Chapter 7

Cellular Transplantation-Based Therapeutic Strategies for Spinal Cord Injuries: Preclinical and Clinical Updates

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Additional information is available at the end of the chapter

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Abstract

Spinal cord injury (SCI) is a distressing neurological condition that causes loss of neural tissue, with subsequent damages to neural circuitry, and loss of sensorimotor function. The SCIs have an estimated incidence rate of ~80 cases per million populations. Till date, no ratified effective therapeutic strategy for SCIs exist; however, recent advancements in regenerative medicines to protect and regenerate damaged/lost neural tissues following SCIs have shown promising results in preclinical and clinical trials. Moreover, there is a greater need to fully understand underlying mechanisms following cellular transplantation that can be achieved through proper differentiation of desired cell type, and their *in-vivo* tracking of migration, proliferation and integration into the host system. Furthermore, techniques that can prevent teratomas formation following cellular transplantation have been reported. In addition to the ongoing comprehensive neuroregenerative and neuroprotective therapeutic strategies for SCIs, novel technologies are emerging including neuroscience-based computational and robotic rehabilitational therapies. These improved strategies in combination with cell-based therapeutic approaches are opening new avenues for future research to completely cure SCIs. Herein, we intended to review pathophysiological mechanisms following SCI, preclinical and clinical updates of cellular transplantation, the extent of success from these transplantations, associated controversies and other emerging technologies.

Keywords: spinal cord injury, pathophysiology, stem cells, preclinical and clinical trials, regenerative medicines, neuromodulation, robotic rehabilitation

1. Introduction

Spinal cord injury (SCI) is an extremely devastating condition with no proper effective treatment strategies till date. Instead of all the recent comprehensive research, SCIs still remain as one of the most intimidating challenge in the field of neurological sciences [1]. The increasing prevalence of SCIs specifically in young generation has caused a serious clinical, social and economical burden across the globe. According to a report by World Health Organization, SCIs has affected people worldwide with an estimated incidence rate of ~80 cases per million population [2]. The causes for SCIs could be a result of traumatic (~90%) or non-traumatic (~10%) events. Although the percentages of traumatic SCIs are high, recently it has been estimated that percentages of non-traumatic SCIs are also increasing majorly due to spinal cord tumors [2, 3].

Following SCIs, severe damages to the neural tissue occur followed by further damages to the neural circuitry, which results in loss of sensorimotor functions [4]. So much of the pathophysiological events cause serious failures in body system that makes it harder or nearly impossible to treat. In addition to neurorehabilitation, the highly established therapeutic strategies for SCIs focus on protocols that can induce early neurological protection and prevent secondary SCIs. While these procedures have revealed to encourage locomotional recovery in affected individuals with incomplete SCIs, the therapeutic outcome in patients with life-threatening incomplete and complete SCIs continues to be disappointing [5]. These kind of therapeutic failures are due to the deficiency of natural regeneration of injured axons where demyelination has occurred. Till date, various number of significant *in vivo* studies that are predominantly experimented on the model of mammalian SCIs in the recent years have contributed to the establishment of several regenerative approaches including neuroprotective therapeutics-coupled regeneration and cellular transplantation with neurotrophic activity. In this review, we are intended to cover pathophysiological mechanisms following SCI, preclinical and clinical updates of cellular transplantation that majorly involve cells population derived from human embryonic stem cells (hESCs), mesenchymal stem cells (MSCs) and human-induced pluripotent stem cells (iPSCs), the extent of success from cellular transplantation, associated controversies and other emerging technologies.

2. Global prevalence of spinal cord injuries

According to World Health Organization (WHO) report, individuals suffering from SCIs hold 2–5 times more chances of premature death compared to non-SCI individuals, whereas the ratio of survival rate get worsen in low and middle income countries [2]. The high morbidity ratio of SCIs has driven widespread exploration into treatments and rehabilitations to recover neural function after SCIs. The incidence and prevalence rate of SCIs, in particular of traumatic SCIs, varies widely among different regions across the globe, mainly due to fluctuating sources of facts and figures and missing or unrecorded data [6]. Apart from including sudden deaths from SCIs, the annual incidence rate of traumatic SCIs across the globe is 2.5–83 cases/per million

population, whereas the highest ratio has been recorded in the USA [6]. Although the incidence rate of traumatic SCI is high, recently it has been reported that the incidence rate of non-traumatic SCIs is also increasing [5]. According to WHO report, there are around 250,000–500,000 people suffering annually from SCIs across the globe, where majority of the cases are due to road vehicle accidents, tumbles and other physical aggressiveness. As per 2016 updated report from National Spinal Cord Injury Statistical Center (NSCISC), the estimated annual incidence rate of SCI is ~54 cases/million population. The estimated number of individuals living with SCIs in 2016 is ~282,000, whereas the ratio is higher in male population accounting for around 80% of newly reported cases of SCIs [7].

3. Pathophysiology of spinal cord injuries

A comprehensive understanding of the neuropathological alterations after a SCI is the crucial part in designing effective therapeutic strategies. The SCI is primarily due to either compression or contusion [8]. The fundamental mechanisms that are involved in initial and later stages of SCIs include vascular complications, inflammation, lipid peroxidation, demyelination and apoptosis [9].

3.1. Vascular disorders

Ischemia, hemorrhage, systemic hypotension and microcirculatory disturbances are the vascular manifestations due to SCI [10]. The major decrease in blood flow at the lesion site occurs immediately after SCI [11], while the ischemia becomes worsen in the first few hours [9]. After a period of ischemia, blood reperfusion occurs with increased free radicals that lead to reperfusion paradoxical damage [12]. The disruption of small blood vessels and hemorrhage affects more of the local microcirculation than the large arteries, which leads to a failure of glutamate-mediated excitotoxicity and autoregulation. Additionally, severe systemic hypotension increases the microcirculation dysfunction and exacerbates injury [13].

3.2. Inflammation

After a SCI, the perniciousness from inflammation to the nervous tissue influences the cells to get into necrosis in the injured site. At this stage, different immune cells, including neutrophils, monocytes, microglia and T-lymphocytes, secrete certain cytokines such as tumor necrosis factor-α, interleukin-1β and interleukin-6, which lead to apoptotic cell death [14]. First, the neutrophils aggregate at the damaged area and release cytokines, proteases and free radicals that lead to more inflammation while involving glial cells in the inflammatory process, which eventually induce cell death [9]. This is followed by the infiltration of monocytes into the injury site, which is followed by differentiation into macrophages. The monocytes and a recently triggered microglia secrete cytokines, free radicals and growth promoting factors. The T-lymphocytes secrete neurotrophins and modulate microglia to protect neurons from degeneration [15].

