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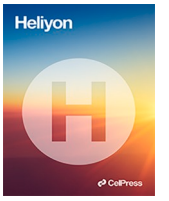

Review article

Hydrogel-based treatments for spinal cord injuries

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ABSTRACT

Spinal cord injury (SCI) is characterized by damage resulting in dysfunction of the spinal cord. Hydrogels are common biomaterials that play an important role in the treatment of SCI. Hydrogels are biocompatible, and some have electrical conductivity that are compatible with spinal cord tissues. Hydrogels have a high drug-carrying capacity, allowing them to be used for SCI treatment through the loading of various types of active substances, drugs, or cells. We first discuss the basic anatomy and physiology of the human spinal cord and briefly discuss SCI and its treatment. Then, we describe different treatment strategies for SCI. We further discuss the crosslinking methods and classification of hydrogels and detail hydrogel biomaterials prepared using different processing methods for the treatment of SCI. Finally, we analyze the future applications and limitations of hydrogels for SCI. The development of biomaterials opens up new possibilities and options for the treatment of SCI. Thus, our findings will inspire scholars in related fields and promote the development of hydrogel therapy for SCI.

1. Introduction

The spinal cord connects the peripheral and central nervous systems and is the center of many simple reflexes [1]. Spinal cord injury (SCI) results in motor, sensory, and autonomic dysfunction, and can be caused by various factors such as external force or inflammation. SCI interrupts the connection between the brain and peripheral nerves, causing life-threatening disruption of sensory and motor functions [2]. The disabling nature and low cure rate of SCI cause chronic patient suffering. Despite medical advances, the clinical prognosis of SCI remains poor due to neuronal loss, astrocyte scarring, and an inflammatory microenvironment [3]. However, advances in tissue engineering and biomaterials have created new possibilities for SCI treatment [4–7].

Hydrogels are a class of polymers with hydrophilic groups that absorb water to form a 3D network with a flexible tissue morphology similar to that of the extracellular matrix (ECM) [8–10]. Biomedical hydrogel materials can be synthetic or natural. Hydrogels used in tissue engineering are biocompatible and have antimicrobial properties; this facilitates tissue repair and integration [10–12]. For SCI repair hydrogels, soft and flexible properties and high conductivity are ideal [13]. Porous structures that mimic the ECM promote nerve cell regeneration after SCI. Therefore, transplantation of hydrogels loaded with different therapeutic components such as bioactive nutritional molecules, stem cells, or drugs is an attractive strategy for SCI treatment [5,14–16].

Herein, we first discuss the basic anatomy and physiology of the human spinal cord, followed by SCI. Next, we describe different treatment strategies for SCI in detail. We further discuss the crosslinking methods and classification of hydrogels and detail hydrogel

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biomaterials prepared by different processing methods for SCI treatment. Finally, we analyze the future applications and limitations of hydrogels for spinal cord regenerative therapy.

2. Spinal cord physiological structure, injury, and treatment

The spinal cord is in the spinal canal, and its lower end, known as the spinal cord cone, is sharpened and conical. A filament that continues from the peak of the cone is called the terminal filament [17]. The spinal cord is a bundle-like nerve tissue that forms the central nervous system along with the brain and brainstem, and its length in adults is 42–45 cm. The spinal cord has three functional areas: cervical dictation, thoracic spinal cord, and lumbosacral distended [18]. The spinal cord is composed of gray matter and white matter nerve tissue. The cross-section of gray matter is H-shaped and mainly comprises neuronal perinuclear bodies, dendrites and their synapses, glial support cells, blood vessels, unsheathed fibers, and a small number of myelinated fibers. Nerve fiber bundles, glia, and blood vessels constitute the white matter, which is dominated by myelinated fibers and is, therefore, lighter in color [19]. The spinal cord transmits nerve signals between the brain and the rest of the body. The posterior horn of the spinal cord receives sensory signals from receptors (e.g., skin, joints, and muscles) in various parts of the body, and the information is transmitted to the intermediate neurons and ascending tracts. The anterior horn, middle band, and descending conduction belt of the spinal cord also receive information from the brain and transmit information to motor neurons throughout the body, thereby serving as a coordinating center for certain reflexes [20].

SCI is a complex neurological system dysfunction that affects the motor and sensory pathways and organ systems below the site of damage [21]. SCI is classified as non-traumatic or traumatic depending on the cause. Non-traumatic SCI is caused by different diseases such as tumors, infections, or degenerative disc diseases. Traumatic injuries to the spinal cord result from external physical impacts, such as car accidents, falls, or violence; falls are the leading cause of traumatic SCI [22]. SCI is further grouped into two phases: primary and secondary (Fig. 1) [5]. The primary injury phase occurs at the time the spinal cord is injured. Secondary injury, depending on the complexity of the neurological cascade in which the injury occurs, occurs in the minutes to weeks after the primary injury and lasts for many years. Primary injury causes massive blood discharge and cell death at the damaged site, followed by ischemia, edema, more cell death (necrosis or apoptosis), excitatory toxicity, ion imbalance, and inflammatory response, further aggravating the severity of SCI [23]. The gray matter breaks down during the secondary injury phase, the white matter is demyelinated, and glial scarring occurs. Some patients may develop ascending myelitis from edema, which can lead to respiratory depression, lung infection, respiratory failure, and death. SCI often results in paralysis of the limbs below the injured segment, incontinence, and sexual dysfunction [24].

Current SCI treatment strategies include early decompression, reduction of inflammatory response, promotion of circulation, continued provision of neuroprotective nutrients, and reduction of scar tissue hyperplasia [25]. Presently, SCI treatment prioritizes early surgical decompression and fixation to minimize the primary injury. Vasopressors are also used to enhance mean arterial blood pressure and improve spinal cord blood perfusion. Corticosteroids are used to reduce pro-inflammatory cytokines, arachidonic acid, adhesion molecule expression, and oxidative stress to enhance the survival of oligodendrocytes and motor neurons. Neurotrophic regenerative agents such as alkaline fibroblastic cytokines, brain-derived neurotrophic factors, and nerve growth factors, which are associated with wound healing and angiogenesis, have been shown to reduce free radical production and excitotoxic cell death [26,

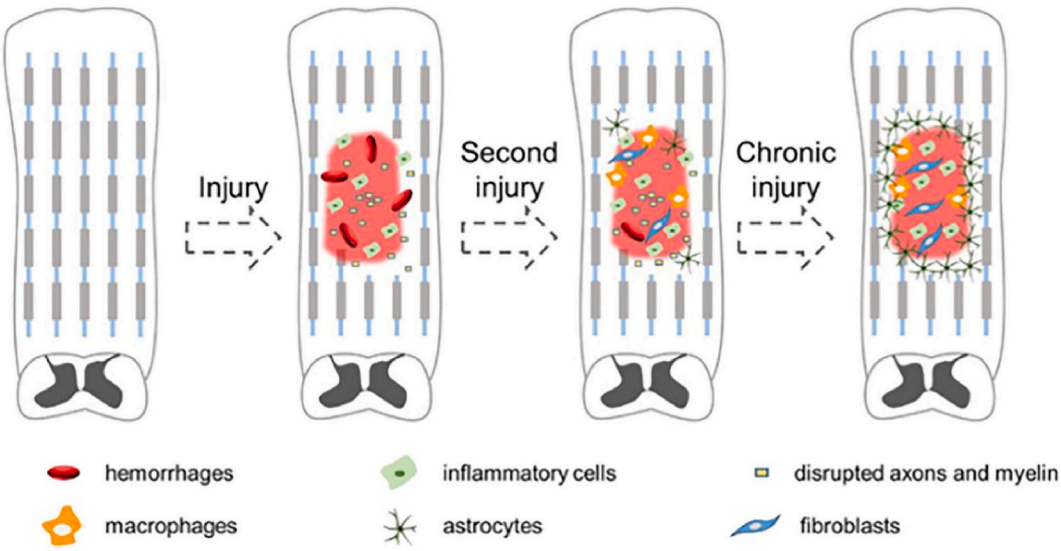

Fig. 1. Schematic representation of disease evolution in spinal cord injury. Initial spinal cord injuries tend to be characterized by acute hemorrhage and cellular necrosis; whereas secondary injuries are accompanied by a stronger accumulation of inflammatory cells and fibroblasts, which is the main reason why spinal cord injuries are difficult to heal. Adapted under the Creative Commons CC-BY license from provide reference [5].

27]. Neurorehabilitation, a noninvasive treatment that provides rhythmic stimulation of the affected area after SCI, promotes muscle maintenance and restores motor and sensory functions [28]. Loss of function following SCI is mainly caused by impaired neurological function, including neuronal death, nerve fiber rupture, and myelin prolapse. As the myelin sheath influences the growth of axons and the establishment of synaptic connections after injury, repair of the myelin sheath is essential for the restoration of neuronal function following SCI [29].

3. Hydrogel crosslinking methods and classification

Different cross-linking methods and polymer compositions affect various properties of hydrogels, including biocompatibility, cross-linking strength, stability, degradation rate, and porosity [30–33]. Rossi et al. investigated the drug release ability of nanoparticles with different particle sizes in hydrogels with different pore sizes by varying the experimental parameters. One of the main priorities in the design of drug delivery systems in SCI repair strategies is to obtain tunable release rates with fine control. Natural polymers can be mainly categorized into proteins and polysaccharides [34]. Natural protein components of hydrogels include gelatin, collagen, silk fibroin (SF), and polypeptides. Natural polysaccharide components of hydrogels include alginate (Alg), hyaluronic acid (HA), chitosan (CS), cellulose, agarose (AG), and dextran. Synthetic materials used to construct hydrogels include polyethylene glycol diacrylate (PEGDA), polyethylene glycol (PEG), and polyvinyl alcohol (PVA) [31,32,35,36].

3.1. Hydrogel crosslinking methods

Depending on the nature of the polymer backbone and its functional groups, hydrogels can be crosslinked using various methods, including physical, and chemical crosslinking [30]. The mode of cross-linking affects the mechanical and chemical properties of the hydrogels, and selecting the most appropriate method is an important part of hydrogel design [30,37] (Table 1).

3.1.1. Physical crosslinking

Physical crosslinking, also known as non-covalent bond crosslinking, is characterized by weak non-covalent bond energy, and is usually not as stable as chemical crosslinking. However, if multiple non-covalent bonds work together, under certain conditions, it can also produce a highly stable, strong bond. The key to robust physical crosslinking lies in the structure of the network and the sum of non-covalent bonds within the network [47]. Physical crosslinking is divided into ion, hydrogen bond, hydrophobic, and crystal crosslinking methods [30].

