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REVIEW

Advancing Spinal Cord Injury Repair: The Role of Conductive Hydrogels in Neurotissue Engineering

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Abstract: Spinal Cord Injury (SCI) is a devastating condition of the central nervous system, affecting a significant number of individuals globally. It leads to irreversible motor, sensory, and autonomic dysfunctions, placing a substantial burden on both patients and society. As a result, there is an urgent need for more effective therapeutic strategies. In recent years, the field of neurotissue engineering has made remarkable progress, offering new avenues for spinal cord injury repair. Among these advancements, conductive hydrogels have gained considerable attention due to their ability to mimic the electrical signaling properties of the spinal cord. These hydrogels not only replicate the complex electrical environment of the spinal cord but also enable non-invasive modulation of electrical signals, which can influence neuronal cell behavior. Additionally, conductive hydrogels provide essential mechanical support and serve as carriers for various drugs, bioactive factors, and cells, which can restore the disrupted microenvironment and promote axonal regeneration, remyelination, and functional recovery after SCI. This paper thoroughly investigates the pathophysiological mechanisms underlying SCI, systematically analyzes the different types of conductive materials used in hydrogels, and evaluates their combinations and functions. Furthermore, it discusses the technical challenges, bottlenecks, and future directions for the development of functional biomaterials aimed at effective SCI repair, offering insights for the creation of innovative therapeutic strategies.

Keywords: conductive hydrogels, neural tissue engineering, electrical stimulation, spinal cord injury

Introduction

Spinal Cord Injury (SCI), one of the most severe traumatic disorders of the central nervous system (CNS), often results in irreversible motor, sensory, and autonomic deficits. These impairments not only significantly reduce patients' quality of life but also impose a substantial economic burden on families and society.[1–3] The pathophysiological cascade of SCI comprises two critical phases: primary damage resulting from mechanical injury, which leads to immediate cell death and axonal shearing, followed by secondary damage driven by ischemia, glutamate excitotoxicity, oxidative stress, neuroinflammation, and glial scar formation.[4–6] Due to the intrinsic regenerative limitations of the central nervous system and the complex pathophysiological microenvironment at the injury site, neurological reconstruction faces significant challenges.[7,8] Despite the use of surgical decompression, pharmacological treatments, and rehabilitation, current therapies fail to restore regenerative connectivity of neural pathways or achieve functional recovery of electrical signaling.[9–12]

The rapid advancements in materials science and technology have highlighted the significant potential of functional biomaterials in remodeling the spinal cord injury microenvironment.[13–15] On one hand, certain biomaterials offer physical support for axonal regeneration.[16,17] On the other hand, they can be pre-modified to serve as carriers of drugs, factors, or cells to restore the dysfunctional microenvironment in SCI.[18–20] In recent years, hydrogels have demonstrated distinct advantages in the field of spinal cord repair.[21–24] These materials offer an ideal platform for reconstructing the molecular microenvironment of the spinal cord due to their excellent biocompatibility, dynamic mechanical properties, cellular interaction interfaces, and controlled degradation.[25,26] Its three-dimensional porous structure not only serves as a physical scaffold for nerve regeneration but also as a carrier for neurotrophic factors, stem cells, and drugs.[27,28] However, conventional hydrogels have significant limitations in mimicking intrinsic

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bioelectrical properties, primarily due to their inherent nonconductivity.[29] This limitation is particularly critical because endogenous electric fields (1–10 mV/mm) are crucial for the growth and development of the spinal cord, particularly in guiding essential developmental processes such as neuronal migration and axonal pathfinding.[30,31] To overcome this bottleneck, the emerging material system of conductive hydrogels has been developed. By integrating conductive polymers such as polyaniline and polypyrrole, or nanomaterials like graphene and carbon nanotubes into hydrogel matrices, the resulting conductive hydrogels exhibit both biointerfacial compatibility and electroactivity.[32,33] Its dynamically adjustable modulus of elasticity, porosity, and other physicochemical properties are tailored to the pathological evolution of the injured area. It can accurately simulate the conductive microenvironment of spinal cord tissues, and its multifunctional design enables the co-delivery of stem cells and small-molecule drugs. Additionally, it can be combined with external electrical stimulation to create a synergistic therapeutic system of "scaffolding-electrical stimulation-bioactivity".[34–37]

