Materials Today Bio 31 (2025) 101536

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Designing hydrogel for application in spinal surgery

Rongpeng Dong, Shuang Zheng, Xueliang Cheng *

Department of Orthopedics, The Second Norman Bethune Hospital of Jilin University, Changchun, 130014, Jilin, China

ARTICLE INFO

Keywords:
Biomedical hydrogel
Spinal surgery
Intervertebral disc degeneration
Spinal cord injury
Dural sealing

ABSTRACT

Spinal diseases and injuries are prevalent in clinical settings and impose a substantial burden on healthcare systems. Current treatments for spinal diseases are predominantly limited to surgical interventions, drug injections, and conservative treatments. Generally, these treatment modalities have limited or no long-term benefits. Hydrogel-based treatments have emerged as potentially powerful paradigms for improving therapeutic outcomes and the quality of life of patients. Hydrogels can be injected into target sites, including the epidural, intraspinal, and nucleus pulposus spaces, in a minimally invasive manner and fill defects to provide mechanical support. Hydrogels can be designed for the localized and controlled delivery of pharmacological agents to enhance therapeutic effects and reduce adverse reactions. Hydrogels can act as structural supports for transplanted cells to improve cell survival, proliferation, and differentiation, as well as integration into adjacent host tissues. In this review, we summarize recent advances in the design of hydrogels for the treatment of spinal diseases and injuries commonly found in clinical settings, including intervertebral disc degeneration, spinal cord injury, and dural membrane injury. We introduce the design considerations for different hydrogel systems, including precursor polymers and crosslinking mechanisms. Herein, we discuss the therapeutic outcomes of these hydrogels in terms of providing mechanical support, delivering cells/bioactive agents, regulating local inflammation, and promoting tissue regeneration and functional recovery.

1. Introduction

Spinal diseases and injuries, including intervertebral disc degeneration, spinal cord injury, and dural membrane injury, are prevalent in clinical settings and impose a significant burden on healthcare systems. Current treatments for spinal diseases are predominantly limited to surgical interventions, drug injections, and conservative treatments. Generally, these treatment modalities have limited or no long-term benefits. Biomaterials have emerged as a potentially powerful paradigm for improving treatment outcomes and the quality of life of patients [1,2].

The intervertebral disc is the fibrocartilaginous part between two adjacent vertebral bodies that contributes to motion and weight bearing. It is composed of an inner gel-like nucleus pulposus and a thick outer ring of fibrous cartilage, known as the annulus fibrosus. Its degeneration begins with the loss of proteoglycans in the nucleus pulposus and disorganization of the lamellar collagen fiber network in the annulus fibrosus. Micro-fissures and tears appear in the annulus fibrosus, leading to herniation of nucleus pulposus. It further compresses surrounding tissues, causing pain and motor deficits [3,4]. Current standard treatment is discectomy with partial nucleotomy, which removes the extruded nucleus pulposus. However, it cannot replenish the lost nucleus pulposus or repair annulus fibrosus defects. Reherniation often occurs in these cases. Biomaterials have shown great potential for the treatment of intervertebral disc degeneration by providing mechanical support, repairing anatomical structures, and rebuilding tissue homeostasis [5–9].

Spinal cord injury is a major challenge in neurological clinical practice. Spinal cord injury is caused by compression, contusion, and spinal cord transection during traffic accidents, falls, or sports activities. This leads to serious motor and sensory disabilities, posing a huge financial burden on patients [10–12]. Current treatment of spinal cord injury relies on spine immobilization, surgical decompression, and pharmacological intervention. However, their efficacies are limited. The inhibitory environment at the injured site and the formation of fibrotic scars impair axonal regeneration and functional recovery of the spinal cord. Biomaterial-based tissue engineering and regenerative medicine strategies have been proposed for spinal cord repair [13–16].

The dural membrane is a fibrous connective tissue that covers the brain and spinal cord. It maintains the cerebrospinal fluid, which

* Corresponding author.
E-mail address: chengxl90@jlu.edu.cn (X. Cheng).

https://doi.org/10.1016/j.mtbio.2025.101536
Received 27 November 2024; Received in revised form 7 January 2025; Accepted 1 February 2025
Available online 3 February 2025

cushions the shock effect and provides essential electrolytes and proteins. In spinal surgeries, an incision of the dural membrane is often required to access the underlying tissues, which leads to cerebrospinal fluid leakage. Cerebrospinal fluid leakage can cause fistulas, hernias, and epidural fibrosis, contributing to extended hospital stays and increased medical costs. The current treatment relies on suturing the dural defect to achieve watertight sealing. However, suturing is technically difficult and time-consuming, particularly in difficult-to-access tissues. In addition, suturing damages the dural membrane and produces needle holes, posing a risk of cerebrospinal fluid leakage [17,18]. Biomaterials, such as liquid sealants, collagen matrices, and synthetic grafts, have been designed to seal dural injury and prevent cerebrospinal fluid leakage [19].

Hydrogels are particularly appealing for tissue repair in the spine because of their high-water content and structural similarity to the native extracellular matrix. They can be injected into target sites, including the epidural, intraspinal, and nucleus pulposus spaces, in a noninvasive manner and fill defects to provide mechanical support. They can be designed for the localized and controlled delivery of pharmacological agents to enhance therapeutic effects and reduce adverse reactions [20]. They can act as structural supports for transplanted cells to improve cell survival, proliferation, and differentiation, as well as integration into adjacent host tissues [21]. In this review, we summarize the recent advances in the design of hydrogels for the treatment of spinal diseases and injuries commonly found in clinical settings, including intervertebral disc degeneration, spinal cord injury, and dural membrane injury (Table 1). We introduce the design considerations for different hydrogel systems, including precursor polymers and crosslinking mechanisms. Herein, we discuss the therapeutic outcomes of these hydrogels in terms of providing mechanical support, delivering cells/bioactive agents, regulating local inflammation, and promoting tissue regeneration and functional recovery.

2. Hydrogel designs

In the realm of spinal surgery, the development of hydrogels necessitates careful consideration of several critical performance criteria. Firstly, biocompatibility and degradability are of utmost importance. Hydrogels must demonstrate non-toxic interactions with human tissues and should not provoke immune rejection or inflammatory responses. Furthermore, they should degrade into non-toxic byproducts or be naturally absorbed by the body. Commonly utilized materials in hydrogel formulation include polyethylene glycol, gelatin, and poly (lactic-co-glycolic acid) (PLGA). Secondly, the mechanical properties of hydrogels are crucial; they must possess adequate mechanical strength and flexibility to withstand the complex post-surgical spinal environment. The integration of dynamic covalent chemical reactions can result in self-healing hydrogels with frequency-dependent hardness, allowing them to absorb energy and mitigate shock, thereby offering effective spinal protection. Thirdly, functionality is a pivotal aspect in hydrogel design, encompassing features such as sustained drug release and responsiveness to microenvironmental stimuli, including variations in pH or reactive oxygen species (ROS). Lastly, personalized design is imperative for hydrogels intended for diverse biomedical applications. For example, hydrogels used for nucleus pulposus replacement should exhibit an appropriate elastic modulus to effectively replicate the mechanical properties of the nucleus pulposus. Conversely, hydrogels employed for dura mater sealing must demonstrate strong adhesion and resistance to tearing. Furthermore, when utilized in the context of spinal cord injury repair, these hydrogels should exhibit specific conductive properties.

2.1. Forms of hydrogel

In spinal surgeries, injectable hydrogels, including *in situ*-formed and shear-thinning hydrogels, can be administered through a needle or catheter into the epidural, intraspinal, and nucleus pulposus spaces. *In situ*-formed hydrogels are injected as precursor solutions and undergo a sol-to-gel transition in the body. This can be achieved through in situ physical or covalent crosslinking. Shear-thinning hydrogels display liquid-like characteristics under shear stress during injection and restore their original mechanical strength within the body [22,23]. These hydrogels are formed based on physical interactions or reversible covalent bonds. Injectable hydrogels are suitable for minimally invasive procedures where the operation space is limited. They are also ideal for covering the delicate spinal cord surfaces and filling irregular nucleus pulposus cavities. Alternatively, preformed hydrogels can be implanted surgically.

2.2. Hydrogel precursors

Various natural and synthetic polymers can be exploited to construct hydrogels for application in spinal surgery. The decellularized matrix was obtained by removing the cells from the tissue and retaining most of matrix components. A decellularized matrix is an ideal tissue-engineering scaffold because of the abundant biochemical signals that encourage cell adhesion and growth. Decellularized rat spinal cord matrix-based hydrogels supported neural cell adhesion and proliferation and promoted motor function recovery in rats with spinal cord injury [24]. A decellularized annulus fibrosus matrix derived from a porcine spine was used to form a hydrogel to seal annulus fibrosus defects. The implanted hydrogel showed good integration with the adjacent annulus fibrosus tissue [25]. Purified natural polymers including proteins and polysaccharides have well-defined compositions. Collagen is one of the main components of the extracellular matrix and is widely used in tissue engineering because of its biocompatibility and biodegradability. Collagen contains numerous integrin binding motifs that promote cell adhesion and proliferation [26]. Collagen has been manufactured into scaffolds to improve neurogenesis and axonal regeneration, and has been applied in clinical studies for spinal cord injury repair [27]. Gelatin is a product of collagen degradation that has been fabricated into hydrogels, sponges, and electrospun fibers for neural regeneration. A gelatin hydrogel loaded with transforming growth factor-beta (TGF-β) promoted intervertebral disc regeneration in a rat nucleotomy model [28]. In addition, polysaccharides, such as hyaluronic acid, chitosan, and alginate, have been extensively used to construct hydrogels for spinal cord repair and intervertebral disc regeneration.

Typically, synthetic hydrogels have precisely controlled compositions and properties. Poly(ethylene glycol) (PEG) has been widely used for drug modification to improve pharmacokinetics [29]. Various medical devices based on PEG have been approved by the Food and Drug Administration as surgical sealants, adhesion barriers, and embolization agents. PEG hydrogels are hydrophilic and bioinert. PEG hydrogels can be readily functionalized with bioactive moieties through end-group modifications.

2.3. Crosslinking strategies

For hydrogels designed for the delivery of cells and bioactive proteins, crosslinking reactions should be efficient under physiological conditions and compatible with the payloads [30]. Amine-involved reactions are convenient for constructing biomedical hydrogels because of the abundance of amino groups in various synthetic and natural polymers. The amino group reacts with an aldehyde to yield a reversible Schiff base bond [31]. Besides, a stable linkage can be formed between the amine and N-hydroxysuccinimide (NHS) ester group. These reactions proceed spontaneously in physiological solutions, yielding nontoxic byproducts. Aldehyde- or NHS-ester-terminated multi-arm PEGs are commercially available and can be readily used for hydrogel preparation. Click reactions, such as Michael addition, azide-alkyne cycloaddition, and Diels-Alder addition, have attracted extensive attention for biomedical hydrogel preparation because of their ambient

Table 1
Representative hydrogels for treatment of spinal diseases and injuries.

Code	Hydrogel types	Materials	Bioactive components	Crosslinking mechanisms	Physical properties	Experimental models	Therapeutic effects	Ref.
Intervertebral disc regeneration								
1	Interpenetrating network hydrogel	Oxidized dextran, gelatin, and four-arm PEG-acrylate	Nucleus pulposus cells	Schiff base bonding and photopolymerization	Compressive modulus of 15.86 ± 1.70 kPa	Porcine nucleotomy model	Enhancing the hydration and regeneration of degenerative nucleus pulposus	40
2	Hydrogel bioadhesive	Polyacrylamide, alginate, chitosan, and coupling agents	/	Radical polymerization and ionic interactions	Adhesion energy of ~159 J m^{-2}	Ex vivo bovine nucleotomy model	Preventing herniation under loading and restoring the biomechanics of bovine discs	47
3	/	Collagen and C16-modified hyaluronic acid	/	Photopolymerization	/	Ovine discectomy model	Promoting annulus fibrosus healing, restoring nucleus pulposus hydration, and maintaining disc mechanical stiffness	48
4	ROS- and pH-responsive hydrogel	Phenylboronic acid-modified gelatin methacryloyl	EGCG	Photopolymerization	Compressive modulus of over 30 kPa	Rat caudal vertebral puncturing model	Maintaining disc height and relieving intervertebral disc degeneration	55
5	Fe^{3+}-scavenging hydrogel	Pluronic F127 diacrylate and tannin	/	Photopolymerization	Compressive modulus of 34.61–55.07 kPa	Rat caudal vertebral puncturing model	Facilitating the recovery of disc structure and function	57
6	/	Four-arm PEG-SH and silver ion	Agomir874 miRNA	Ag–S coordination	Storage modulus of about 600 Pa	Rat caudal vertebral puncturing model	Increasing disc height, water content, and collagen production	60
7	/	Fibrin, genipin, and alginate microbeads	Annulus fibrosus cells	Genipin crosslinking	Young's modulus of 20–30 kPa	Ex vivo bovine caudal intervertebral disc model	Reducing herniation, restoring disc biomechanical properties, and reducing histological signs of degeneration	64
8	/	Decellularized annulus fibrosus matrix	TGF-β1	Photopolymerization	Compressive modulus of 317.2 ± 8.2 kPa	Rat caudal vertebra puncturing model	Reducing nucleus pulposus atrophy and restoring the biomechanical properties of disc	25
Spinal cord injury repair								
1	Conductive and electrogenic hydrogel	Chitosan, silk fibroin, and benzaldehyde-terminated PEG	Black phosphorus nanoplates	Schiff base bonding	Storage modulus of 7–40 Pa	Mouse spinal cord transection model	Promoting the motor and electrophysiological recovery by reducing inflammation, inducing the differentiation of neural stem cells to neurons, and promoting synaptic regeneration	85
2	Granular hydrogel	PEG microgels and PEG annealing linker	Neural progenitor cells	Inverse electron demand Diels–Alder click reaction	Storage modulus of≈438 Pa	Mouse cervical dorsal column lesion model	Supporting the neural progenitor cell graft differentiation toward neuronal lineages and the outgrowth of graft-derived axons into the host tissue	90
3	/	Engineered recombinant protein C7 and eight-arm PEG conjugated with proline-rich peptides	Human induced pluripotent stem cell-derived neurons	Peptide-peptide assembly	Shear modulus of ~10 Pa	Rat cervical spinal cord contusion model	Supporting the survival of transplanted cells, promoting neuritic growth into adjacent tissues, and improving sensorimotor function of rats	88
4	/	Dopamine-grafted hyaluronic acid and a designer peptide	Neurotrophic factor NT3 and curcumin	Pyrocatechol oxidization	/	Rat spinal cord transection model	Promoting neuron accumulation in ventral spinal cord, facilitating the establishment of heterogeneous neural connections via neuronal relays, and improving motor, sensory, and bladder functions	100
5	DAMP-scavenging hydrogel	Methacrylated gelatin and third-generation poly (amidoamine) dendrimer	IL-10	Photopolymerization	Compressive modulus of ~3 kPa	Mouse spinal cord transection model	Inducing M2 polarization of macrophages/microglia, downregulating proinflammatory cytokine expression, and promoting axon growth and neural regeneration	102
6	ROS-responsive hydrogel	Thioketal hyperbranched polymer and	Bone marrow derived stem cells	Photopolymerization	Compressive modulus of over 5 kPa	Rat spinal cord injury model	Reducing scar formation, facilitating neurogenesis, and promoting motor functional recovery	104

