INNM #10.1080/17435889.2026.2672135, VOL 00, ISS 00

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Zoe Giorgi, Valeria Veneruso, Emilia Petillo, Enrico Frigerio, Pietro Veglianese, Giuseppe Perale and Filippo Rossi

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REVIEW

Hydrogels for the treatment of spinal cord injury: progress and promise

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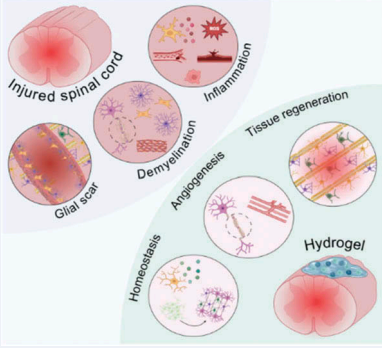
ABSTRACT

Spinal cord injury (SCI) is a devastating condition characterized by complex primary and secondary pathophysiological mechanisms that result in motor, sensory, and autonomic dysfunctions. Despite advances in surgical, pharmacological, and biological therapies, effective treatments remain limited due to the multifactorial nature of SCI and the hostile post-injury microenvironment. In this context, biomaterial-based approaches have emerged as promising platforms, as they can provide both structural support and localized therapeutic delivery. Hydrogel-based systems, in particular, have attracted increasing attention due to their ability to mimic the extracellular matrix, modulate the injury microenvironment, and deliver bioactive molecules or cells in a controlled manner. In particular, combinatorial approaches integrating drugs, growth factors, or cellular components often show enhanced efficacy compared to single-component systems. However, direct comparison across studies is limited by substantial heterogeneity in injury models, outcome measures, and experimental design, as well as by reproducibility challenges associated with complex multi-component constructs. Furthermore, translational progress remains constrained by regulatory classification, manufacturing scalability, and standardization issues. Overall, while hydrogel-based strategies represent a promising platform for SCI repair, future research must prioritize reproducibility, simplification of design, and alignment with regulatory and clinical requirements to enable successful translation.



ARTICLE HISTORY
Received 3 February 2026
Accepted 6 May 2026

KEYWORDS
Hydrogel; polymer; functional recovery; spinal cord injury

1. Spinal cord injury: pathophysiology and therapeutic challenges

Spinal cord injury (SCI) is an acute lesion of the neural elements within the spinal canal resulting in temporary or permanent loss or impairment of motor, sensory, and autonomic functions below the level of injury [1,2]. Depending on the extent of functional loss, SCI can be classified as complete or incomplete, and disease severity is commonly assessed using the American Spinal Injury Association (ASIA) Impairment Scale, which categorizes injuries from grade A (complete loss of function) to grade E (normal function) [3,4] (Figure 1(A)). Beyond paraplegia and tetraplegia, SCI is associated with a wide range of complications, including bladder and bowel dysfunction, sensory disturbances, respiratory and circulatory impairments, as well as chronic pain and urinary tract infections that significantly affect patient quality of life [5–7]. At the biological level, SCI is characterized by a complex and evolving pathophysiological process involving primary and secondary injury mechanisms, which collectively drive tissue damage and hinder regeneration (Figure 1(B)). The primary injury consists of the initial mechanical insult, leading to disruption of neural tissue, vertebral dislocation, fractures, vascular damage, hemorrhage, edema, and breakdown of the blood–spinal cord barrier (BSCB) [4,8]. This event rapidly triggers a secondary injury cascade, a multifactorial process that evolves

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/17435889.2026.2672135

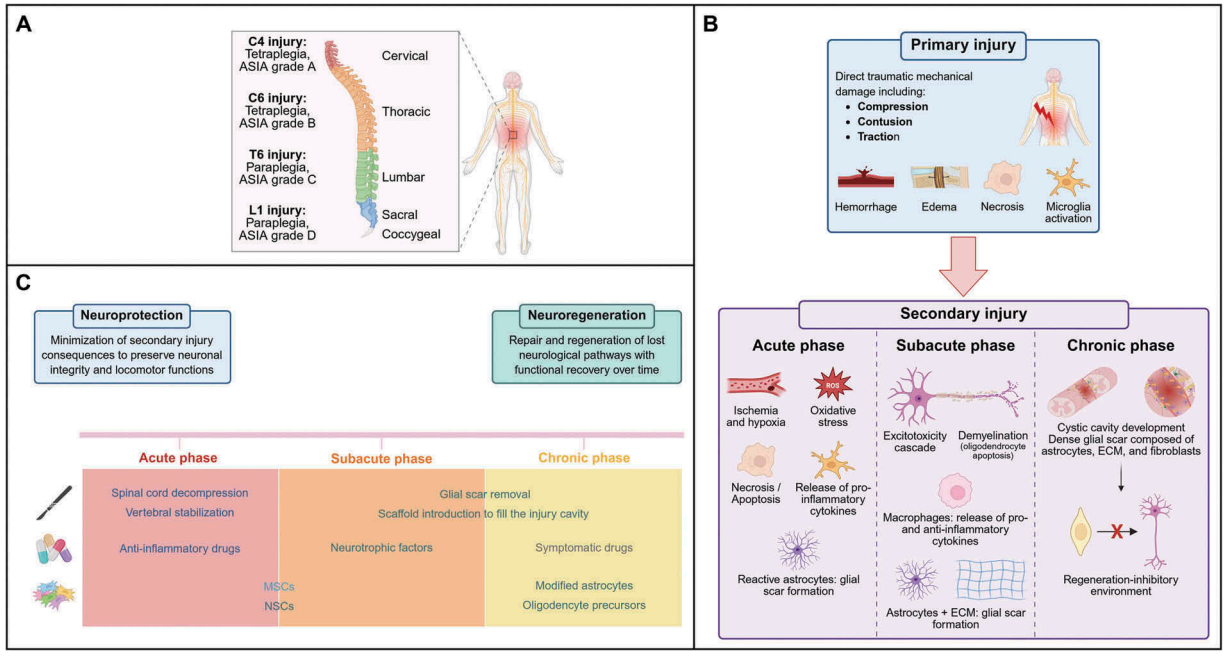

Figure 1. SCI overview. (A) ASIA Impairment Scale grade schematization. (B) Pathophysiology schematization. (C) Current therapeutic approaches. Created in BioRender. Rossi, F. (2026). Panel A: https://BioRender.com/9blcf96; Panel B: https://BioRender.com/4n55tp; Panel C: https://BioRender.com/2gc99gp.

over time and is typically divided into acute (minutes to hours post–injury), subacute (days to weeks post–injury), and chronic (months to years post–injury) phases. During the acute phase, ischemia, hypoxia, and edema are accompanied by early activation of inflammatory pathways, including microglial activation and cytokine release [4,9,10]. In parallel, increased production of reactive oxygen species (ROS), mitochondrial dysfunction, and excitotoxicity contribute to neuronal damage, while multiple forms of regulated cell death, such as apoptosis, ferroptosis, and necrosis, further exacerbate tissue loss [9]. In the subacute phase, sustained inflammation and oligodendrocyte apoptosis lead to progressive axonal demyelination and degeneration [11]. Concurrently, reactive astrocytes proliferate and initiate glial scar formation which, although protective in limiting lesion spread, establishes a physical and biochemical barrier to axonal regeneration [1,12].

In the chronic phase, continued extracellular matrix (ECM) deposition by astrocytes, fibroblasts, and perivascular cells promotes scar maturation and is often associated with the formation of cystic cavities, ultimately resulting in a highly inhibitory microenvironment that severely limits functional recovery [2,10,12]. In light of this pathophysiological complexity, current therapeutic approaches aim to limit secondary damage, promote regeneration, and manage long-term complications (Figure 1(C)). These strategies can be broadly divided into neuroprotective and neuroregenerative approaches, based on their mechanisms of action. Neuroprotective approaches aim to minimize secondary damage by preserving neuronal integrity and motor function [13]. In contrast, neuroregenerative therapies target the repair and regeneration of damaged neural pathways, leading to functional recovery over time [13]. Surgical approaches, including spinal cord decompression and vertebral stabilization, are primarily employed to prevent further mechanical damage and reduce ischemia [14]. In addition, surgical removal of the glial scar and implantation of biomaterial scaffolds have also been explored to address tissue cavitation [15]. Pharmacological therapies focus on modulating inflammation or providing neuroprotection, as well as managing chronic symptoms [16,17]. However, systemic drug administration is often limited by the restrictive nature of the BSCB, resulting in poor bioavailability and insufficient drug concentrations at the injury site [18], while symptomatic treatments are primarily useful for pain control and management of comorbidities without exerting a direct disease-therapeutic effect. Biological approaches include the use of mesenchymal stem cells (MSCs) to harness their paracrine signaling for immunomodulation and trophic factor release, as well as the transplantation of neural stem cells (NSCs) for tissue repopulation owing to their ability to differentiate into spinal cord cellular populations [19]. In addition, genetically or pharmacologically modified astrocyte and oligodendrocyte precursor cells (OPCs) have been investigated to enhance remyelination and improve neural plasticity [10,11]. Despite significant advances, no fully effective therapy is currently available for SCI.

This limitation reflects not only the restricted regenerative capacity of the central nervous system, but also the inability of existing strategies to adequately address the multifactorial nature of the injury [20]. Consequently, increasing attention has been directed toward the development of biomaterial-based strategies, particularly hydrogel systems designed to provide mechanical support, modulate the injury microenvironment,

and enable localized and sustained therapeutic delivery. By simultaneously targeting multiple aspects of the injury microenvironment, these platforms represent a promising strategy to address the current limitations of SCI treatment and will be discussed in detail in the following sections.

2. Hydrogels

Building on these considerations, hydrogels have gained increasing attention as adaptable platforms for SCI repair. Hydrogels are three-dimensional polymeric networks composed of hydrophilic chains that can absorb and retain large amounts of water or biological fluids, thereby creating a microenvironment that closely resembles the physical properties of native soft tissues [21–23].

Owing to their high water content, tunable mechanical properties, and overall biocompatibility, hydrogels have been extensively investigated in tissue engineering and regenerative medicine [24,25]. Their structural similarity to the ECM enables their use as three-dimensional scaffolds that provide physical support, regulate cell behavior, and maintain space for tissue development [26,27]. In addition, their porous architecture allows the encapsulation and controlled release of therapeutic agents directly at the target site, enabling precise dosage control while minimizing systemic side effects [28,29]. In the context of SCI, these properties are particularly advantageous, as hydrogels can be engineered to fill the lesion cavity, restore mechanical continuity, and bridge the injured tissue.

Furthermore, they can serve as multifunctional platforms for the localized delivery of drugs, biomolecules, or cells aimed at promoting neuroprotection, modulating inflammation, and enhancing regenerative processes.

2.1. Methods for literature search and study selection

Given the rapid expansion of hydrogel-based approaches for spinal cord repair, a structured literature search was performed to identify relevant preclinical studies. The PubMed database was queried for articles published between January 2020 and January 2026 using the following search string: *hydrogel[Title/Abstract] AND spinal cord injury[Title/Abstract]*. The retrieved records were screened based on titles and abstracts to assess their relevance. Only original research articles investigating hydrogel-based therapeutic approaches in *in vivo* models of SCI were included. Review articles, editorials, conference abstracts, and studies limited to *in vitro* experiments were excluded.

