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# Synergizing science and therapy: Neurorepair and neurorehabilitation in spinal cord injury recovery

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Resumen

**Introduction:** Devastating motor, sensory, and autonomic deficits with little spontaneous recovery are the outcome of spinal cord injury (SCI). In the past, therapeutic strategies have frequently focused on either biological healing or functional restoration through rehabilitation. Emerging data supports regenerative rehabilitation, which is a synergistic strategy combining regenerative medicine and activity-based rehabilitation, to improve outcomes after spinal cord injury (SCI).

**Objective:** The purpose of this review is to summarize the most recent research on regenerative rehabilitation techniques for SCI, examining their processes, advancements in translation, and possible applications in clinical settings.

**Methods:** A comprehensive literature search was conducted on spinal cord injury, regenerative medicine, neurorehabilitation, stem cells, and neuroplasticity, focusing on peer-reviewed publications discussing combination or synergistic therapies.

**Results:** Stem cell transplantation and rehabilitation training enhance motor recovery, axonal regrowth, synaptic reconfiguration, and task-specific therapy, with neurotrophic factors and bioengineered scaffolds improving endogenous repair.

**Conclusion:** Regenerative rehabilitation is a paradigm change in the treatment of SCI that combines the reparative potential of regenerative medicine with the plasticity-enhancing benefits of rehabilitation. For such combinatory approaches to continue to be successful, timing, dosage, and individualization must be optimized.

**Palabras clave:** Spinal cord injury, Regenerative rehabilitation, Neurorepair, Neuroplasticity, Stem cells, Functional recovery.

# Sinergia entre ciencia y terapia: neurorreparación y neurorrehabilitación en la recuperación de la lesión medular

Abstract

**Introducción:** los déficits motores, sensoriales y autonómicos devastadores, con escasa recuperación espontánea, son el resultado de la lesión de la médula espinal (LME). En el pasado, las estrategias terapéuticas se han centrado con frecuencia en la curación biológica o en la restauración funcional mediante rehabilitación. Los datos más recientes respaldan la rehabilitación regenerativa, la cual es una estrategia sinérgica que combina la medicina regenerativa y la rehabilitación basada en la actividad, para mejorar los resultados tras la LME.

**Objetivo:** el propósito de esta revisión es resumir las investigaciones más recientes sobre las técnicas de rehabilitación regenerativa para la LME, examinando sus mecanismos, los avances en la traslación y sus posibles aplicaciones en entornos clínicos.

**Métodos:** se realizó una búsqueda bibliográfica exhaustiva sobre lesión de médula espinal, medicina regenerativa, neurorrehabilitación, células madre y neuroplasticidad, centrándose en publicaciones revisadas por pares que discutieran terapias combinadas o sinérgicas.

**Resultados:** el trasplante de células madre y el entrenamiento de rehabilitación mejoran la recuperación motora, el recrecimiento axonal, la reconfiguración sináptica y la terapia específica de tareas, mientras que los factores neurotróficos y los andamios bioingenierizados mejoran la reparación endógena.

**Conclusión:** la rehabilitación regenerativa representa un cambio de paradigma en el tratamiento de la LME, al combinar el potencial reparador de la medicina regenerativa con los beneficios potenciadores de la plasticidad propios de la rehabilitación. Para que estos enfoques combinados continúen siendo exitosos, deben optimizarse el momento de intervención, la dosificación y la individualización del tratamiento.

**Keywords:** lesión de médula espinal, rehabilitación regenerativa, neurorreparación, neuroplasticidad, células madre, recuperación funcional.



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## Introduction

One of the most incapacitating neurological disorders is spinal cord injury (SCI), which causes a partial or whole loss of motor, sensory, and autonomic abilities underneath the site of injury. SCI affects between 250,000 and 500,000 people globally each year (1). The combination of rehabilitation and pharmacological or regenerative strategies, termed regenerative rehabilitation, may offer synergistic benefits that surpass the limitations of each approach individually, addressing significant barriers to treatment and rehabilitation with personal and societal implications (2,3).

