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A review on stem cell therapy for spinal cord injury

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Abstract: By enabling improved sensory and motor functions in animal models, stem cells (SCs) offer new hope as a brand-new therapeutic approach for spinal cord injury (SCI). Neural stem cells, mesenchymal stem cells, embryonic stem cells, iatrogenic pluripotent stem cells, and others are among the stem cells used for neuro restoration. A better understanding of the benefits, drawbacks and precise performance of different stem cells in the treatment of SCI could aid in the development of neurorestorative approaches. The most important goal of SC-based medical care for SCI is to replace neurons and interstitial tissue cells that die quickly after injury. Stem cells help to promote remyelination by replacing neuroglia cells with organic process factors that promote neurite outgrowth, nerve fiber elongation, and fiber density, as well as activating resident or transplanted ascendants cells across the lesion cavity. While many SC transplantation methods have shown promising but limited efficacy, the mechanistic proof is frequently lacking, which is arguably the most significant impediment to faster progress and clinical application. The most difficult task ahead is to encourage clinicians, researchers, and patients to work together to define and optimize the mechanisms of SC performance, as well as to identify the best source(s) of SCs that can produce cost-effective and safe therapeutic approaches.

Keywords: Stem cells (SCs); Spinal cord injury (SCI); neural stem cells; mesenchymal stem cells; embryonic stem cells; induced pluripotent stem cells; Differentiation; Remyelination; Inflammation.

INTRODUCTION:

From the bottom of the skull to the middle of the back, the spinal cord is a column of animal tissue. It is protected by three thin layers of protective tissue known as membranes. The backbone is made up of rings of bone called vertebrae that surround the spinal cord. The central nervous system is made up of the spinal cord and the brain. Nerves in the spinal cord send and receive messages between the brain and the rest of the body[1-5].

The spinal cord comprises five segments (Fig 1):

1. The cervical: C1 to C7.
2. Thoracic: T1 to T12.
3. Lumbar: L1 to L5.
4. Sacral: S1 to S5.

Spinal Cord injury:

A spinal cord injury (SCI) occurs when the medulla spinalis is damaged, resulting in a loss of function such as mobility or sensation. A complete injury means that all motor and sensory functions in the vertebral column below the injury site have been lost, whereas an incomplete injury means that some functions have been retained. Trauma (car accidents, gunshots, falls, etc.) and disease (polio, Friedreich's ataxia, etc.) are common causes of medulla spinalis injuries. Back injuries such as ruptured discs, spinal stenosis, or pinched nerves are very different from spinal cord injuries. [9].

Types of spinal cord injury.

There are four types of spinal cord injury:

i. Cervical injury
ii. Thoracic injury
iii. Lumbar injury
iv. Sacral injury [10].

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5. Coccyx [6-8].**Cervical spinal cord injury:**

The top portion of the spinal cord is located in the cervical region of the spine, which is made up of seven vertebrae (C-1 to C-7) in the neck. Cervical spinal cord injuries are the most severe type of spinal cord injury because they affect a larger portion of the body and are closer to the brain. Quadriplegia is the result of a cervical spinal cord injury that causes loss of function in the arms and legs[10-11].

Thoracic spinal cord injury:

The thoracic vertebrae are the 12 vertebrae in the chest area (T-1 to T-12). T-1 is the first thoracic vertebra, and it is to this vertebra that the top rib connects. The chest and legs are usually affected by thoracic injuries, resulting in paraplegia [10-11].

Effects of Injury to Thoracic Spinal Cord Nerves T-1 to T-5: • The abdominal and lower back muscles, as well as the legs, are usually injured, resulting in paraplegia; arm and hand function are usually normal.

Effects of Injury to Thoracic Spinal Cord Nerves–T-6 to T-12:

• Injury usually results in paralysis; • Little or no voluntary control of bowel or bladder, but they can manage on their own with special equipment [12].

