Regenerative Biomedicine

**Production and Hosting:** Shahid Sadoughi University of Medical Sciences

Journal homepage: jrb.ssu.ac.ir

Review Article

# Stem Cell-Based Therapies for Spinal Cord Injury: Mechanisms and Recent Advances

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**Received:**
2025-11-03
**Accepted:**
2025-12-07

**Volume:1**
**Issue no.4**

**Editor-in-Chief:**

Behrouz Aflatoonian Ph.D.



## Abstract

Spinal cord injury is a devastating neurological condition that leads to severe motor, sensory, and autonomic dysfunctions below the site of damage, profoundly affecting patients' quality of life. Despite extensive research, no effective curative treatment currently exists. Conventional therapeutic approaches such as surgical decompression, corticosteroid administration, and intensive rehabilitation primarily aim to reduce inflammation and prevent secondary injury but remain insufficient to promote neural regeneration or functional recovery. In recent years, stem cell–based therapy has emerged as a promising and multidimensional regenerative strategy for repairing injured spinal tissue. The therapeutic benefits of stem cells are mediated through mechanisms including neuronal replacement, modulation of the inflammatory microenvironment, neuroprotection, angiogenesis, and secretion of neurotrophic and growth factors that enhance axonal regeneration. Various types of stem cells—such as mesenchymal stem cells, neural stem cells, embryonic stem cells, and human endometrial stem cells—have been investigated for spinal cord repair, each offering distinct biological advantages as well as translational challenges related to survival, differentiation, and ethical or immunological concerns. Moreover, recent integration of biomaterial scaffolds and three-dimensional bioengineered constructs has further improved the efficacy of stem cell delivery and engraftment within the injured spinal cord. This review provides an overview of the recent advances in stem cell–based therapies for spinal cord injury, highlights the underlying molecular and cellular mechanisms, and discusses emerging bioengineering strategies that may optimize functional recovery and accelerate clinical translation in regenerative medicine.

**Keywords:** Mesenchymal stem cells, Regenerative medicine, Spinal cord injury, Stem cells, Stem cell therapy

**How to cite this article:**
Khandan-Nasab, N., Kuchakzade, F., Ahmadirad, N., Babaloo, H. Stem Cell-Based Therapies for Spinal Cord Injury: Mechanisms and Recent Advances, 2025; 1(4): 271-284.
https://doi.org/10.22034/jrb.2025.12.V1I4A3

## Introduction

Spinal cord injury (SCI) is a devastating neurological disturbance that affects young people and causes significant morbidity and disability. However, there are still no viable treatments available. Following the original injury, the pathological process after SCI involves a succession of secondary disorders, including bleeding, demyelination, edema, and neuronal necrosis (1, 2). There are currently few neuroprotective and regenerative treatments that have direct positive effects (3). Over the last few decades, stem cell (SC) treatment of spinal cord injury has grown in importance as a new area of study. The common SC types for SCI treatment include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), embryonic stem cells (ESCs), and neural stem cells (NSCs) (4). Recent research has revealed that these types of SC can be involved in SCI therapy based on their potential therapeutic mechanisms like tissue repair and replacement, neurotrophic and regenerative effects, promotion of angiogenesis, and antiapoptotic effects which are briefly discussed below. (5). By replacing or repairing injured nerve tissues, including neurons and glial cells, stem cell transplantation can restore nerve function by maintaining the integrity of the nerve conduction system (6). The proximal and distal ends of the spinal cord are linked to the damage site to support the development of new synapses, and interneuron differentiation from transplanted stem cells can trigger axon sprouting (7), While interneurons differentiated from transplanted stem cells can induce axon sprouting, stem cells interact with surrounding tissues to generate a type of neurotrophic factors that alter the microenvironment of the damaged site and speed up the axons growth. As a result, cell treatments with neuroprotective and neurodegenerative potential could open up new avenues for SCI treatment. (7, 8). Even though the fundamental differences between various stem cell types, there are three aspects of these cells benefits that have been identified by recent study (9). First, stem cells can multi- differentiate and play a part in the replacement of degenerative necrotic cells. Furthermore, SCs produce anti-inflammatory substances that suppress the inflammatory response in the injured microenvironment. Eventually, stem cells secrete a variety of cell adhesion factors, growth factors, and cytokines that aid in the improvement of the tissue regeneration and microenvironment (10). With the advent of basic stem cell biology research and translational medicine, the utilization of stimulation of potential stem cell differentiation and stem cell transplantation in vivo to treatment irreversible dysfunction brought on by SCI has seen impressive research in recent years (11).

