Bioactive Materials 39 (2024) 521–543

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Review article

Functional biomaterials for modulating the dysfunctional pathological microenvironment of spinal cord injury

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ARTICLE INFO

Keywords:
Spinal cord injury
Dysfunctional pathological microenvironment
Functional biomaterials
Axon regeneration
Functional recovery

ABSTRACT

Spinal cord injury (SCI) often results in irreversible loss of sensory and motor functions, and most SCIs are incurable with current medical practice. One of the hardest challenges in treating SCI is the development of a dysfunctional pathological microenvironment, which mainly comprises excessive inflammation, deposition of inhibitory molecules, neurotrophic factor deprivation, glial scar formation, and imbalance of vascular function. To overcome this challenge, implantation of functional biomaterials at the injury site has been regarded as a potential treatment for modulating the dysfunctional microenvironment to support axon regeneration, remyelination at injury site, and functional recovery after SCI. This review summarizes characteristics of dysfunctional pathological microenvironment and recent advances in biomaterials as well as the technologies used to modulate inflammatory microenvironment, regulate inhibitory microenvironment, and reshape revascularization microenvironment. Moreover, technological limitations, challenges, and future prospects of functional biomaterials to promote efficient repair of SCI are also discussed. This review will aid further understanding and development of functional biomaterials to regulate pathological SCI microenvironment.

1. Introduction

Spinal cord injury (SCI) is a serious disabling neurological disease, resulting in partial or complete sensor and motor dysfunction below injured cross-section [1,2]. Despite devasting impact of SCI on physical and mental health of patients, there is still no effective treatment owing to relative lack of plasticity and regenerative ability of central nervous system (CNS). A major challenge for SCI repair is occurrence of a series of chemical reactions at injury site, leading to an adverse formation of microenvironment that inhibits axon regrowth [3,4]. Studies in past decades demonstrate that adverse microenvironment for nerve regeneration after SCI mainly comprises of following four aspects: (1) Production of extrinsic inhibitory molecules and formation of glial scars to hinder axon growth [5,6]; (2) A lack of endogenous neurotrophic factors to support axon regeneration [6]; (3) Inactivation of molecular signaling for neuronal regeneration in spinal cord [7]; (4) Uncontrolled inflammatory response after SCI. An exaggerated inflammatory response leads to death of neurons and glial cells, formation of glial scars, and development of cavities [8].

Many studies focused on improving SCI microenvironment to promote functional recovery. For example, antagonizing pro-inflammatory factors and inhibitory molecules in SCI microenvironment through

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https://doi.org/10.1016/j.bioactmat.2024.04.015
Received 13 January 2024; Received in revised form 13 April 2024; Accepted 14 April 2024

administration of anti-tumor necrosis factor-α (TNF-α) antibody or antagonistic peptides of Nogo signaling promoted axon growth [6,9]. However, systemic administration of these antibodies inevitably resulted in off-target effects and limited therapeutic effect on SCI repair. To date, precise mechanisms about underlying cell damage and death in SCI remain a complex area of investigation. Understanding roles of oxidative stress, inflammation, excitotoxicity, and apoptosis will help identify therapeutic targets and develop innovative interventions to mitigate these processes.

With a rapid development of materials science and engineering, there is a great potential in utilizing functional biomaterials for remodeling SCI microenvironment through providing biophysical and biochemical cues. On one hand, some biomaterials provide physical support for axon regeneration and have ideal anti-inflammatory properties; on the other hand, they can be pre-modified to serve as carriers of drugs, factors, or cells to remodel dysfunctional microenvironment in SCI [10,11]. As an example, chitosan (CS) reduces infiltration of immune cells and enhances polarization of M2-type macrophages owing to its innate anti-inflammatory properties, also it delivers anti-inflammatory drugs (*e.g.,* methylprednisolone (MP)) to suppress inflammation after SCI [12,13]. Furthermore, biomaterials play a vital role in regulating stem cell-based therapies to repair SCI microenvironment through promotion of cell survival, engraftment, and neuronal differentiation [14,15].

In this review, we present characteristics of dysfunctional pathological SCI microenvironment in inflammation, presence of inhibitory biomolecules, development of fibrotic or astroglial scars, and summarize several microenvironment-modulating biomaterials for SCI repair, such as inflammatory microenvironment-altering biomaterials, biomolecules-regulating biomaterials, and advanced biomaterials based-technologies (Fig. 1). Current challenges and perspectives facing the use of biomaterials for SCI microenvironment regulation and repair are also discussed. This review aims to provide a reference for future studies and help to construct an innovative approach for SCI repair.

2. Dysfunctional pathological microenvironment in SCI

SCI microenvironment refers to occurrence of the secondary injury cascades including inflammation, presence of inhibitory biomolecules, and development of fibrotic or astroglial scars, which is accompanied by neuronal death, axon degeneration, and demyelination, leading to a series of dramatic changes in nervous, immune, and vascular systems [16–18]. As multiple mechanisms contribute to secondary injury, it is difficult to explain pathological reasons for secondary injury from a single perspective.

2.1. Inflammatory microenvironment post-SCI

After SCI, blood-spinal cord barrier (BSCB) is destroyed and subsequently attracts many peripheral immune cells and microglia to form a complex inflammatory microenvironment [19,20]. These immune cells are continuously recruited to lesion area, and then exert beneficial or harmful effects on SCI repair [21]. For example, microglia/macrophages secret pro-inflammatory factors including TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6) to expand inflammatory response [22,23]. In contrast, activated microglia/macrophages phagocytose cell fragments and secret anti-inflammatory factors including interleukin-4 (IL-4) or interleukin-10 (IL-10) to promote SCI healing [24,25]. Interestingly, a microglial subpopulation is also found to promote axonal regeneration by coordinating scar-free wound healing in SCI neonatal mice [26]. These diverse functions of activated microglia/macrophages are related to cell polarization, which could be divided into pro-inflammatory M1 and pro-repair M2 macrophage subsets [27,28].

Reactive oxygen species (ROS) and oxidative stress are considered as characteristics of SCI and they play a significant role in pathological process of SCI. Microglia/macrophages and neutrophils are major sources of ROS in SCI [22,29,30]. Although ROS is an essential component in physiological process, excessive ROS production results in oxidative stress, which is followed by an activation of mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) signaling pathways to expand secretion of pro-inflammatory cytokines [31]. Hence, eliminating ROS is an effective way to prevent neuronal death after SCI [32,33].

2.2. Biomolecules inhibiting axon regeneration in SCI microenvironment

An inhibitory microenvironment containing a large number of inhibitory molecules is formed after SCI to inhibit regrowth of axons. Myelin-associated inhibitory molecules are main components of the inhibitory microenvironment, which include neurite outgrowth

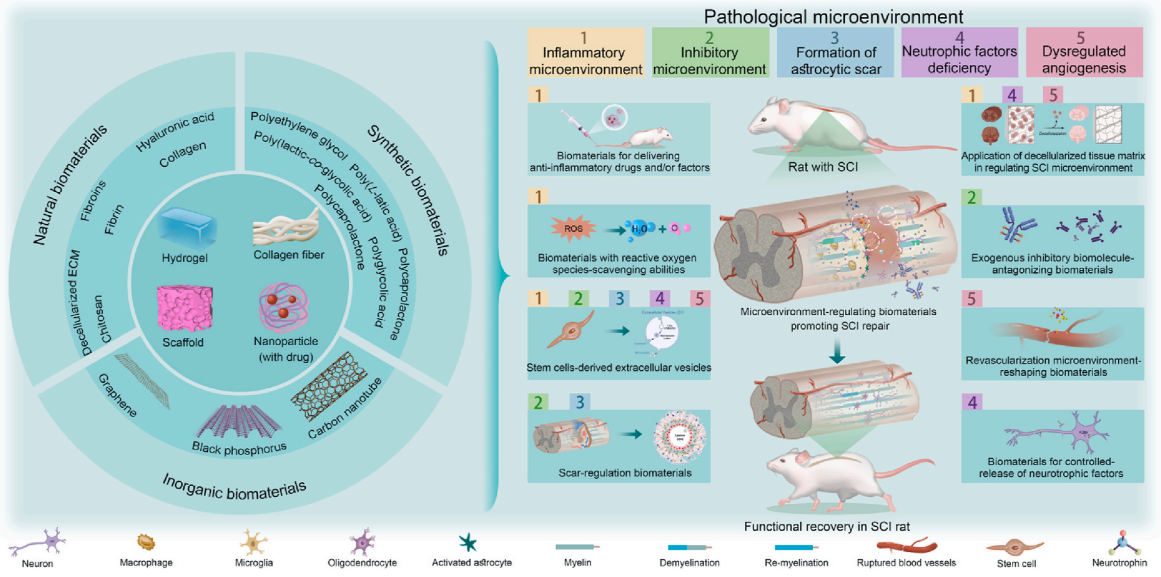

Fig. 1. Schematic illustration of functional biomaterials used to modulate and repair dysfunctional pathological microenvironment of SCI. Existing functional biomaterials are categorized into natural, synthetic, and inorganic biomaterials. Scaffold refers to 3D highly-porous biomaterials that acts as templates to facilitate neural tissue regeneration and repair in SCI.

inhibitor (Nogo), oligodendrocyte-myelin glycoprotein (Omgp), and myelin-associated glycoprotein (MAG). They bind to neuregulin-1 and recruit TROY, Lingo-1, and p75 to form a complex that activate intracellular inhibition signaling and inhibit axon growth [34,35]. Chondroitin sulfate proteoglycans (CSPGs) are also inhibitory molecules that hinder axon regeneration by activating intracellular protein kinase C and Rho signaling pathways [5,36]. Finally, some members of ephrin and semaphorin families, including ephrinB3, Sema3A, and Sema4D, are also involved in inhibition of axonal growth after SCI [37,38]. These inhibitor molecules are axon-guided molecules and have different receptors, but they inhibit axon regeneration by activating RhoA through their downstream signaling pathway [39].

2.3. Formation of fibrotic and astroglial scar border post-SCI

After SCI, pathological microenvironment is roughly categorized into two main types of scar tissues: fibrotic scar and astroglial scar [40]. The fibrotic scar is a non-neural area that consists of interstitial and connective tissues, including stromal cells, fibroblasts, and meningeal fibroblasts. Although the fibrous scar maintains tissue integrity, it also inhibits axonal regeneration. Inhibiting the formation of fibrous scar tissue is helpful to promote functional recovery after SCI [41]. Furthermore, reactive astrocytes migrate around the lesion core and interlace to form a dense and astrocytic scar boundary [42,43]. The new formation of astrocytic scar tissue separates neural and non-neural tissue along healthy tissue at edge of lesion area after 2 weeks. Astrocytic scars limit migration of inflammatory cells from injured site to healthy tissue [44]. In contrast, astrocyte scars also produce CSPGs, tenascin, and NG2 proteoglycans to inhibit axonal growth and remyelination [45].

3. Inflammatory microenvironment-altering biomaterials for SCI repair

3.1. Functional biomaterials for anti-inflammatory regulation

It has been reported that biomaterials with anti-inflammatory components, including polyethylene glycol (PEG), poly−*L*−lactic acid (PLLA), poly(lactide−coglycolide acid) (PLGA), hyaluronic acid (HA), poly−ε−caprolactone (PCL), and CS could reduce secretion of inflammatory factors and infiltration of immune cells [46–48]. The main anti-inflammatory biomaterials are summarized in Table 1. For example, administration of PEG-based nanoparticles enhanced transition from M1 macrophages to pro-regenerative M2 macrophages in a model of SCI [49]. Moreover, Xiao *et al.* developed a hybrid hydrogel by combining dihydroxyphenylalanine (DOPA)-implanted CS with designer peptides (CD) through a dual cross-linking mechanism, which realized an enhanced immune response modulation compared to traditional hydrogels by manipulating phenotypes of immune cells [50]. Similarly, a gelatin hydrogel-based combination treatment was also developed to suppress microglia/macrophages-mediated inflammation for SCI repair. This innovative approach presented a novel cell replacement therapy involving replacing activated microglia/macrophages with resting microglia through use of PLX3397, a colony-stimulating factor 1 receptor (CSF1R) inhibitor, in combination with gelatin hydrogel transplantation. Such combined treatment led to reestablishment of surveillant microglia throughout spinal cord and enhanced an effectiveness of the gelatin hydrogel in reducing neuroinflammation. This integrated therapy is essential, because a single gelatin scaffold transplantation may not sufficiently address inflammation mediated by microglia/macrophages [51].

Although biomaterials possess anti-inflammatory properties, complexity of post-SCI inflammatory microenvironment leads to functional modifications of biomaterials for precise inflammatory-response regulation. Notably, incorporating anti-inflammatory drugs like MP into biodegradable biomaterials for local delivery, such as CS modifications and bioinspired hybrid nano-scaffolds, can minimize side effects

Table 1
List of inflammatory microenvironment-regulating biomaterials for SCI repair.

