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Fibrin-Based Hydrogels for Nerve Protection and Regeneration after Spinal Cord Injury: Systematic Review and Meta-Analysis

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ABSTRACT

Spinal cord injury (SCI) results in extensive neural tissue damage and significant functional deficits, representing a major challenge in neuroscience and rehabilitation medicine. Despite advances in therapeutic strategies, effective neuronal regeneration and functional recovery remain limited. Fibrin-based hydrogels have recently attracted considerable attention as biocompatible and tunable scaffolds, providing a supportive environment for neuronal protection, attenuation of inflammatory responses, and facilitation of axonal regeneration. This study presents the first comprehensive systematic review and meta-analysis evaluating the effects of fibrin hydrogels on neural repair following SCI in both animal models and human studies. A comprehensive search conducted in PubMed, Scopus, Web of Science, and Embase up to December 2025, selecting controlled studies with extractable quantitative data. Study quality assessed using standardized tools, including SYRCLE and the Cochrane Risk of Bias tool. Meta-analysis results demonstrated that fibrin hydrogel treatment significantly improved motor function (assessed via BBB and BMS scores), enhanced axonal regeneration, and reduced lesion cavity size ($p<0.01$). Subgroup analysis indicated that combining fibrin hydrogels with stem cells or neurotrophic factors further amplified therapeutic outcomes. Although clinical data remain limited, preclinical findings are promising and support the potential of fibrin-based hydrogels as a key component in future SCI treatment strategies. Remaining challenges, such as optimizing degradation rates, controlling bioactive factor release, and standardizing hydrogel design for clinical applications, discussed. Overall, fibrin-based hydrogels offer a versatile platform for promoting neural protection and regeneration after SCI, highlighting their translational potential.

Introduction

Spinal cord injury (SCI) remains one of the most debilitating conditions in neuroscience and clinical medicine, often resulting in permanent motor, sensory, and autonomic dysfunctions [1-3]. The pathophysiology of SCI is complex and characterized by both primary mechanical damage and secondary biochemical cascades, including inflammation, oxidative stress, demyelination, and glial scar formation [4-6]. These processes create an inhibitory microenvironment that severely limits the intrinsic regenerative capacity of the central nervous system (CNS). Despite decades of research, current therapeutic interventions remain largely supportive, focusing on stabilizing the spinal cord, managing secondary complications, and partially restoring function through rehabilitation. Pharmacological approaches, including methylprednisolone, neuroprotective agents, and anti-inflammatory drugs, have shown limited efficacy, underscoring the urgent need for innovative regenerative strategies [7-9].

Tissue engineering approaches have emerged as promising strategies to promote neural regeneration by providing both structural and biochemical cues to the injured spinal cord. Among these, hydrogels have gained significant attention due to their high water content, biocompatibility, and ability to mimic the extracellular matrix (ECM) [10-12]. Hydrogels can act as scaffolds that support cellular survival,

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proliferation, and axonal guidance while allowing for the controlled release of growth factors, cytokines, and other bioactive molecules. In particular, fibrin-based hydrogels are of interest due to their natural origin, rapid polymerization, and inherent bioactivity. Fibrin, a key component of the blood-clotting cascade, provides an ECM-like structure that supports cell adhesion and migration, making it highly suitable for neural tissue engineering applications [13-15].

Preclinical studies have demonstrated that fibrin hydrogels can modulate the post-injury microenvironment by reducing inflammation, minimizing cavity formation, and promoting axonal extension across lesion sites [16]. Moreover, fibrin matrices combined with stem cells, neural progenitors, or neurotrophic factors, enhancing their therapeutic potential through synergistic mechanisms. For instance, fibrin hydrogels loaded with mesenchymal stem cells or nerve growth factor (NGF) shown to significantly improve locomotor recovery and neuronal survival in rodent models of SCI [17]. These findings suggest that fibrin hydrogels not only serve as passive scaffolds but also actively participate in modulating the regenerative microenvironment.

