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Insights into Astrogliosis, Inflammation Processes, and Emerging Treatments by Exosome Therapy and Low-Level Laser Therapy for Spinal Cord Injury: A Systematic Review

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Abstract

Introduction: Spinal cord injury (SCI) is among the most severe medical conditions, with profound impacts on global healthcare systems. SCI results in temporary or permanent loss of spinal cord function and is associated with high incidence rates, substantial economic burden, significant disability, and a low average age of onset. Astrogliosis and neuroinflammation play central roles in secondary injury and limit functional recovery. This systematic review examines pathophysiology, mechanisms of recovery, and emerging clinical treatment strategies for SCI.

Methods: A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to identify relevant studies on SCI classification, pathophysiology, and treatment approaches, with a particular focus on Exosome and low level Laser therapy. The search included articles published up to September 2024, and key data were extracted for analysis.

Results: A total of 141 studies met the inclusion criteria. The pathogenesis of SCI involves an initial mechanical injury followed by a secondary cascade of molecular and cellular events that exacerbate tissue damage. Current treatment options primarily provide supportive care for patients with lifelong disabilities. Pharmacological interventions focus on neuroprotection, employing medications and therapeutic agents tailored to modulate degenerative processes. Non-pharmacological approaches, including growth factors, Low level laser therapy, cultured cells, and vitamins, offer additional therapeutic benefits. Laser therapy integration into SCI treatment is increasingly studied due to its anti-inflammatory, neuroprotective, and analgesic effects. Exosome therapies have shown significant neuroprotective and neuroregenerative potential by addressing multiple pathological mechanisms in SCI.

Conclusion: A promising future direction lies in combining conventional pharmacological and surgical strategies with emerging therapies, particularly exosome therapy and LLLT, offers a promising approach to mitigate secondary injury, modulate astrogliosis, and enhance recovery in SCI patients. Comprehensive therapeutic strategies integrating pharmacological and non-pharmacological approaches with cutting-edge cell therapies hold significant promise for improving outcomes in SCI treatment.

Keywords: Spinal cord injury; Inflammation; Neurodegeneration; Low level laser therapy; Exosome therapy.

Introduction

The spinal cord is a highly intricate structure that plays a critical role in transmitting information and commands between the central nervous system (CNS) and the rest of the body. Spinal cord injury (SCI) is classified based on the anatomical site, the functional level affected, and the extent of the injury.[1] SCI can lead to temporary or permanent disruption of spinal cord function, resulting

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in high incidence rates, significant healthcare costs, profound disability, and a relatively young average age of onset.[2] Globally, SCI is one of the most devastating medical conditions, placing a considerable burden on healthcare systems.[3] Epidemiological estimates indicate that approximately 759,302 individuals live with traumatic SCI in China, with 66,374 new cases annually, while in the United States nearly 17,000 new cases are reported each year.[2] SCI is primarily classified into two types: traumatic and non-traumatic. Non-traumatic SCI result from various medical conditions or diseases, such as spinal strokes causing cord ischemia or compression of the spinal cord. From a pathophysiological perspective, acute SCI can be divided into primary and secondary injuries.[4]

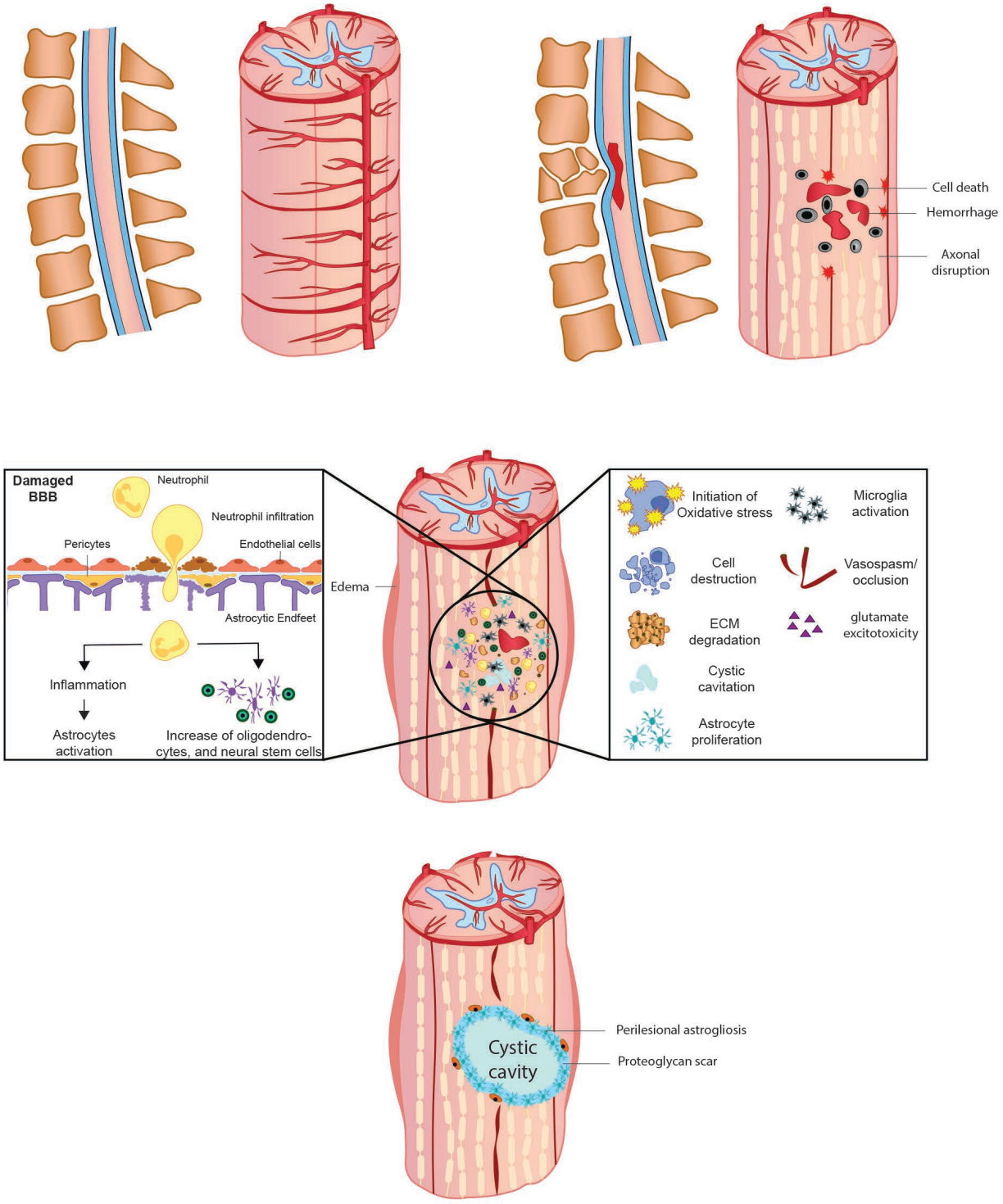

Figure 1. Spinal cord injury (SCI) process. The image shows that after SCI and nerve tissue damage, the nerve cells will be destroyed and the macrophage will phagocytosis the remains of the cells and cavity formation will be started. This figure design by adobe illustrator software