Ion crosslinking is formed by strong electrostatic attractions between molecules. Coordination can be formed by ligands and many divalent or high-valent metal ions, and their interactions can bind and break quickly. Thus, ion-crosslinked high-strength hydrogels generally self-heal well [48]. Hydrogels constructed using single-ion crosslinking are typically weak. Thus, high-strength physical crosslinked hydrogels can be constructed by combining these methods with other mechanisms. Yang et al. crosslinked divalent Ca^{2+} with sodium Alg and complexed it with CS using a polyelectrolyte to form microcapsules. The microcapsules exhibited good swelling, water absorption, degradation, and cargo release properties [38]. Hydrogen bond crosslinking is another common form of physical crosslinking. Yu et al. constructed a typical hydrogen-bonded crosslinked hydrogel with rapid hemostasis and wound healing in uncontrolled unpressurized surface bleeding, in which hydrogen bonds were formed through HA being crosslinked with PVP. HA/PVP complex hydrogels exhibit self-healing properties, good flexibility, and cargo-carrying capacity owing to reversible and dynamic hydrogen bonds [39]. Hydrophobic crosslinking is a method in which hydrophobic polymer structural units aggregate in water to form a physical crosslinking network. An effective crosslinking network can only be formed if the polymer has a high molecular weight and can form sufficient intermolecular hydrophobic associations [49]. Rahmani et al. developed a hydrogel with tough hydrophobic and superabsorbent properties using lauryl methacrylate (LMA), polyacrylamide (PAM), and polyacrylic acid. Their hydrogel exhibited advantageous mechanical properties owing to its multiple physical bonding interactions [40]. In crystal crosslinking, polymer chains crystallize to form crystalline microphases that act as physical crosslinking points. Bilici et al. used semi-crystalline shape memory hydrogels; dots and switching segments were indicated by hydrophobic associations and crystalline domains [41].

Table 1
Crosslinking methods of hydrogels.

Type	Method	Characteristic	Reference
Physical	Ion crosslinking	Good self-healing ability Low strength	[38]
	Hydrogen bond crosslinking	Excellent water absorption	[39]
	Hydrophobic crosslinking	Suitable mechanical properties Excellent swelling rate	[40]
	Crystal crosslinking	Good stiffness and toughness	[41]
Chemical	Dynamic covalent bond crosslinking	Suitable mechanical strength, self-healing	[42,43]
	Non-dynamic covalent bond crosslinking	Excellent mechanical properties	[44]
	Photocrosslinking	Better controllability	[45,46]

3.1.2. Chemical crosslinking

Chemical crosslinking includes dynamic and nondynamic covalent bond crosslinking. Dynamic covalent bonds are a class of reversible covalent bonds that can establish a thermodynamic equilibrium between reactants and products under specific conditions. The formation of dynamic bonds is reversible and changes according to certain environmental conditions [50]. Hua et al. constructed dynamic covalent crosslinking hydrogels in a physiological pH environment using a thiolaldehyde addition reaction. Unstable semisulfide acetal bonds in their dynamic covalent crosslinking hydrogels could be converted to thermodynamically stable bonds, allowing for controlled stabilization; their prepared hydrogels could self-heal, were easily injected, and freely formed owing to the thiolaldehyde addition reaction [42]. Li et al. prepared a novel hydrogel using a benzaldehyde-terminated F127 triblock copolymer (BAF127) and hydrazide-modified HA. Their hydrogels exhibited shear-thinning performance and rapid gelation. In addition, tissue adhesion, liquid absorption, and self-healing properties were observed in their novel hydrogel [43]. Non-covalently cross-linked hydrogels are 3D network systems formed by polymers/low-molecular-weight compounds in aqueous solutions through physical forces between the molecules. In general, most non-covalently crosslinked hydrogels exhibit stimulus responsiveness to a certain ambiguous thought-environment [51]. Huang et al. used hydrophobically modified PAM (HPAM) and-carrageenan (K + C) networks crosslinked with thermoreversible potassium ions to develop a double-network hydrogel. K + C/HPAM DN hydrogels have multiple

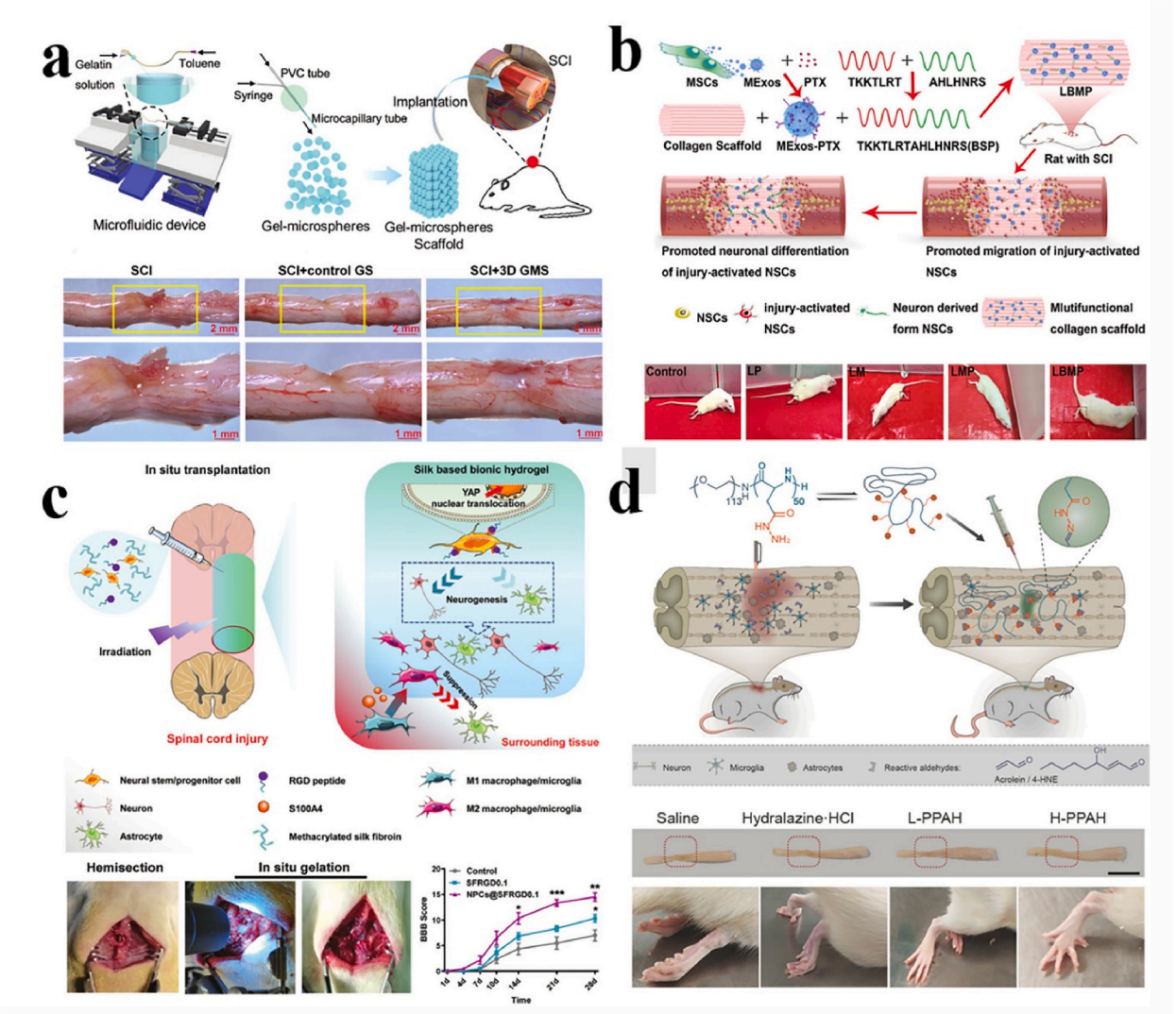

Fig. 2. Natural proteins for hydrogel applications. **(a) Schematic of fabrication of** gelatin microspheres and 3D gelatin microsphere scaffolds, and spinal cord tissue of injury site of different groups. Adapted under the CC BY license from provide reference [63]. **(b) Fabrication and application of** the multifunctional collagen scaffold. Reproduced or adapted with permission from provide reference [64]. Copyright © 2021 Wiley-VCH GmbH. **(c) Schematic of** cell-enhanced bionic silk hydrogel promoting spinal cord repair. Reproduced or adapted with permission from provide reference [65]. Copyright © 2023 Wiley-VCH GmbH. **(d) Schematic of mechanism of** recovery of SCI model rats. Reproduced or adapted with permission from provide reference [66]. Copyright © 2023, Science China Press.

dynamic non-covalent bonds, good mechanical properties, and good self-healing abilities [44].

Photocrosslinking is another chemical crosslinking method, which usually occurs under UV light, and offers unique advantages in 3D printing and tissue engineering [46,52,53]. Methacrylic anhydride-modified polymers are the most commonly polymerized materials for photocrosslinked hydrogels [45]. Gelatin methacryloyl (GelMA) is one of the most researched and is widely used in biomedical applications. The methacrylamide and methacrylate side groups on GelMA chains form covalent bonds after the generation of free radicals by a photoinitiator to produce a network of gelatin chains bound by short polymethacryloyl chains [54]. Han et al. constructed a microneedle patch using GelMA and encapsulated stem cell-derived exosomes in it for SCI repair. The microneedle patch realized the sustained release of exosomes at the site of SCI, avoiding damage that might be caused by repeated injections [55].

3.2. Classification of hydrogel materials

Hydrogels contain natural proteins, polysaccharides, and synthetic materials [37,56]. Natural polysaccharides used in hydrogels include gelatin, collagen, and SF. Natural polypeptides used in hydrogels include Alg, HA, CS, cellulose, AG, and glucan [37,56]. Synthetic components of hydrogels include PEGDA, NIPAM, PEG, and PVA-pHEMA [57–59].

3.2.1. Natural proteins

Gelatin is a degradation product of collagen; it is an important natural biomaterial used in the pharmaceutical, food, and chemical industries. Currently, most gelatin comes from mammalian animal sources, but its use is limited by factors such as mammalian viruses and religious beliefs [60]. Therefore, aquatic gelatin has received significant attention in recent years as a possible alternative. Fish gelatin has properties similar to those of porcine gelatin and can be used in food as an alternative to mammalian gelatin. The production and utilization of fish gelatin can not only improve the use value of fishery by-products but also meet consumer demand [61]. Zhang et al. designed mesoporous silica nanoparticles and coated them with degradable gelatin to deliver anti-inflammatory and inflammatory factors to cells [62]. Furthermore, Ke et al. used microfluidic devices to prepare gelatin microsphere scaffolds at low cost without compromising biodegradability or biocompatibility. In addition, the scaffolds effectively bridged the gap between injuries, established neural connections, promoted signal transduction, reduced the inflammatory microenvironment, and reduced glial scarring (Fig. 2a) [63].