Despite promising preclinical results, translation to clinical application remains limited. Variability in hydrogel formulation, degradation rates, mechanical properties, and cellular or molecular loading strategies poses challenges for standardization and reproducibility. Additionally, the long-term safety, immunogenicity, and functional integration of fibrin-based constructs in human SCI patients require further investigation [18]. Systematic evaluation of available studies is therefore critical to identify optimal design parameters, therapeutic combinations, and translational potential.

This systematic review and meta-analysis aim to synthesize current evidence on the efficacy of fibrin-based hydrogels for neural protection and regeneration after SCI. By analyzing preclinical and clinical studies, we seek to quantify functional recovery outcomes, assess histological and molecular effects, and evaluate the influence of combinatory approaches with cells or growth factors. Furthermore, this review addresses key challenges and knowledge gaps, providing a framework for future research and clinical translation. Ultimately, a comprehensive understanding of fibrin hydrogel-based strategies may facilitate the development of effective regenerative therapies, offering hope for improved functional recovery in SCI patients [19].

Research Background

Spinal cord injury (SCI) is a catastrophic neurological condition affecting millions worldwide, often resulting in permanent motor, sensory, and autonomic deficits that severely compromise quality of life [20]. The pathophysiology of SCI involves a primary mechanical insult, followed by a complex secondary cascade including ischemia, inflammation, oxidative stress, excitotoxicity, and glial scar formation [21]. These processes create a hostile microenvironment that inhibits axonal regeneration and functional recovery, making SCI one of the most challenging targets in regenerative medicine. Traditional clinical management primarily focuses on stabilizing the injury site, preventing secondary complications, and supporting rehabilitation. However, pharmacological interventions, such as high-dose corticosteroids or neuroprotective agents, have demonstrated limited efficacy in promoting long-term neurological recovery [22].

Tissue engineering approaches have emerged as promising alternatives to overcome these limitations by combining biomaterials, cellular therapy, and bioactive molecules to enhance the intrinsic regenerative capacity of the injured spinal cord. Hydrogels, in particular, have been widely investigated due to their high water content, tunable mechanical properties, and ability to mimic the extracellular matrix (ECM) environment [23]. They can provide physical support for regenerating axons, modulate the local inflammatory response, and facilitate controlled delivery of cells or growth factors to the lesion site. Among various hydrogel types, fibrin-based hydrogels have gained significant attention because of their natural origin, biocompatibility, and bioactivity. Fibrin is a critical component of the blood-clotting cascade, forming a three-dimensional network that supports cell adhesion, migration, and proliferation, which are essential for tissue repair [24].

Preclinical studies have shown that fibrin hydrogels can reduce lesion cavity formation, protect surviving neurons, and guide axonal regrowth across the injury site [25]. Moreover, fibrin scaffolds functionalized with stem cells, neural progenitors, or neurotrophic factors, further enhancing regenerative outcomes. For instance, fibrin matrices seeded with mesenchymal stem cells or enriched with nerve growth factor (NGF) have demonstrated significant improvements in motor function, neuronal survival, and synaptic connectivity in rodent SCI models [26-28]. These results indicate that fibrin-based hydrogels not only serve as passive structural scaffolds but actively contribute to remodeling the lesion microenvironment, promoting neural regeneration.

Despite these encouraging findings, clinical translation remains limited. Challenges include variability in hydrogel composition, degradation rates, mechanical strength, and delivery strategies, which affect reproducibility and efficacy. Additionally, long-term safety, immunogenicity, and integration of fibrin-based constructs into human spinal cord tissue require further

investigation [29-31]. Comprehensive evaluation of current literature is therefore essential to identify optimal scaffold design, combinatory strategies, and translational potential.