The goal of neurorepair is to repair the damaged architecture and function of the central nervous system (CNS) via cellular therapies, biomaterials, neurotrophic agents, and genetic interventions. For example, stem cell therapies have demonstrated potential in boosting remyelination, axonal regeneration, and injury environment modification (Figure 1) (4). At the same time, rehabilitation techniques like activity-based therapies, functional electrical stimulation, and locomotor training seek to restore lost functions by utilizing the CNS's plasticity (5). Research indicates that regenerative therapies for severe or chronic spinal cord injury (SCI) are more effective when combined with rehabilitation, due to the principle of activity-dependent plasticity, which enhances the integration and survival of cells in the damaged spinal cord through electrical stimulation or motor training (6).

Additionally, by altering the inflammatory and extracellular matrix environment, rehabilitation may prepare the host tissue to be more responsive to regenerative therapies (7). Task-specific rehabilitation after stem cell transplantation or biomaterial scaffold implantation improves axonal regrowth and functional outcomes in comparison to either treatment alone, as shown by animal models of SCI (8,9). Patients undergoing intense rehabilitation procedures in conjunction with regenerative therapies have demonstrated significant gains in voluntary movement and functional independence in early-stage clinical trials (10). Results emphasize the significance of dosage, timing, and patient-specific factors for improving regenerative rehabilitation. Ongoing challenges include managing injury conditions, identifying optimal treatment times for combined therapies and applying animal model research to humans. Furthermore, ethical, practical, and regulatory challenges impede the establishment and approval of these rehabilitation methods.

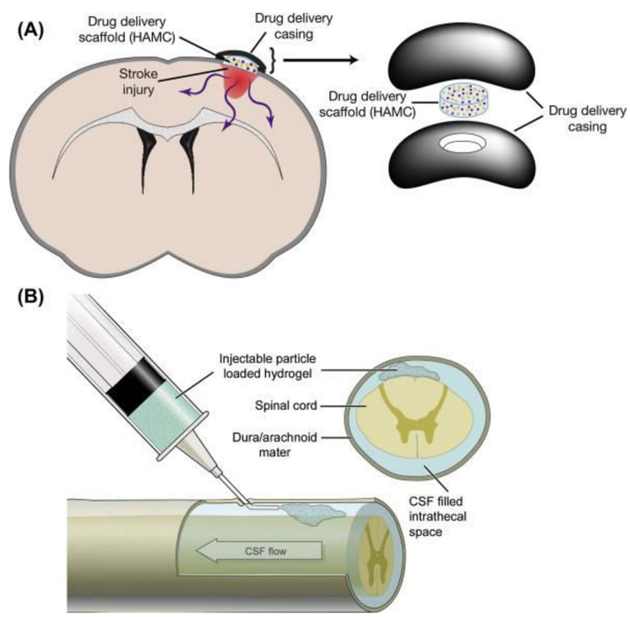


**Figure 1. Neuroregeneration**
**Source:** Adapted from (11).

This review evaluates regenerative rehabilitation for spinal cord injury (SCI), emphasizing molecular insights and evidence from preclinical and clinical studies. It presents a unified approach that integrates neurorepair and neurorehabilitation, marking a significant shift towards a collaborative framework for recovery (12).

## Methods

A structured literature evaluation of integrative techniques for neurorepair and neurorehabilitation, particularly for spinal cord injury (SCI), was conducted. The methodology that followed involved qualitative synthesis and systematic searches of electronic databases from January 2010 to March 2025, with Boolean operators and MeSH terms being utilising. A snowballing strategy helped identify additional relevant studies, ensuring a coherent thematic synthesis aligned with these research objectives and maintaining scientific rigor.

## Criteria for inclusion and exclusion

The eligibility criteria for studies on spinal cord injuries included a focus on regenerative and rehabilitative therapies, unique data from human or animal subjects, and quantifiable results related to neuroplasticity, axon regeneration, motor rehabilitation, or functional enhancement. Studies that were solely pharmaceutical or surgical, lacked detail, or did not provide specific metrics on brain function or repair were excluded.

## Data extraction and study selection

After screening the papers by title and abstract, two reviewers conducted full-text reviews , resolving any disagreements by consensus. Data collected from the included studies consisted of the following: SCI model type and severity; regenerative interventions; rehabilitation regimens; primary and secondary outcomes; and key findings. The Cochrane Risk of Bias instrument (RoB 2) was utilized (13).

