

REVIEW ARTICLE

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Biomaterial-based regenerative therapeutic strategies for spinal cord injury

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Abstract

As one of the most intractable neurological diseases, spinal cord injury (SCI) often leads to permanent neurological impairment in patients. Unfortunately, due to the complex pathological mechanisms and unique postinjury microenvironment, there is currently no way to completely repair the injured spinal cord. In recent years, with the rapid development of tissue engineering technology, the combination of biomaterials and medicine has provided a new idea for treating SCI. Here, we systematically summarize representative biomaterials, including natural, synthetic, nano, and hybrid materials, and their applications in SCI treatment. In addition, we describe several state-of-the-art fabrication techniques for tissue engineering. Importantly, we provide novel insights for the use of biomaterial-based therapeutic strategies to reduce secondary damage and promote repair. Finally, we discuss several biomaterial clinical studies. This review aims to provide a reference and new insights for the future exploration of spinal cord regeneration strategies.

Introduction

Spinal cord injury (SCI) refers to damage to the spinal cord caused by direct or indirect external factors that often results in sensory, motor, and autonomic dysfunctions below the level of injury¹. According to the World Health Organization, between 250,000 and 500,000 people suffer from SCI each year². In Canada, the total annual economic burden of SCI is estimated at \$2.67 billion³. While advances in clinical management have reduced morbidity and improved patient outcomes, there is still a lack of effective repair strategies that promote SCI recovery.

Developing new approaches to spinal cord restoration requires an in-depth comprehension of the drastic changes in the microenvironment following injuries. Dynamic

alterations of cell number, phenotypes, and spatio-temporal distribution are found in the SCI microenvironment. Primary injuries refer to the compression, splitting, twisting or shearing of the spinal cord caused by direct or indirect external mechanical force, resulting in axonal breakage, nerve tissue destruction and neuronal death⁴. These primary injuries trigger a cascade of secondary pathophysiological events. Disruption of the blood–spinal cord barrier (BSCB) triggers inflammatory cells to invade the afflicted region, releasing a large number of inflammatory factors⁵. Phagocytic inflammatory cells produce reactive oxygen species (ROS), further inducing cellular necrosis and apoptosis⁶. Subsequently, glial and fibrous scars form at the lesion site. These secondary injuries inhibit neuroregeneration and prolongs the duration of injury, impeding tissue regeneration and functional recovery⁷ (Fig. 1).

As tissue engineering progresses, biomaterials, predominantly nanoscale materials of various structures, have become pivotal. These materials are tailored to interact with the nervous system with high specificity. They can serve not only as spatial scaffolds or drug/cell

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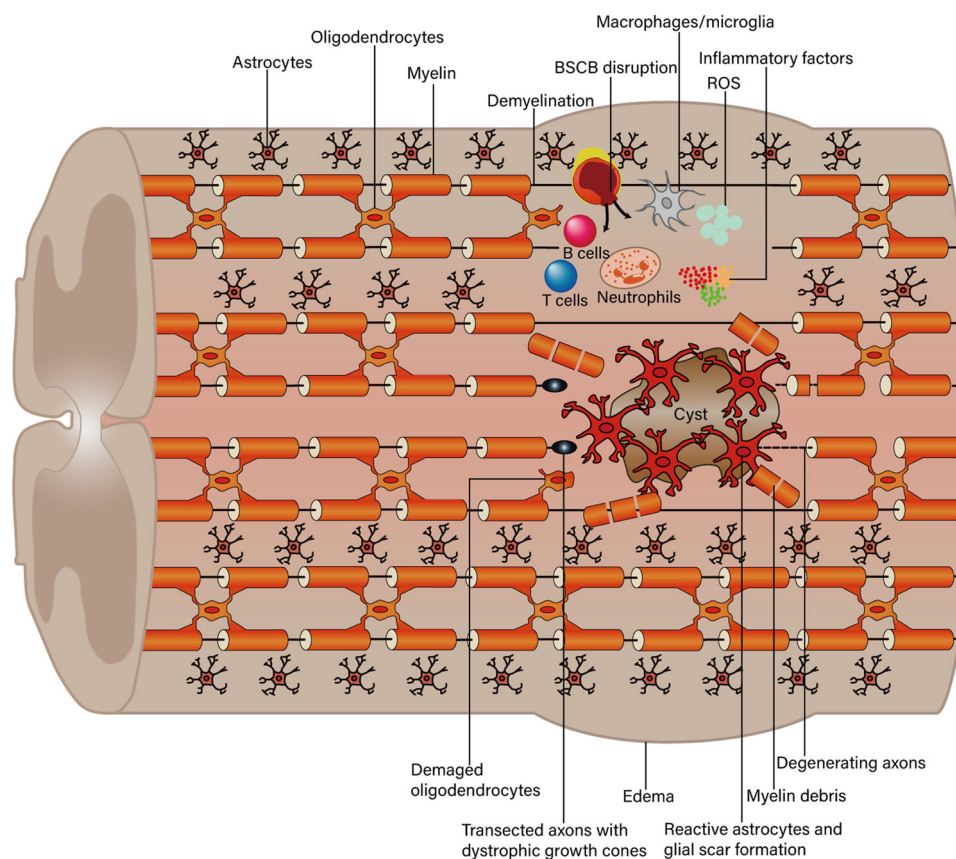


Fig. 1 Schematic representation of the injured spinal cord. Adapted with permission²⁴⁰. Copyright 2023, Springer Nature. All figures in this review should be printed in color.

delivery vehicles⁸ but also as artificial bioactive niches that resemble the extracellular matrix (ECM)^{9,10}. In this review, we summarize representative biomaterials for injured spinal cord repair, advanced tissue engineering fabrication techniques, biomaterial-based therapeutic strategies, and several clinical studies of functional bioscaffolds. This review aims to provide a reference and novel insights for further exploration of spinal cord regeneration strategies.

Biomaterials for SCI repair

Why we use biomaterials for SCI repair

The most common approach to repair peripheral nerve injuries is surgical direct repair/direct coaptation¹¹. When the gap in a peripheral injury exceeds 5 mm, autograft reconstruction is often used as the “gold standard” treatment^{12,13}. However, central nervous system (CNS) injury is accompanied by the formation of an inhibitory milieu, which often restricts nerve regeneration^{14–16}. Therefore, these two conventional strategies are not sufficient for treating CNS injuries. In recent decades, various natural and synthetic biomaterials have been tailored based on selective physical and chemical

properties to promote a favorable microenvironment and CNS nerve regeneration between severed nerve stumps^{17,18}.

Currently, biological approaches to restoring neural connectivity at the lesion site are focused on delivering biomaterials to the lesion to re-establish communication through new relay circuits or to stimulate endogenous axon regrowth. By manipulating the components, morphology and architecture of biomaterials, they can produce suitable topographical and biochemical cues that promote tissue regeneration. These biomaterials can also be modified to offer a permissive substrate for axonal penetration into the injured CNS region^{19,20}.

To promote neural and nonneural cell differentiation as well as axonal growth, bioscaffolds should possess essential characteristics such as degradability and compatibility (Fig. 2). Therefore, the selection of suitable scaffold materials is crucial for the overall design strategy of neural tissue engineering. Moreover, advanced fabrication and tissue engineering techniques are required. In the following sections, we summarize the main scaffold materials and state-of-the-art fabrication techniques.

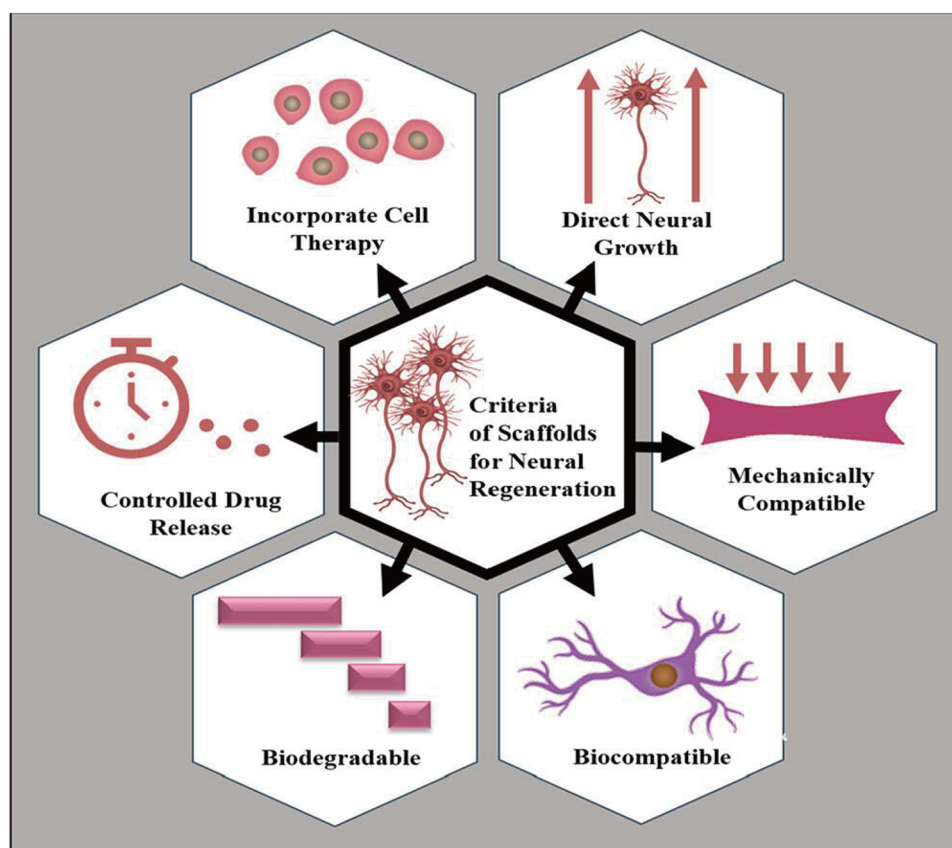


Fig. 2 Characteristics of the scaffolds required for neural regeneration. Reproduced with permission²⁴¹. Copyright 2020, American Chemical Society.

Representative scaffolding materials

Natural Materials

Collagen Collagen is a principal constituent of the ECM and exhibits high conservation across species, making it readily accessible. It stands out for its nontoxicity, biocompatibility, and biodegradability²¹. Furthermore, as a bioprinting material, collagen has the potential to carry targeted tissue, cells, and biomolecules to exert the desired pharmacokinetics and therapeutic effects²². Owing to these advantages, collagen has been extensively used for bioprinting²³ and cell transplantation²⁴ in SCI. Collagen biomaterials can be manufactured into different scaffolds, including hydrogels²⁵, electrospun fibers^{26,27}, linear-ordered collagen scaffolds (LOCS)²⁸, aligned sponges²⁹, and tubes³⁰. Through cross-linking reactions and non-covalent interactions, collagen scaffolds can be further modified to control mechanical properties and biochemical functions³¹. However, due to the shortcomings of collagen scaffolds, including weak biomechanical properties, limited plasticity, and rapid degradation³², recent studies have focused on composite scaffolds, such as collagen/gelatin³³ and collagen/chitosan scaffolds²³.

Fibrin Fibrin, composed of fibrinogen and thrombin, is one of the most important proteins involved in hemostasis and tissue regeneration. In recent years, fibrin-based biomaterials have been extensively investigated in spinal cord tissue engineering. Nazari et al. demonstrated that fibrin hydrogels could increase the viability of cells and trigger the differentiation of induced pluripotent stem cells (iPSCs) into preoligodendrocytes, thereby promoting injured spinal cord repair³⁴. Yao et al. implanted a three-dimensional (3D) aligned fibrin hydrogel (AFG) scaffold into the spinal cords of dorsal hemi-transection model rats, which resulted in faster motor function recovery compared to that of the control group over a 2-week period³⁵. Similar to collagen, its poor mechanical properties can be overcome by combining it with other materials, such as poly- ϵ -caprolactone (PCL)³⁶.

Hyaluronic Acid As the main component of the ECM, hyaluronic acid (HA) is highly concentrated in the nervous system, particularly in the CNS, and possesses excellent biocompatibility and biodegradability. Studies have shown that HA scaffolds can provide neuroprotection and

promote injured spinal cord repair by alleviating secondary damage after SCI³⁷. Nevertheless, HA materials exhibit disadvantages such as poor cell adhesion³⁸. To overcome these drawbacks, HA can be modified, such as with the integrin-binding peptide arginine-glycine-aspartic acid (RGD)³⁹, to enhance cell adhesion and migration to implants. Moreover, 3D hydrogel scaffolds prepared by blending HA with gelatin are effective in promoting endogenous neural stem cell (NSC) migration and neurogenesis⁴⁰.

Chitosan Chitosan is obtained by the deacetylation of chitin, which is widely found in the cell walls of crustaceans, bacilli, and fungi^{41,42}. As a natural polymer with low immunogenicity, nontoxicity, biodegradability, and suitable cell adhesion, chitosan is an ideal scaffold material and has been extensively studied in the repair of SCI. When implanted into the rat spinal cord after bilateral dorsal hemisection, physical chitosan microhydrogels were shown to promote spinal tissue and vasculature reconstitution, diminish fibrous glial scarring, and modulate the inflammatory response⁴³. However, chitosan-based scaffolds also have issues, such as rapid degradation and increased swelling. Compounding chitosan with other materials results in a scaffold with complementary properties, enhancing the overall performance of the scaffold. For example, a composite hydrogel scaffold composed of chitosan and alginate was used as a tissue-engineered spinal cord, which exhibited better mechanical properties, suitable swelling, negligible toxicity, and suitable biocompatibility with adipose-derived mesenchymal stem cells⁴⁴.