### Cell-based Therapy

One of the fields in modern science and health that holds the most promise is cell therapy as a form of regenerative medicine. A wide range of ground-breaking and perhaps effective treatments for some of humanity's deadliest diseases are made possible by such potent technology (12). Regenerative medicine, which seeks to restore normal functions by repairing and possibly replacing damaged cells, tissues, or organs, is swiftly becoming the upcoming breakthrough in


https://doi.org/10.22034/jrb.2025.12.V1I4A3

healthcare (13). To the research communities' strong commitment to exploring the potential applications across a wide range of illnesses, including neurodegenerative ones, the prospect of regenerative medicine as an alternative to conventional drug-based therapies is fortunately becoming a reality by the day (12). Hopes that such regenerative approaches will one day become a treatment approach for a wide range of illnesses have been supported by recent studies showing that stem cell therapies have good patient translation. Any therapy for a disorder or medical condition that requires the utilization of any sort of viable human SCs is characterized as a stem cell-based therapy (14, 15).

**Stem Cell Classification**

SC-based therapy has evolved into a promising and advanced scientific study field in the last few years. The advancement of therapy procedures has sparked high hopes (16). All over the body, human stem cells are unspecialized cells. They possess the ability to self-renew and differentiate into any type of cell in an organism. Both adult and embryonic cells contain stem cells. (17). Totipotent stem cells have the potency to divide and differentiate into any type of cell in the body (18). Pluripotent stem cells (PSCs) stem cells (PSCs) can differentiate into cells from every layer of the germ, but not into extraembryonic tissues, such as the placenta. (19). PSCs are able to specialize in specific cells from particular cell lineages despite having a wider range of differentiation potential than multipotent stem cells. Unipotent stem cells have the smallest differentiation capacity and the unique ability to divide repeated, this characteristic which qualifies them as a potential therapeutic candidate for regenerative medicine (20). Somatic or adult stem cells remain undifferentiated after development and are distributed throughout the body among differentiated cells. These cells have the ability to heal, develop, and replace the cells that are lost every day. There are numerous types of stem cells, listed below: Many tissues contain mesenchymal stem cells. These cells primarily develop into bone, cartilage, and fat cells in bone marrow. They are an exception to the rule of stem cells because of their pluripotent behavior and capacity to specialize in any germ layer cell type.

Neural stem cells produce nerve cells, oligodendrocytes, and astrocytes.

Hematopoietic stem cells are responsible for the formation of all types of blood cells including white, red, and platelets.

Skin stem cells can produce Keratinocytes, which create a protective layer of skin (21, 22).

**Mesenchymal Stem Cells (MSCs)**

Mesenchymal Stem Cells are also recognized as mesenchymal stromal cells and are classified as expanding, non-hematopoietic cells, plastic-adherent, that have been intensively studied since their discovery. MSCs are intriguing candidates for the treatment of a variety of disorders because they may migrate to damaged sites (Fig. 1), engraft, and mature into end-stage functional cells (23). Through paracrine and cell–cell contact effects, as well as extracellular vesicles, these types of SC can stimulate neovascularization, boost angiogenesis, suppress cell death, increase cell survival