In this paper, we systematically analyze the dynamic evolution of the pathological microenvironment following SCI and its barriers to regeneration. We explore the classification and characterization of key materials employed in the construction of conductive hydrogels, with a focus on the molecular and cellular mechanisms underlying nerve regeneration through material functionalization strategies (Figure 1). In comparison to existing studies, this paper not only reviews traditional materials such as conductive polymers and carbon-based composites but also integrates novel two-dimensional conductive materials, including MXene and MoS_2, that have emerged in recent years, highlighting their unique structural and performance advantages. Furthermore, we introduce an innovative approach that explores the synergistic effects of electrical stimulation and conductive hydrogels, demonstrating their promising applications in

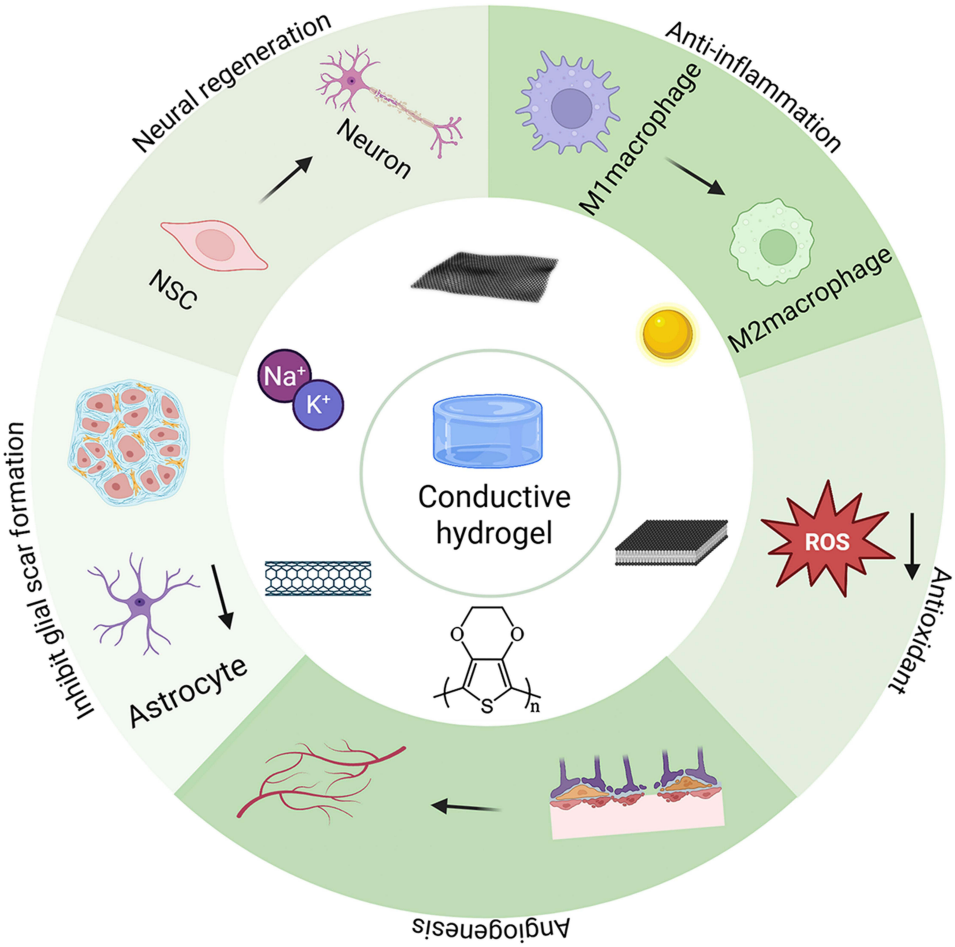

Figure 1 Schematic diagram of functional conductive hydrogel for regulating and repairing spinal cord injuries.

spinal cord injury rehabilitation. We also discuss the primary challenges to clinical translation, including the long-term biocompatibility and safety of materials, the need for individualized optimization, and the development of scalable and standardized preparation processes. Our goal is to provide a robust theoretical foundation for the development of the next generation of efficient, precise, and clinically translatable materials for spinal cord repair.

