Stem cells therapy as a treatment for spinal cord injury

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Abstract

Stem cells therapy holds a great promise to treat several degenerative diseases and repair damaged tissues that are otherwise very difficult to treat by conventional therapies. In future, stem cells therapy will treat spinal cord injury (SCI) which is a major problem associated with demyelination of neurons caused by trauma resulting in cell death that is irreplaceable. Patients usually survive with spinal cord injury but this trauma remains uncured. After SCI, endogenous neuroprogenitor cells migrate towards the affected tissue but many messenger cascades suppress their proliferative activity. Different exogenous stem cells sources are another option to treat SCI patients. Although there is no permanent cure of SCI patients but due to excitatory development in the field of stem cells transplantation, promises a hope for its cure in future. Due to intricacy of factors involved after SCI, there is a need for combinatorial therapies.

Introduction

Spinal cord injury results in severe damage to motor, sensory and autonomic nervous functions and may leads to paraplegia and tetraplegia. Due to cellular loss, regeneration after spinal cord injury is limited1 and current approaches to treat spinal cord injury do not lead to complete cure. Embryonic stem cells transplantation (embryonic central nervous system or human umbilical cord blood stem cells) has been shown to successfully replace host neurons, enhance axonal growth, and improve functional recovery in rat models of spinal cord injury.2-4 Stem cell therapy proves to be promising candidate to treat SCI. Embryonic stem cells (ESCs) are undifferentiated cells that have the ability to proliferate in undifferentiated state both in vitro and in vivo conditions which means they have the capacity of self-renewal and to differentiate into mature specialized cells such as motor neuron. New approaches in stem cell therapy using neuro stem/progenitor cells are widely accepted for the treatment of degenerative diseases for the repair of damaged or lost tissues.5 For stem cell therapy there are several cell sources, including fetal spinal cord tissues6, neural stem cells (NSCs) from adult brains7, and mesenchymal stem cells (MSCs) from bone marrow8 and other organs9, in addition ESCs is another source.10 Human embryonic and adult stem cells both have potential use for cell based regenerative therapies. Of course they differ in many respects like number and differentiated cells types they can be-
cing new cells that have the potential to differentiate and reinte- 

crate into the host tissue to replace lost neuronal tissue. 

NSCs can be directly stimulated in vitro and then neurogene-

sisis can take place in vivo by vascular endothelial growth fac-

tor (VEGF) addition.16

Two mechanisms have been given preferences because of 
their exciting results in promoting regeneration of damaged 
tissues in SCI.17,18 According to first mechanisms differenti-

ated neurons can be introduced in the damaged tissues which 

further make links with surrounding tissues to regenerate neu-

rons. This results in recovery of function. The second possible 

mechanism states that in host tissues different growth factors 

and neurotrophics are released by transplanted stem cells 

which can help in regeneration, repair and survival of that 
damaged host tissue.

**Endogenous neural stem cells after SCI**

Spinal cord injury badly affects axons and myelination which 

interrupts sensory and motor neuronal transmission to and 

from the brain. It does not affect the survival rate but pa-

tients with spinal cord injury are left uncured.19 After the in-

jury, stem cells present around the ependymal layer starts to 

proliferate and differentiate into astroglial cells. But on the 

other hand, there is need of stem cells transplantation be-

cause after injury certain cascades of messengers are pro-

voked which trigger off this proliferation.20 This phenomenon 

can be related to Gliosis which is an attempt to impair the re-

growth and reestablishment of the communications. So far the 
treatments used for SCI are to limit gliosis by suppressing the 

messeger cascades either by steroids or immune modulating 

drugs. This type of endogenous stem cell proliferation and 

functional recovery of neurons by treatments generally leads 
to formation of a glial scar tissue. This glial scar tissue has 
been found to be a major hurdle in the neural regeneration 
after SCI.21 It has been found that that nestin expressing pre-
cursors around the central canal, proliferate and migrate to the 
site of SCI to contribute to the glial scar.21-23 Thus the degree and direction of endogenous stem cell multiplication is 

insufficient (along neural lines) and inappropriate (along glial lines). There are different works which demonstrated 

that repair potential of the adult stem cells mainly depend on 
the epigenetic and growth factors.21 It has been demonstrated that up regulation of the notch pathway is a 

major deterrent in the neural differentiation.21 Finally, it 

seems that limiting factor in endogenous stem cell prolifera-
tion is not dependent on the stem cells availability but it is the 
direction of their multiplication, which can be controlled by 