Primary injury involves direct trauma to the spinal cord, affecting its structure, blood supply, and surrounding supportive tissues, including vertebrae and ligaments. Secondary injury refers to the body's complex biological response to the initial trauma, which involves multiple systems, including the immune, nervous, and vascular systems (Figure 1). This response triggers processes such as ischemia, inflammation, oxidative stress, hemorrhage, demyelination, and neuronal cell death.[1] For instance, hemorrhage following primary injury is accompanied by the infiltration of immune cells, which release pro-inflammatory cytokines within 6–12 hours of the injury. These cytokines exacerbate neuronal inflammation, further intensifying tissue damage.[5] Thus, effective management of acute SCI focuses on addressing the primary injury while mitigating the cascade of secondary injuries.[1] This systematic review, aims to synthesize current evidence on SCI pathophysiology and highlight innovative therapeutic strategies, with a particular focus on nanovesicle-based interventions and their potential integration with established and emerging modalities. By concentrating on these innovative interventions, this review seeks to provide a more targeted perspective than previous broader reviews of SCI therapies which have primarily addressed SCI treatment in a broader context.

Methods

Literature Search Strategy

A systematic and comprehensive literature search was conducted to identify relevant articles on SCI, with a focus on classification, pathophysiology, and treatment strategies, particularly Exosome and Laser therapy. The search was performed across multiple databases, including PubMed, Scopus, and Web of Science, covering studies published up to September 2024 (Figure 2). The following keywords and Medical Subject Headings (MeSH) terms were employed to ensure thorough coverage: *"spinal cord injury," "SCI classification," "pathophysiology," "Low level laser therapy," "cell therapy," "neurodegeneration," "stem cell therapy," "exosome therapy,"* Boolean operators (AND, OR) were applied to maximize sensitivity.

Inclusion Criteria

Studies were included in the review if they met the following criteria:

- Original research articles, review papers, and meta-analyses.
- Publications in English.
- Articles focusing on the classification and pathophysiological mechanisms of SCI.
- Studies discussing various treatment strategies, with an emphasis on Exosome and Laser therapy approaches.

Exclusion Criteria

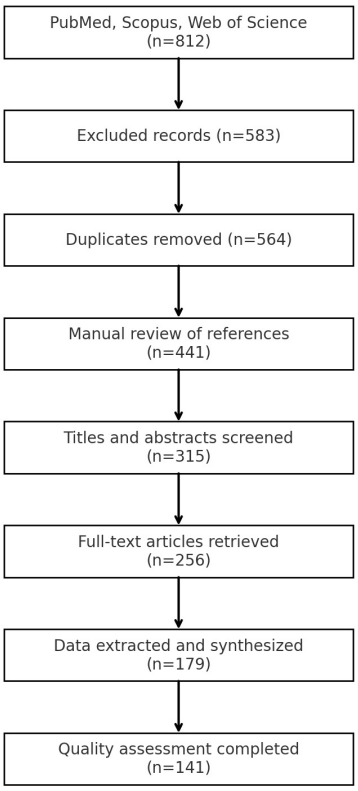

Figure 2. Diagram related to how to find articles and extract data in the desired information databases

Studies were excluded based on the following conditions:

- Articles not directly related to SCI.
- Case reports, conference abstracts, and editorial letters.
- Publications not available in English.

Data Extraction and Synthesis

Data were extracted from selected articles using a structured approach, focusing on:

1. Classification systems for SCI
2. Key pathophysiological mechanisms underlying SCI
3. Treatment modalities, with an emphasis on Exosome and Laser therapy

The extracted data were synthesized to provide a comprehensive and integrative overview of current knowledge in these domains. Particular attention was given to identifying promising treatment strategies and ongoing advancements in Exosome and Laser therapy for SCI (Figure 2).

Quality Assessment

The quality of included studies was rigorously evaluated based on the following criteria:

- Study design (e.g., experimental vs. observational).
- Sample size and statistical rigor.
- Methodological robustness.
- Alignment with the objectives of this review.

Priority was given to high-quality studies to ensure the validity and reliability of the conclusions drawn. Studies were critically appraised to identify limitations and gaps in the existing literature, providing a foundation for future research directions.

Results

Pathogenesis of SCI

The pathogenesis of SCI begins with an initial mechanical injury, followed by a secondary cascade of molecular and cellular events that exacerbate tissue damage. Neuronal damage interrupts essential neural pathways responsible for critical functions such as breathing, movement, bladder control, and autonomic regulation. In response to injury, the body attempts to initiate repair mechanisms by forming new neural connections, resulting in both beneficial and detrimental plasticity.[6] The pathophysiology of SCI involves a series of interconnected events, many of which occur simultaneously, adding complexity to the condition. Immediately after SCI, clinical manifestations often include disrupted blood supply, hypotension, and hypoperfusion, which can result in bradycardia, neurogenic shock, and hypovolemia. These symptoms, primarily due to neurogenic shock and bleeding, lead to ischemia. Persistent vascular ischemia, combined with hypovolemia and altered perfusion, can culminate in necrosis.[7,8] The immune response plays a pivotal role in the outcomes of SCI, contributing to both recovery and further damage. Following SCI, the activation of microglia and the breakdown of the blood-spinal cord barrier allow immune cells to infiltrate the spinal cord. These immune cells release inflammatory mediators, which may hinder healing. However, the precise role of immune responses in SCI recovery remains debated.[9] Astrocytes also become highly activated and proliferate after SCI, exacerbating damage to neurons, oligodendrocytes, and neural stem cells through inflammatory cell infiltration. Microglia contribute to astrocytic scarring by interacting with reactive astrocytes via fibronectin, amplifying inflammatory responses.[10] Various cell types, including fibroblasts, astrocytes, and pericytes, are activated post-SCI, contributing to the formation of fibrotic and glial scars. Transforming growth factor-beta (TGF-β) further intensifies astrocyte activation and promotes the formation of glial scar boundaries, which can both aid in containment and impede recovery.[11] One of the key contributors to post-SCI damage is inadequate blood flow to the spinal cord, caused by impaired vascular regulation and systemic hypotension. Reduced blood supply rapidly depletes cellular adenosine triphosphate (ATP) stores, leading to mitochondrial dysfunction and cell death. The breakdown of the blood-spinal cord barrier exacerbates the injury by causing vasogenic edema, which further impairs perfusion.[6] Ischemic damage and cellular disturbances stimulate the production of free radicals, overwhelming the body's antioxidant defenses. Additionally, ion imbalances, particularly involving calcium and sodium, are critical aspects of the secondary injury phase. The excessive calcium influx into cells triggers a cascade of damaging processes, including mitochondrial dysfunction and activation of destructive enzymes.[12] Another major factor contributing to neuronal death is glutamate excitotoxicity. Following SCI, there is an excessive release of glutamate, a critical excitatory neurotransmitter typically regulated by the calcium ion (Ca^{2+}) flux at the synaptic cleft. This over-release disrupts ionic homeostasis, damages mitochondria, and leads to axonal demyelination and neuronal death.[11]