3.3. Glial-associated damage

In SCI, damage to the myelin sheet that is demyelination causes the exposure of axons to the harmful surroundings that lead to necrosis or apoptosis of overall neurons [9]. Moreover, the process of demyelination delays or blocks signal conduction via axons that leads to ineffective communication between neurons. This process of demyelination is a result of damages to the oligodendrocytes that were generated by glutamate excitotoxicity [16]. Later on, an inflammatory reaction regresses, which is followed by a formation of glial scars. In the initial stages of SCI, astrocytes proliferate at the damaged site to form glial scars, which separate neural tissue to decline neuroinflammation in early phases. Cells in this scar region secrete inhibitory molecules, which inhibit functional recovery [17].

3.4. Necrosis and apoptosis

In the initial stages of SCI, neurons, microglia, oligodendrocytes and astrocytes undergo apoptosis and necrosis, while in later stages apoptosis is mostly limited to white matter [18]. In majority of cases, the SCI results in calcium influx and increased excitotoxicity, which are the major triggers for apoptosis and mitochondrial dysfunction [19].

3.5. Lipid peroxidation

Lipids are abundantly found in tissues of CNS and PNS, which indicate that spinal cord is more vulnerable to lipid peroxidation that can lead to lysis of cell membrane [9]. Since free radicals are abundantly present in injury site, increases in their level will eventually lead to lysis of cell membranes via lipid peroxidation. Consequently, mitochondrial dysfunction occurs as a result of oxidative damage and induces calcium overload [20]. The calcium influx causes ion imbalance and excitotoxicity, which is triggered through acute SCI [9]. Additionally, high level of glutamate is released after SCI, which results in increased calcium influx and damage to the spinal cord by stimulating the AMPA and NMDA receptors that induce neuronal death by apoptosis or necrosis [21]. The oligodendrocytes and neurons are susceptible to glutamate excitotoxicity as they express glutamate receptors [3]. Consequently, excitotoxic injury induces axonal demyelination. Additionally, nitrous oxide is involved in glutamate excitotoxic injury [22]. The increased calcium ions level has a major role in the secondary injury mechanism.

4. Molecular alterations involved in injured spinal cord

An advanced physiopathology induced by SCI affects the cellular growth and overall integrity of nervous system by comprehensive and progressive molecular pathways [23]. The initial stages of SCI are recognized by higher expression of genes mostly involved in inflammation and lower expression of genes involved in tissue architecture and neuronal signal transduction. The later stages of SCI are characterized by upregulation of proteins involved in angiogenesis, cell growth, axon guidance and reformation of extracellular matrix. Other molecular

mechanisms that support the struggle of tissue survival after SCI include higher expression of proteases and stress proteins and lower expression of cytoskeletal and synapsis-based messenger RNA [14]. Following are the molecular alterations after SCI.

4.1. Stress and transcription response

At the initial stage of SCI, different cellular factors such as nuclear factor kappa B (NF-κB) and 70 kD heat shock protein (HSP-70) get activated that last for 24 hours. A stimulation of NF-κB facilitates more expression of genes to moderate regeneration or apoptosis [24]. Moreover, an increased level of HSP-70 with metallothioneins 1 & 2 protects the cells from oxidative stress. An activation of catalase, superoxide dismutases and glutathione peroxidase occurs in later stages [25].

4.2. Inflammatory reaction

During an early phase after SCI, interleukins (IL-6, IL-1β), cyclooxygenase (COX)-2 and TNF-α are activated, which get to normal stage again after 2 weeks. Integrins, vascular and intercellular CAMs, selectins and cadherins are upregulated in early phase of SCI [25]. Inflammatory genes are expressed in several spinal cord cells, which are predominantly studied in microglia. The interleukins IL-6, IL-1β and chemokine ligands, such as 2/M1P2α and 2/MCP-1, help in bringing different immune cells to the injured area [14]. After 3–7 days, microglial gene expression that includes genes, such as *MRF-1* (microglial response factor-1), *cathepsin*, *galectin-3*, *CYBA* (cytochrome b-245, alpha polypeptide), *CASP1* (caspase 1), *MAPK14* (mitogen-activated protein kinase 14), *CCND1* (cyclin D1) and leukocyte surface antigen *CD53*/*OX44*, contributes in immune response, phagocytosis and cell death. Furthermore, other genes such as the classical complement pathway, which related to phagocytosis, showed an insistent upregulation after SCI [25].

4.3. Neuron-related genes

A great number of genes that encode specific proteins for calcium, sodium and potassium pumps, synapsis and cell excitability show a major decrease in the first week following SCI [26]. This reduction reflects alterations of gene profile in neurons and the progress of apoptosis that occurs after SCI. Late axonal regeneration after SCIs is accompanied by overexpression of *CORO1B* (Coronin, actin binding protein, 1B), *RAB13* (Rab13, member RAS oncogene family), *NINJ* (Ninjurin), *ANK* (Ankyrin), cAMP-related genes and myelin oligodendrocyte glycoprotein [27].

4.4. Cell cycle genes

The upregulation of cell cycle genes, including *cyclins*, *c-Myc* (V-myc avian myelocytomatosis viral oncogene homolog) and *GADD45A* (growth arrest and DNA damage-inducible, alpha), is being reported after 24 hours of SCI [27]. Once these genes are activated, it induces apoptosis and astrocytic proliferation through formation of the glial scar [27]. In the initial stages of SCI, upregulation of associated genes, such as *BAX* (BCL2-associated X protein),

BAK-1 (BCL2-antagonist/killer 1) and *CASP3* (caspase 3, apoptosis-related cysteine peptidase), is being reported. In later stages, the upregulation of *STAT3* (signal transducer and activator of transcription 3 (acute-phase response factor)) and *PI3K* (phosphoinositide 3-kinase) and downregulation of *GSK-3* (glycogen synthase kinase 3) are being observed [25]. In addition, earlier upregulation of genes that are involved in preventing apoptosis such as *PDGF* (platelet-derived growth factor), *TGFB* (transforming growth factor-β), *VEGF* (vascular endothelial growth factor) and anti-apoptotic proteins is being reported [24].

4.5. Glial cell alterations

There are well-recognized genes, such as *GFAP* (glial fibrillary acidic protein), *NES* (nestin) and *VIM* (vimentin), that are overexpressed in astrocytes and are found responsible for glial scar formation. They are found upregulated early after SCI [26]. In oligodendrocytes, the gene expression decline due to oligodendrocytic death, while an increase in myelination occurs in later stages [26].

4.6. MicroRNAs

MicroRNAs (miRNAs) have been recognized to play crucial roles in regulating growth signals and immune response [28]. Following SCI, microRNAs play important role in inflammatory pathways or in the invading immune cells. Soon after the SCI, damaged area is infiltrated with blood immune cells [29]. MicroRNAs control upregulation of vascular cell adhesion molecule (*VCAM1*)-mRNA [25] with downregulation of miR-126 [30]. Neutrophil infiltration clarifies upregulation of miR-223 [31], while overexpression of lymphocyte-specific miR-142 [26] associates with the aggregation of immune cells in the injured site during initial days [32]. Moreover, miRNAs are associated with microglia and macrophages activation. Mainly, the downregulation of miR-124 is associated with microglia by directing CCAAT enhancer-binding protein alpha (*CEBPα*), which is a principal transcription factor vital for myeloid cells development [33]. After SCI, MiR-124 shows a constant downregulation that causes microglial activation [32]. Other associated roles of miRNAs during different mechanisms of SCIs have been recently reviewed in [34].