Lumbar spinal cord injury:

The lumbar spine is located below the cervical and thoracic spines in the lower back. L1-L5 are the five vertebrae that make up the lumbar spine. The spinal cord tissue and nerves that control communication between the brain and the legs are found in the lumbar vertebrae (or lumbar bones). Damage to the lumbar spinal cord has ramifications for the hips and groin area, as well as the lower abdominal muscles and thigh flexion [11-13].

Table1. Lumbar spinal cord injury and affected area.

Spinal Nerve Affected.	Specific Muscle Function Affected.
L-1 and L-2.	Hip bending and flexing.
L-3.	Knee straightening.
L-4.	Bend foot upward (Dorsiflexion).
L-5.	Extended toes.

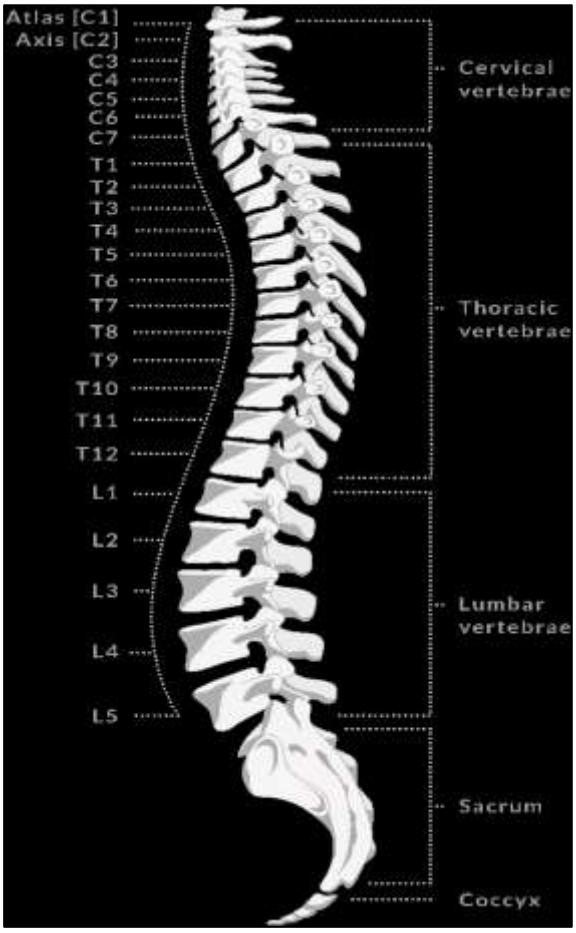

Fig 1. Spine and segments. Spinal cord consists of 5 segments. The cervical: C1 to C7; Thoracic: T1 to T12; Lumbar: L1 to L5.; Sacral: S1 to S5; Coccyx. (Image source: http://www.brainandspineclinic.com/spine/spine-anatomy)

Sacral spinal cord injury:

The sacral spine (sacrum) is situated beneath the lumbar spine and above the coccyx, or tailbone. The triangle-shaped sacrum is made up of five fused bones that are numbered S-1 to S-5. S1 nerves affect the hips and groin area, and each number corresponds to the nerves in that section of the spinal cord: The backs of the thighs are affected by the S2 nerves. The medial buttock is affected by the S3 nerves. The perineal area is affected by the S4 nerves [12-14].

The pathophysiology of SCI can be divided clinically into two phases: primary injury phase and secondary injury phase.

Primary Injury Phase: As a result of a fracture-dislocation or burst fracture of the spine, the spinal cord is directly compressed and contused by fractured and displaced bone fragments and disc material. Axons are disrupted, and neural cell membranes are ruptured, resulting in nerve cell damage. Microhemorrhages in the central grey matter spread out radially and axially after blood vessel injury, resulting in spinal cord swelling and secondary ischemia. A secondary injury cascade is triggered by ischemia, altered ion balance, and toxins released from disrupted neural membranes, which exacerbates SCI.

Secondary Injury Phase: The secondary injury phase is defined as cellular damage caused by an interconnected series of pathophysiological processes such as electrolyte imbalance, ischemia, excitotoxicity, oxidative stress, inflammation, and massive cell death as a result of the injury's immune response. Depolarization and voltage-dependent opening of sodium, potassium, and calcium ion channels initiate secondary injury. Calcium ion overload causes mitochondrial

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dysfunction and the activation of cytoplasmic nitric oxide synthase and phospholipase A2, resulting in microvascular damage and ischemia. Toxic chemicals are released by damaged cells, axons, and blood vessels [10-15].