This selection strategy was designed to focus on translationally relevant evidence. However, it should be noted that the included studies exhibit substantial heterogeneity in terms of injury models, treatment protocols, and outcome measures, which should be carefully considered when comparing results and drawing general conclusions.

2.2. Hydrogels in SCI

Hydrogels for spinal cord injury (SCI) repair encompass a broad spectrum of material designs, which can be organized along a continuum from biomimetic systems to highly engineered multifunctional platforms (Figure 2). This progression reflects a shift from structurally supportive scaffolds toward increasingly complex systems capable of actively modulating the injury microenvironment. Among the earliest and most extensively investigated approaches biomimetic hydrogels derived from ECM components promised great results. These systems are particularly attractive due to their intrinsic ability to recreate a permissive microenvironment for tissue regeneration.

Hyaluronic acid (HA)-based hydrogels, for instance, have demonstrated the capacity to conform to the lesion cavity and restore structural continuity, while supporting endogenous NSC differentiation and angiogenesis, ultimately leading to functional improvements in preclinical models [30,31]. Similarly, anisotropic scaffolds composed of aligned ECM protein fibers provide directional guidance cues that promote neurite outgrowth and axonal extension across the lesion site, enhancing remyelination, vascularization, nerve regeneration, and functional recovery [32,33]. To further mimic the biochemical complexity of native tissue, decellularized extracellular matrix (dECM) hydrogels have been developed. These materials retain tissue-specific bioactive signals and have been shown to modulate the post-injury immune response while promoting regeneration [34]. However, conventional decellularization protocols often lead to rapid material degradation and loss of key bioactive components. To overcome these limitations, alternative tissue lysis–based approaches have been introduced, enabling improved preservation of bioactive components and mechanical properties comparable to those of spinal cord tissue, with consequent beneficial effects on inflammation, axonal growth, and remyelination [35]. In addition to ECM-derived systems, other natural polymers have been explored to achieve specific structural and biological functionalities. Alginate hydrogels, for example, can be engineered into anisotropic capillary scaffolds with stiffness values comparable to native spinal cord tissue, enabling guided axonal growth across the lesion site [36]. Chitosan-based hydrogels have also shown considerable promise; when crosslinked with citric acid and functionalized with dopamine, they enhance cell adhesion and survival, modulate the inflammatory response, and promote axonal regeneration following SCI [37]. Moreover, chitosan–peptide composites further improve immunoregulatory properties while supporting remyelination and functional recovery. For instance, bioactive hydrogels combining chitosan (CS), RADA16 self-assembling nanofibers, and nerve-promoting peptides have been developed to better mimic the injured spinal cord microenvironment and promote the differentiation of neural stem cells into neurons (Figure 2) [38].

Peptides can self-assemble into nanofibrous networks that closely resemble the architecture of native ECM, providing a permissive substrate for neural regeneration. These systems

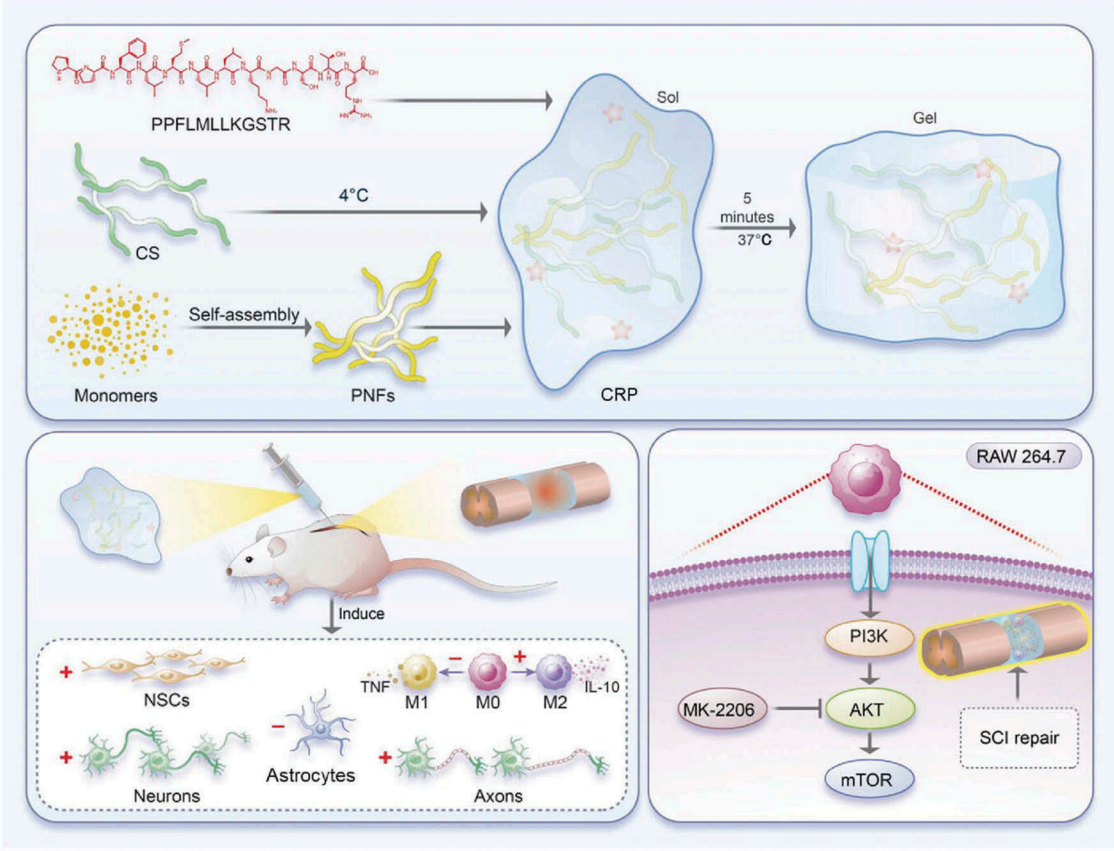

Figure 2. The design of a thermosensitive, neuro-affinitive, and biomimetic hydrogel for the SCI repair. Adapted with permission from [38]. Copyright 2024, John Wiley and Sons.

have been shown to reduce the inhibitory activity of chondroitin sulfate proteoglycans (CSPGs) within the glial scar, thereby facilitating axonal extension [39]. Alternatively, peptides can be grafted onto preformed hydrogel matrices to attenuate fibrotic scar formation and inflammation while promoting angiogenesis and NSC differentiation [40,41]. In addition, specific peptide sequences exhibit bioactive functionalities, including antioxidant and immunomodulatory properties, contributing to microenvironmental stabilization and improved neuronal survival [42]. Despite these biomimetic advantages, natural polymer–based hydrogels often present limitations, including rapid degradation, batch-to-batch variability, and limited mechanical strength. To overcome these constraints, engineered hydrogel systems have been developed to provide enhanced structural stability, tunable degradation profiles, and greater control over physicochemical properties. Among these, gelatin methacrylate (GelMA) has emerged as one of the most widely studied platforms due to its photo–crosslinkable nature, tunable mechanical properties, high biocompatibility, and intrinsic cell-adhesive motifs [43]. Moreover, GelMA can be readily combined with other ECM-derived components to further tailor the post-injury microenvironment [44]. Similar advantages have been reported for methacrylated silk fibroin (SFMA) hydrogels, which combine favorable mechanical strength with excellent biocompatibility, promoting new tissue formation and significant hindlimb locomotion recovery in preclinical SCI models [45,46].

Beyond structural optimization, increasing efforts have been directed toward the development of functionalized hydrogels with additional bioactive or physicochemical properties [47]. Electrical conductivity has been extensively explored due to its relevance in neural signal transmission.

Conductive hydrogels incorporating polymers such as poly-3-amino-4-methoxybenzoic acid (PAMB) [48], polypyrrole (PPy) [49,50], and poly(3,4-ethylenedioxythiophene) (PEDOT) [51], as well as systems based on dynamic metal–ligand coordination [52], have been shown to promote endogenous NSC differentiation toward neuronal and oligodendroglial lineages, thereby supporting tissue repopulation after injury. Similarly, carbon-based nanomaterials provide both electrical conductivity and nanoscale topographical cues that support axonal guidance and remyelination [53–56]. More recently, black phosphorus (BP)-containing hydrogels have attracted attention owing to their combined conductive properties and controlled biodegradability, which enables the release of bioactive phosphate ions and supports tissue remodeling [57–60]. Indeed, biodegradable BP nanosheets can be incorporated into chitosan/gelatin conductive hydrogel at the SCI site to function as wireless power-receiver electrodes (Figure 3) [59]. The resulting configuration generates alternating electrical currents within the conductive scaffold. This effect has been shown to enhance neural tissue repair by promoting remyelination, accelerating axonal regeneration, and inducing endogenous NSC differentiation. In addition to conductive systems, advanced hydrogel platforms incorporating magnetic and

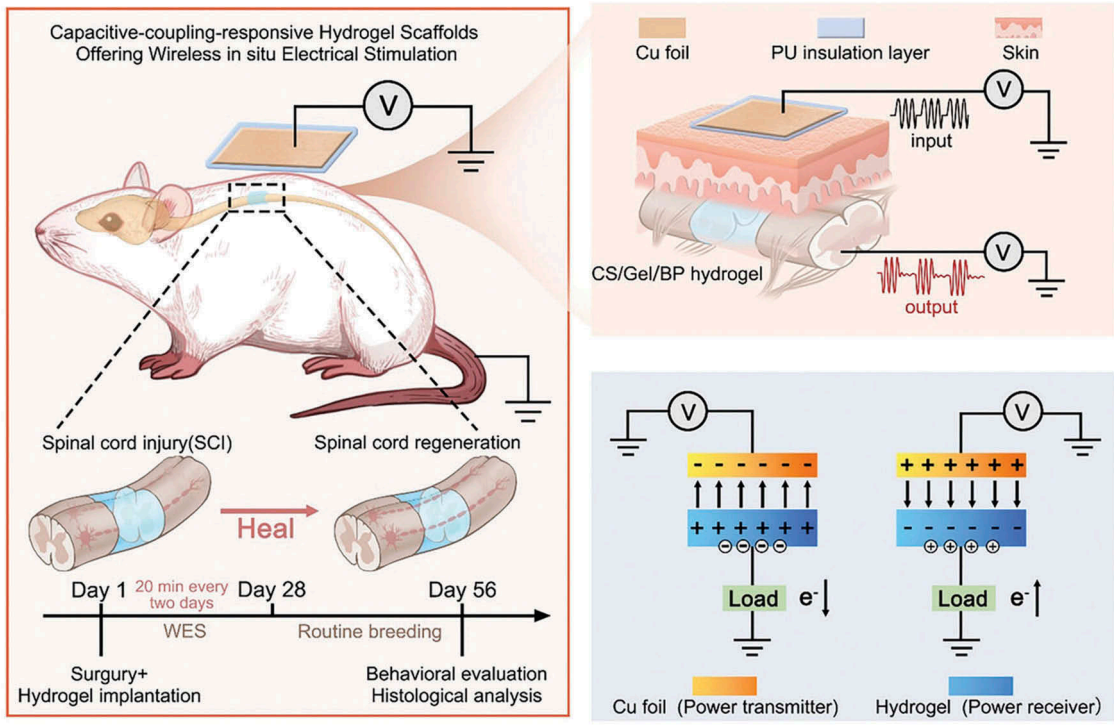

Figure 3. Schematics of wireless electrical stimulation based on conductive and biodegradable hydrogels for spinal cord repair. Owing to the capacitive coupling configuration, the electrostatic induction response of the chitosan/gelatin/black phosphorus (CS/Gel/BP) conductive hydrogel implanted in the lesion site can offer in situ ES without any external metal stimulation electrodes or percutaneous electrical wirings. In a complete transection model of rat SCI, significant nerve regeneration and functional recovery were achieved when a soft insulated metal patch as wireless power transmitter was placed on top of the injury site, and the conductive hydrogel implanted in the injury site could serve as a wireless power receiver. The capacitive coupling of high-frequency electrical field between hydrogel receiver and insulated metal patch transmitter generated alternating current flowing in the hydrogel scaffold owing to electrostatic induction effect (*in vivo* ES parameters: driven voltage, 1.10 V; driven frequency, 5 MHz; pulse width, 10 ms; pulse interval, 0.5 s; 20 min every 2 d for 28 d). Adapted with permission from [59]. Copyright 2024, John Wiley and Sons.