Pathology of Spinal Cord Injury

The pathological process of spinal cord injury (SCI) exhibits significant spatio-temporal dynamics, which can be categorized into two major stages: primary and secondary injury (Figure 2).[13,38] These two stages are interrelated and together determine the final severity of the injury and the neurological prognosis. Primary injury arises from the structural destruction of neural tissue directly caused by mechanical external forces, primarily manifested by blood vessel rupture and hemorrhage, axonal rupture in white matter tracts, and acute necrosis of gray matter neurons. This initial injury irreversibly disrupts bidirectional signaling between the brain and peripheral organs, leading to an immediate loss of sensory and motor functions below the level of injury.[39,40] A key factor in secondary injury is uncontrolled neuroinflammation, which is triggered by the massive release of damage-associated molecular patterns (DAMPs) from injured cells, such as ATP, mitochondrial DNA (mtDNA), reactive oxygen species (ROS), and high-mobility group box 1 (HMGB1). These DAMPs are recognized by pattern recognition receptors (PRRs), initiating an innate immune response.[41] In this process, mitochondria act as both "initiators" and "victims": calcium influx disrupts their membrane potential, leading to the opening of the mitochondrial permeability transition pore (mPTP), which causes mitochondrial dysfunction, an explosion of mitochondrial reactive oxygen species (mtROS), and the release of mtDNA into the cytoplasm. This cascade strongly activates inflammatory pathways. These signals collectively activate the NLRP3 inflammasome, which cleaves Caspase-1, matures pro-inflammatory cytokines IL-1β and IL-18, and induces pyroptosis, resulting in inflammatory lytic cell death and the release of additional DAMPs, further amplifying the inflammatory response.[42–44]

Secondary injuries can be subdivided based on the time course and key features into the following phases: acute phase (< 48 hours), subacute phase (48 hours - 2 weeks), and chronic phase (2 weeks - months). The acute phase is