Category	Material/Drug/Factor	Outcome	Reference
Biomaterials with anti-inflammatory properties	PEG	● FA-PEG/ZIF-8 administration significantly decreased pro-inflammatory macrophages in injured spinal cord	[66]
	PLGA/PLGA-DSC	● PLGA nanoparticles induced macrophage polarization towards pro-regenerative phenotypes ● PLGA-DSC scaffolds polarized macrophages from M1 phenotype to M2 phenotype	[49,67]
	PLLA	● PLLA multi-channel conduits reduced number of macrophages/microglia accumulation at injury site	[68]
	CS-FPHS	● CS microhydrogel promoted polarization of macrophages towards beneficial M2 phenotype ● NT3-CS treatment prevented immune cells infiltration (CD45 labeling)	[69,70]
	HA	● Nanofiber-hydrogel composites facilitated a shift among macrophages towards pre-regenerative phenotype ● HA scaffolds with biomimetic mechanical properties stimulated production of anti-inflammatory cytokine IL-10	[71,72]
	PCL nanofibers	● PCL nanofibers-hydrogel composites promoted polarization of macrophages toward M2 phenotype	[71]
	Gelatin	● Gelatin- and HA-based hydrogels prevented $CD68^+$ cells accumulation ● GelMA reduced inflammatory cells infiltration	[73,74]
	Laminin	● Polylaminin played anti-inflammatory effects by reducing $ED1^+$ immune cells accumulation	[75]
	Decellularized ECM	● Decellularized spinal cord extracellular matrix-gel reduced CD68-positive cells accumulation	[76,77]
	MSCs-derived exosomes	● Transplantation of MSCs-derived exosomes reduced pro-inflammatory cytokines release including IL-1β, TNF-α, and iNOS	[78–80]
	M2 macrophages-derived exosomes	● M2 macrophages-derived exosomes inhibited expression of pro-inflammatory cytokines and promoted	[81,82]

(*continued on next page*)

Table 1 (*continued*)

Category	Material/Drug/Factor	Outcome	Reference
		polarization of macrophages towards M2 phenotype	
	FE@Evs	● FE with sustainable and long-term extracellular vesicle release reduced CD68 and lba-1 cells accumulation	[83]
Functional Biomaterials for delivering anti-inflammatory drugs/factors	PLGA/MP	● Polydopamine-decorated microcomposites promoted function recovery by reducing inflammatory cytokine levels	[46]
	PEG/MC	● PEG-based micelles reduced levels of pro-inflammatory cytokines including TNF-α, IL-6 and IL-1β at lesion site	[84]
	CS/MP	● FA-GC treatment suppressed astrogliosis and ED1^{+} immune cells accumulation	[13]
	PEG/MPSS	● PEG-based multifunctional hydrogels depot with anti-inflammatory drug MPSS reduced CD68 and lba-1 cells accumulation	[85]
	Agarose hydrogel/MC	● Agarose hydrogels for controlled release of minocycline reduced percentage of M1 cells	[54]
	PCL/MC	● PCL-based nanoparticles with minocycline inhibited microglia activation and macrophages recruitment in injury site of SCI	[86]
	PCL-PEG/MC	● PCL−PEG/minocycline deactivated macrophages and reduced expression of pro-inflammatory cytokine IL-6	[55]
	Liposomes/CSB	● Stealth liposomes encapsulated by PEG with CSB induced an increased expression of anti-inflammatory marker arginase I	[87]
	PEI-PEG/Rolipram	● Rolipram-loaded PEI−PEG based nanostructured gel limited inflammatory response in A1 astrocytes	[88]
	PLLA/Ibuprofen	● PLLA loaded with ibuprofen and triiodothyronine improved endogenous regeneration in SCI by inhibiting astrocytes and microglia activation	[89]
	PLGA/Flavopiridol	● Local delivery of flavopiridol in PLGA nanoparticles inhibited astrocytes growth and inflammatory cytokines synthesis	[90]
	Gelatin/IL-10	● Gelatin hydrogels with cationic, DAMP-binding polymer poly(amidoamine) and IL-10	[60]

Table 1 (*continued*)

Category	Material/Drug/Factor	Outcome	Reference
		promoted M2 macrophages phenotype polarization and reduced secretion of inflammatory cytokines	
	PLGA/IL-10	● A multiple channel PLGA deliver IL-10^{+} NT-3 promoted polarization of macrophages towards M2 phenotype	[91]
	Aldehyde cationic liposomes/IL-4	● Immunological electrospun fiber scaffolds reduced secretion of inflammatory factors by releasing IL-4 plasmid-loaded liposomes	[61]
	PLLA/TGFβ3	● PLLA fibers with TGFβ3 decreased expression of neurotoxic A1-specific astrocytes	[92]
ROS-scavenging Biomaterials	MnO_2 nanoparticle-dotted hydrogel	● A MnO_2 nanoparticle-dotted hydrogel alleviated oxidative environment and microglia activation, thereby effectively improved viability of MSCs after SCI	[93]
	PEG/SOD1	● Delivery of SOD1, an efficient ROS scavenger, by PEG-polyglutamic acid mitigated SCI-induced oxidative stress and reduced GFAP expression	[94]
	Se-CQDs	● Se-CQDs with ROS scavenging ability reduced formation of glial scar and accumulation of immune cells	[95]
	CONPs	● Injection of optimal-dosed cerium oxide nanoparticles reduced number of iNOS^{+} immune cells and upregulated anti-inflammatory cytokines	[96]
	SeNPs@GM1/TMP	● SeNPs@GM1/TMP attenuated ROS overproduction and mitochondria dysfunction, thus providing neuroprotection in SCI rats	[97]
	HA-TEMPO	● Implantation of a functional TEMPO-hydrogel promoted nerve regeneration through antioxidant and lesion-bridging regulation of pathological microenvironment regeneration	[98]
	Iridium metal-complex	● Iridium metal-complex eliminated excess ROS by upregulating expression of SOD1, thus reducing secretion of inflammatory cytokines and facilitating neural repair	[99]

Abbreviations: DSC, decellularized spinal cord; MSCs, mesenchymal stem cells; FPHS, fragmented physical hydrogel suspension; FE, F127-polycitrate-polyethyleneimine; EVs, extracellular vesicles; PLG, poly(lactide-*co*-glycolide); Se-CQDs, selenium-doped carbon quantum dots; SOD1, superoxide dismutase type 1; CONPs, cerium oxide nanoparticles; GM1, monosialotetrahexosylganglioside; TMP, tetramethylpyrazine; MC, minocycline; MPSS, methylprednisolone sodium succinate; TEMPO, *2,2,6,6*-tetramethylpiperidinyloxy; ECM, extracellular matrix; PEI, polyethylene-imine; iNOS, inducible nitric oxide synthase; GFPA, glial fibrillary acidic protein.

and enhance therapy effectiveness [52,53]. Similarly, local delivery of minocycline through metal ion self-assembled hydrogels or PCL/PEG-based nanoparticles has more effective than systemic injection, thus suppressing inflammation and promoting neuroprotection post-SCI [54,55]. Curcumin (Cur), a natural product, is also an antioxidant and anti-inflammatory agent that is generally used in combination with biomaterials for SCI repair [56]. As shown in Fig. 2A, retinoic acid (RA) and Cur *co*-loaded nanoparticles exhibited anti-inflammatory and neuroprotective effects on SCI repair [57]. Moreover, nanoparticles also owned ROS-scavenging ability with good antioxidant properties (Fig. 2B–D). Macrophages-related inflammation is a characteristic of neuroinflammation and can be influenced by lipopolysaccharide (LPS) and ROS [58]. Cur-loaded nanoparticles reduced infiltration of inflammatory macrophages and induced polarization of M0/M1 macrophages into the M2 phenotype following LPS stimulation (Fig. 2E–F).

Biomaterials-based strategy for delivery of anti-inflammatory cytokines is also a prospective therapy for SCI repair. For example, IL-10 plays a critical role in reducing inflammation and neuronal loss. However, chronic systemic administration of IL-10 retards SCI recovery and causes serious side effects [59]. To address the problem, Shen *et al.* developed an immunoregulatory hydrogel scaffold with sustained IL-10 release and damage-associated molecular pattern (DAMP) scavenging capability, thus promoting M1 to M2 macrophage transition and reducing pro-inflammatory cytokines expression [60]. Although delivery of anti-inflammatory cytokines was demonstrated with positive therapeutic outcomes in SCI repair, traditional biomaterials inadequately mimic intricate SCI pathological environment. Consequently, precise dosing and release of anti-inflammatory factors remained challenging. Therefore, developing biomaterials capable of being rapid responsive to local microenvironment may offer a solution to the current barriers in SCI treatment. Inspired by acidic microenvironment of SCI, pH-responsive biomimetic electrospun fiber was developed that triggered release of IL-4 from plasmid-loaded liposomes (Fig. 3A). As shown in Fig. 3B–C, biomimetic composite fiber significantly regulated secretions of pro- and anti-inflammatory factors after SCI [61]. Interestingly, the microenvironment-responsive electrospun fiber also presented better effects on functional recovery than conventional biomaterials (Fig. 3D–E).

3.2. Biomaterials with ROS-scavenging abilities

ROS production is another pathological event in SCI that plays a key role in expanding inflammatory pathways and neuronal death, and excessive ROS generation leads to extracellular toxicity in surrounding tissues [30]. Functional biomaterials with ROS-scavenging properties can attenuate expression of proapoptotic proteins, reduce the volume of traumatic lesion, and promote recovery from SCI [62,63]. For example, antioxidant enzymes (superoxide dismutase (SOD) and catalase) delivered by biodegradable nanoparticles efficiently eliminated excessive ROS and reduced neuronal cell apoptosis after SCI [64]. In addition, excess ROS acted as a trigger for drug release, enabling a local and on-demand delivery of drugs, cells, and factors (Fig. 4A). To evaluate therapeutic effect of ROS-responsive hydrogel, a transverse SCI model with a 2 ± 0.5 mm gap was established at T10 level in rats, and then the repair of SCI was analyzed (Fig. 4B). Compared with non-ROS-responsive hydrogels, ROS-responsive hydrogels for encapsulating bone marrow-derived stem cells (BMSCs) attenuated ROS-mediated oxidative damage, thus improving functional recovery in rats with SCI (Fig. 4C, E, F). Additionally, the oxidative DNA damage marker *8*-hydroxy-*2′*-deoxyguanosine (*8*-OHdG) was also stained and analyzed (Fig. 4D, G, H) [65].

4. Biomolecules-regulating biomaterials for axon regrowth post-SCI

4.1. Exogenous inhibitory biomolecules-antagonizing biomaterials

SCI leads to irreversible neuronal death and axial rupture. However, axon regeneration is inhibited due to the presence of many inhibitory molecules in lesion area and surrounding tissues, resulting in neurological deficits and dysfunction of motor recovery [4]. Therefore, removal of inhibitory molecules that impede axonal growth and new axonal myelination has been a goal of recent research. Delivery of anti-NogoA antibody, a myelin-associated inhibitor, is a potential strategy for SCI repair. Although intrathecal catheter delivery of anti-NogoA antibodies has demonstrated efficacy in promoting axonal regeneration and motor function recovery, achieving local, sustained, and bioactive delivery proves to be more effective. This approach reduces the occurrence of off-target effects at long distances and diminishes the requirement for high drug concentrations [100]. Hence, an anti-Nogo antibody-modified injectable hydrogel combined with neurotrophin-3 (NT-3) was developed for local delivery to treat axon dieback and neurological deficit after SCI [101]. The Nogo extracellular peptide residues 1-40 (NEP1-40) peptide blocked myelin-associated inhibitory effects on axonal regeneration by binding to Nogo receptor. Implantation of NEP1-40-loaded PLGA microspheres into the injury site of SCI promoted axonal growth by sustaining local delivery of NEP1-40 [102].

4.2. Biomaterials for controlled-release of neurotrophic factors

Numerous studies have demonstrated that neurotrophic factors play critical roles in promoting nerve growth and are one of the essential factors required to sustain neuronal cell regrowth. However, a lack of endogenous neurotrophic factors after SCI leads to cell dystrophy and inhibits axonal regrowth [103]. Delivery of one or more combined neurotrophic factors to lesion area promotes recovery of sensory and motor functions in animals with SCI. Hence, exogenous delivery of neurotrophins, including brain derived neurotrophic factor (BDNF), NT-3, nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and glial cell-derived neurotrophic factor (GDNF), is an important repair strategy for SCI and has good clinical prospects [104]. However, a major challenge in utilizing neurotrophic or growth factors for SCI treatment lies in the excessive diffusion of protein factors, leading to an unintended accumulation and potential safety risks.