piezoelectric nanoparticles have been developed to enable responsiveness to external stimuli, such as magnetic fields or ultrasound, thereby enhancing neovascularization and locomotor recovery [61–63]. In parallel with material functionalization, innovative hydrogel architectures have been designed to address the spatial and structural complexity of SCI lesions. Open-structured and anisotropic scaffolds with chemically patterned surfaces can guide axonal growth while minimizing immune cell infiltration and scar formation [64]. Modular hydrogel tube constructs tailored to lesion geometries have also demonstrated the ability to reduce glial and fibrotic scarring while modulating immune responses [65]. Furthermore, biomolecularly instructive hydrogels have been engineered to actively direct neural cell fate, promoting differentiation, and accelerating axonal regeneration [66].

In more advanced approaches, hydrogels have been used as supportive matrices for living neural constructs, such as micro–tissue-engineered neural networks (micro-TENNs), which enable axonal survival and integration into host tissue while eliciting minimal astroglial response [67]. Overall, these approaches highlight a progressive evolution from structurally supportive to increasingly functional and bioactive hydrogel systems. However, while material design alone can partially address the hostile post-injury microenvironment, more advanced therapeutic strategies increasingly rely on the integration of hydrogels with bioactive molecules or cellular components, which will be discussed in the following sections.

2.3. Hydrogels as drug delivery systems (DDSs) in SCI

Injectable hydrogels represent a highly attractive platform for localized and in situ delivery of therapeutic agents in SCI, as they enable targeted release while bypassing the restrictive function of the BSCB, which significantly limits the efficacy of systemically administered treatments. Beyond acting as passive carriers, hydrogel-based drug delivery systems (DDSs) can be rationally engineered through tailored crosslinking chemistries and dynamic, stimuli-responsive linkages, allowing precise spatiotemporal control over degradation and therapeutic release in response to local pathological cues such as enzymatic activity, redox imbalance, or pH variations [68–70]. In this context, in situ-crosslinked GelMA hydrogels have been extensively investigated as carriers for neuroprotective agents capable of enhancing neuronal survival and promoting axonal growth [71,72]. For example, the incorporation of candesartan, an angiotensin II type 1 receptor (AT1R) inhibitor, within GelMA hydrogels has been shown to modulate the inflammatory microenvironment by promoting microglial polarization from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 phenotype.

Compared to conventional corticosteroid-based approaches, this strategy enables a more localized and potentially safer immunomodulatory effect (Figure 4) [71]. Similarly, thermosensitive poly(lactic-co-glycolic acid)–poly(ethylene glycol) (PLGA–

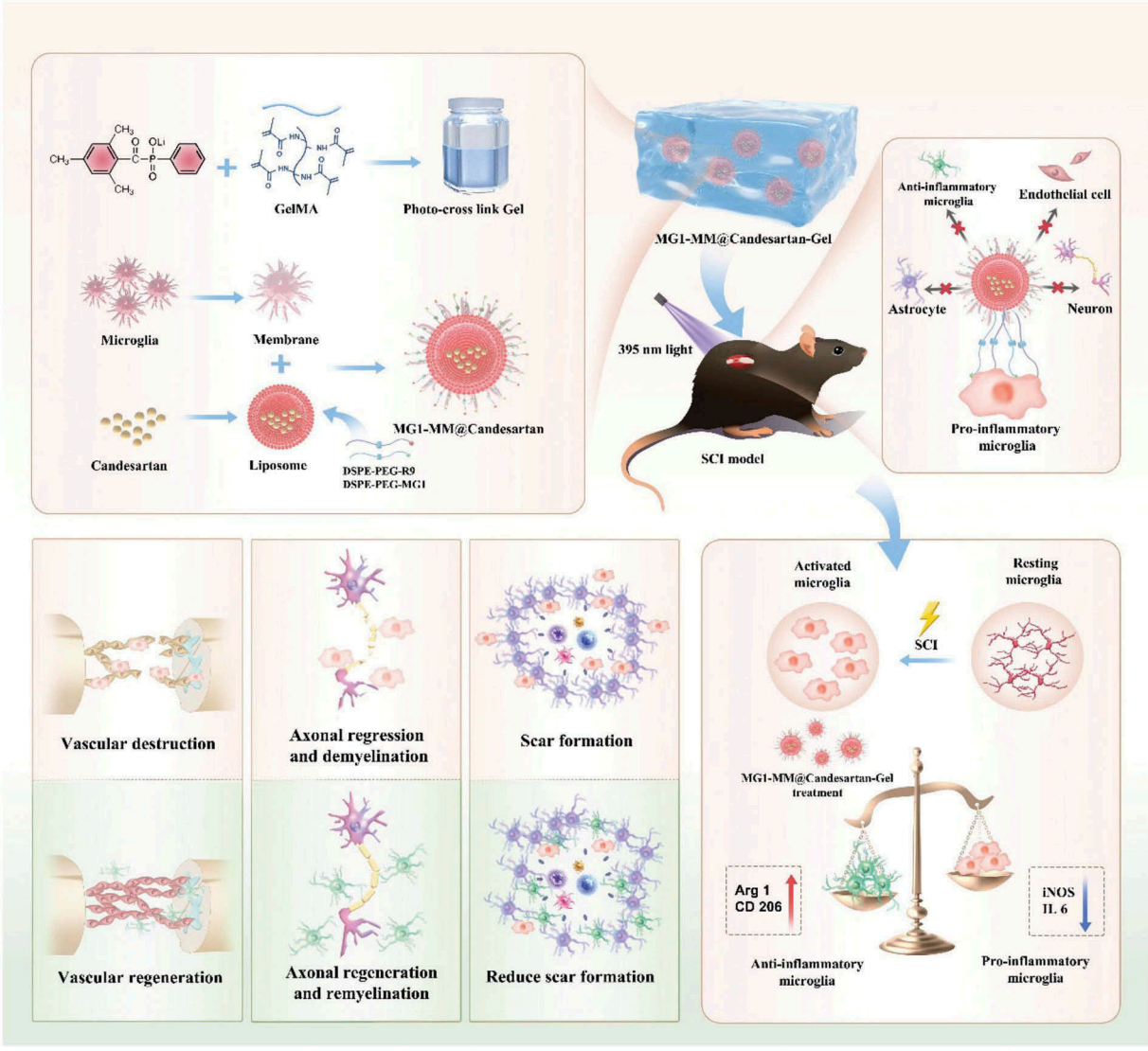

Figure 4. Schematic illustration of the gel design. The sustained-release precision-targeted delivery system consists of MG1-targeting peptide- and R9 cell-penetrating peptide-modified microglial membrane-coated nanoparticles loaded within a photosensitive hydrogel for sustained release. This system specifically recognizes proinflammatory microglia after spinal cord injury (SCI), thereby suppressing neuroinflammation and reprogramming microglia toward an anti-inflammatory phenotype to mitigate scar formation while promoting axonal regeneration and angiogenesis. Reprinted with permission from [71]. Copyright 2025, Elsevier.

PEG)-based hydrogels have been developed for the controlled release of immunomodulatory agents targeting early secondary injury cascades [73,74]. Other natural polymer–based systems have also demonstrated therapeutic potential for drug delivery platforms, supporting neuroprotection and angiogenesis [75–78]. Beyond conventional pharmacological agents, hydrogels have been extensively explored for the localized delivery of neurotrophic factors, whose clinical application is limited by poor stability, short half-life, and rapid degradation within the hostile post-injury microenvironment. In soluble form, these molecules often exhibit transient bioactivity and limited therapeutic efficacy [79]. Hydrogel-based DDSs can overcome these limitations by providing a protective environment that preserves protein structure and enables sustained and localized release. Through the modulation of crosslinking density, affinity interactions, and encapsulation strategies, hydrogels allow fine-tuning of release kinetics, thereby prolonging biological activity. Among the most employed factors, brain-derived neurotrophic factor (BDNF) plays a key role in promoting NSC proliferation, neuronal differentiation, and axonal growth [80,81]. Similarly, basic fibroblast growth factor (bFGF) and fibroblast growth factor 21 (FGF21) enhance NSC survival, inhibit apoptosis, and stimulate angiogenesis, contributing to functional recovery [82–86]. In addition, nerve growth factor (NGF) and neurotrophin-3 (NT-3) have also been incorporated into hydrogel systems owing to their essential roles in regulating neuronal development and synaptic plasticity [87–92]. Hydrogels are increasingly being explored as delivery vehicles for more complex bioactive agents and modulators targeting multiple pathological pathways. These include natural compounds with pleiotropic effects

on inflammation and oxidative stress [93–103], as well as cytokines [104–107], hormones [108–110], nucleotides [111–114], functional proteins [115–121], and enzymes [122,123].

In parallel, hydrogels have been used to deliver specific signaling pathway inhibitors to further modulate detrimental molecular cascades activated after SCI [124–126]. In addition, emerging strategies include the incorporation of systems capable of modulating the injury microenvironment through the controlled release of gasotransmitters such as carbon dioxide (CO_2), nitric oxide (NO), or hydrogen sulfide (H_2S), which contribute to vascular regulation, redox balance, and cellular homeostasis [127–129]. Another emerging strategy involves the incorporation of bioactive ions through nanoparticle-loaded hydrogels. Ions such as iron [63], magnesium [130], zinc [130–134], or selenium [135] can be released in a controlled manner to support neurogenesis, angiogenesis, and redox balance within the injured tissue. At a higher level of biological complexity, hydrogels have also been employed for the delivery of exosomes (Exos), to exploit their intrinsic paracrine activity in modulating cell–cell communication and promoting tissue repair [136–141]. Exosomes can be further engineered to enhance specific therapeutic effects, such as inflammation reduction, axonal regeneration, and angiogenesis [142–146], or can act as secondary drug delivery vehicles [147,148]. Similarly, extracellular vesicles (EVs) can be delivered via hydrogels either alone [149–152] or in combination with encapsulated bioactive substances to achieve synergistic effects [153,154]. Overall, these strategies illustrate a progressive shift from the delivery of single therapeutic agents toward increasingly complex and multifunctional delivery systems. While this evolution enhances the ability to modulate multiple pathological mechanisms simultaneously, it also introduces additional challenges related to formulation complexity, reproducibility, and regulatory classification, particularly when transitioning toward clinically translatable therapies.