(*continued on next page*)

Table 1 (*continued*)

Code	Hydrogel types	Materials	Bioactive components	Crosslinking mechanisms	Physical properties	Experimental models	Therapeutic effects	Ref.
		methacrylated hyaluronic acid						
Dural sealing and prevention of epidural adhesion								
1	Tough adhesive hydrogel	Polyacrylamide, alginate, and coupling agents	/	Radical polymerization and ionic interactions	Toughness of over 5 kJ/m^2	Rat craniotomy model and porcine lumbar dural injury	Sealing dural injury and preventing leakage	111
2	Low-swelling adhesive hydrogel	Gelatin and o-phthalaldehyde terminated four-arm PEG	/	o-phthalaldehyde/ amine condensation	Compressive modulus of 112.0 ± 17.2 kPa	Rat and rabbit models of lumbar and cerebral dural defects	Sealing dural defects and preventing cerebrospinal fluid leakage without noticeable compression on brain and spinal cord	112
3	Anti-swelling adhesive hydrogel	Acryloyl-Pluronic F127, methacrylated hyaluronic acid, and acrylic acid NHS ester	/	Photopolymerization	Tensile modulus of≈90 kPa	Rabbit spinal dura injury model; Implantation in rat spinal epidural space	Sealing dural injury and preventing leakage; Avoiding compression injury to spinal cord and preserving the motor function of rats	113
4	Antioxidant hydrogel bioadhesive	Cysteine/amino-modified gelatin and PEG NHS ester	/	NHS/amine condensation	Compressive modulus of about 3.4 kPa	Rabbit laminectomy and dural injury model	Preventing tissue fluid leakage and epidural adhesion	117

reaction conditions, high efficiency, and outstanding chemo-selectivity [32]. In addition to chemical linkages, physical crosslinks are formed through ionic interactions, hydrogen bonds, and hydrophobic interactions. For example, alginate hydrogels can easily be prepared using Ca^{2+}.

3. Hydrogels for intervertebral disc regeneration

The intervertebral disc is a cartilaginous tissue located between adjacent vertebrae that allows slight movements of the spine, cushions the effect of shock and stress, and prevents friction between vertebrae. It consists of an inner gel-like nucleus pulposus and a thick outer ring of fibrous cartilage, known as the annulus fibrosus. The nucleus pulposus is composed of water, proteoglycans, collagen, and other proteins and has a high osmotic pressure to withstand the compressive load of motion and weight bearing. The annulus fibrosus consists of highly oriented and lamellar collagen fibers that resist high tensile stress during the application of pressure to the central nucleus pulposus. In intervertebral disc degeneration, elevated catabolic processes exacerbate the loss of proteoglycans and osmotic pressure within the nucleus pulposus. These changes are evidenced by the loss of intervertebral disc height and decreased hydration. Meanwhile, the lamellar collagen fiber network lost its organization. Micro-fissures and tears appear in the annulus fibrosus, leading to herniation of nucleus pulposus. It further compresses surrounding tissues, causing pain and motor deficits [33,34]. Current treatments of intervertebral disc degeneration include surgical excision of intrusive intervertebral disc fragments and implantation of artificial disc replacements. However, they cannot repair annular fibrosus defects. Displacement and extrusion of implants may occur because of poor integration with the surrounding tissues, leading to reherniation. Hydrogels are appealing for the treatment of intervertebral disc degeneration because they can be used to fill the nucleus pulposus cavity and seal annulus fibrosus defects [35]. Cellular and pharmacological payloads can be delivered locally by hydrogels and sustained at the target site to improve therapeutic effects and reduce systemic adverse reactions [36–38].

3.1. Tough hydrogels

Most hydrogels are mechanically weak against intervertebral disc loading and lack firm adhesion to tissues, leading to extrusion of the hydrogel from the defect. Various strategies such as crystalline structures, sacrificial bonds, and interpenetrating networks have been exploited to construct tough hydrogels [39] which hold great potential for application in intervertebral disc regeneration. Interpenetrating hydrogels are composed of two or more interpenetrated polymer networks that are individually crosslinked but not connected. Interpenetrating networks can provide hydrogels with excellent mechanical properties, such as stretchability and fracture toughness [39]. Zhou and al. reported an interpenetrating-network-toughened and strengthened hydrogel for nucleus pulposus regeneration [40]. The hydrogel is composed of a rigid four-arm PEG-acrylate network and a soft oxidized dextran/gelatin network. The modulus of hydrogel (15.86 ± 1.70 kPa) is still higher than that of normal nucleus pulposus tissue (5.39 ± 2.56 kPa). When used to encapsulate nucleus pulposus cells, the hydrogel supported long-term cell retention and survival. In a porcine nucleotomy model, the cell-laden hydrogel enhanced hydration and regeneration of the degenerative nucleus pulposus.

Mimicking the hierarchical and complex structures of natural intervertebral disc tissues is challenging. Nucleus pulposus mainly composed of proteoglycans and have a reticular fibrous structure. The annulus fibrosus is made up of multilamellar aligned collagen fibers and fibrocartilage, and is responsible for absorbing mechanical shocks and maintaining the structure of the nucleus pulposus. Chu et al. developed a complete wood framework intervertebral disc containing an anisotropic wood cellulose hydrogel-based annulus fibrosus and an elastic nanocomposite hydrogel-based nucleus pulposus [41]. After removing the colored lignin, the wood framework was immersed in a hydrogel precursor solution under vacuum to allow monomers and crosslinkers to infiltrate the pores and channels of the aligned cellulose framework. After polymerization, an anisotropic wood-cellulose hydrogel with high toughness and energy dissipation was formed.

3.2. Adhesive hydrogels

Tissue-adhesive hydrogels can firmly adhere to biological tissues and withstand biomechanical loading in intervertebral discs. Tissue adhesion can be achieved through the formation of covalent bonds and physical interactions between the hydrogels and tissue surfaces [42–44]. The amine and thiol groups on tissue proteins have been widely exploited to form covalent bonds by reacting with NHS esters, aldehydes, and catechol groups in hydrogels [45,46]. For instance, Li and co-authors developed a tissue-mimetic hybrid hydrogel bioadhesive for intervertebral disc repair (Fig. 1) [47]. This system was composed of

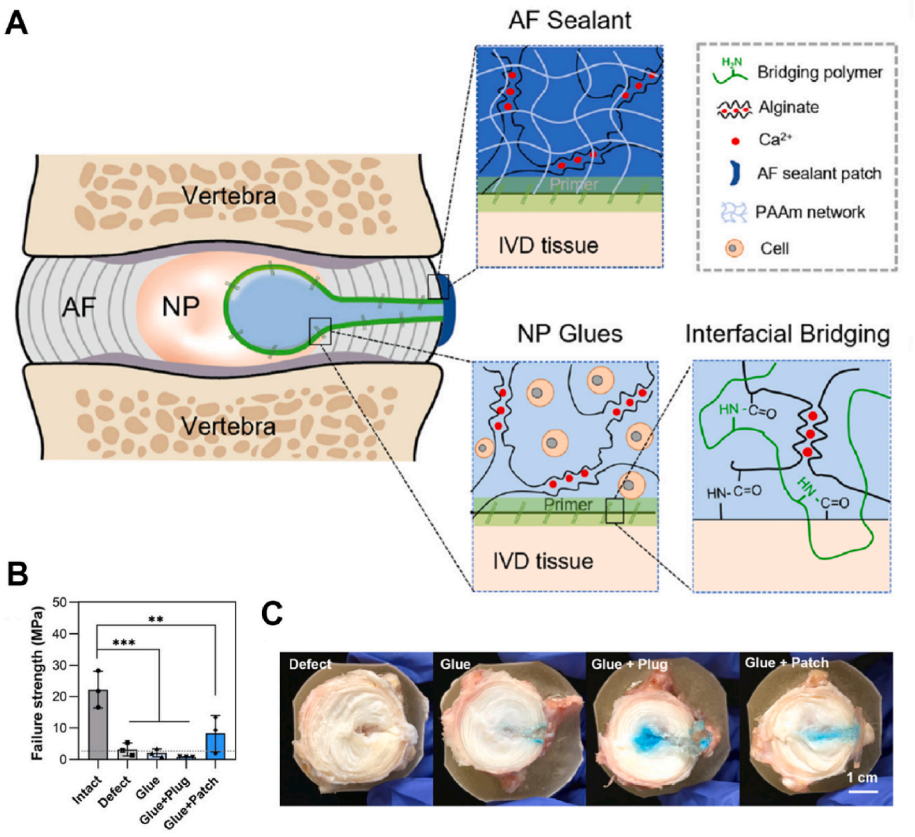

Fig. 1. (A) Mechanism of hybrid hydrogel bioadhesive for intervertebral disc repair and regeneration. Annulus fibrosus defect was sealed using alginate-polyacrylamide tough hydrogel patch (AF sealant), while nucleus pulposus cavity was filled with injectable alginate hydrogel (NP glue). (B) Comparison of failure strength. The dashed line indicates the upper limit of intradiscal pressure. (C) Cross-sectional images of intervertebral disc after mechanical test. Reproduced with permission [47]. Copyright 2023, Royal Society of Chemistry.

nucleus pulposus glue and an annulus fibrosus sealant. The nucleus pulposus glue composed of alginate and calcium sulfate was injected into nucleus pulposus cavity after treatment with a primer solution containing chitosan and coupling reagents. The annulus fibrosus sealant, consisting of an alginate-polyacrylamide tough hydrogel, chitosan, and coupling agents, can seal the annulus fibrosus defect and restore the biomechanics of the repaired disc. Biomechanical tests of bovine intervertebral disc motion segments showed that the hydrogel prevented herniation under loading and restored the biomechanics of bovine discs under cyclic compression. The ramp-to-failure tests were performed to evaluate the ability to prevent re-herniation of intervertebral discs. The results showed that the strength of the hydrogel sealant group is 8.2 ± 4.7 MPa, the strength of the intact group is 22.2 ± 4.8 MPa, and the strength of the defect group is (3.2 ± 1.7 MPa). At the same time, this strength is higher than the intervertebral disc pressure under physiological conditions (2.3 MPa). The results indicates that the prepared hydrogel sealant can promote the repair of the intervertebral disc.

Bonassar et al. reported that a combined strategy of nucleus pulposus augmentation and annulus fibrosus repair could prevent acute intervertebral disc degeneration [48]. C16-modified hyaluronic acid was first injected into the herniated nucleus pulposus space. Subsequently, a high-density collagen patch was photo-crosslinked in situ to fill the annular fibrosus lesion. In the ovine lumbar spine after discectomy, this combined strategy effectively promoted the healing of annulus fibrosus defects, restored nucleus pulposus hydration, and maintained the mechanical stiffness of the vertebra-intervertebral disc-vertebral segments for 6 weeks. Simultaneously, to assess the prolonged impact of increased hydrogel application in intervertebral disc repair, Gullbrand and colleagues developed endplate-modified disc-like angle ply structures (eDAPS). This study demonstrated that, in a rat caudal disc replacement model, the compromised intervertebral disc regained its mechanical properties under physiological conditions after a 20-week repair period. Similarly, in a goat cervical disc replacement model, the damaged intervertebral disc restored its mechanical properties under physiological conditions after an 8-week repair period [49].

3.3. *Targeting inflammation and ROS*

Inflammation plays a crucial role in the initiation and progression of intervertebral disc degeneration [50]. Anti-inflammatory agents can be loaded onto hydrogels to resolve inflammation. Reactive oxygen species (ROS), pH, and enzymes have been investigated as triggers for the responsive release of drugs in the inflammatory intervertebral disc microenvironment [51–55]. For instance, Wu et al. designed a pathological microenvironment-responsive hydrogel for the controlled release of anti-inflammatory compounds to promote the repair of degenerated intervertebral discs [56]. The hydrogel was formed by the photo-crosslinking of phenylboronic acid-modified gelatin methacryloyl. The naturally derived anti-inflammatory epigallocatechin-3-gallate (EGCG) was conjugated to the hydrogel via dynamic boronic ester linkage. The responsive release of EGCG was achieved under high ROS and acidic conditions. The hydrogel could maintain the viability of nucleus pulposus cells in 2 mM H_2O_2 and an inflammatory medium containing 10 ng/mL tumor necrosis factor-α. In a rat model of intervertebral disc degeneration, the hydrogel maintained the disc height and relieved intervertebral disc degeneration.

Ferroptosis also plays an important role in intervertebral disc degeneration [57]. Excessive Fe^{3+} contributes to reactive oxygen species production, oxidative stress, and inflammation. Scavenging of Fe^{3+} effectively inhibits ferroptosis of nucleus pulposus cells and delays

intervertebral disc degeneration. Chen et al. developed an Fe^{3+}-scavenging hydrogel to reshape iron metabolism and promote tissue repair in intervertebral disc degeneration [58]. The hydrogel was formed by the photocrosslinking of Pluronic F127 diacrylate. Tannin was incorporated into the hydrogel to provide the ability to adsorb Fe^{3+} through coordination interactions and to remodel the iron metabolism of cells. In a rat caudal vertebral puncture intervertebral disc degeneration model, the hydrogel effectively facilitated the recovery of disc structure and function.