To overcome this limitation, many studies have investigated modified functional biomaterials that could be used as a carrier for realizing a sustained or/and controlled delivery of neurotrophic factors to regulate SCI [105–107]. In Table 2, we summarized various newly-synthesized biomaterials developed for achieving a controlled release of neurotrophic factors, and meanwhile the main components, mechanisms, and functionalities of different scaffold biomaterials are also compared. For example, to dissolve and release hydrophobic molecules, amphiphilic diblock *co*-polypeptide hydrogel formulations were developed with diverse hydrophobic segments in terms of amino acid type and chain length [108]. These formulations underwent biodegradation over multiple weeks *in vivo* and provided continuous release of bioactive growth factors such as fibroblast growth factor (FGF), NGF, and BDNF for two weeks or longer, which promoted axon regeneration throughout complete SCI after administration [106]. Similarly, a nanocapsule system efficiently transported NGF and aided neural regeneration in SCI mice. Dependent on *in situ* polymerization, MPC and PLA diacrylate were

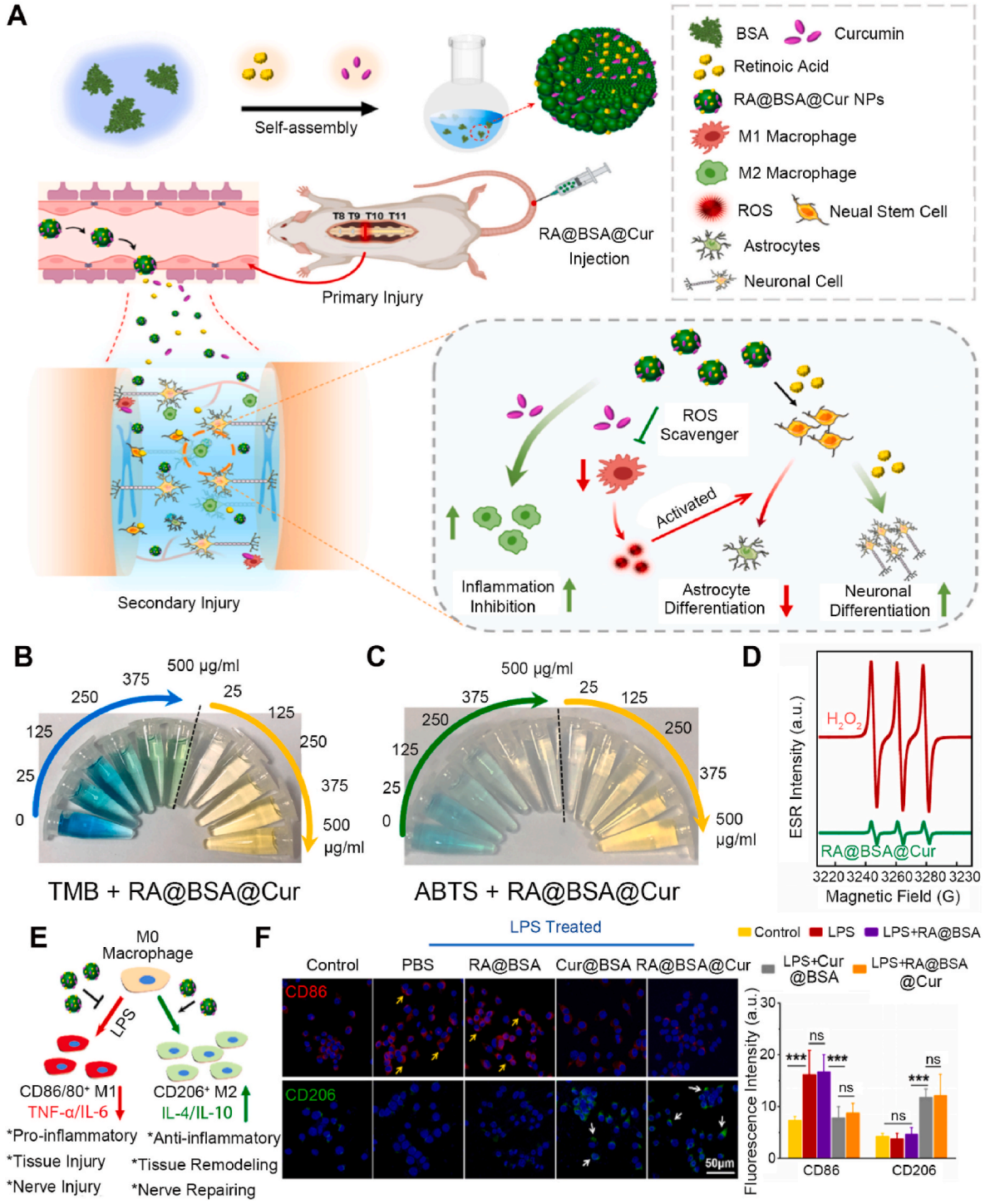

Fig. 2. Anti-inflammatory nanoplatform for facilitating pro-regenerative macrophage polarization in complete transection SCI. A) Schematic illustration of RA@BSA@Cur nanoparticles for SCI repair, which were formed by bovine serum albumin (BSA)-encapsulated nanoparticles of RA and Cur. B, C) Color changes of *3,3,5,5*-tetramethylbenzidine (ROS probe) and *2,2*′-azinobis-(*3*-ethylbenzthiazoline-6-sulphonate), which were treated with different RA@BSA@Cur nanoparticles. D) ESR spectroscopy analyze of ROS scavenging capacity of RA@BSA@Cur nanoparticles. E) Schematic illustration of macrophage polarization regulated by RA@BSA@Cur nanoparticles stimulated by LPS. F) Immunofluorescence and quantitative analyses of $CD68^+$ and $CD206^+$ RAW 264.7 macrophages in each treatment group stimulated by LPS [57]. Copyright 2022, KeAi Publishing Communications Ltd.

utilized as monomer and crosslinker, respectively, enabling sustained NGF release by breaking down the nanocapsule shell through crosslinker hydrolysis. More importantly, post-SCI healing involved a pH shift from acidic to alkaline, accelerating NGF release with neuroprotective and neurotrophic effects [105]. Moreover, Feng *et al.* developed a hybrid hydrogel using functional self-assembling peptide (F-SAP) and large-molecule functional hydrogel (SF) components to enhance axon and myelin sheath regeneration through controlling release of NT-3. Unique self-assembly mechanism involved large SF micelles merging with small F-SAP nanofibers through osmotic pressure and electrostatic interactions, ultimately forming a double nanofiber network. This hybrid hydrogel mimicked ECM structure with individually tunable

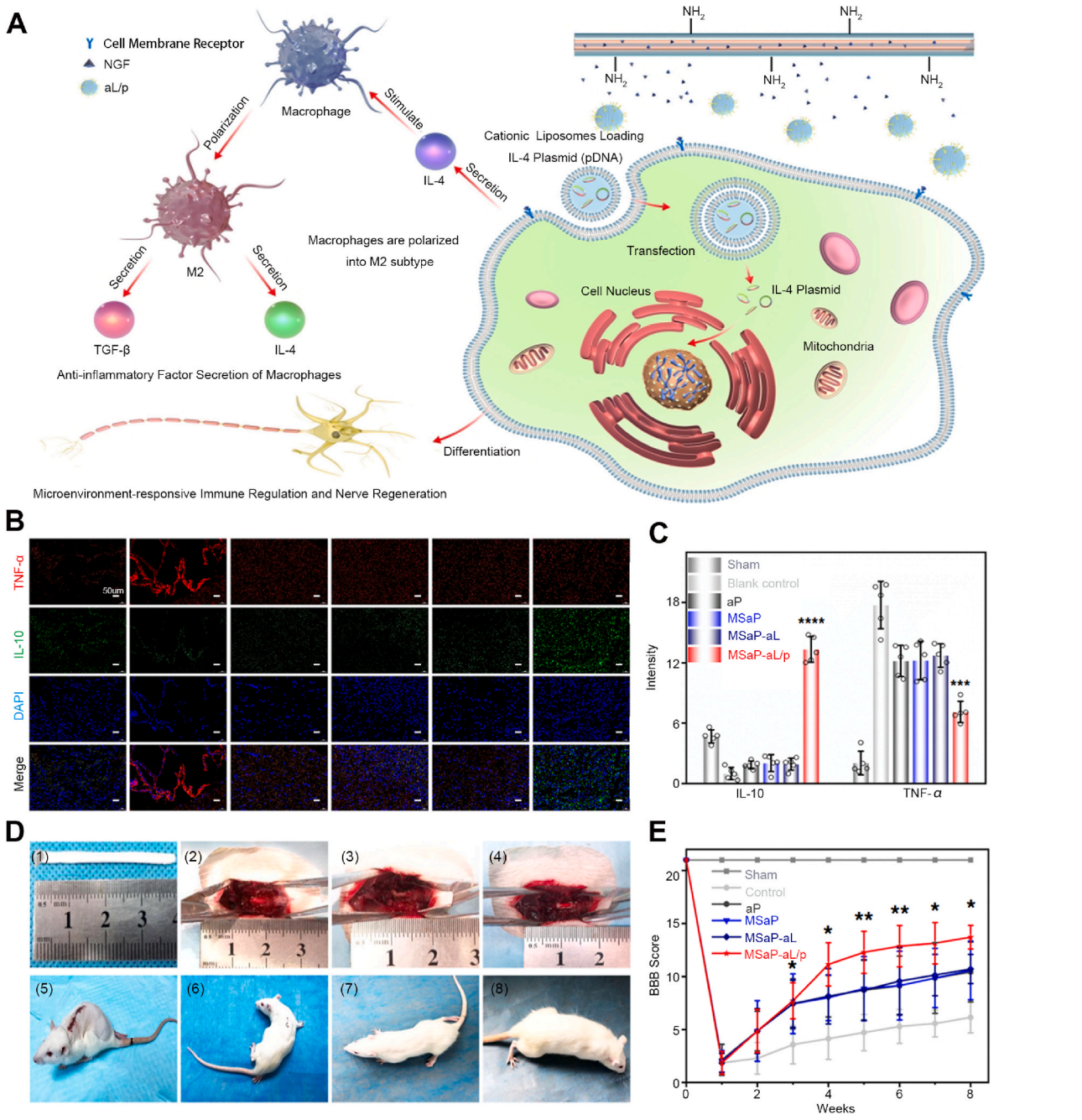

Fig. 3. Microenvironment-responsive electrospun fibers for delivery of IL-4 plasmid in a model of SCI. A) Schematic illustrating formation of microenvironment-responsive scaffolds for immunological regulation and nerve regeneration. B) Representative images of TNF-α and IL-10 immunofluorescence of each treatment group. C) Quantitative analyses of TNF-α and IL-10 fluorescence intensity. D) Representative images of SCI rats at 7 days, 4 weeks, and 8 weeks. E) Quantitative analyses of Basso-Beattie-Bresnahan scores in each group after treatment for 0−8 weeks [61]. Copyright 2020, Springer Nature.

biochemical properties, providing high biosafety due to noncovalent interactions [109]. To synchronize with different repair phases following SCI (such as from acute inflammation to scar formation and long-term repair), modulated release rate of different types of bioactive factors in the same scaffold was also realized. Recently, a multilevel-responsive nanovesicle for precise *co*-delivery of multiple drugs in a spatially and temporally selective manner was developed. In acidic microenvironment around lesion, the nanocarrier was disassembled and led to preferential release of insulin-like growth factor 1 to protect survival neurons. Subsequently, another *co*-loaded drug named p38 inhibitor was released to facilitate M1 to M2 macrophages conversion for long-term modulation of inflammatory response at lesion site, adapting to disease progression through self-cascaded disintegration [110].

Additionally, recent studies demonstrated that three-dimensional (3D) printed scaffolds bound with growth factors efficiently promoted axon regrowth after SCI (Fig. 5A) [111]. For example, Liu *et al.* developed a 3D-printed BDNF/collagen/CS scaffold by low-temperature extrusion 3D printing, which released BDNF into transected lesion area over a long period, thus facilitating tissue regeneration (Fig. 5B−C). Conventional 3D-printing technologies involve high temperatures or chemicals, which maybe compromise biological activity of growth factors during printing process. This approach of incorporating growth factors into pulp preparation process using 3D printing technology at

