Perspective

Current stem cell treatments for spinal cord injury

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Introduction

Spinal cord injury (SCI) is a devastating condition associated with significant functional and sensory deficits, emotional, social, and financial burdens, and an increased risk of cardiovascular complications, deep vein thrombosis, osteoporosis, pressure ulcers, autonomic dysreflexia, and neuropathic pain.

The estimated annual global incidence of SCI is 15–40 cases per million. In the USA, approximately 1.275 million individuals are affected, with over 12,000 new cases each year.[1-5] The most common causes of traumatic SCI are road traffic accidents, falls, occupational and sports-related injuries that result in contusion and compression of the spinal cord.[1] Approximately 55% of SCIs occur at the cervical level (C1 to C7-T1) with a mortality of 10% in the first year following injury and an expected lifespan of only 10–15 years post-injury, and thoracic (T1–T11), thoracolumbar (T11–T12 to L1–L2) and lumbosacral (L2–S5) injuries each account for approximately 15% of SCI.[1-4] Depending on the age of the patient, severity, and levels of SCI, the lifetime cost of health care and other injury-related expenses can reach $25 million.[1-5]

Despite advances in pre-hospital care, medical and surgical management and rehabilitation approaches, many SCI sufferers still experience substantial neurological disability. Intensive efforts are underway to develop effective neuroprotective and regenerative strategies.

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Pathophysiology

SCI involves a primary (the physical injury) and a secondary injury (the subsequent cascade of molecular and cellular events which amplify the original injury).[6] The primary injury damages both upper and lower motor neurons and disrupts motor, sensory and autonomic functions. Pathophysiological processes occurring in the secondary injury phase are rapidly instigated in response to the primary injury in an attempt to homeostatically control and minimize the damage. Paradoxically, this response is largely responsible for exacerbating the initial damage and creating an inhibitory milieu that prevents endogenous efforts of repair, regeneration and remyelination. These secondary processes include inflammation, ischemia, lipid peroxidation, production of free radicals, disruption of ion channels, axonal demyelination, glial scarring (astrogliosis), necrosis and programmed cell death. Nevertheless, endogenous repair and regenerative mechanisms during the secondary phase of injury minimize the extent of the lesion (through astrogliosis), reorganize blood supply through angiogenesis, clear cellular debris, and reunite and remodel damaged neural circuits. The spatial and temporal dynamics of these secondary mediators[7] are fundamental to SCI pathophysiology and as such offer exploitable targets for therapeutic intervention.

Cell Therapy

A multitude of characteristics of cells tested pre-clinically and clinically make them attractive to potentially address the multifactorial nature of the pathophysiology of secondary SCI – they are anti-inflammatory, immunomodulatory,[8-12] anti-gliotic,[13] pro-oligodendrogliogenic,[14] pro-neuronogenic,[15] and secrete various anti-apoptotic and pro-angiogenic neurotrophic factors. Given the pathophysiological targets of SCI,[7] transplanted cells should: 1) enable regenerating axons to cross barriers; 2) functionally replace lost cells; and/or 3) create an environment supportive of neural repair.[16] However, given the multifactorial nature of SCI and its dynamic pathophysiological consequences, the success of future clinical trials of cell therapy will likely depend on the informed co-administration of multiple strategies, including pharmacological and rehabilitation therapies.[7]

Different sources and types of cells have been and/or are being tested in clinical trials for SCI, including embryonic stem cells (ESCs), neural progenitor cells (NPCs), bone marrow mesenchymal cells (BMSCs) and non-stem cells such as olfactory ensheathing cells and Schwann cells.[17] Other cell types are being developed for the clinic, including other sources of mesenchymal cells (fetal blood,[18] adipose tissue, umbilical cord[19-36]), adult[21,37] and immortalized neural progenitors (PISCES, NCT01151124), skin-derived progenitors,[38-47] induced pluripotent stem cells[48-52] and endogenous spinal cord progenitors[53-58] [Table 1]. The advantages and disadvantages of each cell source and type being considered or already in clinical trials for SCI have been extensively described and compared elsewhere,[17,59-63] and reflect their potential in the clinic [Table 1]. There are currently more than a dozen cell therapy clinical trials for SCI listed on clinicaltrials.gov.[64] Most are Phase I or I/II clinical safety and feasibility studies, indicating that cellular treatments for SCI developed in the laboratory are still in the very early stages of clinical translation.

This editorial will focus specifically on the most widely studied progenitor cells currently in clinical trials for SCI: BMSCs and NPCs.