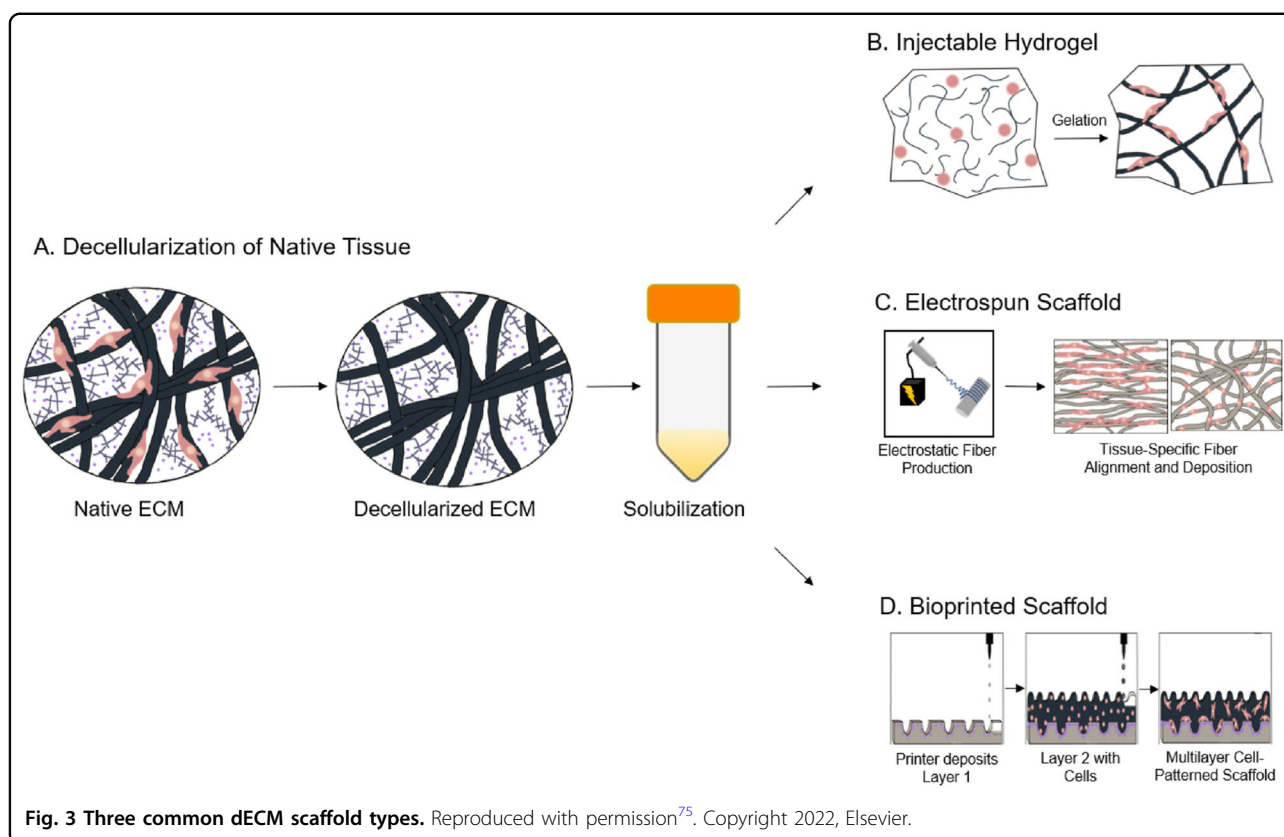
Alginate Alginate is a natural polysaccharide carbohydrate extracted from the cell walls of brown algae. As a tissue engineering biomaterial, in addition to its advantages of biocompatibility, low toxicity and low cost, alginate can be cross-linked with divalent cations (e.g., Ca^{2+}) to form alginate hydrogels under mild conditions. Depending on the divalent cation used, the physical properties (e.g., mechanical strength, elasticity, or stability) vary⁴⁵. The use of alginate-based hydrogels in regenerative medicine has grown exponentially. Nonfunctionalized soft alginate hydrogels showed potential in preventing fibrous scarring and promoting functional recovery after a severe SCI⁴⁶; for chronic SCI, implants of alginate hydrogels showed the ability to restore the anatomical continuity of the spinal cord, slightly improve motor function, and restore partial electrophysiological conductivity⁴⁷. Likewise, to enhance the repair effect, alginate is often combined with other natural materials, cells, and growth factors^{48–50}.

Polysialic Acid Polysialic acid (PSA) is an endogenous polysaccharide attached to nerve cell adhesion molecules that control CNS development by regulating cell adhesion

and promoting axonal growth. Induction of endogenous PSA expression through cell- or gene-based approaches, such as broad or selected targeting at neurons⁵¹, astrocytes⁵², or transplanted Schwann cells^{53,54}, is a strategy for the treatment of SCI. There is no solid evidence for the efficacy of exogenous PSA infusion in repairing injured spinal cord, but several PSA mimetics, such as PSA cyclic mimetic peptide (PR-21)⁵⁵, linear mimetic peptide H-NHTDPYIYPID-OH⁵⁶, tegaserod⁵⁷, and 5-nonyloxytryptamine oxalate⁵⁸ have shown therapeutic effects in animal models of SCI. In recent years, drug-loaded PSA scaffolds or micelles have shown therapeutic effects on SCI^{59,60}. The exact mechanism of exogenous PSA in the treatment of SCI remains to be elucidated.

Gelatin Gelatin is a macromolecular hydrophilic colloid partially hydrolyzed from collagen that promotes cell attachment and proliferation due to the presence of abundant RGD sequences and integrin-binding motifs⁶¹. Using gelatin-based biomaterial scaffolds for the treatment of SCI has been extensively studied. For example, a photosensitive gelatin hydrogel scaffold was loaded with collagen-binding stromal cell-derived factor-1 α and Taxol liposomes to promote their sustained release, thereby synergistically promoting neurovascular unit regeneration and motor function improvement⁶². Moreover, 3D gelatin methacrylate (GelMA) hydrogel combined with iPSC-derived NSCs reduced the cavity areas, inhibited glial scar formation, and promoted axonal regeneration⁶³. Furthermore, gelatin hydrogels can be modified with enzymes. For example, a dual-enzymatically cross-linked gelatin hydrogel by hydrogen horseradish peroxidase and galactose oxidase could enhance the survival, proliferation, and neural differentiation of human umbilical cord MSCs (hUC-MSCs)⁶⁴. In conclusion, gelatin-based scaffolds have great therapeutic potential.

Agarose Agarose, a linear polymer derived from seaweed, has been shown in a previous in vitro study to promote cell attachment and neurite outgrowth⁶⁵. Further studies found that after the implantation of agarose scaffolds with uniaxial channels into the injured rat spinal cord, the scaffolds could be well integrated with host tissue, where axons grew in a strikingly linear fashion⁶⁶. Combining materials is a common strategy. The experimental results of Han et al. demonstrated that an agarose scaffold containing Matrigel could enhance linear axon regeneration and promote the reconnection of functional axons after SCI⁶⁷. An agarose/gelatin/polypyrrole (PPy) hydrogel with similar conductivity and modulus as the spinal cord can fill the cavity, mimicking the physiological properties of the spinal cord to promote injured spinal cord repair⁶⁸. Agarose can also be used for cell delivery^{69–71}, drug delivery⁷², and bioink preparation⁷³.



Decellularized extracellular matrix scaffolds Decellularized extracellular matrix (dECM) scaffolds are constructed by removing cells from the matrix (namely, decellularization)⁷⁴. Injectable hydrogels, electrospun scaffolds and bioprinted scaffolds are three common types of dECM scaffolds⁷⁵ (Fig. 3). In addition to the advantages of suitable histocompatibility, low immunogenicity, suitable degradability and nontoxicity of degradation products, dECM scaffolds can also simulate an optimal nonimmune environment with native 3D structures and various bioactive components⁷⁶. For the treatment of SCI, acellular spinal cord (ASC) scaffolds have been widely studied. They are commonly used as carriers for stem cells, drugs, and neurotrophic factors^{77,78}. To enhance mechanical properties, ASC scaffolds are often modified or compounded with other materials^{79,80}. In addition to ASC scaffolds, dECM scaffolds derived from other tissue have also been reported, such as decellularized meningeal scaffolds⁸¹ and decellularized optic nerve scaffolds⁸².

Synthetic materials

Compared with natural scaffolds, synthetic materials show the advantages of high raw material availability, controllable biodegradability and customizable physical

and mechanical properties and have been widely used in scientific research.

Synthetic polymeric materials

There are many kinds of synthetic polymeric materials, including degradable polymers (e.g., PCL) and non-degradable polymers (e.g., poly(2-hydroxyethyl methacrylate)). In Table 1, we summarize some commonly used synthetic polymeric materials in the construction of bioscaffolds.

In addition to the materials summarized in Table 1, studies on conductive polymers such as polyaniline and PPy are emerging. After SCI, the electrical properties of tissue cells at the injury site are altered, generating an extracellular endogenous electric field with the ability to guide cell migration and promote tissue repair. However, in the case of severe SCI, current conduction is blocked, inhibiting self-repair of the injured spinal cord⁸³, which is the theoretical basis for the application of conductive polymers in spinal cord tissue engineering. Wang et al. assessed an electroactive polyaniline-poly(lactic acid) scaffold that promoted the adhesion, survival and proliferation of olfactory ensheathing cells⁸⁴. However, further in vitro experiments are needed to observe the various behavioral changes of cells on the scaffold surface under different electrical stimuli. A soft conducting polymer

Table 1 Summary of synthetic polymeric materials commonly used in constructing bioscaffolds.

Materials	Advantages	Disadvantages	Examples of research in the past five years
PCL	Well-controllable properties and high biological safety ²⁴⁴ ; high crystallinity, suitable mechanical strength, bioabsorbable and biocompatible nature ²⁴⁵ .	Slow degradation rate in vivo ²⁴⁶ ; hydrophobicity-mediated poor cell attachment ^{247,248} .	PCL scaffolds loaded with activated Schwann cells and iPSCs-NSCs increased tissue remodeling and promoted motor function recovery in transected spinal cord model rats ²⁴⁹ . Using PCL as a drug delivery system to deliver uric acid, Singh and coworkers successfully protected spinal cord tissue from excitotoxic injury in an in vitro injury model ²⁵⁰ .
PEG	Stability, nontoxicity, biocompatibility ²⁵¹ .	Relatively low drug loading capacity ²⁵¹ ; poor efficacy when applied alone ²⁵² .	Polyethylene glycol microgel scaffolds can be used to deliver human bone marrow MSCs (hMSCs) and promote their secretory potential to repair nerve damage ²⁵³ . Before cell transplantation, utilizing macroporous PEG tubes to serve as a soft substrate can create a more permissive injection site, thus improving the survival of mouse embryonic day 14 spinal progenitors ²⁵⁴ .
PLA	Suitable processability, mechanical strength, biocompatibility and biodegradability ^{255,256} .	Hydrophobicity, low impact toughness and slow degradation rate ²⁵⁷ .	Polypyrrole/PLA nanofibrous scaffolds loaded with bone marrow MSCs can inhibit glial scarring, promote axonal regeneration, bridge lesion gaps, and restore nerve electrical conduction ⁸³ . In an SCI animal model, codelivery of DHA and BDNF from a PLA/DHA/BDNF electrospun aligned core-shell fibrous membranes could provide neuroprotection and promote neuroplasticity changes in recovered neuronal tissue ²⁵⁸ .
PLGA	Adjustable physicochemical properties ²⁵⁹ ; favorable thermal stability, biocompatibility, biodegradability, sustained-release properties, and film-forming ability ²⁴⁵ .	Weak electrical conductivity ²⁶⁰ ; high hydrophobicity ²⁶¹ .	Local delivery of IGF-1 and BDNF immobilized to PLGA/GO hybrid nanofibers could reduce cavity formation, increase the number of neurons at the injury site, and significantly improve functional locomotor recovery after SCI in rats ²⁶² . In SCI model mice, copolymer PLGA-PEI-mPEG loaded ACPP and etanercept suppressed the inflammation and promoted neuronal survival and locomotor recovery ²⁶³ .
PVA	Hydrophilicity, swellability, nontoxicity, biodegradability, and ease of conversion to hydrogel ²⁴⁵ ; sufficient mechanical strength for tissue engineering ⁷⁴ .	Relatively low biocompatibility and slow degradability ⁷⁴ .	As an implantable drug delivery system, genistein based on chitosan/PVA nanofibers decreased the levels of nitric oxide (NO), malondialdehyde and tumor necrosis factor- α (TNF- α), while causing an increase in the activity of super oxide dismutase and the level of interleukin-10 (IL-10) in the injured spinal cord tissue of rats, thereby ameliorating the marked oxidative damage and inflammation induced by SCI ²⁶⁴ .

Table 1 continued

Materials	Advantages	Disadvantages	Examples of research in the past five years
pHEMA	Low interfacial tension in the liquid state and similar mechanical properties to the spinal cord in the hydrogel state ^{265,266} .	Nonbiodegradability; insufficient functional recovery after SCI after hydrogel implantation ⁷⁴ .	Following the implantation of iPSC-NPs into laminin-coated pHEMA-MOETACL hydrogels, the material was found to integrate into the chronic injured spinal cord, reducing cavitation and supporting iPSC-NPs survival; however, the recovery of motor function was not statistically significant ²⁶⁷ .
pHPMA	Similar physical and chemical properties to pHEMA; positive effect on functional recovery after SCI after hydrogel implantation ²⁶⁸ .	Similar properties to pHEMA such as nonbiodegradability.	There is little research on pHPMA in the past five years; examples of research in the earlier years are as follows: Implantation of pHPMA hydrogel into hemisected T10 rat spinal cord resulted in improvements in locomotor and neurophysiology ²⁶⁸ . A form of pHPMA hydrogel with RGD modification enhanced axonal growth across the reconstructed lesion, displaying the potential to repair tissue defects in the CNS ²⁶⁹ .