## Evaluation of quality

The SYRCLE risk of bias tool was used in animal research to assess the methodological quality, including elements such as randomization, blinding, and housing conditions (14). The Cochrane Risk of Bias instrument (RoB 2) was used to clinical research (13). To guarantee the validity of the conclusions, only studies with a low or moderate risk of bias were incorporated into the final synthesis.

## Data information/synthesis

A qualitative narrative synthesis approach was used to address heterogeneity in research involving various species, intervention types, and outcome measures. Themes were organized based on translational advancement, preclinical discoveries, and synergistic mechanisms, highlighting trends, challenges, and potential directions for future research.

## Mechanisms of regenerative rehabilitation's synergistic recovery

Activity-based therapies intended to support functional recovery are combined with cellular or molecular interventions targeted at neuronal repair in regenerative rehabilitation (15). Physical rehabilitation improves the integration and efficacy of regenerative therapies by encouraging neuronal activity, synaptic remodeling, and axonal sprouting, which is supported by activity-dependent plasticity (3).

By replacing injured cells, promoting axon growth, and modifying the injury microenvironment, neurorepair techniques like stem cell transplantation, growth factor delivery, and biomaterial scaffolds offer the biological substrate for regeneration (4). To direct neuronal reconnection, these treatments frequently call for the right kind of stimulation. When combined with regenerative techniques, rehabilitation interventions such as electrical stimulation, locomotor training, and robotic-assisted movement have been demonstrated to enhance neuronal survival, synaptic strength, and remyelination (Figure 2) (9).

## Preclinical research in favour of combined treatments

The advantages of integrating regenerative treatments with rehabilitation have been shown in numerous animal studies. In rats with spinal cord transection, for instance, (8) demonstrated that while neural stem cell transplantation resulted in axonal regeneration, substantial functional recovery was only attained when combined with treadmill training. Similarly, (7) found that when paired with regular physical therapy, bioengineered scaffolds seeded with stem cells improved axonal development and motor outcomes.

Additionally, compared to mice receiving monotherapies, animals receiving combined treatments exhibited increased cortical-spinal tract integrity and greater motor evoked potentials, according to electrophysiological investigations (Figure 3) (17). According to these results, rehabilitation may be crucial for converting biological repair into functional improvements in addition to serving as a supplement to regenerative therapies.

The main non-vascular models of spinal cord injury illustrated involve excitotoxicity from excessive glutamate release, mechanical impact, and compression leading to tissue breakdown. Immunological and inflammatory responses further worsen cellular damage through cytokine signalling. Additionally, the production of free radicals induces oxidative stress, causing further neuronal and glial damage. Apoptosis leads to the progressive loss of these cells, while demyelination disrupts axonal conduction. Together,