2.4. Hydrogels as scaffolds for stem cells in SCI

Building on drug delivery strategies, cell-based therapies have emerged as a promising approach for SCI repair due to their potential to replace damaged cells, secrete neurotrophic factors, and modulate the post-injury microenvironment. Among the different cell populations investigated, neural stem cells (NSCs) and neural progenitor cells (NPCs) are commonly employed in preclinical SCI models because of their intrinsic differentiation potential and their ability to contribute to tissue remodeling while stimulating the recruitment of endogenous NSCs toward the injury site [155,156]. However, the clinical translation of stem cell-based approaches remains challenged by several safety and biological concerns. In particular, highly proliferative stem cell populations may exhibit uncontrolled proliferation or tumorigenic potential, especially when their differentiation is not tightly regulated. In addition, transplanted cells may undergo lineage drift within the complex post-injury microenvironment, leading to the generation of nonfunctional or undesired cell populations. A critical issue in SCI therapy is the balance between neuronal and astroglial differentiation, as excessive astrocyte formation may contribute to glial scar formation and further inhibit axonal regeneration. Importantly, the long-term survival and functional integration of transplanted cells into host neural circuits remain significant challenges, as the hostile post-injury environment, characterized by inflammation, metabolic stress, and limited vascularization, may compromise nutrient and oxygen supply, thereby limiting effective cell engraftment. Collectively, these limitations underscore the need for supportive delivery platforms capable of stabilizing cell fate and improving cell survival and integration. In this context, hydrogels are frequently employed as scaffolds for stem cell-based therapies owing to their ability to provide a supportive three-dimensional microenvironment that enhances cell retention, survival, and proliferation [157–159]. Moreover, hydrogel scaffolds act not only as passive carriers but also as instructive biomaterials capable of modulating stem cell behavior and fate [160–163].

By tuning mechanical stiffness, it is possible to direct NSC fate commitment, as softer matrices have been shown to favor neuronal differentiation, whereas stiffer environments may promote astroglial lineage specification [164]. Additionally, the incorporation of conductive components, ECM-derived motifs, or immobilized growth factors can further enhance neuronal maturation and support synaptic connectivity. In this context, amino-modified gelatin and aniline tetramer grafted onto oxidized hyaluronic acid have been used to generate conductive hydrogel microenvironments. When loaded with NSCs, these systems facilitate electrical signaling and promote neuronal differentiation, ultimately contributing to the inhibition of glial scar formation (Figure 5) [163]. MSCs have emerged as a practical alternative to NSCs owing to their robust anti-inflammatory, immunomodulatory, and neurotrophic properties [165,166]. Their availability from accessible tissue sources, together with their relative ease of isolation, expansion, and multilineage differentiation potential, has further supported their widespread use in SCI research [167–171]. However, their therapeutic effects are largely mediated by paracrine signaling rather than direct cell replacement, which may limit long-term tissue integration. In addition, MSCs can be co-transplanted with NSCs within hydrogel matrices to enhance neuronal differentiation and improve overall regenerative outcomes through complementary paracrine signaling mechanisms [172,173]. Despite these advantages, MSC survival within the hostile post-injury environment remains a major challenge, highlighting the importance of hydrogel-based scaffolds in improving cell retention, viability, and therapeutic efficacy [174,175]. To address ethical concerns, immunological responses, and the risk of tumor formation associated with certain stem cell sources, alternative cell types have also been explored. Epithelial cells (ECs) delivered within hydrogel scaffolds have shown potential due to their expression of pluripotency- and neural-associated markers, as well as their ability to secrete neurotrophic factors. Moreover, ECs can be preprogrammed *in vitro* to acquire NSC-like phenotypes prior to transplantation, thereby representing a promising alternative cell source [171,176,177]. Finally, central nervous system-associated cell types have also been investigated in combination with hydrogel platforms.

Schwann cells, for example, secrete a broad range of trophic factors, cell-adhesion molecules, and ECM components

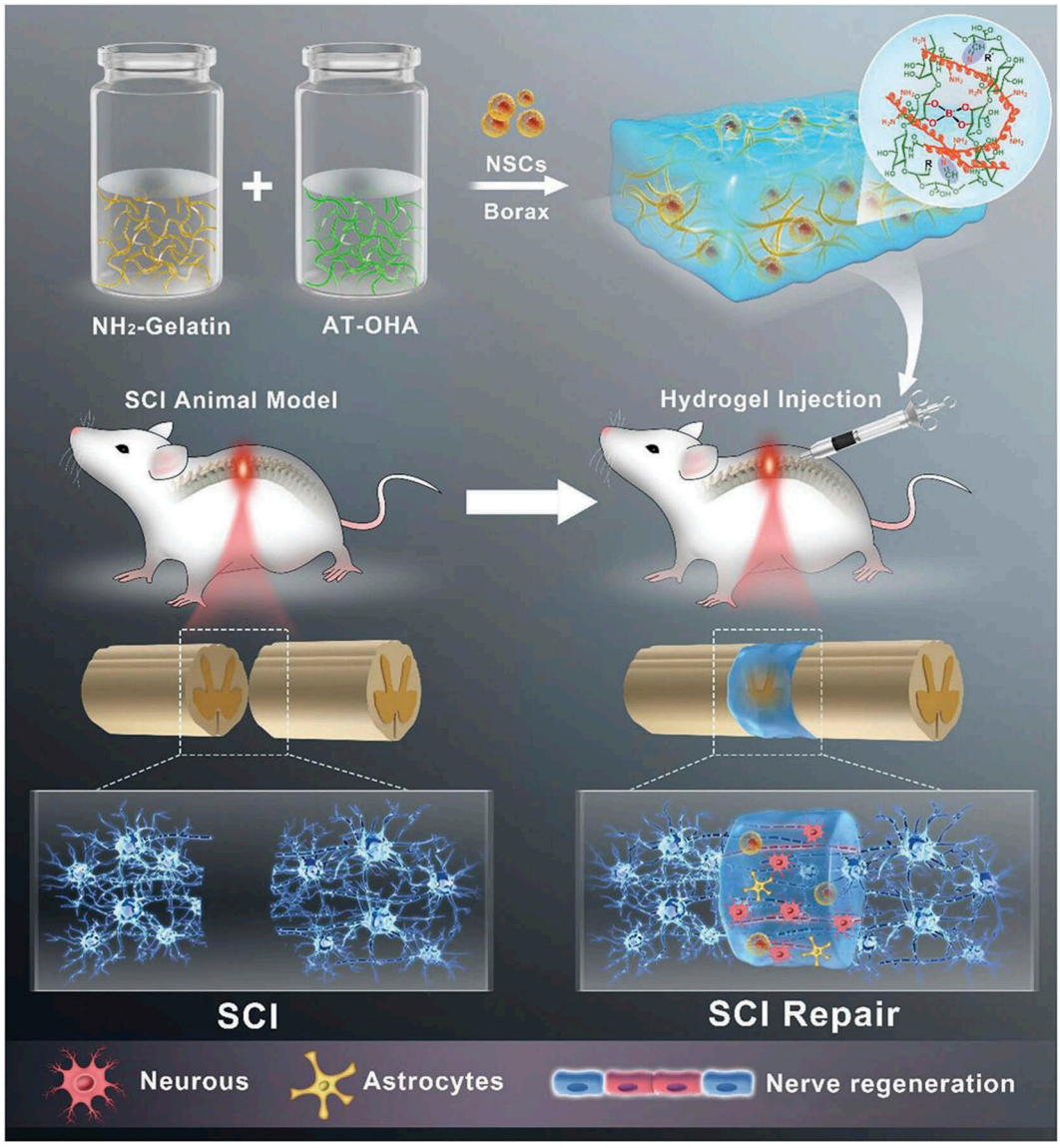

Figure 5. Schematic illustration of the preparation of Injectable Conductive ICH Hydrogel Scaffold and its application in Spinal Cord Injury repair. Reprinted with permission from [163]. Copyright 2023, American Chemical Society.

to support and guide neuronal regeneration [178]. Similarly, microglia incorporated within hydrogel systems can release anti-inflammatory cytokines that contribute to tissue homeostasis and repair following SCI [179]. These approaches further highlight the versatility of hydrogel-based scaffolds in supporting diverse cell populations for spinal cord repair.

2.5. Combined approaches

Owing to the remarkable versatility of hydrogels and the multifaceted pathophysiology of SCI, combinatorial therapeutic strategies have emerged as particularly effective approaches. These systems enable the simultaneous or sequential delivery of multiple bioactive cues, such as drugs, biomolecules, and cells, within a single platform, thereby addressing different pathological mechanisms in a synergistic manner. Dual-delivery hydrogel systems are increasingly designed to concurrently target multiple aspects of SCI pathology. For instance, neurotrophic factors can be co-delivered with antioxidants, or immunomodulatory molecules to mitigate the hostile post-injury environment while enhancing nerve regeneration [180–184]. Similarly, strategies aimed at restoring tissue homeostasis and inhibiting ferroptosis have combined the controlled release of therapeutically relevant ions with ferroptosis inhibitors, neuroprotective agents, or growth factors, resulting in synergistic effects on neuronal survival and axonal repair [185–188]. Inflammation modulation and stimulation of endogenous repair processes can be further enhanced through the combined delivery of chemokines and oligonucleotides, which reduce inflammatory signaling and promote progenitor cell recruitment, thereby potentiating the trophic effects of growth factors [189–191].