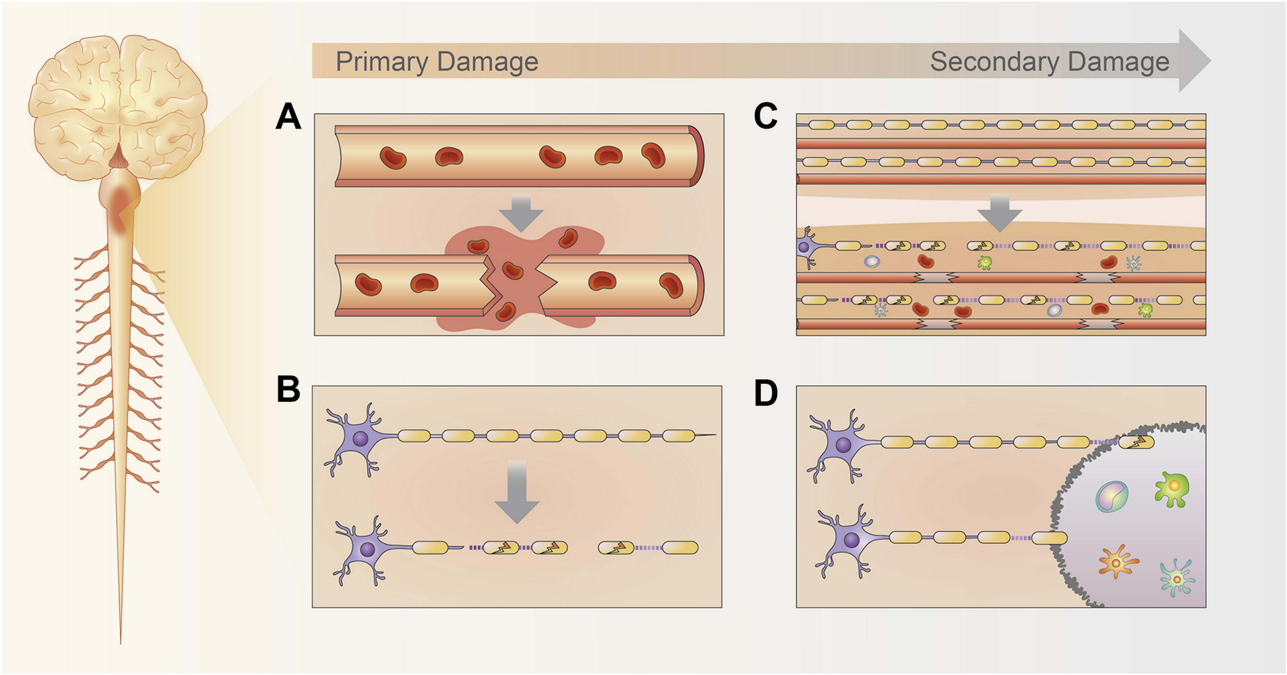

Figure 2 Primary and secondary injuries after the occurrence of spinal cord injury. Primary injury: (**A**) rupture of blood vessels in the spinal cord; (**B**) disruption of the myelin sheath, freeing of red blood cells from the injured area. Secondary injury: (**C**) various activated inflammatory cells accumulate to the injured area, producing an inflammatory cascade response; (**D**) forming glial scars, and inhibiting injury repair. Adapted with permission from [Ref.[38]]. Copyright 2021, Elsevier.

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characterized by a vigorous inflammatory response and significant changes in the microenvironment. Persistent hemorrhage, vasospasm, and endothelial cell injury lead to disruption of the blood-spinal cord barrier.[45] The inward flow of Na^+ and Ca^{2+}, along with increased outward flow of K^+, causes cytotoxic and vasogenic edema. The release of excitatory neurotransmitters, such as excess glutamate, overactivates neuronal receptors (especially NMDA receptors), leading to Ca^{2+} overload. This overload activates phospholipases, proteases, and nitric oxide synthase (NOS), which generate large quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS), subsequently attacking cell membrane lipids, proteins, and DNA.[46,47] Concurrently, numerous neutrophils are recruited by factors such as IL-1β. Stimulated by mitochondrial reactive oxygen species (mtROS) and inflammatory cytokines, these neutrophils undergo NETosis, forming neutrophil extracellular traps (NETs).[48,49] NETs not only physically obstruct microcirculation and directly damage neurons but also release components such as histones and DNA, which act as DAMPs, reactivating NLRP3 inflammasomes and creating a vicious cycle that exacerbates tissue damage.[49–51] Surgical decompression combined with high-dose methylprednisolone is the primary intervention strategy in the acute phase to attenuate secondary injury by inhibiting lipid peroxidation and inflammation. However, its effectiveness is limited by a strict time window and hormone-related side effects, such as an increased risk of infection, gastrointestinal bleeding, and hyperglycemia.[52,53]

During the subacute phase, microglia and macrophages—the principal inflammatory effectors—exhibit profound dysregulation of their polarization.[54] Early infiltrating immune cells and M1 macrophages/microglia dominate the response. Activated by IFN-γ, NETs, and IL-1β, these cells produce large amounts of reactive oxygen species (ROS) via NADPH oxidase (NOX) and secrete pro-inflammatory cytokines such as TNF-α and IL-6, thereby exacerbating tissue destruction. In contrast, the reparative M2 phenotype is suppressed, resulting in insufficient secretion of neurotrophic factors and impaired tissue repair.[55,56] ROS permeates this entire process, functioning both as a cytotoxic agent that directly damages lipids, proteins, and DNA, and as a crucial signaling molecule that activates NLRP3 inflammasomes, induces NETosis, and sustains the M1 pro-inflammatory state.[57,58] These events ultimately lead to extensive neuronal and oligodendrocyte death, demyelination, and axonal injury.[59,60] Concurrently, activated astrocytes proliferate and migrate to the injury margins, where they begin to form a glial scar in an attempt to isolate the damaged area. However, this process also generates a physical and chemical barrier that hinders axonal regeneration.[61–64]