and/or proliferation, and alter immunological responses (24, 25). MSCs have recently been employed in numerous clinical trials around the world to recover a variety of disorders. Interestingly, some human trials have found no therapeutic benefit of MSCs, despite some promising outcomes from animal studies (26, 27). It is possible to extract MSCs or MSC-like cells, from practically any tissue in the human body, while bone marrow is the most common source. Adipose tissue, gingiva, amniotic fluid, dermis, placenta, dental pulp lung, skeletal muscle, compact bone, brain, human islets, synovium, peripheral blood, umbilical cord, and other tissues have all been found to contain MSC-like cells (28, 29). There has been a lot of interest in employing MSCs in a range of therapies due to their distinct therapeutic properties. The use of mesenchymal stem cells is efficient in engraftment in various organs, the repair of cardiovascular (30), autoimmune diseases (31), bone and cartilage diseases (32) and spinal cord injuries (33). The possible administration of MSCs either locally or systemically exposed to paracrine action has a role in determining the success of MSC therapy. There are three different ways to infuse MSCs including; Systemic delivery (intravenous (IV) and intra-arterial (IA), as well as inhalation) each with its own set of benefits and drawbacks. The second type of distribution is local, topical, or regional (cell spray, gel, or subcutaneous injection with a carrier hydrogel, intra-peritoneal (IP), intramuscular, or intracardiac (IC), and intrathecal injection), and the third type is scaffold/bioengineered construct (cells implanted in a scaffold) (34). Plastic adherence, the potential for differentiation in the adipogenic, chondrogenic, and osteogenic lineages, cell surface expression of CD90, CD105, CD73, and the absence of hematopoietic markers or CD14, CD19, CD45, CD34, or CD11b, CD79, and HLA-DR were all recognized as Mesenchymal Stem Cells characteristics by the International Society for Cellular Therapy. In addition, Mesenchymal Stem Cells, do not express membrane-bound molecules associated with immunological rejection, allowing for allogeneic transplantation. Despite these positive results, there are still safety issues with MSC-based therapy, particularly when it comes to long-term follow-up. The main issue is the transplanted MSCs' capacity to block anti-tumor immune responses and produce new blood arteries, which could support tumor development and metastasis (35).

**Stem Cell-based Therapy**

Progress in SC treatment and regenerative medicine has been fueled by the clinical need for innovative therapeutic approaches. To put it another way, SC-based therapies are becoming more significant in chronic and long-term illnesses treatment (36). However, to maximize the potential of SC-based therapies, various criteria must be addressed. Different scientific and clinical research on the effects of stem cell-based therapies on diseases with no definitive treatments has been conducted in this field (14, 37). Adult stem cells have been tested as a potential cell-based therapy for various disorders in preliminary studies. The characteristics of stem cells which make them suitable candidates for cell-based therapy are as follows:


https://doi.org/10.22034/jrb.2025.12.V1I4A3

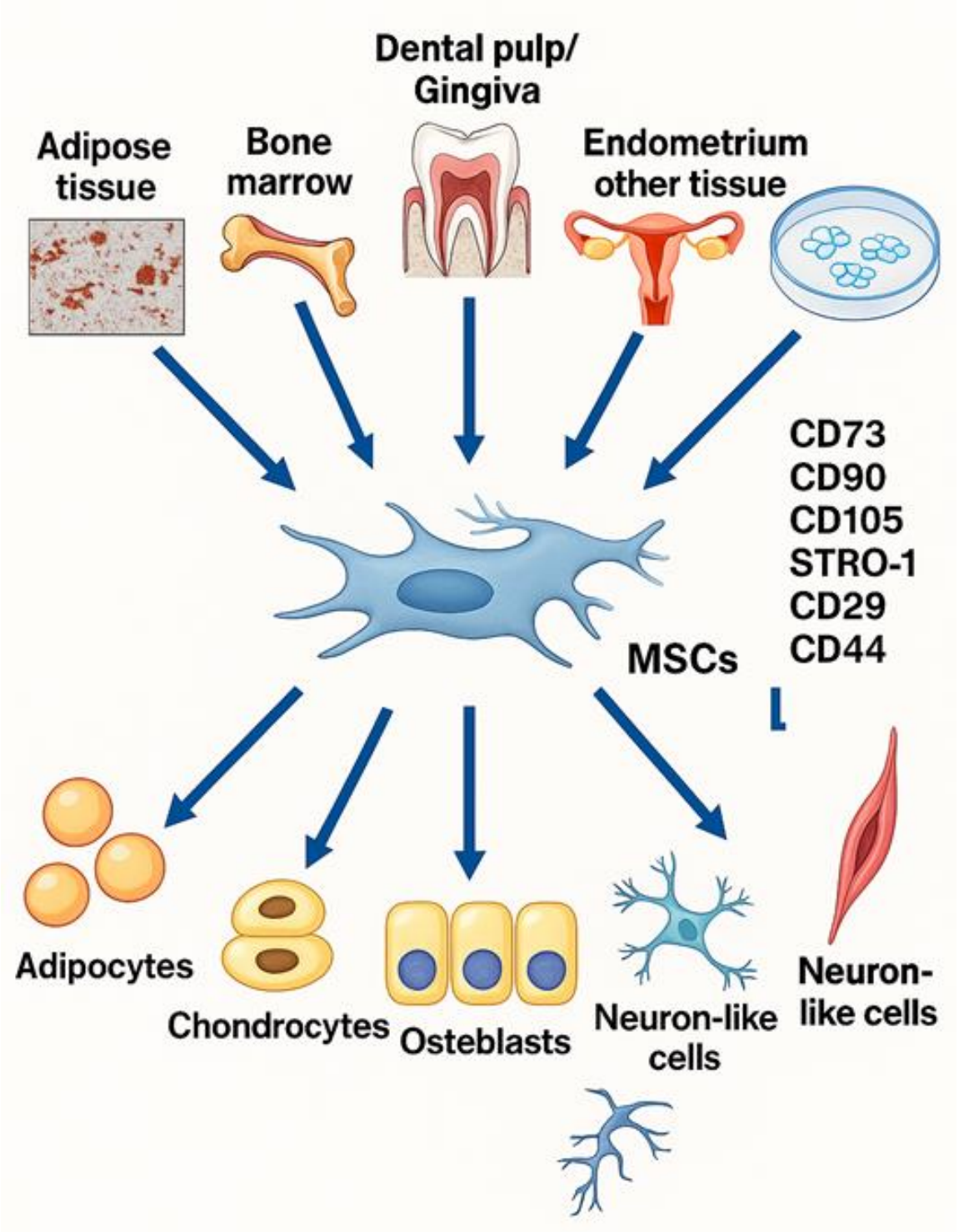


**Figure 1.** Differentiation ability of MSCs . Image adapted from (28) with permission from the publisher.

The Cell can be harvested from patients, In culture, cells have a high proliferative ability, Gene splicing methods make it simple to replace existing nonfunctional genes, the ability to move to specific tissues in the host (homing), The potency to integrate into host tissues and interact with the tissues around it (22). Numerous clinical trials are now being conducted around the world as a result of the

phenomenal success of animal studies. Various treatment programs are investigating the role of cell replacement therapy in illnesses such as cancer, heart failure, diabetes, hematological disease, spinal cord injury, arthritis, Parkinson's disease, and peripheral vascular disease in pilot or proof-of-concept studies (22, 38).

**Neurodegenerative disease prevention with stem cell-based therapy**

Neurodegenerative disease is a type of chronic, advanced nervous system marked by neuron death or degeneration. Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are examples of neurodegenerative disorders determined by a progressive loss of function, structure, or quantity of neurons in the spinal cord or brain. Regrettably, the present therapy choices are insufficient to stop the progression of neurodegenerative diseases. For millions of people throughout the world living with neurodegenerative disorders, the cost of care, the loss of quality of life, and the lack of viable medications are huge burdens (39-41). The traditional therapy of neurodegenerative illnesses has not yielded optimum outcomes due to the brain's limited ability to repair and regenerate (42). Stem cell therapy now recommends promising treatment options for practically all types of neurodegenerative diseases. These techniques include neuronal network stabilization, neurotrophic support brain tissue regeneration, and neurodegeneration alleviation at various neuronal circuitry levels (43). Spinal cord injuries are another neurologic reason for stem cell usage. Though the transplantation of various types of neural stem cells and oligodendrocyte progenitors has resulted in axon growth as well as neural connections, suggesting the possibility of repair, confirmation of restored function has yet to be proven in rigorous clinical studies. Nonetheless, stem-cell treatment for spinal cord injuries has recently received permission in Japan. Based on unpublished clinical trials involving 13 patients who had just suffered a spinal cord injury, this approval was granted. The patients were able to regain some sensation and motion when the Japanese doctors injected stem cells from their bone marrow. This is the first SC-based therapy for SCI to be approved by the government for use in patients (12, 14).