Collagen is a major structural protein of the ECM in mammals. Collagen is abundant in the skin, bone, muscle, and other tissues, where it plays important roles in supporting, repairing, and protecting cells [67]. As the major component of the ECM, collagen is the most abundant protein in vertebrates and has low immunogenicity and high biocompatibility. As a natural biological resource, collagen is considered a critical raw material in the biotechnology industry. The development of collagen products and industrial innovation are research hotspots worldwide [68]. Zhang et al. used a novel dual biospecific peptide to link exosomes extracted from human umbilical cord-derived mesenchymal stem cells (MSCs) onto collagen scaffolds, which successfully increased the migration of neural stem cells (NSCs). This versatile scaffold technology improved motor function recovery in a rat model of SCI by enhancing nerve regeneration and reducing scar deposition (Fig. 2b) [64]. In another study, Liu et al. developed microRNA 21 (miR21)-loaded exosomes that could be wrapped in collagen I scaffolds to repair SCI; miR21 has been shown to have protective effects against SCI [69].

SF is a natural polymer fibroprotein with excellent mechanical properties, good biocompatibility, easy shaping and bioresorption, as well as good biodegradability, non-immunogenicity, and osteogeneity [70]. Scientific research and application technology developers favor SF in the field of biomedical materials. The mechanical strength and degradability of SF can be adjusted, and the carrier performance of loaded cells, bioactive factors, and drugs is sufficient for different fields [71]. For instance, Ling et al. designed a cell-enhanced photocrosslinked filament protein hydrogel that mimicked the mechanical properties of the ECM. Their hydrogel was able to fill the area of injury by gelling to regulate neuroinflammation caused by injuries and accelerate neurite regeneration. Importantly, nerve stem/progenitor cell (NPC)-coated hydrogels (NPCs@SFRGD0.1) effectively reshaped the post-SCI inflammatory microenvironment to promote healing (Fig. 2c) [65]. Zhou et al. synthesized a methacrylate-silk fibroprotein (SilMA) hydrogel for basic fibroblast growth factor (bFGF) delivery (SilMA@bFGF). SilMA@bFGF exhibited controlled release of bFGF and accelerated axonal regeneration. Another study confirmed that SilMA hydrogels repair nerve function by inhibiting local inflammatory response [72].

Sericin and albumin are also hotspots for current research in the biomedical field. Sericin is rich in hydroxyl, amino, and carboxyl groups, which can be used for functionalization and tuning of its chemical and mechanical properties [52]. Albumin is an abundant protein in organisms and is highly biocompatible while being easily accessible [73,74]. Owing to their physical similarity with tissues and biocompatibility, peptide hydrogels have excellent application potential in bio-related fields [75]. The removal of toxic reactive aldehydes can effectively treat secondary SCI. For instance, Liu et al. designed and synthesized a drug-free polypeptide (PPAH) to treat secondary SCI by removing toxic aldehydes (Fig. 2d) [66].

3.2.2. Natural polysaccharides

Alg, a linear polysaccharide, comprises repeating units of L-guluronic acid (G) and D-mannouronic acid (M). Alg is a natural biological material used for hydrogel synthesis, and through simple ion crosslinking, it can undergo an “egg carton reaction” with polyvalent inorganic cations such as Ca^{2+} [76]. There are many –OH and –COOH polar groups on the Alg backbone, which are modified by chemical or physical methods to achieve controlled release of loaded cells or bioactive molecules. Alg is one of the most widely used polymeric polysaccharides in drug delivery systems [77]. In recent years, biocompatible materials have been combined with bioactive molecules and cells to promote the regeneration of damaged tissues. Hydrogel materials have the potential to protect embedded cells and mimic the natural ECM. As such, Alg is widely used because of its gelation properties and good biocompatibility

[78]. Zhu et al. combined fibroblast growth factor 21 (FGF21) and dental pulp stem cells to design a calcium Alg hydrogel for hemi-amputated SCI treatment (Fig. 3a) [79].

HA is involved in many cellular physiological processes such as differentiation and proliferation. Three-dimensional network-like hydrogels can simulate the ECM to a certain extent, and synergistic stem cells can play an active role in tissue repair [82]. HA hydrogels are widely used because of their superior biocompatibility and biological activity. To enhance the long-term repair capacity of HA hydrogels in various types of tissue damage, it is possible to alter the mechanical properties of the hydrogel and load different types of therapeutic cargo for controlled delivery [83]. Xu et al. designed biocompatible HA and methylcellulose loaded with fat extract to treat

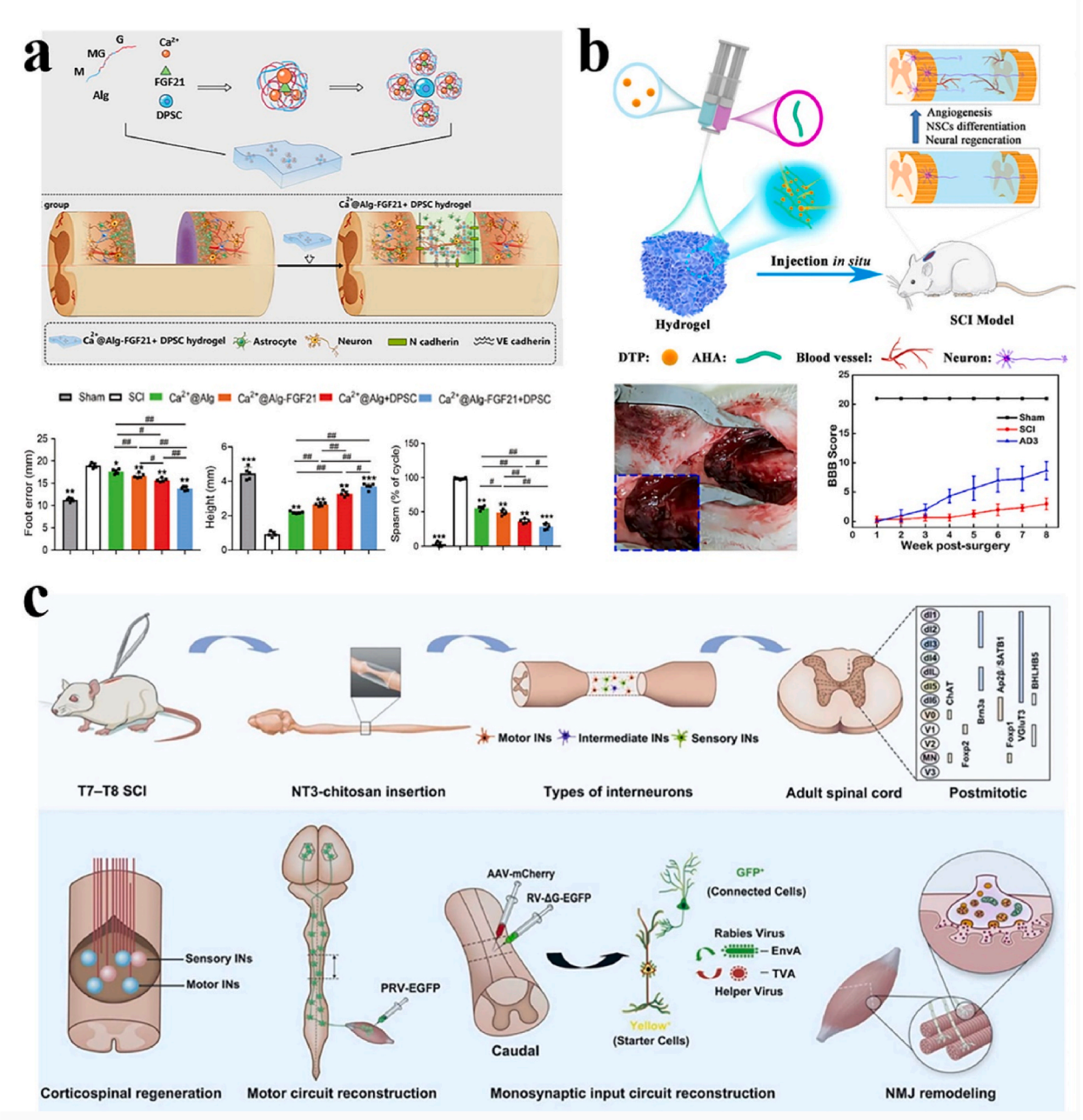

Fig. 3. Natural polysaccharides and their hydrogel applications. **(a) Schematic of fabrication and application of** Ca^{2+}@Alg-FGF21+dental pulp stem cell hydrogel. Adapted under the Creative Commons CC-BY–NC–ND license from provide reference [79]. **(b) Schematic of** injection into lesion area. Reproduced or adapted with permission from provide reference [80]. Copyright © 2022 Elsevier Ltd. All rights reserved. **(c)** Schematics of newborn neurons subtypes after spinal cord injury in rats and **corticospinal regeneration, motor circuit reconstruction, monosynaptic input circuit reconstruction, and NMJ remodeling.** Adapted under the Creative Commons CC-BY–NC–ND license from provide reference [81].

mouse spinal cord contusion. The composite not only inhibited the death of nerve and vascular cells but also protected nerve and vascular structures and regulated the inflammatory phenotype of macrophages in locally injured areas [84]. Furthermore, Li et al. developed an injectable, self-healing hyaluronate hydrogel that improved motor recovery in SCI rats by promoting nerve regeneration and myelination (Fig. 3b) [80].

CS is a natural polymer that can exist in liquid form in an acidic environment and is a product of the partial deacetylation of chitin. CA is naturally antibacterial, biodegradable, and biocompatible [85]. CA is a natural polysaccharide with multiple biological activities and participates in a variety of physiological processes. Wang et al. designed an implanted CA scaffold that promoted functional recovery by improving the shape of relay neural circuits and the differentiation of mature neurons (Fig. 3c) [81].

Cellulose and its derivatives are a large class of renewable natural polymer materials that are non-toxic. Cellulose-based hydrogels have good water absorption, biocompatibility, and biodegradability, and can be used in medical, environmental, agricultural, and other industrial fields [86]. Zhang et al. developed an injectable gel hydrogel based on CS and sodium carboxymethylcellulose for the topical delivery of cannabidiol (CBD). Their results confirmed that CBD-loaded hydrogels achieved urinary and motor function recovery (Fig. 4a) [87].