5. Types of cells used in transplantation for spinal cord injuries

The use of cellular transplantation in SCIs has been reported to encourage regeneration of neural circuitry and recover the associated compromised function of nervous system. Transplanted cells are being observed to perform this job via secretion of indulgent neurotrophic factors at the injury site to boost the reformative capability, followed by developing a scaffold for axonal regeneration, myelination and replacement of damaged nerve cells [35], as depicted in **Figure 1**. Following are the type of cells that have been shown success in preclinical trials and currently being evaluated in clinical phase trials for treatment of SCIs.

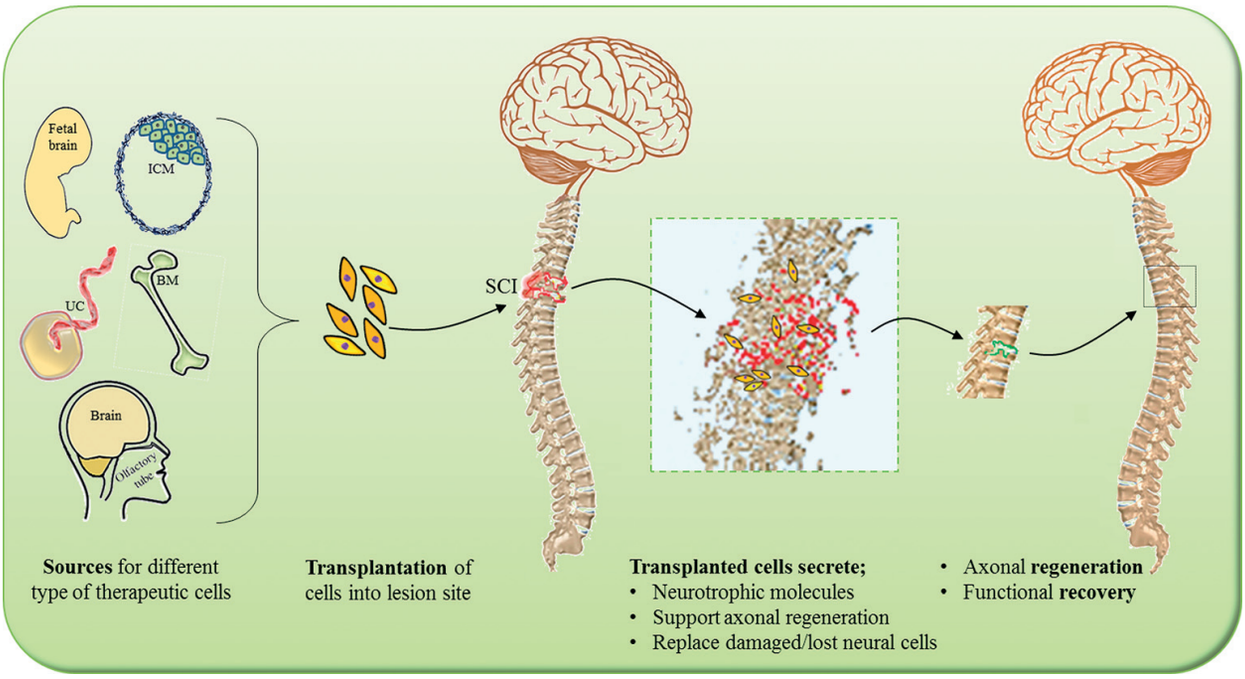

Figure 1. Graphical representation of cellular transplantation and functional recovery from SCI. Therapeutic cells are derived from different types of sources. Following cellular transplantations into injury site, the transplantable cells secret indulgent neurotrophic molecules to boost the regenerative capability, support axonal regeneration and myelination and replace damaged/loss neurological cells, resulting functional recovery from SCI.

5.1. Embryo-derived cell population

Although ethical issues are associated with the origin of embryonic stem cells (ESC), their potential use might significantly results into numerous scientific and clinical applications, especially if they are differentiated into desired cell types and are utilized to develop functional body organs [36]. The ESCs have been considered as a leading candidate of therapeutic cells for numerous types of disorders triggered by loss of cells/tissue or any abnormal body function [37]. A gap that has been produced in spinal cord after traumatic or non-traumatic injury can be refilled via new cell transplantation. To date, embryonic stem cells are considered as the most appropriate type of cells that can be used for this purpose. These are the immature cells that can differentiate into any of a cell type in human body including the cells of CNS and PNS. ESCs have been reported to form a bridge across the injury site, as well as they are capable of excreting neuroprotective factors that reduce the harmful effects from inflammation [38–40].

5.1.1. Human embryonic stem cell-derived oligodendrocyte progenitors (hESCs-ODPs)

Since the major problem associated to SCIs is "demyelination," a potential treatment option to replace the myelin-forming cells will be of significant interest. For this purpose, a transplantation of hESCs-ODPs into SCI rat model has shown to increase remyelination and promoted improvement in recovery of locomotory function [41]. This study paved the ways for the use of hESCs-ODPs for treatment of SCIs and supported the notion that pre-differentiation of hESCs into active oligodendrocytes progenitors will offer therapeutic option at early time points after

SCIs. After preclinical success, the uses of hESCs-ODPs are being evaluated into clinical trials on patients with SCIs. The hESCs-ODPs are currently known as ASTOPC1, while previously it was known as GRNOPC1. It was permitted for clinical trials by US FDA in 2009; however, the proper trials begin in 2010 after being evaluated for safety reason in patients as it developed cysts in animal models [42, 43]. While for some unknown reasons Geron-Corporation ceases the trials, another corporation Asterias Biotherapeutics begin the same trials in phase 1 (NCT01217008) on individuals suffering from subacute thoracic SCIs. The trial was concluded in year 2013 with positive results where safety and tolerability was achieved with no serious fallouts [44, 45]. A year after, Asterias Biotherapeutics initiated a new clinical trial of phase I/IIa (NCT02302157) involving the use of hESCs-ODPs for treatments of sensorimotor complete cervical SCIs, which is expected to complete in year 2018 [44]. Since direct transplantation of hESCs poses a risk of forming teratomas and problem of differentiating into exact cells progeny within a body [41], the highly purified ODPs that are freshly derived from hESCs will offer a best treatment option for patients with SCIs.