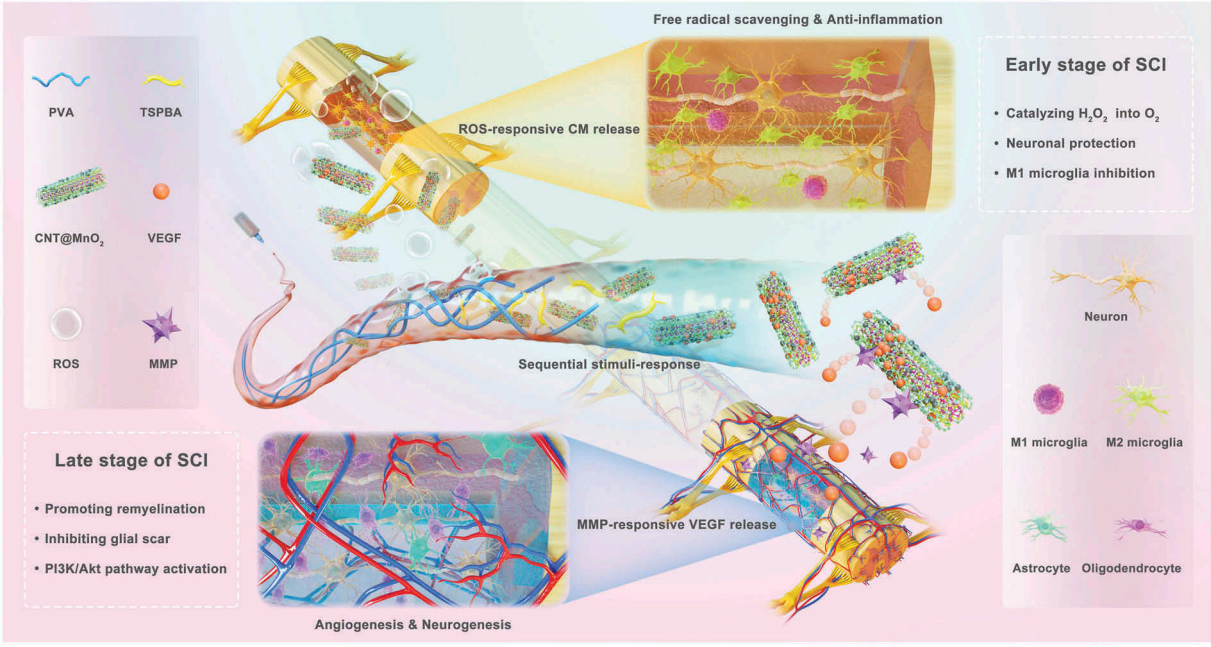

Figure 6. Schematic illustration of the application of CMV-RM hydrogel in SCI treatment. CNT@MnO2 nanodrugs (favoring ROS scavenging) loaded with an MMP-sensitive VEGF recombinant protein (favoring angiogenesis and neurogenesis) were doped into ROS-responsive PVA/TSPBA hydrogel. The resultant CMV-RM hydrogel could first respond to SCI-related oxidative stress microenvironment and release the nanodrugs to relieve inflammation and protect neurons in the early stage of SCI. Subsequently, the accumulation of MMPs in injured spinal cord region during the late stage of SCI could evoke the release of VEGF from the nanodrugs, resulting in the accelerated regeneration of spinal cord and vessels. This dynamically controllable drug delivery strategy efficiently promotes both anatomical and functional recovery of spinal cord in clinically relevant SCI models with only a single injection of CMV-RM hydrogel. Reprinted with permission from Elsevier, Copyright 2025 [192].

Synergistic outcomes have also been reported through the co-delivery of neurotrophic factors and conventional pharmacological agents [192–194].

For example, hydrogel systems incorporating carbon nanotube/manganese dioxide nanodrugs enable early-stage reduction of oxidative stress and inflammation, while matrix metalloproteinase (MMP)-responsive mechanisms subsequently trigger the release of vascular endothelial growth factor (VEGF), promoting angiogenesis and NSC differentiation (Figure 6) [192]. In a similar direction, clinically approved anti-inflammatory drugs such as methylprednisolone and minocycline have been integrated into combinatorial hydrogel platforms and co-delivered with complementary bioactive agents, including ferroptosis inhibitors, cytokines, and regulatory nucleic acids. This approach enables the concurrent attenuation of secondary injury cascades, modulation of immune responses, and promotion of axonal regeneration [195–199]. More broadly, pharmacological agents originally developed for other therapeutic indications, such as Metformin, Taxol, or Paclitaxel, can be repurposed and combined with chemokines, hormones, metal ions, or EVs within hydrogel systems to achieve synergistic neuroprotective and neuroregenerative effects by targeting multiple pathological pathways involved in SCI [200–203].

Beyond drug-drug combinations, the delivery capability of hydrogels can be further exploited to enhance the efficacy of cell-based therapies by modulating the post-injury microenvironment. In this context, the incorporation of conductive moieties [204], immunomodulatory agents [205–210], and ROS-scavenging molecules [211–214] within hydrogel matrices has been shown to improve cell survival, engraftment, and differentiation. For instance, hydrogels incorporating hollow cerium oxide nanospheres within chitosan methacryloyl and alginate methacryloyl matrices exhibit strong antioxidant properties, protecting encapsulated NSCs from apoptosis. In addition, cerium oxide nanospheres loaded with L-arginine can promote nitric oxide (NO) release, inducing calcium influx and activating the cAMP–PKA pathway, ultimately enhancing NSC differentiation (Figure 7) [212]. Moreover, multiple bioactive molecules can be co-encapsulated to sustain the survival, proliferation, and neuronal differentiation of transplanted NSCs or NPCs [215–222] or to potentiate the paracrine activity of MSCs, thereby further promoting nerve regeneration and functional recovery [223–227].

Overall, these combinatorial approaches underscore the importance of simultaneously targeting multiple components of the secondary injury cascade, thereby reflecting the multifactorial nature of spinal cord injury. At the same time, increasing system complexity introduces additional challenges related to formulation design, reproducibility, and clinical translation, which will be further discussed in the following sections.

2.6. Next-generation hydrogel platforms

Building upon the strategies discussed above, recent research is increasingly moving toward more advanced and biologically inspired hydrogel platforms aimed at further enhancing the

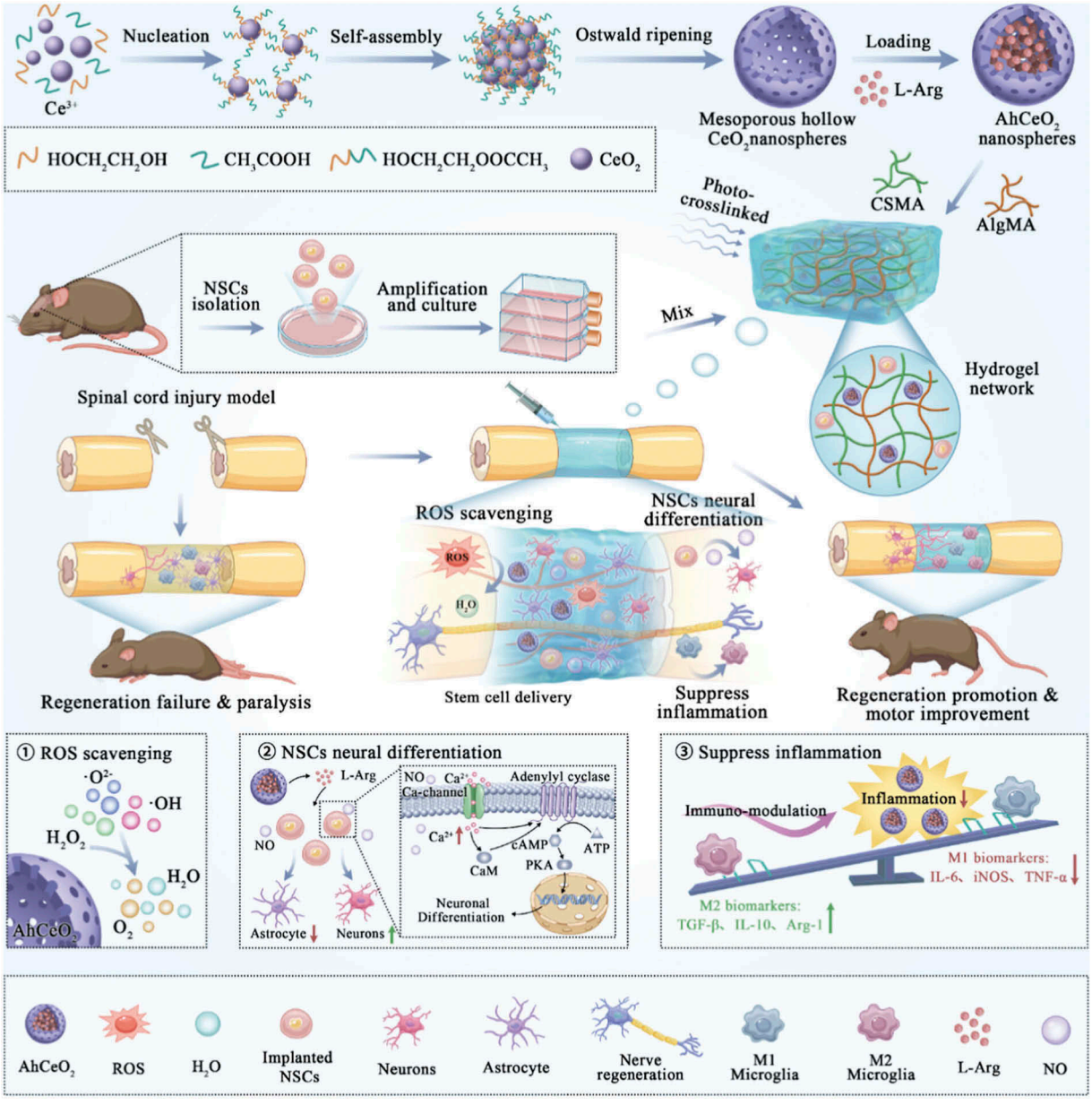

Figure 7. Schematic diagram of a composite hydrogel loaded with NO-releasing mesoporous hollow CeO2 nanospheres in coordination with NSCs transplantation for the treatment of rats with severe long-span SCI. AhCeO2 nanospheres remodeled the local microenvironment by alleviating oxidative stress and reducing neuroinflammation and promoted neural tissue regeneration and motor function recovery by enhancing neural differentiation of implanted NSCs and local neural circuit integration through the sustained release of NO. Reprinted with permission from [212]. Copyright 2023, American Chemical Society.

regenerative potential of SCI therapies. Rather than replacing existing paradigms, these emerging directions expand the functional versatility of hydrogels, positioning them as integrative interfaces capable of orchestrating biochemical, biophysical, and cellular cues within the injured microenvironment. The integration of hydrogels with physical and neuromodulator-based therapies, such as neurostimulation [228] and electrical stimulation [229], or complementary neuromodulatory approaches such as acupuncture [230], offers a promising avenue to synergistically enhance neural plasticity and regeneration. In parallel, highly innovative biological strategies are being explored, including hydrogels combined with adipose-derived tissues extracts to exploit their rich paracrine signaling [231], or with metabolically active mitochondria to directly support neuronal bioenergetics and neuroprotection [232].

Moreover, the incorporation of neural organoids [233], engineered microtissues, or even cell-free approaches based on conditioned media [234], exosomes, or secretomes [235] highlights a paradigm shift toward exploiting the regenerative power of paracrine signaling while mitigating the risks associated with direct cell transplantation. Recent research is also exploring the development of adaptive or feedback-responsive hydrogel systems capable of dynamically responding to changes in the injury microenvironment. These "smart" biomaterials can incorporate biosensing elements that detect local biochemical or mechanical cues and modulate therapeutic release or scaffold properties accordingly. Such systems may enable real-time regulation of drug delivery, inflammation modulation, or electrical stimulation within the injured spinal cord. In this context, injury-responsive hydrogels are

emerging as particularly promising platforms, as they can trigger the release of therapeutic agents in response to pathological signals characteristic of the injured spinal cord, including elevated levels of ROS, MMPs, inflammatory mediators, or local pH alterations. By incorporating stimulus-sensitive linkages or degradable motifs within the polymer network, these systems enable on-demand therapeutic delivery synchronized with the progression of the injury microenvironment, thereby improving spatiotemporal control of treatment while minimizing off-target effects. Another emerging concept involves the development of "4D hydrogels," defined as biomaterials capable of dynamically modifying their structural or biochemical properties over time in response to environmental stimuli [236]. In the context of SCI, such systems may progressively adjust their stiffness, degradation kinetics, or bioactive signaling profiles throughout the different phases of injury progression, thereby better matching the evolving regenerative requirements of spinal cord tissue. Beyond biochemical responsiveness, increasing attention is also being directed toward the integration of hydrogel platforms with bioelectronic interfaces. Conductive or electroactive hydrogels may serve as soft biointerfaces capable of transmitting electrical signals while simultaneously delivering therapeutic molecules or cells [237].