Astrogliosis and information

Astrogliosis refers to a series of functional, cellular, and molecular changes in astrocytes in response to CNS damage and various diseases.[13] It significantly impacts outcomes in a wide range of CNS disorders.[14] Reactive astrogliosis is a complex and regulated process characterized by cellular hypertrophy, changes in gene expression, scar formation, and long-term structural alterations. Rather than a single uniform response, this process involves dynamic and multifaceted changes.[15] Reactive astrocytes can have detrimental effects and are associated with the progression of neurodegenerative diseases.[16] Inflammation is a protective immune response to harmful stimuli such as damaged cells, toxic metabolites, pathogens, and physical trauma.[17] It involves the activation of microglia, macrophages, and neutrophils. Macrophage infiltration occurs around twelve hours post-injury, with the inflammatory response peaking at 72 hours.[18] Recent research has emphasized the diverse roles of reactive astrocytes in SCI recovery, including their capacity to reduce inflammation.[19] SCI remains a significant challenge in clinical medicine, affecting thousands of people.[20] Despite substantial research, there is still no method to fully repair SCI. More research is needed to better understand the processes that can mitigate the inflammatory response and promote regeneration.[21] A major barrier to advancing medical treatments for SCI is the multifactorial nature of SCI under both normal and pathological conditions. The mechanisms of damage in SCI are complex and involve many factors.[22] The plasticity of astrocytes, which can adopt either proinflammatory or anti-inflammatory phenotypes, presents a potential target for therapeutic intervention.[23] Understanding the characteristics and regulatory mechanisms of astrocytes could improve our understanding of neurological disorders and lead to novel treatment strategies. Reactive astrocytes appear to contribute to pathological damage through the NF-κB signaling pathway while also supporting lesion recovery via the STAT3 pathway.[24] Activated astrocytes enhance inflammation by secreting cytokines such as interleukin-1 and TNF-α.[25] They also respond to pro-inflammatory cytokines released by CNS

resident cells and peripheral immune cells recruited to the CNS, influencing the overall response of surrounding cells throughout the CNS.[26] Astrocyte signaling pathways often converge on common transcriptional regulators during inflammation, particularly NF-κB.[27] The nuclear translocation of NF-κB is a key step in astrocyte activation, contributing to the progression of CNS pathologies, including SCI.[26] Blocking NF-κB signaling in astrocytes has been shown to improve clinical outcomes by reducing pro-inflammatory cytokines and oxidative stress. NF-κB activation in astrocytes is triggered by pro-inflammatory stimuli such as IL-17, IL-1β, TNF-α, reactive oxygen species (ROS), phagocytosed myelin, Toll-like receptor (TLR) engagement, and other factors related to CNS inflammation.[27] Understanding the stages of astrogliosis is crucial for addressing the detrimental effects of glial scar formation. Various therapies, such as hydrogels, stem cells, and steroids, are being explored in preclinical and clinical settings to modify astrocyte activity and improve SCI outcomes.[13] The pathophysiological processes underlying neurodegenerative diseases are not fully understood, but inflammation plays a critical role. Microglial cells in the CNS detect harmful pathogens and initiate neuro-inflammatory processes to maintain cellular homeostasis. However, persistent inflammation by microglial cells can become toxic, leading to neuronal degeneration and initiating a cycle of neurodegeneration.[28] Neuroinflammation involves the movement and accumulation of cells that support tissue damage and recovery.[29] Evidence suggests that increased age is linked to higher levels of inflammation, which may contribute to neurodegenerative diseases.[30] Activated astrocytes release inflammatory mediators, which can have either neurotoxic or neuroprotective effects, playing key roles in CNS disorders like SCI.[31] Despite these discoveries, the research community lacks a comprehensive understanding of astrogliosis. There is a growing need to clarify how specific astrocyte functions are altered during astrogliosis to develop evidence-based therapeutic approaches. While surgery and medication are the primary clinical treatments, advances in tissue engineering suggest the potential of cellular therapies for injury repair, with promising results.[32]

Mechanism of Spinal Cord Recovery Pathways

Following SCI, neuronal death and axonal disruption lead to a breakdown of neural circuits, resulting in both motor and sensory dysfunction. Recent research has emphasized the crucial role of interneurons in bridging neurons and facilitating the formation of alternative neural pathways, a promising strategy for SCI repair (Figure 3). While the body has an inherent, albeit limited, capacity for self-repair following SCI, external interventions are necessary to enhance recovery outcomes. Stem cells have shown promise in this regard, as they can differentiate into various neural cell types, secrete growth factors, and modulate inflammation, thereby supporting nerve repair and tissue regeneration.[9] SCI triggers both motor and sensory deficits, primarily due to a cascade of harmful processes initiated by the injury. While the initial injury causes direct neuronal damage, it also activates a series of secondary destructive events that complicate recovery and limit the effectiveness of many treatment strategies. Current therapeutic approaches can generally be categorized into three main strategies: neuro-regenerative, immune-modulating, and neuroprotective.[3] Tissue regeneration after SCI follows three main stages: 1) inflammation and cell death, 2) tissue replacement and cell proliferation, and 3) remodeling of tissue. The initial response to SCI is hemostasis, followed by inflammation, which helps clear cellular debris from the injury site. Platelet aggregates are involved in recruiting macrophages and neutrophils to the injury site. Additionally, endogenous mesenchymal stem cells migrate to the site to assist in tissue repair and regeneration.[33]

Clinical Treatment

Currently, there is no effective treatment for SCI that can fully preserve or restore function post-injury. Existing treatments are largely limited to providing supportive relief for patients facing lifelong disabilities. Many researchers agree that mitigating secondary injury following SCI remains a primary target for effective treatment strategies.[34] Pharmacological interventions focus on neuroprotection by targeting various molecular pathways involved in the degenerative processes after SCI. These strategies include: 1) neurotransmitter agonists and antagonists, 2) antioxidants, 3) anti-apoptotic agents, 4) ion channel blockers, and 5) herbal and natural compounds. At present, Methylprednisolone (MP) is the only FDA-approved medication for SCI treatment. Clinical trials are currently underway for new drug treatments, which aim to promote neural regeneration, regulate the post-injury microenvironment, and improve drug delivery methods.[9] Non-pharmacological approaches for SCI treatment include the use of growth factors, cultured cells, and vitamins. Cellular therapies, for example, utilize neuroprotective growth factors such as BDNF (brain-derived neurotrophic factor), TGF-β (transforming growth factor beta), and IGF-1 (insulin-like growth factor 1). Although various bioengineering technologies are being investigated for their potential in SCI treatment, many of these are still in preclinical or laboratory stages.[3] The choice of therapeutic approach can significantly impact the inflammatory response, as well as the anatomical and functional outcomes following SCI. Developing therapies that specifically target the regulation of the inflammatory response, particularly by modulating

