. Geffner, L. F. et al. Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: comprehensive case studies. *Cell Transplant*. 17, 1277–1293 (2008).
4. Baptiste DC, Fehlings MG.Update on the treatment of spinal cord injury .Prog Brain Res. 2007:161:217-233.
5. Jos G Jasper, Sankaranarayanan S, Baskar S and Senthil KR, Autologous Stem Cell Therapy in Spinal Cord Injury, Journal of stem cells and regenerative medicine,Vol.IV Issue: I: Abstract: PASRM 2008-005 (JSRM code: 004010700007).
6. A.Mackay-Sim, F. Féron, J. Cochrane,L. Bassingthwaighte,C. Bayliss,W. Davies P. Fronek, C. Gray, G. Kerr,P. Licina,A. Nowitzke,C. Perry, P.A.S. Silburn,S. Urquhart, and T. Geraghty /Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial/Brain. 2008 September; 131(9): 2376–2386. /Published online 2008 August 8. doi: 10.1093/brain/awn173.
7. Carlos Lima, MD, José Pratas-Vital, MD, Pedro Escada, MD, Armando Hasse-Ferreira, MD, Clara Capucho, MD, and Jean D Peduzzi, PhD /Olfactory Mucosa Autografts in Human Spinal Cord Injury/ J Spinal Cord Med. 2006; 29(3): 191–203. PMCID: PMC1864811.
8. Http://www.sci-recovery.org/stem cell research in spinal cord injury treatment.
9. Yamamoto Y, Mochida J, Sakai D, Nakai T, Nishimura K, Kawada H, Hotta T (2004) Upregulation of the viability of nucleus pulposus cells by bone-marrow-derived stromal cells: significance of direct cell-to-cell contact in co-culture system. Spine 29:1508–1514.
10. Sakai D, Mochida J, Yamamoto Y, Nomura T, Okuma M, Nishimura K, Nakai T, Ando K, Hotta T (2003) Transplantation of mesenchymal stem cells embedded in Atelocollagen gel to the intervertebral disc: a potential therapeutic model for disc degeneration. Biomaterials 24:3531–3541.
11. G. La Rosa; and M. Crostelli. The use of mesenchymal stem cells and growth factor bmp-7 in paediatric spinal surgery. Journal of Bone and Joint Surgery - British Volume, Vol 87-B, Issue SUPP_II, 185-197. May 30, 2008.
12. MESA, Ariz. (Ivanhoe Newswire) .Stem Cells for Scoliosis. Ortopedic channel, Reported May 30, 2008.
13. International Society for Stem Cell Research. Guidelines for Clinical Translation of Stem Cells, 2008 Dec 3.
14. International Society for Stem Cell Research. Patient Handbook on Stem Cell Therapies, 2008 Dec 3.