3.4. Gene therapy

Gene therapy has emerged as an effective tool for the treatment of intervertebral disc degeneration [59,60]. Due to the avascular structure of intervertebral disc, intervertebral injection may be a promising delivery route compared with systemic administration. However, due to

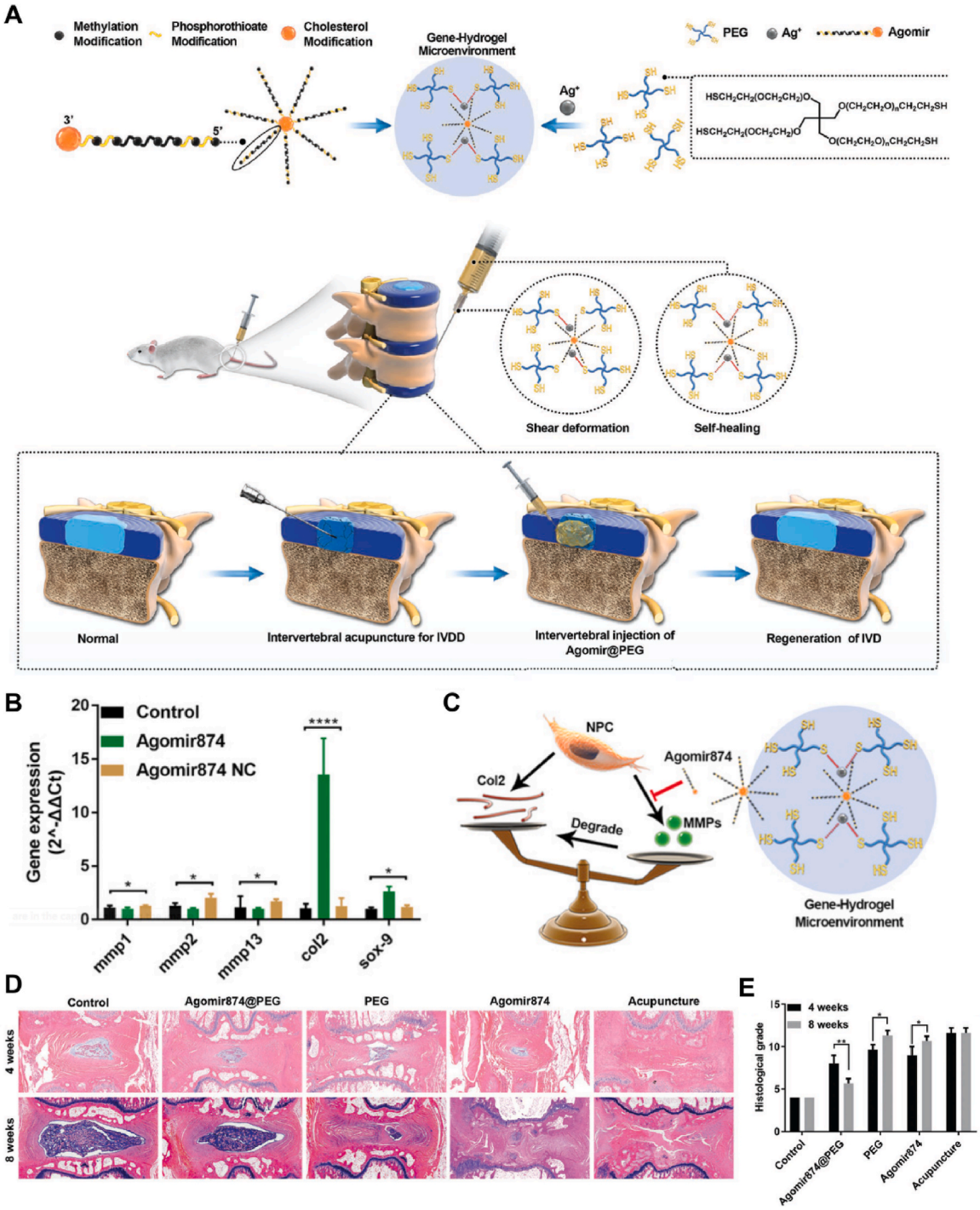

Fig. 2. (A) Gene-hydrogel microenvironment for treatment of intervertebral disc degeneration. Agomir, a cholesterol-, methylation-, and phosphorothioate-modified miRNA mimic, was loaded in an injectable and self-healing hydrogel composed of four-arm PEG-SH and silver ion. (B) Gene expression in NPCs treated with Agomir874 or Agomir874. (C) The mechanism of gene-hydrogel microenvironment regulating the synthesis/catabolism balance. (D) H&E staining images of rat caudal intervertebral discs after different treatments. (E) Histological grade at different time points. Reproduced with permission [60]. Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

high intradiscal pressure, liquid therapeutics are prone to leak out of the intervertebral space, which reduces therapeutic effects and causes undesired adverse reactions. Hydrogels are used to maintain miRNAs at their site of action. For instance, Shen et al. loaded agomir miRNA into a PEG hydrogel to regulate the synthesis and catabolism of the tissue extracellular matrix for the treatment of intervertebral disc degenerative diseases (Fig. 2) [61]. The hydrogel was prepared by the coordination of four-arm PEG-SH and silver ions. Agomir874 was used to downregulate the expression of matrix metalloproteinases in the nucleus pulposus, thereby reducing the degradation of the extracellular matrix produced by nucleus pulposus cells and regulating the synthesis/catabolism balance. In a rat caudal intervertebral disc degeneration model, treatment with the Agomir874-loaded hydrogel resulted in increased disc height, water content, and collagen production.

3.5. Cell therapy

Previous studies have suggested that the progression of intervertebral disc degeneration is closely related to a decrease in the number of intervertebral disc-resident cells. Supplementing degenerated intervertebral discs with regenerative cells, such as nucleus pulposus cells, induced pluripotent stem cells, and adipose-derived mesenchymal stem cells, is a promising strategy for treating intervertebral disc degeneration [62–64]. However, the intradiscal injection of cells showed limited efficacy owing to cell leakages and the harsh environmental conditions in degenerated intervertebral discs, including low nutrient levels, metabolic product accumulation, and high intradiscal pressure. Hydrogels can be engineered to provide an artificial microenvironment that supports the attachment and proliferation of transplanted cells. Thus, delivering cells to intervertebral disc with injectable hydrogels is a promising strategy for preventing herniation and promote intervertebral disc regeneration. For instance, Iatridis et al. designed a genipin-cross-linked fibrin hydrogel seeded with oxidized alginate microbeads for intervertebral disc cell therapy (Fig. 3) [65]. The working principle of the hydrogel balances the biomechanics and biological properties. On the one hand, it can provide immediate biomechanical stability, and on the other hand, promote functional cell synthesis of ECM for long-term healing, which can be used for IVD repair. The hydrogel can maintain stable mechanical properties within 42 days, which provides enough time for the repair of the intervertebral disc. Annulus fibrosus cells encapsulated in microbeads could maintain high viability, and display phenotypic cell morphology and gene expression after release. In a long-term bovine caudal intervertebral disc organ culture bioreactor, cell-laden composites can reduce the risk of herniation, restore intervertebral disc biomechanical properties, and reduce the histological signs of degeneration.

Incorporating bioactive peptides and proteins into hydrogels can promote cell-material interactions and improve cell survival and proliferation. Naturally derived proteins such as collagen and cytokines can be introduced into hydrogels by physical mixing. Alternatively, bioactive peptides can be covalently conjugated to a polymer network [66, 67]. Ye et al. reported that a composite hydrogel modified with collagen mimetic peptide and TGF-β1 could promote annulus fibrosus repair through annulus fibrosus cell recruitment and microenvironment regulation [68]. The composite hydrogel was composed of oxidized hyaluronic acid, dopamine, and polyacrylamide. The hydrogel exhibited good mechanical properties, bioadhesive strength, and self-healing ability. After modification with collagen mimetic peptide and TGF-β1,

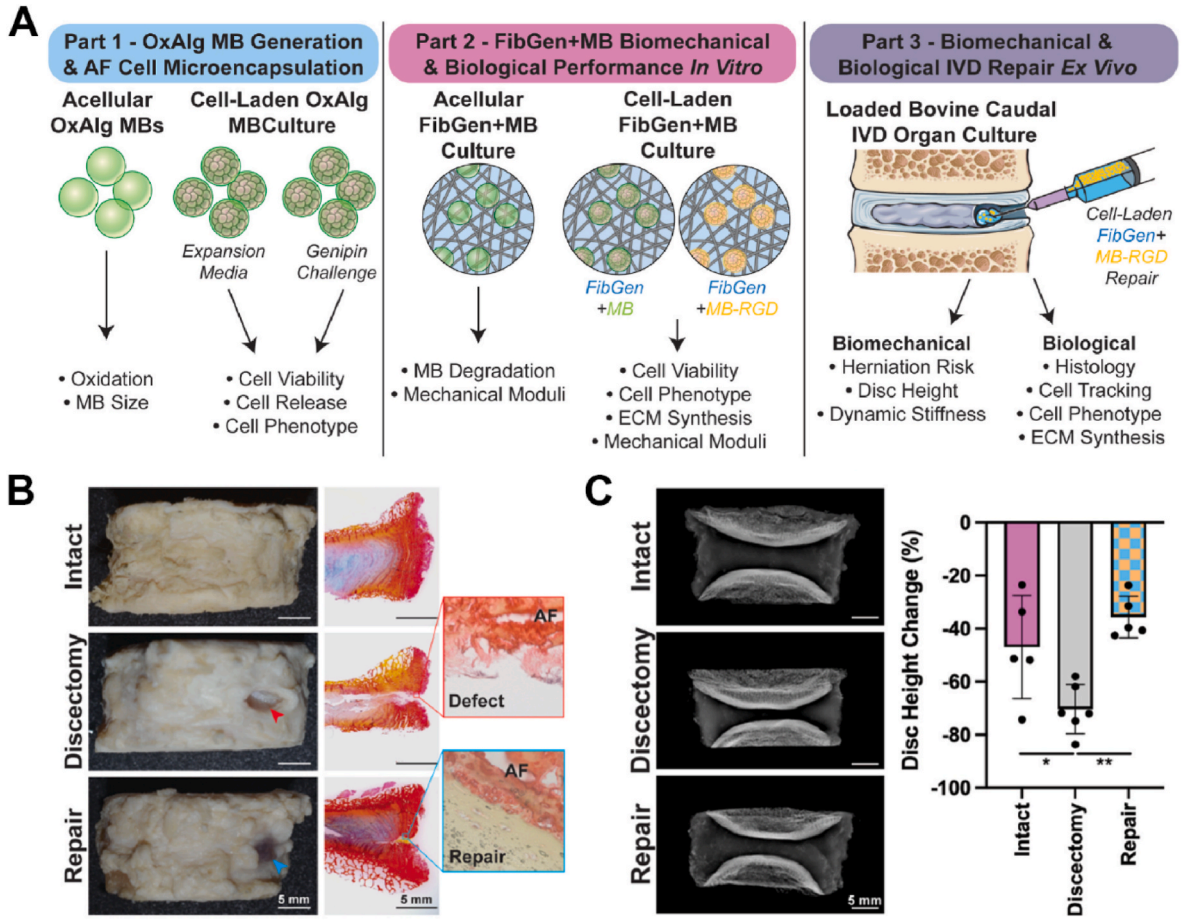

Fig. 3. (A) Genipin-crosslinked fibrin hydrogel (FibGen) seeded with oxidized alginate microbeads (OxAlg MBs) for encapsulation of annulus fibrosus (AF) cells. (B). (C). Reproduced with permission [64]. Copyright 2022, Elsevier.

the hydrogel could recruit annulus fibrosus cells, promote extracellular matrix synthesis, and relieve lipopolysaccharide-induced inflammatory response. In a rat tail annulus fibrosus defect model, the composite hydrogel effectively sealed defects and alleviated intervertebral disc degeneration. Li et al. reported that TGF-β1-supplemented decellularized annulus fibrosus matrix hydrogels supported the adhesion, proliferation, and extracellular matrix production of annulus fibrosus cells [25]. Decellularized annulus fibrosus matrix obtained from porcine spines exhibited similarity in composition and structure to native tissue. In a rat caudal vertebra puncturing model, the hydrogel was infiltrated by host cells and integrated into the surrounding tissue after implantation. The hydrogel effectively reduced nucleus pulposus atrophy and restored the biomechanical properties of discs.

One of the major risks associated with cell-based therapy is the immune rejection of transplanted cells. Extracellular vesicles such as exosomes have the potential to achieve therapeutic effects similar to those of cell transplantation [69–71]. Exosomes contain proteins, nucleic acids, and bioactive components that play crucial roles in various physiological processes. For instance, mesenchymal stem cell-derived exosomes have been reported to protect nucleus pulposus cells from apoptosis, promote the synthesis of the extracellular matrix, and relieve the inflammatory response in discs [72]. Zhang and co-authours developed an injectable extracellular matrix hydrogel functionalized with adipose-derived mesenchymal stem cell exosomes for the treatment of intervertebral disc degeneration by regulating metabolism and pyroptosis [73]. In vitro studies have shown that the sustained release of exosomes from hydrogels downregulates the expression of matrix metalloproteinase-13 and reduces pyroptosis of nucleus pulposus cells. Liu et al. reported that cartilage endplate stem cells loaded into a cartilage matrix hydrogel released exosomes for intervertebral disc regeneration [74]. The exosomes can regulate autophagy and senescence of nucleus pulposus cells and relieve disc degeneration by activating the PI3K/AKT signaling pathway.

The role of hydrogels in intervertebral disc repair encompasses both mechanical and biological functions. Mechanically, hydrogels can occupy the cavity of the nucleus pulposus and seal defects in the annulus fibrosus, thereby restoring the biomechanical integrity of the intervertebral disc and preventing recurrent herniation. Biologically, nucleus pulposus adhesives exhibit anti-inflammatory and antioxidant properties and facilitate the delivery of exogenous cells, thereby promoting disc repair and matrix regeneration. Upon initial application into the intervertebral space, the hydrogel primarily serves as mechanical support, subsequently facilitating the repair and regeneration of the intervertebral disc. While the hydrogel demonstrates effective functionality in the short term, its efficacy may diminish over time. This decline could be attributed to the degradation of the hydrogel itself, the reduction in mechanical properties, or alterations in the biological environment. Therefore, the permanent integration of implant materials with natural tissues is essential. Current research has successfully extended the functional lifespan of hydrogels to exceed six weeks. The gradual degradation of the intervertebral disc creates space for ECM growth, thereby providing a critical time window for disc repair.

4. Hydrogels for spinal cord injury repair

Spinal cord injury can result from traffic accidents, falls, or sports injuries. Besides, infections, tumors, inflammation, and vertebral column degenerative disorders are also possible to occur. In the primary phase of spinal cord injury, immediate mechanical forces exerted on the spinal cord can destroy neural and vascular tissues, leading to edema, hematoma, and ischemia. Subsequently, a cascade of molecular and cellular reactions persists for days to months, leading to the formation of fibrotic scars and cystic cavities [75,76]. Spinal cord injury can lead to mild to severe sensory, motor, and autonomic impairments. Currently, clinical treatments for acute spinal cord injury include spinal immobilization, surgical decompression, and injection of corticosteroids, such as methylprednisolone. Physical rehabilitation can improve the self-care ability of patients with chronic spinal cord injury and reduce complications. However, no effective treatment to restore neurological function is available [77–79].

For spinal cord injury repair, hydrogels should have the following properties: biocompatibility and minimal inflammatory response; biodegradability with suitable degradation time; the ability to support neural cell adhesion, proliferation, and differentiation; and electrical and biochemical activities that promote axonal growth and neurogenesis.