In this review, the use of different kinds of stem cells for spinal cord injury has been discussed.

STEM CELLS (SCs) FOR TREATING SPINAL CORD INJURY:

Stem cells are self-renewing cells that can differentiate into different cell types. High proliferative potential, self-renewal through asymmetric cell division (production of one daughter cell identical to the mother cell and another cell that progresses down an alternative differentiation pathway), and the ability to differentiate into multiple cell types are three fundamental properties of stem cells. When it comes to the types of cells that stem cells can generate, there are significant differences. Totipotent stem cells are those that can generate an entire organism; a fertilized egg is a good example. Pluripotent stem cells, such as embryonic stem (es) cells, can give rise to lineages derived from all three primary germ layers—namely, ectoderm, mesoderm, and endoderm. Multipotent stem cells are cells that can give rise to multiple cell types within a germ layer; because multipotent stem cells can be found in both adult and embryonic organs, they are sometimes referred to as adult stem cells in the literature [11-17].

Mesenchymal stem cells (MSCs):

Because of their ability to differentiate into various cellular lineages, MSCs, also known as mesenchymal stromal cells, are classified as multipotent stem cells. Although BM is the most well-studied source of MSCs, MSCs can also be extracted from adipose tissue, umbilical cord, blood, Wharton's jelly, amniotic fluid, skeletal muscle tissue and periosteum, liver tissue, lung tissue, menstrual blood, gingiva, and periodontal tissue [16-18].
In an in vivo contusion SCI model, intramedullary transplantation of hNSCs, hUC-MSCs, or hNSC, UC-MSCs in the subacute phase all significantly improved outcomes. The best method[17] is the co-transplantation of hNSCs and hUC-MSCs, which can increase the survival of transplanted stem cells in vivo.

Bone Marrow stem cells (BMSC):

BMSCs are the most abundant cells in bone marrow, as well as the stroma of body tissue and organs. Within the bone marrow, BMSCs are still hematopoietic and functional support cells. Bone marrow stromal cells (MSCs) have some advantages over other cell sources in cell therapies: they're relatively easy to isolate from bone marrow, they grow well in tissue cultures, they'll be used in autologous transplantation protocols, and bone marrow as a cell source has already been approved for the treatment of hematopoietic diseases. Preclinical studies on rats with a medulla spinalis injury have shown that transplanted cells survive, migrate into the host tissue, and result in axonal regeneration and motor function recovery [18-24]. This was accomplished not just through the implantation of cells with a low percentage of mesenchymal cells in the bone marrow (MSC), but also by the introduction of freshly collected bone marrow with nuclear cells (BMCs) [18,20,21,25,26]. So far, two clinical studies[25,27] have demonstrated the safety of such an approach as well as a partial improvement in function in acute patients. According to immunostaining as per MSC classification criteria, rat BM-MSCs express positivity for the panel of markers CD29, CD54, CD73, CD90, and CD105, and negativity for hematopoietic cells. The potential of bone marrow cell transplantation as a means of repairing the injured CNS could be used for a wide range of therapeutic purposes [28]. Animal studies have shown that transplanted MSCs alter the inflammatory environment in the acute setting and reduce the effects of inhibitory connective tissue in the subacute/chronic setting, resulting in an environment that is conducive to axonal extension. Furthermore, grafted cells may act as a source of growth factors, promoting axonal elongation across lesions in the medulla spinalis. HSCs and MSCs may even transdifferentiate to replace lost or damaged neuronal tissue, according to another research. Preliminary clinical results suggest that autologous bone marrow cell transplant and/or GM-CSF administration are frequently used without severe complications to treat SCI patients. These data are promising. However, future studies still need to determine if bone marrow cell treatment can be used to treat the injured CNS securely and functionally. The bone marrow harvested BM-MSCs may be distinguishable from the mesodermal cells. Several studies have shown the powerful capacity of BM-MSCs in the differentiation of neurons and glial cell types from osteoblasts, chondrocytes, chondroblasts, adipocytes, and fibroblasts. BM-MSCs have been shown to cause tissue repair damaged by activating different mechanisms. BM-MSCs mainly exhibited anti-inflammatory properties by decreasing the rate of proliferation and differentiation of lymphocytes. Furthermore, by providing various growth factors BDNF, VEGF, NGF, GDNF, Neurotrophine-3 (NT-3), Fibroblast Growth Factor (FGF), and Epidermal Growth Factor (EGF)), BM-MSCs provide tropical assistance and neuroprotection. BM-MSCs seem ready to remedy the area affected by additional neuronal losses[29-33].