involving messenger cascades.24

**Need for stem cells transplantation**

Stem Cell manipulation in basal ganglionic disorders such as 

Huntington’s chorea25, Parkinson’s disease26 and ischemic inju-

ry27 showed promising results, in addition transplantation of 
exogenous neural stem cells in traumatic brain injury (TBI) 

animal models have given successful outcome in promoting 

motor and behavioural recovery and remyelination.28 Enh-

ancing the endogenous regenerative stem cell response by 

transplanting neural stem cells in spinal cord repair was ef-

fective in both complete SCI and incomplete SCI which may 

not have sufficient residual multipotent cells to respond to 
stimulation by exogenous agents.24 One of the major func-
tional deficits in SCI is progressive chronic demyelination. 

Therefore, neural stem cells or glial restricted progenitor cells 

have been used preferentially to target demyelination because 

of their directed differentiation to oligodendrocyte lineage 

prior to transplantation. It has also been an effective stra-

tegy to favour the oligodendroglial differentiation in SCI to 

increase the extent of remyelination. Transplanted NSCs 

work as scaffolds for growing axons and also promote ax-

onal regeneration. For axonal growth mesenchymal stromal 

cells have been proved to be effective.29 Likewise, another 

firm functional benefit has been achieved by the addition of 

sonic hedgehog genes.30 To enhance the efficacy of cellular 

transplantation strategies for SCI, several approaches have 

been using polymer scaffolds to fill the lesion cavity and in-

roducing regeneration promoting genes.31

Another approach, in which many researchers are interested, 
is to replace the damaged tissue with the transplantation of 

NSCs and olfactory ensheathing glia, and Schwann cells into 

the spinal cord at or near the site of injury to repair the sen-

sorimotor function and to promote recovery. Given that stem 

cells can differentiate into a particular cell type, NSC trans-

plantation is proved to be very successful and practical in 
goal directed repair of SCI. Recently it has been shown that 

transplantation of Schwann cells derived from skin derived 

precursor cells32 and oligodendrocyte precursor cells33 can 

myelinate demyelinated axons and can repair sensorimotor 

function in SCI rodent models. The properties of olfactory 

ensheathing cells (OECs) make them promising candidates for 

transplantation in SCI experimental models. Olfactory en-

sheathing cells include glial cells from olfactory system which 

promote axonal regeneration24, 35, remyelination over sev-

eral millimeters of axons and bringing back the axonic con-

duction velocities36, and neural protection.37, 38 In a recent 

study it has been proved that transplantation of stem cells 

with other modalities seems to be very helpful in veterinary 

medicines. Another very interesting approach is the culturing 
of ODCs assist in relocation of SCs to the injury site due to 

release of nerve growth factors, which has been previously 

blocked in injury.39 The monomodal approaches for treating 

spinal cord injury remains to be very successful in treating 

experimental SCI. There are now many researchers inter-

ested in using combinatorial or multi-model therapies. But the 
time of investigation for multi model therapies might take a 

longer period of time due to intricacy of factors involved and 
an appropriate functional and practical therapy for human 

and veterinary models is put forward for SCI.40

**Functional Recovery by Remyelination**

Previous treatments for SCI like immune modulating drugs 
had been helpful in promoting restoration of the long tracts. 

However, recent approaches are mostly directed for the re-

pair re-growth and functional recovery of the axons by pro-

moting remyelination which is supported by oligodendrocyte
and glial re-growth of the axons by astrocytes. Cell replacement therapies are effective in two ways. Firstly it replaces the damaged neurons and enhances axonal regeneration or plasticity and secondly it repairs the supportive cells like oligodendrocytes to enhance myelination.\textsuperscript{41} The first approach for treating SCI is to stimulate the proliferative activity of endogenous neuro progenitor/stem cells (NPSCs) along the neural line to replenish the anterior horn cells injured at the time of injury. The functional recovery of damaged tissues depends on the direction and degree of proliferation not on the extent of endogenous stem cells. So it is important to control the switches or messengers, for example sonic hedgehog to push neural stem cells along neuronal lines.\textsuperscript{11}