As a natural polymer, AG is hydrophilic, and its molecular chain contains many hydrogen bonds, which can give the material a water stimulation response through the breaking and recombination of hydrogen bonds. Furthermore, the low melting point of AG

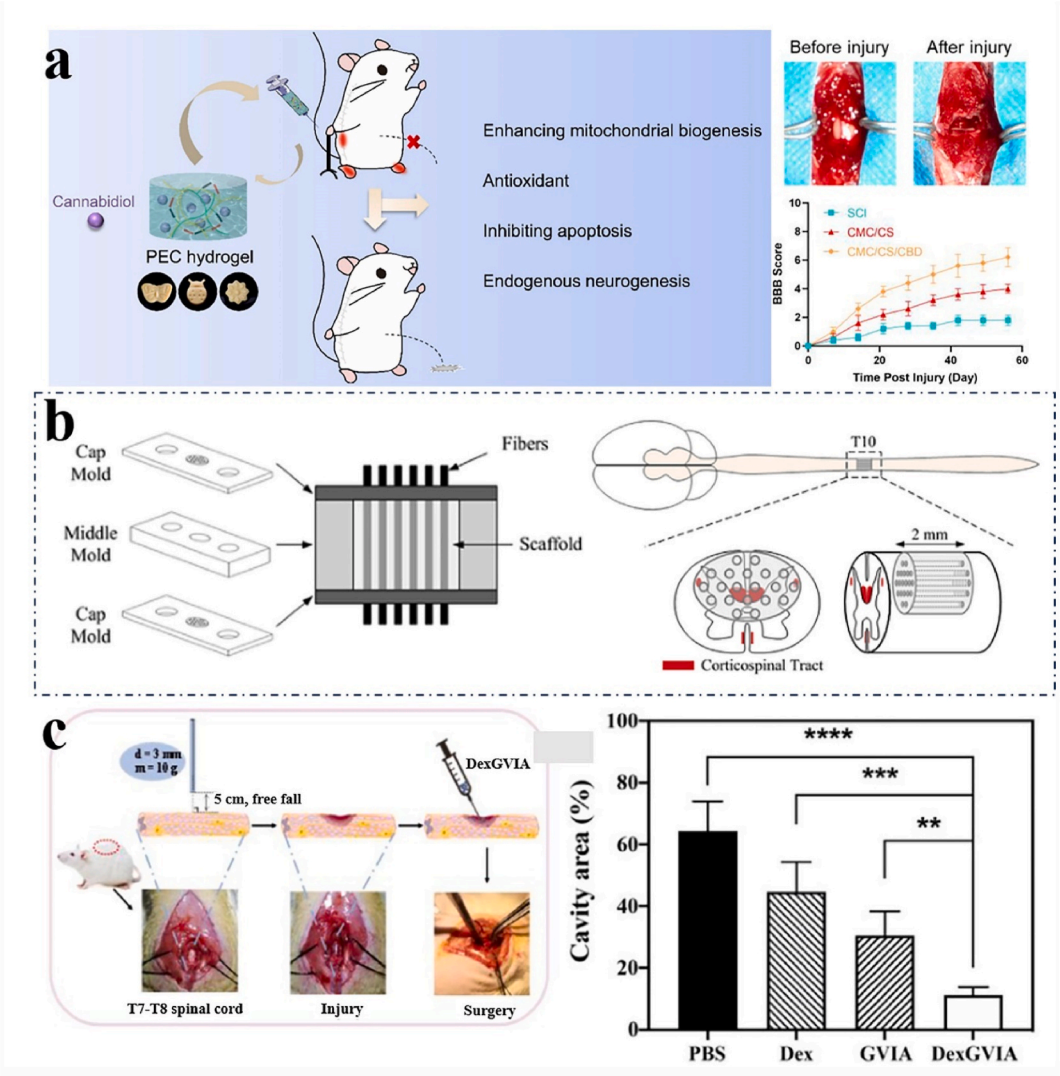

Fig. 4. Natural polysaccharides and their hydrogel applications. **(a) Schematic of** cannabidiol-loaded hydrogels. Reproduced or adapted with permission from provide reference [87]. Copyright © 2022 Published by Elsevier B.V. **(b) Schematic of** agarose scaffold production, and **schematic of** scaffold implantation. Reproduced or adapted with permission from provide reference [88]. Copyright © 2018 Elsevier Inc. All rights reserved. **(c) Schematic of T7-T8 spinal cord injury and repair in** rats. Reproduced or adapted with permission from provide reference [89]. Copyright © 2021 Elsevier Ltd. All rights reserved.

allows for the material to have a thermal stimulation response [90]. Cryogel technology can be used to easily prepare AG-based scaffold materials with macroporous structures, which may be useful for biomedical applications [91]. In agreement with this notion, Han et al. found that axon regeneration of linear tissues can be supported and enhanced by AG scaffolds containing Matrigel (Fig. 4b) [88].

β-glucan is a typical representative of lactic acid bacterial exopolysaccharides, which are similar polysaccharides linked by D-glucose units through single or multiple-glycosidic bonds (α-1,6, α-1,4, α-1,3 and α-1,2) [92]. According to its bond composition and structural characteristics, β-glucan is divided into four main categories: dextran, roy sugar, variable sugar, and alternating sugar. β-glucan is mainly found in plant and microbial cell walls, is composed of dextran monomers, and has a variety of structures and biological functions [93]. Zhao et al. designed a bifunctional microgel for the delivery of GVIA to enable combination therapies that reduce the concentrations of Ca^{2+} and glutamate and suppress the influx of Ca^{2+} into the ECM. Their results showed that motor function was significantly restored in the SCI rats that received the hydrogels (Fig. 4c) [89].

3.2.3. *Synthetic materials*

PEG is a linear polyether polymer with good thermal and chemical stability. Modification of the PEG end group yields a highly reactive PEG derivative. PEG and its derivatives are widely used for material engineering modifications [94]. PEG derivatives have good hydrophilicity, low toxicity, low immunogenicity, strong chemical stability, good tolerance to acids and bases, and energy

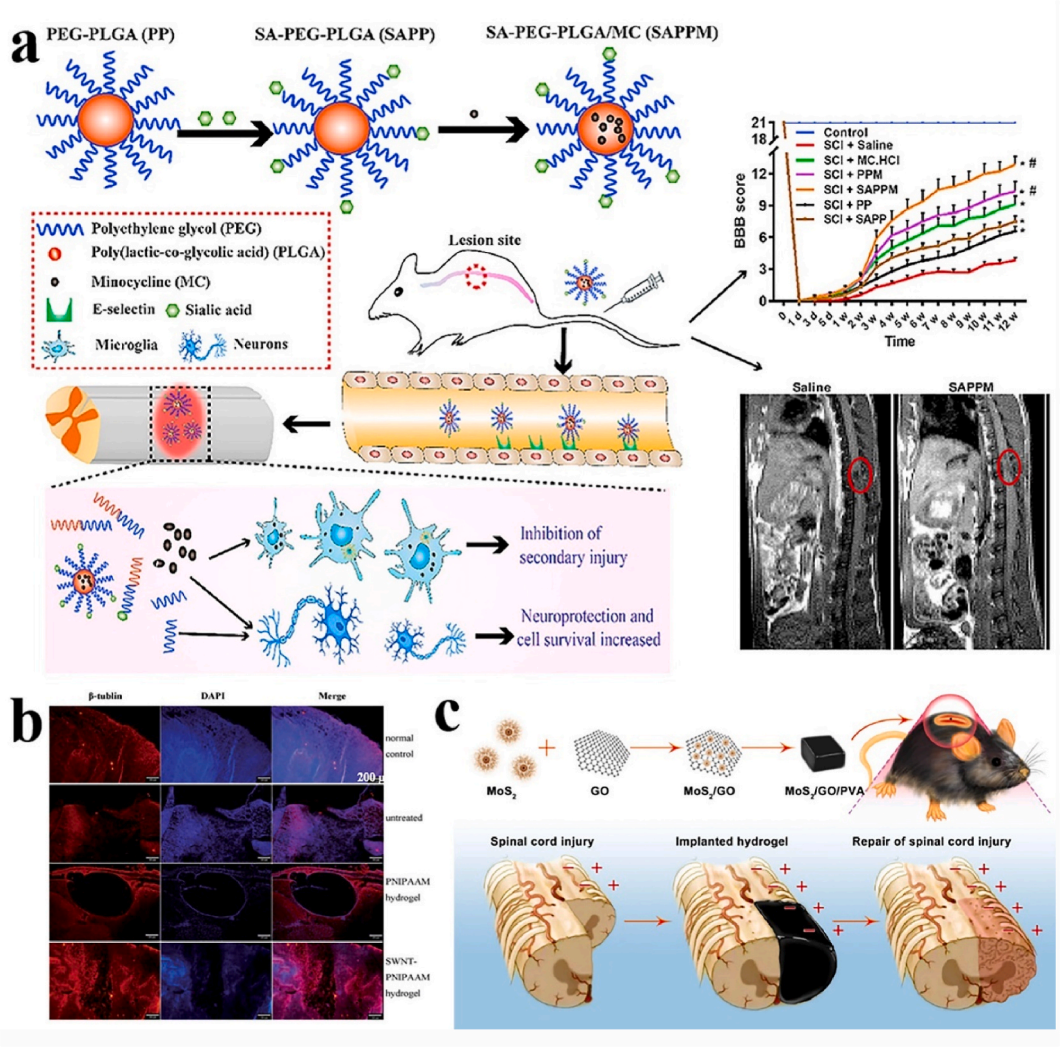

Fig. 5. Synthetic materials and their hydrogel applications. **(a) Schematic of** fabrication and application of SA-PEG-PLGA/MC, and blood-brain barrier (BBB) scores of SCI rats and T1-weighted MRI images of different groups. Reproduced or adapted with permission from provide reference [96]. Copyright © 2019 Elsevier Ltd. All rights reserved. **(b)** Immunofluorescence staining of different groups. β-tublin (red) and DAPI (blue). Reprinted with permission from Ref. [97]. **(c) Schematic of** fabrication and application of MoS2/GO/PVA nanocomposite hydrogels. Adapted under the CC BY license from provide reference [98].

storage temperature regulation. PEG is a water-soluble polymer, and its biosafety and compatibility make it attractive for biomedicine; it has also been studied for its ability to repair nerve damage [95]. Wang et al. designed a SAPP copolymer targeting an E-selective protein to deliver hydrophobic minocycline for SCI combination therapy. The prepared SAPPM exhibited continuous drug release and good neuroprotective capacity in vitro. In vivo, lesion cavity areas were significantly reduced and hind limb function recovery was increased in SCI rats treated with SAPPM (Fig. 5a) [96].