These multifunctional platforms may bridge regenerative biomaterials with implantable neuroprosthetic technologies, potentially enabling combined electrochemical and biological modulation of neural repair. Finally, advances in computational modeling and artificial intelligence are beginning to support the rational design and optimization of hydrogel systems for SCI repair [238]. Data-driven approaches may help predict optimal biomaterial compositions, degradation profiles, and therapeutic combinations based on injury characteristics. Such strategies could ultimately facilitate the development of personalized hydrogel therapies, in which scaffold composition and therapeutic payloads are tailored to the specific pathological features of individual spinal cord lesions. Together, these emerging strategies highlight the transition from passive biomaterial scaffolds toward adaptive, multifunctional, and potentially personalized hydrogel platforms capable of responding to the dynamic complexity of spinal cord injury and improving the efficacy of future regenerative therapies.

3. Comparative analysis and design principles of hydrogel therapies for SCI

Although numerous hydrogel systems have been proposed for SCI repair, their therapeutic performance depends on combination of key design parameters, as their physicochemical properties must be carefully engineered to interact with the complex pathological microenvironment of SCI. A comparative analysis of these design strategies helps identify material properties trade-offs that ultimately influence regenerative outcomes. In addition, a conceptual mapping between key pathological mechanisms of SCI and hydrogel-based therapeutic strategies is summarized in Table 1 and Figure 8.

Table 1. Mapping of SCI pathological mechanisms to hydrogel design strategies and therapeutic targets.

SCI pathological mechanism	Biological consequence	Therapeutic goal	Hydrogel design strategy	Key design parameters
BSCB disruption	Infiltration of immune cells and neurotoxic molecules, edema	Reduce secondary damage and restore barrier integrity	Injectable in situ–gelling hydrogels forming protective barriers	Rapid gelation, injectability, tissue adhesion
Excitotoxicity	Glutamate accumulation leading to neuronal death	Protect neurons during acute phase	Hydrogels delivering neuroprotective agents	Controlled and sustained release ability
Oxidative stress	ROS-mediated cellular damage	Limit oxidative injury and cell death	Antioxidant-loaded or ROS-scavenging hydrogels	Redox-responsive materials, or sustained release ability
Ferroptosis	Iron accumulation leading to lipid peroxidation (LPO) and cellular death	Prevent ferroptotic cell death and LPO (increase iron metabolism)	Hydrogels delivering ferroptosis inhibitors or iron chelators	Targeted release
Acute inflammation	Activation of microglia/ macrophages (M1 phenotype)	Reduce early inflammatory damage	Hydrogels delivering anti-inflammatory molecules or modulators to promote M2 phenotype	Release profile tuning, immunomodulatory cues
Chronic inflammation	Persistent immune activation and inhibitory microenvironment	Promote regenerative environment		
Axonal degeneration	Loss of connectivity and signal transmission	Guide axonal regrowth and reconnection, restore signal transmission and functional connectivity	Aligned, anisotropic, or conductive hydrogels	Topographical cues, electrical conductivity
Demyelination	Loss of oligodendrocytes and impaired signal conduction	Promote remyelination	Cell-laden hydrogels (OPCs) or factor-releasing scaffolds	Cell viability support, differentiation cues
Glial scar formation	Physical and biochemical barrier to axonal growth	Enhance axonal penetration and plasticity	Enzyme-loaded (e.g., chondroitinase ABC) or ECM-mimetic hydrogels	Sustained delivery, matrix remodeling capacity
Cystic cavity formation	Structural void preventing tissue bridging	Provide structural support and bridge lesion	Injectable bulk-filling hydrogels acting as scaffolds	Stiffness comparable to spinal cord tissue, shape conformity, stability

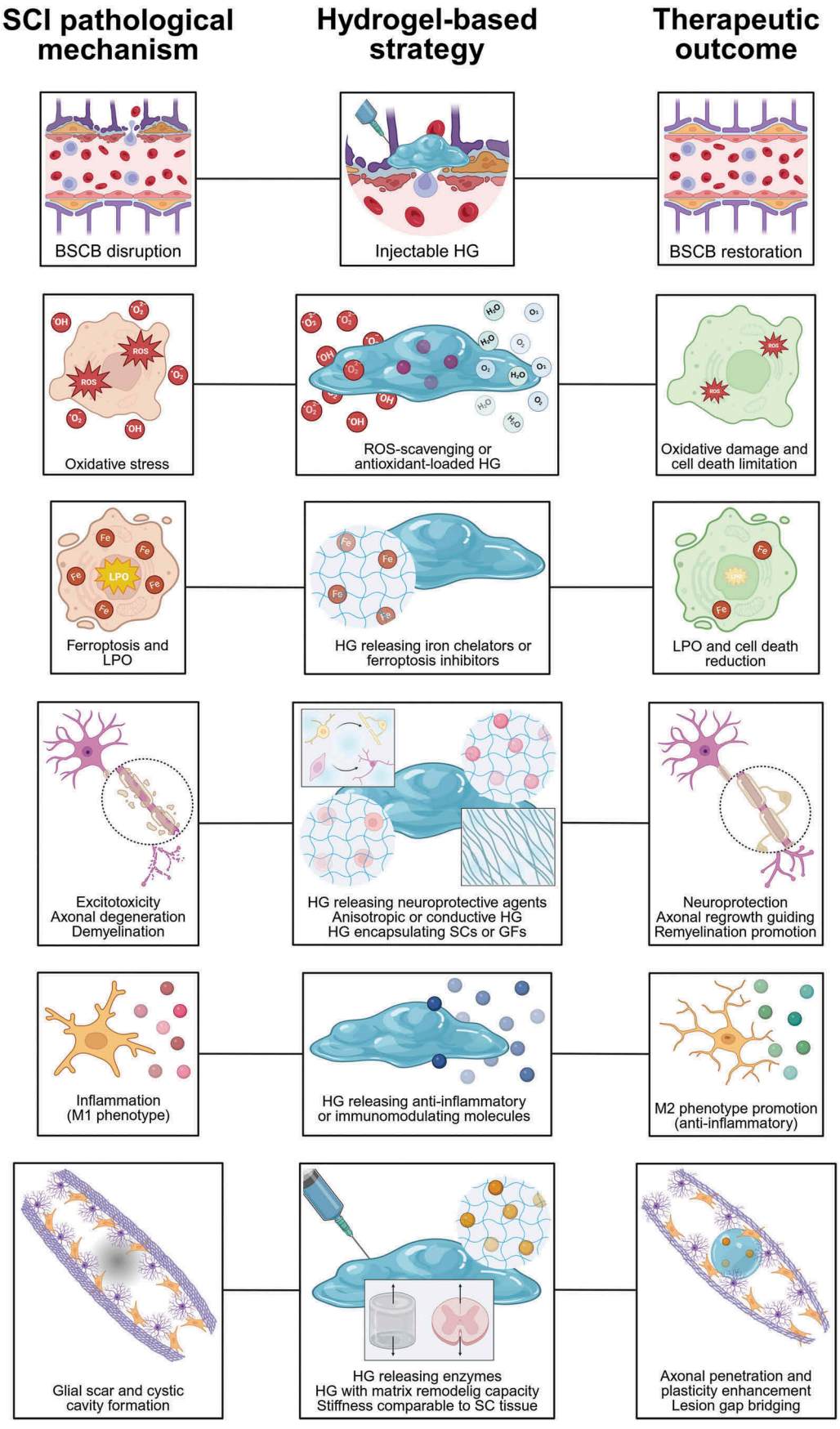

Figure 8. Conceptual mapping of SCI pathological mechanisms to hydrogel-based therapeutic strategies. Created in BioRender. Rossi, F. (2026) https://BioRender.com/q7pzsn7.

Natural-based hydrogels are widely employed due to their intrinsic biocompatibility and their ability to mimic components of the extracellular matrix. These materials often support cell adhesion, migration, and axonal growth, making them particularly suitable for regenerative applications and cell-based therapies. However, their mechanical properties and degradation rates are often difficult to precisely control, and batch-to-batch variability may affect reproducibility.

In addition, many natural hydrogels exhibit relatively low mechanical stability, which may limit their ability to provide long-term structural support within the lesion cavity. Conversely, synthetic hydrogels and engineered polymer systems offer greater tunability in terms of stiffness, degradation kinetics, and chemical functionalization, enabling the precise modulation of scaffold architecture and drug release profiles. However, synthetic polymers generally lack intrinsic biological cues and therefore often require functionalization with extracellular matrix–derived motifs, peptides, or growth factors to promote cell adhesion and compatibility. Another key design parameter concerns the mechanical properties of the hydrogel matrix, which should closely match the mechanical environment of the native spinal cord to avoid additional mechanical stress on the injured region. The spinal cord exhibits relatively low stiffness, typically within the range of approximately 0.1–10 kPa, and hydrogels designed for neural applications are often engineered within similar ranges to support neuronal differentiation and axonal extension [239]. Matrices that are excessively stiff may promote astroglial differentiation and scar formation, whereas excessively soft materials may lack the structural integrity required to maintain the lesion cavity and guide regenerating axons. Conductive hydrogels have been developed to address the electrophysiological nature of neural tissues by facilitating electrical signaling and enhancing neuronal differentiation and axonal regeneration. These materials typically exhibit electrical conductivities in the range of 10^{-5} to 10^{-2} S/cm, which is considered sufficient to support electroactive cellular responses [240]. Despite their promising regenerative potential, the incorporation of conductive nanomaterials may introduce additional challenges related to long-term stability, potential cytotoxicity, and the control of degradation products. Degradation kinetics also represent a critical design parameter for hydrogel-based therapies. Ideally, scaffold degradation should occur over weeks to months, allowing sufficient time for tissue remodeling and axonal regeneration while avoiding chronic compression of the surrounding neural tissue. Hydrogels that degrade too rapidly may fail to provide adequate structural support, whereas overly persistent materials may interfere with long-term tissue integration.

Another important design aspect concerns the incorporation of therapeutic payloads. Cell-laden hydrogels aim to provide both structural support and a source of regenerative cells capable of replacing damaged neural tissue or secreting trophic factors. However, challenges related to cell survival, immune compatibility, tumorigenic potential, and regulatory approval remain significant barriers to clinical translation. Alternatively, acellular hydrogels can be engineered to deliver bioactive molecules, offering greater control over release kinetics and potentially representing a more scalable and clinically translatable strategy. Beyond biomaterial composition, the delivery route also represents an important variable in the design of hydrogel-based therapies. While many hydrogel systems have been developed for direct implantation within the lesion cavity, alternative delivery strategies are increasingly being explored. Intrathecal [241,242] and epidural [243,244] administration routes enable hydrogels to act as biointerfaces capable of locally modulating the injury microenvironment without requiring direct intraparenchymal injection. Such approaches may be particularly advantageous when hydrogels are primarily designed as drug delivery systems, as they allow localized therapeutic exposure while reducing surgical invasiveness. In contrast, direct implantation within the spinal cord parenchyma is typically required when hydrogels are intended to function as regenerative scaffolds that support axonal growth or transplanted cells [245]. The choice of delivery route is also closely linked to the timing of intervention in a clinical context. Intrathecal or epidural hydrogel administration may be performed relatively early after injury, for example during decompression surgery, enabling the delivery of therapeutics targeting early secondary injury mechanisms. Conversely, intraparenchymal implantation is often delayed until the formation of a cystic cavity within the injured spinal cord. Anatomical barriers such as the dura mater may further influence drug diffusion depending on the delivery route, as the intact dura can limit the penetration of large biomolecules delivered from epidural hydrogels [245].