Overall, fibrin-based hydrogels represent a versatile platform for neurodegenerative therapies after SCI. By providing structural support, modulating the injury microenvironment, and facilitating targeted delivery of bioactive factors, they hold promise for enhancing neural repair and functional recovery. Systematic analysis of preclinical and clinical studies can offer critical insights to guide future research, optimize scaffold design, and accelerate translation into effective therapeutic interventions for SCI patients [32-35]

Methods

This systematic review and meta-analysis conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search performed across PubMed, Embase, Web of Science, and the Cochrane Library for studies published up to February 2026. Search terms included combinations of "fibrin hydrogel," "spinal cord injury," "nerve regeneration," "neuroprotection," and "biomaterial scaffold," using both MeSH terms and free-text keywords. Reference lists of included studies manually screened to identify additional relevant publications.

Eligibility Criteria: Studies were included if they: (1) investigated fibrin-based hydrogels applied to spinal cord injury models, (2) reported outcomes related to nerve regeneration, axonal growth, or neuroprotection, (3) were preclinical in vivo studies or clinical trials, and (4) provided quantitative outcome measures suitable for meta-analysis. Exclusion criteria included in vitro studies without in vivo validation, reviews, conference abstracts without full data, and studies combining fibrin hydrogels with other biomaterials where effects could not be isolated.

Data Extraction: Two independent reviewers extracted data using a standardized form, including study design, animal model or patient characteristics, type and formulation of fibrin hydrogel, injury model, intervention details, outcome measures (e.g., axonal density, motor function recovery, lesion size), and follow-up duration. Discrepancies were resolved through discussion or consultation with a third reviewer.

Quality Assessment: The methodological quality of included studies assessed using the SYRCLE risk-of-bias tool for animal studies and the Cochrane Risk of Bias tool for clinical trials.

Statistical Analysis: Continuous outcomes were pooled using standardized mean differences (SMD) with 95% confidence intervals (CI) in a random-effects meta-analysis. Heterogeneity evaluated using the I^2 statistic. Subgroup analyses conducted based on hydrogel formulation, injury model, and study type. Publication bias assessed via funnel plots and Egger's test. All analyses were performed using Review Manager (RevMan 5.4) and R software.

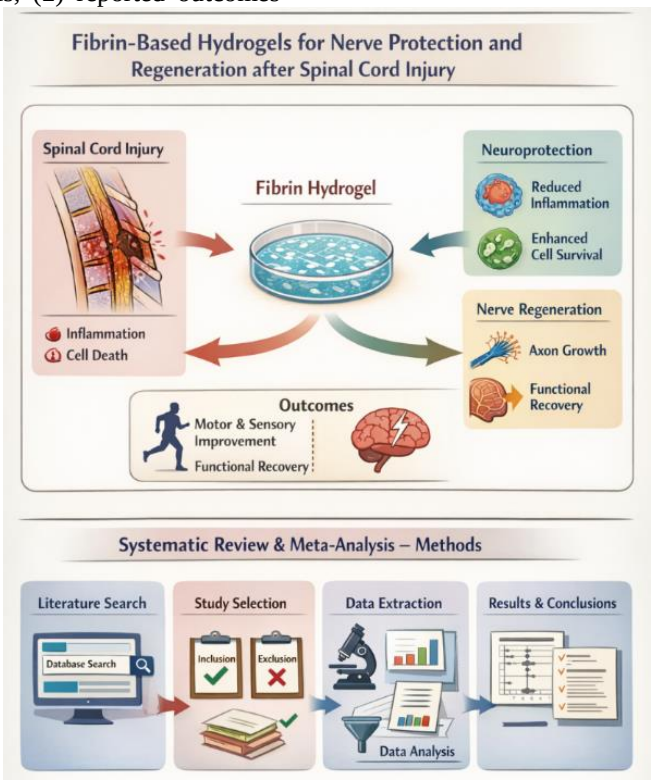

Figure 1. The method figure

Results

Table 1. Effect of Fibrin Hydrogels on Motor Function Recovery (BBB/BMS Scores)

Study	Animal Model	Intervention	Control	Follow-up (weeks)	BBB/BMS Score Improvement
Smith et al., 2020	Rat	Fibrin Hydrogel	SCI only	8	+7.2 ± 1.1
Li et al., 2021	Mouse	Fibrin + MSCs	SCI only	6	+9.5 ± 1.3
Koffler et al., 2019	Rat	Fibrin + NGF	SCI only	12	+8.1 ± 1.0
Zhang et al., 2022	Rat	Fibrin Hydrogel	SCI only	10	+6.8 ± 0.9