ACPP activated cell-penetrating peptides, BDNF brain-derived neurotropic factor, DHA docosahexaenoic acid, GO graphene oxide, IGF-1 insulin-like growth factor 1, iPSC-NPs induced pluripotent stem cell-derived neural progenitors, iPSCs-NSCs induced pluripotent stem cell-derived neural stem cells, mPEG methoxypolyethylene glycol, MOETACL [2-(methacryloyloxy) ethyl] trimethylammonium chloride, PEG polyethylene glycol, PEI poly (ethylene imine), pHEMA poly(2-hydroxyethyl methacrylate), PLA polylactic acid, pHPMA poly [N-(2-hydroxypropyl) methacrylamide], PLGA poly (lactic-co-glycolic acid), PVA polyvinyl alcohol.

hydrogel (CPH) prepared by mixing tannic acid (TA), pyrrole (Py), and Fe³⁺ has been shown to promote NSC differentiation into neurons rather than astrocytes in vitro and to activate new endogenous neurogenesis in vivo⁸⁵ (Fig. 4). These studies reveal the unlimited potential of conductive biomaterials in the treatment of SCI.

Synthetic Peptide Materials

Consisting of short and repeating amino acid units, self-assembling peptides (SAPs) have been widely applied to SCI regeneration due to their suitable mechanical strength, suitable water solubility and excellent biocompatibility⁸⁶. Four main SAP systems and representative examples are shown in Fig. 5. SAP scaffolds can function as carriers. SAP hydrogels loaded with chondroitinase ABC (ChABC) facilitated host neural regeneration and behavioral recovery in chronic SCI model rats, since the stable and sustained release of ChABC attenuated the inhibitory effect of chondroitin sulfate proteoglycans (CSPGs)⁸⁷. To further improve the properties of SAP scaffolds, they can be modified. For example, by mixing RADA₁₆ (the SAP) and FGL (the motif from a neural cell adhesion molecule), researchers prepared an FGLmx peptide hydrogel scaffold with the function of promoting NSC proliferation and migration⁸⁸. Hong et al. showed that RADA₁₆ modified with substance P

stimulated angiogenesis and enhanced functional improvement in rats with spinal cord contusion injury⁸⁹.

Nanomaterials

Some nanomaterials have electronic and catalytic properties that positively affect neural regeneration. GO and carbon nanotubes are two typical examples. By genipin crosslinking and lyophilization, Yang and coworkers fabricated a conductive GO-composited chitosan scaffold⁹⁰. It was shown to promote the oriented growth of nerve cells, angiogenesis, neuron migration and neural tissue regeneration. However, there is still debate regarding the toxicity of graphene-derived materials⁹¹. Bendable microfibers composed of reduced graphene oxide have been shown to promote cell adhesion without evident signs of subacute local toxicity⁹². In addition, to GO, Usmani et al. reported an artificial carbon nanotube-based scaffold that could improve motor function recovery in SCI model rats, possibly owing to regenerating fibers successfully crossing the lesion site⁹³. Some nanoparticles (NPs) have oxidation and reduction catalytic capabilities to relieve oxidative stress following SCI. For example, by dispersing manganese dioxide (MnO₂) NPs in a PPFLMLLKSTR peptide-modified hydrogel, Li et al. fabricated an MnO₂ NP-dotted HA hydrogel⁹⁴. In addition to promoting stem cell adhesion, growth and neural

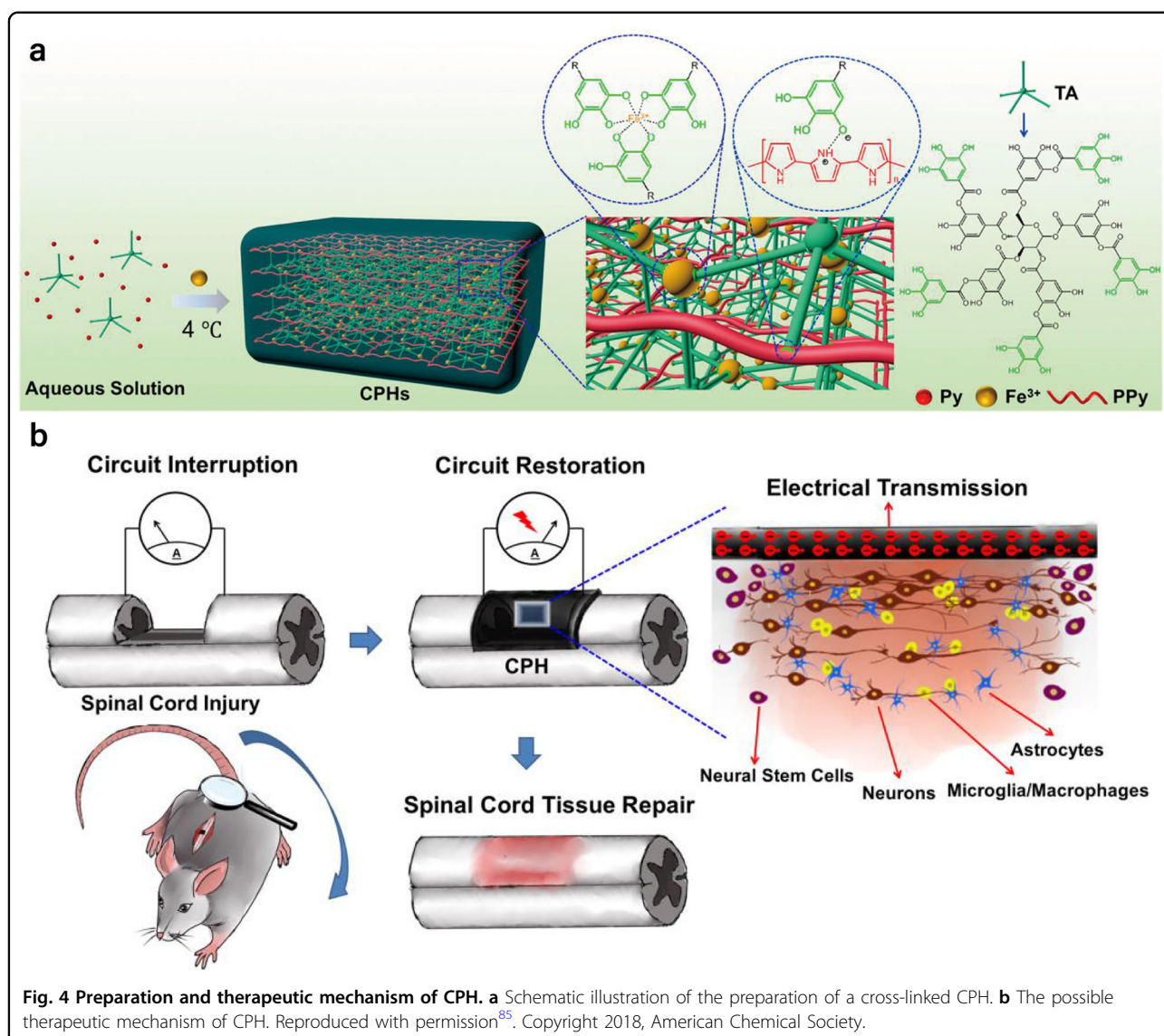


Fig. 4 Preparation and therapeutic mechanism of CPH. **a** Schematic illustration of the preparation of a cross-linked CPH. **b** The possible therapeutic mechanism of CPH. Reproduced with permission⁸⁵. Copyright 2018, American Chemical Society.

tissue bridging, it also alleviated the oxidative environment to effectively improve MSC viability (Fig. 6).

Hybrid Materials

Hybrid materials are mixtures of two nano- or molecular-scale components. They possess superior spinal cord tissue engineering properties with the advantages of synthetic, natural, and nanomaterials and have become a research hotspot in recent years. The RADA₁₆ hybrid hydrogel scaffold constructed by Zhai et al. possessed enhanced mechanical properties and slower degradation while retaining the nanostructure of the peptide and achieved remarkable results in animal experiments⁹⁵. By using Fmoc-grafted chitosan and Fmoc peptide, an injectable and self-healing hybrid hydrogel was developed with the ability to release curcumin slowly and persistently⁹⁶. It could facilitate functional recovery

after SCI by locally reassembling the ECM, modulating the local inflammatory response and recruiting Schwann cells to remyelinate the regenerated nerves. By constructing porous PLGA microcapsules loaded with neurotrophin-3 (NT-3) within GelMA hydrogel, Chiang et al. established a hierarchical hybrid GelMA-microcapsule hydrogel (HGMH)⁹⁷. As shown in Fig. 7, the HGMH platform provided a four-dimensional (4D) spatiotemporal distribution of NT-3, which induced NSC differentiation and migration, thereby promoting the full recovery after SCI in rats.

Fabrication Techniques

Hydrogel

Hydrogel is a functional polymeric material with 3D network structures that can swell and retain plenty of water in its structure⁹⁸. Many natural materials that are