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Human umbilical mesenchymal stem cells (hUCMSC):

Human umbilical mesenchymal stem cells (hUCMSCs) appear to have several advantages over other MSCs. They provide a noncontroversial, readily available source of cells that can be collected in a low-cost, non-invasive manner [34]. Furthermore, hUCMSCs are isolated from fetal structures during the perinatal period and are better tolerated after transplantation than other types of postnatal MSCs, resulting in a lower incidence of graft versus host disease [35]. In culture, the isolated hUCMSCs had a fibroblast-like morphology in confluent layers. All of the hUCMSCs were immunopositive for vimentin, laminin, and fibronectin, which was consistent with previous findings. Nestin and Ki67 expression in hUCMSCs was 9.371.4 percent and 56.6575.35 percent, respectively [36]. The hUCMSCs did not express CD34, indicating that they did not come from a hematopoietic lineage. Because of the numerous potential mechanisms that obstruct medulla spinalis recovery, SCI treatment necessitates a multifaceted approach. Following SCI, a study found that combining Taxol infusion with hUCMSC transplantation has greater therapeutic effects than either Taxol or hUCMSCs alone [37]. UC-MSCs are easily obtained from infants' ducts or cord blood, and they can be stored at cryogenic temperatures until needed. When compared to other stem cells, these cells have higher immunogenicity and a lower risk of rejection after transplantation. The release of cytokines and trophic factors such as IL-1, IL-10, neutrophil activator, NT-3, BDNF, VEGF, FGF, and neural cell adhesion molecule, which promote nerve tissue repair, induce axon growth, and activate damaged neurons, is primarily responsible for their biological effects. In several experimental models of SCI, much preclinical evidence shows that UC-MSCs have broad curative effects with a combination of multiple factors efficacy, such as neurotrophic, anti-inflammatory, anti-apoptotic, and angiogenic effects. Wharton's Jelly (WJ-MSCs) is a gelatinous matrix from which UM-MSCs are normally harvested. WJ-MSCs have a higher proliferative capacity than BM-MSCs, according to some researchers, so they will be propagated more quickly and widely. Furthermore, it was discovered in a preclinical study that administering human WJ-MSCs caused the release of trophic factors within the lesion area, as well as axonal regeneration. These findings show that these cells improve motor function [37-42].

Adipose-derived mesenchymal stem cells (AD-MSC):

While there are some similarities between AD-MSCs and BM-MSCs in terms of morphology and cell surface matter expression, they differ in terms of proliferation rates and multilineage capabilities. Because animal tissue contains more corporal stem cells than bone marrow, AD-MSCs are a good candidate for MSCs, especially because animal tissue is readily available. In both chronic and acute SCI, AD-MSC transplantation has shown to be effective. Intravenous administration of AD-MSCs improves hindlimb motor function by activating ontogenesis and upregulating ERK and Akt. By increasing the expression of beta3-tubulin, BDNF, and ciliary neurotrophic factor(CNTF), AD-MSCs also promotes cell survival and tissue repair. In rats with SCI, AD-MSCs may protect neurons and reduce impotence. Liposuction and lipoclastic surgery are used to isolate AT-MSCs from animal tissue [36]. AT-MSCs' ability to secrete a variety of neurotrophic factors (such as BDNF and GDNF), extracellular matrix substances, proteases, cytokines (such as IL-6, IL-7, IL-1, IL-8, and TNF-) and immunomodulatory molecules (such as IL-10 and reworking Growth Factor-beta [TGF-]) demonstrates their promising neurodegenerative, anti-apoptotic, angiogenic and wound healing effects [43]. In addition to those mechanisms of action, AT-MSCs can differentiate into a variety of cell lines, including vegetative cell cells and epithelial cells. AT-MSCs are interested in changing/enriching the lesion space of vegetative cell cells broken or undergoing necrosis because of their multi-differentiation properties; thus, they require the ability to repair nervous tissue broken in patients with SCI. Several studies in both animal and human models of SCI have shown that AT-MSCs when administered directly within the lesion space after injury, can have a regenerative effect [44-45].