In the chronic phase, the injury site stabilizes, establishing a persistent inhibitory microenvironment. Necrotic tissue is cleared, and fluid-filled cystic cavities gradually develop.[65] Chondroitin sulfate proteoglycans (CSPGs) continue to be expressed, and their glycosaminoglycan (GAG) side chains bind to neuronal surface receptors such as PTPσ and LAR, thereby activating downstream signaling pathways, including RhoA/ROCK, which inhibit growth cone extension.[66,67] Axons that fail to regenerate undergo progressive proximal degeneration. Fibroblast-derived connective tissue infiltrates the lesion core and integrates with the glial scar. Meanwhile, adaptive or maladaptive reorganization of neural circuits occurs around the injury site.[68,69] Therapeutic strategies in the chronic phase focus primarily on managing complications —including pain, spasticity, abnormal autonomic reflexes, pressure ulcers, and urinary tract infections—while promoting functional compensation and rehabilitation to maximize patients' quality of life and preserve residual function.[70,71]

Emerging Strategies for Spinal Cord Repair-Conductive Hydrogel

Promoting substantial spinal cord neuroregeneration with functional loop reconstruction remains a central challenge in SCI treatment, despite the growing understanding of the pathological process.[72] Global research has focused on several strategies, including stem cell transplantation to provide replacement cells, secretion of neurotrophic factors, modulation of immunity, and promotion of myelin regeneration.[73,74] Targeted delivery of neurotrophic factors, anti-inflammatory agents, axonal growth inhibitor antagonists, and agonists of regeneration-promoting signaling pathways aims to stimulate nerve growth.[75–78] However, a key bottleneck is the lack of supporting structures for the cystic cavities or voids formed in the core of the injury. Mature scarring creates a strong physicochemical barrier, making it difficult for transplanted cells or bioactive factors to effectively colonize, survive, and function in the injured area due to the poor local microenvironment and the lack of anchoring sites caused by cerebrospinal fluid impact.[69,79]

In recent years, hydrogel scaffolds have emerged as highly promising carriers for spinal cord repair due to their excellent biocompatibility, adjustable mechanical properties, injectability, and ability to mimic the three-dimensional structure of the extracellular matrix (ECM), supporting cell adhesion and migration.[19,28,80,81] However, traditional

hydrogels lack electrical conductivity and are unable to effectively transmit neuroelectric signals within the spinal cord, making it difficult for them to directly participate in the reconstruction of neuroelectrophysiological activities. This led to the development of conductive hydrogels, which combine the physical and chemical advantages of hydrogels with the electrochemical properties of conductive materials, such as PANI, PPy, CNT, and MXene, achieving a key breakthrough: the simulation of the neurophysiological microenvironment. This innovation provides an electrical signaling pathway, guiding the directional growth of neuronal cells and facilitating electrical activity.[35,82,83] It can also respond to external signals, such as electrical stimulation, and regulate cell proliferation, differentiation, migration, and other behaviors.[84] By overcoming the limitations of conventional hydrogels, it provides an electrochemical environment that more closely resembles the physiological state for nerve regeneration. As a result, it has emerged as a promising strategic platform to advance spinal cord injury repair.

Classification of Conductive Materials

Implantable scaffolds for nerve regeneration after SCI must meet specific requirements for mechanical properties, biocompatibility, biodegradability, and biophilicity, in addition to electrical conductivity. Properly designed conductive hydrogels not only bridge tissues within and around the lesion but also promote potential propagation to restore natural bioelectricity and facilitate nerve cell communication by spreading electrical activity across a wider area. The various types of conductive materials used in SCI are described in detail below. Table 1 provides a comprehensive list of the advantages and disadvantages associated with each of these materials.