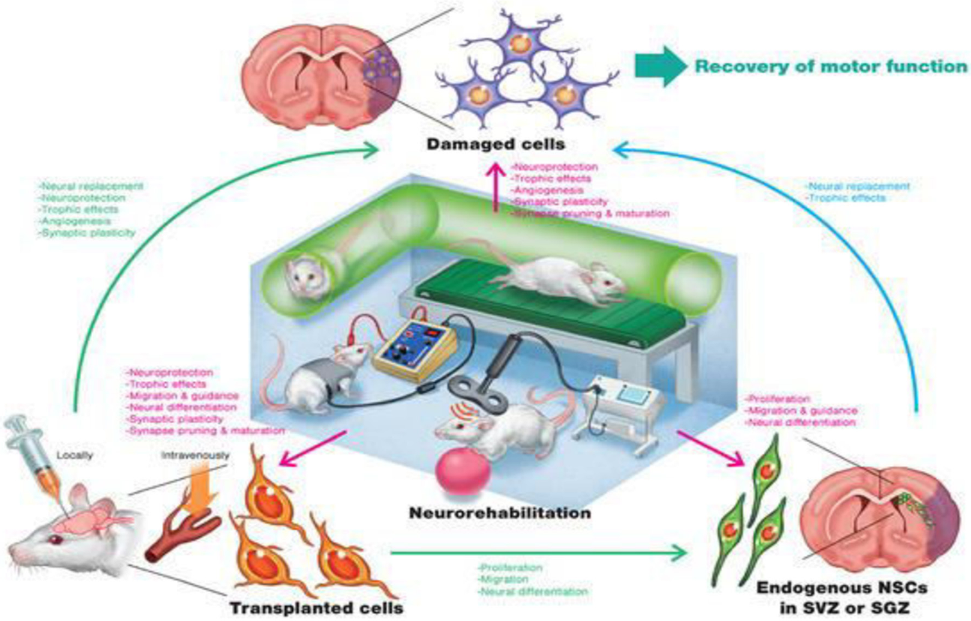


**Figure 2. A schematic visualization of an animal model's recovery after stroke via regenerative therapy.**

**Source:** Adapted from (16).

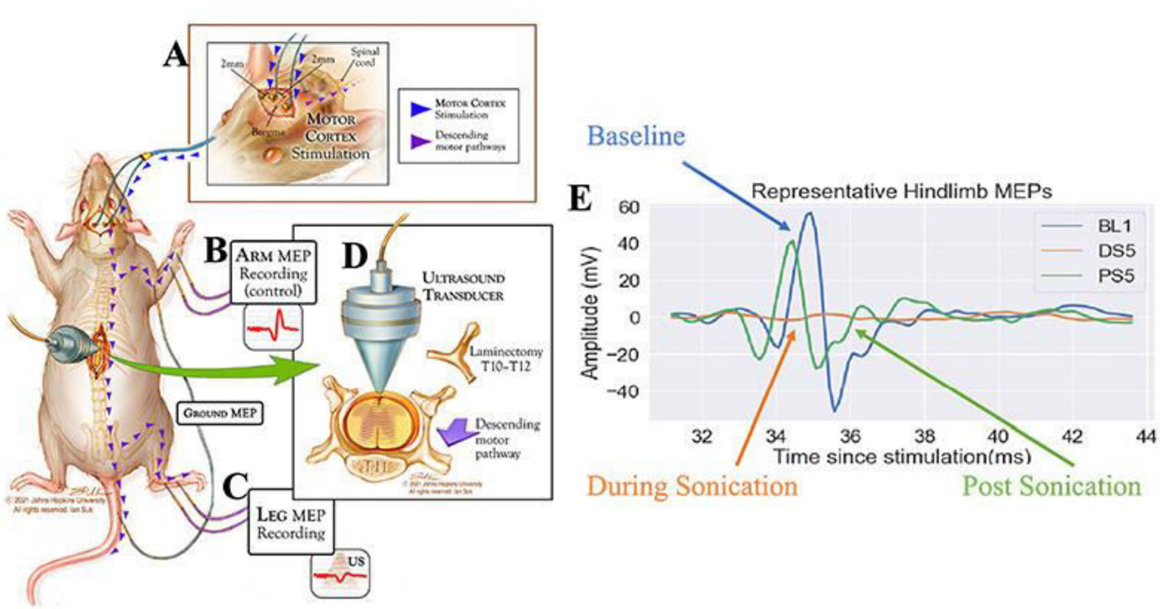


**Figure 3. Spinal Cord Injury**

**Source:** Adapted from (18).

these mechanisms contribute to functional impairments and hinder neurological recovery after spinal cord injury (Figure 4).

## Challenges and clinical translation

Early-phase clinical trials suggest that regenerative rehabilitation may improve voluntary motor control in chronic spinal cord injury (SCI) patients, particularly the use of autologous stem cells alongside locomotor training. However, challenges such as variability in injury severity, timing of intervention, ethical issues with stem cells, and insufficient randomized controlled trials complicate the field. Continued comprehensive research with long-term follow-ups is crucial, as current rodent model findings have limited human relevance. The document also addresses translational challenges and reviews significant clinical trials (19).