MSCs are derived from the embryonic mesodermal layer and retain the cardinal abilities of stem cells for self-renewal and multipotentiality to differentiate to the various connective tissues cell types. It has been reported that MSCs that have been derived from human umbilical cord blood (hUCB) stem cells hold a great potential for repair after SCI. After transplantation into the spinal cord after injury hUCB stem cells differentiate into oligodendrocyte and neurons, and promote enhanced locomotor function.\textsuperscript{42} So neurotrophic function\textsuperscript{43} of hUCB stem cells cannot be neglected as these cells improve functional recovery by remyelination.\textsuperscript{43} MSCs alleviating the need for long-term immunosuppression and are used in experimental models of SCI and are in preliminary clinical trials for the improvement for SCI. It’s still remains to be investigated that MSCs can be transdifferentiate.\textsuperscript{43} In CNS injuries, MSCs transplantation provides the target tissue with some important growth factors or they can modulate the immune system, so these can be used in combinatorial therapies.\textsuperscript{44}

NSC transplantation is therapeutically effective in that these cells show extensive migration to demyelinated axons and spread throughout the damaged tissue after SCI.\textsuperscript{45}

Cell death is inevitable after SCI. However, endogeneous neural progenitor cells have too limited proliferative activity and self recovery after SCI. Thus, other transplantation approaches are required in SCI models.\textsuperscript{46} It has been recently reported that after transplantation into a SCI model, fetal derived stem cells differentiated into neurons and oligodendrocytes and showed recovery.\textsuperscript{47}

Adult derived stem cells when ectopically transplanted in tissues like spinal cord, some evidences suggested that these cells can trans-differentiate into other cell types. The benefit of these cells is that they avoid the ethical and biological issues of using ESCs and fetal derived stem cells for regenerative therapies.

It is obvious from previous studies that a Schwann cell seems to be very helpful in promoting remyelination.\textsuperscript{48} These cells can easily be obtained from patient’s peripheral nerves and it requires comparatively short time to produce appropriate material for autologous transplantation. It has been reported that Schwann cells are helpful in promoting regeneration of axons through secretion of neurotrophic factors\textsuperscript{49} and extracellular matrix\textsuperscript{50} which ultimately myelinate axons and some improvements in the hindlimb functions.\textsuperscript{51} MSCs have been used in experimental models of SCI\textsuperscript{52} and showed improvement of behavioural outcome through neuroprotective pathways and by inhibition of Fas-mediated apoptosis.\textsuperscript{53} Recently several groups have reported that,\textsuperscript{54,55} neural tissue markers nestin and GFAP in MSCs or their neuron like morphological characteristics in certain tissue culture conditions make them a possible replacement of NSCs. Some researchers also proved the fact that,\textsuperscript{55} transplantation of bone marrow MSCs, can induce axonal growth through the glial scar in a model of chronic SCI in rats through release of neurotrophins. However, these approaches are not completely effective for functional recovery after chronic SCI.

The cell replacement therapy helps to cure injury in mainly two ways that is axonal regeneration to recover axonal conduction and repair of oligodendrocytes to prevent demyelination. Transplanted neural stem cells have the potential to extensively migrate to the lost axons.

**Disadvantages / Risk Factors**

Despite of many advantages there are certain disadvantages of stem cell therapy which are mainly related with the use of ESCs for SCI that include limited tissue availability, immunosuppression, impaired cell survival, political issues etc. More specifically some ethical issues and the risk of tumorigenesis are related with ESCs.\textsuperscript{44} The risk profile of stem cell therapy depends on many risk factors, which include the type of stem cells, their differentiation and proliferation capacity, administration route, \textit{in vitro} culture, irreversibility of treatment, need for tissue regeneration in case of irreversible tissue loss, and long-term survival of engrafted cells.

ESCs are a possible approach for SCI therapy because they have the potential and capacity to differentiate in any type of the cells. Creation of induced pluripotent stem cells (iPSC) has opened new ways in the field of stem cell therapy to increase development and scientific knowledge.\textsuperscript{5} The pluripotent cells derived from the inner cell mass of the developing blastocyst can differentiate into three primary germ layers and these iPSCs have the same potential of differentiation. These iPSCs has gained much attention of researchers in functional recovery after SCI.\textsuperscript{56-60}

**Conclusion**

Stem cell transplants after SCI may help to improve regeneration and spinal cord function. Several attempts have been made to find a strategy in experimental animals that could be translated into human application. But still, more research is required so that preclinical findings can be transferred from animal models to humans. Transplantation of neural stem/progenitor cells offers promise for improvement of function after SCI. MSCs and hUCB stem cells are also under trials to treat SCI patients and showing promising results. However many answers regarding the risks of using stem cell therapy have not been answered yet. In short devising new stem cell strategies to improve regeneration of the damaged
neuronal cells holds great assurance for millions of individuals.

References