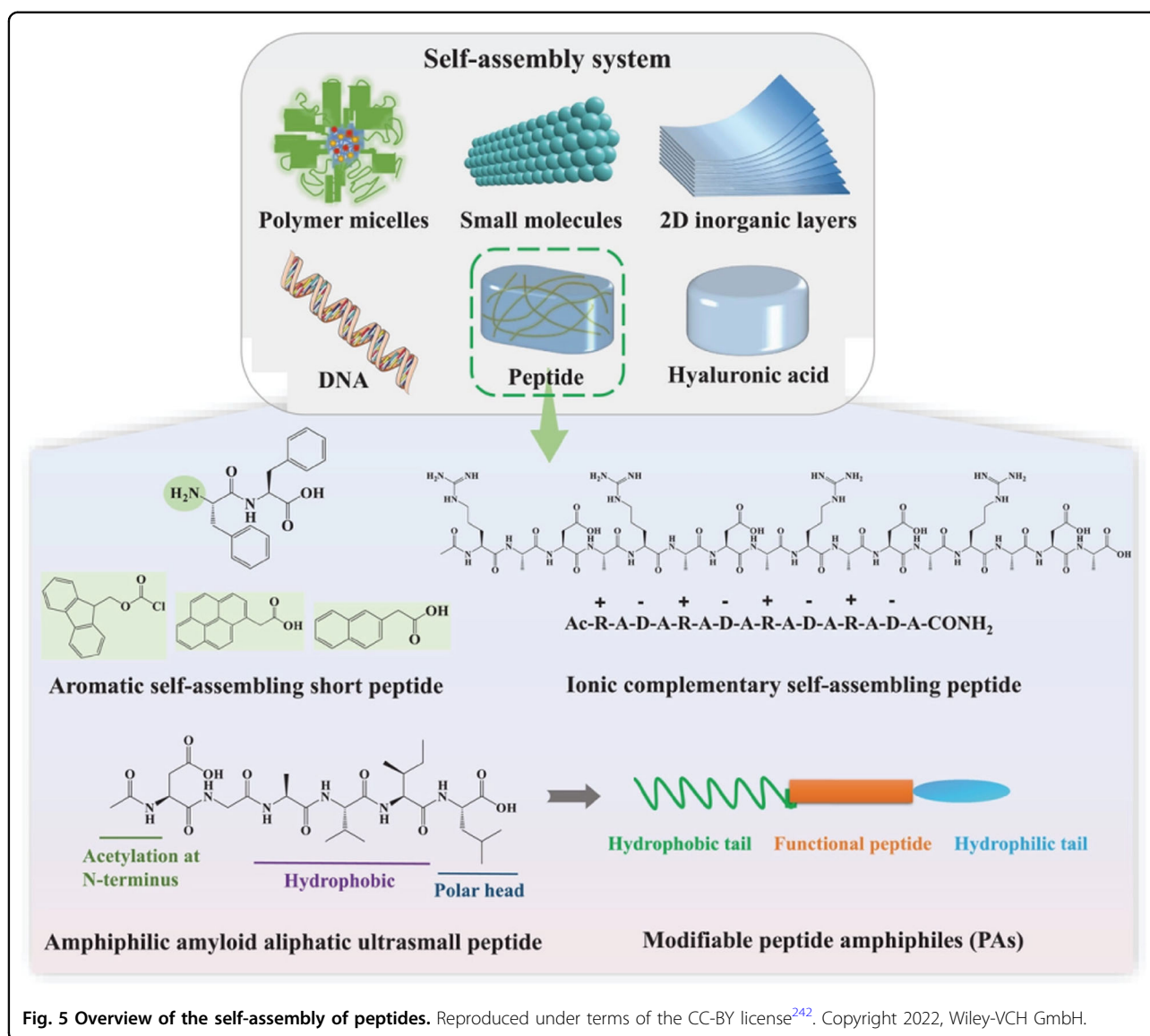


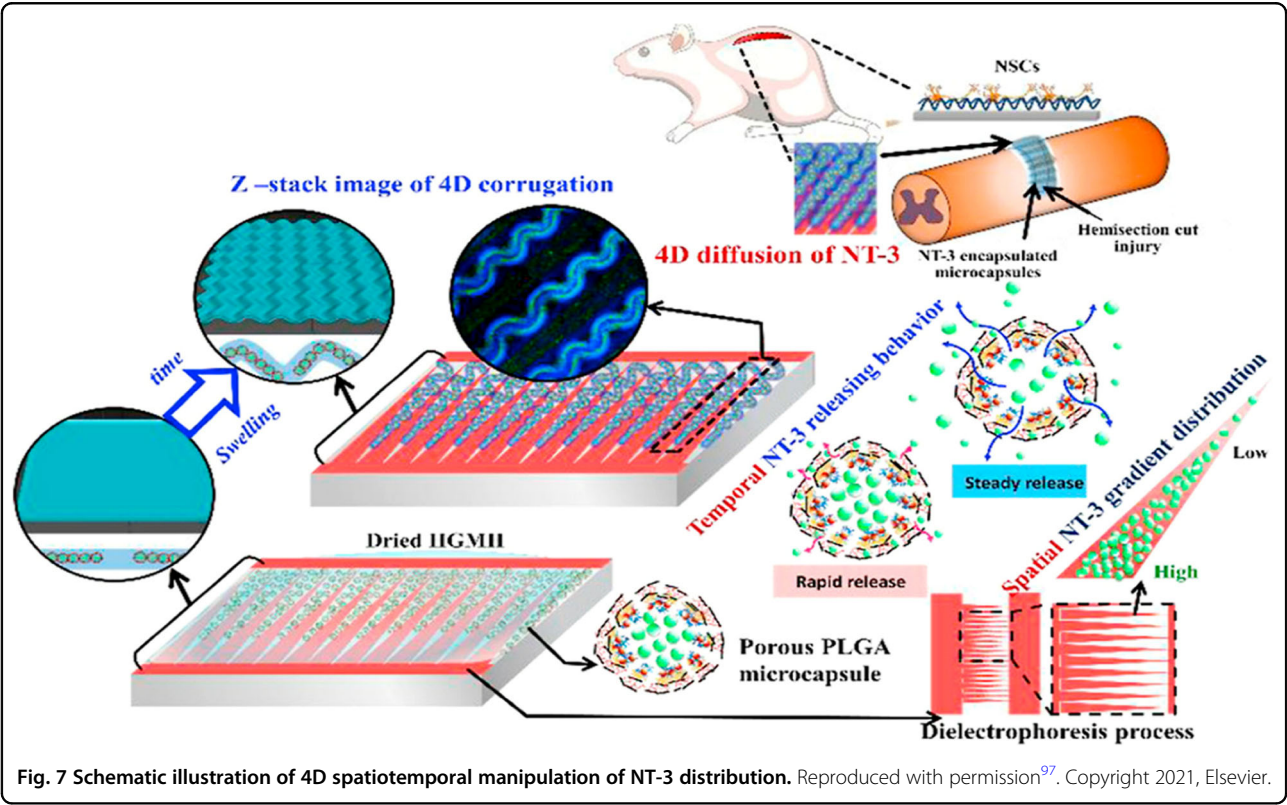
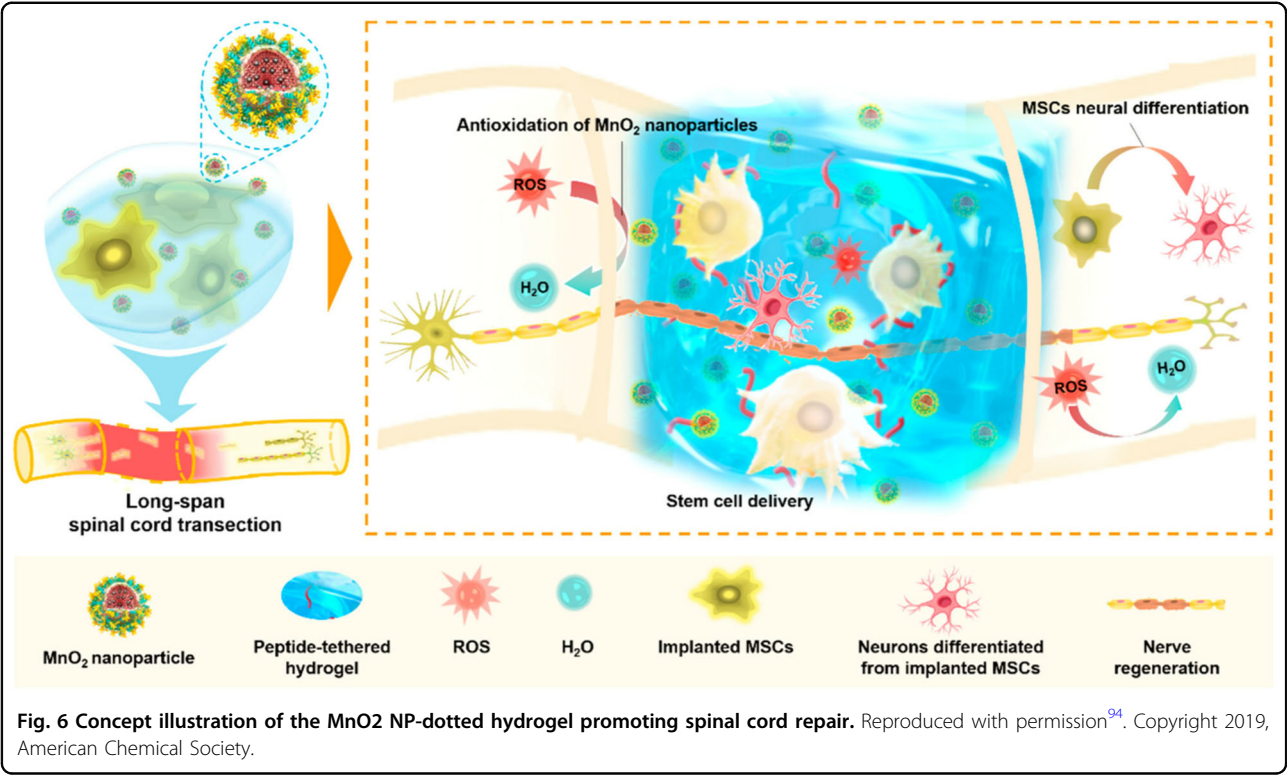
Fig. 5 Overview of the self-assembly of peptides. Reproduced under terms of the CC-BY license²⁴². Copyright 2022, Wiley-VCH GmbH.

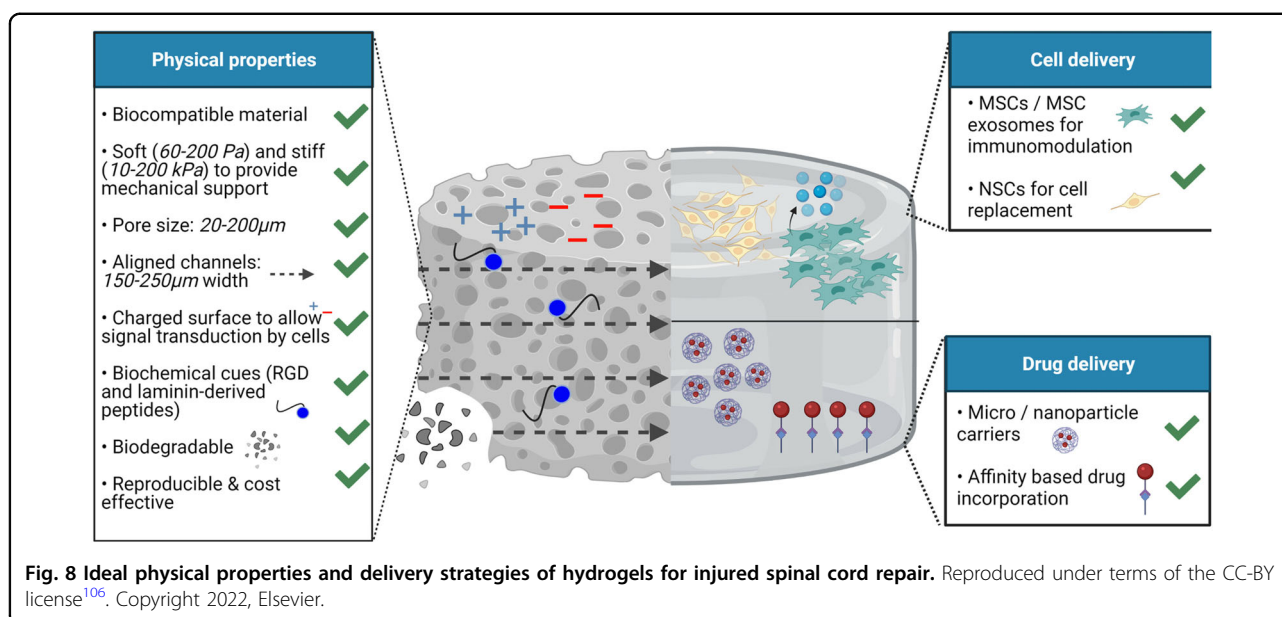
widely available and inexpensive can be prepared into hydrogels. Recently, the research and application of hydrogels have become increasingly abundant. However, simplex hydrogel scaffold materials often have difficulty accurately matching the size and shape of the defect in SCI, and the invasive implantation process can easily lead to secondary injuries⁹⁹. Injectable hydrogels offer a solution, as they can fill pathological defects with minimal surgical trauma by injecting flowable hydrophilic materials in situ. In addition, as suitable carriers for sustained drug release, injectable hydrogels have high drug loading efficiency, as well as the ability to uniformly and continuously release the loaded substances^{100,101}. They can also carry stem cells, such as NSCs⁶³ or MSCs¹⁰², to promote nerve regeneration and local microenvironment repair. Stimulus-responsive smart hydrogels, such as

conductive hydrogels^{68,103} and thermosensitive hydrogels¹⁰⁴, are another promising class of hydrogels that have provided new directions for SCI treatment. With multiple controllable properties in terms of time or space, these smart hydrogels can quickly respond to changes in the external environment to achieve the controlled release of drugs¹⁰⁵. Nevertheless, there are still many issues to be solved, including relatively weak mechanical properties (especially natural polymer hydrogels) and excessively high swelling properties. Walsh et al. summarized the ideal physical properties of hydrogels for injured spinal cord repair¹⁰⁶ (Fig. 8).

Electrospinning

The electrospinning technique refers to the process in which polymers in a molten or dissolved state are formed





into fibers under the action of a high-voltage electrostatic field. As a technique for preparing fibers with nano- to micron-scale diameters²⁶, it is widely used to create nerve scaffolds not only for its simple experimental equipment but also for its feasibility in controlling the morphological characteristics of fibers and porosity of fiber surfaces^{83,107}. The previously described AFG scaffold is a typical example³⁵, suggesting that oriented scaffold structures can promote cell migration and tissue regeneration, which is exactly the advantage of electrospinning. In addition, the electrospinning process enables the incorporation of all kinds of substances into nanofibers, such as proteins, low-molecular lipophilic drugs and nucleic acids.

3D Printing

Because of the highly spatially ordered cellular distribution and 3D structure of native spinal cord tissue, conventional 3D scaffolds have limitations in adequately and accurately controlling the external shape and internal architecture¹⁰⁸⁻¹¹⁰. An emerging technology, 3D printing, offers a solution because it enables the fabrication of individualized scaffolds that match the precise structure of SCI and provide a suitable microenvironment to stimulate and guide axon regeneration. Koffler et al. used the 3D printing technique to precisely construct the transverse architecture of gray and white matter of the spinal cord in rats and then grafted neural progenitor cells (NPCs) within the 3D scaffold¹¹¹ (Fig. 9). In this study, the combination of 3D biomimetic scaffolds and NSC grafts significantly enhanced host axonal regeneration into the lesion site and supported partial motor functional recovery, as assessed by the Basso, Beattie and Bresnahan (BBB) locomotor scale^{112,113}. In addition, astrocytic processes were strikingly

rearranged, penetrating into scaffold channels rather than forming a “wall” at the host/scaffold interface.

Decellularization Techniques

A variety of dECM scaffolds have been introduced above and have many advantages, such as suitable histocompatibility and low immune rejection. Furthermore, decellularization can remove inhibitory components to restore the balance of the SCI immune microenvironment¹¹⁴. The preparation methods of decellularized scaffolds include physical, chemical, and biological methods. In general, two or more methods are used in combination to preserve more of the physiological structure and biological activity of the ECM under the premise of maximizing decellularization¹¹⁵. In addition, the preparation method can be further improved. For instance, Xing et al. combined 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide cross-linking with chemical extraction methods, significantly improving the preparation efficiency of ASC scaffolds¹¹⁶. It is worth noting that appropriate and sufficient biological tissue sources are the biggest dilemmas limiting the development of this technology. The cryopreservation technique of meningeal tissues studied by Vishwakarma et al. solved this problem to a certain extent¹¹⁷. The different challenges that can be encountered during decellularization are summarized in Fig. 10.