4.1. Conductive hydrogel

Electrical stimulation facilitates tissue repair in the nervous system by regulating stem cell differentiation and by alleviating inflammation [80,81]. However, metal-based electrode and electroacupuncture may produce discomfort to patients, and traditional implementation of electrical stimulation by subcutaneous electrode implantation is invasive and associated with the risk of infection. To overcome these issues, injectable and conductive hydrogels have been designed [82–85]. Wei et al. have designed a conductive electrogenic hydrogel for spinal cord injury repair [86]. The hydrogel was formed via a Schiff base reaction between chitosan, silk fibroin, and benzaldehyde-terminated PEG. Black phosphorus nanoplates were incorporated into the hydrogel via electrostatic interactions. Under a rotating magnetic field, hydrogels produce electrical signals and promote the differentiation of neural stem cells into neurons. In a mouse model of spinal cord transection, the hydrogel promoted motor and electrophysiological recovery by reducing inflammation, inducing differentiation of neural stem cells into neurons, and promoting synaptic regeneration. Luo et al. constructed a conductive hydrogel composed of chitosan, gelatin, and black phosphorus to promote nerve regeneration by providing in situ electrical stimulation (Fig. 4) [87]. After placing a soft, insulated metal plate on the injury site, an alternating current was generated in the conductive hydrogel via electrostatic induction. The hydrogel can provide electrical stimulation with adjustable time line, duration and intensity in vivo as required. In a rat model of spinal cord transection, hydrogel-assisted electrical stimulation promotes functional recovery and neural tissue repair by facilitating remyelination, axon regeneration, and neural stem cell differentiation.

4.2. Cell therapy

The transplantation of neural progenitor cells is a promising strategy for the treatment of spinal cord injury [88]. However, traditional cell transplantation usually leads to low cell viability, with a reported survival rate of only 1 % [89]. The injection of cells into saline may lead to mechanical membrane damage and cell death due to shear force. In addition, the transplanted cells can extravasate under positive spinal cord pressure, resulting in minimal cell deposition at the target site. Injectable and shear-thinning hydrogels can be used to encapsulate and deliver cells to improve the efficacy of cell therapies [90]. Alge and al. proposed clickable granular hydrogel scaffolds for the delivery of neural progenitor cells for the treatment of spinal cord injury (Fig. 5) [91]. PEG microgels functionalized with cell-adhesion peptides and MMP-cleavable peptides were synthesized in a PEG-dextran aqueous two-phase system using thiol-norbornene click chemistry. The granular hydrogel was then assembled by mixing with a tetrazine-terminated PEG annealing linker. The granular hydrogel exhibited highly tunable physicochemical properties and inherently interconnected microporosity. When used to deliver neural progenitor cells, the granular hydrogel can support neural progenitor cell graft differentiation toward neuronal lineages and the outgrowth of graft-derived axons into the host tissue.

By incorporating biophysical and biochemical cues, hydrogels can provide an artificial microenvironment that promotes the integration of

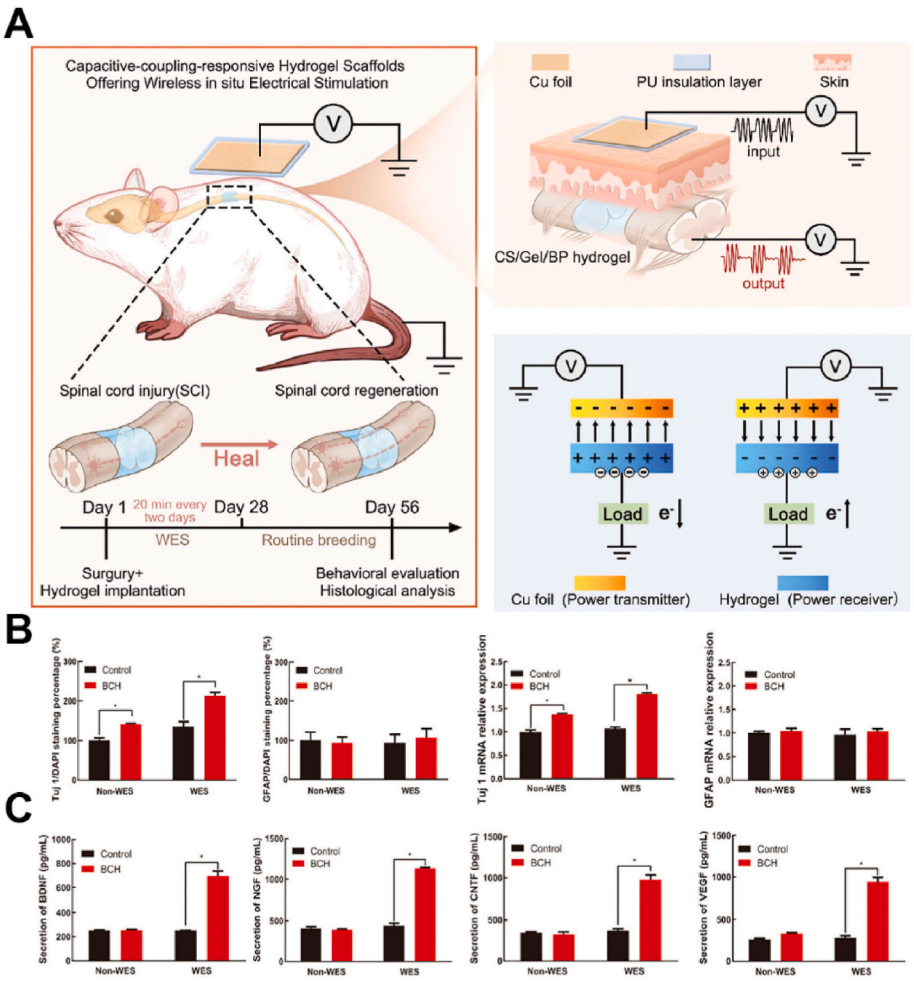

Fig. 4. (A) Schematic illustration of conductive hydrogel-assisted electrical stimulation for spinal cord injury repair. In situ electric stimulation was produced in conductive hydrogel by electrostatic induction with a soft insulated metal patch. (B) Hydrogel-assisted wireless electrical stimulation (WES) promoted neural stem cell differentiation. Tuj1, a marker for neuron-specific microtubule element; GFAP, a marker for astrocyte. (C) WES increased neurotrophic factor secretion. BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; CNTF, ciliary neurotrophic factor; VEGF, vascular endothelial growth factor. Reproduced with permission [86]. Copyright 2024, Wiley-VCH GmbH.

transplanted cells with native tissues. Heilshorn et al. developed an injectable hydrogel to deliver human-induced pluripotent stem cell-derived neurons for cervical spinal cord injury repair [89]. The hydrogel was formed from engineered recombinant protein C7 with folded WW domains and eight-arm PEG conjugated with proline-rich peptides through peptide-peptide assembly. Poly(N-isopropylacrylamide) was conjugated to the PEG-peptide copolymer to provide additional physical crosslinking at physiological temperatures. In a rat cervical spinal cord contusion model, the cell-laden hydrogel supported the survival of transplanted cells, promoted neuritic growth into adjacent tissues, and improved sensorimotor function in rats.

DNA-based supramolecular hydrogels have emerged as outstanding candidates for regenerative medicine because of their defined sequences, tunable structures, and precise recognition [92–94]. Liu and al. developed a DNA supramolecular hydrogel that promotes neurogenesis and functional recovery in spinal cord transection injury [95]. The supramolecular hydrogel was built from a DNA duplex with a persistence length of approximately 50 nm. The distance between the two crosslinking points was approximately 20 nm, making the DNA hydrogel more permeable than traditional hydrogels. In rats with a 2 mm spinal cord gap, the neural stem cell-laden DNA hydrogel promoted the formation of a renascent neural network and the recovery of hindlimb function.

For cell transplantation, the use of animal-derived scaffolds is limited because of batch-to-batch variations. Self-assembling peptide-based hydrogels with well-defined sequences and physicochemical properties exhibit high translational potential [96]. Gelain and al. developed a self-assembling peptide hydrogel scaffold that facilitated human neural stem cell maturation and neural regeneration to treat spinal cord injury [97]. In the culture medium, the cell-peptide constructs self-assemble into solid-like scaffolds with nanofibrous β-rich structures and stiffness in the range of nervous tissues. *In vitro* studies showed that the scaffolds induced differentiation of encapsulated cells into neural phenotypes. In a rat model of spinal cord hemisection injury, cell-laden hydrogels reduced inflammation and astrogliosis while significantly promoting axon regeneration and motor functional recovery.

Furthermore, several challenges in cell-based therapies are present, including limited cell sources and expensive and time-consuming *in vitro* cell expansion procedures [88]. Neural stem cells need to be harvested from allogeneic donor brain and spinal cord tissues. Alternatively, neural stem cells that differentiate from induced pluripotent stem cells are a more practical source, because they can be obtained from autologous somatic cells. In addition, isolated cells, including multiple cell types, require purification and testing to circumvent undesired adverse reactions or tumorigenicity. Cell expansion is a time-consuming and expensive procedure requiring good manufacturing practices for regulatory approval.

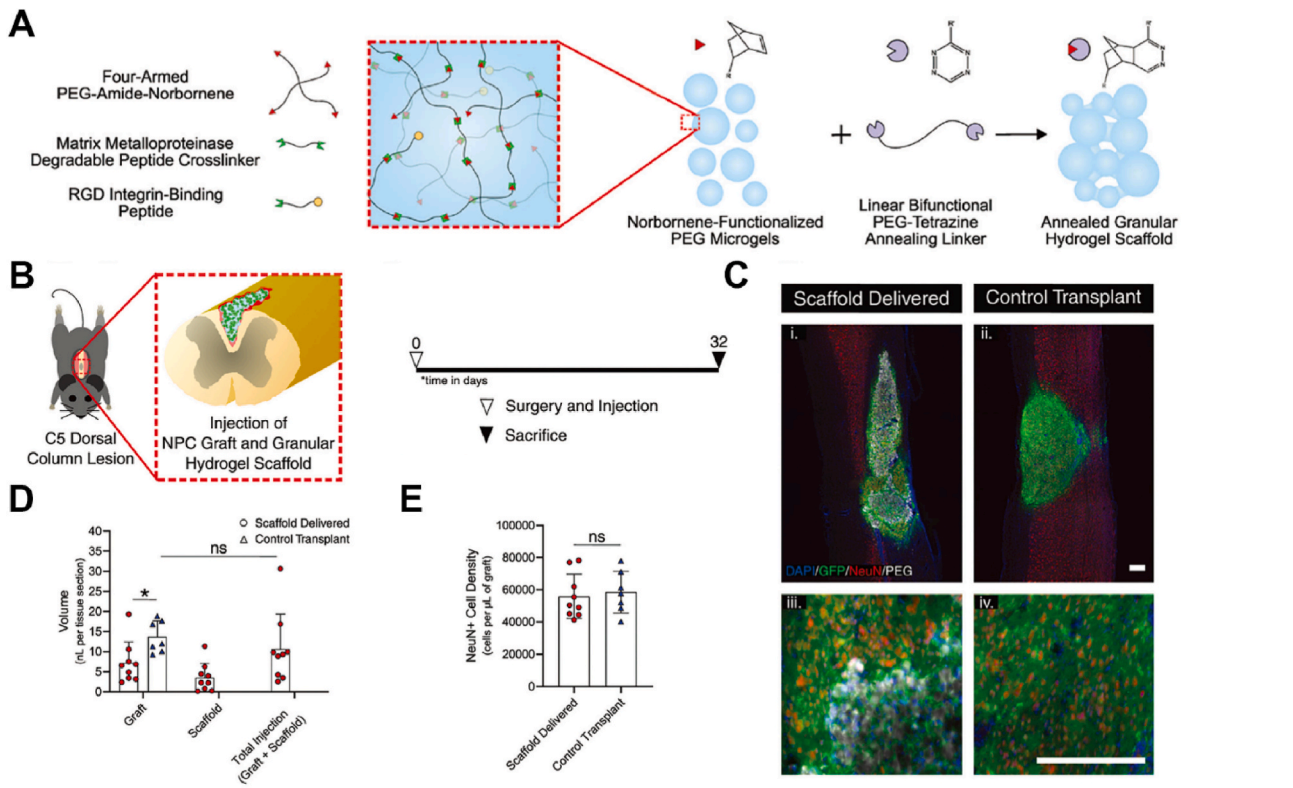

Fig. 5. (A) Schematic illustration for preparation of granular hydrogel. PEG microgels functionalized with cell adhesion peptide and matrix metalloproteinase-cleavable peptide were first synthesized. Then, the granular hydrogel was assembled by mixing PEG microgels with a tetrazine-terminated PEG annealing linker. (B) Hydrogel delivery of neural progenitor cells to mice. (C) Immunofluorescent staining images of PEG hydrogel (white), neuronal nuclear protein (Red), and neural progenitor cell grafts (green). Scale bar, 200 μm. (D) Quantification of graft and scaffold volume. (E) Quantification of neuronal nuclear protein positive cell density. Reproduced with permission [90]. Copyright 2024, Wiley-VCH GmbH.

4.3. Delivery of bioactive payloads

Several small-molecule drugs and proteins have been reported to treat spinal cord injury by reducing apoptosis, relieving inflammation, and improving functional recovery. Owing to the slow regeneration of the nervous system, the delivery of drugs and bioactive agents usually requires multiple dosages to maintain the therapeutic effect. Systemic delivery of drugs is inefficient because of the blood-spinal cord barrier. To reduce the systemic off-target effects and toxicity, therapeutics can be delivered using hydrogels and released in a localized and sustained manner [98]. Gao and al. loaded human mesenchymal stem cell-derived exosomes into an adhesive hydrogel to treat spinal cord injury [99]. The hydrogel was formed by the Schiff base reaction between oxidized hyaluronic acid and adipic dihydrazide-modified hyaluronic acid, and modified with a laminin-derived adhesive peptide. Exosomes show prolonged retention and sustained release profiles *in vitro*. The hydrogel effectively relieved inflammation, promoted the recovery of hindlimb motor function, and protected urinary tissues from neurogenic injury.

Trauma induces a cascade of pathophysiological events that leads to the formation of fibrotic scars [100]. This hostile environment impedes axonal growth and neural regeneration. Various strategies have been explored to reduce fibrotic scar formation, such as degradation of the extracellular matrix and suppression of extracellular matrix deposition. He et al. developed a tissue-integratable hydrogel for the delivery of neurotrophic factor NT3 and curcumin to prevent fibrotic scarring and promote spinal cord injury repair [101]. The hydrogel was composed of dopamine-grafted hyaluronic acid and the designer peptide HGF-(RADA)$_4$-DGDRGDS. In a rat spinal cord transection model, the hydrogel promoted neuronal accumulation in the ventral spinal cord, facilitated the establishment of heterogeneous neural connections via neuronal relays, and improved motor, sensory, and bladder functions in rats.