Dental pulp stem cells (DPSCs):

Ectodermal cells migrate from the neural tube into the oral cavity and differentiate into mesenchymal cells, giving rise to human dental pulp stem cells (hDPSCs). The lack of environmental differentiation stimuli in the dental pulp, a niche sealed by mineralized dentin, preserves the staminal feature of hDPSCs in adult tissue. hDPSCs can maintain and repair periodontal tissue, have a high proliferation rate, and can differentiate into multiple lineages with plasticity. Several in vitro studies have shown that hDPSCs can be used to make osteoblasts, chondrocytes, adipocytes, odontoblasts, neural, and myocyte-like cells [46]. In the treatment of SCI, DMSC-based therapies have shown promising results [47]. DPSC can be differentiated into Schwann-like glial cells, which can secrete neurotrophic factors (NTF) and promote neurite outgrowth and survival. However, there are still several challenges in using DMSCs for SCI regeneration, including a low rate of cell engraftment and survival after transplantation [48]. To address these issues, engineered 3D scaffolds for DMSC delivery after SCI have been proposed, which may provide a mechanically supportive environment that promotes cell adhesion, migration, and in vivo differentiation [49]. Various in vivo studies have demonstrated the significant impact of DMSCs as a promising strategy for neuronal repair, functional recovery, and tissue regeneration following SCI. A preliminary study in animal models of SCI showed that DPSCs have therapeutic potential via a paracrine-mediated mechanism that promotes axon regeneration and the survival of endogenous neurons and glia within and around the lesion site [49]. Transplanted neural-induced SHED improves locomotion in a rat SCI site [50]. In a chronic contusive SCI rat model, some researchers used neural differentiated DPSCs in combination with a chitosan scaffold [51]. A higher

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amount of BDNF, GDNF, b-NGF, and NT3 was found in the site of the lesion in this DPSC/chitosan scaffold-treated group, which was responsible for hind limb locomotor recovery. A thermosensitive heparin poloxamer (HP) hydrogel containing DPSCs and Fibroblast growth factors (FGF) was recently used as the best combination of the scaffold, cells, and growth factors for neuronal regeneration and functional recovery after SCI [52].

Neural stem cells (NSCs) or neural progenitors (NPS):