Biomaterial-based therapeutic strategies for SCI

Strategies to limit the impact of secondary events

As mentioned above, the initial SCI triggers various secondary cascades that result in an inhibitory neuroregenerative microenvironment as well as an expanded lesion area. To restore normal function, managing these

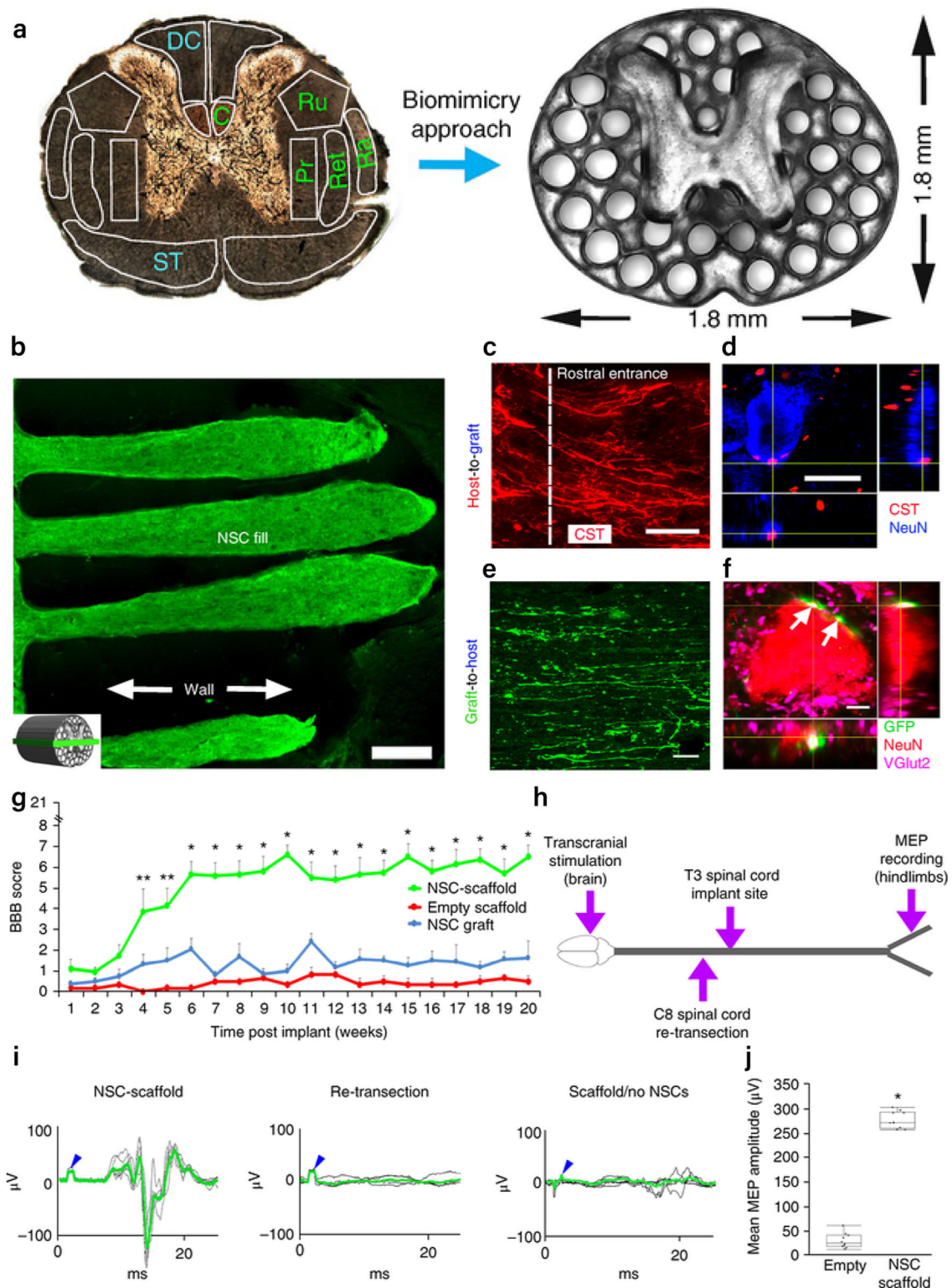
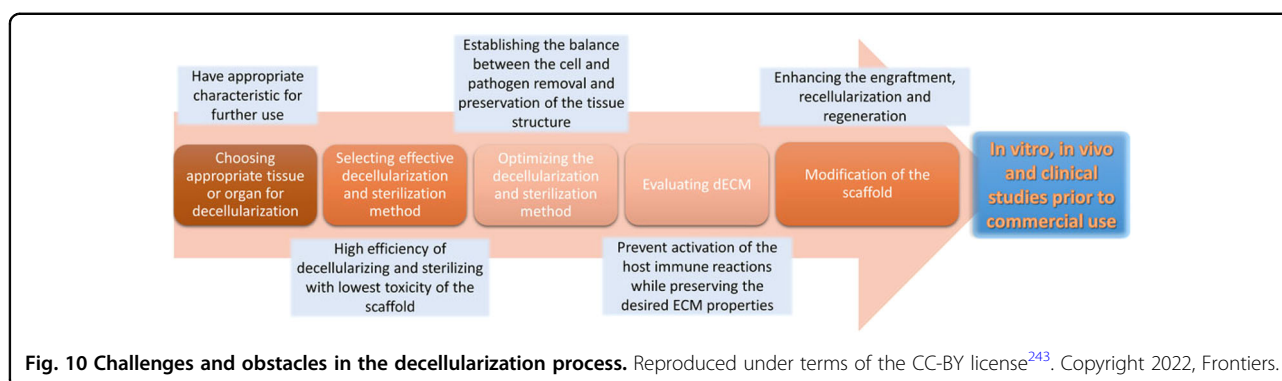


Fig. 9 3D-printed scaffold for injured spinal cord repair. **a** Schematic diagram of the 3D-printed scaffold. Fluorescence images of **b**) NPCs, **c**) Corticospinal axons, **d**) Corticospinal axons converging on a neuron, **e**) NPC-derived axons and **f**) Excitatory contacts (VGlut2) forming between NPC-derived axons and host neurons. **g** BBB motor scores. **h** Schematic diagram of the electrophysiology study. **i** Motor evoked potential (MEP) responses. **j** Mean MEP amplitude. Reproduced with permission¹¹¹. Copyright 2019, Springer Nature.



secondary cascades is an important first step¹¹⁸. Below, we identify four broad targets for intervention.

Managing inflammation

After SCI, activated immune cells infiltrate the lesion site, releasing inflammatory factors and ROS. These prolonged immune and inflammatory cascades lead to secondary damage. Hence, it is beneficial to deliver anti-inflammatory treatments to modulate the immune microenvironment of SCI¹¹⁹.

Biomaterials commonly function as carriers for the local delivery of anti-inflammatory drugs. For example, by using PLGA NPs embedded in agarose gel, low doses of 17- β estradiol were focally delivered to the contused spinal cord, eliciting rapid anti-inflammatory effects¹²⁰. An injectable PLGA-PEG-PLGA thermosensitive hydrogel designed by Zheng et al. controllably released the JAK1/2 inhibitor baricitinib, which led to decreased expression levels of inflammatory cytokines and improved functional recovery¹²¹. Intriguingly, local delivery of flavopiridol, a proliferation inhibitor originally developed to treat chronic lymphocytic leukemia¹²², in PLGA NPs was also proven to improve recovery from SCI by inhibiting inflammatory factor synthesis¹²³. In addition to conventional drugs, biomaterials can deliver endogenous biological signaling molecules to suppress inflammation. By activating nuclear factor-erythroid 2-related factor 2 protein, H₂S exerted a series of neuroprotective effects on SCI model rats, including reducing the secretion of inflammatory factors, oxidative stress, and nerve cell apoptosis¹²⁴. Jiang et al. reported a near-infrared light-triggered NO-releasing system, which was constructed with upconversion NPs coated by zeolitic imidazolate framework-8 and an NO photochemical donor¹²⁵. In vivo experiments proved that NO can effectively inhibit gliosis and inflammation, promote neural regeneration and protect neurons from apoptosis.

Biomaterials can have innate anti-inflammatory properties. Chitosan, for example, can control inflammation by inhibiting the secretion of TNF- α and IL-6¹²⁶. Ferulic acid-modified glycol chitosan NPs can not only suppress

astrogliosis and inflammation but also preserve axons and myelin¹²⁷. Partially reduced GO scaffolds were able to attenuate the inflammatory response while supporting angiogenesis¹²⁸. Polylaminin, a polymeric form of laminin, also exerts an unsuspected anti-inflammatory effect, which may involve interfering with macrophage recruitment to the lesion site¹²⁹. Austin et al. proved that intrathecal injection of a hyaluronan and methyl cellulose hydrogel could dampen SCI-related arachnoiditis and improve functional recovery¹³⁰.

Reducing oxidative stress

Superoxide, hydrogen peroxide, and hydroxyl radicals are three physiologically relevant ROS, the production and elimination of which are tightly controlled. After SCI, excess ROS are released into the extracellular microenvironment, disrupting this equilibrium. Reducing ROS is often a byproduct of reducing inflammation, but it equally deserves attention, given that inflammation is not the only source of ROS¹¹⁸. The intake of antioxidant molecules is a countermeasure to reduce ROS, but they have limitations such as easy degradation, poor water solubility, and low bioavailability¹³¹. Fortunately, the antioxidant properties of natural and synthetic compounds have been extensively studied, leading to the development of new therapeutic strategies.

Some materials can reduce ROS levels as a result of their intrinsic properties or ROS-responsive functional groups. Taking PEG as an example, without the ability to scavenge free radicals by itself, it can still inhibit injury-induced ROS production by mediating plasma membrane repair¹³². Further studies have shown that PEG may also interact with mitochondria directly to inhibit abnormal oxidative metabolism, which plays a dominant role in the later stage of repair¹³³. However, the application of PEG has limitations in terms of concentration and molecular weight. Cho et al. thus developed PEG-decorated silica NPs (PSiNPs), which showed better membrane-sealing properties than uncoated particles or PEG alone. Further in vivo tests demonstrated that PSiNPs significantly reduced ROS production¹³⁴. Unlike

PEG, some polymers have the ability to scavenge ROS. In general, these chemical functional groups can be present in biomaterials, and the mechanisms by which they can reduce ROS levels mainly involve solubility or chemical bond changes¹³⁵. For instance, in the presence of ROS, thioether can be converted to hydrophilic sulfoxide and sulfone groups. Zhang et al. synthesized a high-density thioether-containing polymer to construct ROS-scavenging lipid-polymer NPs, denoted as PELPNPs¹³⁶. The results showed that PELPNPs could readily scavenge overproduced ROS, thereby reducing secondary injury and promoting functional recovery in a rat spinal cord contusion model (Fig. 11).

Developing delivery systems for antioxidant drugs is an effective strategy. For example, as the main active ingredients of the traditional Chinese medicines Huangqi and Danshen, Astragalus polysaccharide (APS) and tanshinone IIA (TSIIA) have suitable antioxidant activities. Rao et al. utilized selenium NPs as delivery vehicles to improve the bioavailability of APS and TSIIA, demonstrating a positive therapeutic antioxidative effect on SCI¹³⁷. Resveratrol (RES) is a nonflavonoid polyphenol compound with important functions, such as antioxidant and anti-free radicals. Based on this, researchers prepared functional resveratrol-biodegradable manganese-doped silica NPs, referred to as PMMSN-RES. As a sustained-release formulation, PMMSN-RES effectively delivered resveratrol to the spinal cord, mitigated oxidative stress, reduced neuronal apoptosis and inhibited inflammation, thus promoting the recovery of mouse motor function¹³⁸.

Nanozymes refer to nanomaterials with enzyme-like characteristics that can mimic natural antioxidant enzymes to react with ROS¹³⁹. A type of well-known nanozyme is cerium oxide NPs (CONPs), which can be either a superoxide dismutase mimic or a catalase mimic depending on the Ce^{3+}/Ce^{4+} ratio¹⁴⁰. Administration of CONPs to SCI model rats can improve their motor function and attenuate inflammation and apoptosis¹⁴¹. It is noteworthy that there is an optimal therapeutic dose range, above which CONPs might be cytotoxic and adversely affecting functional recovery. MnO_2 , another type of nanozyme, can effectively improve the viability of MSCs by alleviating the oxidative environment⁹⁴, which reveals the synergistic role of cell-based therapy and microenvironment regulation in SCI treatment. Iron oxide NPs (IONPs) also have the ability to scavenge free radicals¹⁴². The combination of IONP implantation and magnetic field exposure has been shown to significantly promote functional recovery and reduce lesion volume in SCI model rats.

Restoring the Blood–Spinal Cord Barrier

The BSCB is a blood–brain barrier-like structure that exists in spinal cord tissue. Normally, the diffusion of

molecules and cells across the BSCB is highly regulated by tight junctions (TJs), allowing the CNS to function as an isolated system¹⁴³. Structural disruption and increased permeability of the BSCB are universal consequences of SCI, leading to the infiltration of immune cells and inflammatory factors into the stroma¹⁴⁴. Moreover, BSCB damage is long-lasting. Dynamic contrast-enhanced MRI showed that the BSCB remained impaired 56 days post-SCI¹⁴⁵. Given that BSCB disruption mediates secondary and long-term damage, its restoration appears particularly important.

Biomaterials can restore the BSCB by delivering drugs to certain targets. For example, curcumin has been proven to improve the integrity of the BSCB by attenuating inflammatory factors and upregulating TJ protein expression¹⁴⁶. Incorporating curcumin into a polyacetal increased its bioavailability and stability, thereby enhancing neuroprotection and improving functional recovery in acute SCI¹⁴⁷. Joshi et al. incorporated carbon monoxide–releasing molecule-2 (CORM-2) into a solid lipid NP (CORM-2-SLN) to improve its short carbon monoxide release half-life¹⁴⁸. In vivo experiments showed that compared with CORM-2 alone, CORM-2-SLN effectively rescued endothelial cell damage and prevented BSCB disruption, but the exact mechanism remains to be clarified. In another study, a thermosensitive heparin-polyoxamer hydrogel was developed to load and deliver acidic fibroblast growth factor, which has an SCI-protective effect¹⁰⁴. This composite hydrogel reduced the loss of junction proteins and thus prominently attenuated BSCB disruption, providing a successful SCI protection strategy.

Cell transplantation is another way biomaterials can restore the BSCB. For instance, a two-component polymer implant seeded with NPCs and endothelial cells promoted the formation of stable, functional blood vessels, half of which stained for endothelial barrier antigen, indicating that BSCB was being re-established¹⁴⁹. After transplantation of microvascular cells within the self-assembling polypeptide scaffold RADA-16I, microvessels with BSCB integrity were successfully formed, alleviating secondary SCI events such as inflammation and scar formation¹⁵⁰. MSCs also exert a positive effect on BSCB recovery. Intravenous delivery of MSCs reduced the permeability and leakage of the BSCB, resulting in its stabilization^{151,152}. Providing a carrier material for MSCs may enhance this effect. A unique PLGA scaffold can augment the stemness, engraftment, and function of hMSCs¹⁵³. These scaffolds of nontransdifferentiated hMSCs exhibited multimodal effects, including angiogenesis-promoting effects. Nevertheless, this study did not explore BSCB recovery.