Table 1 Classification of Conductive Materials

Classification	Representative Materials	Advantages	Limitations	Reference
Conductive Polymers	PPy	Good biocompatibility, surface modifiable, low cost.	Relatively low conductivity, non-degradable	[85–87]
	PANI	Wide range of conductivity adjustment, good stability, low cost	Poor biocompatibility, non-degradable	
	PEDOT	High conductivity, high stability, good biocompatibility.	non-degradable	
Carbon-Based Materials	rGO	High electrical conductivity, excellent mechanical properties	Non-degradability, poor dispersion, aggregation problems	[88–90]
	GO	Excellent hydrophilicity and biocompatibility; easy chemical modification	Lower conductivity	
	CNT	Ultra-high electrical conductivity, excellent mechanical properties, high aspect ratio	Complexity of synthesis, non-degradability, high cost	
Metallic conductive nanomaterials	AuNPs	Excellent electrical conductivity, surface functionalization, enhanced mechanical properties	Potential long-term toxicity, easy to aggregate	[91, 92]
	AgNPs	Highly effective antimicrobial properties, low cost	Oxidizing and aggregating tendency, Dose-dependent toxicity	
Phosphorus-Based Materials	BPNSs	Excellent electrical conductivity and carrier mobility, good biocompatibility and degradability	Environmental instability, decentralization challenges	[93-95]
	BPQDs	Ultra-high surface area and active sites, excellent optical properties	Complicated preparation process, lack of stability, increased specific surface area and increased oxidization	

(*Continued*)

Table 1 (Continued).

Classification	Representative Materials	Advantages	Limitations	Reference
Ionic conductive hydrogels	Na^+, K^+, Li^+, Cl^-	Highly bionic, excellent biocompatibility	Low conductivity, ion loss, poor stability	[96,97]
Emerging two-dimensional conductive materials	MXene	Ultra-high electrical conductivity, excellent mechanical properties, tunable surface chemistry	Easy to oxidize, not easy to disperse	[98–101]
	MoS_2	Controllable semiconductor properties, efficient photothermal, environmental stability	Relatively low conductivity, difficult to strip and disperse	

Conductive Polymers

Conductive polymers (CPs) are a class of polymers with a conjugated π-bond structure in the carbon backbone, widely used in biomedicine due to their high electrical conductivity, large specific surface area, low specific gravity, and non-toxicity. Common conductive polymers include PPy, PEDOT, and PANI. When combined with hydrogel materials, conductive polymers form conductive polymer-based hydrogels, which can be adjusted by altering the content of conductive polymers to regulate electrical conductivity. These hydrogels exhibit excellent biocompatibility, adjustable mechanical properties, and electrical conductivity.[85–87] Song et al prepared a conductive composite hydrogel scaffold loaded with NSCs using 3D bioprinting. They synthesized a novel conductive polymer (PEDOT:CSMA, TA) and introduced it into a photocrosslinked gelatin/polyethylene glycol physico-gel matrix, resulting in a composite bio-ink with excellent shear-thinning and self-repairing properties. The scaffold exhibits high shape fidelity and physicochemical properties similar to those of natural spinal cord tissue, forming strong physical contact with neighboring cells and the conductive matrix. It supports major neuronal differentiation in vivo, with a small amount of astrocytogenesis, promoting neural tissue development and accelerating motor function recovery in rats.[102]

Carbon-Based Materials

Carbon-based materials hold great potential for application in hydrogel matrices due to their unique physicochemical properties, including high electrical conductivity, large specific surface area, and abundant surface functional groups. The incorporation of carbon-based materials not only significantly enhances the electrical conductivity of hydrogels but also improves their mechanical properties. Notable applications of carbon-based materials include, but are not limited to, graphene oxide (GO) and carbon nanotubes (CNT).[89,90,103] Graphene, a single-layer carbon material, combines ultra-high electrical conductivity, thermal conductivity, mechanical strength, and a large specific surface area. Its functionalized derivative, graphene oxide, has a wide range of applications in biomedical and neural devices.[88,104] Wang et al proposed graphite nanosheets combined with neural stem cells (NSCs) as electromagnetic cellularization patches, leveraging the high electrical conductivity and electromagnetic induction properties of graphite. These patches generate wireless pulsed electrical signals in situ under a rotating magnetic field, regulating the neuronal differentiation of NSCs to treat spinal cord injury. By adjusting the rotational speed of the magnetic field, the intensity and frequency of the induced voltage can be controlled. The generated pulsed electrical signals promoted the differentiation of NSCs into functionally mature neurons, increasing the proportion of neurons from 12.5% to 33.7%.[105] Carbon nanotubes (CNTs), cylindrical nanotubes with a high aspect ratio, can significantly enhance the thermal stability and electrical conductivity of hydrogels. However, it is important to note that CNTs are not biodegradable and may cause tissue damage if left in place for extended periods. To address this, CNTs are often converted into single-walled or multi-walled carbon nanotubes (SWNTs/MWCNTs) with improved biocompatibility through chemical modification. Xing et al demonstrated that CNT hydrogels functionalized with poly(styrenesulfonic acid)-alginic acid-dopamine (CNT-PSS-SA-DA) can effectively inhibit LPS-induced expression of pro-inflammatory factors (IL-6, IL-1β), providing a novel strategy for drug delivery in spinal cord regeneration.[106]