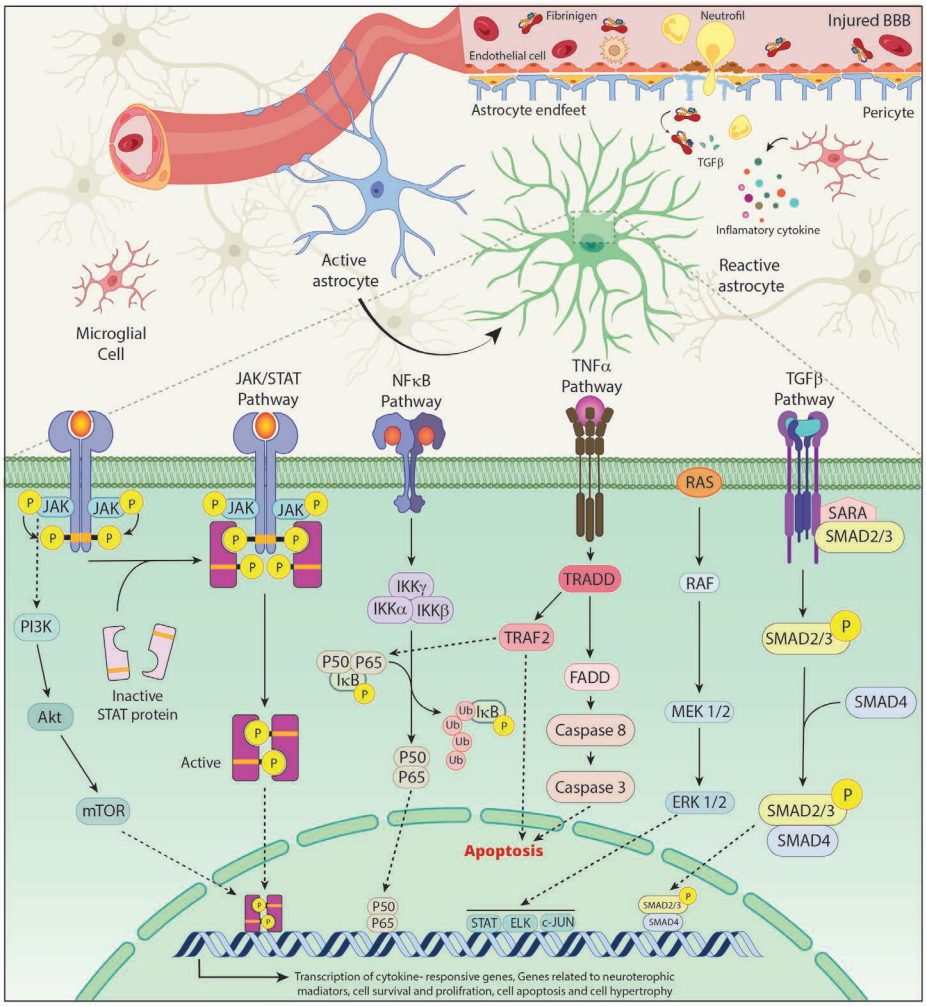

Figure 3. Several factors in the creation of cellular inflammatory cascades and molecules caused by SCI. This procedure starts by activation and proliferation of microglia and astrocytes; infiltration of safe cells inside blood circulation, including neutrophils, monocytes and lymphocytes; increased synthesis and release within the spinal cord and other reactive materials (such as histamine and protein supplements) by types of nerve cells (microglia and astrocytes) Endothelial cells and cells and non-neural factors. This figure design by adobe illustrator software

cytokines, is essential for improving treatment efficacy.[35]

The therapeutic potential of mesenchymal stem cells (MSCs) can be enhanced further by integrating them with emerging biological treatments, such as stem cell secretome therapy, immunotherapy, and scaffold-based approaches.[36] Several studies have explored the use of bioactive materials to modulate the injury microenvironment and facilitate SCI repair.[37]

In general, SCI treatment strategies vary depending on the stage of injury. In the acute stage, the focus is on neuroprotection and controlling neuroinflammation. Pharmacological agents are used to reduce inflammatory cell infiltration and minimize oxidative stress. In the chronic phase, recovery strategies focus on restoring neural function, which may include physical therapies, removal of glial scars, and the reconstruction of neural circuits using biomaterials and stem cells. A promising approach is the trans-differentiation of astrocytes into neurons through reverse transcription, which can support neural recovery.[38,39]

Laser Therapy in Inflammation Control and Pain Modulation of SCI

Low-level laser therapy (LLLT), also termed Photobiomodulation (PBM)', uses low-power (600–850 nm) red or near-infrared light to stimulate cellular processes.[40] Its integration into SCI treatment is increasingly studied due to its anti-inflammatory, neuroprotective, and analgesic effects.[41] LLLT downregulates pro-inflammatory mediators such as TNF-α, iNOS, IL-1β and IL-6 at the lesion site, while promoting anti-inflammatory (M2) macrophage polarization. For instance, in rat contusive SCI models, laser treatment significantly reduced TNF-α and iNOS expression, paralleling improved motor recovery.[42] In systematic reviews of preclinical SCI models, 79% of studies reported reduced cytokine levels and enhanced neuroprotection after LLLT, with initiation within 2 hours post-injury yielding the strongest results.[40] Nevertheless, heterogeneity in laser parameters

(wavelength, dose, duration) highlights the need for standardized protocols.[43] Neuropathic pain after SCI is notoriously difficult to treat. LLLT has demonstrated efficacy in reducing hyperalgesia and allodynia in animal models by modulating pro-inflammatory cytokines (e.g., IL-6) and neurotrophic factors.[42] One rat study showed that two weeks of LLLT reduced IL-6, mechanical hyperalgesia, and heat hyperalgesia comparably to methylprednisolone, without corticosteroid side effects.[44] Clinical systematic reviews also support LLLT's analgesic benefits across peripheral and central neuropathic pain settings, though optimal dosing remains under investigation.[45,46] Emerging studies combine LLLT with stem-cell therapies to harness synergistic effects. In SCI rat models, the co-administration of human adipose-derived stem cells (hADSCs) and lasers significantly improved motor outcomes, axonal regeneration, and reduced hyperalgesia more than either treatment alone. This suggests that LLLT may potentiate vesicle-mediated regenerative effects and reduce astrogliosis.[47] Preclinical evidence positions LLLT as a promising adjunctive therapy, particularly when started early post-injury. However, clinical data in SCI patients remain sparse. Moreover, the optimal wavelength, dose, timing, and delivery devices are still debated. Light scattering through tissue raises questions about sufficient energy delivery to spinal targets, though fiber-optic and intrathecal methods are under study[9,48,49] Finally, LLLT is safe, well-tolerated, and non-invasive, but its cost-effectiveness needs evaluation in clinical trials.[50]

Across multiple experimental models, LLLT has been shown to reduce pro-inflammatory cytokine expression and neuroinflammation,[51,52] shift microglia and macrophages toward an anti-inflammatory M2 phenotype, modulate astrocytic responses by decreasing A1 and enhancing A2 astrocytes, and improve mitochondrial bioenergetics through the activation of the AMPK/PGC-1α/TFAM pathway.[53-55] These biological effects translate into meaningful improvements in neuropathic pain control, tissue preservation, and locomotor recovery.[55-57] The benefits appear to be wavelength- and dose-dependent, underscoring the need for optimized treatment parameters.[52] Although most of the available evidence is derived from animal studies, systematic reviews and transcriptomic analyses further support the role of LLLT in suppressing inflammation and promoting regeneration.[48] Collectively, these findings highlight LLLT as a promising adjunctive therapy for SCI. Future clinical trials are essential to validate these results, establish standardized protocols, and evaluate long-term outcomes in humans (Table 1).