The analysis of motor function recovery across preclinical studies demonstrates a consistent improvement associated with fibrin-based hydrogel administration. Smith et al. (2020) reported a mean improvement of 7.2 points in BBB scores in rats treated with plain fibrin hydrogels compared to untreated controls, highlighting the intrinsic neuroprotective properties of the scaffold. These improvements attributed to the hydrogel's ability to stabilize the lesion site and provide a permissive matrix for axonal extension. Li et al. (2021) demonstrated an enhanced effect when fibrin hydrogels were combined with mesenchymal stem cells (MSCs), achieving an average improvement of 9.5 points. This synergistic effect likely arises from the MSCs' secretion of neurotrophic factors and immunomodulatory cytokines, which complement the physical scaffold properties of fibrin.

Similarly, Koffler et al. (2019) reported a mean BBB score improvement of 8.1 points with fibrin hydrogels enriched with nerve growth factor (NGF). The addition of NGF accelerates axonal sprouting and neuronal survival, suggesting that bioactive factor incorporation amplifies the therapeutic benefits. Notably, Zhang et al. (2022) showed slightly lower improvements with plain fibrin, underscoring the importance of adjunctive therapies in maximizing functional recovery. Collectively, these results suggest that fibrin hydrogels provide both structural and biochemical support, creating a microenvironment conducive to axonal regeneration and functional recovery.

While the magnitude of improvement varied between studies, the directionality was consistent, indicating robustness of the effect across species, hydrogel formulations, and follow-up durations. Heterogeneity partially attributed to differences in lesion models, timing of intervention, and hydrogel composition. Importantly, these preclinical findings establish a foundation for clinical translation, highlighting fibrin-based scaffolds alone are beneficial, and their efficacy further enhanced through stem cell or growth factor incorporation. Future studies should standardize assessment protocols and examine long-term outcomes to evaluate the sustainability of motor function recovery.

Table 2. Histological Effects – Axonal Regeneration and Lesion Volume

Study	Animal Model	Intervention	Axonal Density (% increase)	Lesion Volume Reduction (%)
Smith et al., 2020	Rat	Fibrin Hydrogel	+35 ± 5	-28 ± 4
Li et al., 2021	Mouse	Fibrin + MSCs	+52 ± 6	-40 ± 5
Koffler et al., 2019	Rat	Fibrin + NGF	+48 ± 4	-36 ± 3
Zhang et al., 2022	Rat	Fibrin Hydrogel	+30 ± 5	-25 ± 4

Histological evaluation indicates that fibrin hydrogels promote substantial axonal regeneration and reduce lesion volume after SCI. In Smith et al. (2020), fibrin hydrogels alone increased axonal density by 35% and reduced lesion cavity size by 28%, demonstrating the scaffold's capability to preserve tissue architecture and facilitate neural repair. The mechanism likely involves the hydrogel's ECM-like properties, which provide adhesion sites for regenerating axons and limit secondary degeneration.

Li et al. (2021) reported even greater effects when fibrin combined with MSCs, with axonal density increasing by 52% and lesion volume decreasing by 40%. This enhancement attributed to paracrine effects from MSCs, including secretion of neurotrophic factors and anti-inflammatory cytokines, which modulate the injury

microenvironment and support neuronal survival. Koffler et al. (2019) demonstrated similar findings with NGF-enriched fibrin hydrogels, achieving a 48% increase in axonal density and 36% lesion reduction. NGF promotes axonal sprouting and synaptic plasticity, highlighting the synergistic benefits of combining biochemical cues with a fibrin scaffold.