5.1.2. Fetal brain-derived human central nervous system stem cell/neural precursors

The skill of isolation, proliferation and genetic manipulation of ESCs is one of the most important accomplishments in experimental stem cells biology [46]. An isolation of ESCs and their controlled proliferation into neural precursors population has been achieved in variety of preclinical models. After transplantation of ESC-derived neural precursors into the CNS of animal models, the cells have been observed to assimilate well into the recipient tissue and have also shown to improve locomotional recovery in injured rat spinal cord [46, 47]. To evaluate *in vivo* differentiation of hESC-derived neural precursors, a study has shown that these cells were able to integrate, migrate and differentiate into a host tissue [40]. After the preclinical validations and successful outcomes from ESC-derived neural precursors, they are being evaluated in clinical trials with a name HuCNS-SC. The HuCNS-SCs are highly purified fetal brain-derived human CNS stem cells, which have been shown to promote neuroprotection after SCIs [48]. In addition to its use for SCIs, HuCNS-SCs have been used in clinical trials for other disorders including neuronal ceroid lipofuscinosis, age-related macular degeneration and Pelizaeus-Merzbacher disease [48–51]. Following transplantation, HuCNS-SCs are shown to differentiate into neurons and glia and also retained semipermanent survival ability in host tissues. They have been recently evaluated in phase I/II clinical trials (NCT01321333) for safety and preliminary efficacy in patients with subacute SCI via intramedullary transplantation into thoracic spinal cord region [44]. In the clinical outcome from this trial (NCT01321333) that involved 5-year follow-up period, absolutely no safety issues have been documented [52].

5.1.3. Umbilical cord blood-derived mononuclear cells

Transplantation of human umbilical cord blood-derived stem cells has been reported to migrate well and promote therapeutic recovery from neurological injuries such as stroke and SCIs [53]. Following intravenous administration of human umbilical cord blood-derived stem cells, a study has demonstrated that the transplanted cells were able to improve behavioral properties of induced SCI [53]. Another preclinical study has reported functional locomotory effect following the administration of human umbilical cord blood cells in combination with

brain-derived neutrophic factor into the SCI rat model [54]. In addition to preclinical studies on animal models, a case study on human (37-year-old female) patient with SCI has reported an injection of human umbilical cord blood-derived stem cells. In this study, it was shown that cell transplantation ameliorates sensory perception and movement of body parts, based on functional and morphological analysis [55]. Recently, the transplantation of umbilical cord blood-derived mononuclear cells (UCBMC) has been tested in phase I/II clinical trials (NCT01354483; NCT01471613) for treatment of acute, subacute and chronic SCIs in combination with neuroprotective agents such as lithium carbonate and methylprednisolone [44]. Following transplantation, these cells have been observed to decrease sensimotor injury and other associated cerebral deficiency [56]. In one of the clinical trial outcomes involving UCBMC (NCT01354483), the cellular transplantation was observed to be safe while some recipients were appeared to regain sensorimotor function [57].

5.1.4. Human ES-derived motor neurons

It has been reported that growth signaling pathway-related factors are able to prompt mouse ESCs differentiation into vertebral progenitor cells, followed by subsequent differentiation into motor neurons [58]. These ESC-derived motor neurons have been recognized with a potential to occupy the embryonic medulla spinalis, lengthen axons and develop synaptic connections with respective muscle tissues [58]. Another study has reported that earlier neuroectodermal cells derived from hESCs population, which expressed *Pax6* but not *Sox1,* were able to differentiate into spinal motor neurons in the presence of retinoic acid and sonic hedgehog. Whereas the neuroectodermal cells in later stages that were expressing both *Pax6* and *Sox1* were unable to differentiate into spinal motor neurons [59]. Following transplantation, these motoneurons have the ability to quickly engraft, maintain proper phenotype and project axonal elongation into peripheral regions in recipient's tissues [60]. These evidences of *in vivo* subsistence of hESC-derived motoneurons are a major way forward to treat SCIs via cellular therapy using motoneurons' transplantation.

5.2. Mesenchymal stem cells

The lineage of mesenchymal stem cells (MSCs) is characterized with self-renewal capacity and multipotent stem cells-like abilities. They were originally isolated from the bone marrow [61, 62] and have been reported to differentiate into several cell types [63–68]. The MSCs have also been shown to transdifferentiate into variety of neuronal cells in different animal models [69–72]. The MSCs that qualify transplantational procedure are known as multipotent mesenchymal stromal cells [73], which are having several subtypes that are being therapeutically evaluated for SCIs in different clinical trials. After their transplantation into lesion site, they are thought to be regulated by secretion of trophic factor, which stimulates new vessels formation and anti-inflammatory factors [74]. Moreover, MSCs are being reported to secrete different cytokines and associated growth promoting factors that exhibit both paracrine and autocrine characteristics. These biologically active secreted factors have been shown to suppress the intrinsic immunological repsonse, prevent apoptosis and formation of glial scars, improve angiogenesis and stimulate cell cycle to enhance regenerative activities [75].

5.2.1. Autologous bone marrow-derived mesenchymal stroma cells

The autologous bone marrow-derived mesenchymal stromal cells (ABM-MSCs) have been reported *in vivo* to treat different disorders like fistulising Crohn's disease, refractory luminal Crohn's disease and chronic paraplegic SCI [76–78]. In addition to other rodent models, transplantation of ABM-MSCs has shown locomotional recovery in adult mini-pigs models after the induction of SCI [78]. After preclinical evaluation, these ABM-MSCs have been reported to make their way into phase I/II clinical trials for treatment of chronic SCIs [1, 74].

Till date, a couple of the completed clinical trials that involve ABM-MSC transplantation have provided clinical outcomes. In one of the most recent clinical trial (NCT02482194 completed in March 2016) involving ABM-MSCs to treat subacute and chronic SCIs, the transplantation procedure has been documented as safe and doable. This also reported improved sensorimotor functions as well as revealed bladder and bowel improvement [79]. The phase 1 clinical trial (NCT01325103), which has been completed in December 2012 involved ABM-MSC transplantation in patients with chronic traumatic SCIs, has reported that direct cellular transplantation into lesion site is safe, viable and may encourage sensorimotor functions. In this trail, eight patients improved lower limbs motor function, mainly in the flexor muscles of hip, while seven patients advanced American Spinal Injury Association Impairment Scale (AIS) grades to B or C and nine patients improved urological functions [80]. Another phase 1/2 clinical trial that has been completed in October 2010 involving patients of subacute thoracic SCIs has reported that following ABM-MSC transplantation, noticeable recovery was observed in five patients (45.5%). ASIA sensorimotor score increased and patients were able to walk using a support [81].

In addition to the clinical trials mentioned above, there are several ongoing clinical trials from phase 1/2 to 2/3 that involve the use of ABM-MSC transplantation in patients with chronic cervical, thoracic and lumbar SCIs. These clinical trials (NCT02574585; NCT01676441; NCT02570932; NCT01730183; NCT01446640; NCT02687672; NCT02981576; NCT02260713; NCT02923817; NCT02574572; NCT02009124) are expected to be completed in the upcoming years, and the clinical outcomes from these trials are still pending as mentioned in **Table 1**.