Across the literature analyzed in this review, several hydrogel classes emerge as particularly promising based on the consistency of functional recovery outcomes, mechanistic targeting of secondary injury pathways, and translational feasibility. In particular, injectable ECM-mimetic hydrogels, multifunctional composite hydrogels combining drug delivery with structural scaffolding, and conductive hydrogels designed to support neuronal signaling have repeatedly demonstrated robust regenerative effects in preclinical SCI models. These platforms typically achieve a favorable balance between mechanical compatibility with spinal cord tissue, controlled degradation, and the ability to modulate key pathological processes such as inflammation, oxidative stress, and axonal degeneration. From a translational perspective, hydrogel platforms based on clinically established polymers, scalable manufacturing processes, and well-defined regulatory pathways may ultimately represent the most realistic candidates for future clinical applications.

4. Functional recovery and influence of SCI models

The ultimate goal of hydrogel-based therapies for SCI is the restoration of neurological function. Accordingly, the evaluation of therapeutic efficacy in preclinical studies relies on a combination of behavioral, electrophysiological, and anatomical outcome measures that assess different aspects of motor and sensory recovery. Behavioral assessment remains the most widely used approach to quantify functional improvement following SCI. In rat models, the Basso, Beattie, Bresnahan (BBB) locomotor rating scale is the most commonly applied scoring system, ranging from 0 to 21 and evaluating

progressive improvements in hindlimb joint movement, stepping coordination, trunk stability, and paw placement. For mouse models, the Basso Mouse Scale (BMS) provides a comparable evaluation framework adapted to species-specific locomotor patterns, with scores ranging from 0 to 9.

These open-field locomotor assessments are often complemented by more sensitive behavioral tests, including grid walk and ladder rung walking tasks, as well as automated gait analysis systems such as CatWalk, which quantify paw placement accuracy, interlimb coordination, and gait symmetry. Electrophysiological recordings provide complementary information on the functional integrity of neural pathways. In particular, motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs) are commonly used to assess signal conduction across the injured spinal cord. Improvements in signal amplitude or reductions in latency are often interpreted as indicators of restored neural connectivity. Quantitative kinematic analyses and automated gait tracking systems can further provide objective locomotor parameters that strengthen the interpretation of behavioral outcomes. Although some studies also report autonomic outcomes such as bladder function or sensory recovery, these endpoints remain less consistently evaluated across preclinical investigations. A major challenge in interpreting the efficacy of hydrogel-based interventions lies in the heterogeneity of experimental SCI models [246]. Commonly employed models include contusion, compression, hemisection, and complete transection injuries, each reproducing distinct aspects of spinal cord pathology. Among these, contusion injuries are generally considered the most clinically relevant because they reproduce the mechanical trauma and progressive secondary injury cascade observed in human SCI, while preserving partial tissue continuity. Compression models, typically generated through sustained mechanical pressure on the spinal cord, reproduce prolonged tissue deformation and ischemia and are frequently used to model injuries associated with vertebral fractures or spinal canal narrowing. Hemisection and complete transection models involve precise surgical disruption of the spinal cord and are often used to investigate axonal regeneration under controlled experimental conditions. While these models facilitate the study of axonal bridging across the lesion site, they represent more severe and less clinically representative injuries compared with contusion models. As a result, regenerative outcomes observed in transection paradigms may not directly translate to the more heterogeneous pathology seen in human SCI.

Additional variability arises from differences in injury severity, spinal level (cervical vs thoracic), species and strain, and the timing of therapeutic intervention relative to the acute, subacute, or chronic phases of injury. These experimental parameters can significantly influence inflammatory responses, scar formation, and regenerative potential, ultimately affecting the functional outcomes observed after treatment. Despite the diversity of hydrogel formulations reported in the literature, therapeutic efficacy is most frequently evaluated through changes in locomotor scores and electrophysiological recovery. Across many studies, hydrogel implantation results in moderate improvements in BBB or BMS scores, typically reflecting partial restoration of hindlimb movement and coordination rather than complete recovery of locomotor function. Hydrogel systems that combine structural scaffolding with bioactive components often report greater functional improvements compared with inert biomaterial scaffolds alone. Similarly, conductive hydrogels designed to facilitate electrical signaling have shown encouraging results in some studies, where enhanced electrophysiological conduction correlates with improved behavioral recovery. However, direct comparison of therapeutic efficacy across studies remains challenging due to differences in injury models, outcome measures, and experimental protocols. To facilitate a clearer synthesis of the available evidence, Table S1 summarizes the key experimental parameters and functional outcomes reported for representative hydrogel-based therapies in preclinical SCI models. The increasing complexity of hydrogel-based therapeutic systems also introduces challenges related to reproducibility and experimental standardization. Many studies employ multi-component constructs, combining biomaterial scaffolds with cells, extracellular vesicles, growth factors, or pharmacological agents. While these combinatorial approaches may enhance therapeutic efficacy, they also complicate the interpretation of results and may hinder reproducibility across laboratories. Additional sources of variability include batch-to-batch differences in biologically derived materials as well as incomplete reporting of hydrogel cross-linking chemistry, including initiators, reaction conditions, and potential residual reagents.

To improve experimental rigor and facilitate cross-study comparisons, greater adherence to standardized reporting practices is needed. Key methodological elements should include clear descriptions of randomization and blinding procedures, sample size justification, handling of experimental exclusions, and the concordance between functional and histological outcomes. In line with ARRIVE guidelines [247], a minimal reporting framework for hydrogel-based SCI studies is proposed in Table 2, highlighting core methodological parameters that should be clearly documented to enhance transparency, reproducibility, and translational relevance in future investigations.

5. Clinical translation and regulatory considerations

The clinical translation of hydrogel-based therapies for SCI requires careful consideration of both regulatory classification and manufacturing constraints, as these factors directly determine development pathways, evidentiary requirements, and overall feasibility. Depending on their composition and intended mechanism of action, hydrogel systems may be regulated as medical devices, medicinal products, or combination products. In the United States, products integrating multiple components are classified as combination products under 21 CFR 3.2(e), a regulation issued by the U.S. Food and Drug Administration (FDA), with categorization based on the primary mode of action (PMOA). Hydrogels functioning primarily as structural scaffolds are generally regulated as medical devices, whereas systems enabling controlled delivery of pharmacologically active agents are classified as drug–device combination products and require additional pharmacological and

Table 2. Proposed ARRIVE-aligned reporting checklist for preclinical hydrogel-based SCI studies.

Reporting element	Description	Reason of importance
Randomization	Animals randomly allocated to treatment groups	Reduces selection bias
Blinded outcome assessment	Functional outcomes evaluated by blinded investigators	Prevents observer bias in locomotor scoring
Sample size justification	Power calculation or rationale for group size	Ensures adequate statistical power
Reporting of exclusions	Clear documentation of excluded animals or failed procedures	Prevents selective reporting
Animal characteristics	Species, strain, sex, age, and weight reported	Influences injury response and reproducibility
Injury model description	Detailed reporting of SCI model type, level, and severity	Enables comparison across studies
Housing and husbandry	Description of animal housing conditions and care	Affects physiological and behavioral outcomes
Experimental procedures	Detailed surgical methods, anesthesia, and treatment protocols	Ensures reproducibility
Outcome measures	Definition of primary and secondary outcomes	Improves clarity and interpretation
Statistical methods	Description of statistical tests and data analysis	Ensures validity of conclusions
Ethical statement	Approval by institutional animal care committee	Ensures compliance with ethical standards
Concordance between functional and histological outcomes	Behavioral recovery supported by structural repair evidence	Strengthens interpretation of therapeutic efficacy
Hydrogel characterization	Composition and physicochemical properties clearly reported	Influences tissue response, integration, and therapeutic outcome
Payload description	Type, dose, and release profile of incorporated therapeutic agents and cells specified	Determines biological activity and treatment efficacy
Delivery strategy	Route, timing, and method of hydrogel administration described	Route, timing, and method of hydrogel administration described

toxicological evaluation. More complex constructs incorporating cells, extracellular vesicles, or other biologically active elements are typically regulated as biologic–device combination products, substantially increasing regulatory complexity. In the European Union, classification is governed by the EU Medical Device Regulation (MDR 2017/745), with additional clarification provided by the Medical Device Coordination Group for borderline products.

Hydrogels exerting predominantly physical effects are typically classified as medical devices, while those delivering pharmacologically active substances or biological components may be regulated as medicinal products. Notably, when the hydrogel primarily acts as a carrier for therapeutic cells or gene-related components, the product may fall within advanced therapy frameworks, including Advanced Therapy Medicinal Products (ATMPs), or tissue-engineered products (TEPs), under the oversight of the European Medicines Agency (EMA). This distinction is critical, as device pathways focus on safety and performance, whereas medicinal and ATMP pathways require comprehensive demonstration of clinical efficacy, long-term safety, and strict traceability. Consequently, early consideration of regulatory classification is essential, as increasing system complexity is directly associated with more demanding development and approval processes. Beyond regulatory classification, several practical challenges limit clinical translation. Sterilization remains a major barrier, particularly for hydrogels based on natural polymers, hybrid materials, or systems incorporating bioactive molecules and living components. Conventional methods such as irradiation, ethylene oxide, or autoclaving may alter polymer networks, affect crosslinking density, or compromise biological functionality, often necessitating aseptic manufacturing strategies. In parallel, stringent control of bioburden and endotoxin levels is required for clinical-grade materials, especially for injectable formulations targeting the central nervous system. Product stability and shelf life also represent critical limitations. Many hydrogel systems rely on in situ crosslinking mechanisms or contain labile biological components, which can reduce storage stability and impose cold-chain requirements. Variability in degradation kinetics and progressive loss of bioactivity further complicate clinical use. Reproducibility challenges are not limited to biologically derived materials (e.g., dECM, EVs), but extend more broadly to complex and multi-component hydrogel systems, including those incorporating NPs, GFs, or chemically modified polymers. Such systems may exhibit variability related to raw material sourcing, functionalization efficiency, and formulation protocols.

In addition, insufficient reporting and control of crosslinking chemistry can significantly impact cytocompatibility, degradation behavior, and regulatory assessment. Translation to clinical use further requires compliance with Good Manufacturing Practice (GMP) standards, including rigorous control of raw material quality, batch consistency, and process validation. These requirements become increasingly demanding for multi-component or biologically active systems, reinforcing the need for simplified, well-defined, and scalable formulations. Despite extensive progress in preclinical research, clinical translation remains limited. Most hydrogel-based approaches for SCI have been evaluated predominantly in rodent models, with only limited progression toward large-animal studies or early clinical investigation, and no hydrogel-based therapy has yet achieved widespread clinical adoption for SCI. This gap reflects not only the biological complexity and heterogeneity of SCI, but also the challenges associated with reproducibility, manufacturing scalability, and regulatory approval of multifunctional systems. While combinatorial strategies integrating biomaterials with cells, growth factors, extracellular vesicles, or drugs may enhance regenerative potential, they also introduce additional layers of complexity that can hinder standardization and translation. Overall, bridging the gap between promising preclinical outcomes and clinical application will require not only advances in biomaterial design, but also early integration of regulatory

considerations, simplification of therapeutic strategies, and the development of robust, scalable manufacturing processes aligned with clinical and regulatory requirements.