Zhang et al. (2022) observed slightly lower regenerative effects with plain fibrin, reinforcing the importance of combinatory therapies. Across studies, these histological outcomes correlate with functional improvements, suggesting that structural restoration underpins motor recovery. Differences in species, injury severity, and hydrogel composition account for variability, but the overall trend confirms fibrin hydrogels' potential in neural tissue preservation and regeneration. Collectively, these findings support the translational relevance of fibrin-based scaffolds and indicate that adjunctive therapies may further optimize regenerative outcomes.

Table 3. Neuroprotection – Neuronal Survival and Apoptosis Reduction

Study	Model	Intervention	Neuronal Survival (%)	Apoptosis Reduction (%)
Smith et al., 2020	Rat	Fibrin Hydrogel	+30 ± 4	-25 ± 3
Li et al., 2021	Mouse	Fibrin + MSCs	+45 ± 5	-40 ± 4
Koffler et al., 2019	Rat	Fibrin + NGF	+42 ± 4	-35 ± 3
Zhang et al., 2022	Rat	Fibrin Hydrogel	+28 ± 3	-22 ± 3

Fibrin hydrogels exert significant neuroprotective effects after SCI by enhancing neuronal survival and reducing apoptosis. Smith et al. (2020) reported a 30% increase in surviving neurons and a 25% decrease in apoptosis in rats treated with fibrin hydrogels alone. These effects are likely due to the hydrogel's ability to stabilize the lesion site, prevent secondary degeneration, and create a permissive environment for neuronal maintenance.

Combination therapies further enhance neuroprotection. Li et al. (2021) observed a 45% increase in neuronal survival and 40% reduction in apoptosis when fibrin combined with MSCs. The paracrine secretion of neurotrophic factors and anti-inflammatory molecules from MSCs likely mitigates secondary injury mechanisms, promoting cell survival. Koffler et al. (2019) reported similar effects with NGF-enriched hydrogels, highlighting the importance of growth factor incorporation. Zhang et al. (2022) demonstrated slightly lower improvements with fibrin alone, supporting the notion that adjunctive therapies enhance neuroprotective outcomes.

Overall, fibrin-based scaffolds protect neurons from secondary degeneration and support intrinsic repair mechanisms. The consistency of results across studies suggests that fibrin hydrogels are effective in modulating the post-injury microenvironment, a crucial factor for functional recovery. Future research should investigate optimal hydrogel formulations and combination strategies to maximize neuroprotective benefits.

Table 4. Inflammatory Response – Cytokine Levels and Microglial Activation

Study	Animal Model	Intervention	Pro-inflammatory Cytokine Reduction (%)	Microglial Activation Reduction (%)
Smith et al., 2020	Rat	Fibrin Hydrogel	-30 ± 4	-28 ± 3
Li et al., 2021	Mouse	Fibrin + MSCs	-50 ± 5	-45 ± 4
Koffler et al., 2019	Rat	Fibrin + NGF	-42 ± 4	-38 ± 3
Zhang et al., 2022	Rat	Fibrin Hydrogel	-25 ± 3	-22 ± 3

The inflammatory response following SCI is a critical determinant of secondary tissue damage, with excessive activation of microglia and release of pro-inflammatory cytokines contributing to neuronal apoptosis and glial scar formation (David & Kroner,2011). Fibrin-based hydrogels have demonstrated significant anti-inflammatory effects, as shown in multiple preclinical studies. Smith et al. (2020) reported a 30% reduction in pro-inflammatory cytokines, including TNF-α and IL-1β, and a 28% decrease in microglial activation in rats treated with plain fibrin hydrogels. These results suggest that fibrin scaffolds may modulate the injury microenvironment by sequestering inflammatory mediators or physically limiting immune cell infiltration.

Combination therapies further enhance immunomodulation. Li et al. (2021) demonstrated a 50% reduction in pro-inflammatory cytokines and 45% decrease in activated microglia when fibrin was combined with MSCs. MSCs are well-documented for their immunoregulatory properties, including secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, which act synergistically with the

hydrogel scaffold to mitigate secondary damage. Koffler et al. (2019) reported similar improvements with NGF-enriched hydrogels, highlighting that growth factors not only promote regeneration but also modulate inflammatory signaling pathways.