## Mechanisms of disease initiation and tissue response following neurotrauma

Spinal cord injury (SCI) triggers a complex cascade of secondary damage that includes glutamate excitotoxicity, calcium influx, oxidative stress, mitochondrial dysfunction, and a strong inflammatory response (20,21). Beyond initial mechanical trauma, spinal cord injury leads to further neurological impairments through mechanisms like demyelination, cavitation, and cell death at the lesion site. Neuroinflammation, depicted in Figure 5, involves various cytokines and phenotypic characteristics that contribute to neurodegeneration, which are critical factors to consider during recovery from spinal cord injury.

Astrogliosis: it is characterized by the proliferation of reactive astrocyte, increased levels of glial fibrillary acidic protein (GFAP) and remodelling of the-extracellular matrix. It is a key aspect of the tissue response in the myelinated central nervous system (CNS) (22). This because of their function in creating the glial scar and secreting inhibitory chemicals such chondroitin sulfate proteoglycans (CSPGs), reactive astrocytes were formerly thought to be significant inhibitors of regeneration (23). Recent research, however, shows that astrocytes have a dual role: they maintain tissue integrity, stop the spread of inflammation, and promote early repair responses, even though they do limit axonal growth in chronic stages (24,25).

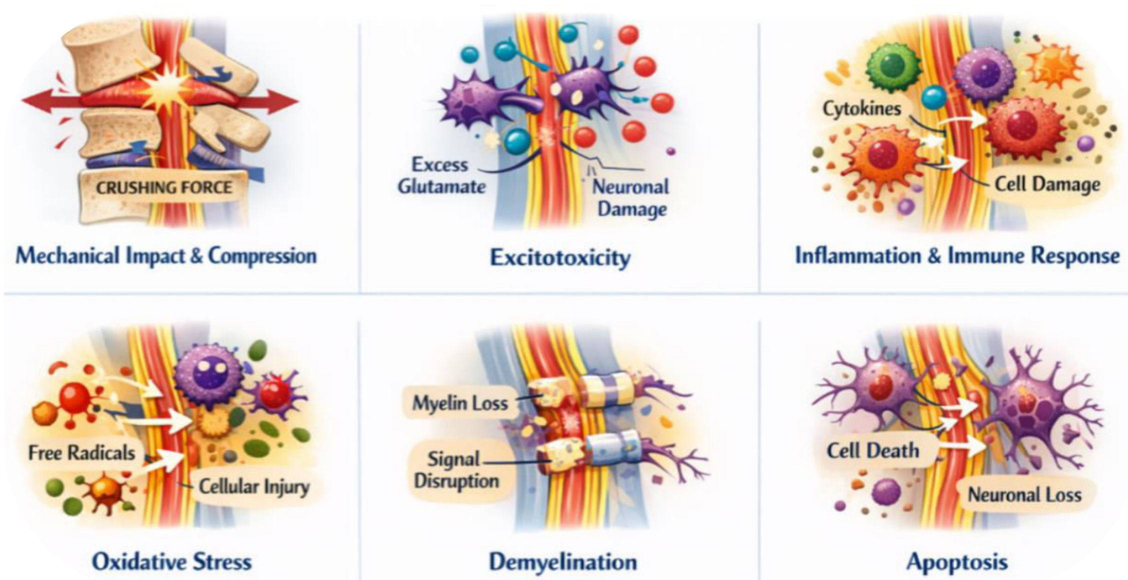


**Figure 4. Major non-vascular mechanisms involved in spinal cord injury pathophysiology**

**Source:** Own elaboration.

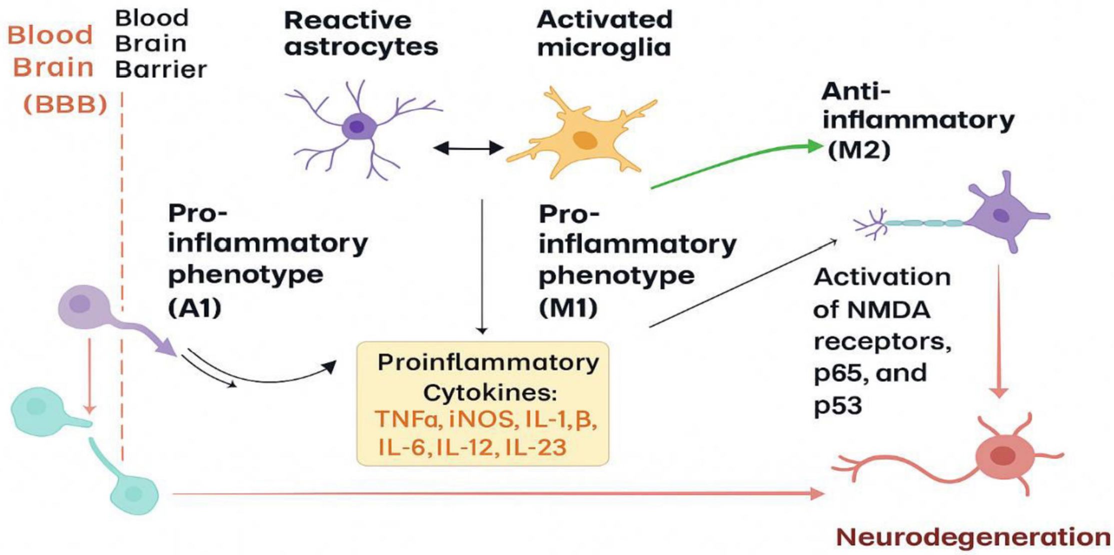


**Figure 5: Neuroinflammation**

**Source:** Own elaboration.

Axonal regeneration: Both internal and external factors restrict the ability to axons to regenerate in the adult central nervous system. Adult neurons have limited regenerative ability by nature, as growth-promoting genes are suppressed. It has been demonstrated that reactivating growth programs is possible with experimental models that target molecular pathways like PTEN/mTOR, SOCS3/STAT3, and KLF family transcription factors (26,27). Axonal extension is hampered by an extrinsic non-permissive environment that is produced by inhibitory signals from myelin debris (such as Nogo-A, MAG, and OMgp) and the glial scar (28,29).

Researches are exploring new approaches to combat these inhibitory effects. These include the enzymatic breakdown of CSPGs using chondroitinase ABC, the administration of neurotrophic factors such as BDNF, NT-3, and GDNF to promote axonal elongation, and the use of biomaterial scaffolds to close the lesion gap (30,31).