**Neurodegenerative Disorders and MSCs**

Because of their excellent self-renewal valence while keeping multipotency, MSCs offer the tremendous therapeutic capability and can be a favorite source for cell transplantation in neurodegenerative disorders. Owing to the relatively simple collection procedures and fewer relevant ethical, religious, and immune rejection concerns, Functional neurons produced from MSCs, in terms of neurodegenerative illnesses than embryonic stem cells seem more promising. Furthermore, unlike other primitive stem cells like mesenchymal stem cells embryonic stem cells, do not organize tumors. As a result of their potential abilities, MSCs are a prospective platform for neurodegenerative disease research. Contrary to the existence of tight junctions that would ordinarily restrict such routes, mesenchymal stem cells have been found to traverse the blood-brain barrier (BBB) via paracellular channels. MSCs' therapeutic efficiency in various neurodegenerative illnesses is now being evaluated in preclinical investigations and ongoing clinical trials (39, 44-46).


https://doi.org/10.22034/jrb.2025.12.V1I4A3

**Mechanisms of MSCs in Neurodegenerative Disease Treatment**

MSCs' putative strategies for treating neurodegenerative illnesses include (1) homing to damaged brain areas, (2) paracrine neuroprotective factors, and (3) immune cell regulation (42). When the body is harmed, MSCs can spontaneously move to the affected region, which is known as homing (47). Paracrine Mesenchymal stem cells(MSCs) can release a variety of growth factors, chemokines, and cytokines, all of which help regulate cell migration and immunity (48). MSCs have the ability to regulate immune cell function by preventing B cells from producing antibodies, T cells from activating, and NK cells from secreting cytokines (49).

**Treatment of SCI with SC-Based Therapies**

For many years, spinal cord injury as a result of severe injury or disease has been a difficult condition to solve (50). SCI is more common in boys under 30 years with frequency and incidence ranging from 8 to 906 instances per million persons according to nations and regions. The loss of neurons, axon breaking, and hemorrhagic necrosis are all symptoms of primary injury, which is an irreversible process that destroys the spinal cord tissue. In contrast to the peripheral nervous system (PNS), the spinal cord has a lower regeneration ability as a result of post-traumatic factors such as ischemia, inflammation, immunological response, and glial scar formation old (51, 52). Surgery to stabilize the injured area, pharmaceutical intervention to stop further injury, rehabilitation to stop function loss and help restore lost functions are the main components of traditional SCI treatment. However, because these remedies do not promote spinal cord regeneration, they are unsuccessful (51, 53, 54). Therapeutic developments have held many of hope for patients with SCI during the last two decades, but none of the known therapies has resulted in the restoration of the morphological structure of the spinal cord or its functions (55). In a small number of cases, different treatment interventions improve the wounded person's outcomes and quality of life, but in the vast majority of cases, they are unable to repair serious neurologic abnormalities and regain lost functions. Surgical techniques for SCI repair try to restore the orthopedic anatomy of the spinal canal, however, the results are mixed. The current definition of a SCI includes the impossibility of returning to a former way of life as well as the restoration of prior capacities for working and reproducing, with consequently considerable social and economic losses (56). Several innovative therapeutic adjuncts and therapy techniques, such as immunotherapy, stem cell secretory product-based therapy, and scaffold-based therapy can be utilized in conjunction with mesenchymal stem cell therapy to improve MSC survival, engraftment, proliferation, and migration (51). According to the findings, stem cell or progenitor transplantation may aid spinal cord healing (57). Mesenchymal stem cells, Fetal-derived neural stem cells, ESC-derived oligodendrocyte precursor cells, and central nervous system stem cells have all been surveyed or are being investigated clinically for the treatment of spinal cord injury (51, 58). Lost neuron replacement,