PEGDA is an example of a PEG derivative. High cytotoxicity and poor degradability limit PEGDA applications in the biomedical field [99]. However, PEGDA hydrogels have good biocompatibility and are extensively used to prepare biological scaffolds; their structures are more complex and porous [100]. For instance, Sang et al. reported a thermosensitive hydrogel prepared by copolymerization of an oligomeric amphiphilic crosslinker using n-isopropyl acrylamide, single-walled carbon nanotubes, and PEGDA-DD-AEP. In their SCI model, the hydrogels promoted the regeneration of neural tissues. Thus, hydrogels are potential restorative biomaterials for spinal cord regeneration (Fig. 5b) [97].

PVA is a widely used water-soluble material that can be crosslinked to form hydrogels. PVA hydrogels exhibit good hydrophilicity, biodegradability, biocompatibility, high crystallinity, and feasibility for mixing with nanocellulose. PVA-conductive hydrogels also have good electrical conductivity, making them widely used in biomedical applications, flexible sensing, and other fields [101]. Chen et al. used molybdenum sulfide/graphene oxide (MoS2/GO) nanomaterials and PVA to develop a composite hydrogel with excellent inflammatory attenuation. After the implantation of the complex hydrogel, endogenous regeneration of the spinal cord was activated, thereby restoring motor function in a preclinical SCI model (Fig. 5c) [98].

4. Treatment strategies for spinal cord injury

SCI treatments can be divided into bioactive factor therapy, stem cell therapy, drug therapy, exosomes, and nanozymes [56,

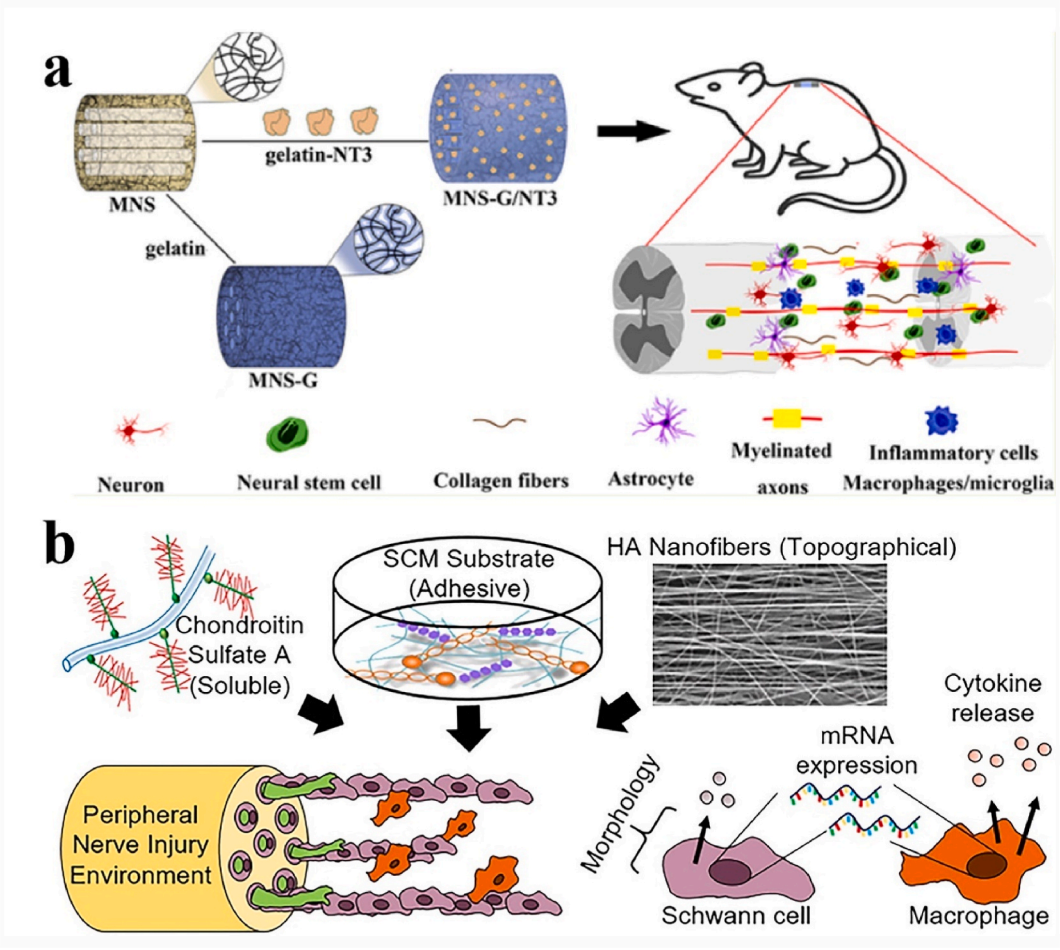

Fig. 6. Biological active factors for spinal cord injury therapy. (a) **Schematic of fabrication of** MNS-G/NT3. Reprinted with permission from Ref. [112]. Copyright © 2020, American Chemical Society. (b) **Schematic of** the effects of chondroitin sulfate proteoglycan (CSPG), chondroitin sulfate A (CSA), spinal cord matrix (SCM), and HA fibers on macrophages and Schwann cells (SCs). Reprinted with permission from Ref. [114]. Copyright © 2018 IBRO. Published by Elsevier Ltd. All rights reserved.

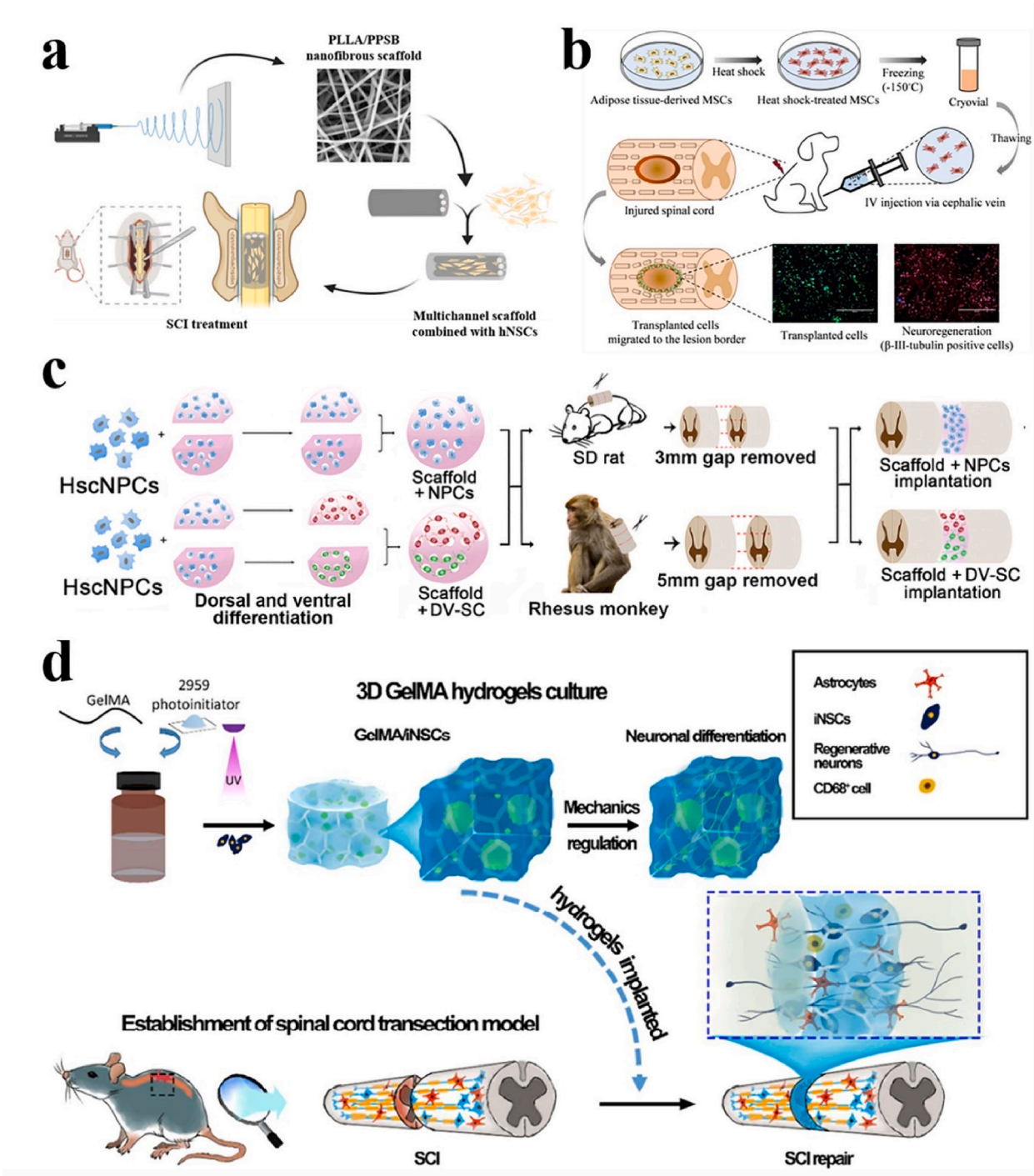

Fig. 7. Stem cell therapy of spinal cord injury (SCI). **(a)** Schematic of fabrication and SCI treatment of PLLA/PPSB nanofibrous scaffolds. Reprinted with permission from Ref. [119]. Copyright © 2023, American Chemical Society. **(b)** Schematic of F-HSP-HO-MSCs for SCI. Reprinted with permission from Ref. [121]. Copyright © 2022, The Author(s), under exclusive licence to Springer Science Business Media, LLC, part of Springer Nature **(c)** Schematic of DV-SC transplantation in SCI rats and rhesus monkeys. Adapted under the CC BY license from provide reference [122]. **(d)** Schematic of fabrication of hydrogel and animal experiment. Reprinted with permission from Ref. [123]. Copyright © 2023, American Chemical Society.

102–104]. Bioactive factors include neurotrophic growth factors that promote neuronal growth and survival such as insulin-like growth factor-1 (IGF-1), neurotrophic factor-3 (NT-3), ciliary neurotrophic factor (CNTF), and glial cell-derived neurotrophic factor (GDNF) [103]. Stem cell therapies include NSCs, induced pluripotent stem cells (iPSCs), NPCs, and MSCs, which can either support regeneration through direct cell replacement or bystander effects such as secretion of anti-inflammatory or neurotrophic molecules [102].