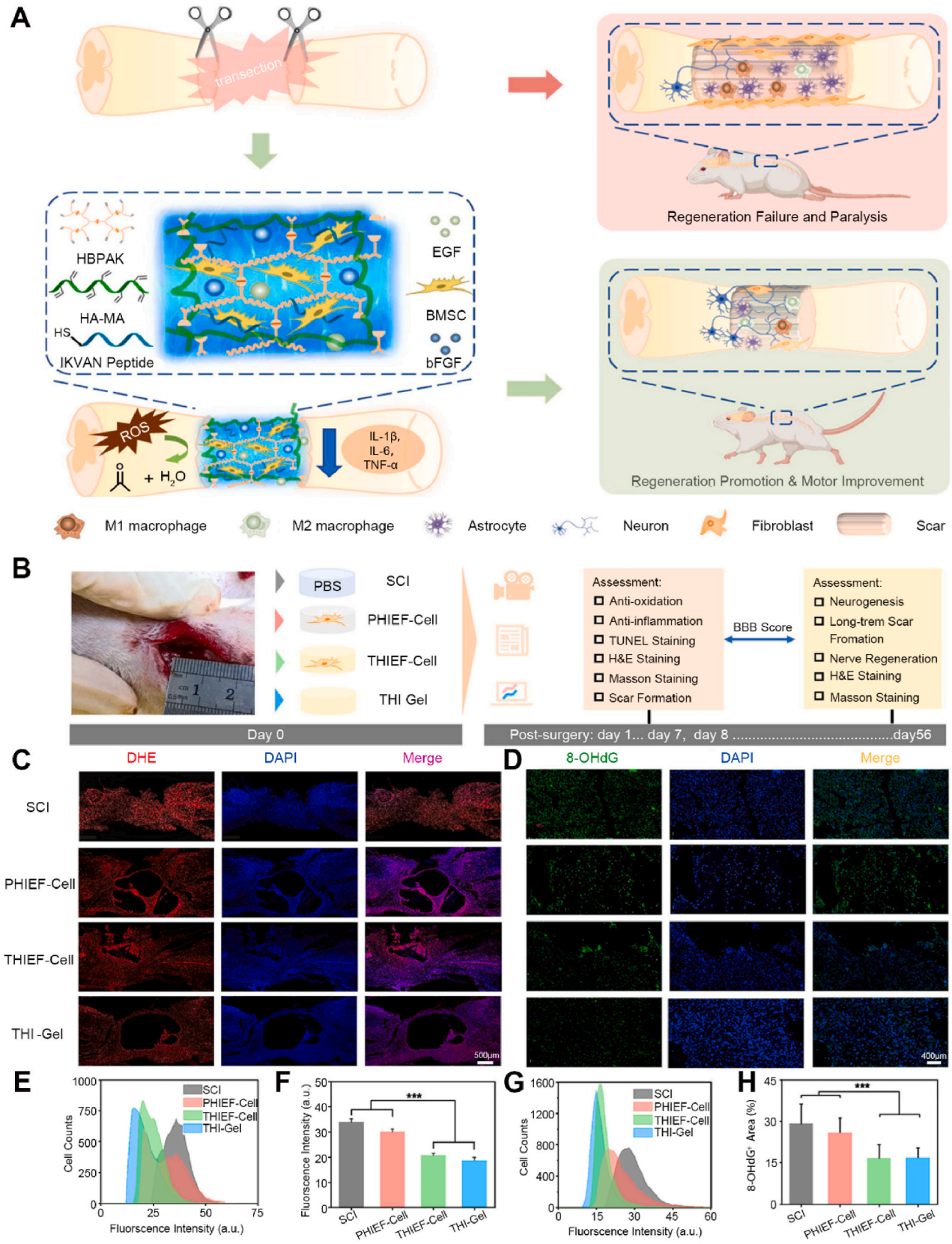

Fig. 4. ROS-scavenging hydrogel for encapsulation of BMSCs to promote SCI repair. A) Schematic illustrating BMSCs-encapsulated ROS-scavenging hydrogel for attenuation of inflammation and improvement of motor function in rats with SCI. B) Schematic illustrating transplantation of BMSC-loaded non-ROS-responsive hydrogels (PHIEF cells), BMSC-loaded ROS-responsive hydrogels (THIEF cells), and ROS-responsive hydrogels (THI hydrogel) into injured spinal cord of rats with SCI. C, D) Dihydroethidium (DHE) and *8*−OHdG staining showing superoxide anion levels and antioxidation property of ROS-responsive hydrogel. E, F) Quantitative analyses of DHE fluorescence intensity. G, H) Quantitative analyses of fluorescence intensity and *8*−OHdG-positive area [65]. Copyright 2022, KeAi Publishing Communications Ltd.

Table 2
Main components, mechanisms, and functionalities of different biomaterial scaffolds for SCI repair.

Types of biomaterials	Main components	Mechanisms	Functionalities
Biomaterials for anti-inflammatory regulation	PEG PLLA PLGA HA PCL CS Gelatin Exosome IL-4 IL-10	● Reduce number of macrophages/ microglia accumulation ● Induce macrophages polarization from M1 to M2 phenotype ● Reduce secretion of inflammatory factors	● Regulate inflammatory microenvironment ● Protect nerve cells
Biomaterials with ROS-scavenging abilities	MnO_2 SOD1 Catalase Se-CQDs CONPs SeNPs@GM1/TMP HA-TEMPO Iridium metal complex	● Attenuate expression of pro-apoptotic proteins ● Reduce volume of traumatic lesion	
Exogenous inhibitory biomolecules-antagonizing biomaterials	NEP1-40 LOTUS	● Removal of inhibitory molecules of Nogo-A and CSPGs	● Promote axonal regeneration and motor function recovery
Biomaterials for controlled-release of neurotrophic factors	Amphiphilic diblock copolypeptide MPC and PLA diacrylate	● Degradation	● Controllable release of neurotrophic factors
	BDNF/collagen/CS		● Promote nerve growth
	F-SAP and large-molecule SF	● Osmotic pressure ● Electrostatic interactions	● Promote recovery of sensory and motor functions
	SB203580/IGF-1-HPAA-BM@CD-HPG-C GSH-modified gelation (PTX/VEGF) @DMWCNTs/GG	● pH, MMP, and NIR response	
Revascularization microenvironment-reshaping biomaterials	FA RADA16 with neuropeptide substance P ECM	● Promote angiogenesis signaling pathways ● Induce VEGF expression	● Transport oxygen and nutrient ● Promote angiogenesis
	PEG PLGA PLLA Poly−*L*−Lysine Cerebrospinal fluid ECM	● Deliveries of angiogenic factors, EVs, or vascular cells	
BSCB-regulating biomaterials	Bazedoxifene Dexamethasone UCMSC-Exos SCs-Exos Elamipretide (SS-31) G protein-coupled receptor 124	● Activate BSCB-related pathways (NF-κB and JAK1/STAT3) ● Enhance mitochondrial function and suppress lipid peroxidation	● Repair disrupted BSCB ● Maintain homeostasis
Astroglial scar-regulating biomaterials	Chondroitinase ABC Chondroitinase AC Arylsulfatase B Epoxide hydrolase Hyaluronidase Imidazole-poly (organophoaphazenes)	● Cut chain structure of CSPGs for biodegradation ● Reduce astrocytes activation ● Minimize chronic fibrotic host responses	● Alleviate fibrotic microenvironment ● Support axonal regrowth

Abbreviations: LOTUS, lateral olfactory tract usher substance; MPC, 2-methacryloyloxyethyl phosphorylcholine; F-SAP, self-assembling peptide; SB203580, co-loading p38 inhibitor; IGF-1, insulin-like growth factor 1; HPAA, hyperbranched poly (amido amine); BM, benzimidazole; HPG, hyperbranched polyglycerol; CD, β-cyclodextrin; C, lesion-targeting NH2-Cys-Ala-Gla-Lys-OH peptide; GSH, glutathione; PTX, paclitaxel; VEGF, vascular endothelial growth factor; DMWCNTs, drug-loaded multiwalled carbon nanotubes.

low temperatures can preserve the activity of the growth factors well. Six weeks post-implantation, the scaffold with a collagen/CS mass ratio of 2:1 was completely degraded, making it ideal for SCI repair process. Importantly, transplantation of this 3D scaffold demonstrated encouraging results in promoting functional recovery (Fig. 5D−F).

Despite significant advancements, growth factor-delivery platforms still face challenges that must be addressed. Further development is needed to combine growth factors with other drugs in hydrogel for enhancing therapeutic efficacy and minimizing side effects. Additionally, investigating these mechanisms will facilitate targeted design and optimization of growth factors delivery hydrogels in the future [112]. More importantly, further research is needed to explore integrating administration of growth factors-loaded bioactive hydrogels into clinical procedures to facilitate clinical application of these delivery systems [113].

4.3. Revascularization microenvironment-reshaping biomaterials for SCI repair

Vasculature of spinal cord is a spatial proximity neural system, which plays a crucial role in maintaining function and activity of neurons [114]. As importance of angiogenesis in axonal regeneration and functional recovery is mediated through oxygen and nutrient transport, promoting angiogenesis has emerged as a promising therapeutic strategy for SCI repair [115]. To date, owing to lower occurrence of side effects than systemic administration of drugs, implantation of biomaterials with innate angiogenic properties or in combination with angiogenic factors for localized delivery is a potential strategy for blood vessel formation [18,116–118]. For example, natural biomaterials including aligned fibrin hydrogel and collagen have been widely used to enhance revascularization *via* their intrinsic angiogenic properties or

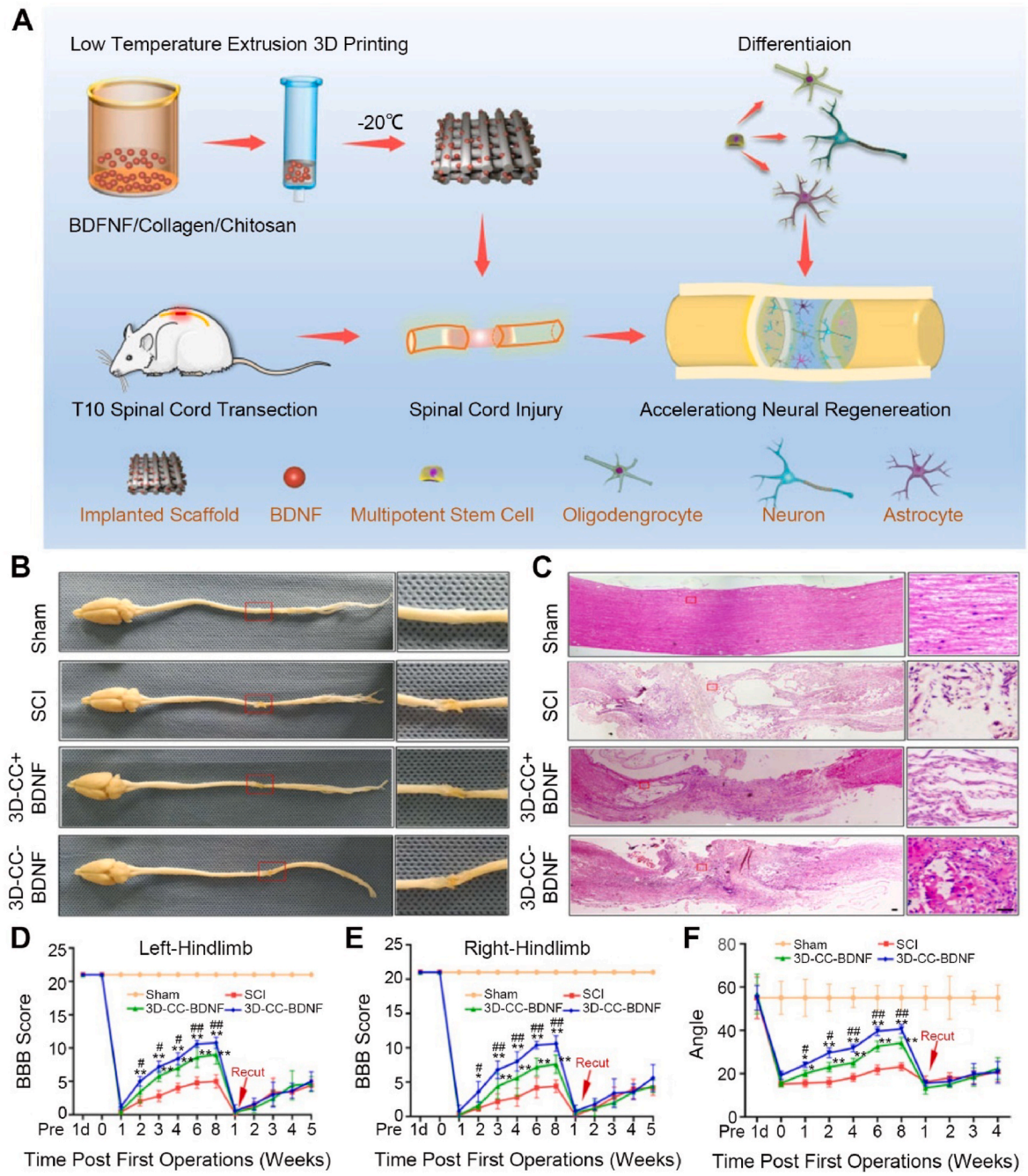

Fig. 5. BDNF/collagen/CS scaffolds prepared by 3D printing for BDNF delivery to promote axon regeneration and reduce glial scar formation. A) Schematic illustrating construction of BDNF/collagen/CS scaffolds by low-temperature extrusion 3D printing that accelerated axonal regeneration in a model of SCI. B) Low-magnification and high-magnification images of macroscopic histology. C) Low-magnification (50 ×) and high-magnification (400 ×) images of hematoxylin and eosin staining of spinal cord sections in each treatment group. D, E) Quantitative analyses of Basso–Beattie–Bresnahan score of the left and right hindlimbs of rats with SCI over time. F) Quantitative analyses of inclined-grid climbing test results for rats with SCI over time [111]. Copyright 2021, Oxford Academic.

delivery of angiogenic factors [119–121]. Implantation of 3D hierarchically-aligned fibrin hydrogel supported rapid vascularization along with axon regrowth in rats with SCI [122]. Moreover, *in situ* injection of hyaluronic-ferulic acid conjugate containing bucladesine nanoparticles promoted angiogenesis after SCI [123]. Recently, an angiogenic self-assembling peptide modified with substance P effectively stimulated angiogenesis and subsequent functional improvement in SCI rats [124]. For long-distance SCI, combing living nerve-like fibers with neural stem cells (NSCs) is one of suitable ways to promote angiogenesis and refine ecological niche of SCI defect site [77].

In addition to natural biomaterials, synthetic biomaterials (*e.g.*, PEG, PLGA, and Poly−*L*−Lysine) are widely used for revascularization and angiogenesis owing to their degradation characteristics, excellent biocompatibility, and stable physical performance [123,125]. For example, Estrada *et al.* implanted three graft materials such as matrigel, alginate hydrogel, and PEG to compare their therapeutic effect on chronic SCI repair. Results showed that the PEG implantation had significant benefits regarding revascularization, axon regeneration, and functional recovery after SCI [126]. Apart from implantation of biomaterials alone, a local and sustained delivery of VEGF and NT-3 from synthetic PLGA nanoparticles to epicenter of injury also has a beneficial effect on vascular remodeling for SCI [127].