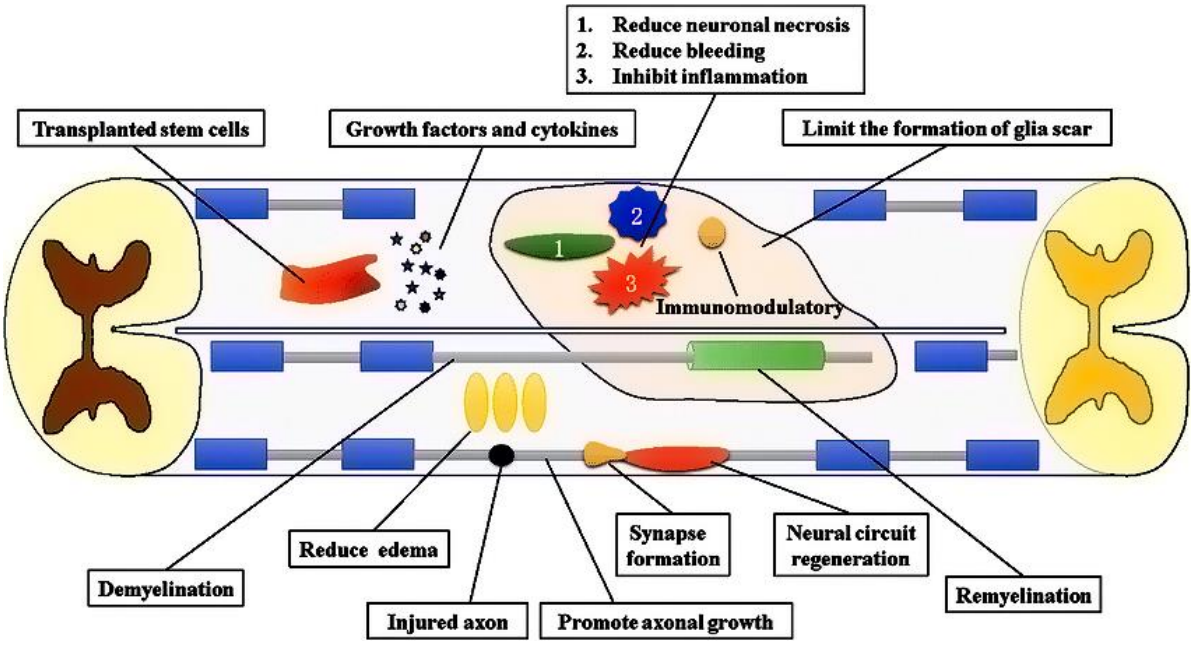


**Figure 2.** The link between stem cells and spinal cord damage . Image adapted from (8) with permission from the publisher.

axonal regeneration, apoptosis inhibition, and myelination are all promoted by stem cell-based therapy (59, 60). With varied targets and responses to stimuli, including modulating inflammatory responses, enhancing plasticity, and giving dietary assistance, cell treatments have neuroprotective and neuronal regeneration potential in SCI. Different cells from various tissue sources, such as adipose-derived mesenchymal stem cells (AD-MSCs), bone marrow mesenchymal stem cells (BM-MSCs), umbilical mesenchymal stem cells (U-MSCs), embryonic stem cells (ESCs), and neural stem cells (NSCs), were studied with these excessive potential mechanisms (61) (Fig. 2).

### Embryonic Stem Cells (ESCs)

ESCs are cells with the potential to develop into a variety of distinct cell types, such as neuronal and glial cells. As a result, these cells can be employed to heal neurological illnesses and traumas, such as SCI, as a prospective source of differentiated oligodendrocytes and motoneurons. Nonetheless, there is various anxiety about the safety of ESC transplantation in humans, including the controversies surrounding the creation of teratomas after hESC-derived brain cell engraftment (62-64).