Bone Marrow Stromal Cells

BMSCs are isolated from the stromal compartment of bone marrow, and fractioned from hematopoietic stem cells by virtue of their adherence to tissue culture plastic and/or their expression of distinct cell surface antigenic markers. They are non-teratogenic, have anti-inflammatory and immunomodulatory effects[65,66] and secrete neurotrophic factors, making them attractive candidates in CNS cell rescue and as autologous transplanted cellular sources of trophic support for endogenous and co-implanted cells. Despite recurring claims of their neurogenic differentiation potential *in vitro* or *in vivo*, there is no conclusive evidence to support this.[67]

Most studies of BMSCs have found beneficial effects of BMSC administration after thoracic SCI, largely as a result of neurotrophic factor secretion[68,69] and possibly also anti-inflammatory cytokine secretion. Intraspinal as well as intrathecal and systemic (intravenous) routes of delivery have been successful.[70-72] Porcine and non-human primate studies have been carried out to further support their clinical use,[73,74] and as in rodent studies, it has been found that BMSCs promote a certain degree of axonal regrowth and sprouting, at least in transection models,[75] especially when treated with growth factors prior to being implanted.[68]

The inflammatory component of SCI and subsequent demyelination of surviving axons are serious limiting factors in the efficacy of early cell therapy for SCI, as implanted cells are more likely to be eliminated by the host.[76] The immunomodulatory effect of bone marrow-derived cells has been demonstrated in the Canadian Bone Marrow Transplant (BMT) clinical trials for multiple sclerosis led by Freedman.[65,66] It is therefore worth considering interventions to modify the inflammatory milieu in order to enhance donor cell survival and efficacy, as in the newly initiated clinical trial of autologous BMSCs in children suffering from SCI [Table 2] (NCT01328860).

Table 1: A comparison of the different cell types and sources currently in (*) or under consideration for clinical trials for SCI

	WJ/UCM	fMPC	BMSC*	ES*	iPS	fNPC*	aNPC	OEC*	SC*	SKP	Adip MSC
Isolation Practicalities Ethical considerations	Easy None	Chal-lenging Signifi-cant	Chal-lenging Consid-erable	Challenging Significant	Challenging None	Challeng-ing Signifi-cant	Challeng-ing Consider-able	Chal-lenging Few	Chal-lenging Consid-erable	Less challenging Few	Easy Few
Differentiation potential											
Bone	✓	✓	✓	Pluripotent	Pluripotent	Neural	Neural	-	-	Peripheral myelin	✓
Fat	✓	✓	✓								✓
Cartilage	✓	✓	✓								✓
Storage											
Pre-isolation	✓	×	×	×	×	×	×	×	×	×	?
Post-isolation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunogenicity	Low	Low	Low	Low/?	Low/?	Low	?	Low	Low	Low	Low
Immunosuppressant/ anti-inflammatory	✓	×	✓	?	?	✓	?	?	?	?	?
Tumorigenicity	×	×	×	✓	✓	×	×	×	×	?	×
Transfection	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	?
Safety/risk	✓	✓	✓	✓	?	✓	✓	✓	✓	?	✓
Pathotropism	✓	✓	✓	?	?	✓	?	?	?	?	?
Autologous	Potential	No	✓	×	Potential	×	×	✓	✓	✓	✓

WJ – Wharton's jelly; UCM – umbilical cord matrix; BMSC – Bone marrow stromal cells; ES – Embryonic stem; iPS – Induced pluripotent; fNPC and aNPC – Fetal and adult neural precursor cells; OEC – Olfactory ensheathing cells; SC – Schwann cells; SKP – Skin-derived progenitors; AdipMSC – Adipose tissue-derived mesenchymal cells, *cells in current or pas clinical trials for SCI.

Table 2: Clinical trials of cell therapy for SCI listed on www.clinicaltrials.gov.