4.4. Targeting inflammation and ROS

After trauma, inflammation and oxidative stress cause secondary injuries at the lesion site. Tissue-resident macrophages and circulating neutrophils recognize damage-associated molecular patterns (DAMPs) released from injured tissues and produce proinflammatory factors and ROS. Targeting inflammation and ROS is a promising strategy for improving hostile environments, protecting transplanted cells, and facilitating neurogenesis [102]. Dai et al. designed a hydrogel to scavenge DAMPs and release the anti-inflammatory cytokine IL-10 to promote neural regeneration and motor function recovery [103]. The hydrogel was formed by the visible light crosslinking of methacrylated gelatin with a cationic third-generation poly(amidoamine) dendrimer and IL-10. The hydrogel can scavenge negatively charged DAMPs through electronic interactions and relieve the pro-inflammatory responses of macrophages and microglia. In a mouse spinal cord transection model, the hydrogel induced the polarization of macrophages/microglia toward the M2 phenotype, downregulated proinflammatory cytokine expression, and promoted axonal growth and neural regeneration. Cheng et al. proposed a self-assembled hydrogel based on Mg/Mn layered double hydroxides and silk fibroin for spinal cord injury repair (Fig. 6) [104]. The hydrogel scavenges ROS and releases oxygen to relieve oxidative stress and hypoxia. In vitro studies showed that the hydrogel promoted PC12 the growth and differentiation. In a mouse model of spinal cord injury, the hydrogel reduced scar formation and promoted the recovery of motor function. Gao et al. constructed an ROS-responsive hydrogel to encapsulate bone marrow-derived stem cells for spinal cord injury repair [105]. The hydrogel was formed by photocrosslinking an ROS-cleavable thioketal hyperbranched polymer, methacrylated hyaluronic acid, and CQAASIKVAV peptide, and physically loaded with epidermal growth factor

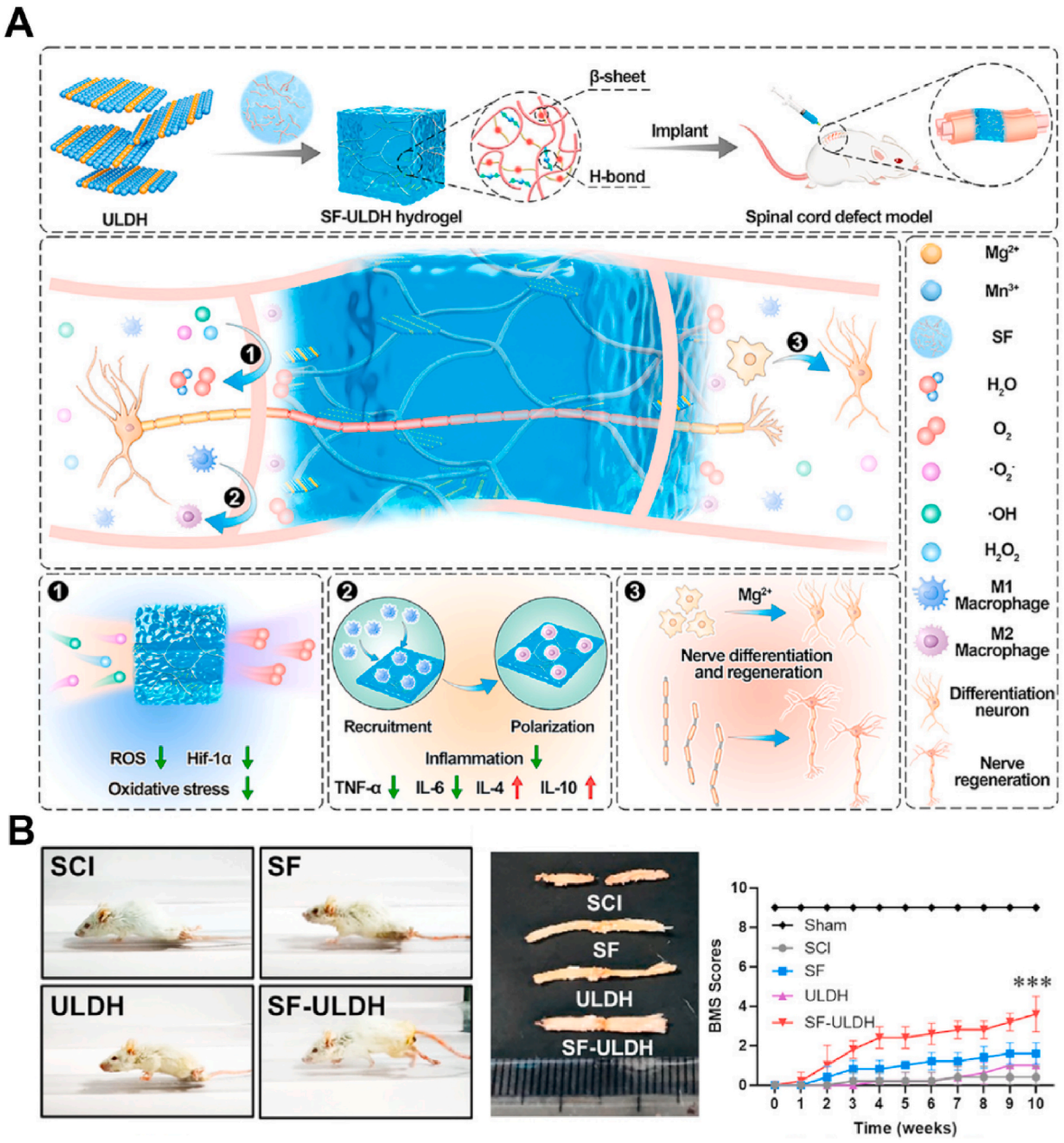

Fig. 6. (A) Metal ion-based hydrogel converts ROS to O_2 to relieve oxidative stress and inflammation, and releases Mg^{2+} to promote neural growth and differentiation. The hydrogel was formed from silk fibroin (SF) and Mg/Mn layered double hydroxides (ULDH) through hydrogen bonding. (B) In vivo assessment in a mouse spinal cord transection model. Behavioral recovery, images of spinal cord tissues, and Basso Mouse Scale (BMS) score of lower limb motor function. Reproduced with permission [103]. Copyright 2023, Elsevier.

and basic fibroblast growth factor. The hydrogel relieved the ROS-mediated oxidative damage and downregulated the production of inflammatory cytokines. In a rat model of spinal cord injury, the cell-laden hydrogel reduced scar formation, facilitated neurogenesis, and promoted functional motor recovery.

5. Hydrogels for dural sealing and prevention of epidural adhesion

The dura mater is a fibrous connective tissue membrane that covers the brain and the spinal cord. In spinal surgery, an incision in the dura mater is often required to access the underlying tissues. One of the complications is cerebrospinal fluid leakage, which has an incidence rate of 4–32 % [106]. Cerebrospinal fluid leakage can cause fistulas, hernias, and epidural fibrosis, leading to extended hospital stays and increased medical costs. Durable watertight sealing of dural defects is crucial for dural regeneration because of the lack of intrinsic clotting mechanisms. Current treatment relies on suturing the dural defect. However, suturing is technically difficult and time-consuming, particularly in difficult-to-access tissues. In addition, suturing damages the dural membrane and produces needle holes, posing a risk of cerebrospinal fluid leakage.

Hydrogel adhesives and sealants have received extensive attention for dural sealing because of their outstanding biocompatibility, biodegradability, and biological functions [107–109]. Hydrogel adhesives utilize various covalent bonds and physical interactions to adhere to tissue surfaces [110,111]. For example, primary amines derived from lysines in tissue proteins are the most widely used targets. They can covalently couple with the NHS ester, aldehyde, and catechol groups of the hydrogel adhesives. Mooney et al. developed a tough adhesive

hydrogel for the intraoperative sealing of the dural membrane (Fig. 7) [112]. A mixture of chitosan and coupling reagents was applied to the surface of an alginate-polyacrylamide tough hydrogel, which was compressed into tissue surfaces. The hydrogel showed stronger adhesion (5 kJ/m^2) and higher burst pressure (>200 mmHg) than commercially available DuraSeal and Adherus. The hydrogel could attach to the dura for more than 4 weeks after application in rats, which would provide sufficient time for the repair of the dura mater.

Existing dural sealants tend to excessively swell and compress the spinal cord, leading to severe complications. He et al. designed a tissue-adhesive and low-swelling hydrogel for the watertight sealing of dural defects [113]. The hydrogel was covalently crosslinked with o-phthalaldehyde-terminated four-arm PEG. The hydrogel displayed a burst pressure of over 200 cmH_2O, far surpassing the normal cerebrospinal fluid pressure. The hydrogel exhibited low swelling ratios both *in vitro* and in vivo. In rat and rabbit models of lumbar and cerebral dural defects, the hydrogel outperformed fibrin glue in sealing the dural injury and preventing cerebrospinal fluid leakage without noticeable compression of the brain and spinal cord. Zhao et al. proposed an anti-swelling adhesive hydrogel for hemostasis and dural sealing (Fig. 8) [114]. The hydrogel was formed by photo-crosslinking acryloyl-functionalized Pluronic F127, methacrylated hyaluronic acid, and an acrylic acid NHS ester. Pluronic F127 self-assembles into micelles at room temperature. When exposed to body temperature, the

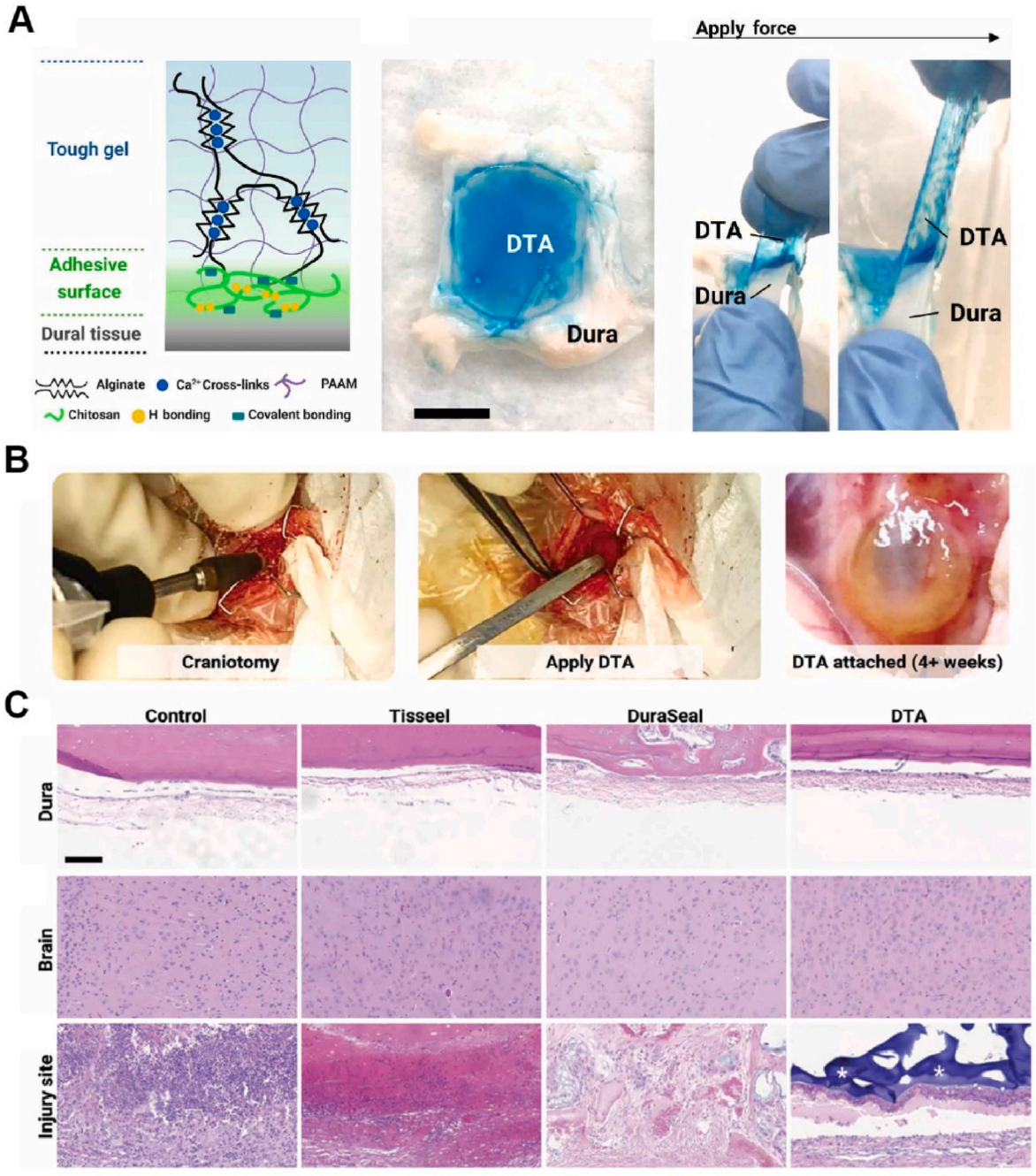

Fig. 7. (A) Schematic illustration of dural tough adhesive (DTA) composed of alginate-polyacrylamide tough hydrogel and chitosan-based adhesive surface, and images showing the adhesion and peel test of DTA on porcine dura. (B) Implantation of DTA on rat dural membrane for 4 weeks. (C) H&E staining images of dura, brain, and craniotomy injury site 4 weeks after implantation of DTA and commercial sealants Tisseel and DuraSeal. Reproduced with permission [111]. Copyright 2024, AAAS.

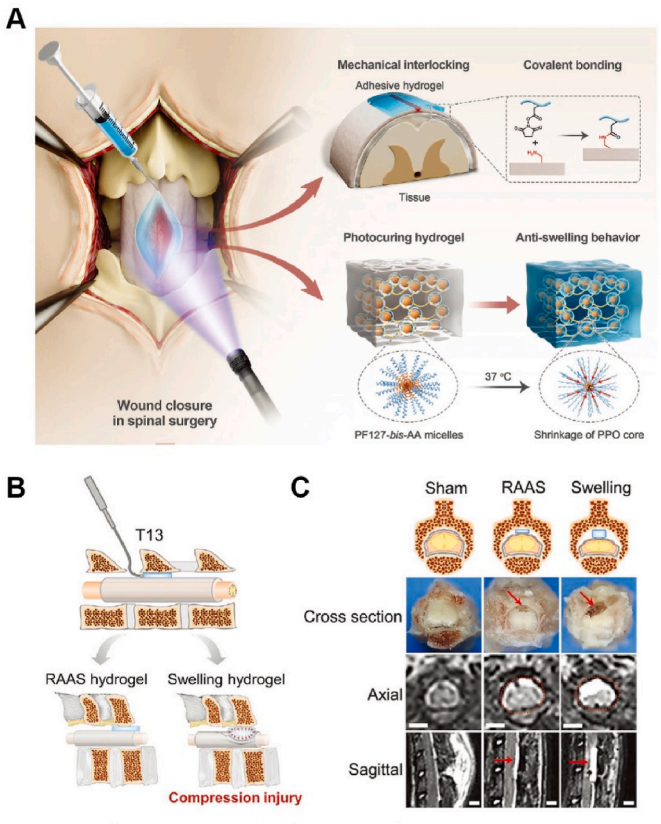

Fig. 8. (A) Schematic illustration of the rapid-adhesion and anti-swelling (RAAS) hydrogel. The tissue adhesion was achieved by forming covalent bonding, and the anti-swelling property was attributed to the shrinkage of Pluronic F127 micelles upon temperature increase. (B) Scheme showing the intraspinal implantation of hydrogels. (C) Photographs and axial/sagittal magnetic resonance imaging of spinal cords treated with RAAS gel and swelling gel at 3 days. Reproduced with permission [113]. Copyright 2022, Wiley-VCH GmbH.

hydrophobic interactions strengthened, and the micelles shrunk, leading to the anti-swelling property of the hydrogel. The hydrogel showed a burst pressure of over 230 mmHg on the porcine dura mater and sealed spinal dura injury to prevent cerebrospinal fluid leakage in rabbits. After implantation in the spinal epidural space of rats, the non-swelling hydrogel prevented compression injury to the spinal cord and preserved the motor function of the rats.