5.2.2. Umbilical cord-derived MSCs

Since the clinical use of ABM-MSCs might be unfavorable due to the practice of vastly invasive method, as well as the ratio of BM-MSCs decreases while differentiation increases with passage of age, the utilization of umbilical cord blood-derived MSCs is a best substitute for BM-MSCs [82]. It has been reported that umbilical cord blood-derived MSCs can be grown for longer time period and are having maximum proliferation potential. In contrast, BM-MSCs require less time to grow and possess low proliferation capacity [82]. A study has reported the transplantation of human umbilical cord-derived MSCs into animal SCI model, which has shown that these cells were able to migrate well into the lesion site and were positive to anti-nuclei antibody (clone 235-10) MAB1281 [83]. Following their preclinical validation, the umbilical cord-derived MSCs have reached to phase I/II clinical trials for the treatment of chronic and/or acute SCIs [1]. One of the most recent clinical trial that involves umbilical cord

Source	Type of therapeutic cells	Combination therapy	Type of spinal cord injury	Clinical phase reached	Year of completion	Outcome	Clinical trials identifiers/ References
Embryo-derived cell population	GRNOPC1 (hESCs-ODPs)	_	Complete, subacute SCI	Phase 1	Jul-2013	Safety and tolerability were achieved with no serious fallouts	NCT01217008 [45]
	AST-OPC1	_	Subacute cervical SCIs	Phase 1/ 2a	Dec-2018	Pending	NCT02302157
	HuCNS-SC	_	Thoracic chronic SCIs	Phase 1/ 2	Apr-2015	After 5 years of clinical follow-up, absolutely no safety issues have been documented	NCT01321333 [52]
	UCBMC	Methylprednisolone and lithium carbonate	Chronic SCIs	Phase 1/ 2	Dec-2013	UCBMC' transplantation was observed to be safe while some recipients were appeared to regain sensorimotor function	NCT01354483 [57]
	UCBMC	Lithium carbonate	Acute and subacute SCI	Phase 1/ 2	Jan-2014	No study results posted	NCT01471613
Mesenchymal stem cells	ABM-MSCs	_	Subacute and chronic SCI	Phase 1	Mar-2016	Transplantation appeared to be safe and viable, resulted in improved sensorimotor functions and also revealed bladder and bowel improvement	NCT02482194 [79]
	Autologous bone marrow MSC	_	Chronic traumatic SCI	Phase 1	Dec-2012	Intralesional transplantation of ABM-MSCs is safe, feasible and may promote neurological improvements	NCT01325103 [80]
	ABM-MSCs	_	Subacute thoracic SCI	Phase 1/ 2	Oct-2010	Noticeable recovery was observed in five patients (45.5%). ASIA sensorimotor score increased and patients were able to walk using a support	[81]
	AMB-MSCs	_	Thoracic and lumbar chronic and complete SCI	Phase 2	Dec-2017	Pending	NCT02574585
	ABM-MSCs	_	Cervical SCI	Phase 2/ 3	Dec-2020	Pending	NCT01676441

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Source	Type of therapeutic cells	Combination therapy	Type of spinal cord injury	Clinical phase reached	Year of completion	Outcome	Clinical trials identifiers/ References
	ABM-MSCs	_	Chronic SCI	Phase 2	Feb-2018	Pending	NCT02570932
	ABM-MSCs	_	Cervical, thoracic and lumbar SCIs	Phase 1/ 2	11 Jan-2014	Pending	NCT01730183
	ABM-MSCs	_	Thoracic and lumbar SCIs	Phase 1/ 2	Jun-2014	Pending	NCT01446640
	ABM or Leukapheresis-derived MSCs	_	Chronic traumatic SCI	Phase 1/ 2	Dec-2021	Pending	NCT02687672; NCT02981576
	ABM-MSCs	_	Acute SCI	Phase 1/ 2	Nov-2017	Pending	NCT02260713
	ABM-derived mononuclear cells	_	SCIs	Phase 2	Jun-2019	Pending	NCT02923817
	ABM-MSCs	_	Cervical chronic and complete SCI	Phase 1	Dec-2016	No study results posted	NCT02574572
	Autologous bone marrow mononuclear cell	_	SCIs	Phase 2	Dec-2016	No study results posted	NCT02009124
	Umbilical cord Wharton's jelly-derived MSCs	Placebo/XCEL-UMC-BETA	Chronic traumatic thoracic SCIs	Phase 1/ 2a	Apr-2020	Pending	NCT03003364
	Human umbilical cord-derived MSCs (allogeneic)	Bone marrow mononuclear cells (BMMC)	SCIs	Phase 1/ 2	Oct-2019	Trial withdrawn prior to enrollment	NCT02237547
	Umbilical cord-derived MSCs	_	Complete or incomplete cervical and thoracic SCIs	Phase 1/ 2	Dec-2018	Pending	NCT02481440
	Human autologous adipose tissue-derived MSC (hAdMSC)	_	SCIs	Phase 1	Feb-2010	Following cellular transplantation in SCI patients, no safety issues were seen and also the transplanted cells did not develop teratomas	NCT01274975 [85]
	N-Ad-MSC (autologous adipose tissue-derived	Hematopoietic stem cells	Traumatic lumbar SCIs	Phase 1	Oct-2012		[86]

Source	Type of therapeutic cells	Combination therapy	Type of spinal cord injury	Clinical phase reached	Year of completion	Outcome	Clinical trials identifiers/ References
	MSCs differentiated neuronal cells)					Coadministration of N-Ad-MSC and hematopoietic in patients' CSF is safe and feasible treatment option for SCIs	
	Autologous adipose-derived stem cells	_	Acute SCIs	Phase 1/ 2	3 Jan-2015	Pending	NCT02034669
	Spinal cord-derived neural stem cells	_	Chronic cervical and thoracic SCIs	Phase 1	Dec-2022	Pending	NCT01772810
	MSC-autologous neural stem cells	RMx Biomatrix	Acute, sub-chronic and chronic lumbar and thoracic SCIs	Phase 1/ 2	Dec-2018	Pending	NCT02326662
	MSC-derived neural stem cells	NeuroRegen scaffold	Cervical and thoracic SCIs	Phase 1/ 2	Jun-2018	Pending	NCT02688049
Peripheral myelinating cells	Autologous human Schwann cells (ahSC)	_	Subacute lumbar SCIs	Phase 1	Aug-2016	Following 1-year assessment, no signs were observed for serious side effects that could be specifically associated to the nerve harvest, cellular transplantation protocol or to the transplanted cells in lesion site	NCT01739023 [91]
	Autologous human Schwann cells (ahSC)	Rehabilitation	Chronic lumbar and thoracic SCIs	Phase 1	Jan-2018	Pending	NCT02354625
	Autologous olfactory ensheathing glia and olfactory fibroblasts	_	Subacute or chronic SCIs	Phase 1	N/A	Pending	NCT01231893

Table 1. Results of clinical trials of stem cell-based therapy for spinal cord injury.

Wharton's Jelly expanded MSCs with Placebo/XCEL-UMC-BETA intervention is being evaluated against thoracic SCIs in phase 1/2a, which is expected to be completed in April, 2020 (NCT03003364). Another phase 1/2 clinical trial that was testing the use of UC-MSCs in combination with bone marrow mononuclear cells was expected to complete in October 2019; however, it was withdrawn prior to enrolment (NCT02237547). One of the ongoing phase 1/2 clinical trial that purely involves the use of allogenic UC-MSCs is evaluating its safety and viability using intrathecal injections. This trial involves patients with complete or incomplete cervical and thoracic SCIs, which is expected to be completed in December 2018 (NCT02481440).