Reducing Glial Scarring

After SCI, astrocytes proliferate, become hypertrophic and form glial scars¹⁵⁴. Glial scars not only act as a

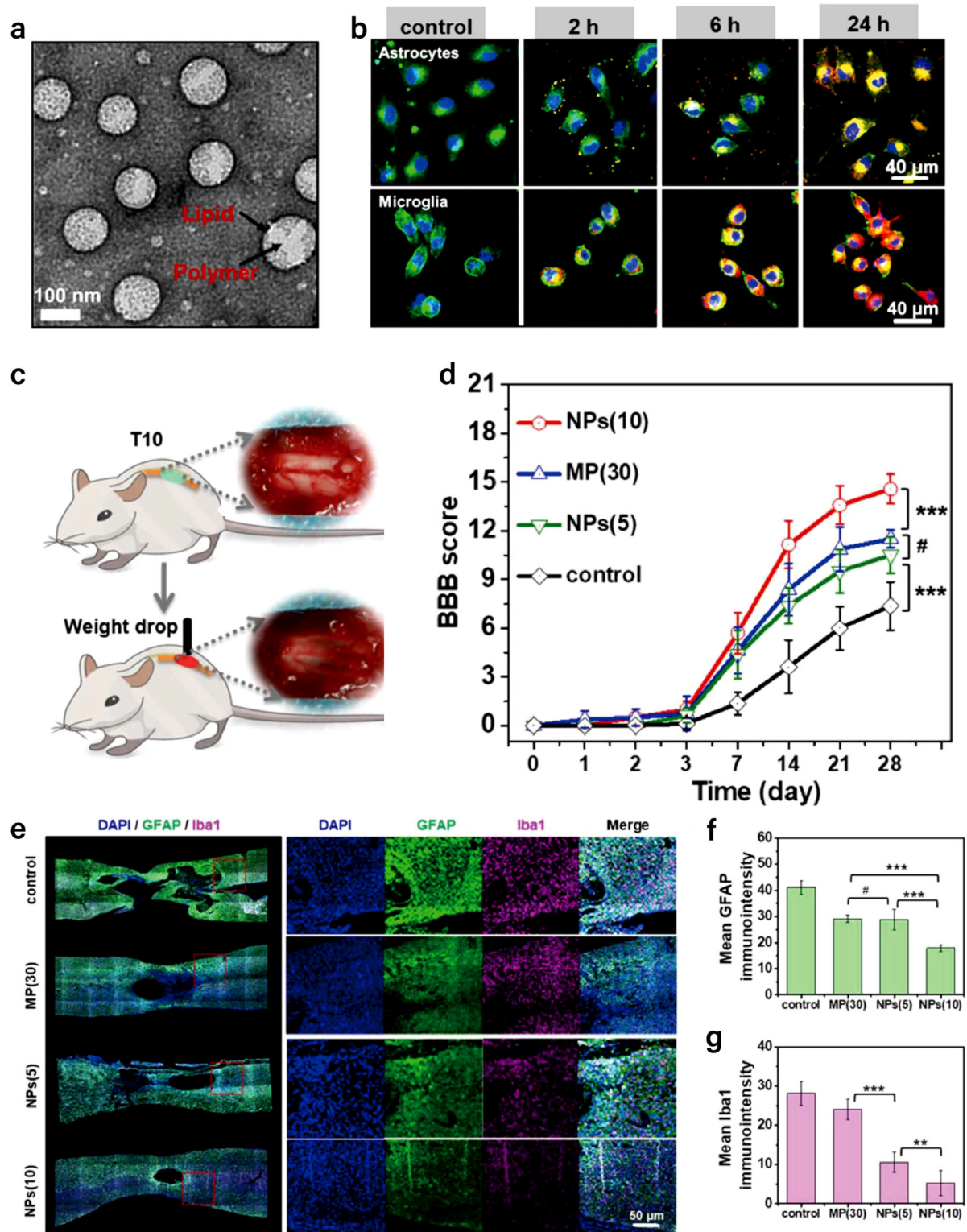


Fig. 11 PELPNPs for ROS scavenging. **a** Transmission electron microscope image of PELPNPs. **b** Cellular uptake of PELPNPs (red). **c** An SCI model of T10 contusion. **d** BBB scores of rats injected with 5% glucose solution (control group), 10 mg kg⁻¹ PELPNPs (NPs (10) group), 5 mg kg⁻¹ PELPNPs (NPs (5) group), and 30 mg kg⁻¹ methylprednisolone (MP (30) group). **e** Immunohistochemistry images of GFAP and ionized calcium binding adapter molecule 1 (Iba1) in the damaged spinal cord on day 28 after injury. Quantitative analysis of the mean immunointensity of **f** GFAP and **g** Iba1. Reproduced with permission¹³⁶. Copyright 2021, Elsevier.

physical barrier to axon regeneration but also contain inhibitory chemical components represented by CSPGs^{155–157}. In 2002, a study demonstrated that ChABC could reduce glial scar formation to promote SCI recovery¹⁵⁸. Since then, numerous SCI studies have concentrated on regulating glial scarring, either by altering astrocyte behavior or targeting CSPGs¹¹⁸. Therefore, our subsequent discussion will thoroughly explore into these two aspects.

Glial scar formation can be reduced by alleviating astrocyte activation or infiltration, which is mainly applicable to acute SCI. Biomaterials can function through inherent properties. For example, alginate/chitosan/genipin hydrogel composites reduced astrocyte reactivity in vitro while sequestering extracellular Ca^{2+} to prevent Ca^{2+} -induced secondary injury¹⁵⁹. A new aligned hydrogel microfiber scaffold constructed using photocrosslinked gelatin methacryloyl and electrospinning technology significantly reduced astrocyte activity in vivo, thus inhibiting glial scar formation¹⁶⁰. For biomaterial-based drug delivery systems, targeting the injury site could improve efficacy and avoid systemic side effects of high-dose therapy. A peptide CAQK identified via in vivo phage display screening can specifically target brain and nerve injury sites^{161,162}. Accordingly, Sun et al. grafted the FITC fluorescent molecule and CAQK peptides onto the surface of arctigenin-loaded mesoporous silica NPs to target the SCI site¹⁶³. Arctigenin is an anti-inflammatory agent isolated from the Chinese medicinal herb *Arctium lappa*. In addition, the size of this nanocarrier, approximately 100 nm, enabled it to penetrate the BSCB. Experiments showed that this nano-drug platform can inhibit the activation of astrocytes, a process in which the molecular mechanisms involve IL-17. Compared to targeting damaged sites, directly targeting astrocytes is apparently a more attractive strategy. A nanogel consisting of copolymers of PEG and PEI with high selectivity toward astrocytes was developed¹⁶⁴. Functionalization with both NH_2 and Cy5 groups limited uptake by macrophages, allowing it to be exclusively internalized in astrocytes. After endocytosis, nanogels undergo degradation by lysosomes to release compounds with potential therapeutic effects, such as rolipram.

Existing scars can be degraded by targeting CSPGs, which is mainly suitable for chronic SCI. As the most commonly used scar-degrading biomolecule, ChABC can specifically and efficiently cleave glycosaminoglycan (GAG) chains inside CSPGs¹⁶⁵. However, its low bioavailability and poor thermal stability may limit its applications, for which biomaterials could provide a solution. For example, ChABC was encapsulated in a hydrogel based on SAPs named FAQ for long-term release with high activity for up to 42 days in vitro⁸⁷. Injection of this hydrogel resulted in the degradation of gliotic scars and

locomotor recovery improvement in chronic SCI model rats. PLGA NPs were also able to protect enzymes from decomposition while controlling their release¹⁶⁶. The immunohistochemistry results demonstrated glial scar degradation in the ChABC-treated particle group, with the BBB score indicating remarkable functional improvement compared with the other groups. However, this study did not include a direct ChABC-treated control group, so it was not possible to specifically assess the improvement brought by NP administration. For greater therapeutic efficacy in vivo, combination with other drugs or neurotrophic factors is appealing. Sustained and combinatorial delivery of ChABC and NT-3 facilitated by a hydrogel-microtube scaffold system can enhance axonal sprouting and functional recovery after SCI¹⁶⁷. Notably, the chondroitin sulfate GAG levels remained markedly decreased for up to 6 weeks.

However, a study demonstrated that the lack of reactive astrocytes after SCI led to an obvious inflammatory response, BSCB repair failure, and pronounced motor defects¹⁶⁸. Anderson et al. used a gene-targeted knockout approach in adult mouse SCI models to show that none of preventing astrocyte scar formation, attenuating scar-forming astrocytes or deleting chronic astrocytic scars resulted in the spontaneous regrowth of transected corticospinal, sensory or serotonergic axons²⁰. Hence, the hypothesis that axonal regeneration can be promoted by only reducing glial scars may be oversimplified, as it ignores that early glial scars can limit the spread of inflammation. Transplantation of peripheral blood-derived MSCs may provide a solution. In this study, the levels of the astrocyte biomarker glial fibrillary acidic protein (GFAP) were initially increased followed by a decrease, suggesting that PB-MSC transplantation could promote glial scar formation in the early stage but inhibit it in the later stage¹⁶⁹. Furthermore, simply targeting CSPG or astrocytes to modulate glial scar formation may lead to inaccurate conclusions because other cells and extracellular components are also involved in the formation of the glial scar¹⁵⁴. Taken together, there is still a long way to go to fully and correctly understand the effects of reducing glial scars in SCI.

Strategies to enhance neurorestoration

On the basis of managing secondary inflammatory cascades, neurorestoration should also be strengthened, as it is indispensable to achieve functional recovery, the ultimate goal of injured spinal cord repair. The following sections outline three biomaterial-based strategies to enhance neural repair.

Stimulation of axonal regeneration

The overwhelming cell death in SCI causes the formation of multiloculated, perilesional microcysts, which

eventually combine to form larger cavities that are detrimental to axonal regeneration¹⁷⁰. Therefore, bioscaffolds that can act as a bridge and guide axon regeneration are attractive. Among them, injectable hydrogels have been extensively studied because they can conform to the irregular shape of the lesions, providing ideal contact between the severed spinal cord stumps and the biomaterial¹⁷¹. Porous scaffolds, a more advanced biomaterial implant, are effective in regenerating axons because they not only exhibit higher mechanical stability and longer degradation periods than hydrogels but also support and guide the organized and linear growth of injured axons^{172,173}. However, the geometry of porous scaffolds is determined before implantation, while injury sites tend to be quite irregular, making it difficult to find an optimal design for each unique spinal lesion^{171,174}. Additionally, scaffolds of synthetic molecules that mimic proteins can transmit cellular signals to promote tissue regeneration. Recently, a study published in *Science* reported the development of a supramolecular scaffold of nanoscale fibrils that integrates two different orthogonal biological signals to activate the transmembrane receptor β -1 integrin, the basic fibroblast growth factor 2 receptor and their respective downstream effectors¹⁷⁵. Intensifying the motions of molecules within scaffold fibrils could optimize cell signaling, leading to significant improvements in axonal regeneration, myelination, and functional recovery.

Scaffolds can incorporate growth-promoting molecules to accelerate axonal growth through the lesion. For instance, as a class of small, well-conserved noncoding RNAs, microRNAs (miRs) play a vital role in neural development and function¹⁷⁶. The delivery of a cocktail of miR-132/miR-222/miR-431 along with glial cell-derived neurotrophic factor (GDNF) using a 3D fiber-hydrogel scaffold significantly promoted and preserved mature axon regeneration and survival¹⁷⁷. Additionally, when combined with methylprednisolone (MP), functional recovery was further enhanced without alteration in axon regeneration (Fig. 12). Courtine and Sofroniew demonstrated that a combination of temporally controlled and spatially targeted delivery of neuronal intrinsic growth factors, growth-supportive substrates, and chemoattractant factors could stimulate robust propriospinal axon regrowth¹⁷⁸. Unfortunately, little improvement in locomotor function was detected. Another common strategy is to seed scaffolds with cells that produce neurotrophic factors, such as bone marrow stromal cells^{69,71} and genetically altered fibroblasts^{179–181}. Optimized scaffolds with porous structures may facilitate the long-term survival of these transplanted cells¹⁷⁴.