In addition to regeneration, axonal plasticity, or the adaptive remodelling of intact neuronal networks, is a crucial component of functional recovery. It has been demonstrated that rehabilitation techniques, including as activity-based therapies and epidural electrical stimulation, improve synaptic connection and strength in spared pathways (32,33). This neuroplastic adaptation helps to restore motor and sensory functions by compensating for lost connections. In summary, glial reactivity, inflammatory signals, and failure of regeneration interact dynamically in spinal cord injury (SCI). Effective treatments for promoting repair and recovery in patients with neurotrauma require a deep understanding of these mechanisms.

## Discussion

Spinal cord injury (SCI) is a severe neurological disorder that causes lasting deficits in motor function, sensory perception, and autonomic control. The absence of standardized, evidence-based rehabilitation protocols, particularly with regard to the timing and sequencing of interventions, has complicated clinical management. Despite physical therapy being widely used in the treatment of SCI, there is no consensus on the optimal starting point for rehabilitation, how to integrate new regenerative techniques, or which patients would benefit most from specific methods (8). Recent advancements in neurorepair, including stem cell transplantation and biomaterial scaffolds, have increased the range of available treatments. However, these treatments often yield inconsistent functional recovery, highlighting the importance of activity-dependent processes in achieving neurological improvement. Research suggests that regenerative therapies are most effective when combined with timely rehabilitation techniques, resulting in the concept of regenerative rehabilitation (34).

Cellular and molecular processes contribute to the synergy of enhanced synaptic plasticity and improved survival and integration of transplanted cells, due to the activity-dependent release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (35). Rehabilitation can alter the inflammatory environment following spinal cord injury. Chronic inflammation can lead to the formation of a glial scar and the production of inhibitory molecules like chondroitin sulfate proteoglycans (CSPGs), which can obstruct axonal regeneration. However, the initial inflammatory response is essential for removing debris (36). Exercise can reduce chronic inflammation, supporting axonal development and repair. The timing of rehabilitation is crucial; early intervention may exacerbate secondary damage, whereas delaying treatment can reduce its effectiveness. Research indicates that the best outcomes with combination therapies can be achieved within a few days to weeks of injury (37).