Laminectomy is a common spinal procedure that removes a part of the lamina to relieve pressure on the spinal cord. After surgery, fibrous scar tissue can form around the surgically treated spinal tissues, leading to epidural adhesions and fibrosis. Current clinical methods to prevent epidural fibrosis rely on the use of liquid (e.g., sodium hyaluronate and carboxymethyl cellulose) or film (Seprafilm and Interceed) products as physical barriers. However, most cases require surgical fixation by suturing because of weak adhesion to tissues. Excessive ROS production induced by trauma can contribute to fibrosis either directly or indirectly through enhancing inflammation. Therefore, adhesive and ROS-scavenging hydrogels have been designed to reduce epidural adhesions and fibrosis [115–117]. For instance, Bu et al. reported an antioxidant hydrogel bioadhesive prepared by mixing cysteine/amino-modified gelatin and PEG NHS ester (Fig. 9) [118]. The hydrogel can scavenge free radicals and protect cells from oxidative damage owing to its abundant thiol groups. In rabbit laminectomy and dural injury models, the hydrogel prevented tissue fluid leakage and epidural adhesion. Zhang et al. designed a multifunctional supramolecular hydrogel to prevent epidural adhesions after laminectomy [119]. The supramolecular hydrogel was composed of a thermosensitive triblock copolymer poloxamer 407, tannic acid, and ROS-scavenging nanoparticles containing tempol and phenylboronic acid pinacol ester functional groups. The hydrogel effectively prevented epidural fibrosis and adhesion after laminectomy in rat and rabbit models by reducing the local oxidative stress and inflammatory responses.

6. Challenges and perspectives

The regeneration and restoration of intervertebral disc faces critical challenges. The ideal hydrogels for intervertebral disc repair should have similar mechanical properties and integration strength as natural annulus fibrosus tissue and should maintain long-term physiological function under daily motion and weight-bearing. The intervertebral disc is an avascular and largely aneural tissue with low oxygen and poor nutritional availability. Further research is required to promote the integration of biomaterials into native tissues. Currently, the rat caudal intervertebral disc puncture model is one of the most widely used models for intervertebral disc degeneration research. There are huge differences in histology and biomechanics between humans and small animals. Large animals, such as sheep, could be suitable models for evaluating new intervertebral disc regeneration strategies.

The pathophysiology of spinal cord injury is complex and poorly understood. This process is dynamic and evolves through the interplay between miscellaneous molecular and cellular events. Combination therapy is a promising approach for the treatment of spinal cord injury. Hydrogel-assisted cell delivery and drug release systems can improve axonal regrowth and neurogenesis, enhance synaptic connections and neuronal relays, and promote neural function recovery. Future studies should focus on designing hydrogels with various types of biological and physiochemical cues according to the heterogeneous and dynamic interactions between neurons, astrocytes, and immune cells. In addition, sequential and spatial delivery of multiple drugs, growth factors, and neuroprotective agents can be achieved using smart hydrogel delivery systems for specific phases of spinal cord repair.

Watertight sealing of the dural membrane incision is crucial due to the lack of intrinsic clotting mechanisms. Various tissue-adhesive hydrogel sealants have been developed for use as dural sealants. Future studies are needed to improve the tissue adhesion and sealing performance of hydrogels under wet conditions, and to investigate their performance in larger animal models. A comprehensive evaluation of the safety, degradation, and long-term metabolism of these hydrogels is necessary to achieve clinical translation.

In summary, the utilization of hydrogels in spinal surgery demonstrates significant promise, particularly in addressing intervertebral disc degeneration, spinal cord injury, dural injury, and in the prevention and management of epidural fibrosis. Hydrogels can be administered to specific sites via minimally invasive techniques, providing mechanical support and functioning as localized delivery systems for pharmaceuticals, cells, and genes. Furthermore, the design of hydrogels is carefully tailored to ensure biocompatibility, appropriate mechanical properties, and functionality to accommodate diverse clinical requirements. Enhancing the cross-linking mechanisms and physical characteristics of hydrogels could further augment their efficacy in treating spinal disorders.

CRediT authorship contribution statement

Rongpeng Dong: Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Shuang Zheng:** Data curation, Funding acquisition. **Xueliang Cheng:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

This is a review article and has no ethics approval and consent to participate to declare.

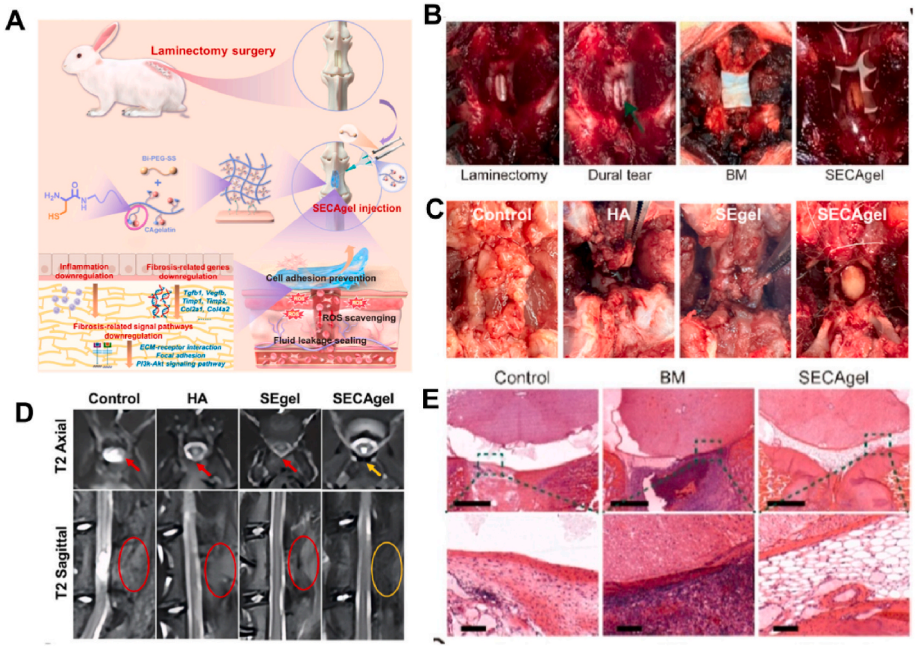

Fig. 9. (A) Scheme showing the antioxidant bioadhesive hydrogel to prevent epidural adhesion. After laminectomy, the SECAgel formed by mixing PEG NHS ester and cysteine/amino-modified gelatin could prevent postoperative adhesion by sealing cerebrospinal fluid leakage, reducing cell adhesion, and scavenging ROS. (B) Images showing the rabbit dural tear model after laminectomy. Commercially available biological membrane (BM) and SECAgel were then applied. (C) Macroscopic observation of laminectomy sites after 4 weeks of treatment. (D) T2-weighted axial and sagittal MR images of laminectomy sites after 4 weeks of treatment. Red arrows indicate the location of epidural adhesion, while orange arrows indicate a smooth surface with very little scar tissue. (E) H&E staining images showing the dural tear sites (upper row; scale bar, 1 mm) and adhesion sites (lower row; scale bar, 100 μm). Reproduced with permission [117]. Copyright 2024, American Chemical Society.

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.

Acknowledgments

This work was supported by the Jilin Provincial Department of Health [grant numbers JYTJF2022030] and Jilin Provincial Science and Technology Agency [grant numbers 2021SJ002].

Data availability

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

References

[1] Q.Z. Zhang, B. Shi, J.X. Ding, L.S. Yan, J.P. Thawani, C.F. Fu, X.S. Chen, Polymer scaffolds facilitate spinal cord injury repair, Acta Biomater. 88 (2019) 57–77.
[2] R. Qiu, K. Cai, K. Zhang, Y. Ying, H. Hu, G. Jiang, K. Luo, The current status and development trend of hydrogel application in spinal surgery, J. Mater. Chem. B 12 (7) (2024) 1730–1747.
[3] J. Clouet, M. Fusellier, A. Camus, C. Le Visage, J. Guicheux, Intervertebral disc regeneration: from cell therapy to the development of novel bioinspired endogenous repair strategies, Adv. Drug Deliv. Rev. 146 (2019) 306–324.
[4] L. Jin, A.L. Shimmer, X. Li, The challenge and advancement of annulus fibrosus tissue engineering, Eur. Spine J. 22 (5) (2013) 1090–1100.
[5] X. Zhao, H. Ma, H. Han, L. Zhang, J. Tian, B. Lei, Y. Zhang, Precision medicine strategies for spinal degenerative diseases: injectable biomaterials with in situ repair and regeneration, Materials Today Bio 16 (2022) 100336.
[6] R.D. Bowles, L.A. Setton, Biomaterials for intervertebral disc regeneration and repair, Biomaterials 129 (2017) 54–67.
[7] M. D'Este, D. Eglin, M. Alini, Lessons to be learned and future directions for intervertebral disc biomaterials, Acta Biomater. 78 (2018) 13–22.
[8] I.L. Mohd Isa, S.A. Mokhtar, S.A. Abbah, M.B. Fauzi, A. Devitt, A. Pandit, Intervertebral disc degeneration: biomaterials and tissue engineering strategies toward precision medicine, Adv. Healthcare Mater. 11 (13) (2022) 2102530.
[9] A. Zhang, Z. Cheng, Y. Chen, P. Shi, W. Gan, Y. Zhang, Emerging tissue engineering strategies for annulus fibrosus therapy, Acta Biomater. 167 (2023) 1–15.
[10] A. Anjum, M.D.i. Yazid, M. Fauzi Daud, J. Idris, A.M.H. Ng, A. Selvi Naicker, O.H. R. Ismail, R.K. Athi Kumar, Y. Lokanathan, Spinal cord injury: pathophysiology, multimolecular interactions, and underlying recovery mechanisms, Int. J. Mol. Sci. 21 (20) (2020) 7533.
[11] A. Alizadeh, S.M. Dyck, S. Karimi-Abdolrezaee, Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms, Front. Neurol. 10 (2019) 282.
[12] C.S. Ahuja, S. Nori, L. Tetreault, J. Wilson, B. Kwon, J. Harrop, D. Choi, M. G. Fehlings, Traumatic spinal cord injury-repair and regeneration, Neurosurgery 80 (3) (2017) S9–S22.
[13] N. Ghane, M.-H. Beigi, S. Labbaf, M.-H. Nasr-Esfahani, A. Kiani, Design of hydrogel-based scaffolds for the treatment of spinal cord injuries, J. Mater. Chem. B 8 (47) (2020) 10712–10738.
[14] D. Silva, R.A. Sousa, A.J. Salgado, Hydrogels as delivery systems for spinal cord injury regeneration, Materials Today Bio 9 (2021) 100093.
[15] R.C. Assuncao-Silva, E.D. Gomes, N. Sousa, N.A. Silva, A.J. Salgado, Hydrogels and cell based therapies in spinal cord injury regeneration, Stem Cell. Int. 2015 (2015) 948040.
[16] A.E. Haggerty, I. Maldonado-Lasuncion, M. Oudega, Biomaterials for revascularization and immunomodulation after spinal cord injury, Biomed. Mater. 13 (4) (2018) 044105.
[17] E.H. Choi, A.Y. Chan, N.J. Brown, B.V. Lien, R. Sahyouni, A.K. Chan, J. Roufail, M.Y. Oh, Effectiveness of repair techniques for spinal dural tears: a systematic review, World Neurosurgery 149 (2021) 140–147.
[18] J. Gandhi, A. DiMatteoa, G. Joshi, N.L. Smith, S.A. Khan, Cerebrospinal fluid leaks secondary to dural tears: a review of etiology, clinical evaluation, and management, Int. J. Neurosci. 131 (7) (2021) 689–695.
[19] A. Kinaci, T.P.C. Van Doormaal, Dural sealants for the management of cerebrospinal fluid leakage after intradural surgery: current status and future perspectives, Expet Rev. Med. Dev. 16 (7) (2019) 549–553.
[20] Z. Zhang, C. He, X. Chen, Designing hydrogels for immunomodulation in cancer therapy and regenerative medicine, Adv. Mater. 36 (4) (2024) 2308894.
[21] G. Huang, F. Li, X. Zhao, Y. Ma, Y. Li, M. Lin, G. Jin, T.J. Lu, G.M. Genin, F. Xu, Functional and biomimetic materials for engineering of the three-dimensional cell microenvironment, Chem. Rev. 117 (20) (2017) 12764–12850.
[22] P. Bertsch, M. Diba, D.J. Mooney, S.C.G. Leeuwenburgh, Self-healing injectable hydrogels for tissue regeneration, Chem. Rev. 123 (2) (2023) 834–873.
[23] K. Zhang, Q. Feng, Z. Fang, L. Gu, L. Bian, Structurally dynamic hydrogels for biomedical applications: pursuing a fine balance between macroscopic stability and microscopic dynamics, Chem. Rev. 121 (18) (2021) 11149–11193.
[24] X.C. Zhao, X.Z. Lu, K. Li, S.Q. Song, Z.H. Luo, C.C. Zheng, C.L. Yang, X.M. Wang, L.Q. Wang, Y.J. Tang, C. Wang, J. Liu, Double crosslinked biomimetic composite