6. Conclusions

Hydrogel-based strategies for SCI have evolved from passive scaffolds to multifunctional platforms capable of modulating multiple aspects of the injury microenvironment. As highlighted in this review, these systems can combine structural support with localized delivery of bioactive molecules and, in some cases, cellular therapies, enabling simultaneous targeting of inflammation, oxidative stress, and axonal degeneration.

Despite these advances, the functional improvements reported in preclinical studies remain generally partial and highly dependent on experimental variables, including injury model, treatment timing, and outcome measures. Beyond biological complexity, the clinical translation of these systems is further constrained by significant regulatory and manufacturing challenges. Increasing formulation complexity, particularly in multi-component systems, directly impacts regulatory classification, often shifting products toward combination or advanced therapeutic categories with more demanding evidentiary requirements. At the same time, practical limitations related to scalable manufacturing, reproducibility, sterilization compatibility, and product stability continue to hinder the transition from preclinical proof-of-concept to clinically viable therapies.

7. Future perspectives

Future research in hydrogel-based therapies for SCI should move beyond increasing system complexity and instead prioritize strategies that enhance translational feasibility. While multifunctional and combinatorial approaches have demonstrated promising biological effects, their clinical applicability is often limited by challenges in reproducibility, scalability, and regulatory approval. A key direction will be the development of simplified and modular hydrogel platforms with well-defined composition and controllable properties, enabling better standardization and manufacturing consistency. In parallel, greater emphasis should be placed on identifying the minimal set of functional components required to achieve meaningful therapeutic effects, rather than relying on highly complex multi-component constructs. From a translational perspective, early integration of regulatory considerations into material design will be essential. This includes selecting chemistries compatible with sterilization, ensuring low endotoxin risk, and adopting materials and processes that can be readily adapted to GMP production. In addition, future studies should increasingly incorporate clinically relevant experimental designs, including contusion-based injury models, delayed treatment paradigms, and standardized functional outcome measures.

Greater alignment between preclinical study design and clinical reality will be critical to improve the predictive value of experimental findings. Finally, minimally invasive delivery strategies, such as injectable or perilesional hydrogels, may offer more clinically feasible alternatives to invasive implantation approaches and should be further explored in translational studies.

Author contributions

CRediT: **Zoe Giorgi:** Investigation, Methodology, Writing – original draft; **Valeria Veneruso:** Methodology, Writing – review & editing; **Emilia Petillo:** Methodology, Writing – review & editing; **Enrico Frigerio:** Methodology, Writing – review & editing; **Pietro Veglianese:** Methodology, Writing – review & editing; **Giuseppe Perale:** Supervision, Writing – review & editing; **Filippo Rossi:** Project administration, Resources, Supervision, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This paper was not funded.

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PDF Alt-text Coversheet

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uf0001	**Alt-Text:** Spinal injury: inflammation, demyelination, scar, angiogenesis, homeostasis, regeneration, hydrogel.
uf0001	**Long Description:** The illustration depicts various stages and processes related to spinal cord injury and recovery. The injured spinal cord is shown with a focus on inflammation, represented by reactive oxygen species and cellular damage. Demyelination is illustrated with disrupted nerve fibers and affected cells. A glial scar is depicted with dense cellular structures. Angiogenesis is shown with new blood vessel formation. Homeostasis is represented by balanced cellular activity. Tissue regeneration is illustrated with organized cellular structures and healing processes. Hydrogel is depicted as a supportive material aiding in recovery, shown applied to the spinal cord. Each section highlights different aspects of injury and healing mechanisms.
Figure 1.	**Alt-Text:** Three-part infographic on spinal cord injury: ASIA scale, pathophysiology and therapeutic approaches.
Figure 1.	**Long Description:** Image A illustrates the ASIA Impairment Scale for spinal cord injuries: C4 (tetraplegia, grade A), C6 (tetraplegia, grade B), T6 (paraplegia, grade C) and L1 (paraplegia, grade D), with regions labeled cervical, thoracic, lumbar, sacral and coccygeal. Image B details spinal cord injury pathophysiology, showing primary causes like compression and contusion leading to hemorrhage and necrosis and secondary phases: acute (ischemia, necrosis, cytokine release), subacute (excitotoxicity, demyelination, glial scar formation) and chronic (cystic cavity, dense glial scar). Image C presents therapeutic approaches focusing on neuroprotection and neuroregeneration, with treatments for each phase: acute (decompression, anti-inflammatory drugs), subacute (glial scar removal, neurotrophic factors) and chronic (oligodendrocyte precursors, modified astrocytes).
Figure 2.	**Alt-Text:** Illustration of hydrogel formation, application in SCI repair and cellular interactions.
Figure 2.	**Long Description:** The illustration shows the process of hydrogel formation and its application in spinal cord injury (SCI) repair. The top section depicts the chemical structure PPFLMLLKGSTR, which undergoes self-assembly with monomers to form peptide nanofibers (PNFs) at 4 degrees Celsius. These PNFs transition from sol to gel at 37 degrees Celsius in 5 minutes, forming a cross-linked polymer (CRP). The bottom left section illustrates a mouse being injected with the hydrogel, inducing neural stem cells (NSCs), neurons, astrocytes and axons, while modulating immune responses involving TNF, M1, M0, M2 and IL-10. The bottom right section shows the PI3K/AKT/mTOR signaling pathway in RAW 264.7 cells, with MK-2206 inhibiting AKT, contributing to SCI repair.
Figure 3.	**Alt-Text:** Illustration of wireless electrical stimulation for spinal cord repair using hydrogel scaffolds in a rat model.
Figure 3.	**Long Description:** The illustration shows a rat model for spinal cord repair using capacitive-coupling-responsive hydrogel scaffolds. The top left section depicts a rat with a spinal cord injury, where a hydrogel is implanted for regeneration. The timeline below indicates the process from surgery and hydrogel implantation on day 1, wireless electrical stimulation every two days for 20 minutes until day 28, followed by routine breeding and evaluation until day 56. The top right section illustrates the setup with copper foil, polyurethane insulation and skin layers, showing input and output of electrical signals through the chitosan/gelatin/black phosphorus hydrogel. The bottom section shows diagrams of the power transmitter and receiver, with copper foil as the transmitter and hydrogel as the receiver, indicating the flow of electrons and load. This setup facilitates wireless electrical stimulation for spinal cord healing.
Figure 4.	**Alt-Text:** Gel design for spinal injury: microglia modulation and tissue regeneration illustration.
Figure 4.	**Long Description:** The illustration depicts a gel design for spinal cord injury treatment. The top section shows the creation of a photo-crosslink gel using GelMA and Candesartan, combined with microglia membranes and liposomes to form MG1-VM at Candesartan. This gel is applied to a spinal cord injury model under 395 nanometer light, targeting pro-inflammatory microglia and promoting anti-inflammatory

	microglia, astrocytes, endothelial cells and neurons. The bottom section illustrates the effects of the treatment: vascular destruction and regeneration, axonal regression and remyelination and scar formation reduction. The right section shows activated and resting microglia, with a balance between anti-inflammatory and pro-inflammatory states, indicated by Arg 1 CD 206 and iNOS IL 6 markers.
Figure 5.	**Alt-Text:** Illustration of hydrogel scaffold preparation and application in spinal cord injury repair in mice.
Figure 5.	**Long Description:** The illustration depicts the preparation and application of a hydrogel scaffold for spinal cord injury repair in mice. At the top, two jars labeled NH2-Gelatin and AT-OHA are shown, with an addition sign between them, indicating their combination. Nearby, NSCs and Borax are depicted, leading to the formation of a hydrogel. A detailed view of the hydrogel structure is shown with chemical components. Below, two mice are illustrated. The first mouse represents the SCI animal model with a highlighted spinal cord injury. The second mouse shows the hydrogel injection into the injured area. Below each mouse, cross-sections of the spinal cord are displayed. The SCI section shows disrupted neural connections, while the SCI Repair section shows improved nerve regeneration with neurons and astrocytes. A legend at the bottom identifies neurons, astrocytes and nerve regeneration elements.
Figure 6.	**Alt-Text:** Illustration of CMV-RM hydrogel application in SCI treatment showing early and late stage responses.
Figure 6.	**Long Description:** The illustration depicts the application of CMV-RM hydrogel in spinal cord injury treatment. On the left, components like PVA, TSPBA, CNT at MnO subscript 2, VEGF, ROS and MMP are shown. The top section highlights the early stage of spinal cord injury, focusing on free radical scavenging and anti-inflammation, catalyzing hydrogen peroxide into oxygen, neuronal protection and M1 microglia inhibition. The central part illustrates a sequential stimuli-response with ROS-responsive CM release. The bottom section details the late stage of spinal cord injury, emphasizing MMP-responsive VEGF release, promoting remyelination, inhibiting glial scar and PI3K/Akt pathway activation. Various cell types like neurons, M1 and M2 microglia, astrocytes and oligodendrocytes are depicted on the right. The illustration conveys angiogenesis and neurogenesis processes during spinal cord injury treatment.
Figure 7.	**Alt-Text:** Hydrogel with AhCeO2 aids spinal injury in rats by promoting NSCs differentiation and reducing inflammation.
Figure 7.	**Long Description:** The diagram shows a composite hydrogel with AhCeO2 nanospheres for spinal cord injury treatment in rats. It starts with forming mesoporous CeO2 nanospheres loaded with L-arginine, mixed with CSMA and AlgMA to create a hydrogel. The injury model shows regeneration failure and paralysis, followed by stem cell delivery, ROS scavenging, NSCs differentiation and inflammation suppression. The hydrogel aids regeneration and motor improvement. ROS scavenging involves AhCeO2 reacting with H2O2 to produce O2. NSCs differentiation is boosted by NO release, calcium influx and cAMP–PKA pathway activation. Inflammation suppression includes immuno-modulation, reducing M1 biomarkers and increasing M2 biomarkers. Neurons, astrocytes and microglia are illustrated.
Figure 8.	**Alt-Text:** Illustration links SCI mechanisms to hydrogel strategies for BSCB repair and axonal regrowth.
Figure 8.	**Long Description:** The illustration maps spinal cord injury mechanisms to hydrogel therapies. BSCB disruption is addressed by injectable hydrogels, restoring BSCB. Oxidative stress is countered by ROS-scavenging hydrogels, limiting oxidative damage and cell death. Ferroptosis and lipid peroxidation are treated with hydrogels releasing iron chelators, reducing lipid peroxidation and cell death. Excitotoxicity, axonal degeneration and demyelination are managed by hydrogels releasing neuroprotective agents, promoting neuroprotection, axonal regrowth and remyelination. Inflammation (M1 phenotype) is addressed with hydrogels releasing anti-inflammatory molecules, promoting M2 phenotype. Glial scar and cystic cavity formation are treated with hydrogels releasing enzymes and matrix remodeling hydrogels, enhancing axonal penetration and lesion gap bridging.