Status	Study	NCT	Cells	Administration route	Phase	Country	Sponsor/ Investigator	Duration	Numbers enrolled
Recruiting	Transfer of bone marrow derived stem cells for the treatment of SCI	NCT 01162915	Autologous BMSCs, expanded *ex vivo*	Intrathecal infusion, single dose	I, single center	USA	TCA Cellular Therapy, LLC; Gabriel P. Lasala	July 2010–June 2012	10
Completed	Cell transplant in SCI patients Condition: Chronic SCI Procedure: Physical therapy	NCT 00816803	Autologous bone marrow	?	I/II	Egypt	Cairo University, Cancer Institute of New Jersey, UMDNJ/RWJMS; Hatem E. Sabaawy	May 2005–Dec 2008	80
Recruiting	Transplantation of autologous OECs in complete human SCI Other: Rehabilitation	NCT 01231893	Autologous olfactory mucosa ensheathing cells (OECs) and fibroblasts	Intraspinal	I	Poland	Wroclaw Medical University; Wlodzimierz Jarmundowicz, Pawel Tabakow	May 2008	10
Terminated	Treatment for acute SCI	NCT 00695149	BMSC	Into cerebrospinal fluid	I/II	Japan	Translational Research Informatics Center	July 2005–March 2010	23
Completed	Autologous adipose derived MSCs transplantation in patients with SCI	NCT 01274975	Autologous adipose derived MSCs	Intravenous infusion, 4×10^8 cells	I	Korea	RNL Bio Company Ltd, SangHan Kim	July 2009–Feb 2010	8
Recruiting	Safety and feasibility of umbilical cord blood cell transplant into injured spinal cord Drug: ± Methylprednisolone Drug: ± Lithium	NCT 01046786	Umbilical cord blood mononuclear cell, dose comparison	Intraspinal	I/II	China	China Spinal Cord Injury Network	Jan 2010–June 2012	20
Completed	Safety and efficacy of autologous bone marrow stem cells in treating SCI Condition: Acute, subacute and chronic SCI Procedure: Laminectomy	NCT 01186679	Autologous bone marrow	Intrathecal	I/II	India	International Stemcell Services Limited, Arvind Bhateja	Jan 2008–Aug 2010	12
Enrolling by invivation	Umbilical cord blood mononuclear cell transplant to treat chronic SCI Other: Methylprednisolone, sodium succinate or lithium carbonate plus rehabilitation	NCT 01354483	HLA-matched umbilical cord blood mononuclear cells		I/II	China	Treating Center of Spinal Cord Injury Chengdu Army Kunming General Hospital (Dr Hui Zhu)	Sep 2010–Dec 2012	20
Suspended	Autologous incubated macrophages for patients with complete SCIs condition: Acute SCI	NCT 00073853	Autologous incubated macrophages	Intraspinal	II	USA, Israel	Proneuron Biotechnologies, Marcus Foundation B.I.R.D. (Israel-U.S. Binational Industrial Research and Development); Daniel Lammertse, Nachshon Knoller, Marca Sipski, Edward Benzel	Sep 2003	61

Table 2 contd/-

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Status	Study	NCT	Cells	Administration route	Phase	Country	Sponsor/ Investigator	Duration	Numbers enrolled
Recruiting	Safety study of GRNOPC1 in SCI Condition: Complete T3–T9 level subacute (7–14 days post-injury) SCI	NCT 01217008	GRNOPC1 (ES cell-derived oligodendrocytic progenitors)	Intraspinal, single dose of 2 million cells	I	USA	Geron, Gary K. Steinberg, David Apple, Richard G Fessler, James S Harrop, Shekar Kurpad	Oct 2010–Oct 2012	10
Recruiting	Autologous stem cells for SCI in children Condition: Primary SCI, to minimize secondary SCI	NCT 01328860	Autologous BMSCs	Intravenous infusion	I	USA	Memorial Hermann Healthcare System, James E. Baumgartner	April 2011–Oct 2014	10
Recruiting	Autologous bone marrow stem cell transplantation in patients with spinal cord injury	NCT 01325103	Autologous BMSC	Intraspinal	I	Brazil	Hospital Sao Rafael; Ricardo R. dos Santos	July 2010–Jan 2013	20
Recruiting	Study of human CNS stem cells (HuCNS-SC) in patients with thoracic spinal cord injury Condition: Subacute thoracic (T2–T11) SCI	NCT 01321333	HuCNS-SC cells	Single dose, intramedullary	I/II	Switzer-land	StemCells, Inc.; Armin Curt	March 2011–March 2016	12

Ongoing clinical studies and those carried out to date have enrolled small patient numbers and have used autologous marrow-derived cells rather than purified stromal cells.[77-80] A recently published dose-escalation trial examined autologous BMSCs in patients with chronic SCI.[66] Although BMSCs were safe, they were not found to be beneficial in this cohort of patients. Having clearly established the safety and feasibility of the clinical use of BM-derived cells specifically for SCI in these trials, the continued testing of BMSCs in the context of SCI appears justified although the use of this intervention in complete thoracic cases may not be optimal. Based on the mechanism of action of BMSCs, which appear to provide trophic support to the penumbra zone of the acutely and subacutely injured cord, trials in patients with subacute severe, but incomplete spinal cord lesions are a consideration.