Metallic Conductive Nanomaterials

Metallic conductive nanomaterials, primarily composed of pure metals or their compounds, have become commonly used conductive fillers in hydrogels due to their high electrical conductivity and large specific surface area. These materials are widely applied in electrochemistry, batteries, and electronic conductors. The combination of metal nanomaterials and hydrogels not only significantly enhances the conductivity and mechanical properties of the hydrogels but also imparts unique flexibility and ductility to traditional metal materials.[91,107] Common metal-conducting nanomaterials include gold and silver nanoparticles. Gold nanoparticles (1–100 nm) are known for their high electron density, excellent dielectric properties, and catalytic activity, as well as their good biocompatibility. They can effectively bind a wide range of biomolecules without affecting their function. Additionally, metal nanoparticles are generally resistant to corrosion and oxidation, have a high specific surface area, and are easy to functionalize, making them attractive for use in biological systems. Due to these excellent biological properties, gold nanoparticles have been widely applied in biomedical fields such as drug delivery, disease diagnosis, bioimaging, and photothermal therapy.[108] Silver nanoparticles exhibit excellent antimicrobial properties, including significant inhibition and killing of Gram-positive bacteria, Gram-negative bacteria, fungi, some viruses, and even drug-resistant strains.[109] Despite these advantages, both AuNPs and AgNPs raise concerns regarding long-term toxicity. Their biocompatibility and toxicological profiles are strongly influenced by particle size, surface modifications, and administration routes.[110] AuNPs generally exhibit favorable short-term biocompatibility. However, prolonged exposure can lead to their accumulation in the liver and spleen, and high doses may trigger inflammatory responses and histopathological alterations.[111] Sengupta et al evaluated the hematological effects of intravenous AuNP administration in mice at doses of 1, 2, and 10 mg/kg. Blood samples collected at 6, 12, 24, 48, and 72 hours post-injection revealed a dose-dependent increase in hemoglobin concentration and red blood cell (RBC) counts at higher doses (2 and 10 mg/kg), whereas no significant changes were observed at 1 mg/kg.[112] Notably, AuNP toxicity is highly size-dependent: particles as small as 1.5 nm exhibit strong cytotoxicity, while those larger than 15 nm demonstrate markedly reduced toxicity.[113] In contrast, AgNPs generally display more pronounced toxicity through mechanisms that are mechanistically complex. A major contributor is the sustained release of silver ions (Ag^+), which interact with biomolecules to induce oxidative stress, apoptosis, and other cytotoxic effects.[114,115] Their toxicity is also heavily influenced by particle size and morphology. For example, zebrafish exposed to different particle sizes demonstrated that 10 nm AgNPs induced more severe reactive oxygen species (ROS) generation and developmental toxicity compared to 50 nm particles.[116] Surface modification and rational material design play a pivotal role in mitigating the long-term toxicity of metal nanoparticles. Polyethylene glycol (PEG) functionalization, for instance, enhances metabolic clearance and reduces toxicity, thereby improving nanoparticle stability and biocompatibility.[117,118] Taken together, careful control of particle size, surface engineering, and exposure strategies is essential to maximize the biomedical potential of metal nanoparticles while minimizing long-term safety risks. Zhao et al developed an electroactive hydrogel composed of oxidized sodium alginate, carboxymethyl chitosan, and silver nanoparticles (OSA/CMCS/AgNPs). The aldehyde group of OSA rapidly forms dynamic imine bonds with the amino group of CMCS and generates AgNPs in situ through UV irradiation. The resulting electroactive hydrogel demonstrates good injectability, strong self-repairing ability, excellent biocompatibility, and high antimicrobial activity. Under electrical stimulation, it exhibits multiple beneficial effects, such as anti-inflammation, promotion of fibroblast proliferation, angiogenesis, and collagen deposition.[92]