These are multipotent cells that can differentiate into neurons, oligodendrocytes, and astrocytes, among other things. NSCs can be isolated and expanded in vitro or prepared as differentiated derivatives from embryonic or induced pluripotent stem cells. They are found in both the adult and developing central nervous systems (iPSCs). When using NPs to repair a damaged medulla spinalis, the focus is usually on loss replacement as well as trophic support of the remaining host nerve tissue. Several authors have reported functional improvement in SCI animals after NSC transplantation, as measured by the Basso, Beattie, and Bresnahan (BBB) locomotor scale. The origin of implanted NSCs appears to be important in determining their impact and fate after SCI. Because fetal tissue is difficult to obtain in sufficient quantity and quality, immortalized cell lines are created using a variety of techniques all over the world [53,54,55]. Conditionally immortalized neuroepithelial somatic cell lines are one of these approaches, in which the immortalizing gene is downregulated after transplantation into the host tissue [56]. Conditional growth control technology (c-mycERTAM) could be a fusion protein made up of a growth-promoting gene (c-myc) and a hormone receptor controlled by an artificial drug, 4-hydroxy-tamoxifen (4-OHT). CTX0E03, one of these cell lines, was recently approved for a clinical phase II clinical trial in stroke patients in the United Kingdom (http://clinicaltrials.gov/show/NCT02117635). In vitro differentiation of human iPSCs into region-specific NPCs was successful in a study. These NPCs grafted onto the injured medulla spinalis in mice showed good engraftment properties and retained their regional identities [56,57]. We discovered that only NPCs with a medulla spinalis identity promoted functional recovery in SCI mice when comparing the engraftment effects of the two types of NPCs with different regional identities, highlighting the importance of the regional identity of cells used for engraftment in cell therapy for SCI [58]. NPCs primarily differentiate into oligodendrocytes, which improve hindlimb function by increasing myelination. One study also found that transplanting NPCs from the subventricular zone improved respiratory recovery after SCI, even though differentiation did not work. The expression of NGF, CNTF, BDNF, IGF-1, and GDNF was increased after NPC transplantation, which is beneficial for SCI recovery. NPCs also influence the inflammatory response41 by inhibiting reactive macrophage and T cell secretion and releasing neuroprotective cytokines. Previous research has found that NPC transplantation during the acute stage is more effective than transplantation during the subacute and chronic stages and that transplantation in intact soft tissue may be more effective than transplantation in the injury site during the subacute period [59-63].

Embryonic Stem Cells (ESC):

They're multipotent stem cells that can differentiate into a variety of different cell types in the body. To replace nonfunctional cells or tissues in SCI, ESCs differentiate into neurons and glial cells [64]. However, because of the risk of tumorigenicity, their undifferentiated form is rarely used. Previous research has shown that ESC transplantation can help people recover from spinal cord injuries. ESCs transfected with L1, a cell adhesion molecule that promotes neuronal survival and neurite sprouting, showed promise in the treatment of SCI. In SCI animal models, ESC-derived definitive neural stem cells express myelin basic protein, support nodal architecture, and show multilayer myelination. Oligodendrocytes or oligodendrocyte progenitor cells and motoneuron progenitors derived from human embryonic stem cells promote astrogliosis and improve motor recovery. Axons can pass through chondroitin sulfate proteoglycan (CSPG), which is a huge barrier to axonal regeneration and has therapeutic potential for SCI treatment, thanks to ESC-derived neural lineage cells. This process is aided by the expression of nerve glial antigen 2 and MMP9. The use of GABAergic neurons derived from mouse ESCs reduced neuropathic pain and raised the paw withdrawal and vocalization thresholds [65-67].

Induced pluripotent stem cells (iPSCs):

Takahashi and Yamanaka first described iPSCs, which are derived from differentiated cells using a variety of reprogramming techniques that include the introduction of specific transcription factors that promote pluripotency. To date, some methods for obtaining iPSCs have been developed [7]. Human NSCs derived from iPSCs have already shown promise in the treatment of SCI in the lab. Despite some unresolved concerns (such as teratoma formation, the immunogenicity of iPSC-derived cells, and epigenetic factors), Japan has begun the first clinical trial using iPSCs in damaged retinas. In nonhuman primates, the possibility of clinical application of allogenic precursor cells derived from iPSC lines has recently been investigated. With a better understanding of the biochemical regulators of stem cell maturation, terminally differentiated somatic cells like fibroblasts and peripheral blood cells can be “un-differentiated” into pluripotent cells called induced pluripotent stem cells. Drs. Takahashi and Yamanaka were the first to create iPSCs, identifying Oct3/4, Sox2, c-Myc, and Klf4 as the four factors required to reverse differentiate adult fibroblasts into stem-