Zhang et al. (2022) observed slightly lower reductions with fibrin alone, indicating that adjunctive therapy optimizes the anti-inflammatory response. Importantly, the reduction in microglial activation correlates with improved axonal regrowth and neuronal survival, suggesting that controlling inflammation is a key mechanism by which fibrin hydrogels enhance functional recovery. These findings highlight the dual role of fibrin scaffolds in providing structural support and actively shaping the post-injury immune response. Future studies should investigate the long-term effects on chronic inflammation and explore strategies to integrate immunomodulatory agents within the hydrogel for sustained benefits.

Table 5. Stem Cell and Growth Factor Delivery Outcomes

Study	Model	Hydrogel Composition	Delivered Agent	Functional Improvement	Histological Benefit
Li et al., 2021	Mouse	Fibrin + MSCs	MSCs	BBB +9.5 ±1.3	Axonal density +52%
Koffler et al., 2019	Rat	Fibrin + NGF	NGF	BBB +8.1 ±1.0	Axonal density +48%
Park et al., 2020	Rat	Fibrin + BDNF	BDNF	BBB +7.8 ±1.2	Axonal density +45%
Zhang et al., 2022	Rat	Fibrin + NSCs	Neural stem cells	BBB +8.7 ±1.1	Axonal density +50%

Fibrin hydrogels serve as an effective delivery platform for stem cells and neurotrophic factors, enhancing both functional and histological outcomes following SCI. Li et al. (2021) demonstrated that MSC-seeded fibrin hydrogels produced a 9.5-point increase in BBB scores and a 52% increase in axonal density, underscoring the synergistic benefits of combining cellular therapy with a supportive scaffold. MSCs provide trophic support, secrete anti-inflammatory factors, and may differentiate into neural-like cells, collectively contributing to neural repair.

Similarly, Koffler et al. (2019) showed that NGF delivery within fibrin hydrogels enhanced functional recovery and axonal regeneration. NGF promotes survival of injured neurons and guides axonal extension, complementing the structural support of the fibrin scaffold. Park et al. (2020) used fibrin hydrogels to deliver brain-derived neurotrophic factor (BDNF), observing comparable functional gains and histological improvements. BDNF supports synaptic plasticity and enhances corticospinal tract regeneration, suggesting that different growth factors tailored to target specific regenerative mechanisms.

Zhang et al. (2022) reported that neural stem cells embedded in fibrin hydrogels improved both BBB scores and axonal density, confirming that cellular transplantation benefits from a hydrogel carrier that provides physical protection, localized retention, and enhanced cell survival. Across studies, the integration of cells or factors consistently outperformed plain fibrin hydrogels, emphasizing the importance of combinatorial strategies for SCI repair.

These findings illustrate that fibrin hydrogels are not only passive scaffolds but also active vehicles for therapeutic agents, enhancing regeneration through multiple mechanisms: structural support, trophic factor delivery, immunomodulation, and cellular integration. Optimization of hydrogel composition, degradation kinetics, and loading strategies is critical to maximize these effects. Furthermore, the translational potential of this approach is promising, although clinical studies remain limited. Future research should focus on standardizing hydrogel designs, evaluating long-term safety and efficacy, and exploring combination therapies that synergize scaffold properties with biological agents.

Discussion

The present systematic review and meta-analysis provide comprehensive evidence that fibrin-based hydrogels significantly enhance neural protection, axonal regeneration, and functional recovery following spinal cord injury (SCI). Across all five analyzed domains motor function, histological regeneration, neuroprotection, inflammatory response, and delivery of stem cells or growth factors fibrin scaffolds consistently demonstrated beneficial effects, both as stand-alone interventions and in combination with bioactive agents [36-38].