In addition to delivery of pro-angiogenic factors, implantation of vascular cells is a promising method for remodeling angiogenesis and neurovascular interactions. For example, implantation of NeuroRegen scaffolds containing microvascular endothelial cells promoted neovascularization and functional recovery in lesion area [128]. Moreover, self-assembled peptide scaffolds are seeded with microvascular cells to support BSCB integrity and vascularization in rats with SCI [118]. Interestingly, transplantation of a 3D scaffold with aligned micro-vessels guides axon regeneration from neural progenitor cells along microvasculature [129]. In conclusion, application of biomaterials to repair vascular rupture induced by SCI not only has innate angiogenesis-promoting properties, but also locally delivers pro-angiogenic factors to remodel revascularization, which is a potential treatment for vascular regeneration after SCI.

4.4. BSCB-regulating biomaterials

BSCB plays a critical role in maintaining homeostasis of CNS, and its disruption following SCI can lead to detrimental consequences [20,129]. Recent research underlined importance of bioactive scaffolds and targeted drug-delivery systems in repairing the BSCB post-SCI. To address challenge of targeted drug delivery in BSCB repair post-SCI, Wang et al. introduced a novel biocarrier material of bazedoxifene (BZA)-loaded HSPT@Be, which was made of HA, sodium alginate (SA), polyvinyl alcohol (PVA), and tetramethylpropane (TPA). This system comprised an outer layer of biodegradable hydrogel and an inner layer of drug-loaded hydrogel. The outer hydrogel was degraded in an oxidative-stress microenvironment at 1 day post SCI, facilitating a gradual release of BZA from the inner layer over a week. The HSPT@Be offered a sustained drug delivery, enhancing treatment efficacy and supporting BSCB recovery [130]. Similarly, a recombinant G protein-coupled receptor 124 (GPR124) was discovered to help repair the disrupted BSCB post-SCI partially by restoring tight junctions and supporting endothelial cell functions. However, limited physicochemical stability hindered a widespread application of the GPR124. To address this issue, a thermosensitive heparin-poloxamer (HP) hydrogel was developed to sustain GPR124 release and preserve its bioactivity for rebuilding the BSCB, finally being helpful to improve motor function recovery post-SCI [131].

Recent studies highlighted the role of exosomes in promoting BSCB repair following SCI in addition to drugs and peptides. For instance, specific subpopulations of $CD146^{+}CD271^{+}$ umbilical cord MSCs (UCMSC) were isolated to generate engineered exosomes with targeted neovascularization function. These UCMSC-Exos shown great efficacy in targeting neovascularization in SCI mice, stabilizing the BSCB, and enhancing functional recovery after SCI. Furthermore, deep microRNA sequencing was utilized in this study to explore the biological mechanisms underlying the impact of UCMSC-Exos on BSCB permeability and identified significant role of miR-501-5p/MLCK axis in this process [132]. In addition, it was discovered that miR-210 derived from pericytes enhanced mitochondrial function and suppressed lipid peroxidation in vascular endothelial cells following traumatic SCI by activating JAK1/STAT3 signaling pathway [133]. In conclusion, by leveraging the advances in biomaterial science and bioengineering, researchers strive to develop targeted therapies that not only repair the BSCB but also facilitate neural regeneration and functional recovery in patients with SCI.

4.5. Astroglial scar-regulating biomaterials

Astroglial scar formation is a complex process that occurs in response to SCI, leading to formation of a physical and chemical barrier that inhibits neural regeneration [134]. CSPGs which are secreted by astroglial scar, have been widely studied for its ability to inhibit axonal growth [5]. Administration of chondroitin sulfate to degrade the CSPGs deposited in lesion area of SCI and surrounding tissues is able to promote axon regeneration [36,135]. However, enzyme activity of chondroitinase ABC (chABC) is inactivated at 37 °C. Delivering chABC through biomaterials can effectively degrade the CSPGs in the astroglial scar, promoting axonal regeneration and function recovery. Recently, a tailor-made random copolymer with an ability to stabilize the chABC at physiological temperature was developed, which was able to promote sustained neural regeneration [136]. To further improve enzyme activity time of chABC, Raspa *et al.* constructed two self-assembling peptides (SAPs) hydrogels for prolonging the enzymatic activity of chABC from 72 h to 42 days *in vitro*, and this extended activity proved to be beneficial in promoting neural regeneration and locomotor recovery [137]. Furthermore, a dual-functional hydrogel was developed for localized delivery of arylsulfatase B (a human enzyme to degrade CSPGs), significantly alleviated scar microenvironment and supported axonal regrowth (Fig. 6A) [76]. Imidazole-conjugated poly(organophosphoronitrile) hydrogels (I-5) prevented tissue defects following an injection into a SCI animal model [138]. Consequently, delivery of CSPGs-degrading enzymes by I-5 hydrogel effectively reduced CS carbohydrate chains and chondroitin-*4*-sulfate (C4S) by an immunoreaction (Fig. 6B–D). In addition, injection of the dual-functional hydrogel reduced level of sulfated glycosaminoglycans (GAGs) by GAG assays after SCI (Fig. 6E).

In addition to counteracting CSPGs released by astroglial scar, strategies aimed at reducing astrocytes activation have been explored to regulate glial scar formation. In the context of downregulating astrocytes activation, biomaterials with superior biocompatibility are more suitable as they have an ability to minimize chronic fibrotic host responses [139]. Several biomaterials derived from ECM component, including CS, collagen, and gelatin, have been explored for SCI repair [140]. For instance, CS-based nanoparticles with biocompatibility and pH-responsive behavior were developed for targeting reactive astrocytes in SCI [141]. However, majority of the nanoparticles were sequestered by microglia/macrophages and CD45 positive cells due to their heightened phagocytic activity, resulting in limited accumulation within astrocytes. To address this issue, Irma Vismara *et al.* developed a functionalized nanogel-based nanovector that was modified with PEG and polyethylene-imine (PEI) and then loaded with the drug of Rolipram. This method accomplished a targeted release aimed at A1 astrocytes in SCI, involving clathrin-mediated endocytosis for internalization and lysosome-oriented degradation. Additionally, absence of lysosome colocalization in microglia indicates alternative uptake pathways for NG like caveolae-mediated endocytosis, which prevents lysosomal degradation [88]. Similarly, Simonetta Papa functionalized a nanogel-based nanovector with both NH2 and Cy5 groups, effectively limiting uptake by macrophages and facilitating internalization into cytoplasm of astrocytes [142].

Although significant progress has been made in utilizing biomaterials for glial scar modulation in preclinical studies, translation to clinical applications is still a challenge. An optimization of biomaterial properties, such as biocompatibility, degradation rate, and mechanical strength, is crucial for realizing a successful clinical translation. Additionally, long-term safety and biocompatibility studies are necessary to ensure the effectiveness and safety of these biomaterial-based interventions.

5. Advanced technologies for regulating SCI microenvironment

5.1. Application of decellularized tissue matrix in regulating SCI microenvironment

ECM is an external environment composed of secreted proteins, which is crucial in maintaining tissue homeostasis, damage repair, and remodeling [143]. In this regard, the ECM-mimicking hydrogels and decellularized extracellular matrix (dECM) scaffolds derived from blood vessels, optic nerve, brain, and spinal cord tissues are promising biomaterial formulations to promote tissue regeneration and repair after

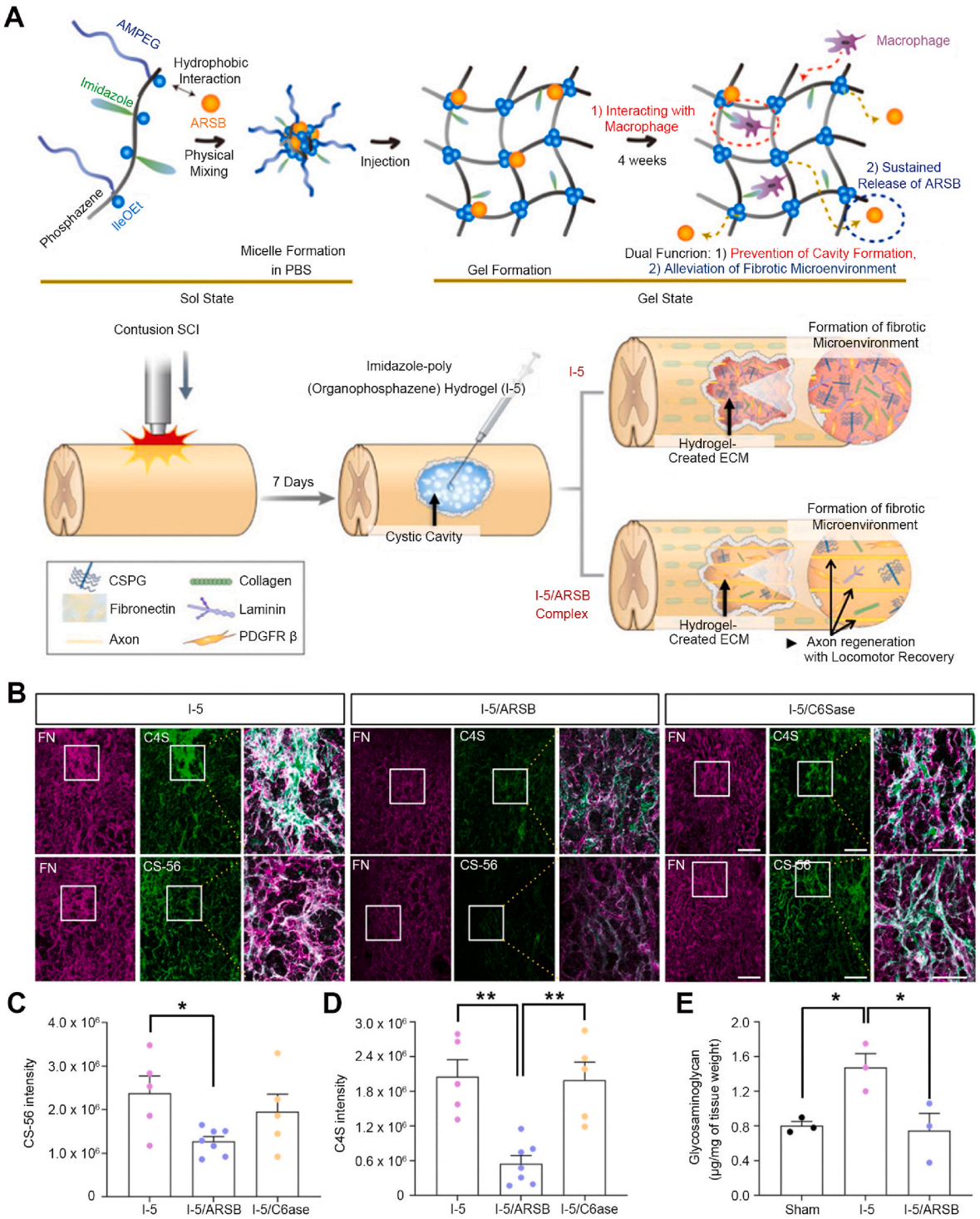

Fig. 6. Dual-functionalized hydrogel for localized delivery of arylsulfatase B to alleviate fibrotic microenvironment after SCI. A) Schematic illustrating construction of dual-functionalized hydrogel for CSPGs degradation and axonal regeneration in a model of SCI. B) Representative images of fibronectin and chondroitin-*4*-sulfate (C4S) or CSPGs (CS-56) immunofluorescence of each treatment group. Scale bars indicate measurements of 200 μm for lower magnification images and 100 μm for higher magnification images. C, D) Quantitative analyses of C4S and CSPGs fluorescence intensity. E) Quantitative analyses of CSPGs in spinal cord tissue by glycosaminoglycan assay [76]. Copyright 2022, Elsevier.

SCI [144–146]. Recently, a decellularized tissue matrices hydrogel from spinal cord (DSCM-gel) was developed and injected into SCI rats for neural stem/progenitor cell microenvironment remodeling after SCI [147]. The gel reestablished a regenerative microenvironment for endogenous neural stem/progenitor cells (eNSPCs) recruitment and neuronal differentiation. In additional to regulating eNSPCs recruitment and differentiation, the DSCM gel/GelMA hydrogel also promoted survival, proliferation, and differentiation of transplanted mesenchymal stem cells through reconstruction of the SCI microenvironment *via* reduced inflammatory response and proliferation of reactive astrocytes [145].

A variety of organ or tissue-derived dECM have been demonstrated to provide a suitable microenvironment for neuronal differentiation of stem cells and axon regeneration. For example, brain-derived dECM

hydrogels were reported to enhance polarization of macrophages towards M2 and functional improvements after SCI [148]. Similarly, optic nerve-derived dECM functional scaffolds also improved SCI microenvironment through alleviating inflammation and reducing CSPGs levels [144]. These results fully verified that other neural tissue-derived dECM also effectively promoted SCI repair as a replacement for DSCM-derived scaffolds. This was because that although functional proteins of DSCM were similar to normal spinal cord, spinal cord was prone to be collapsed after decellularization due to tubular structure, and therefore affected the resultant axon regeneration.