Cell Therapy in SCI

Despite significant advances in medical research, effective regenerative therapies for SCI remain elusive.[58] Neurons at the injury site have a limited capacity for regeneration, posing a major challenge to recovery. Rapid progress of stem cell science is the driving potential of cell therapies that help individuals with SCI.[59-60] Cell-based therapies offer potential for treating SCI (Figure 4), driven by rapid progress in stem cell science. These therapies have the ability to target various aspects of SCI pathology, including cellular and molecular responses to injury. However, despite promising results from clinical studies, the efficacy of these therapies in SCI treatment remains limited.[59-60] Given the complexity of SCI, a multifaceted therapeutic approach is essential to improve patient outcomes.[58] Cell-based therapies show substantial neuroprotective and neuroregenerative potential by targeting multiple mechanisms involved in SCI. Researchers have explored various stem cell types derived from different sources to harness their therapeutic benefits.[61-63]

Stem Cell Types for SCI Treatment

Table 1. Preclinical and experimental studies on the use of laser therapy for inflammation control and pain modulation in SCI.

Study (Authors, Year)	Model / Species	Laser Parameters (wavelength, fluence, duration)	Inflammation / Pain Outcomes	Mechanisms Highlighted
Svobodová et al 2019	Rat contusion SCI	808 nm + 905 nm concurrent, multiwave locked system, daily post-injury	↓ Thermal hyperalgesia; ↑ M2/CD206, ↓ M1/CD86 macrophages; tissue sparing	Shift of microglia/macrophage polarization toward anti-inflammatory (M2).[51]
Janzadeh et al 2023	Rat SCI model	PBMT 2 vs 4 W, weekly for 2–4 weeks	↓ Neuropathic pain, improved allodynia; motor benefit; immunomodulation of IL1α, IL10, P2RX receptors	Regulation of immune-gene expression, pain-receptor modulation.[52]
Zhu et al 2022	Rat SCI	PBM daily irradiation (810 nm?) over up to 28 days	↓ Neuronal apoptosis; improved motor recovery; restored mitochondrial function	Activation of AMPK/PGC-1α/TFAM pathway, improved mitochondrial bioenergetics.[53]
Wang et al 2021	Clip-compression SCI in rats	PBM daily for 2 weeks	Lesion cavity reduction; motor recovery; reduced A1 astrocytes, ↑ A2 astrocytes	Modulation of A1/A2 astrocyte phenotypes, upregulation of bFGF and TGF-β.[54]
Da Silva et al 2016	Rat impact SCI	808 nm, fluences: 500, 750, 1000 J/cm², daily × 14 days	↑ Locomotor and tactile recovery, ↓ CD68 expression at higher fluences	Dose-dependent anti-inflammatory effect, microglial/macrophage reduction.[55]
Stevens et al 2025	Mouse SCI (omics)	PBM acute post-injury (transcriptomic analysis)	Gene expression shifts favouring regeneration and inflammation suppression	Down-regulation of apoptosis/metabolic pathways; modulation of macrophage genes (e.g. Fabp4).[56]
Zhang et al 2024	Mouse T9 clamp SCI	810 nm, 50 mW/cm² × 50 min × 7 days	↓ Chondroitin sulfate proteoglycan (versican) expression; improved motor function	Inhibition of Smad3/Sox9 and MAPK/Sox9 pathways in astrocytes.[57]

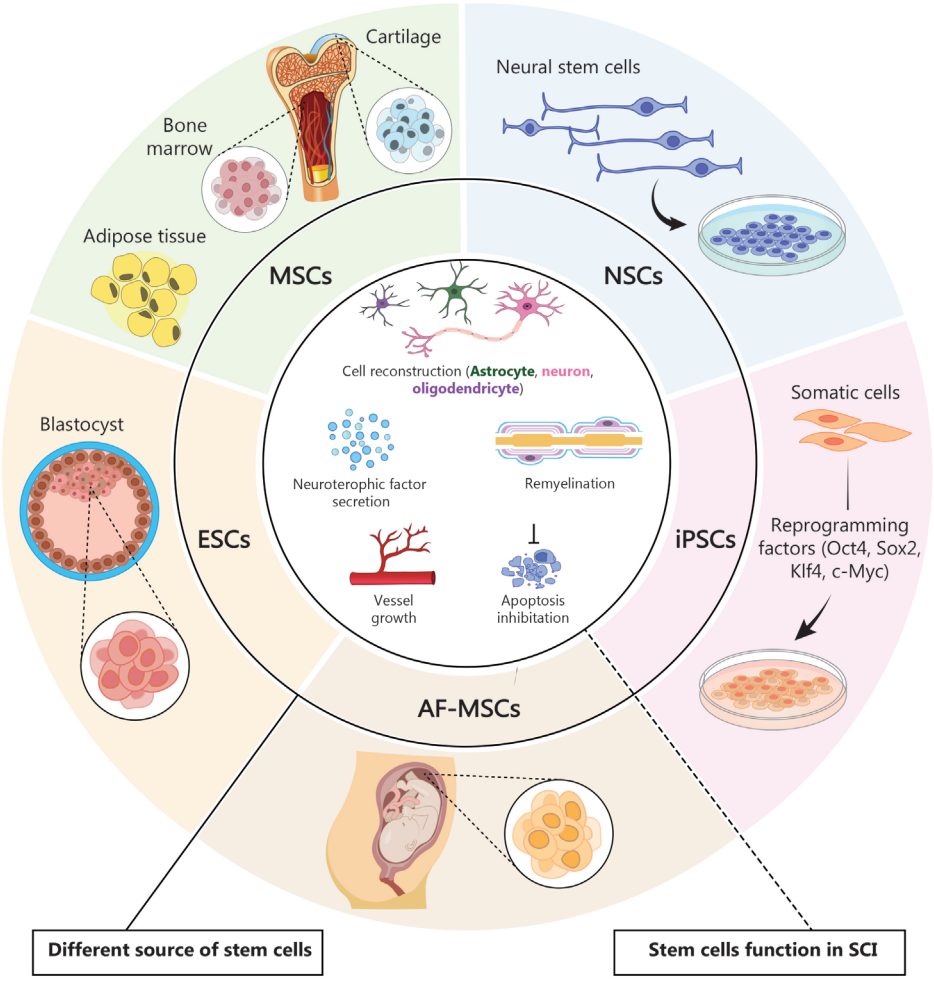

Figure 4. Stem cells have shown potential in the treatment of spinal cord injuries. These cells can repair or replace damaged nerve cells and tissues, including nerve cells and glial cells, and contribute to the integrity of the nerve conduction pathway and, as a result, restore nerve function. On the other hand, stem cells interact with the surrounding tissues to create different nerve factors, change the conditions of the damaged area, and accelerate the growth of nerve fibers. This figure design by adobe illustrator software