hydrogels containing topographical cues and WAY-316606 induce neural tissue regeneration and functional recovery after spinal cord injury, Bioact. Mater. 24 (2023) 331–345.
[25] Q. Wei, D.C. Liu, G.L. Chu, Q.F. Yu, Z. Liu, J.Y. Li, Q.C. Meng, W.S. Wang, F. X. Han, B. Li, TGF-β1-supplemented decellularized annulus fibrosus matrix hydrogels promote annulus fibrosus repair, Bioact. Mater. 19 (2023) 581–593.
[26] Z.W. Cai, Y.B. Gan, C.Y. Bao, W.J. Wu, X.B. Wang, Z.T. Zhang, Q. Zhou, Q.N. Lin, Y. Yang, L.Y. Zhu, Photosensitive hydrogel creates favorable biologic niches to promote spinal cord injury repair, Adv. Healthcare Mater. 8 (13) (2019) 1900013.
[27] Y. Zhao, F. Tang, Z. Xiao, G. Han, NuoWang, N. Yin, B. Chen, X. Jiang, C. Yun, W. Han, C. Zhao, S. Cheng, S. Zhang, J. Dai, Clinical study of NeuroRegen scaffold combined with human mesenchymal stem cells for the repair of chronic complete spinal cord injury, Cell Transplant. 26 (5) (2017) 891–900.
[28] J. Luo, A. Darai, T. Pongkulapa, B. Conley, L. Yang, I. Han, K.-B. Lee, Injectable bioorthogonal hydrogel (BIOGEL) accelerates tissue regeneration in degenerated intervertebral discs, Bioact. Mater. 23 (2023) 551–562.
[29] M. Ibrahim, E. Ramadan, N.E. Elsadek, S.E. Emam, T. Shimizu, H. Ando, Y. Ishima, O.H. Elgarhy, H.A. Sarhan, A.K. Hussein, T. Ishida, Polyethylene glycol (PEG): the nature, immunogenicity, and role in the hypersensitivity of PEGylated products, J. Contr. Release 351 (2022) 215–230.
[30] Y. Gao, K. Peng, S. Mitragotri, Covalently crosslinked hydrogels via step-growth reactions: crosslinking chemistries, polymers, and clinical impact, Adv. Mater. 33 (25) (2021) 2006362.
[31] Z. Zhang, C. He, X. Chen, Hydrogels based on pH-responsive reversible carbon–nitrogen double-bond linkages for biomedical applications, Mater. Chem. Front. 2 (10) (2018) 1765–1778.
[32] Y. Jiang, J. Chen, C. Deng, E.J. Suuronen, Z. Zhong, Click hydrogels, microgels and nanogels: emerging platforms for drug delivery and tissue engineering, Biomaterials 35 (18) (2014) 4969–4985.
[33] J. Dowdell, M. Erwin, T. Choma, A. Vaccaro, J. Iatridis, S.K. Cho, Intervertebral disk degeneration and repair, Neurosurgery 80 (3) (2017) S46–S54.
[34] P.P.A. Vergroesen, I. Kingma, K.S. Emanuel, R.J.W. Hoogendoorn, T.J. Welting, B.J. van Royen, J.H. van Dieen, T.H. Smit, Mechanics and biology in intervertebral disc degeneration: a vicious circle, Osteoarthr. Cartil. 23 (7) (2015) 1057–1070.
[35] T.C. Schmitz, E. Salzer, J.F. Crispim, G.T. Fabra, C. LeVisage, A. Pandit, M. Tryfonidou, C. Le Maitre, K. Ito, Characterization of biomaterials intended for use in the nucleus pulposus of degenerated intervertebral discs, Acta Biomater. 114 (2020) 1–15.
[36] G. Fontana, E. See, A. Pandit, Current trends in biologics delivery to restore intervertebral disc anabolism, Adv. Drug Deliv. Rev. 84 (2015) 146–158.
[37] F. Colella, J.P. Garcia, M. Sorbona, A. Lolli, B. Antunes, D. D'Atri, F.P.Y. Barre, J. Oieni, M.L. Vainieri, L. Zerrillo, S. Capar, S. Haeckel, Y. Cai, L.B. Creemers, Drug delivery in intervertebral disc degeneration and osteoarthritis: selecting the optimal platform for the delivery of disease-modifying agents, J. Contr. Release 328 (2020) 985–999.
[38] L. Frapin, J. Clouet, V. Delplace, M. Fusellier, J. Guicheux, C. Le Visage, Lessons learned from intervertebral disc pathophysiology to guide rational design of sequential delivery systems for therapeutic biological factors, Adv. Drug Deliv. Rev. 149 (2019) 49–71.
[39] X. Zhao, X. Chen, H. Yuk, S. Lin, X. Liu, G. Parada, Soft materials by design: unconventional polymer networks give extreme properties, Chem. Rev. 121 (8) (2021) 4309–4372.
[40] Y.B. Gan, P. Li, L.Y. Wang, X.M. Mo, L. Song, Y. Xu, C. Zhao, B. Ouyang, B. Tu, L. Luo, L.Y. Zhu, S.W. Dong, F.Y. Li, Q. Zhou, An interpenetrating network-strengthened and toughened hydrogel that supports cell-based nucleus pulposus regeneration, Biomaterials 136 (2017) 12–28.
[41] J.M. Liu, D.Q. Wang, Y.Y. Li, Z.Q. Zhou, D.Y. Zhang, J.S. Li, H.T. Chu, Overall structure construction of an intervertebral disk based on highly anisotropic wood hydrogel composite materials with mechanical matching and buckling buffering, ACS Appl. Mater. Interfaces 13 (13) (2021) 15709–15719.
[42] Z. Ma, G. Bao, J. Li, Multifaceted design and emerging applications of tissue adhesives, Adv. Mater. 33 (24) (2021) 2007663.
[43] Y. Shen, Z. Zhang, X. Chen, C. He, Tissue-adhesive, antibacterial, naturally-derived polymer hydrogels as wound dressings for infected and chronic wound healing, J. Polym. Sci. 62 (11) (2024) 2320–2339.
[44] H. Ren, Z. Zhang, X. Chen, C. He, Stimuli-responsive hydrogel adhesives for wound closure and tissue regeneration, Macromol. Biosci. 24 (3) (2024) 2300379.
[45] H. Ren, Z. Zhang, X. Cheng, Z. Zou, X. Chen, C. He, Injectable, self-healing hydrogel adhesives with firm tissue adhesion and on-demand biodegradation for sutureless wound closure, Sci. Adv. 9 (33) (2023) adh4327.
[46] Z. Zou, Z. Zhang, H. Ren, X. Cheng, X. Chen, C. He, Injectable antibacterial tissue-adhesive hydrogel based on biocompatible o-phthalaldehyde/amine crosslinking for efficient treatment of infected wounds, Biomaterials 301 (2023) 122251.
[47] X. Li, Y. Liu, L. Li, R. Huo, F. Ghezelbash, Z. Ma, G. Bao, S. Liu, Z. Yang, M. H. Weber, N.Y.K. Li-Jessen, L. Haglund, J. Li, Tissue-mimetic hybrid bioadhesives for intervertebral disc repair, Mater. Horiz. 10 (5) (2023) 1705–1718.
[48] S.R. Sloan, C. Wipplinger, S. Kirnaz, R. Navarro-Ramirez, F. Schmidt, D. McCloskey, T. Pannellini, A. Schiavinato, R. Hartl, L.J. Bonassar, Combined nucleus pulposus augmentation and annulus fibrosus repair prevents acute intervertebral disc degeneration after discectomy, Sci. Transl. Med. 12 (534) (2020) aay2380.
[49] S.E. Gullbrand, B.G. Ashinsky, E.D. Bonnevie, D.H. Kim, J.B. Engiles, L.J. Smith, D.M. Elliott, T.P. Schaer, H.E. Smith, R.L. Mauck, Long-term mechanical function and integration of an implanted tissue-engineered intervertebral disc, Sci. Transl. Med. 10 (468) (2018) eaau0670.
[50] M. Molinos, C.R. Almeida, J. Caldeira, C. Cunha, R.M. Goncalves, M.A. Barbosa, Inflammation in intervertebral disc degeneration and regeneration, J. R. Soc. Interface 12 (104) (2015) 20141191.
[51] T. Gao, G. Xu, T. Ma, X. Lu, K. Chen, H. Luo, G. Chen, J. Song, X. Ma, W. Fu, C. Zheng, X. Xia, J. Jiang, ROS-responsive injectable hydrogel loaded with slc7a11-modRNA inhibits ferroptosis and mitigates intervertebral disc degeneration in rats, Adv. Healthcare Mater. (2024) 2401103.
[52] H. Yu, Y. Teng, J. Ge, M. Yang, H. Xie, T. Wu, Q. Yan, M. Jia, Q. Zhu, Y. Shen, L. Zhang, J. Zou, Isoginkgetin-loaded reactive oxygen species scavenging nanoparticles ameliorate intervertebral disc degeneration via enhancing autophagy in nucleus pulposus cells, J. Nanobiotechnol. 21 (1) (2023) 99.
[53] H. Ding, X. Zhang, Z. Liu, J. Wang, C. Zhu, Q. Chen, Y. Huang, Y. Ai, R. Wu, G. Feng, L. Zhang, L. Liu, Construction of MOFs nanoplatform with pH-triggered release of protocatechuic acid for intervertebral disc degeneration therapy, Mater. Des. 225 (2023) 111493.
[54] Y. Wang, M. Deng, Y. Wu, C. Hu, B. Zhang, C. Guo, H. Song, Q. Kong, Y. Wang, Sustained gene delivery from inflammation-responsive anti-inflammatory hydrogels promotes extracellular matrix metabolism balance in degenerative nucleus pulposus, Compos. B Eng. 236 (2022) 109806.
[55] Z. Zheng, A. Chen, H. He, Y. Chen, J. Chen, A.A. Albashari, J. Li, J. Yin, Z. He, Q. Wang, J. Wu, Q. Wang, J. Kang, M. Xian, X. Wang, J. Xiao, pH and enzyme dual-responsive release of hydrogen sulfide for disc degeneration therapy, J. Mater. Chem. B 7 (4) (2019) 611–618.
[56] L. Liu, W. Wang, L. Huang, Y. Xian, W. Ma, J. Fan, Y. Li, H. Liu, Z. Zheng, D. Wu, Injectable pathological microenvironment-responsive anti-inflammatory hydrogels for ameliorating intervertebral disc degeneration, Biomaterials 306 (2024) 122509.
[57] R.-Z. Yang, W.-N. Xu, H.-L. Zheng, X.-F. Zheng, B. Li, L.-S. Jiang, S.-D. Jiang, Involvement of oxidative stress-induced annulus fibrosus cell and nucleus pulposus cell ferroptosis in intervertebral disc degeneration pathogenesis, J. Cell. Physiol. 236 (4) (2021) 2725–2739.
[58] Y. Xu, F. Cai, Y. Zhou, J. Tang, J. Mao, W. Wang, Z. Li, L. Zhou, Y. Feng, K. Xi, Y. Gu, L. Chen, Magnetically attracting hydrogel reshapes iron metabolism for tissue repair, Sci. Adv. 10 (33) (2024) ado7249.
[59] Y. Takeoka, T. Yurube, K. Nishida, Gene therapy approach for intervertebral disc degeneration: an Update, Neurospine 17 (1) (2020) 3–14.
[60] E.J. Roh, A. Darai, J.W. Kyung, H. Choi, S.Y. Kwon, B. Bhujel, K.T. Kim, I. Han, Genetic therapy for intervertebral disc degeneration, Int. J. Mol. Sci. 22 (4) (2021) 1579.
[61] W. Chen, H. Chen, D.D. Zheng, H.B. Zhang, L.F. Deng, W.G. Cui, Y.H. Zhang, H. A. Santos, H.X. Shen, Gene-hydrogel microenvironment regulates extracellular matrix metabolism balance in nucleus pulposus, Adv. Sci. 7 (1) (2020) 1902099.
[62] D. Sakai, G.B.J. Andersson, Stem cell therapy for intervertebral disc regeneration: obstacles and solutions, Nat. Rev. Rheumatol. 11 (4) (2015) 243–256.
[63] A.L.A. Binch, J.C. Fitzgerald, E.A. Growney, F. Barry, Cell-based strategies for IVD repair: clinical progress and translational obstacles, Nat. Rev. Rheumatol. 17 (3) (2021) 158–175.
[64] N. Henry, J. Clouet, J. Le Bideau, C. Le Visage, J. Guioheux, Innovative strategies for intervertebral disc regenerative medicine: from cell therapies to multiscale delivery systems, Biotechnol. Adv. 36 (1) (2018) 281–294.
[65] C.J. Panebianco, S.J. Rao, W.W. Hom, J.H. Meyers, T.Y. Lim, D.M. Laudier, A. C. Hecht, M.D. Weir, J.R. Weiser, J.C. Iatridis, Genipin-crosslinked fibrin seeded with oxidized alginate microbeads as a novel composite biomaterial strategy for intervertebral disc cell therapy, Biomaterials 287 (2022) 121641.
[66] A.T. Francisco, R.J. Mancino, R.D. Bowles, J.M. Brunger, D.M. Tainter, Y.T. Chen, W.J. Richardson, F. Guilak, L.A. Setton, Injectable laminin-functionalized hydrogel for nucleus pulposus regeneration, Biomaterials 34 (30) (2013) 7381–7388.
[67] H. Wang, D. Wang, B. Luo, D. Wang, H.R. Jia, P.D. Peng, Q.L. Shang, J.X. Mao, C. Gao, Y. Peng, L. Gan, J.J. Du, Z.J. Luo, L. Yang, Decoding the annulus fibrosus cell atlas by scRNA-seq to develop an inducible composite hydrogel: a novel strategy for disc reconstruction, Bioact. Mater. 14 (2022) 350–363.
[68] Z. Wei, H. Ye, Y. Li, X. Li, Y. Liu, Y. Chen, J. Yu, J. Wang, X. Ye, Mechanically tough, adhesive, self-healing hydrogel promotes annulus fibrosus repair via autologous cell recruitment and microenvironment regulation, Acta Biomater. 178 (2024) 50–67.
[69] Z. Krut, G. Pelled, D. Gazit, Z. Gazit, Stem cells and exosomes: new therapies for intervertebral disc degeneration, Cells 10 (9) (2021) 2241.
[70] W. Liang, B. Han, Y. Hai, D. Sun, P. Yin, Mechanism of action of mesenchymal stem cell-derived exosomes in the intervertebral disc degeneration treatment and bone repair and regeneration, Front. Cell Dev. Biol. 9 (2022) 833840.
[71] Z.-L. Hu, H.-Y. Li, X. Chang, Y.-Y. Li, C.-H. Liu, X.-X. Gao, Y. Zhai, Y.-X. Chen, C.-Q. Li, Exosomes derived from stem cells as an emerging therapeutic strategy for intervertebral disc degeneration, World J. Stem Cell. 12 (8) (2020) 803–813.
[72] K. Lu, H.-y. Li, K. Yang, J.-l. Wu, X.-w. Cai, Y. Zhou, C.-q. Li, Exosomes as potential alternatives to stem cell therapy for intervertebral disc degeneration: in-vitro study on exosomes in interaction of nucleus pulposus cells and bone marrow mesenchymal stem cells, Stem Cell Res. Ther. 8 (2017) 108.
[73] H.Y. Xing, Z.J. Zhang, Q.J. Mao, C.G. Wang, Y.L. Zhou, X.P. Zhou, L.W. Ying, H. B. Xu, S.J. Hu, N. Zhang, Injectable exosome-functionalized extracellular matrix hydrogel for metabolism balance and pyroptosis regulation in intervertebral disc degeneration, J. Nanobiotechnol. 19 (1) (2021) 264.
[74] L.W. Luo, J.F. Gong, Z.G. Wang, Y. Liu, J.M. Cao, J.H. Qin, R. Zuo, H.Y. Zhang, S. Wang, P. Zhao, D. Yang, M.J. Zhang, Y.Q. Wang, J.F. Zhang, Y. Zhou, C.Q. Li,