5.2.3. Autologous adipose-derived MSCs

In comparison to the umbilical cord blood, another source that has been reported to hold more number of MSCs is adipose tissue. It had been shown that 100% of MSCs can be isolated from adipose tissues compare to 63% of isolation from umbilical cord blood [82]. Since the adipose-derived MSCs have been recognized by immunosuppressant characteristics and less immunogenic behavior, they have been considered as a potential source of treatment for SCIs [84]. A study has reported that after an intravenous administration of human adipose-derived MSCs in murine models (Balb/c-nu nude mice) and humans (n = 8) clinical trial (NCT01274975) for SCIs, no safety issues were seen and also the transplanted cells did not develop teratomas [85]. The use of adipose-derived MSCs has been evaluated in phase I and I/II clinical trials for treatment of different SCIs [1, 44]. A phase 1 clinical trial that has been completed in October 2012 reported that co-administration of autologous adipose-derived MSCs' differentiated neuronal cells (N-Ad-MSC) and hematopoietic in patients' CSF is safe and feasible treatment option for SCIs [86]. Another phase 1/2 clinical trial has evaluated adipose-derived MSCs in patients with acute SCIs, which was expected to be completed in 2015; however, the clinical outcomes are still pending (NCT02034669).

5.2.4. MSC-derived neural stem cells

A specific cell progeny can be derived from MSCs, which has been tested in different clinical trials that mainly involve MSC-derived neural stem cell (NSC) population. In one of the most recent phase 1 clinical trials, human spinal cord-derived neural stem cells population has been used for transplantation to treat patients with chronic cervical and thoracic SCIs. The clinical outcome form this trial is still pending as the trial is expected to be completed in December 2022 (NCT01772810). A phase 1/2 clinical trial is currently evaluating MSCs-autologous NSC transplantation together with RMx Biomatrix (3D biomatrix) as scaffold for treatment of acute, sub-chronic and chronic lumbar and thoracic SCIs, which is expected to be completed in December 2018 (NCT02326662). Another phase 1/2 clinical trial that is currently ongoing for treatment of patients with cervical and throracic SCIs is utilizing the transplantation of MSCs-NSCs in combination with "NeuroRegen" scaffolds. This trial is expected to be completed in June 2018 (NCT02688049).

5.3. Peripheral myelinating cells

In addition to other type of cells, the most relevant cell types for treatment of SCIs are the peripheral myelinating cells, which are mainly damaged during primary and secondary injury

process. Such types of peripheral myelinating cells that have shown promising results in preclinical trials for SCIs and are currently being evaluated in clinical trials include the following.

5.3.1. Autologous human Schwann cells

Schwann cells have been reported to display significant flexibility in performing a wide range of functions in nervous system through major involvement in ensheating and myelination of axons. Schwann cells are playing crucial regenerative role in supporting regeneration of axons in the PNS, which indicates that the uses of Schwann cell transplantation and autografting will offer regenerative role in damaged CNS [87]. Different studies have reported the differentiation of adult precursor cells into Schwann cells, including a study where precursor cells isolated from skin were able to produce myelinating Schwann cells. Upon transplantation, these Schwann cells were able to improve remyelination and supported locomotional recovery from contusion SCI [88]. Following transplantation, the Schwann cells are characterized by remyelination of damaged axons and maintaining an environment favorable for axonal regrowth by secreting important growth and trophic factors [89]. One of a renowned study has shown that a combination of Schwann cell transplantation and regulation of cyclic adenosine monophosphate (cAMP) levels by using rolipram and/or a cAMP analog (db-cAMP), might improve the overall regenerative roles of Schwann cells in treatment of SCIs [90].

In clinical trials, the autologous human Schwann cells have been evaluated in phase I trials (NCT01739023; NCT02354625) for chronic and subacute SCIs [44]. In one of the most recently completed phase 1 clinical trial, transplantation of autologous human Schwann cells (ahSC) has been evaluated in patients with subacute lumbar SCIs (NCT01739023). In the clinical outcome following 1-year assessment, no signs were observed for serious side effects that could be specifically associated to the nerve harvest, cellular transplantation protocol, or to the transplanted cells in lesion site [91]. Another phase 1 clinical trial that is utilizing ahSCs in combination with rehabilitation to treat chronic lumbar and thoracic SCIs is expected to be completed in January 2018 (NCT02354625).

5.3.2. Autologous olfactory ensheathing glia and olfactory fibroblasts

The olfactory ensheathing glial cells are belong to a class of macroglia, which are involved in ensheathing demyelinated axons of olfactory neurons. In olfactory bulb, typical and transected olfactory axonal structures are able to move in, regenerate and restore damaged synaptic communications with their respective targets [92]. Moreover, transplantation of olfactory ensheathing glial cells has been reported to improve axonal remyelination within a damaged nervous system [92]. A preclinical study has reported a transplantation of adult rat's olfactory bulb-derived ensheathing glia cells in a SCI's site, where the cells filled the lesion gap through regeneration [93]. In addition to the preclinical success of olfactory ensheathing cell transplantation, a study has reported the feasibility of transplantation of autologous olfactory ensheathing cells into three spinal cord injured patients where the cells were found safe without any serious complication for up to 12 months after transplantation [94]. A subsequent study has reported that transplantation of olfactory ensheathing cells is viable and safe for promoting motor and sensory activities [95]. Therapeutically, the olfactory ensheathing cells

are most likely to maintain their effects via secretion of specific growth promoting factors that develop new olfactory axons and promote axonal regeneration following SCI [96]. At present, the olfactory ensheathing glial and fibroblastic cells are being evaluated in phase I clinical trial (NCT01231893) for treatment of complete SCIs [44].

5.4. Induced pluripotent stem cells (iPSCs)

Pluripotency, a special ability of a pluripotent cell to differentiate into any type of body cell, was shown to be induced in adult differentiated cells via the activity of only four embryonic transcription factors—Oct3/4, Sox2, Klf4 and c-Myc. These induced adult cells gaining the ability of pluripotency were termed as "induced pluripotent stem cells" (iPSCs) [97]. This discovery offered a very forthright procedure of how to induce pluripotency in mature cells in a basic laboratory setup, yet the scope of this cell-rewinding discovery was extraordinarily vast in biomedical sciences and regenerative medicine, which earned the principle investigator, Yamanaka, a Nobel Prize in year 2012 [98].