Among the diverse stem cell types, Mesenchymal Stem Cells (MSCs) stand out for their ability to repair SCI. MSCs can differentiate into various tissue types, including cartilage, bone, adipose tissue, and nervous tissue.[64] Compared to other stem cell sources, MSCs are particularly attractive due to their ease of isolation and preservation, as well as their inherent therapeutic properties.[65] They show significant potential in repairing nervous tissue damage after SCI. Furthermore, MSCs possess immune-modulatory properties, releasing cytokines that help reduce neuronal loss and support SCI recovery. However, the clinical effectiveness, safety, and feasibility of using adipose-derived and umbilical cord MSCs for SCI remain underexplored.[64]

Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) are of particular interest for SCI treatment, owing to the high abundance of somatic stem cells in adipose tissue and the relative ease of obtaining this tissue. AD-MSCs secrete various cellular components and immune agents, contributing to their potential in promoting neuroregeneration, providing anti-apoptotic effects, supporting angiogenesis, and facilitating wound healing.[66]

Although studies comparing the effectiveness of autologous bone marrow-derived MSCs (BM-MSCs) and AD-MSCs have been conducted, the results have not yet been published.[64]

Neural Stem Cells (NSCs) have demonstrated the ability to promote remyelination in demyelinated rat spinal cords, producing patterns of myelination comparable to Schwann cells. These cells also reduce glial scar formation, decrease secondary tissue damage, and preserve nerve tracts.[67] While NSCs improve functional recovery through neuroprotective and neuroregenerative mechanisms, most studies involving NSC transplantation have reported only modest improvements in spinal cord recovery.[60]

Embryonic Stem Cells (ESCs), derived from the inner cell mass (ICM) of blastocysts, have the capacity to

differentiate into ectodermal cells such as neurons and glial cells, showing potential for neurological recovery without adverse effects.[68] However, ESCs raise ethical concerns and their clinical use is limited.

Amniotic Fetal Mesenchymal Stem Cells (AF-MSCs) are notable for their high proliferation capacity and low immunogenicity. Despite these advantages, preclinical studies have yielded only modest benefits, including decreased inflammation, enhanced angiogenesis, and nutritional support.[69]

Induced Pluripotent Stem Cells (iPSCs) hold promise for SCI treatment, offering an alternative to ESCs by bypassing ethical concerns and immune rejection issues. iPSCs provide autologous cells capable of generating various neural cell types, which are critical for successful cell-based therapies. Research has shown that iPSCs can differentiate into mature neural cells, including dopaminergic neurons, motor neurons, and GABAergic interneurons.[68]

There are several challenges in applying cell-based therapies to SCI treatment. One of the primary hurdles is selecting the appropriate stem cell types and sources, as each type has its own distinct advantages and limitations. Another challenge is ensuring the survival and differentiation of transplanted cells, as maintaining their therapeutic potential remains critical. Additionally, quality control and consistency throughout the process of isolating, expanding, and transplanting stem cells are essential for successful outcomes. Determining the optimal dosage and timing for stem cell transplantation is another area of ongoing research. Furthermore, translating findings from animal models to human physiology poses additional difficulties, underscoring the need for further research. While stem cell transplantation offers significant promise, it is important to recognize that it cannot fully repair SCI on its own. A more comprehensive approach that combines stem cell-based therapies with established treatments, such as surgery and pharmacotherapy, holds greater potential for improving recovery from SCI.[58,68]

Managing Patient Expectations

As clinical trials have yielded only limited results, it is crucial to manage patient expectations. Current therapies for SCI remain in the early stages of development, and patients should be informed of the limitations of these treatments to prevent unrealistic expectations and minimize the psychological impact of unmet hopes.[70]

A summary of these sources is provided in the table below (Table 2).

Exosome Therapy in SCI

Extracellular vesicles (EVs) are membrane-bound particles secreted by various cells into the extracellular space, playing a crucial role in intercellular communication and tissue repair.[91] Among these, exosomes—a specific type of EV released by stem cells—have shown significant potential in promoting tissue repair following injury.[92]

Exosomes derived from mesenchymal stem cells (MSC-Exo) have emerged as promising therapeutic agents in the treatment of various neurological disorders. These exosomes are capable of reducing neuronal inflammation and supporting neural repair,[93] making them an essential component in the pathophysiology of SCI.[94] After SCI, extensive vascular damage leads to hemorrhage, ischemia, and inflammation, which contribute to significant neuronal cell death, microglial activation, and axonal loss at the injury site.[95] Therefore, early intervention strategies aimed at reducing apoptosis, stimulating neuronal and axonal regeneration, modulating microglial activation, and suppressing inflammation are critical for mitigating SCI progression and improving patient outcomes. Exosomes, with their content of bioactive molecules and microRNAs, have garnered increasing attention for their role in treating CNS disorders, including SCI.[94] While direct transplantation of MSCs holds therapeutic promise, it involves several risks, including the development of chromosomal abnormalities in bone marrow-derived stem cells (BMSCs) during early cell passages, which can lead to malignant tumor formation.[96] MSC transplantation also faces challenges such as low cell survival rates and immune rejection, complicating its use in SCI treatment.[97] In contrast, exosomes derived from MSCs offer a significant advantage: they are non-tumorigenic and circumvent many of the complications associated with whole-cell therapies. Umbilical cord mesenchymal stem cells (UCMSCs) appear to be a particularly promising source of exosomes. UCMSCs are more accessible than BMSCs and do not raise the same ethical concerns.[98] Exosomes can be derived from various sources, and many studies have reported the beneficial effects of exosomes from different origins in SCI treatment.[99] Additionally, recent research has highlighted the role of microRNAs (miRNAs) in the pathophysiology of SCI. Studies have shown that exosomes carrying miRNAs can be utilized to enhance SCI treatment.[100]

A systematic review of 32 studies indicated that exosomes can significantly improve motor function in SCI models by reducing pro-inflammatory factors and apoptotic proteins. Exosomes derived from human tissues demonstrated superior reparative effects compared to those from animal tissues (Table 3). Moreover, longer treatment durations were correlated with more substantial improvements in SCI outcomes. However, the review also identified methodological limitations in the current animal studies.[101] Future research should focus on improving the safety, targeting, and stability of exosomes to optimize their therapeutic potential for SCI recovery. The table below summarizes key studies in this area to date.