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like cells. At the same time, the authors discovered that Oct4, Sox2, NANOG, and LIN28 are all that is required to reprogram fully differentiated somatic cells to express ESC-like characteristics. Studies have increasingly turned to iPSCs as an ethical and readily available alternative to ESCs as our understanding of differentiation and developmental biology has progressed. In vitro and in vivo, iPSC-derived neural progenitor cells (NPCs) have been shown to have ESC-like neural differentiation potential. Transplantation of these iPSC-derived NPCs has been linked to a reduced injury profile, tract regeneration, remyelination, and serotonergic reinnervation in animal models of SCI [58]. [59] Prescreening of NPCs was required in one study because teratomas formed in a subset of transplanted NPC neurospheres, resulting in functional deterioration. The viral mechanism used to generate iPSCs has been linked to increased tumorigenic potential, as constitutional reactivation of the c-Myc transgene occurs frequently as a result of viral integration into the host cell genome. The development of nonviral methods for creating iPSCs using transposon-based reprogramming is one recent solution to this conundrum. Transplantation of transposon-induced, iPSC-derived NPCs is safe and promotes motor function recovery in mice with spinal cord injuries. Although human clinical trials to determine the feasibility of iPSC-based cell therapy for SCI have yet to be completed, recent research has looked at iPSC-derived NPC grafts in larger systems, such as minipig SCI models. To investigate changes in functional recovery, iPSC-derived NPCs were grafted into syngeneic recipients using a nonintegrating viral model. NeuN, synaptophysin, and GFAP immunofluorescence staining, markers for identifying terminal neural cell subtypes, confirmed differentiated cell populations, while gene expression analysis revealed distinct neuronal and glial subtypes resembling the cellular organization of non-SCI mature pig CNS tissue. However, positive results from various in vivo models hint at their therapeutic potential [68-71]. Further safety evaluation of iPSC-derived transplant therapies is required before administration in human acute SCI patients.

Human umbilical cord blood stem cells (hUCB):

They hold a lot of promise for healing the medulla spinalis after an injury (SCI). [72] Human umbilical blood stem cells were found to be effective in reversing the behavioral effects of medulla spinalis injury when infused 7 days after the injury, according to a study. Furthermore, hUCB-derived cells were found in injured areas of rat spinal cords but not in non-injured areas. A behavioral recovery of this magnitude has previously been demonstrated in acute injury models. To see the potential of hUCB in promoting functional recovery in SCI rats, we used a cyclosporine-treated group as a control group in this study. In hUCB-treated rats, cyclosporine may have a synergistic effect with hUCB in improving significant functional recovery. The findings support the theory that hUCB-derived stem cells migrate to and participate in the healing of neurological defects caused by trauma [38,73,74].

STRATEGIES FOR TREATING SCI WITH SCs THERAPY:

Various strategies are used for stem cell therapy to treat spinal cord injury they include mode of treatment, pathways of transplantation, number of stem cells, time window, Application of Immunosuppressive Therapy. Let's understand each of them briefly,

Modes of Treatment:

In vivo and in vitro induction are the two main modes of SC transplantation. The goal is to directly implant the appropriate SCs into the body, where the in vivo environment and specific signaling molecules will guide these SCs into mature cells that can perform the required functions. The latter involves isolating, culture, purifying, and amplifying a specific SC, inducing differentiation into cells with the desired function in vitro, and then transplanting these mature cells into a human body for treatment. The best effect on the patient may be achieved by combining the two techniques properly [75].