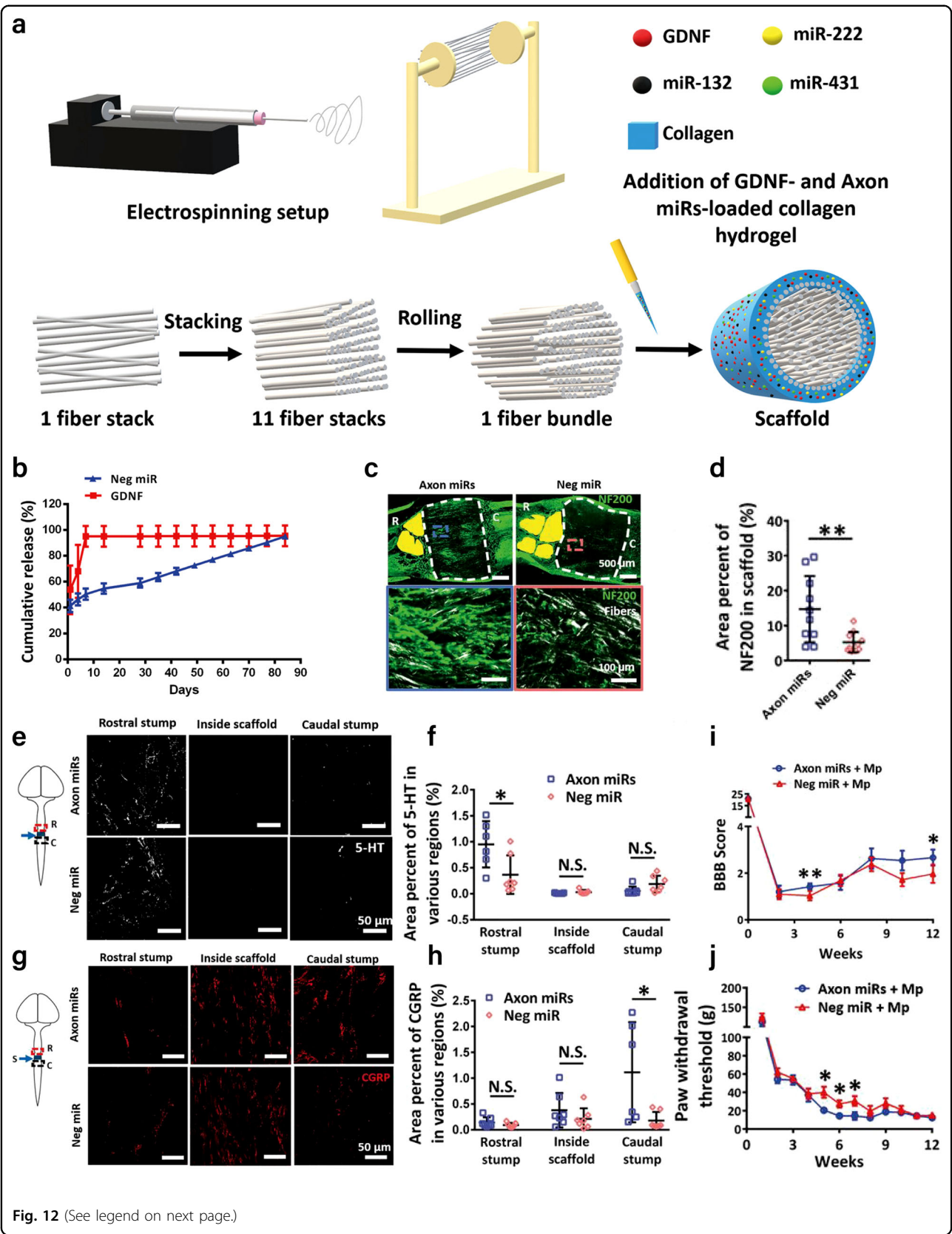
Formation of a neuronal relay network

Although axon regeneration after SCI has been extensively studied, it remains difficult to stimulate the

regeneration of brain-derived descending axons, such as the corticospinal tract (CST), across the SCI area to innervate target neurons¹⁸². Providing an interneuronal network to relay neural information through the defect area may be a feasible solution. This neuronal relay repair strategy has been detailed in many reviews^{182–187}. This article only provides a brief overview from the perspective of biomaterials.

The endogenous neuronal relay strategy refers to activating and inducing endogenous stem cells to differentiate into neurons to form a neural network at the SCI site. Based on this concept, scientists have developed a series of functionalized bioscaffolds to specifically induce adhesion, migration, proliferation, and neuronal differentiation of endogenous NSCs. For example, a combined treatment of photocrosslinked hydrogel transplantation and PLX3397, a colony-stimulating factor 1 receptor inhibitor, suppressed inflammation mediated by microglia/macrophage, thereby promoting the neurogenesis of endogenous neural stem/progenitor cells and improving functional recovery in complete transection SCI model mice¹⁸⁸. Recently, a novel biodegradable material called “Bio-C” was constructed by combining collagen with high molecular weight HA. This material has been shown to enhance neural regeneration and motor-functional restorations in SCI model mice¹⁸⁹. Further in vitro experiments showed that Bio-C promoted the proliferation of NSCs and their differentiation toward neuronal lineages. These studies suggest that programming endogenous NSCs might be a feasible strategy for motor function recovery rather than exclusively pursuing CST regeneration. However, the complexity and diversity of endogenous spinal cord NSCs cannot be ignored. Different endogenous NSCs postinjury might have distinct activation-inducing factors, signalling pathways, time courses, and differentiation capacities and profiles¹⁸³. Further research is needed to improve and optimize this repair strategy.

In cases of severe SCI (e.g., completely transected SCI), depletion or insufficient mobilization of endogenous NSCs may occur, necessitating supplementation with exogenous NSCs. This supplementation is a part of the exogenous neuronal relay repair strategy. For example, researchers developed a functional collagen scaffold by loading liposomes encapsulated with the microtubule-stabilizing agent paclitaxel into a collagen microchannel scaffold¹⁹⁰. Animal experiments proved that this scaffold provided a suitable microenvironment for mature neuronal differentiation of grafted NSCs. Recently, a highly permeable DNA supramolecular hydrogel was designed to repair completely transected SCI in rats¹⁹¹. This DNA hydrogel was found to facilitate both implanted and recruited NSCs to migrate, proliferate, and differentiate sufficiently, thereby promoting the formation of a



(see figure on previous page)

Fig. 12 Delivery of miRs and GDNF for axonal regeneration. **a** Schematic diagram of the fabrication of the 3D fiber-hydrogel scaffold. **b** Cumulative release of negative miR (Neg miR) and GDNF. **c** Representative fluorescence images of neurofilament 200 (NF200) staining. **d** Quantification analysis of NF200⁺ area. **e** Representative fluorescence images of 5-hydroxytryptamine (5-HT) staining. **f** Quantification analysis of 5-HT⁺ area. **g** Representative fluorescence images of calcitonin gene-related peptide (CGRP) staining. **h** Quantification analysis of CGRP⁺ area. **i** BBB scores in the presence of MP. **j** Von Frey Hair test in the presence of MP. NF200 is a marker of mature axons; 5-HT and CGRP are markers for different types of axons, labeling serotonergic and sensory axons, respectively. Reproduced under terms of the CC-BY license¹⁷⁷. Copyright 2021, Wiley-VCH GmbH.

continuous regenerative neural network. Within 8 weeks, the rats recovered basic hindlimb function with detectable motor-evoked potentials. However, challenges persist with exogenous neuronal relay strategies, including abnormal proliferation, slow differentiation and maturation, and long-distance migration of transplanted NSCs in vivo¹⁸². In terms of clinical translation, there are also enormous challenges to face, such as immune rejection, the risk of neoplasm and teratoma formation¹⁸³. In short, a considerable amount of work remains to be done before exogenous NSCs can be applied in SCI treatment.

Recently, tissue engineering strategies for nerve repair and regeneration have been rapidly developed. For complete SCI, this strategy can meet the diverse needs of spinal cord structural and functional repair through a delicate combinatorial design of biomaterials, seed cells, and bioactive factors. Based on this, Zeng's team constructed exogenous neural network tissue^{192–195}, proposing the hypothesis of tissue-engineered neuron relays to repair spinal cord defects¹⁹⁶. By combining NSCs, a collagen scaffold, and neurotrophic factors and their receptors, they further constructed spinal cord-like tissue (SCLT) in vitro for the first time¹⁹⁷. Transplantation of this SCLT into a 2 mm completely transected spinal cord defective area significantly promoted the regeneration of brain-derived descending axons and the neurons derived from NSCs established synaptic connections with descending axons to transmit brain-derived excitatory neural information and promote motor function recovery. However, nascent neurons serving as relays typically require months to functionally integrate into the host spinal cord neural networks¹⁸⁷. Before that, functional silencing or disuse atrophy can occur. Therefore, the stem cell-derived neuronal relay strategy should be combined with rehabilitation physiotherapy, such as functional electrical stimulation, to restore the innervation of spinal cord motor neurons to target muscles as soon as possible¹⁸².

Promotion of remyelination

Another pathway to functional recovery after SCI is to promote axonal remyelination, which depends on the health and availability of oligodendrocyte progenitor cells (OPCs)¹⁷⁴. However, the highly inhibitory postinjury microenvironment not only hinders the migration of

remaining endogenous OPCs to the demyelinating site but also strongly influences the fate of transplanted exogenous OPCs^{198–200}. A possible solution is to use biomaterial systems that can create supportive niches for transplanted cells, thus enhancing remyelination.

Some biomaterials can serve as candidates for OPC transplantation. ECM-mimicking hydrogels are useful biomaterials for regeneration. For example, a highly biocompatible HA/gelatin hydrogel crosslinked by poly(ethylene glycol) diacrylate was developed to provide a permissive microenvironment for the survival, oligodendrogenic differentiation, and remyelination of transplanted OPCs²⁰¹. This study also found that hydrogels of medium stiffness (at an elastic modulus of approximately 120 Pa) can best support the natural oligo-morphology and proliferation of OPCs. Similarly, Führmann et al. synthesized a hyaluronan and methylcellulose (HAMC) hydrogel modified with an RGD peptide and platelet-derived growth factor (PDGF-A)²⁰². In addition to promoting early survival and integration of transplanted OPCs, this hydrogel could also promote their differentiation to attenuate teratoma formation, which is one of the major challenges in the transplantation of pluripotent stem cells and their differentiated counterparts (Fig. 13). Electrospun fibers are another instructive biomaterial. For instance, PCL electrospun nanofibers have been shown to support the growth and differentiation of OPCs, and copolymerization with gelatin could further enhance myelination²⁰³. In another study, electrospun fibers were utilized as artificial axons to investigate how fiber (axon) diameter affects OPC myelination²⁰⁴. Researchers determined the minimum fiber diameter threshold to be 0.4 μm , above which the fiber diameter was sufficient to initiate concentric wrapping by rat primary oligodendrocytes. In summary, OPCs differ from other CNS cell types in many ways and thus may have different requirements for biomaterial properties²⁰⁰.

NSCs also have the potential to differentiate into oligodendrocytes, providing new ideas for promoting remyelination. For instance, a soft methacrylamide chitosan hydrogel with a Young's elastic modulus ($E(Y)$) < 1000 Pa promoted NSC differentiation into neurons and astrocytes, while stiffer scaffolds ($E(Y)$ > 7000 Pa) drove oligodendrocyte differentiation²⁰⁵. By providing instructive physical cues, a unique graphene-nanofiber hybrid

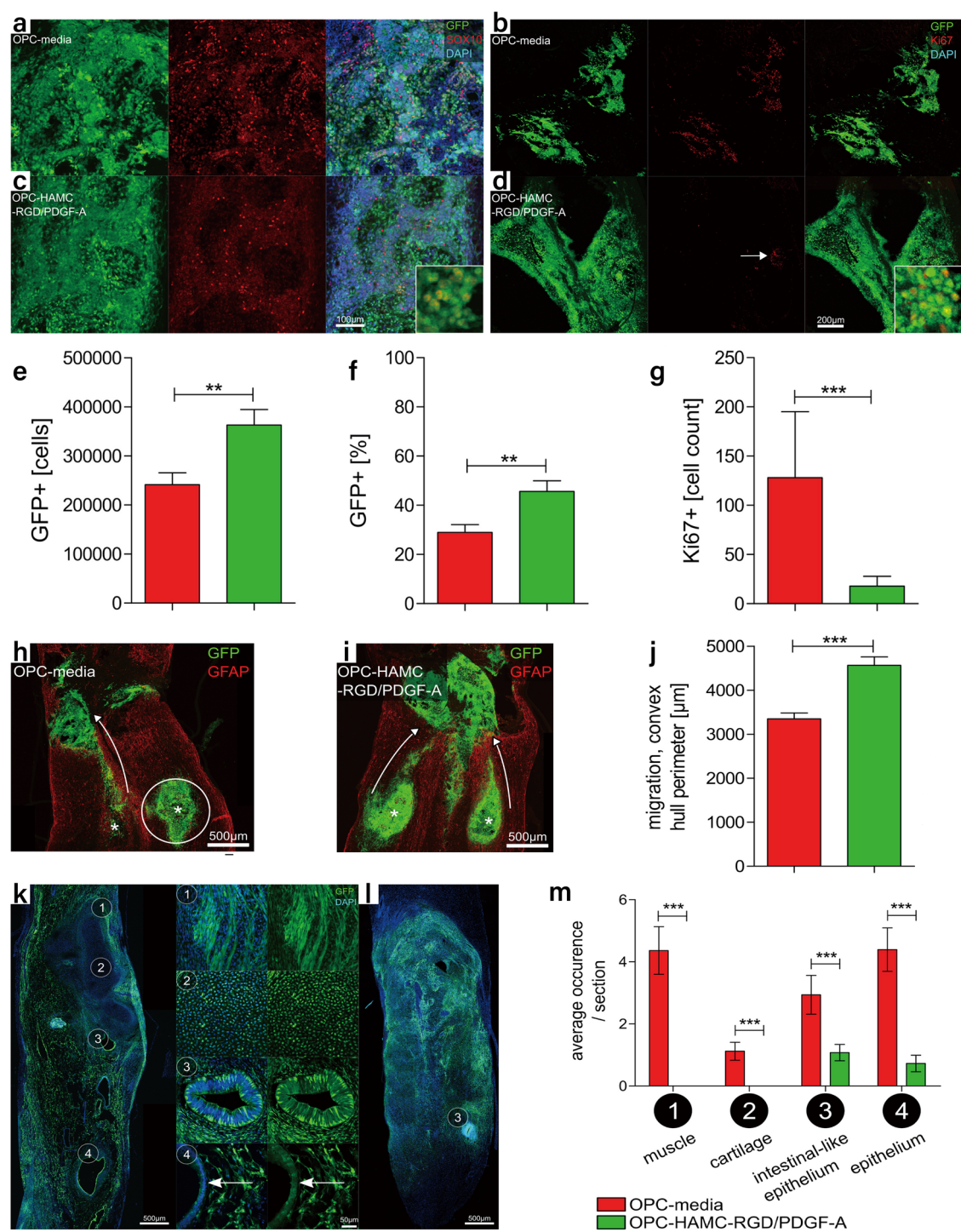


Fig. 13 HAMC-RGD/PDGF-A for OPC transplantation. **a, b** Representative fluorescence images of SOX10 (the OPC marker) and Ki67 (the proliferation marker) staining after cells were transplanted in media. **c, d** Representative fluorescence images of SOX10 and Ki67 staining after cells were transplanted in HAMC-RGD/PDGF-A. **e** Count of green fluorescent protein-positive (GFP⁺) cells. **f** Proportion of GFP⁺ cells to initial cells. **g** Count of Ki67⁺ cells. **h, i** Migration of injected cells in media and HAMC-RGD/PDGF-A. **j** Quantification of migration degree. **k, l** Nonspinal cord structures in the OPC-media group and OPC-HAMC-RGD/PDGF-A group. **m** Quantification of the four structures. Reproduced with permission²⁰². Copyright 2016, Elsevier.

scaffold could lead to selective differentiation of NSCs into mature oligodendrocytes without requiring culture media differentiation inducers²⁰⁶. Another combinatorial therapy to enhance remyelination is using novel material to carry Schwann cells. For example, Chen et al. seeded Schwann cells, which highly expressed GDNF, into multichannel positively charged oligo [poly (ethylene glycol) fumarate] scaffolds and implanted them into transected rat spinal cords²⁰⁷. Experimental results demonstrated that these GDNF-Schwann cells enhanced remyelination of regenerating axons. However, it should be noted that remyelination was most likely a result of endogenous Schwann cell recruitment, as myelinating cell and axon complexes were not formed by implanted cells but by host Schwann cells. Recently, a porcine decellularized optic nerve scaffold loaded with NT-3-overexpressing Schwann cells was also proven to enhance remyelination in the injured dorsal white matter of the rat spinal cord⁸².