A review has highlighted the absence of a cohesive model in spinal cord injury (SCI) research that links damage, glial responses and the challenges of regeneration. It proposes a dynamic framework for phase-specific strategies to improve glial regulation, regenerative techniques, and neuroprotection. The findings reveal that astrocytes have dual roles as protective agents and scar formers, which contradicts the previously held view that they have solely inhibitory functions (20,21). Depending on context and timing, inflammation can act as both destructive and reparative. Advances in glial scar remodelling using drugs such as chondroitinase, ABC and intrinsic axonal reprogramming via PTEN/mTOR and KLF signalling, demonstrate the importance of combined, temporally specific therapies (22,23). Rather than total regeneration, neuroplasticity in spared circuits is increasingly recognized as the main driver of functional recovery (24).

Encouraging findings from clinical trials suggest that spinal cord epidural electrical stimulation (EES) can help individuals with chronic spinal cord injury (SCI) to regain some voluntary motor control, especially when combined with rehabilitative gait training (38). While these treatments do ot directly repair the spinal cord, they appear to activate dormant circuitry that may have been stimulated by prior restoration techniques. In a similar vein, (39) showed that prolonged virtual walking could result in a partial neurological recovery for paraplegic patients with the use of BMIs (brain-machine interfaces). These cases demonstrate that combining repair with intensive training can improve the functionality of chronic spinal cord injuries (SCIs), although generalization is hindered by the variability of SCI types. Most biological treatments are still in the experimental stage and produce mixed results. A comprehensive restructuring of clinical practices is essential to merge neurorepair with neurorehabilitation, and advocate for a multidisciplinary strategy. It is vital to manage patient expectations, especially given the rising trend of unregulated stem cell clinics. Innovations such as closed-loop neuromodulation and bioengineered scaffolds, coupled with personalized medicine via biomarkers, could significantly improve rehabilitation outcomes for people with SCI (40).

Alongside electrical stimulation and stem cell therapy, other techniques are crucial for regenerative rehabilitation after spinal cord injury (SCI). Pharmacological treatments such as minocycline, riluzole, and anti-Nogo-A antibodies have shown potential in enhancing neuroprotection and promoting axonal regeneration (41). These substances enhance regenerative outcomes by altering growth-inhibitory, excitotoxic, and inflammatory pathways. New technologies such as brain-computer interfaces (BCIs) and virtual reality (VR)-assisted rehabilitation are being incorporated into the recovery of patients with (SCI) to encourage foster cortical restructuring and motor learning in interactive environments. Future research should explore multimodal approaches that combine biological therapies with cellular, electrical, pharmaceutical, and digital rehabilitation platforms to improve functional recovery for SCI patients (3,39).

Combining neurorepair and neurorehabilitation is essential for effective spinal cord injury (SCI) treatment. Neurorehabilitation addresses functional deficiencies, while neurorepair focuses on structural recovery. Their collaboration is crucial because recovery requires behavioural and biological support, rather than just tissue restoration or movement training (42).

Recent research highlights the importance of combining regenerative and rehabilitative therapies, particularly the use of stem cells alongside rehabilitation techniques such as electrical stimulation and task-specific training. This combined approach has been shown to significantly enhance cell survival, integration, and functional recovery compared to using either treatment alone (9,43). It is believed that activity-induced changes such as the release of neurotrophic factor, synaptic plasticity and neurovascular remodelling contribute to the synergistic effect on recovery. Moreover, the timing and sequencing of interventions, particularly early rehabilitation, have been shown to maximize the benefits of regeneration (44).

Considering the individual diversity in injury level, severity, age, comorbidities, and neuroplastic capability, personalized rehabilitation strategies are essential, highlighting the need for customized approaches for various therapeutic populations (45). For example, due to their greater plasticity, younger patients often respond better to regenerative therapies, whereas older patients may derive greater benefit from assistive technology and medication (46). Recent insights suggest that hormonal factors and healing patterns in spinal cord injury (SCI) outcomes differ by sex. Advanced tools such as wearable sensors, functional imaging and AI evaluations enable real-time monitoring and adaptation of therapy plans to individual needs. Integrating precision medicine techniques into rehabilitation could significantly improve functional recovery and long-term outcomes (47).