4.1. Biological active factor treatment

SCI results in significant neuron loss. Sustainable delivery of exogenous neurotrophic factors is important because cells that make up the CNS require neurotrophic factors to survive, proliferate, and differentiate [103,105].

4.1.1. IGF-1

IGF-1 is a single-chain protein comprising 70 amino acids with a molecular weight of 7649 Da that plays regulatory roles in apoptosis, differentiation, proliferation, growth, and development of nerve cells. Recent research has shown that IGF-1, whether systemic or topical, can promote SCI repair [106]. Li et al. established a mouse model of microvascular endothelial cell damage and transfected the cDNA of IGF-1 into microvascular endothelial cells [107]. The area of the damaged cores was reduced and the microenvironment of neural tissue repair was corrected after administration of excess IGF-1 into SCI mice [107].

4.1.2. GDNF

GDNF plays a crucial role in the development, growth, and repair of the nervous system; GDNF protects against ischemic cerebrovascular and neurodegenerative diseases [108]. GDNF is involved in the formation and maintenance of neural circuits and synaptic plasticity [109]. Silva et al. prepared a human adipose tissue-derived stem cell secretion proteome delivery system based on hydrogels. Secreted proteome induces neurite growth and cell differentiation. Moreover, hydrogels loaded with secreted proteins effectively improved motor function in rats with SCI [110].

4.1.3. NT-3

The neurotrophin (NTs) family contains neurotrophic factors with important functions in maintaining the survival and regeneration of nerve cells; NT-3 is the third member with a wide range of biological activities [111]. Sun et al. prepared a multi-channel nanofiber scaffold, and the gelatin-coated nanofiber effectively combined with NT-3 and highly promoted neuronal differentiation and synaptic formation of seeded neural stem cells. After the nanofiber stent was implanted into the fully transcribed spinal cord of rats, the inflammatory response and collagen/astrocyte scarring were limited. Additionally, functional neuronal and myelin regeneration were promoted postoperatively, greatly improving functional recovery (Fig. 6a) [112]. Chen et al. designed a PPF scaffold with a high mechanical strength. Multichannel PPF scaffolds can be combined with collagen biomaterials to develop new biocompatible delivery systems. Indeed, combination therapy consisting of PPF and CBD-NT3-loaded collagen is reported to promote axon and neuron regeneration, myelination, and synaptic formation after SCI [113].

4.1.4. CNTF

CNTF contains four reversed-phase alpha-helical structures and is mainly involved in neuronal cell growth and the repair of damaged neurons. CNTF provides pro-growth and pro-survival signals to many types of neurons and regulates the in vitro proliferation and differentiation of nerve cells [115]. Hu et al. found that activating signal transducers, transcriptional activators, and IL-6 in neurons could mediate neuroinflammatory responses via CNTF [116]. Wrobel et al. evaluated nanofibers for Schwann cells and macrophages. The results showed that, when cultured with biomaterial cues, anti-inflammatory cytokines, including CNTF, were released from the cells. This suggests that the biomaterial has a regenerative function in both cell types (Fig. 6b) [114].

4.2. Stem cell therapy

Cell therapy is a major strategy for future SCI treatment. NSCs, MSCs, NPCs, and iPSCs are widely used to treat SCI in preclinical studies [102].

4.2.1. NSCs

NSCs are present in the lateral ventricles, dentate area of the hippocampus, and the central canal of the spinal cord. As adult pluripotent stem cells, NSCs can differentiate into oligodendrocytes and neurons, and they do not have the problem of malignant transformation that ESCs do, thus improving safety for clinical applications [117]. NSC transplantation can re-establish the neural circuit at the site of injury by direct replacement of lost or damaged neurons, thereby promoting SCI recovery. Under normal conditions, endogenous NSCs are dormant, but when SCI occurs, they migrate to damaged areas for nerve repair, which is often insufficient to fully rectify the damage [118]. Therefore, transplantation of exogenous NSCs and support of endogenous NSCs are strategies for SCI treatment. Dai et al. prepared a biomimetic nanofiber scaffold through electrospinning, which could be combined with human NSCs to treat SCI. Nanofiber transplantation loaded with human NSCs enhanced neuronal regeneration and improved the inflammatory responses in the rat spinal cord (Fig. 7a) [119]. Qi et al. designed injectable hydrogels that bind NSCs to strengthen tissue regeneration in a fully transected rat SCI model. After transplantation into a fully cross-sectioned SCI rat model, NSC-cf Gels enhanced the neuronal differentiation of transplanted NSCs and promoted neural circuit reconstruction and axon regeneration [120].

4.2.2. MSCs

MSCs are widely studied for the treatment of SCI because of their wide availability and low immunogenicity. The main mechanism of MSC therapy is the secretion of many anti-inflammatory and growth factors through paracrine signaling, thereby improving the lesion microenvironment and promoting the self-repair of host cells. However, MSC differentiation and subsequent replacement of lost cells is weaker compared to other stem cell types [124]. Kim et al. used heat shock (HS) to enhance the properties of cryopreserved MSCs and to induce HS protein (HSP) expression. They reported that the HSP-induced group had improved hind limb motility, higher expression of neuromarkers, fibrotic changes with less intervention, and improved myelination (Fig. 7b) [121]. Similarly, Xie et al. reported that transplantation of umbilical cord MSCs could effectively promote SCI repair [125]. Yao et al. fabricated microfibers of 3D MSCs through electrospinning in spun cell cultures to mimic neural tissues and facilitate their integration with host tissues. Microfiber implantation with MSCs enhances the neural differentiation of donor MSCs, encourages host neurons to migrate to damaged sites, and promotes nerve fiber regeneration at damaged sites [126]. Maintaining cell viability and differentiation potential of MSCs is an important prerequisite for exerting therapeutic effects on SCI injury. Caron et al. [127] constructed a three-dimensional biomimetic hydrogel to enhance the attachment ability of MSCs in the hydrogel and maintain the biological activity of MSCs by mimicking the structure and components of the natural extracellular matrix.

4.2.3. NPCs

Transplanting NPCs is a promising method for replacing neurons lost after SCI. NPCs transplanted into subacute contusions

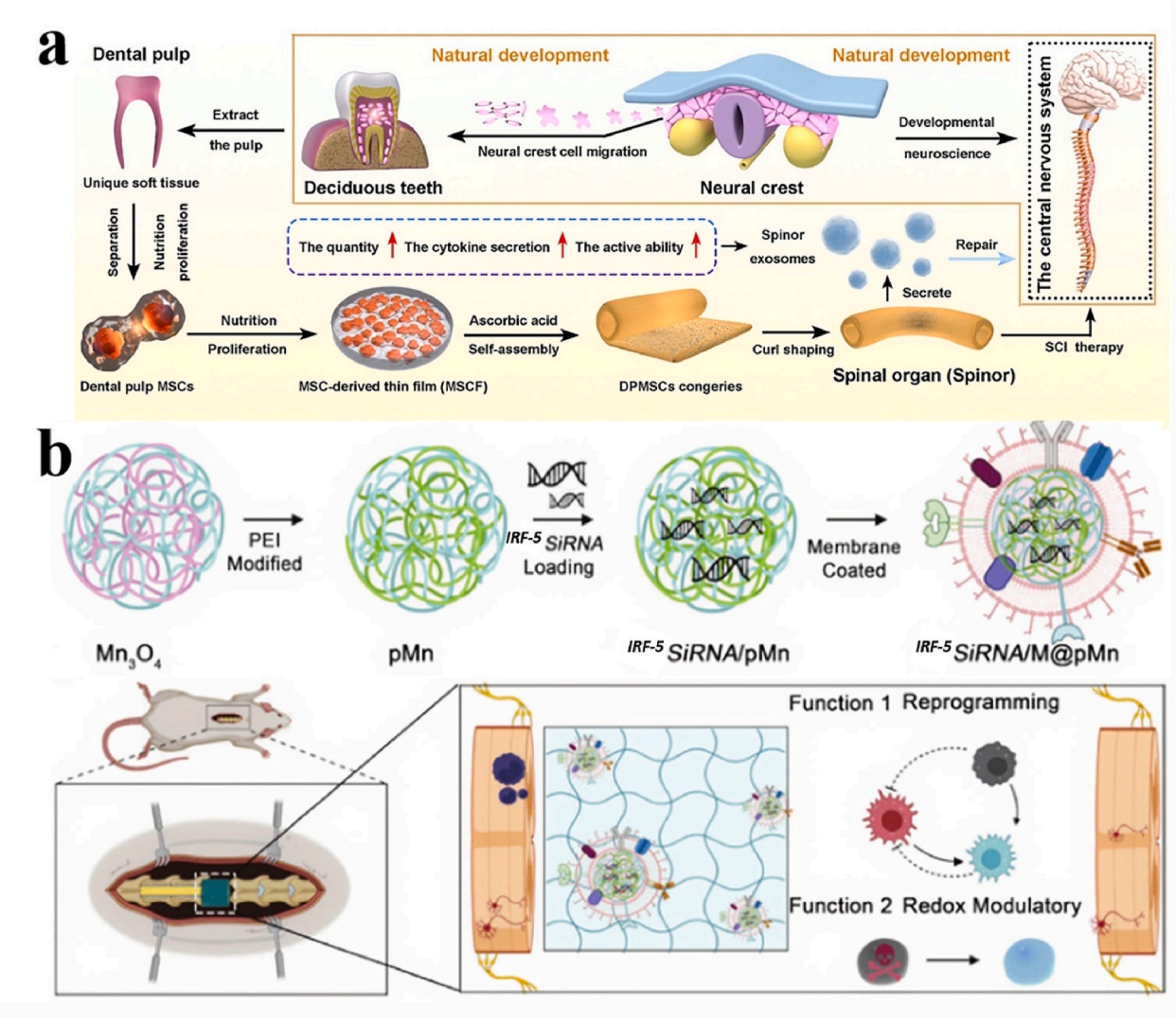

Fig. 8. Drug therapy, exosomes, and nanozyme therapies for spinal cord injury (SCI). **(a) Schematic of fabrication of** Spinor. Reprinted with permission from. Adapted under the CC BY license from provide reference [137]. **(b) Schematic of** $^{IRF-5}$SiRNA/M@pMn nanozyme fabrication, and the multifunctional therapeutic ability of nanozymes. Adapted under the CC BY license from provide reference [138].

improve motor, sensory, and bladder function [128,129]. Xu et al. engineered a human embryonic spinal cord-like tissue (DV-SC), which improved hindlimb function in SCI after transplantation into SCI models (Fig. 7c) [122]. Chen et al. reported a collagen fibrillary protein (Col-FB) fibrous hydrogel. Softly arranged fibrous hydrogels can be in close contact with the host stump by mimicking the features of the native spinal cord and providing adhesion. The induced endogenous NPCs were released and migrated to the lesion sites, leading to the recovery of hind limb motion. The proposed strategy was shown to effectively utilize endogenous NSPC, thereby significantly facilitating SCI remediation [130].