B. Ni, Z.Q. Tian, M.H. Liu, Injectable cartilage matrix hydrogel loaded with cartilage endplate stem cells engineered to release exosomes for non-invasive treatment of intervertebral disc degeneration, Bioact. Mater. 15 (2022) 29–43.
[75] S. Kabu, Y. Gao, B.K. Kwon, V. Labhasetwar, Drug delivery, cell-based therapies, and tissue engineering approaches for spinal cord injury, J. Contr. Release 219 (2015) 141–154.
[76] E.A. Kiyotake, M.D. Martin, M.S. Detamore, Regenerative rehabilitation with conductive biomaterials for spinal cord injury, Acta Biomater. 139 (2022) 43–64.
[77] T. Fuhrmann, P.N. Anandakumaran, M.S. Shoichet, Combinatorial therapies after spinal cord injury: how can biomaterials help? Adv. Healthcare Mater. 6 (10) (2017) 1601130.
[78] H. Shen, C. Fan, Z. You, Z. Xiao, Y. Zhao, J. Dai, Advances in biomaterial-based spinal cord injury repair, Adv. Funct. Mater. 32 (13) (2022) 2110628.
[79] L. Li, B. Xiao, J. Mu, Y. Zhang, C. Zhang, H. Cao, R. Chen, H.K. Patra, B. Yang, S. Feng, Y. Tabata, N.K.H. Slater, J. Tang, Y. Shen, J. Gao, A MnO(2) nanoparticle-dotted hydrogel promotes spinal cord repair via regulating reactive oxygen species microenvironment and synergizing with mesenchymal stem cells, ACS Nano 13 (12) (2019) 14283–14293.
[80] A. Burton, Z. Wang, D. Song, S. Tran, J. Hanna, D. Ahmad, J. Bakall, D. Clausen, J. Anderson, R. Peralta, K. Sandepudi, A. Benedetto, E. Yang, D. Basrai, L. E. Miller, M.C. Tresch, P. Gutruf, Fully implanted battery-free high power platform for chronic spinal and muscular functional electrical stimulation, Nat. Commun. 14 (1) (2023) 7887.
[81] Y. Kong, F. Liu, B. Ma, J. Duan, W. Yuan, Y. Sang, L. Han, S. Wang, H. Liu, Wireless localized electrical stimulation generated by an ultrasound-driven piezoelectric discharge regulates proinflammatory macrophage polarization, Adv. Sci. 8 (13) (2021) 2100962.
[82] C. Fan, W. Yang, L. Zhang, H. Cai, Y. Zhuang, Y. Chen, Y. Zhao, J. Dai, Restoration of spinal cord biophysical microenvironment for enhancing tissue repair by injury-responsive smart hydrogel, Biomaterials 288 (2022) 121689.
[83] Q. Yu, S. Jin, S. Wang, H. Xiao, Y. Zhao, Injectable, adhesive, self-healing and conductive hydrogels based on MXene nanosheets for spinal cord injury repair, Chem. Eng. J. 452 (2023) 139252.
[84] J. Cai, H. Zhang, Y. Hu, Z. Huang, Y. Wang, Y. Xia, X. Chen, J. Guo, H. Cheng, L. Xia, W. Lu, C. Zhang, J. Xie, H. Wang, R. Chai, GelMA-MXene hydrogel nerve conduits with microgrooves for spinal cord injury repair, J. Nanobiotechnol. 20 (1) (2022) 460.
[85] Y. Feng, Z. Yu, H. Liu, L. Guan, X. Yang, A.V. Zvyagin, Y. Zhao, X. Yang, B. Yang, Q. Lin, Biomimicking 3D soft scaffold combined with electrical stimulation to manipulate neural stem cell differentiation for guidance spinal cord injury repair, Mater. Today 71 (2023) 50–62.
[86] M. Liu, W. Zhang, S. Han, D. Zhang, X. Zhou, X. Guo, H. Chen, H. Wang, L. Jin, S. Feng, Z. Wei, Multifunctional conductive and electrogenic hydrogel repaired spinal cord injury via immunoregulation and enhancement of neuronal differentiation, Adv. Mater. 36 (21) (2024) 2313672.
[87] P. Wu, C. Xu, X. Zou, K. Yang, Y. Xu, X. Li, X. Li, Z. Wang, Z. Luo, Capacitive-coupling-responsive hydrogel scaffolds offering wireless in situ electrical stimulation promotes nerve regeneration, Adv. Mater. 36 (14) (2024) e2310483.
[88] P. Assinck, G.J. Duncan, B.J. Hilton, J.R. Plemel, W. Tetzlaff, Cell transplantation therapy for spinal cord injury, Nat. Neurosci. 20 (5) (2017) 637–647.
[89] V.M. Doulames, L.M. Marquardt, M.E. Hefferon, N.J. Baugh, R.A. Suhar, K. R. Dubbin, J.M. Weimann, T.D. Palmer, G.W. Plant, S.C. Heilshorn, Custom-engineered hydrogels for delivery of human iPSC-derived neurons into the injured cervical spinal cord, Biomaterials 305 (2024) 122400.
[90] Y. Wan, Y. Lin, X. Tan, L. Gong, F. Lei, C. Wang, X. Sun, X. Du, Z. Zhang, J. Jiang, Z. Liu, J. Wang, X. Zhou, S. Wang, X. Zhou, P. Jing, Z. Zhong, Injectable hydrogel to deliver bone mesenchymal stem cells preloaded with azithromycin to promote spinal cord repair, ACS Nano 18 (12) (2024) 8934–8951.
[91] T.J. Tigner, G. Dampf, A. Tucker, Y.-C. Huang, V. Jagrit, A.J. Clevenger, A. Mohapatra, S.A. Raghavan, J.N. Dulin, D.L. Alge, Clickable granular hydrogel scaffolds for delivery of neural progenitor cells to sites of spinal cord injury, Adv. Healthcare Mater. 13 (25) (2024) 2303912.
[92] Y. Shao, H. Jia, T. Cao, D. Liu, Supramolecular hydrogels based on DNA self-assembly, Accounts Chem. Res. 50 (4) (2017) 659–668.
[93] J.S. Kahn, Y. Hu, I. Willner, Stimuli-responsive DNA-based hydrogels: from basic principles to applications, Accounts Chem. Res. 50 (4) (2017) 680–690.
[94] L. Zhou, X. Jiao, S. Liu, M. Hao, S. Cheng, P. Zhang, Y. Wen, Functional DNA-based hydrogel intelligent materials for biomedical applications, J. Mater. Chem. B 8 (10) (2020) 1991–2009.
[95] T.Y. Yuan, Y. Shao, X. Zhou, Q. Liu, Z.C. Zhu, B.N. Zhou, Y.C. Dong, N. Stephanopoulos, S.B. Gui, H. Yan, D.S. Liu, Highly permeable DNA supramolecular hydrogel promotes neurogenesis and functional recovery after completely transected spinal cord injury, Adv. Mater. 33 (35) (2021) 2102428.
[96] K.A. Tran, P.P. Partyka, Y. Jin, J. Bouyer, I. Fischer, P.A. Galie, Vascularization of self-assembled peptide scaffolds for spinal cord injury repair, Acta Biomater. 104 (2020) 76–84.
[97] A. Marchini, A. Raspa, R. Pugliese, M. Abd El Malek, V. Pastori, M. Lecchi, A. L. Vescovi, F. Gelain, Multifunctionalized hydrogels foster hNSC maturation in 3D cultures and neural regeneration in spinal cord injuries, Proc. Natl. Acad. Sci. U.S. A. 116 (15) (2019) 7483–7492.
[98] Y. Yang, Y. Fan, H. Zhang, Q. Zhang, Y. Zhao, Z. Xiao, W. Liu, B. Chen, L. Gao, Z. Sun, X. Xue, M. Shu, J. Dai, Small molecules combined with collagen hydrogel direct neurogenesis and migration of neural stem cells after spinal cord injury, Biomaterials 269 (2021) 120479.
[99] L.M. Li, Y. Zhang, J.F. Mu, J.C. Chen, C.Y. Zhang, H.C. Cao, J.Q. Gao, Transplantation of human mesenchymal stem-cell-derived exosomes immobilized in an adhesive hydrogel for effective treatment of spinal cord injury, Nano Lett. 20 (6) (2020) 4298–4305.
[100] E.J. Bradbury, E.R. Burnside, Moving beyond the glial scar for spinal cord repair, Nat. Commun. 10 (2019) 3879.
[101] Z. Tan, L. Xiao, J. Ma, K. Shi, J. Liu, F. Feng, P. Xie, Y. Dai, Q. Yuan, W. Wu, L. Rong, L. He, Integrating hydrogels manipulate ECM deposition after spinal cord injury for specific neural reconnections via neuronal relays, Sci. Adv. 10 (27) (2024) ado9120.
[102] D.J. DiSabato, N. Quan, J.P. Godbout, Neuroinflammation: the devil is in the details, J. Neurochem. 139 (2016) 136–153.
[103] H. Shen, B. Xu, C. Yang, W.W. Xue, Z.F. You, X.M. Wu, D.Z. Ma, D. Shao, K. Leong, J.W. Dai, A DAMP-scavenging, IL-10-releasing hydrogel promotes neural regeneration and motor function recovery after spinal cord injury, Biomaterials 280 (2022) 121279.
[104] X. Cui, L. Wang, X. Gao, J. Wu, T. Hu, J. Zhang, X. Zhou, K.-Q. Zhang, L. Cheng, Self-assembled silk fibroin injectable hydrogels based on layered double hydroxides for spinal cord injury repair, Matter 7 (2) (2024) 620–639.
[105] Z.M. Li, T.F. Zhao, J. Ding, H.C. Gu, Q.X. Wang, Y.F. Wang, D.T. Zhang, C.Y. Gao, A reactive oxygen species-responsive hydrogel encapsulated with bone marrow derived stem cells promotes repair and regeneration of spinal cord injury, Bioact. Mater. 19 (2023) 550–568.
[106] G. Hutter, S. von Felten, M.H. Sailer, M. Schulz, L. Mariani, Risk factors for postoperative CSF leakage after elective craniotomy and the efficacy of fleece-bound tissue sealing against dural suturing alone: a randomized controlled trial, J. Neurosurg. 121 (3) (2014) 735–744.
[107] T. Zhu, H. Wang, Z. Jing, D. Fan, Z. Liu, X. Wang, Y. Tian, High efficacy of tetra-PEG hydrogel sealants for sutureless dural closure, Bioact. Mater. 8 (2022) 12–19.
[108] J. Li, J. Tian, C. Li, L. Chen, Y. Zhao, A hydrogel spinal dural patch with potential anti-inflammatory, pain relieving and antibacterial effects, Bioact. Mater. 14 (2022) 389–401.
[109] X. Liu, X. Cheng, Y. Sun, J. Nie, M. Cheng, W. Li, J. Zhao, Peptide/glycyrrhizic acid supramolecular polymer: an emerging medical adhesive for dural sealing and repairing, Biomaterials 301 (2023) 122239.
[110] G.M. Taboada, K. Yang, M.J.N. Pereira, S.S. Liu, Y. Hu, J.M. Karp, N. Artzi, Y. Lee, Overcoming the translational barriers of tissue adhesives, Nat. Rev. Mater. 5 (4) (2020) 310–329.
[111] S. Nam, D. Mooney, Polymeric tissue adhesives, Chem. Rev. 121 (18) (2021) 11336–11384.
[112] K.C. Wu, B.R. Freedman, P.S. Kwon, M. Torre, D.O. Kent, W.L. Bi, D.J. Mooney, A tough bioadhesive hydrogel supports sutureless sealing of the dural membrane in porcine and ex vivo human tissue, Sci. Transl. Med. 16 (739) (2024) eadj0616.
[113] X. Cheng, Z. Zhang, H. Ren, Z. Zou, Y. Zhang, Y. Qu, X. Chen, J. Zhao, C. He, A low-swelling hydrogel as a multirole sealant for efficient dural defect sealing and prevention of postoperative adhesion, Natl. Sci. Rev. 11 (6) (2024) nwae160.
[114] S. Bian, L. Hao, X. Qiu, J. Wu, H. Chang, G.M. Kuang, S. Zhang, X. Hu, Y. Dai, Z. Zhou, F. Huang, C. Liu, X. Zou, W. Liu, W.W. Lu, H. Pan, X. Zhao, An injectable rapid-adhesion and anti-swelling adhesive hydrogel for hemostasis and wound sealing, Adv. Funct. Mater. 32 (46) (2022) 2207741.
[115] M. Han, J. Tang, H. Zhao, Y. Sheng, Z. Li, W. Shi, J. Wang, C. Ma, K. Xi, Y. Gu, L. Chen, Bio-adhesive barrier with active ROS-scavenging ability for simultaneous management of dura tear and epidural inflammatory fibrosis, Chem. Eng. J. 484 (2024) 149308.
[116] S. Wang, K. Shi, J. Lu, W. Sun, Q. Han, L. Che, D. Zhang, Microsphere-embedded hydrogel sustained-release system to inhibit postoperative epidural fibrosis, ACS Appl. Bio Mater. 4 (6) (2021) 5122–5131.
[117] Y.S. Wang, M. Liang, Z.Z. Zheng, L.C. Shi, B. Su, J. Liu, D.L. Kaplan, B. Zhang, X. Q. Wang, Adhesion prevention after laminectomy using silk-polyethylene glycol hydrogels, Adv. Healthcare Mater. 4 (14) (2015) 2120–2127.
[118] Y. Gong, B. Zhu, Y. Chen, F. Li, W. Duan, S. Martin-Saldana, R. Yang, X. Gao, B. Zhang, L. Luo, Z. Xiao, B. Du, L. Yan, Y. Bu, Organism-inspired antioxidant bioadhesive with strong sealing ability to prevent epidural adhesion, ACS Nano 18 (32) (2024) 21411–21432.
[119] Y. Wang, L.L. Li, Y.C. Ma, Y. Tang, Y. Zhao, Z.M. Li, W.D. Pu, B. Huang, X. Wen, X. J. Cao, J.F. Chen, W. Chen, Y. Zhou, J.X. Zhang, Multifunctional supramolecular hydrogel for prevention of epidural adhesion after laminectomy, ACS Nano 14 (7) (2020) 8202–8219.