5.4.1. Reprogramming factors

The reprogramming factors, also known as pluripotency markers, are the main regulators of inducing pluripotency in mature cells via a process of activating pluripotent genes expression. The induction of pluripotency can be achieved via expression of only four reprogramming factors, i.e. OCT3/4, SOX2, KLF4 and c-Myc [99]. POU class 5 homeobox 1 (POU5F1 or OCT4) is being reported to play a significant role in developing embryo and maintaining pluripotent status. It has been observed to bind an octamer motif (ATGCAAAT) of DNA, where it is involved in regulation of several genes that play important part in pluripotency. Oct4 has been observed to frequently regulate in association with Sox2 [100–102]. SRY (sex determining region Y)-box 2 (SOX2) is a transcription factor encoded by *SOX2* intronless gene. It plays an important role to regulate embryonic development and determine cell fate and is usually expressed in developing embryo and neuronal cells [100]. It has been reported that expression of SOX2 is fundamental for maintaining pluripotent status of evolving embryos, whereas its downregulation is associated with mesodermal and endodermal differentiation. Embryos with no expression of SOX2 were found unable to grow and proliferate after implantation [102, 103]. Kruppel-like factor 4 (KLF4 or EZF), a zinc finger protein is a transcription factor that is involved in regular growth of the barrier properties of body skin [100]. KLF4 has been reported to have a higher expression in non-dividing cells and is associated with induction of cell cycle arrest [104, 105]. KLF4 has been shown to specifically regulate genetic stability [106, 107] and promote cellular growth and survival [108]; however, in some cases, KLF4 has been reported to induce cell death [109, 110]. c-Myc, a nuclear phosphoprotein, has been recognized to play multiple functions, including cell cycle multiplication, programmed cell death and cellular propagation, via transcriptional regulation of particular genes [100]. The efficacy of OCT3/4, SOX2 and KLF4 is shown to be enhanced by the expression of an enhancer factor c-Myc [111].

5.4.2. Mechanisms of cellular reprogramming

In mechanism of cellular reprogramming, three pluripotency markers (OCT3/4, SOX2 and KLF4) have been observed to greatly influence multiple genes expression in iPSCs [112]. In

iPSCs, the augmented factors binding at promoter regions are linked with elevated level of transcription, signifying the fact that OCT3/4, SOX2 and KLF4 are involved in genes regulation predominantly as activators of transcription [113].

For induction of cellular reprogramming in adult cells, four strategies can be employed that include nuclear transfer, fusion of cells, cellular explantation and infection through retroviral vectors [114]. In the mechanism of nuclear transfer, direct administration of a viable donor somatic nucleus into an enucleated egg cell, followed by implantation in a surrogate mother, can develop a reproductive clone. If the enucleated egg cell with implanted somatic nucleus is grown *in vitro*, it can generate inherently matched ESCs population. In mechanism of cell fusion, culture of adult body cells with ESCs can give rise to hybrid progeny of cells that can entirely exhibit pluripotency. In another strategy of cellular explantation, adult body cell cultures can be directly induced to gain pluripotency via reprogramming factors. In fourth strategy of cellular reprogramming, infection through retroviral vectors carrying distinct factors can induce reprogramming to generate iPSCs [114].

5.4.3. Trials involving iPSCs for SCIs

A preclinical study has reported that following transplantation of human iPSC-derived neurospheres into spinal cord-injured mice model, a locomotional recovery from SCI was achieved, signifying the importance of human iPSC-derived neurospheres in regenerative medicines [115]. Another study has reported the transplantation of human iPSC-derived neural stem cells into monkeys' specie that promoted locomotory function after SCI, without inducing teratomas [116]. One of a report has stated that iPSCs have the ability to generate three important functional cell types of the CNS, i.e. astrocytes, oligodendrocytes and neurons [117]. An optimization of efficient protocols that can be utilized to generate constant and long-term population of neural stem cells from ESCs and iPSCs has been demonstrated [118, 119]. These types of cells have displayed stable features, for example constant expanding properties, consistent differentiation into neurons and glia and the ability of producing efficient established neurons *in vitro*. Another study has reported that following transplantation of such long-term stemness-rich cells (iPSC-derived neural stem cells) into SCI mice model, improved remyelination and axonal regrowth were observed with additional support for subsistence of endogenic neurons [120].

In one of an important study, cells from a healthy man of 86 years of age were induced to generate iPSCs, from which neural stem cells were generated and transplanted into rats exhibiting immunodeficiency following SCI. After 12 weeks of C5 lateral hemi-sections, iPSCs endured and generated neuronal and glial cells, extending large number of axons from injured area to almost the complete distance of rat CNS that subsequently developed synaptic communications with host neurons [121]. Another study on human iPSC-derived neural progenitors known as IMR90 has reported functional recovery after IMR90 transplantation in SCI rat models. It was shown that iPSCs have the ability to generate functional neurons, which resulted in long-term functional recovery from SCI [122]. Altogether, several studies have reported that following transplantation of iPSC-derived neural stem/precursor cells, locomotory function was improved/recovered in spinal cord-injured animal models [115, 116, 120, 123, 124]. In contrast, other studies have reported that transplantation of clones containing

human iPSC-derived neural stem/precursor cells, e.g. clone-253G1 and 836B3, has been reported to induce teratomas and suppress locomotory function after long-term follow-up. In addition, the induced teratomas were made up of undifferentiated Nestin-positive cells of human origin [125, 126]. For this purpose, one of a recent study is paving the ways to tackle such problems of teratoma formation and locomotory inhibition. In this study, it was shown that human iPSC-derived neural stem/precursor cells that were pre-treated with γ-secretase inhibitor (GSI) induce differentiation and development of neuronal cells, whereas it also recovers host neural circuitry. Moreover, the incredible results showed that following transplantation of these cells with GSI pre-treatment after SCI, tumorigenesis was prevented and locomotory function was maintained [126].

6. Safety concerns regarding the use of cell transplantation

Therapeutic approaches of cellular transplantation are revolutionizing the field of regenerative medicine; however, it also raises different safety concerns regarding several associated risk factors including tumorigenesis, adverse immunogenic response, transmission of extrinsic factors and differentiation into unwanted cellular progeny [127, 128].

6.1. Cyst/tumor formation

The intrinsic characteristics of ESCs and adult stem cells (ASCs) correlate to cancerous cells, for instance, their extended lifespan, comparative apoptotic resistance and potential to divide for longer time period [129]. Moreover, maintenance of required growth signals and other tightly regulated mechanisms can be observed in both cancerous and stem cells [130, 131]. Thus, the pluripotency of ESCs and multipotency of adult stem cells are regarded as the crucial aspect of developing tumors. The tumorigenic potential of cellular transplantation therapy could be intrinsic or adventitious, depending upon the microenvironment of transplanted cells [130]. It has been reported that following differentiation of stem cells into mature cells, the later can induce tumorigenesis due to acquiring several mutations in the process of parent-stem cells culture [132].

6.2. Immune rejection

An immune rejection is another apparent safety concern that could escalate after cellular transplantation therapy. A transplanted cell could either directly prompt an immunogenic reaction or could have a regulatory influence on the immune system [133]. Several factors may impact the host-induced immunogenicity depending upon the location of cellular transplantation and number of administered doses [134]. MSCs and other ESC-derived progeny are being described as immunoprivileged and hold little immunogenicity [135]. It has been shown that MSCs can cause suppression of T cell to proliferate, prevent monocytes to differentiate [136] and can also hinder B cell to proliferate and/or differentiate [137]. In addition, extracts from both mouse and hESCs have been shown to maintain immune regulatory characteristics of ESCs [138].