4.2.4. IPSCs

IPSCs can be transformed from self-extracted somatic cells and are widely used in SCI research. Joung et al. placed clusters of iPSC-derived cells on scaffolds. The platform can generate scaffolds to mimic in vitro central nervous system tissue structures and treat neurological diseases by developing novel clinical methods [131]. Fan et al. combined a GelMA hydrogel with iNSCs to accelerate SCI repair. Overall, IPSCs reduce inflammation and exert significant therapeutic effects by promoting axon regeneration (Fig. 7d) [123].

4.3. Others

There are other treatments for SCI in addition to bioactive factor and stem cell therapies. Examples include drug therapies, exosomes, and nanozymes.

4.3.1. Drug therapy

In terms of clinical treatment, patients are continuously monitored after SCI to prevent complications, such as dyspnea, cardiovascular aberrations, and hypoxia. After the condition stabilizes, the doctor performs internal and external decompression and internal fixation surgically to create good conditions for spinal cord recovery [132]. However, the disruption of the ascending and descending nerves caused by SCI, as well as the mass death of neuronal cells, makes it difficult to reconnect and regenerate the tissue through surgical means. The immunosuppressive drug methylprednisolone sodium succinate (MPSS) is used as a pharmacological adjunct in patients with SCI to improve the neurological function [133]. Ye et al. proposed a one-step solution to repair serious SCI by self-assembling a multifunctional hydrogel library with local punctual release of growth factors and MPSS. The synergistic release of growth factors and MPSS in hydrogel libraries can lead to significantly improved bridges for axonal regeneration [134].

4.3.2. Exosomes

Exosomes are vesicles that are secreted by cells into the extracellular environment and contain nucleic acids, proteins, lipids, and amino acids. Compared with the cells they are derived from, exosomes have the following advantages: (1) they are more stable, (2) they are enriched with growth factors, (3) they are more biocompatible, (4) they are safer, and (5) they can easily cross the blood–brain barrier. Owing to their biological advantages, exosomes have gradually become a popular topic in regenerative medicine and have been used in the treatment of cancer and degenerative neurological diseases [135]. Fan et al. developed conductive hydrogels loaded with BMSC-derived exosomes for SCI repair. Exosome-bound conductive hydrogels enhance the recruitment of local NSCs and accelerate the regeneration of neurons and axons, thus achieving functional recovery in the initial stages of SCI [136]. Yan et al. established a developmental engineering strategy to assemble DPMSCs into biological assemblies called spinors at three levels. Spinor exhibits a geometry like that of spinal cord tissue and obtains an optimized quantity and quality of autonomously released exosomes to inhibit scarring and inflammation and promote axon regeneration (Fig. 8a) [137].

4.3.3. Nanozymes

Xiong et al. designed novel “nanoflower” Mn_3O_4 integrated with “pollen” IRF-5SiRNA for antioxidant and anti-inflammatory combination therapy after SCI [138]. Nanozymes can effectively catalyze the production of O_2 from ROS, which is beneficial for reducing oxidative stress and hypoxia and promoting angiogenesis [104]. In SCI rats, multifunctional nanozymes enhance the proliferation and recovery of motor function in various neuronal subtypes, suggesting that remodeling of the extrinsic neural environment is a promising strategy for promoting neural regeneration (Fig. 8b) [138].

5. Hydrogel-based novel treatment strategies for SCI

There are many methods for processing biological materials, including 3D printing, injectable hydrogels, microspheres, electrospinning, and sponge scaffolds. Different processing methods give rise to biomaterials with different properties for select applications.

5.1. 3D printing scaffold

3D printing technology uses bioactive molecules and cells to precisely and effectively build complicated biomimetic functional scaffolds. 3D printing is fast, efficient, and has greater design freedom than other processing methods [139]. In fact, 3D printing technology is now widely used in orthopedics. However, 3D printing of biomaterials and cells is technically challenging [140]. In 3D printing of bone tissue engineering scaffolds, the use of single-material-printed bone tissue engineering scaffolds often has disadvantages. However, composites composed of different materials can improve the biocompatibility and mechanical properties of the stent [141]. With the rapid development of 3D printing technology, researchers are beginning to mix printing-related cytokines with cells to construct therapeutic biological scaffolds [142]. For instance, Liu et al. designed an NSC-loaded scaffold composed of HA

derivatives, CS, and matrix gum via 3D bioprinting. The NSCs encased in the scaffold maintained good viability. Furthermore, the in vivo scaffold promoted axon regeneration and deposition of reduced glial scars, resulting in a significant recovery of motor function in SCI rats (Fig. 9a) [143]. Similarly, Yang et al. prepared living nerve-like fibers composed of NSCs embedded in a designed hydrogel using extrusion-based 3D bioprinting. Their NSC hydrogels mimicked the ECM and improved immunomodulation, angiogenesis, neurogenesis, neural relay formation, and neural circuit remodeling, resulting in excellent functional recovery [144].

5.2. Injectable hydrogel

Hydrogels are soft materials with high water content and flexibility. Injectable drug-loaded hydrogels may be directly inserted into lesion sites to form a drug reservoir, which can significantly improve drug delivery to target tissue and reduce off-target toxicity [147]. In recent years, injectable hydrogels have shown great potential as new biomedical polymer materials. Natural hydrogel biomaterials derived from the ECM are of particular interest because they have properties similar to natural neural tissues and have a 3D network structure, inherent biocompatibility, and biodegradability [148]. Injectable ECM hydrogels have great potential for the treatment of traumatic SCI because they can fill lesion cystic cavities and adapt to the irregular form caused by lesion area defects through minimally invasive techniques [149]. Additionally, the self-healing performance of injectable ECM hydrogels may be crucial for prolonging their service life in vivo and restoring their structure and function after injection. Moreover, the presence of an electrical microenvironment favors the growth of neurons and myelination axon regeneration. Therefore, the design of injectable, conductive, ECM hydrogel materials may provide a new treatment modality for traumatic SCI [150]. For instance, Luo et al. developed a native

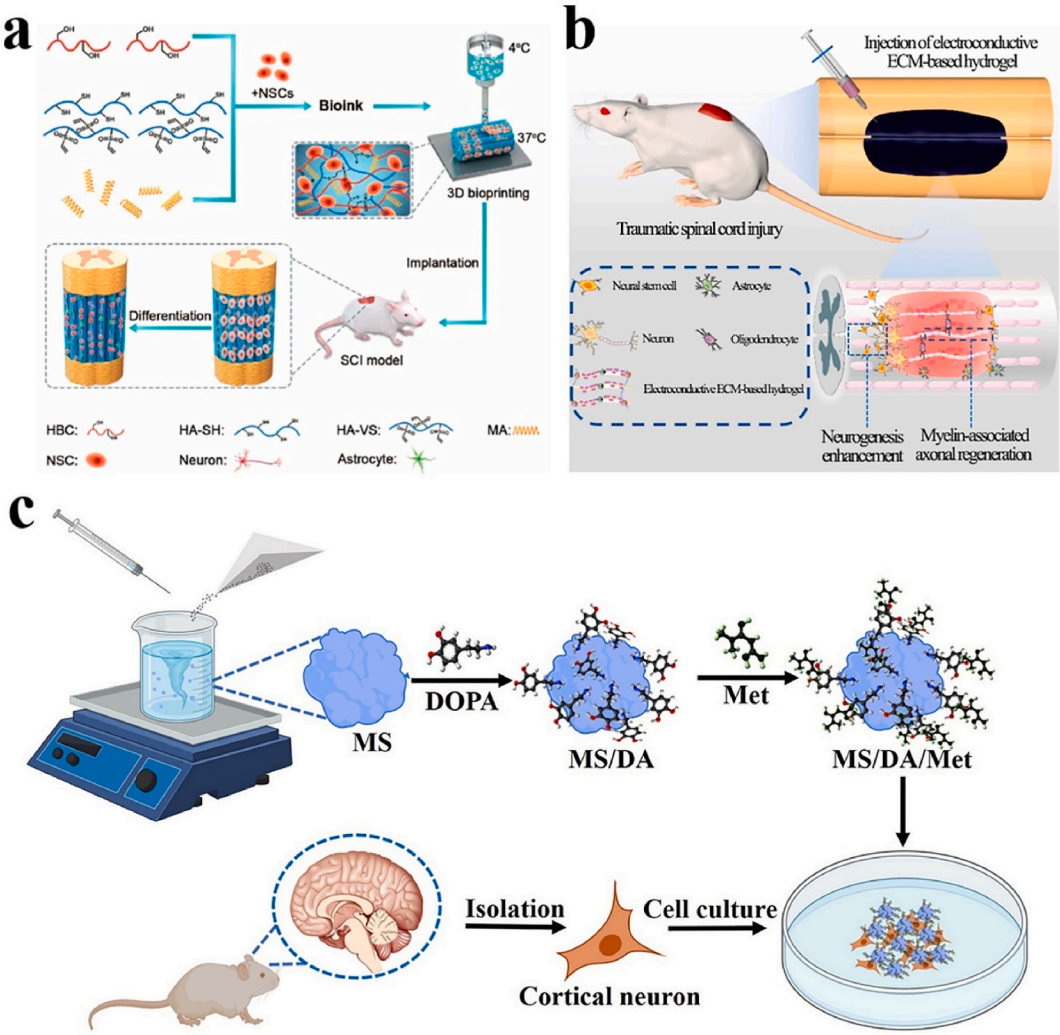

Fig. 9. 3D printing, injectable hydrogels, microspheres, and their applications. **(a) Schematic of** scaffold fabrication by 3D printing. Reprinted with permission from Ref. [143]. Copyright © 2021 Elsevier Ltd. All rights reserved. **(b) Schematic of** the application of electroconductive extracellular matrix (ECM)-based hydrogels. Adapted under the CC BY license from provide reference [145]. **(c) Schematic diagram of** fabrication of metformin loaded microsphere. Reprinted with permission from Ref. [146]. Rights managed by Taylor & Francis.