Because ESCs differentiate into neurons, they are also used to treat neurological disorders as a highly effective neuronal cell replacement (65, 66). Many publications on the employ of embryonic stem cells to develop into glial cells and neurons for the treatment of SCI have been published in recent years (67, 68). Human embryonic stem cell-derived cells have been observed to develop into mature oligodendrocytes and neurons in patients with SCI in a variety of animal investigations (69, 70).

### Neural Stem Cells (NSCs)

NSCs are multipotent cells that can differentiate into neurons, oligodendrocytes, and astrocytes and can be effectively


https://doi.org/10.22034/jrb.2025.12.V1I4A3

reproduced in vitro. They are situated in the central canal of the spinal cord, the dentate gyrus of the hippocampus, and the lateral ventricle of the brain. These cells are derived from the spinal cord, and their properties differ from those of Neural Stem Cells derived from the forebrain (62, 71).

The main mechanisms of neural stem cells' therapeutic effects on neurological diseases are the modulation of astrocyte contribution to the glial scar, enhancement of neuronal differentiation and oligodendrocyte differentiation, replacement of missing nerve cells in SCI, and secretion of pro-regenerative factors to support injured tissue cells and neuritis (8, 72). NSC transplantation has been shown in numerous studies to aid in the recovery of neurological function after spinal cord injury (73). Glial scar astrocytes produced by neural stem cells have advantageous roles, such as protecting tissue integrity and providing neurotrophic protect for surviving neurons. After spinal cord injury, endogenous neural stem cells have been observed to have beneficial effects, making them a potential therapeutic target. Investigating the recognition, potential, and regulation of endogenous brain stem cells is crucial to effectively controlling their damage response. Increased neural stem cell progeny generation and neural stem cell redirection to generate more oligodendrocytes following spinal cord injury are two promising avenues to investigate (74).

**Hematopoietic Stem Cells (HSCs)**

Currently, research have increasingly concentrated on the use of HSCs in the treatment of SCI (75, 76). Andrey S. Bryukhovetskiy and colleagues, investigated the short- and long-term effects of complicated cell therapy (hematopoietic stem cells and progenitor cells) in 202 instances with SCI. According to the findings, the approach is safe and effective, that also, significantly improves the quality of life for spinal cord injury patients. The therapy has received approval to be used in clinical settings as a first-line therapy (56).

**Mesenchymal Stem Cells (MSCs)**

As stem cell technology has improved, the immunomodulatory function of stem cell transplantation has been a hot issue for the treatment of spinal cord injury (SCI), particularly that of mesenchymal stem cells (77). Mesenchymal Stem Cells have been extensively employed in both experimental and clinical settings and have been shown to have therapeutic potential in a diversity of CNS disorders, including ischemic stroke (78), multiple sclerosis (79), and SCI (80). Mesenchymal stem cells have evolved into the preferred seed cells in preclinical and clinical regenerative medicine due to their abundant source, extensive biological effects, lack of ethical concerns, and minimal immunogenicity (60). Bone marrow mesenchymal stem cells (BM-MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), and umbilical cord mesenchymal stem cells (UC-MSCs), are the most often employed MSCs in clinical practice (4). Types of research have demonstrated that BM-MSC transplantation may help SCI rats restore their neurological functions and reduce their neurological impairments (81). Mesenchymal stem cells from bone marrow have been demonstrated to promote spinal cord regeneration in a variety of ways. First, in the spinal cord injury region, bone marrow mesenchymal stem cells protect against