As mentioned above, most of studies have found that dECM improves microenvironment of SCI, while multimodal therapeutic effect of the dECM in combination with other materials or/and biomedical factors remains unclear. Recently, a composite scaffold containing a HA-based hydrogel, decellularized brain matrix (DBM@Gel), and bioactive compounds (such as polydeoxyribonucleotide (PDRN), TNF-α/IFN-γ induced mesenchymal stem cell-derived extracellular vesicles (TIEVs), and human embryonic stem cell-derived neural progenitor cells (NPCs)) was developed for improving SCI microenvironment (Fig. 7A–B) [149]. As shown in Fig. 7C, to examine *in-vivo* neural regeneration effectiveness of

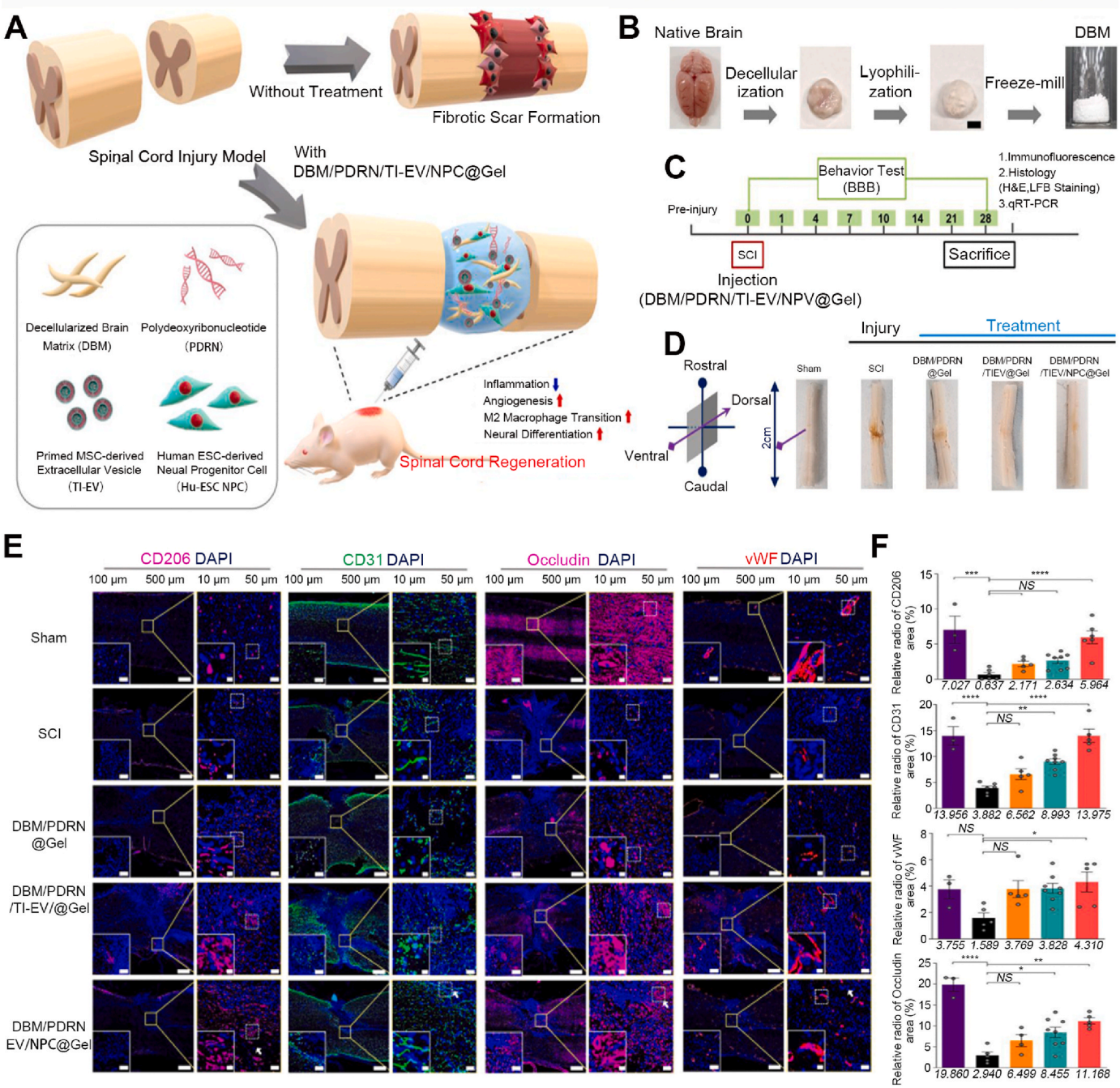

Fig. 7. Injection of DBM/PDRN/TI-EV/NPC@Gel after SCI inhibits pro-inflammation and promotes angiogenesis and M2 macrophage transition. A) Schematic illustrating DBM/PDRN/TI-EV/NPC@Gel for SCI repair. B) Image of DBM preparation process (scale bar: 500 μm). C) Schematic illustrating experimental plan process in SCI rats. D) Image of morphology changes of fibrotic scar after injection of DBM/PDRN/TI-EV/NPC@Gel 28 days in SCI rats. E) Representative images of CD206, CD31, tight junction-related protein marker occludin, and vWF immunofluorescence of each treatment group. The yellow box in the 500 μm image represents a 50 μm area. The image in the lower left is an enlarged version of the corresponding area, showing a scale of 100 μm and a detailed view of 10 μm within that area. F) Quantitative analyses of CD206, Occludin, CD31, and vWF fluorescence area [149]. Copyright 2023, Elsevier.

DBM/PDRN/TI-EV/NPC@Gel, behavioral analysis, immunofluorescence, and qRT-PCR experiments were conducted 28 days after administration of the hydrogel. Visual examination of spinal cord samples revealed accelerated wound healing and reduced scarring after implantation of the DBM/PDRN/TI-EV/NPC@Gel in SCI rats (Fig. 7D). The injection of DBM/PDRN/TI-EV/NPC@Gel improved anti-inflammatory M2 macrophage transition in SCI rats by analysis of cluster of differentiation 206 (CD206). The DBM/PDRN/TI-EV/NPC@Gel also promoted angiogenesis by evaluating expressions of cluster of differentiation 31 (CD31) and von willebrand factor (vWF). Additionally, expression of tight junction-related protein marker, occluding, was higher in the DBM/PDRN/TI-EV/NPC@Gel group compared to other groups. This founding suggested that the DBM/PDRN/TI-EV/NPC@Gel promoted the restoration of the blood-brain-spinal cord barrier (BSCB) after SCI (Fig. 7E–F). As dysfunctional pathological microenvironment of SCI is generally very complex, and thus a comprehensive treatment will be more effective than single therapy. This study provides a multifaceted combination treatment including stem cells, dECM, and exosomes, which will be able to afford a promising technology for future therapy in SCI patients. Along with advancements in contemporary animal husbandry, it is easy to source porcine spinal cord, brain, and muscle tissues for large-scale production. However, if the dECM can be utilized in clinical treatment in the near future, limited standardized production of spinal cord tissue may pose a significant obstacle to its clinical applications [150].

5.2. *Application of stem cells-derived EVs and 3D stem cell spheroids for SCI repair*

Exogenous stem cell transplantation replenishes excess of dead neurons or glial cells and creates a favorable microenvironment for regeneration of injured spinal cord tissue [151,152]. MSCs are pluripotent cells in mesenchymal tissues and have various beneficial effects on SCI microenvironment; however, low survival rate and risk of tumor formation have limited their widespread applications in treatment of SCI [153,154]. Hence, MSCs-derived EVs containing valuable MSCs-secreted factors are considered as a promising strategy to replace MSC transplantation for the treatment of SCI (Fig. 8A). Recently, a BMSCs-derived exosomes-loaded electroconductive hydrogel with a highly porous 3D structure was developed, and it was shown to promote M2 microglial polarization significantly (Fig. 8B). Expression of M1-markers, such as iNOS, IL-6, and TNF-α were lower in

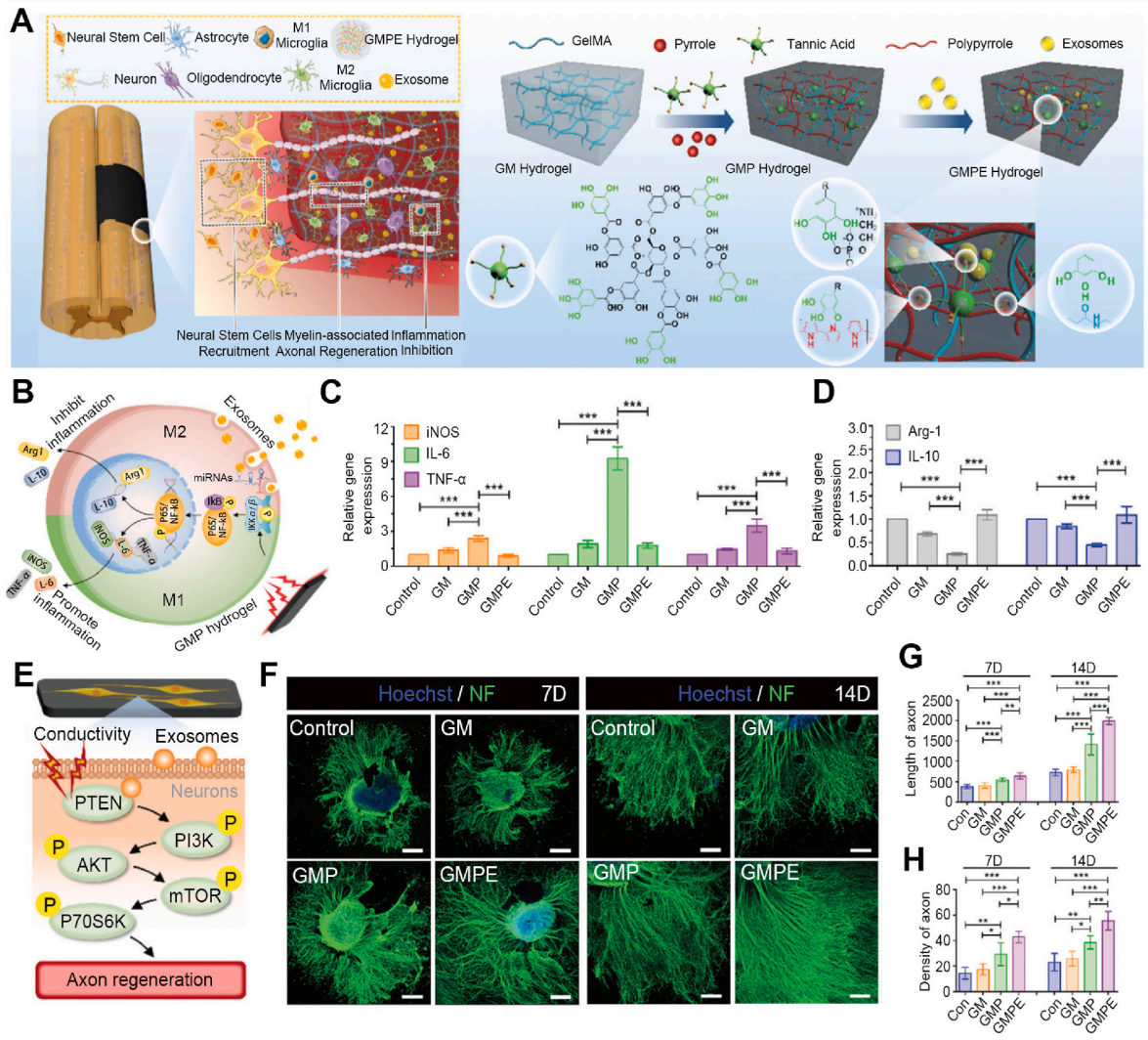

Fig. 8. Electroconductive hydrogels loaded with BMSC-exosomes facilitate pro-regenerative macrophage polarization and myelinated axon growth. A) Schematic illustrating synthesis of GMPE hydrogel, which reduced inflammation and promoted myelinated axonal regrowth. B) Schematic illustration of M1 to M2 conversion through NF-κB pathway activity. C, D) mRNA expression of pro-inflammatory factors including iNOS, IL-6, TNF-α, Arg1, and IL-10. E) Illustration of GMPE hydrogel promoted axon growth through regulating activity of PTEN/PI3K/AKT/mTOR pathways. F) Representative immunofluorescence image of NF-positive axons in DRGs for 7 and 14 days. G, H) Quantification of axon density and length [155]. Copyright 2022, Wiley.