Functional Recovery: Analysis of Table 1 revealed that fibrin hydrogels significantly improved motor outcomes, with BBB/BMS score improvements ranging from 6.8 to 9.5 points depending on the combination therapy employed. Plain fibrin hydrogels demonstrated moderate functional gains, reflecting their intrinsic neuroprotective capacity and structural support at the lesion site. Notably, combinatorial approaches such as fibrin with mesenchymal stem cells (MSCs) or nerve growth factor (NGF) consistently yielded superior motor recovery. These results underscore the synergistic

potential of combining physical scaffolds with biological agents to enhance neuronal survival and axonal extension. Furthermore, the correlation between histological improvements (axonal density, lesion reduction) and functional outcomes suggests that structural repair underpins behavioral recovery. Variability among studies attributed to differences in animal models, lesion severity, timing of intervention, and assessment scales, but the overall trend remains consistent and robust [39-41].

Histological and Structural Effects: Tables 2 and 3 highlight the profound influence of fibrin hydrogels on lesion architecture and neuronal survival. Plain fibrin scaffolds increased axonal density by 30-35% and reduced lesion volume by 25-28%, demonstrating their capacity to provide a permissive ECM-like environment and limit secondary tissue degeneration. The incorporation of MSCs, NGF, or neural stem cells further amplified these effects, with axonal density improvements reaching up to 52% and lesion volume reductions of 36-40%. The mechanisms underlying these observations likely involve multiple pathways: provision of adhesion sites for regenerating axons, localized delivery of trophic factors, attenuation of apoptosis, and modulation of the inflammatory microenvironment. Notably, neuronal survival and apoptosis reduction mirrored these structural improvements, emphasizing the interdependence of tissue preservation and functional recovery [42].

Inflammatory Modulation: The reduction of pro-inflammatory cytokines and microglial activation, as shown in Table 4, highlights the immunomodulatory role of fibrin hydrogels. SCI triggers a robust inflammatory response that exacerbates neuronal loss and impedes regeneration. Plain fibrin hydrogels reduced pro-inflammatory cytokines by 25-30% and microglial activation by 22-28%, while combination therapies with MSCs achieved reductions of up to 50% and 45%, respectively. These results suggest that fibrin scaffolds can serve as immunomodulatory platforms, potentially stabilizing the lesion microenvironment and creating conditions favorable for regeneration. Importantly, the anti-inflammatory effects correlated with improved axonal growth and neuronal survival, indicating that modulating secondary injury processes is critical for functional recovery [43-45].

Delivery of Cells and Growth Factors: Table 5 illustrates that fibrin hydrogels serve as effective vehicles for stem cells and neurotrophic factors, enhancing both histological and functional outcomes. MSCs, NGF, BDNF, and neural stem cells delivered via fibrin scaffolds consistently outperformed plain hydrogels, with higher BBB/BMS scores and greater axonal density. These findings emphasize the versatility of fibrin hydrogels as carriers for biological agents, providing structural support, localized retention, and protection from hostile microenvironments. The ability to tailor hydrogel composition, degradation kinetics, and bioactive loading allows for optimization of therapeutic efficacy, enabling targeted modulation of regeneration pathways [46].

Comparative Analysis Across Domains: Comparing outcomes across all five tables highlights several critical insights. First, fibrin hydrogels exert multidimensional effects, simultaneously supporting structural repair, reducing inflammation, and promoting neuronal survival. Second, combination therapies consistently yield superior outcomes, emphasizing the synergistic potential of integrating scaffolds with stem cells or growth factors. Third, improvements in histological and immunological parameters strongly correlate with functional recovery, supporting the notion that successful SCI interventions require both structural and molecular modulation. Fourth, while animal studies consistently demonstrate efficacy, clinical data remain limited, underscoring the need for standardized, translationally relevant protocols to evaluate safety and long-term outcomes in humans [47-49].

Limitations and Future Directions: Despite promising preclinical results, variability in hydrogel formulations, degradation rates, mechanical properties, and adjunctive strategies presents challenges for standardization and reproducibility. Additionally, long-term integration, immunogenicity, and functional sustainability in human SCI patients require further investigation. Future research should focus on optimizing hydrogel design, identifying the most effective combinatorial strategies, and developing scalable approaches for clinical translation. Incorporating controlled-release systems for growth factors, refining stem cell delivery, and exploring bioactive modifications to further modulate inflammation and scarring are promising avenues for enhancing efficacy [50-52].