inflammatory reactions, suppress the immune system, and decrease lymphocyte proliferation and differentiation. Second, in the damaged area, BM-MSCs encourage the conversion of M1 macrophages to M2 macrophages. Furthermore, a variety of growth factors are secreted by BM-MSCs to protect spinal cord tissue that has already been harmed. (8, 82, 83). UC-MSCs are MSCs that come from the umbilical cord or cord blood., and they are straightforward to acquire and expand in vitro. Numerous preclinical studies have shown that UC-MSC implantation into SCI mice significantly improves functional impairments. (84). SCI has also been treated using UC-MSCs in animals and humans (85, 86). A-MSCs (adipose-derived mesenchymal stem cells) can be obtained during liposuction and are produced from adipose tissue. A-MSCs have advantages including being easy to collect in large quantities, causing minimal trauma damage, allowing for autologous transplantation, and not being connected to ethical issues. By secreting several neurotrophic agents, such as GDNF and BDNF, which control immune cell activation, promote nerve regeneration, and have anti-apoptotic properties, AD-MSCs can treat SCI and improve regeneration (87, 88). Because they are easy to obtain and have outstanding proliferation and differentiation capabilities, AD-MSCs are one of the best sources accessible (89). AD-MSCs have been shown in numerous studies to reduce the infiltration of ED1-positive macrophages and inhibit the inflammatory response following CNS damage (90). A growing number of clinical studies and procedures advise AD-MSC transplantation for the recovery from spinal cord damage in light of these findings (8).

**Human Endometrial Stem Cells (hEnSCs) as a Novel Source of Neural Cells Programming**

For the first time, research in 2004 identified stem cells in endometrial tissue (91). Through clonogenicity experiments, plastic adhesion, fibroblast-like morphology, and in vitro differentiation to adipogenic, chondrogenic, and osteogenic fates, the characterization of endometrial stromal cells illustrated MSC properties of these cells (92, 93).

Endometrial MSCs can also differentiate into cardiomyocytes, respiratory epithelial cells, pancreatic cells, neuronal cells and, hepatic cells (94, 95). Antibody panels used to further characterize human endometrial stromal cells revealed expression of MSI1, CD105, CD90, CD73, CD44, CD29 and, NOTCH1 (92, 96, 97). To date, only a few EnSC transplantation investigations have been undertaken, which including those on EnSC development into neuron-like cells (98). Endometrial stem/progenitor cells are thought to be important in mediating endometrial healing and subsequent tissue regeneration after menstruation. However, getting human endometria has the downside of being a very invasive procedure. Several investigations have recently revealed that menstrual blood contains a distinct population of cells with features comparable to AD-MSCs (99, 100). As autologous therapeutic agents, endometrial stromal cells have a a unique potential since they are simple to separate, multiply quickly without raising serious ethical or practical concerns, and have a higher overall clonogenicity (101-103). As a result, endometrial could be a viable alternative supply of MSC-like cells for


https://doi.org/10.22034/jrb.2025.12.V1I4A3

tissue engineering, with no higher morbidity than any other stem cell source (101).

## Conclusion

Stem cell–based therapy has emerged as one of the most promising strategies for treating spinal cord injury (SCI), offering the potential not only for neuroprotection but also for structural and functional regeneration. Over the past decade, significant progress has been made in elucidating how different stem cell populations—such as mesenchymal, neural, and embryonic stem cells—contribute to spinal cord repair through mechanisms including trophic factor secretion, immune modulation, and axonal regeneration. Despite these advances, several challenges remain before stem cell–based therapies can be fully translated into routine clinical use. Issues such as limited cell survival, potential immune rejection, and the inhibitory microenvironment of the injured spinal cord continue to restrict therapeutic outcomes. Future studies should focus on optimizing cell delivery methods, improving engraftment efficiency, and ensuring long-term safety and functional recovery. In conclusion, stem cell therapy represents a rapidly evolving and highly promising approach for spinal cord repair. Continued advances in stem cell biology, neuroregeneration research, and clinical translation will be essential to unlock its full potential and move closer to effective treatments for patients with spinal cord injury.

## Conflict of interest

The authors declare that they have no competing interests.

## Acknowledgements

The authors would like to express their sincere gratitude to Shahid Sadoughi University of Medical Sciences (Yazd), Mashhad University of Medical Sciences, and Iran University of Medical Sciences for their valuable academic support and scientific collaboration during the preparation of this manuscript.

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https://doi.org/10.22034/jrb.2025.12.V1I4A3