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6.3. Other physiological side effects

One of a recent study has reported that a male dominant hormone testosterone has the ability to stimulate proliferation of human adult MSCs and endothelial precursor cells, while preserving their stemness properties [139]. Transplantation of these cells in a hyper testosterones secreting recipient will raise several safety concerns.

7. Techniques for "*in-vivo* tracking" of transplanted cells

One of the most essential and obvious steps to follow after cellular transplantation is to track down the implanted cells in host tissues. To date, several studies have reported the use of *in vivo* tracking system where an investigator can observe and analyze transplanted cells to evaluate their extensive status including site of cell transplantation, cellular migration, proliferation, differentiation into desired cell types, long-term self-renewal and their integration within a host tissue [140]. Using MRI technique where a superparamagnetic iron oxide works as a contrast mediator, transplanted cells can be tracked down *in vivo* [141]. One of a study has shown that using 3D microtopographic scaffolds, reprogrammed neuronal cells were capable of colonizing damaged neural cells to replace with transplantable cells [142]. It has been reported that transplanted MSCs, labeled with established gadolinium-based MRI contrast agent, i.e. Gadoteridol, were effectively traced via *in vivo* tracking in a SCI mouse model. A procedure that was employed during the *in vivo* tracking was established on hypo-osmotic shock that induced an osmolality-contingent permeabilization and physical alterations in cellular membrane [143]. Hence the *in vivo* cell tracking techniques are evolving; further development in these technologies will help to optimize future cellular transplantation therapy protocols for SCIs.

8. Success story and controversies of cell transplantation in patients with SCIs

Researchers in the field of cellular therapy and regenerative medicines are restraining to directly inject hESCs or iPSCs in humans, but rather more inclined to evaluate hESCs- or human iPSC-derived cell population, i.e. ODPs, HuCNS-SC, Schwann cells, olfactory ensheathing cells, umbilical cord blood mononuclear cells, autologous BMSCs and umbilical cord blood- and adipose-derived MSCs, as evident from the recent and ongoing clinical trials —**Table 1**. In contrast to direct transplantation of ESCs or iPSCs, direct administration of the above-mentioned derived cells is only limited to form single-specific cell progeny and also possesses lower risk of developing teratomas in host specie [144].

Till date, success has been made in cellular transplantation therapies for SCIs as their usages and procedures have now reached to clinical trials; however, these procedures are still at their early stages with no further than phase I or phase I/II clinical trials [5]. Nevertheless, all the

preclinical and clinical studies have improved our understanding of repair mechanism following cellular transplantations. As mentioned earlier, novel methods are emerging to tackle all the associated risks with cellular transplantation, where tumorigenesis can be prevented by using specialized protocols [126]. Up till now, even after reaching into clinical trials, fundamental associations between locomotory functional development and specific mechanisms in SCIs have rarely been achieved [145]. Yet, some studies have reported clinical success by using cellular transplantation therapies for SCIs. One of such study has been conducted in 2003, where a clinician directly transplanted OECs derived from aborted fetuses in Chinese hospital. In this contentious experiment, 171 spinal cord-injured patients were reported to have recovered from SCIs without any associated risk [146, 147]. Two years later, a Korean research division claimed that umbilical cord blood-derived MSCs have the ability to recover locomotory function in a patient who was suffering from a complete disability for several years [55]. The claims made in these studies received controversial responses because they were associated with ethical challenges, greater risk association and still require appropriate and accurate clinical confirmations [147]. Nonetheless, cellular transplantation therapies for SCIs are becoming more exciting and interesting, especially when research studies of lower immune rejections and preventing teratoma formation are paving the ways for future regenerative research [126, 148].

9. Future prospects

In the current era of regenerative medicine, cell-based transplantation therapies have advanced our approaches to an extent that these therapies soon will be capable of treating subacute and chronic SCIs in the very near future. The ongoing improvements and assessments of associated risks with cellular transplantation, improved relevance of preclinical models, long-term enhanced recovery, *in vivo* tracking of transplanted cells and preventing teratoma formations are advancing the future aspects of these therapies for SCIs [5, 126, 145]. Cells that are derived from hESCs and iPSCs are showing promising results in preclinical and clinical trials, indicating their dominance in the prospective field of personalized and regenerative medicines. In particular, the iPSC-derived cell progeny that is disease and patient-specific, is evidently the best option as it carries lower immune rejection and is limited to particular cell types [149]. In addition to the ongoing comprehensive neuroregenerative and neuroprotective therapeutic strategies for SCIs [5], newer technologies are evolving including neuroscience-based computational and robotic rehabilitational therapies. In 2014, a group of Swiss scientists reported an innovative discovery for treatment of complete SCI using neuroscience modulation-based therapeutic approach to control spinal sensorimotor network, without involving cellular transplantation techniques. In this study, an electric stimulus-based procedure was used to assist a non-standing paralytic rat model with complete injured spinal cord to move the paralyzed feet again and even climbed staircases [150]. The neurorobotic techniques-based therapies for SCIs are also emerging, as recently being reported where a volunteer-driven exoskeleton was used as an innovative robotic device for rehabilitation in chronic SCIs [151]. These exoskeleton

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robotic devices work as a wearable outfit that regulates the external movements by detecting internal nerve signals in patients with SCIs. However, such neuroscience-based computational and robotic rehabilitation therapies are evolving for treatment of SCIs, yet they are in the initial phases of development and do not offer a complete cure to fully repair and regenerate injured spinal cord. Nevertheless, any sort of therapeutic strategy that can rehabilitate and improve functional recovery will always be considered a therapy-of-future for SCIs, as being phrased "something is better than nothing." In a nutshell, the only therapeutic approach that could be able to completely cure SCIs in near future is the use of cell-based transplantation strategies.

10. Conclusion

Spinal cord injury, a devastating condition where patient feels sharpest pain shooting from vertebrae through the neck up head and subsequent paralysis has unfortunately no proper treatment. In recent times across the globe, a renewed attention has been diverted to find and develop a complete treatment for SCIs. In addition to neuroregenerative, neuroprotective and neuro-computational strategies, cellular transplantations are considered the most relevant, inspiring and encouraging therapies for treatment of SCIs. To date, numerous preclinical and clinical studies have confirmed cellular regeneration and locomotory functional recovery from SCIs following cellular transplantation. Instead of direct transplantation of hESCs and iPSCs, their derived cell population is the most preferred type of cells for successful transplantational recovery, as evident from their extents into the clinical trials. Novel approaches have revealed to specifically generate desired cell type, track the transplanted cells *in vivo* and prevent associated risks of tumorigenesis and loss of locomotional functions. Accomplishments from these newer improved strategies are opening new avenues for future research to completely cure SCIs.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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