Table 2. Clinical trials and animal studies on different cell therapies

Cell Type	Study by	Year	Model / Species	Important Findings
BM-MSCs (bone marrow-derived mesenchymal stem cells)	Mendonça et al	2014	Human	Neurological and MRI Findings: Increased sensitivity in the injury site was detected. MRI results demonstrated stability in hyperintense signals, with no lesion size expansion or new areas of gliosis, suggesting recovery of motor function and a decreased risk of secondary damage.[71]
	El-Kheir et al	2014	Human	Safety and Efficacy: Over an 18-month period post-surgery, transplantation was deemed safe, with improvements in motor function, modest neurological enhancements, and reduced spinal cord compression.[72]
	Satti et al	2016	Human	Tolerance: After one year, all patients tolerated the procedure well, with MRI revealing no alterations in hyperintense signals or ectopic tissue formation.[73]
	Vanquero et al	2016	Human	Functional Improvements: Notable improvements were reported in sphincter control, sensation, spasticity reduction, motor and sexual function.[74]
	Guadalajara et al	2018	Human	Bowel Function: Patients had better anal sensation pressure, neurogenic bowel dysfunction scores, and MRI findings.[75]
AD-MSCs (adipose-derived mesenchymal stem cells)	Ra et al	2011	Human	Cardiac and Physical Condition: No alterations noted in vital signs, heart function, or physical condition compared to control measurements. However, MRI did show a slight, non-significant reduction in the size of the lesion in the spinal cord at 12 weeks.[76]
	Hur et al	2016	Human	Motor and Sensory Scores: ASIA[1]motor scores enhanced in five out of 14 patients, with sensory recovery in ten out of 14. One patient experienced worsened sensation, and some reported headache, nausea, and vomiting.[77]
U-MSCs (umbilical mesenchymal stem cells)	Cheng et al	2014	Human	Cell Therapy vs. Rehabilitation: In the cell therapy group, 7/10 patients showed motor score improvements, better self-care, and reduced muscular tension. In comparison, five out of 14 in the rehabilitation-only patients saw improvements, with the cell therapy patients similarly showing better urodynamics.[78]
NSCs (neural stem cells)	Curtis et al	2018	Human	Safety and Improvements: No major adverse events were reported. EMG[2], ISNCSCI[3] and BMCA[4] scores improved, but there were no significant improvements in quality of life.[79]
	Levi et al	2018	Human	Cell Delivery: Manual injection of up to 4×10^7 cells was feasible and protected.[80]
	Levi et al	2019	Human	GRASSP Score: Although there were improvements in GRASSP[5] scores, the trial was terminated early due to futility analysis.[81]
NPCs (neural progenitor cells)	Jin et al	2016	Animal	Challenges in Chronic SCI: Neural progenitor cells did not survive well in chronic spinal cord injuries, leading to no improvements in motor and sensory function, although bladder function significantly improved [82].
ESCs (embryonic stem cells)	Faulkner et al	2005	Animal	Remyelination and Repair: The study reported evidence of remyelination and functional repair.[83]
	Shroff et al	2015	Human	Good Outcomes: All patients exhibited notable improvements in sitting balance, bowel and bladder control, and limb movement, with no adverse events reported.[84]
	Salewski et al	2015	Animal	dNSCs Benefits: Clonally derived dNSCs from pluripotent cells improved motor function after SCI, enhanced neural tissue preservation, and were safe and clinically relevant.[85]
AF-MSCs (amniotic fetal mesenchymal stem cells)	Zhou et al	2016	Animal	Neurotrophic Effects: Treatment significantly increased BDNF and VEGF levels, promoted angiogenesis and axonal regeneration, and improved neurobehavioral recovery.[86]
iPSCs (induced pluripotent stem cells)	Tsuji et al	2010	Animal	Axonal Regrowth and Locomotion: Induced remyelination and axonal regrowth of serotonergic fibers, leading to recovery of locomotor function.[87]
	Romanyuk et al	2015	Animal	Differentiation: Observed neuronal regeneration, up-regulation of trophic factors and tissue preservation.[88]
	Pomeshchik et al	2015	Animal	Graft Survival: A poor graft survival rate was noted, with no functional recovery.[89]
	Kawabata et al	2016	Animal	Myelination and Recovery: Some studies reported robust myelination and functional recovery.[90]

[1]American Spinal Injury Association
[2]electromyography
[3]International Standards for Neurological Classification of Spinal Cord Injury
[4]brain motor control assessment
[5]graded redefined assessment of strength, sensibility and prehension

Discussion

SCI remains a major global health challenge, driven by complex injury mechanisms and limited therapeutic options.[134] This review emphasizes the multifaceted nature of SCI, exploring its pathophysiology and emerging treatment strategies. Understanding the cascade of primary and secondary injury mechanisms is essential for identifying critical windows for intervention to prevent irreversible damage. The intricate interplay between neuroinflammation, oxidative stress, and apoptosis presents key targets for therapeutic modulation. A central finding of this review is the dual role of astrogliosis. On the one hand, it contributes to repair by forming a protective barrier; on the other hand, it restricts axonal regrowth through glial scar formation. Therefore, future strategies should focus on modulating astrocyte activity, enhancing its beneficial functions while limiting inhibitory effects.[135,136] In clinical treatment, while pharmacological

Table 3. Clinical trials and animal studies on different source for exosome therapy

Cell Type	Loaded with	Study by	Important Outcomes
MSC-Exo	Phosphatase and Tensin Homolog siRNA	Guo et al 2019	• Attenuated PTEN expression in the injured spinal cord region. • Enhanced neovascularization and axonal growth, while decreasing astrogliosis and microgliosis. • Improved both structural and electrophysiological function.[102]
	immobilized in a peptide-modified adhesive hydrogel (Exo-pGel)	Li et al 2020	• Significantly alleviated adverse conditions in the SCI microenvironment. • Demonstrated effective retention and prolonged release within host nerve tissues, contributing to substantial nerve recovery. • Successfully reduced inflammation and oxidative stress, thereby preserving urinary tissue.[103]
	fibrin glue (FG-Exo)	Mu et al 2021	• Emergency interventions effectively mitigated ROS and the inflammatory system, leading to a significant improvement in function and nerve tissue repair.[104]
	exosomes derived from pericytes	Yuan et al 2019	• Reduces pathological changes associated with SCI. • Enhances angiogenesis and oxygen levels. • Improves endothelial capacity, reduces edema, and protects the blood-spinal cord barrier. • Safeguards the spine in hypoxic conditions.[105]
	BMSCs-Exos	Li et al 2019	• Effectively promotes function. • Inhibits neuronal apoptosis. • Activating the Wnt/β-catenin signaling pathway plays a role in SCI treatment.[106]
	BMSC-Exos	Gu et al 2020	• Attenuates neuronal apoptosis by promoting autophagy, enhancing functional behavior recovery potential.[107]
	derived from miR-133b-modified	Li et al 2018	• Facilitated better recovery of hindlimb functionality.[108]
	exosomes derived from MSCs transfected with PTENP1 short hairpin RNA (shRNA)	Wang et al 2020	• Suppresses neuronal apoptosis by downregulating PTEN expression.[109]
	exosomes derived from the human urine stem cell (USC-Exo) embedded in hydrogel	Cao et al 2021	• Enhances spinal cord neurological function recovery through angiogenesis.[110]
	neuron-derived exosomal miRNA	Jiang et al 2020	• Promotes functional behavioral recovery by suppressing M1 microglia activation.[111]
	loaded with electroconductive hydrogel	Fan et al 2022	• Promotes axon outgrowth, oligodendrocyte and neuronal differentiation. • Stops astrocyte differentiation. • Significantly reduces CD68-positive microglia and enhances NSC, leading to early-stage functional recovery.[112]
	BMSCs transfected with miRNA-29b	Yu et al 2019	• Effective in repairing.[113]
	miR-494-modified exosomes (Exo-miR-494)	Huang et al 2021	• Inhibits apoptosis and inflammation. • Upregulates miR-494 and anti-inflammatory elements, protecting the neural system, stimulating neurofilament regeneration, and improving behavioral function.[114]
Human umbilical cord mesenchymal stem cells (hucMSC)		Sun et al 2018	• Elicited significant recovery, particularly in locomotor functions. • Regulated the secretion of cytokines.[92]
		Kang et al 2022	• Improved motor function by reducing apoptosis and inflammation. • Reduced transcription levels of astrocyte marker GFAP and microglia marker IBA1, indicating decreased inflammation.[115]
		Zhang et al 2021	• Supported the migration of NSC, leading to better recovery in the rat model of SCI. • Stimulated neural regeneration and minimized scar tissue formation.[116]
AD–MSCs	human epidural adipose tissue-derived MSCs (hEpi AD–MSCs)	Sung et al 2022	• Enhances locomotor function • Regulates the inflammatory response.[117]
	derived from MiR-133b-modified	Ren et al 2019	• Promotes neurological function recovery after SCI, potentially through pathways related to axon regeneration.[118]
Dental pulp stem cell (DPSC)		Liu et al 2022	• Disrupts the cycle between ROS and M1 macrophage polarization.[119]
neural stem cells (NSCs-Exos)	loaded with FTY720	Chen et al 2021	• Alleviates pathological changes • Improves hindlimb function and oxygen supply. • Ameliorates neuron morphology, • Reduces inflammatory infiltration and edema.[120]
		Zhong et al 2020	• Promotes migration and tube formation, and increases microvascular endothelial cells, with exosomal VEGF-A mediating pro-angiogenic consequences. • Increases microvascular density, reduces spinal cord cavity size, and supports motor function recovery.[121]
		Zhang et al 2022	• miR-374-5p in exosomes was highly expressed, reducing injured neural cell apoptosis by activating autophagy flux.[122]