The use of BMSCs in SCI does, however, present certain issues. BMSC migration beyond the injection site (for intraspinally delivered cells) is limited, and inter-donor variability in efficacy and immunomodulatory potency might confer variable clinical outcome,[81] making evaluation of efficacy difficult. Studies of BMSCs in cervical contusion–compression models have yet to be carried out. BMSCs have, in all but two studies by the same group, been used in subacute and acute models.[82-85] Based on the limited number of pre-clinical studies in chronic models, it is not yet possible to evaluate their efficacy. It is also not known whether BMSCs provide functional preservation of axons or *de novo* axonal regrowth across the lesion site in contusion–compression models, which are more appropriate models to distinguish these processes than transection models.[86-89]

Neural Progenitor Cells

NPCs can be generated from ESCs, which are derived from the blastocyst-stage embryo. These cells have indefinite self-renewal capacity and are pluripotent, with the potential to generate all cell types of the body, making them a potentially limitless source of cells for therapy. However, they are not without problems [Table 1], including the moral issues and practical constraints of their embryonic derivation, their karyotypic instability with repeated freeze–thaw cycles,[90,91] and their teratogenic potential in the host.

Pre-clinical studies have shown that animals transplanted with human ESC-derived oligodendrocytic progenitors cells (OPCs) show improvement in functional recovery following SCI.[12,92-96] With this background, extensive pre-clinical studies were conducted by Geron to characterize the safety and efficacy of hESC-OPCs exclusively in rodent models prior to the conduct (not without considerable objection and controversy) of a clinical trial of human ESC-derived OPCs implanted within 2 weeks into patients with thoracic SCI.[97-99] This Geron-sponsored clinical trial is further supported by behavioral and histological data from studies implanting

glial restricted progenitors (GRPs)[100] and OPCs[101,102] isolated from embryonic and post-natal rodents in SCI models, albeit indirectly. Whilst these show predominantly astroglial differentiation of GRP implanted within the blunt contusion-induced thoracic lesion site, there is a shift toward oligodendrocytic specification beyond the injury site correlated with the degree of functional improvement,[103-105] both of which can be enhanced by transduction of factors such as D15A, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3).[106] GRP implantation was also shown to be neuroprotective and inhibited neuropathic pain.

Neural progenitor cells can also be derived from several regions of the fetal, post-natal and adult CNS, including the sub-ventricular zone of the brain, the central canal of the spinal cord and the hippocampus. They can be expanded in culture as non-adherent neurospheres and have the potential to generate all three neural cell types under the appropriate conditions. The key advantage of this NPC source is the amenability to *in vitro* manipulation (including immortalization) prior to implantation as well as the lack of tumorigenicity. However, autologous derivation of CNS NPCs would be unfeasible for cell therapy purposes.

On the basis of promising results in clinically relevant primate[107-109] and canine cervical contusion models of SCI and cell number-dependent locomotor recovery in acute, subacute and chronic thoracic rodent models,[110-113] a StemCells Inc-sponsored clinical trial is underway to treat SCI sufferers with non-immortalized fetal human CNS stem cells (HuCNS-SC, NCT01321333). The lack of trials of NPCs in SCI is in spite of the bulk of pre-clinical findings to date in support of the potential of fetal and adult NPCs (particularly the former) in experimental SCI models,[17] and is likely to reflect ethical concerns over their origins and practical issues hindering their isolation and directed differentiation. Another possible explanation for the absence of clinical trials of NPCs for SCI is that the mechanisms through which NPCs provide functional benefit (including immunomodulation and angiogenesis) are only now beginning to be understood. Also, aims of axonal regeneration through the injury site have been replaced pre-clinically by more realistic objectives of remyelination[17] and provision of trophic support for endogenous precursors and axons. This makes NPCs much more promising candidates for cell therapy for SCI and probably heralds their increased use in clinical trials.

Conclusion

Cell therapy can potentially enhance the quality of life of those affected by SCI. The significant advances that have been made on the basis of pre-clinical studies carried out in rodent models of SCI have enabled clinical trials demonstrating the safety of cell therapy for SCI to proceed and have informed researchers of the knowledge gaps that remain to be addressed. However, rodent contusion/compression models of SCI are generally "incomplete" with partial sparing of motor and sensory functions, and mimic most closely patients with severe, partial lesions with an American Spinal Injury Association (ASIA) impairment scale rating of AIS B or C. Given that most trials of cell therapy have been carried out in AIS A patients (the safest to treat but also the least likely to show cell therapy-induced benefit), there is a need for future clinical trials to include patients modeled in the laboratory. There is a compelling need for preclinical researchers to develop valid models of compressive/contusive cervical SCI given that approximately 50–60% of human SCI involves the cervical region.

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