In summary, cell transplantation strategies based on biomaterials can enhance remyelination and achieve some reparative effects. However, there is still a considerable amount of work to be done. In terms of mechanisms, oligodendrogenesis is an understudied process, and the regulatory mechanisms of OPCs and differentiated oligodendrocytes remain elusive²⁰⁰. The pathophysiological process and regulatory mechanism of Schwann cells involved in myelin repair after SCI also need to be further elucidated²⁰⁸. In the aspect of clinical translation, a study has questioned whether remyelination is a validated target after moderate spinal cord contusion because experimental data demonstrated that oligodendrocyte remyelination was not necessary for the spontaneous recovery of walking²⁰⁹.

Combination biomaterial and cell transplantation strategies

With the ongoing advancement in cell culture technology, cell transplantation has emerged as an innovative approach in SCI treatment, serving not only to replace or protect damaged tissue but also to promote axonal regrowth through both physical and trophic support²¹⁰. Several candidate cell types have been studied in clinical trials in SCI patients, such as autologous Schwann cells²¹¹, olfactory ensheathing cells^{212,213}, BMSCs^{214,215}, and neural stem/progenitor cells²¹⁶. However, the efficacy of cell transplantation is often compromised by the flow of cerebrospinal fluid and the hostile microenvironment at the injury site, resulting in ineffective colonization, a low cell survival rate, and uncertain differentiation. To better address these issues, researchers often employ a combination of biomaterials and cell transplantation. In the preceding sections, we have listed numerous research examples of biomaterial and cell transplantation strategies. Below, we concisely explore this combination strategy in depth.

Biomaterial scaffolds can benefit cell transplantation in a variety of ways: (1) Specific 3D microstructures can be engineered into small “chambers” or aligned channels/fibers suitable for cell seeding and directional linear growth of axons⁶⁹. (2) They can serve as a physical matrix for cell adhesion, thus enhancing the survival and retention of transplanted cells at the lesion site^{217,218}. (3) They can separate the transplanted cells from the host tissue, thereby providing an independent microenvironment for cell differentiation and proliferation. (4) They can effectively fill cavities and bridge lesions, significantly reducing the number of cells for transplantation. This is particularly appealing for clinical applications, as the availability of autologous cells from patients is limited²¹⁰. Biomaterials dictate the fate of transplanted cells through complex physical properties. The morphology (internal structure, pore size, etc.) and mechanical properties (stiffness, viscoelasticity, and rheological properties) of biomaterials influence the survival, proliferation, and adhesion of transplanted cells via different signalling pathways²¹⁹. For example, the crosslinking of hydrogels typically improves the long-term stability of biomaterials, yet it also results in increased stiffness. This balance between stiffness and stability is delicate for cell adhesion, migration and nerve regeneration^{220,221}. Injectable in situ polymerized hydrogels facilitate the direct delivery of cells and factors to the lesion site, thereby reducing the invasiveness of surgical intervention. They form a homogeneous 3D matrix that mimics the natural ECM microstructure to modulate cell fate^{102,202}. Appropriate modifications to biomaterials can enhance the therapeutic effect of cell transplantation. For example, surface modification with ECM components can create a less hostile molecular microenvironment within biomaterials, thereby improving cell adhesion and survival^{222,223}. In summary, biomaterials that possess excellent biocompatibility, appropriate mechanical parameters, microenvironment manipulation or neuroprotective capability all have the potential to enhance the efficacy of cell transplantation in SCI treatment.

Cell transplantation based on biomaterials can be categorized into four approaches. The first is the transplantation matrix, referring to the in vitro mixture of cells with biomaterials to form a tissue-like matrix, which is then implanted into the injury site. This technique has been widely employed as a delivery system to confine transplanted cells to the site of injury. The second, injection and in situ gelling, entails the coinjection of self-assembling biomaterials and cells into the injury site to assemble seeded scaffolds in vivo. This technique has gained popularity for filling irregular lesion cavities formed post-SCI. The first two approaches are primarily applied to gel materials. The third approach uses pre-seeded scaffolds, which refer to cells seeded onto prepared bioactive scaffolds before implantation. This technique is

Table 2 Clinical trials of functional bioscaffolds to treat SCI.

Scaffold type	NCT number	Treatment	SCI phase/Location	AIS grade	Clinical phase	Country
Neuro-spinal scaffold	NCT02138110	Scaffold implantation	Acute T2-T12	A	N/A	The United States
Neuro-spinal scaffold	NCT03762655	Standards of care open spine surgery with or without scaffold implantation	Acute T2-T12	A	N/A	The United States
Functional collagen scaffold	NCT02510365	Scaffold transplant	Acute C4-T12	A	I	China
Functional collagen scaffold	NCT03966794	Epidural electrical stimulation versus Scaffold transplant with epidural electrical stimulation	Acute or chronic C4-T12/L1	A	I/II	China
NeuroRegen scaffold	NCT02352077	Scaffold transplant with MSCs or BMSCs	Chronic C5-T12	A	I	China
NeuroRegen scaffold	NCT02688062	Scaffold transplant with BMSCs versus Surgical intradural decompression and adhesiolysis	Chronic Thoracic level	A	I/II	China
NeuroRegen scaffold	NCT02688049	Scaffold transplant with 10 million cells of MSCs or NSCs	Chronic C5-T12	A	I/II	China

predominantly utilized for solid scaffolds with a pre-determined shape. The fourth approach aims to promote the integration of the scaffold into the host tissue to increase axonal bridging. This is achieved by implanting a prefabricated scaffold into the injury site and then injecting cells around it. The latter two approaches are primarily applied to solid biomaterials^{210,224}.

Clinical trials of functional bioscaffolds

Although many biomaterials have been applied in SCI research, few have actually entered clinical trials. Current clinical trials mainly focus on the implantation of two functional bioscaffolds: the Neuro-Spinal scaffold and NeuroRegen scaffold (Table 2).

Neuro-spinal scaffold

The Neuro-Spinal scaffold made of PLGA and poly (L-lysine) has been shown to promote functional recovery in acute SCI model rats and incomplete SCI model African green monkeys^{225,226}. Based on these studies, InVivo Therapeutics initiated a series of clinical trials to evaluate the efficacy of this scaffold in treating acute traumatic thoracic SCI, collectively known as the INSPIRE trials.

The first INSPIRE trial started in 2014 and is estimated to be completed in 2024 (NCT02138110). Selected participants in this trial must have complete nonpenetrating SCI defined as an American Spinal Injury Association Impairment Scale (AIS) grade A at T2-T12. The researchers first reported a case study of one patient with a T11 AIS grade A traumatic SCI²²⁷. They observed an improvement in AIS grade from A to C at 3 months after implantation. However, it remains uncertain whether the improvement could be attributed solely to the implanted scaffold and not related to surgical decompression. Recently, published 6-month follow-up data from the INSPIRE 1 trial reported no serious adverse events (SAEs) related to the scaffold or the implantation procedure²²⁸. AIS grade improvements were observed in 7 of 16 patients (43.8%). These results illustrate the efficacy and safety of the Neuro-Spinal scaffold in the short term. To further evaluate the safety and probable benefits of the Neuro-Spinal scaffold, the INSPIRE 2 trial was initiated in May 2019 and estimated for completion in July 2028 (NCT03762655).

NeuroRegen Scaffold

Since 2009, several animal experiments have demonstrated that LOCs linked to multiple functional molecules are effective in the treatment of SCI^{229–232}. To further examine the therapeutic effect of LOCs, they have been applied in five clinical trials under the product name NeuroRegen.

On January 16, 2015, a phase I trial was carried out to examine the safety and efficacy of bone marrow

mononuclear cell (BMMC)- and MSC-loaded NeuroRegen scaffolds in chronic SCI patients (NCT02352077). Five patients who received transplantation of the NeuroRegen Scaffold with BMBCs showed autonomic and electrophysiological improvements during a 12-month follow-up²³³. Unfortunately, no other meaningful motor or sensory improvements were reported. In contrast, some positive results in motor function and sensation level were observed in eight patients after implantation of the same scaffold loaded with hUC-MSCs²³⁴. A summary of 2-5 years of follow-up data involving this trial has been recently published²³⁵. Among the 51 patients enrolled, no SAEs associated with functional scaffold transplantation were observed. Data analysis suggested that younger patients might be more likely to regain sensation. Another phase I trial was conducted to examine the use of the NeuroRegen scaffold in patients with acute SCI (NCT02510365). Two patients with acute SCI at T11 and C4 were followed up for one year after receiving a transplantation of the NeuroRegen scaffold with hUC-MSCs²³⁶. Both patients experienced significant improvements in sensory and motor functions, especially an improvement in injury status from AIS grade A to C. Similarly, seven patients with acute thoracic SCI of AIS grade A underwent the implantation of NeuroRegen scaffolds loaded with autologous BMBCs²³⁷. During the 3-year follow-up, some patients exhibited improvements in sensation and autonomic nervous functions. Unfortunately, no recovery of motor function was observed, nor was there obvious improvement in the AIS grade. During the 2-5 year follow-up period, none of the 15 enrolled patients experienced SAEs related to scaffold transplantation²³⁵. More than one-third of the patients, particularly those with shorter injury lengths, showed significant recovery of sensory and motor functions. Notably, four patients even recovered their voluntary walking ability.

While some therapeutic effects of biomaterial implantation have been observed in these clinical trials of SCI, there is currently a lack of large-scale clinical studies supporting their routine clinical use. Additionally, it is essential to properly assess and monitor the safety of biomaterial implants before and during clinical trials to avoid premature human studies, a scenario that has occurred in the past²³⁸. Undeniably, with the initiation of these clinical trials, the blueprint for SCI treatment is unfolding. In the near future, biomaterials are expected to be part of combinatorial treatments alongside other interventions, such as electrical stimulation, stem cell treatment and growth factor administration, to facilitate neurological recovery in SCI patients.

Conclusions and outlook

A series of complex pathophysiological processes post-SCI result in the formation of microenvironments that

inhibit nerve regeneration, while the role of many cells remains controversial. For instance, as a natural source of myelinating cells, OPCs can ameliorate pathological deterioration in SCI³¹. However, there is evidence that OPCs may also participate in glial scar formation²³⁹. In addition to OPCs, astrocytes have complex functions. Recent findings indicated that astrocyte scar formation may actually promote, rather than inhibit, CNS axon regeneration²⁰. Elucidating the mechanisms underlying the actions of these cells will advance the development of novel therapeutic strategies for SCI. Furthermore, components within the cellular microenvironment do not act in isolation. In the future, researchers should elucidate the regulatory relationships between the components to better aid neural repair following SCI.

Tissue engineering scaffolds for SCI treatment are rapidly evolving. After years of research and exploration, biocompatibility, low toxicity, and degradability have become the basic properties of tissue engineering scaffolds. In addition to serving as a bridge to reconnect the lesion gap, bioscaffolds can carry various bioactive molecules, cells, and drugs to promote the reconstruction of the microenvironment. However, numerous issues remain unresolved. For example, the detailed mechanism through which bioscaffolds regulate cell behavior and microenvironments is unclear. Concerning the safety of scaffold materials, unified international evaluation standards are still lacking. Moreover, the timing of transplantation and the location and degree of SCI require careful consideration.

In the future, research should focus on the development and application of novel regenerative biomaterials⁷⁴. Building on this, exploring the optimal combination of scaffold materials, seed cells, cytokines and drugs is also essential. In short, further optimization of biomaterial-based combinatorial strategies will be the core of future injured spinal cord repair research. Tissue engineering scaffolds are a topic with enormous research potential and application value. As research deepens, it is believed that more novel scaffolds will be transitioned into clinical applications, promoting the treatment of SCI patients.

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Author contributions

K.C. and W.Y. wrote the main manuscript text. G.Z. and Z.X. prepared figures. C.Y., Y.W. and Z.Y. helped search and collect relevant articles. W.Y., * and B.H. * made instructive revisions to the article. H.C. *General design for the article and financial support. All authors reviewed the manuscript. K.C. and W.Y. contributed equally to this work.

Conflict of interest

The authors declare no competing interests.

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