Table 3. Continued.

Cell Type	Loaded with	Study by	Important Outcomes
		Pan et al 2022	• Increased autophagy and decreased apoptosis, leading to better motor function. • Upregulated autophagy levels, inducing microtubule acetylation and polymerization.[123]
Schwann cell-derived exosomes (SCDEs)		Huang et al 2023	• Promoted angiogenesis • Attenuated tissue damage • Improved functional recovery[124]
		Ren et al 2023	• Improved functional recovery • Anti-inflammatory effects • Inhibited neuronal apoptosis[125]
		Pan et al 2021	• Reduced deposition of chondroitin sulfate proteoglycans is achieved by upregulating TLR2 expression on astrocytes through the NF-κB/PI3K signaling pathway[126]
M2 macrophage-derived exosomes (M2-Exos)	loaded with OTULIN protein	Luo et al 2021	• Positively influenced vascular regeneration and neurological function recovery[127]
		Huang et al 2022	• Enhancing neurogenesis and angiogenesis.[128]
		Peng et al 2021	• Promoted M2 macrophage polarization through a potential miRNA-mRNA network, which can be effective for SCI treatment.[129]
Vascular endothelial cell-derived exosomes (VECs-Exos)		Ge et al 2023	• Shifted microglia/macrophages towards M2 polarization, and ameliorated mitochondrial impairment • Decreased ROS. • Improved motor function.[130]
microglia-derived exosomes (MG-Exos)		Peng et al 2021	• Decreased the level of ROS • Facilitated cell proliferation and vascular regeneration, contributing to improved functional recovery.[131]
iPSCs-Exo	loaded with miR-199b-5p	Li et al 2023	• Improved motor function • Promoted neural regeneration • Regulated the expression of inflammatory factors.[132]
Treg cell-derived exosomes	loaded with miR-709	Xiong et al 2022	• Improved motor recovery by inhibiting microglia pyroptosis.[133]

and surgical interventions have made progress, they often fall short of fully restoring function. Recent advances in cell-based therapies, including stem cell transplantation and exosome-mediated delivery, have demonstrated considerable promise.[99] These approaches aim to replace damaged cells, modulate the immune response, and enhance the spinal cord intrinsic repair capacity. However, challenges such as immune rejection, tumorigenicity, and delivery efficiency still hinder their widespread clinical application.[137] Complementary approaches are also emerging. LLLT has demonstrated neuroprotective effects by attenuating inflammatory signaling and reducing astrocyte reactivity. Preclinical studies report significant decreases in pro-inflammatory cytokines such as TNF-α and IL-6 after LLLT, suggesting a role in mitigating secondary injury cascades.[41,138] The integration of LLLT into the broader therapeutic framework of SCI, especially in combination with regenerative cell therapies, may represent a multi-pronged strategy to address the inflammatory and neurodegenerative components of injury.[47] While these combined approaches are promising, the current evidence is primarily derived from preclinical studies. Robust clinical trials are still lacking; therefore, the translational potential of these combination therapies remains uncertain. Exosome therapy, a relatively new and exciting field, offers a non-cellular alternative with significant advantages in terms of bioavailability and reduced immunogenicity.[139] Exosomes derived from stem cells have shown potential in delivering neurotrophic factors and microRNAs to injured sites, promoting neuroregeneration and functional recovery. Nonetheless, the lack of standardized protocols for exosome isolation, characterization, and delivery remains a major barrier to successful translation into clinical practice.[140] Taken together, advancing SCI treatment will require a multidisciplinary approach. Future research should prioritize combination therapies that act synergistically on multiple injury mechanisms. Incorporating innovations in biomaterials, gene editing, and personalized medicine may further enhance treatment efficacy. Importantly, rigorous preclinical studies and carefully designed clinical trials are needed to establish safety, reproducibility, and long-term benefits. In conclusion, while substantial progress has been made, effective SCI treatment remains an unmet goal. Collaborative efforts between neuroscientists, clinicians, and bioengineers will be crucial in overcoming current limitations and unlocking the full therapeutic potential of emerging strategies.

Conclusion

SCI remains one of the most formidable medical challenges, driven by complex mechanisms and a lack of fully restorative therapies. Although pharmacological, surgical, and cell-based approaches have advanced considerably, they rarely achieve complete functional recovery. Emerging modalities such as exosome-based

therapies are particularly promising, given their ability to modulate neuroinflammation, oxidative stress, and apoptosis simultaneously. Notably, exosomes derived from human umbilical cord blood exhibit strong neuroprotective and regenerative potential, but their translation into clinical practice will require standardized protocols for isolation, characterization, and delivery. LLLT also warrants attention as a non-invasive and safe adjunct. Its capacity to attenuate inflammation, reduce neuropathic pain, and synergize with regenerative therapies makes it a valuable candidate for future clinical evaluation.

Looking forward, progress in SCI treatment will likely depend on multidisciplinary and combination-based approaches. Integrating pharmacological, surgical, and regenerative strategies with cutting-edge technologies—such as biomaterials, gene editing, and personalized medicine—offers the best chance of improving neurological outcomes. Ultimately, well-designed clinical trials and cross-disciplinary collaboration will be essential to transform these promising experimental therapies into effective, accessible treatments that enhance the quality of life for SCI patients.

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

This study is under the support of the Medical Research Ethics Committee at Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1403.144).

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