ECM biopolymer-based hydrogel containing polypyrrole that exhibited similar mechanical and conductive properties as native spinal cord tissue; the hydrogels enabled significant motor function recovery in the spinal cord of rats (Fig. 9b) [145]. Liu et al. prepared conductive hydrogels loaded with NSCs that could establish a fine cellular electrical signaling pathway, and an appropriate degradation cycle was conducive to the growth of new nerves [151].

5.3. Microspheres

SCI can lead to paraplegia or quadriplegia. The massive death of nerve cells and insufficient neurogenesis and angiogenesis hinder SCI repair. Currently, exogenous neurotrophic factors have great potential to promote SCI repair [152]. However, augmenting neurogenesis with exogenous nutrients or drugs to treat SCI remains challenging. Owing to their porosity and injectability, hydrogel microspheres have wide application prospects in the biomedical field, such as in the delivery of cells and bioactive factors/drugs, and the construction of tissue repair scaffolds [153,154]. Hydrogel/bead platforms that can be loaded with neurotrophic factors and cells are of great interest for SCI therapy. For example, Wu et al. prepared a hydrogel microsphere (PDGF-MPHM) using a piezoelectric ceramic-driven thermospray device that could maintain the proliferation of NSCs and inhibit their apoptosis in vitro to exert a strong neuroprotective effect. PDGF-MPHM + NSCs promote neuronal differentiation and NSC survival, and significantly improve motor function recovery in SCI rats [155]. Han et al. developed a metformin SF microsphere functionalized with dopamine using surface modification technology and the emulsification diffusion method, which exhibited good injectability and stability. Metformin-loaded silk microspheres significantly improve the growth of cortical neurons and have excellent potential for spinal cord regeneration (Fig. 9c) [146].

5.4. Electrospinning

Electrospinning is a common method for preparing nanoscale fiber membrane materials; it has the advantages of high porosity, adjustable pore size, and high surface volume ratio, and corresponds to the morphology of the ECM, which also makes it advantageous

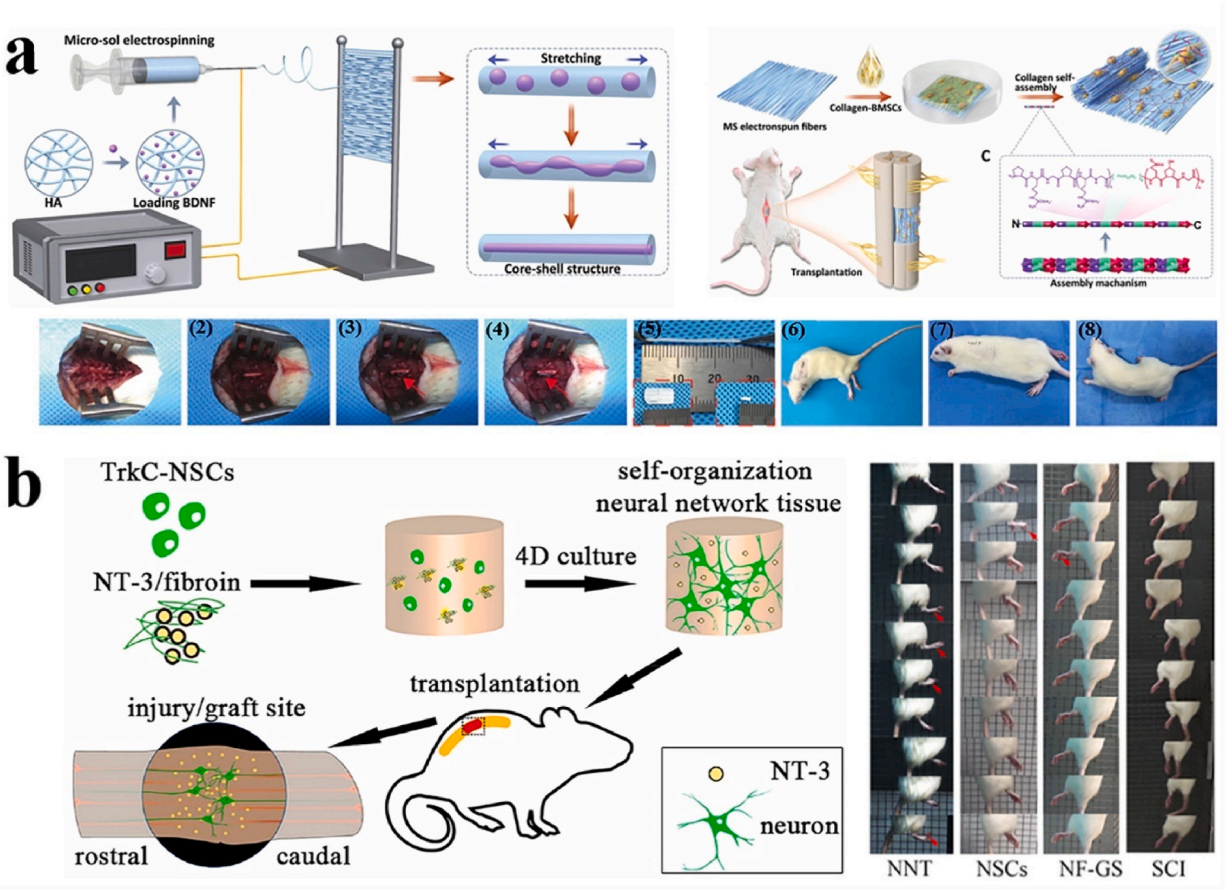

Fig. 10. Electrospinning, sponge scaffolds, microneedles, and their applications. **(a) Schematic of** fabrication and application of electrospinning fibers. **Photographs of** animal experiments. Reprinted with permission from Ref. [159]. Copyright © 2023 Wiley-VCH GmbH. **(b) Schematic of** fabrication and application of the NT-3/silk protein-coated gelatin sponge scaffold. Adapted under the CC BY license from provide reference [160].

in the biomedical field [156]. SCI is a neurological injury associated with a high rate of disability. Bio-scaffolds with biomimetic structures can be used as "bridges" to reconnect the tissue and promote regeneration. Liao et al. used electrospinning to prepare a biomimetic multichannel nanofiber catheter for promoting axon regeneration. The prepared nanofibers exhibited appropriate surface wettability. In vivo experimental results showed that TUBA-loaded nanofibers have great potential for clinical SCI healing [157]. In addition, the inflammatory cascade following SCI leads to local stem cell-necrotizing apoptosis, thereby limiting nerve regeneration. Thus, it is crucial to accelerate central nervous system recovery by coordinating NSC function and the inflammatory response. For example, Tang et al. constructed "concrete" composite scaffolds that repair nerve damage. The fiber composite improved local inflammatory responses. Novel fiber composites can serve as new treatments for SCI [158]. Xu et al. prepared directed living fiber bundles using collagen self-assembly and microsol electrospinning, which enhanced the dynamic regulation of stem cells in the inflammatory process (Fig. 10a) [159].

5.5. Sponge bracket

Liu et al. prepared spongy collagen scaffolds, which had excellent drug release properties and biocompatibility and could accelerate axon and neuron regeneration simultaneously after implantation into an SCI model. The results showed that hind limb motility and optimal neuroelectrophysiological recovery were improved in the SCI rats that received the scaffolds [161]. In summary, an ideal scaffold can coordinate axon and *in situ* neuronal regeneration and promote the restoration of neural function and reconstruction of neural circuits. Furthermore, Li et al. designed TrkC-modified NSC-derived neural network tissues in NT-3/silk protein-coated gelatin sponge scaffolds, which significantly improved motor function recovery in rats with SCI (Fig. 10b) [160].

5.6. Other

Microneedles are another biomaterial being actively researched for SCI drug and cell delivery. Huang et al. used miniature 3D printing technology to create a PPy-coated microneedle array. Inflammation was reduced by a PPy microneedle to release the steroid dexamethasone (Dexa) in a transdural model, demonstrating that this microneedle is feasible for delivering anti-inflammatory drugs into the central nervous system [162]. Fang et al. fabricated an MSC-containing patch (MN-MSC) with a porous microstructure and reasonable mechanical strength for treating SCI. The microneedle effectively delivered EXO, reduced cavity formation, and improved axonal survival. The treated rats demonstrated strong hind limb motor function recovery [163]. Similarly, Han et al. prepared a 3D-exohydrogel hybrid microneedles array patch for the *in situ* treatment of SCI. Glial scarring and SCI-induced inflammation were effectively reduced by 3D-Exo [55]. Cai et al. fabricated a GelMA-MXene hydrogel nerve conduit with electrical conductivity and internal-facing longitudinal grooves for SCI treatment. The resulting grooved GelMA-MXene hydrogels effectively promoted NSC adhesion, proliferation, and differentiation in vitro. Additionally, when a GelMA-MXene conduit loaded with NSCs was implanted into the injured spinal cord site, effective repair capability for complete transection of SCI was observed [164].

6. Challenges and perspectives

SCI is a complex neurological disorder with limited treatment options to date. The distinct anatomical structure of the spinal cord and the pathophysiological features of SCI are the main reasons for the limited efficacy of current therapeutic options. There are many drugs, bioactive substances, and stem cell derivatives that have shown promising results for the treatment of SCI. However, each option has its limitations due to difficulties working with the blood–spine barrier and the limited efficacy of oral and intravenous administration of drugs at the site of SCI. Local injections allow the drug or biologically active substance to be applied directly to the site of injury, but due to rapid clearance by the circulatory system, multiple injections may be necessary to achieve satisfactory results. Multiple injections can be traumatic and can even lead to complications such as infection.

Hydrogels have been increasingly researched in recent years for their good biocompatibility and loading capacity for local delivery and prolonged slow release of drugs; they have shown potential in the treatment of SCI. Owing to the good biocompatibility and plasticity of hydrogels, they can fill the defective spinal cord area and continuously release active ingredients. However, issues and challenges remain that need to be addressed by researchers. Designing hydrogels that are more compatible with the stiffness and elasticity of spinal cord tissue can help to better repair SCIs, but few researchers have worked on this to date. A particularly important feature that needs to be investigated is the swelling of the hydrogel. Hydrogel swelling may lead to compression of normal spinal cord tissues or even increase intracranial pressure, resulting in more serious complications. In addition, most previous research has focused on animal models and determining whether their findings can be applied to humans. Animal models similar to humans, such as primates, can be used. However, clinical trials in humans are required before any definitive conclusions can be drawn. Overall, SCI is a complex disorder that can occur in different regions of the spinal cord and results from different causes. Thus, SCI repair is a long-term, individualized, and multidisciplinary process that requires further research.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Notes

Any additional relevant notes should be placed here.

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