GM/PPy/exosomes (GMPE) group than GM/PPy (GMP) group. Conversely, M2-markers, including IL-10 and Arg-1 were higher in GMPE group (Fig. 8C–D). To evaluate role of GMPE hydrogel in axon outgrowth, dorsal root ganglions (DRGs) were harvested to be cultured onto different hydrogels. Results showed that electroconductive hydrogels loaded with BMSCs-exosomes had a strong therapeutic effect on axon outgrowth in DRGs through regulating PTEN/PI3K/AKT/mTOR pathways after SCI (Fig. 8E–H) [155]. Nonetheless, an efficient transportation of EVs to damaged spinal cord can inadvertently harm nearby healthy tissues, resulting in potential unforeseen side effects. In a recent study, Fang *et al.* introduced a novel approach utilizing porous microneedles (MNs) to deliver EVs directly to spinal cord lesion beneath spinal dura, without causing any damage to the lesion itself. To ensure a sustained delivery of MSC-EVs, the microneedle arrays with appropriate pore sizes were combined with a gelatin methacryloyl (GelMA) hydrogel embedded with MSCs during the surgery. Moreover, this combination

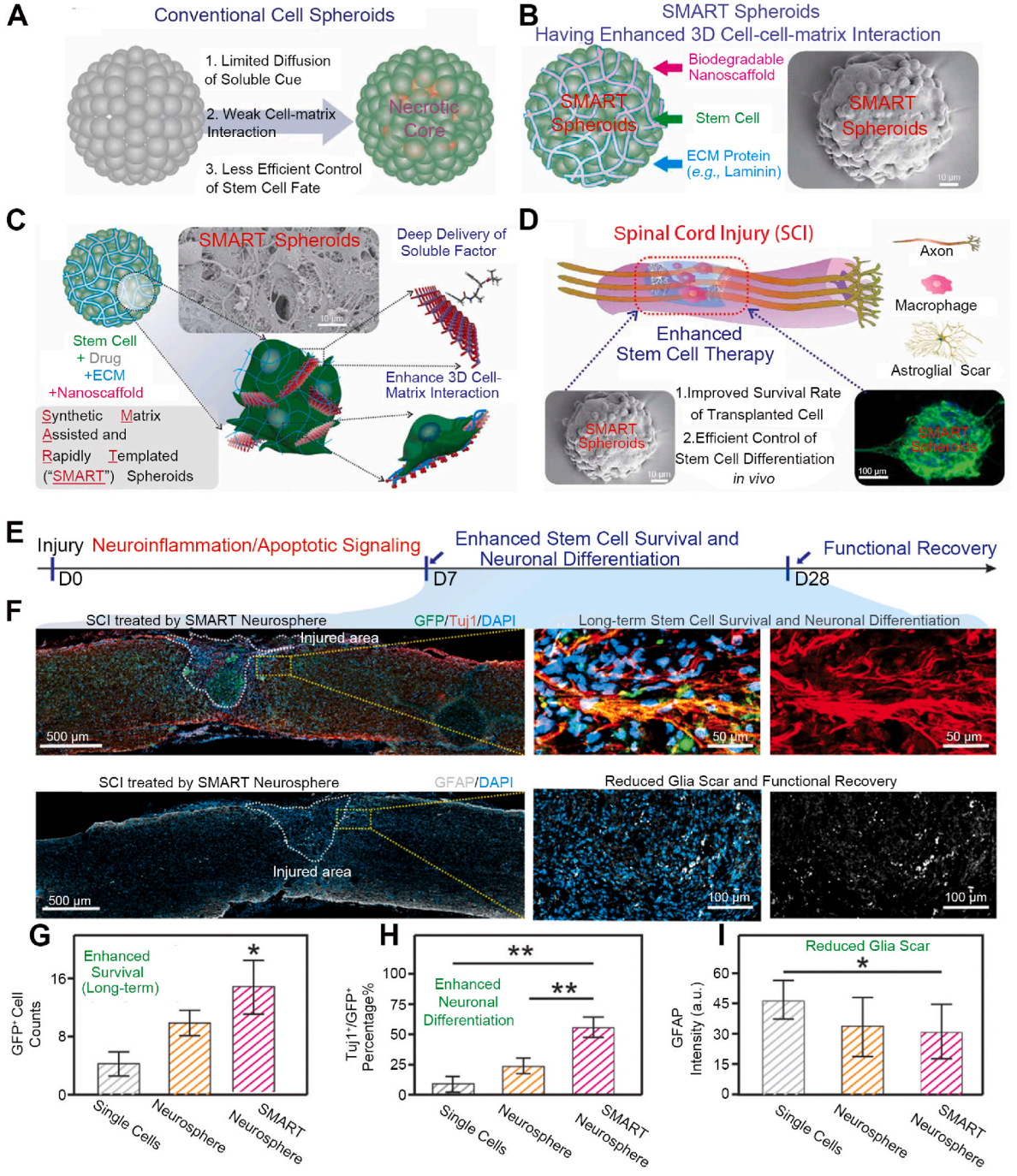

Fig. 9. Hybrid SMART spheroids enhance stem cell-based therapy for SCI. A, B) Schematic illustrating of advantages of SMART spheroids over conventional cell spheroids. C) Schematic illustrating formation of SMART spheroids with controlled drug release and cell-extracellular matrix proteins interactions by 2D nanosheets of manganese dioxide. D) Schematic illustration of implantation of SMART spheroids into mice with SCI improved survival rate and neuronal differentiation of stem cells. E) Schematic illustrating survival, differentiation, and functional recovery after implantation of SMART spheroids into mice with SCI. F) Representative images of GFP, GFAP and Tuj1 immunofluorescence after treatment with SMART neurospheres post-SCI. G–I) Quantitative analyses of GFP-positive cells, $GFP^+/Tuj1^+$ (percentage neural differentiation) and GFAP-positive glia scar fluorescence intensity post-SCI [160]. Copyright 2022, American Association for the Advancement of Science.

allowed for continuous deliver MSCs secretomes to spinal cord lesion, due to the porous MNs [156]. Despite promising preclinical data on EVs for SCI treatment, clinical research is still limited. Standardizing EVs size, purity, and components from different culture conditions and separation methods are crucial. Ensuring a large-scale production of EVs compliant with good manufacturing practices is vital for successful translation of EVs-based therapies [157].

However, limited cell sources and ethical issues hinder application of stem cells in SCI treatment. The use of somatic cells derived from induced pluripotent stem cells (iPSCs) addresses these challenges and is considered as a potential therapeutic approach for SCI [158]. Recent study conducted by V. M. Doulames *et al.* developed custom-engineered hydrogels with *in situ* stiffening properties to retain cells within injury site and thus promoting cell attachment and neurite extension and delivering human iPSCs-derived neurons into injured spinal cord [159]. In addition, stem cells-based spheroids and organoids are also potential treatment strategies to address low survival and inefficient differentiation of stem cells. Recently, Christopher *et al.* developed a nanobiomaterial-templated 3D cells-assembly method to form hybrid stem cell spheroids capable of controlling drug release and cell-matrix interactions, which were called "synthetic matrix-assisted and rapidly templated (SMART) spheroids" (Fig. 9A–B). The development of this SMART spheroid technology enabled us to combine scaffold-based and scaffold-free methods effectively, facilitating induction of neuronal differentiation in stem cell spheroids both *in vitro* and *in vivo*. This advancement held promise for future treatment of CNS injuries, including SCI and traumatic brain injury (TBI) (Fig. 9C–D). To confirm therapeutic efficacy of the SMART spheroid for CNS injuries, survival and differentiation abilities of implanted cells were assayed after SCI (Fig. 9E). Results showed that SMART-based hiPSC-NSCs implantation enhanced survival and neuronal differentiation of stem cells [160] (Fig. 9F–H). Moreover, glia scar formation was also reduced after transplantation of the SMART-based hiPSC-NSCs (Fig. 9F, I).

5.3. Bioengineered biomaterials-based 3D spinal cord-like tissue transplantation

Stem-cell transplantation provides promising prospects for modulating microenvironment and replenishing dead neurons after SCI, but most transplanted stem cells differentiate into astrocytes rather than mature functional neurons due to an inhibitory nature of this microenvironment. Moreover, it is noteworthy that spinal cord contains more than 20 types of neurons, and how to ensure exogenous stem cells differentiate into a variety of neurons after transplantation is an ongoing challenge. Therefore, combined technology that replenishes various neurons and improves SCI microenvironment to help survival of transplantable multiple neurons of spinal cord is a new trend of SCI treatment in the future. Lately, engineered biomaterials-based spinal cord-like organoids with multiple functional dorsal and ventral neurons generated from neural stem/progenitor cells or even human astrocytes have been explored for supplementing lost neurons and forming a targeted connection with host neurons in SCI model [161–163]. Similarly, Jin *et al.* successfully constructed a unique centimeter-scale, linearly-ordered spinal cord-like structure on linear-ordered collagen scaffold (LOCS), and then synaptic connections with host cells as well as a favorable biological microenvironment following implantation into SCI rats were observed [164]. To further address personalized treatment for SCI, Wu *et al.* devised a functional neural network tissue by utilizing TrkC-modified iPSC-derived NSCs and CBD-NT3-modified LOCS, with a goal of both replenishing defective spinal tissue and improving microenvironment [165]. More importantly, the authors revealed potential mechanisms for SCI repair through RNA-seq and metabolomics analyses, by which implantation of functional neural-network tissue contributed to extracellular matrix remodeling, material transport activation, intercellular message conduction, and ion channel capacity.

Recently, Lai *et al.* developed a bioengineered transplantable spinal white matter-like tissue (WMLT) module derived from decellularized optic nerve scaffolds loaded with NT-3 overexpressing oligodendrocyte precursor cells [166]. Implantation of WMLT reduced scar formation, inhibited inflammation, and reconstructed a favorable microenvironment to support directional axon regeneration and myelination after SCI. The most prominent advantage of WMLT module was its microstructure and bioactive matrix, which allowed for formation of neural construction with a niche rich in NT-3, laminin, and OL cells after SCI. However, spinal cord-like tissue module always lacks properties of gray matter-like tissue, which contains a variety of nerve cells in different sizes, shapes, and functions to receive and emit impulses. Hence, a spinal cord-like tissue incorporated both WMLT (including CNTF-overexpression oligodendrocytes) and gray matter-like tissue (GMLT) (including NT-3/TrkC-overexpression neurons) was fabricated recently using collagen sponge scaffold [167]. Transplantation of this spinal cord-like tissue into SCI rats enhanced their neuronal regrowth and remyelination, also improved microenvironment of muscle tissue, finally promoting functional recovery.

6. Conductive biomaterials for repair of SCI

In recent years, development of conductive biomaterials emerged as a promising strategy to enhance neural regeneration and functional recovery. Conductive biomaterials possess unique electrical properties that allow application of electrical stimulation to promote nerve regeneration [168]. Within neural tissues, activation of neural cell ion channels initiates a cellular gap, leading to membrane polarization and creation of inherent electric signals [169]. Some commonly-used conductive biomaterials including polypyrrole (PPy), poly(*3*,*4*-ethylenedioxythiophene) (PEDOT), and carbon nanotubes (CNTs) are incorporated into scaffolds or implanted directly into injured spinal cord, thus promoting axonal growth, enhancing neuronal survival, and modulating inflammation and scar formation *via* external electrical stimulation and transmission of electrical signals [170]. For example, Yang *et al.* developed a PPy-based conductive supramolecular agarose/gelatin/polypyrrole (Aga/Gel/PPy, AGP3) hydrogel to rebuild a biocompatible microenvironment for increasing neurogenesis-related gene expression after SCI [10]. In terms of mechanism, RNA-seq analysis showed that the AGP3 hydrogel boosted neurogenesis-related gene expression by altering NSC behavior through mechanotransduction mismatches. In addition to stiffness, electroactive materials amplify weak local electric field generated by cell membrane, leading to transmembrane voltage gradients that impact ion influx. Intracellular signaling greatly affects NSC proliferation and differentiation, potentially elucidating that neurogenesis is stimulated by intracellular Ca^{2+} signaling cascades.

Furthermore, conductive biomaterials could also be served as scaffolds for stem cell transplantation, providing a conducive environment for cell adhesion, proliferation, and differentiation [170,171]. Recently, Song *et al.* integrated PEDOT into a composite conductive hydrogel loaded with NSCs (CCH/NSCs), which enhanced survival, migration, and neural differentiation of transplanted NSCs *in vivo* [172]. The mechanism behind promotion of neurogenesis by CCH/NSCs was attributed to the self-healing properties of CCH, which sustained electroactivity and supported stable transmission of electrical signals. This contributed to restoration of interrupted spinal circuits, enabling continuous transmission of endogenous electrical signals within the spinal cord. A controlled degradation timeline of CCH ensured that the hydrogel did not hinder growth and connection of new axons, optimizing the functions of NSC carrier and external electroactive microenvironment. These studies highlight the capability of conductive materials to enhance stem cell survival and integration in injured spinal cord.

Conductive biomaterials provide a promising strategy for promoting nerve regeneration and functional recovery in SCI. Their unique electrical properties enhance neurite outgrowth, stem cell survival, and

neural differentiation through effective electrical stimulation. While significant advancements have been achieved in preclinical research, it is essential that future studies concentrate on improving stability and biocompatibility of these materials to ensure their safe and effective use in clinical applications over extended periods [170]. Conductive biomaterials have a great potential to revolutionize treatment of SCI, offering new hope for patients in regaining lost neurological function.

So far, functional biomaterials-based combinatorial strategies have shown great promise in reconstructing a permissive and favorable microenvironment. Table 3 lists advantages, disadvantages, and modification methods of biomaterial scaffolds for SCI. It can be seen that scaffold component such as natural polymers and bioactive small molecules have good biocompatibility and ideal bioactivity, and the synthetic biomaterials always exhibit sufficient mechanical properties, all of which lay a solid theoretical basis for promoting axon growth and nerve regeneration. Furthermore, some of the biomaterial scaffold even can meet the clinical requirements for SCI repair after surface modification or optimization of processing techniques. Table 4 summarizes numerous clinical and preclinical trials involving use of biomaterials relevant to SCI repair. However, current repair strategies primarily target singular aspects of SCI microenvironment. Future research should focus on developing multifunctional biomaterials capable of regulating various aspects of the SCI microenvironment.