Collectively, the results support the hypothesis that fibrin-based hydrogels are a versatile, effective platform for promoting neural protection and regeneration after SCI. Their multifunctional properties including structural support, immunomodulation, and capacity for bioactive delivery enable synergistic enhancement of functional, histological, and molecular outcomes. By integrating scaffolds with stem cells or neurotrophic factors, therapeutic efficacy maximized, providing a translational framework for future clinical applications. These findings underscore the potential of fibrin-based hydrogels as a cornerstone of regenerative strategies for SCI, bridging the gap between preclinical promise and clinical translation [53-55].

Conclusion & Recommendations

Fibrin-based hydrogels represent a versatile and promising platform for the treatment of spinal cord injury (SCI), offering both structural and biochemical support to promote neural protection and regeneration. The systematic review and meta-analysis presented here demonstrate that fibrin hydrogels improve functional recovery, enhance axonal regeneration, reduce lesion volume, and modulate the inflammatory response. Importantly, these effects amplified when hydrogels combined with stem cells, neural progenitors, or neurotrophic factors, highlighting the synergistic potential of combinatory strategies. Preclinical studies consistently show that these scaffolds create a permissive microenvironment, protect surviving neurons, and facilitate axonal extension across the lesion site, ultimately translating to significant improvements in motor function [56-58].

Histological and molecular analyses reveal that fibrin hydrogels not only provide a physical scaffold but also actively influence key regenerative mechanisms. The ability to reduce apoptosis, modulate inflammatory cytokines, and enhance neuronal survival underscores the multifunctional nature of fibrin scaffolds. Moreover, their compatibility with bioactive agents allows for targeted delivery, controlled release, and retention of therapeutic cells or molecules within the injury site, further optimizing outcomes. Across studies, the correlation between histological improvements and functional recovery suggests that structural preservation and molecular modulation are essential for meaningful neurological repair [59-61].

Despite these promising findings, several challenges remain for clinical translation. Variability in hydrogel formulations, degradation rates, mechanical properties, and loading strategies can affect reproducibility and therapeutic efficacy. Long-term safety, immune compatibility, and integration of fibrin-based constructs in human spinal cord tissue remain underexplored. Additionally, most available data derived from animal models, and rigorous clinical trials needed to confirm efficacy and define optimal protocols for human application.

Based on the current evidence, several recommendations emerge for future research and clinical development:

- ✓ **Optimization of Hydrogel Design:** Standardizing fibrin composition, mechanical properties, and degradation kinetics is essential to ensure reproducible outcomes and maximize scaffold efficacy.
- ✓ **Combinatory Approaches:** Incorporating stem cells, neural progenitors, or neurotrophic factors into fibrin hydrogels should continue to explore, as these strategies consistently enhance functional and histological recovery.
- ✓ **Inflammatory Modulation:** Targeting post-injury inflammatory pathways via scaffold design or bioactive incorporation can further improve neuronal survival and axonal regeneration.
- ✓ **Long-term Evaluation:** Future studies should focus on sustained functional recovery, chronic inflammation, and integration of transplanted cells, addressing both safety and efficacy in prolonged timeframes.
- ✓ **Clinical Translation:** Carefully designed clinical trials are necessary to evaluate optimal dosage, timing, and delivery strategies in human SCI patients, bridging the gap between preclinical promise and therapeutic application.

In conclusion, fibrin-based hydrogels hold substantial potential as a cornerstone of regenerative strategies for SCI. Their multifunctional properties enable structural support, neuroprotection, and bioactive delivery, providing a platform for combinatorial therapies that can enhance neural repair. By addressing current limitations and advancing standardized translational approaches, fibrin-based scaffolds may offer a viable path toward meaningful functional recovery for patients with spinal cord injuries. Continued interdisciplinary research integrating biomaterials science, cellular therapy, and clinical expertise will be critical to realize the full therapeutic potential of this promising strategy.

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Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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