It is challenging to find the therapeutic window for integrating regenerative and rehabilitative therapies due to the significant impact of timing on outcomes. For example, early rehabilitation can exacerbate injuries, while delays can reduce neuroplasticity. The absence of standardized protocols complicates clinical trials and reduces the effectiveness of treatment. The proliferation of unregulated stem cell clinics is raising ethical concerns as they are offering untested treatments to vulnerable patients. The new regenerative rehabilitation paradigm emphasizes therapeutic timing, dosage, and individualization, linking rehabilitation directly to neurorepair processes rather than treating it as a mere supportive intervention (48).

In addition to causing immediate suffering through negative consequences, such actions can erode public confidence in reliable research and delay patients' access to evidence-based care (49). Ethical frameworks emphasize informed consent, patient autonomy, and therapeutic accountability, all of which are often at risk with uncontrolled treatments. To address this issue, increased awareness, regulatory enforcement and patient education are needed, alongside the promotion of rigorous clinical trials and the prevention of misinformation by publications and professional associations (50).

### Strengths

This review emphasizes the synergy between neurorepair and neurorehabilitation for spinal cord injury recovery by integrating current research on cellular treatments, biomaterials, and neuroplasticity. It advocates coordinated therapy approaches from a multidisciplinary perspective to enhance functional outcomes.

## Limitations

The evaluation process is dominated by preclinical and early-phase clinical studies, which limits applicability to broader patient groups. Variations in damage models, intervention timings and treatment regimens also complicate translation. Additionally, the lack of established protocols for biological and restorative treatments highlights the discrepancy between experimental potential and clinical application.

## Future directions

Advances in the treatment of spinal cord injury (SCI) have been made through regenerative rehabilitation, combines neurorepair and neurorehabilitation to improve functional recovery. This approach combines biological repair with activity-based interventions to promote neuroplasticity, and overcome limitations of traditional therapies. Research indicates that regenerative therapies, such as growth factor delivery and stem cell transplantation are most effective in neuronal environments created by rehabilitation. Early intervention can boost neuroplasticity, but challenges such as inflammation and graft rejection in chronic SCI must be managed. This requires strategies to manipulate inhibitory molecules for regeneration (36). Personalization in SCI rehabilitation is complicated by factors like age and comorbidities, necessitating tailored protocols. Technologies such as wearable sensors, neuroimaging, and biomarker profiling support real-time monitoring and adjustments, enabling customized treatment plans (51). Ethical and regulatory challenges hinder the adoption of stem cell treatments, necessitating standardized manufacturing, long-term safety, and proven efficacy via randomized trials. Rehabilitation research should integrate neurobiological outcomes with traditional measures to substantiate stem cell regeneration mechanisms. Notably, combining electrical neuromodulation with stem cell therapy may yield synergistic effects (52). Targeted and continuous administration of regeneration stimuli is possible by bioengineered scaffolds implanted with genetically modified cells or controlled drug release systems (53).

Emerging technologies like artificial intelligence (AI) and closed-loop systems are significant in rehabilitation. AI analyzes biomechanical data to enhance therapy personalization and predict recovery. Closed-loop neuroprosthetic systems aid in brain plasticity and sensorimotor integration, offering promising outcomes for restoring motor functions in spinal cord injury patients (38,54).

## Conclusion

Regenerative rehabilitation combines neurorepair and evidence-based neurorehabilitation to aid recovery from spinal cord injuries (SCIs) by leveraging brain plasticity to promote functional recovery. The review emphasizes the importance of multidisciplinary collaboration between neuroscience, rehabilitation, bioengineering and clinical practice, advocating integrated solutions over isolated approaches. It highlights innovative methods such as neuromodulation and digitally assisted rehabilitation, prioritizing patient-centered outcomes and ethical treatment use. This paradigm is crucial for achieving lasting functional recovery and enhancing the quality of life for SCI patients while adapting therapeutic development to evolving clinical data.

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