7. Challenges and perspectives

A main challenge in clinical treatment of SCI is how to construct a complex and inhibitory microenvironment that hinders axon regrowth [184]. Although understanding mechanisms behind this microenvironment has already been advanced, there are still many debated subjects, such as interaction of various recruited immune cells, cells heterogeneity in fibrous scars, and function of immune cells in transition after SCI. Therefore, gaining a thorough understanding of the complex interactions between various cells and microenvironment, including diverse functions and transitions of various cell subpopulation, are crucial for developing strategies to leverage positive aspects while mitigating negative effects of a compromised microenvironment.

Over past decades, a range of biomaterials such as stem cell-based biomaterials, biomaterial scaffolds, and drug delivery systems, have been crucial in creating a favorable microenvironment for tissue repair and regeneration [140,185]. These biomaterials vary in their mechanisms and efficacy in promoting tissue healing. Specifically, stem cells-based biomaterials incorporate living cells into matrices to directly replace damaged cells and improve microenvironment, while serious challenges exist in achieving optimal cell survival and well integration into host tissue. Biomaterial-based scaffolds, such as hydrogels, electrospun fibers, and porous scaffolds, act as structural frameworks to guide nerve fiber growth and provide mechanical stability, but they do

Table 3
Advantages, disadvantages, and modification strategies of biomaterial scaffolds.

Types of biomaterials	Biomaterial scaffold composition	Advantages	Disadvantages	Modification strategies
Natural polymers	Alginate CS SF PEG HA Cellulose	● Good biocompatibility and biodegradability ● Provide suitable physical support for cell adhesion and proliferation	● Limited mechanical strength ● Poor toughness ● High swelling ratio	● Modulate composition, control cross-linking degree ● Dope nanomaterials
	Collagen Gelatin Proteoglycans Glycoproteins	● Non-cytotoxicity ● Provide suitable mechanical property ● Mimic natural environment of tissue regeneration	● Presence of potential immunogenic reactions and thrombosis	● Improve decellularization techniques ● Optimize extraction and purification methods
Synthetic polymers	PLA PLLA PCL PAAm PVDF	● Easy processing ● Sufficient mechanical strength ● Support cell attachment, proliferation, and differentiation	● Slow degradation rate	● Grafting modification
Metal ions	Mn^{3+} Mg^{2+} Zn^{2+}	● Alleviate oxidative stress and hypoxia ● Inhibit activity of MMP-9 to facilitate neurons differentiation	● Lack of biocompatibility ● Poor degradation	● Surface modification ● Control concentration precisely
Inorganic compounds	$BaTiO_3$ ZnO BP PPy rGO CNTs	● Good conductivity and piezoelectricity to induce cellular phenotypic differentiation ● Excellent anti-inflammatory properties to regulate immune microenvironment and promote tissue regeneration	● Potential toxicity ● Slow degradation rate	● Surface grafting modification
Bioactive molecules	NGF βFGF GDNF BDNF CNTF NT-3 NT-5 Nrg-1	● Enhance survival and differentiation of nerve cells ● Promote axon extension and regeneration	● Poor permeability ● Short half-life ● Low utilization rate	● Develop new carriers ● Realize sustained-release ● Extend *in-vivo* time and improve utilization
	IL-4 IL-10	● Regulate inflammation and provide positive microenvironment for nerve regeneration		
	VEGF aFGF Ang-1 Ang-2 TGF-β EPO EGF IL-6	● Promote vascular endothelial cell proliferation, migration, and polarization ● Accelerate neovascularization		

Abbreviations: PAAm, poly (allylamine); PVDF, poly (vinylidene fluoride); $BaTiO_3$, barium titanate; ZnO, zinc oxide; BP, black phosphorous; CNTF, ciliary neurotrophic factor; Nrg-1, neuregulin-1, Ang-1, angiopoietins 1; TGF-β, transforming growth factor-β; EPO, erythropoietin; EGF, epidermal growth factor; MMP-9, matrix metalloproteinase 9; rGO, reduced graphene oxide.

Table 4
List of biomaterials-based clinical and preclinical trials for SCI repair.

Clinical or Preclinical trials	Biomaterials	NCT number	Combinatory agent	Phase	Injury location	Status
Clinical trials	NeuroRegen scaffold	NCT02352077	BMSCs/MSCs	1	Cervical/thoracic level (C5-T12)	Unknown
	Poly(lactic-*co*-glycolic acid)-*b*-poly(l-lysine) scaffold	NCT02138110	–	–	Thoracic level (T2-T12)	Terminated
	Collagen scaffold	NCT03966794	Epidural electrical stimulation	1, 2	Cervical, thoracic/lumbar level C4-T12/L1	Unknown
	Collagen scaffold	NCT02510365	–	1	Cervical/thoracic level (C4-T12)	Unknown
	NeuroRegen scaffold	NCT02688049	NSCs/MSCs	1,2	Cervical/thoracic level (C5-T12)	Unknown
	NeuroRegen scaffold	NCT02688062	BMSCs	1,2	Thoracic	Unknown
	Poly(lactic-*co*-glycolic acid)-*b*-poly(l-lysine) scaffold	NCT03762655	–	–	Thoracic level (T2-T12)	Terminated
	Self-assembling peptide nanofiber hydrogel	NCT05967325	Stromal vascular fraction (SVF)	–	Thoracic level (T2-T12)	Recruiting
	CS-laminin scaffold	Amr SM et al. [173]	BMSCs and sural nerve grafts	–	Thoracic	–
Preclinical trials	PLGA scaffold	Christopher D Pritchard et al. [174]	Human neural stem cells	–	Thoracic (T9–T10)	–
	Collagen scaffold	Han et al. [175]	NT3	–	Thoracic (T9)	–
	Collagen scaffold	Li et al. [176]	Cetuximab (FDA approved)	–	Thoracic (T8)	–
	CS scaffold	Rao et al. [70]	NT3	–	Thoracic (T8)	–
	Collagen scaffold	Fan et al. [177]	Cetuximab (FDA approved)	–	Thoracic (T9)	
	Fibrin/carbon microfiber	Alexandra Alves-Sampaio et al. [178]	bFGF	–	Thoracic	–
	PEG-CS	Michael Lebenstein-Gumovski et al. [179]	–	–	Thoracic (T7-T9)	–
	Gelatin sponge scaffold	Zeng et al. [180]	–	–	Thoracic	–
	Collagen scaffold	Yin et al. [181]	Taxol (FDA approved)	–	Thoracic (T8)	–
	Collagen scaffold	Liu et al. [182]	Taxol (FDA approved) or human MSCs	–	Thoracic (T8)	–
	Collagen scaffold	Yin et al. [183]	Taxol (FDA approved)	–	Thoracic (T8)	–

Abbreviations: NTC, National Clinical Trial; FDA, Food and Drug Administration.

not directly replace lost cells due to limited bioactivity. Drug delivery systems mainly include nanoparticles, microspheres, and liposomes, which target specific pathways by releasing therapeutic agents to modulate inflammation and thus enhancing tissue repair [186]. However, current approaches for treating SCI produced unsatisfactory results in functional recovery. A promising approach is to combine drug delivery systems with spinal cord optogenetics through nanotechnology, so as to stimulate damaged neurons using the delivered photosensitive proteins. This innovative method has potential to improve neural network reconnection and repair near SCI sites, providing a new avenue for restoring motor and sensory functions. Furthermore, leveraging artificial intelligence and machine learning with patient data allow researchers to develop cutting-edge biomaterials-based treatments. By analyzing extensive datasets and imaging information, new biomaterials for personalized therapies can be identified, leading to predictive models that enhance patients' rehabilitation and clinical decision-making. These innovative approaches collectively contribute to ongoing advancement of SCI treatment.

Biomaterials-based SCI research aims to translate laboratory finding into clinical applications, but most studies are currently done on rodent models that differ greatly from humans [187]. Therefore, it is essential to conduct studies on large animals, particularly non-human primates that closely resemble humans, to advance preclinical trials for *in-vivo* testing of scaffolding strategies. Researchers have utilized canine and non-human primate models to assess the effectiveness of scaffolds-based strategies for SCI repair [70,175,176]. To analyze mechanism of scaffolds-based treatment in SCI monkeys, Fan *et al.* used single-cell transcriptomics to investigate the mechanism, demonstrating improvements of pathological microenvironment through regulating glial cells and fibroblasts as well as reducing inhibitory neurons [177]. In addition to non-human primates, pigs are also commonly used for *in-vivo* testing of scaffolds-based strategies for SCI repair [178,179].

Besides the preclinical trials, advancements in SCI microenvironment remodeling such as combining NeuroRegen scaffolds with MSCs to improve partial function recovery have been achieved in clinical settings [188–190]. Despite these advancements, challenges including safety, efficiency, ethics, and regulatory compliance limitations still remain in the widespread clinical applications of microenvironment-regulating biomaterials. To address these issues, transplantation protocols are continuously optimized to maximize stem cells survival and desired neural differentiation, through preconditioning stem cells, modifying biomaterial properties, affording biochemical or physical guidance cues, and modulating gene expressions. Another significant issue is absence of a globally agreed-upon safety and management standard for clinical use of functional scaffold materials in transplantation. For instance, the clinical use of CS scaffold in SCI patients leads to a slight improvement in functional recovery, while it also causes postoperative seroma complications due to CS decomposition [173]. Hence, it is important to establish a unified clinical-evaluation standard for biomaterials, including comprehensive safety evaluation and monitoring of biodegradation kinetics. The standard should outline protocols with clear safety thresholds and guidelines for monitoring adverse events and risks, such as seroma formations or wound healing delays. Furthermore, the ethical dilemma regarding the utilization of experimental treatments or therapies for SCI patients is notable. Although these interventions offer potential benefits for enhancing therapeutic efficiency, they may also bring risks, particularly if they lack rigorous testing or if their long-term effects remain uncertain. Striking a balance between offering potential benefits to patients and ensuring their safety is paramount in such cases. Consequently, regulatory compliance plays a crucial role in supervising the development and implementation of treatments for SCI. Notably, the FDA imposes stringent criteria for approving novel therapies of SCI, and it is extremely essential of ensuring compliance with these regulations for protecting patient safety in medical interventions. Addressing these

ethical and regulatory concerns demands careful approaches that prioritize patient safety, autonomy, and scientific integrity.

In summary, there is promising research on using biomaterials for SCI treatment, while the challenges of translating these findings to clinical applications are significant. Future efforts should focus on refining biomaterials design with ideal biosafety and long-term efficacy, promoting host tissue integration, fostering functional neural-connection restoration, and conducting well-designed clinical trials to overcome these challenges. In addition, considering each patient has specific medical history, injury characteristics, and overall health status, personalized scaffolds with customized anatomical dimensions composition and degradation rates should be designed, and meanwhile incorporating stem cells like autologous, allogeneic, or iPSCs will further enhance the overall therapy effectiveness. Furthermore, multidisciplinary collaborations among materials scientists, bioengineers, neuroscientists, pharmacologists, and clinicians, are expected to further enhance the effectiveness of SCI treatment approaches significantly. By leveraging the diverse expertise and perspectives of these professionals, some innovative solutions or models have been developed to address the complex challenges associated with SCI. For instance, a brain-spine interface (BSI) comprising by implanted recording and stimulation system, was developed through collaboration among bioengineers, neuroscientists, and clinicians. The BSI allowed individuals with paralysis from SCI to achieve natural and adaptive control over standing and walking by voluntarily controlling the timing and amplitude of muscle activity [191]. Similarly, multidisciplinary collaborations have led to the development of bioactive scaffolds with enhanced supramolecular motion, significantly promoting recovery from SCI [192]. On the whole, interdisciplinary teamwork facilitates the translation of research findings into clinical applications, ultimately benefiting SCI patients.

Ethics approval and consent to participate

None.

CRediT authorship contribution statement

Dezun Ma: Writing – original draft. **Changlong Fu:** Writing – original draft. **Fenglu Li:** Writing – original draft, Supervision, Methodology, Investigation. **Renjie Ruan:** Writing – original draft. **Yanming Lin:** Supervision, Methodology. **Xihai Li:** Writing – review & editing, Supervision, Conceptualization. **Min Li:** Writing – review & editing. **Jin Zhang:** Writing – review & editing.

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 review.

Acknowledgements

This study was supported by the National Key R&D Program of China (Grant No. 2022YFB3808000/2022YFB3808001), the National Natural Science Foundation of China (Grant Nos. 82301554, 51903050 and 82104888), Scientific Research Foundation for the High-level Talents Fujian University of Traditional Chinese Medicine (X2021007−talents, X2019011−talents) and School management project of Fujian University of traditional Chinese Medicine (X2023019). The authors also gratefully acknowledged the kindly financial support provided by the Top Young Talents of Foal Eagle Program of Fujian Province and the Youth Promotion Talent Project of Fujian Province to Jin Zhang.

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