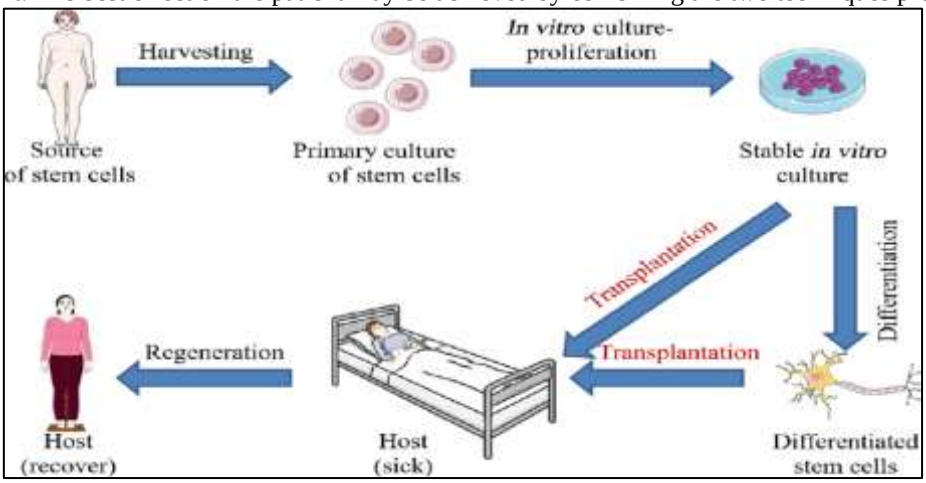

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Fig. 2: A basic cell transplantation procedure for the treatment of spinal cord injury. Isolation and extraction of cells, purification and screening in vitro and stable culture, and cell transplantation into patients are the three main steps in the basic process of cell transplantation in the treatment of spinal cord injury. In some studies, however, the purified cells were induced to differentiate in vitro, which is not a common procedure but is becoming more common.
(Image source: https://www.nrronline.org/viewimage.asp?img=NeuralRegenRes 2021 16 3 405 293130 f1.jpg&hcb=1)

Pathways of Transplantation:
In various SCI models, there are a variety of ways to transplant SCs, including:

- Intravenous injections
- Transarterial injections
- Intranasal injections
- Intraperitoneal injections
- Intrathecal injections
- Intramedullary injections

It was determined that various routes of SC administration could be used to treat SCI.

Number of SCs:
The number of SCs has a significant impact on the therapeutic outcome. It will be difficult to achieve therapeutic effects if there aren't enough transplanted cells. The majority of SC treatments for SCI studies used tens of thousands to millions of cells and had significant therapeutic effects.
They used an 8 105 number of MSCs to treat SCI mice via intravenous or intraperitoneal administration, and they discovered that the nerve fibers damaged in the mice's spinal cord after administration were reduced, and the mice's motor function was improved.

Time Window:
The time window for SC treatment of SCI is viewed differently in different studies. Some of them believe that SC transplantation should be used early in the treatment of SCI. Early SC transplantation can effectively reduce the occurrence of secondary injury and promote the recovery of nerve function because SCI usually causes secondary damage such as inflammation and apoptosis within a week.

Application of Immunosuppressive Therapy:
The immune barrier is a major impediment to allogeneic SC transplantation therapy's clinical transformation. The immunosuppressive regimen is constantly improved, increasing the chances of successful transplantation. Nonspecific immunosuppression, on the other hand, can lead to infection and cancer, as well as hypertension, diabetes, nephrotoxicity, and high blood lipid levels [76-78].

CONCLUSION:

Neuron replacement and neurological, structural, and functional restoration are the main goals of stem cell-based therapies for SCI. Stem cell-based therapies have a lot of potential as a treatment option for SCI. Although some types of stem cells will function as a renewable cell source in cell-based therapy for patients suffering from SCI, it is still unclear which type of stem cell is best suited for cell replacement therapy in SCI patients. Furthermore, stem cell-based replacement therapy's efficacy, safety, and ethical concerns are still being debated.
Numerous studies have suggested that SCs can aid recovery after SCI, but no single SC type appears to be sufficient to support a robust regenerative response that will result in complete SCI recovery when transplanted. A better understanding of SC differentiation pathways and SC survival after transplantation is required for successful SC-based therapy for SCI. Protocols for transforming ESCs, MSCs, NSCs, DPSCs, and iPSCs into a pure population of functional neural cells must be improved. More reliable animal models, particularly primate models, should be used to investigate the precise mechanisms of reconstructing pathways and synapses, integration, survival, and action of transplanted SCs in the injured medulla spinalis. As a result, the primary long-term results of trials examining the impact of stem cell-based therapies for SCI are eagerly anticipated. Until then, finding the ideal source of SCs for effective and safe cell-based therapy for SCI remains a difficult task that requires more research and ongoing collaboration among clinicians.

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