Phosphorus-Based Materials

Phosphorus-based conductive fillers are emerging as functional materials in the field of conductive hydrogels, attracting significant attention due to their unique biocompatibility, degradability, intrinsic conductivity, and optoelectronic properties. Phosphorus, an essential element for life, imparts the key advantage of eventual degradation to non-toxic phosphates in physiological environments. This property is notably superior to the difficult-to-degrade graphene, carbon nanotubes, or metal-based fillers, making phosphorus-based conductive hydrogels highly promising for implantable bioelectronic devices, resorbable sensors, and tissue-engineered scaffolds. These hydrogels can circumvent the risk of long-term foreign body reactions and the need for secondary surgeries. Common phosphorus-based conductive materials include black phosphorus nanosheets (BPNSs) and black phosphorus quantum dots (BPQDs). Black phosphorus nanosheets are novel two-dimensional materials consisting of phosphorus atoms that form a pleated honeycomb-like layered structure.

They exhibit high specific surface area, anisotropic electrical and mechanical properties, and surfaces enriched with lone-pair electrons, making them easily functionalized for modification or loading with other materials to enhance their properties. Their excellent biocompatibility and environmental degradability further reduce the risk of long-term retention in the body.[93,94] Black phosphorus quantum dots (BPQDs), as zero-dimensional nanomaterials, exhibit enhanced properties due to quantum-limited domain effects.[95] Xie et al designed black phosphorus quantum dots (BPQDs) encapsulated in a polymeric gel of epigallocatechin-3-gallate (EGCG) (E@BP) for spinal cord injury treatment. The E@BP conductive hydrogel demonstrated good stability, biocompatibility, and safety. It not only attenuates LPS-induced neuronal inflammation and promotes neuronal regeneration in vitro but also restores the structural and functional integrity of spinal cord tracts, induces cell-cycle reactivation, and promotes neural regeneration, thereby significantly enhancing the recovery of motor function in rats with SCI.[119]

Ionic Conductive Hydrogels

The electrical conductivity of ionic conductive hydrogels (ICH) arises from the migration of free ions within their polymer network. This conductivity is exclusively due to the free-moving ions dissociated by electrolyte salts or ionic liquids incorporated into the hydrogel network. The large amount of water trapped within the porous structure provides ion transport channels, while the high mobility of ions in water serves as the foundation for functionalized material design. Compared to other conductive hydrogels, ICH offers three distinct advantages: high transparency and optical compatibility, ease of processing, and a biomimetic ionic conductivity mechanism that closely resembles the electrical signaling in biological tissues. Furthermore, molecular design can impart strong water retention, low-temperature resistance, and anti-freezing properties, making it an ideal core material for flexible electronic devices.[96,97,120] Ye et al developed an injectable silk fibroin/ionic liquid (SFMA@IL) conductive hydrogel that can be rapidly formed in situ under UV light. The silk fibroin (SF) provides mechanical support and promotes nerve regeneration, while the electrical conductivity is facilitated by the designed ionic liquid (IL). In vivo electrophysiological studies in fully transected SCI rats have demonstrated that SFMA@IL supports electrical transmission in sensory nerves, remodels the microenvironment, reduces inflammation, and promotes nerve fiber growth.[82]

Emerging Two-Dimensional Conductive Materials

MXene

MXenes refer to a class of two-dimensional, ultrathin metallic carbide and nitride materials, characterized by their layered structure.[98] The "M" represents a transition metal element, "X" denotes carbon or nitrogen, and "T" signifies the end group attached to the M layer. This composition enables MXenes to exhibit both the electrical conductivity of a transition metal and the physicochemical properties of carbon or nitride.[99,121] The abundance of functional groups on the surface of MXenes imparts hydrophilicity and rich modifiability, making them suitable for various applications in bioengineering.[122] Furthermore, MXenes are biodegradable and can be safely metabolized and excreted by the body. Unmodified MXene nanosheets also exhibit an inherent ability to scavenge reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and superoxide anions (O_2•−). Yu et al developed a novel conductive hydrogel for spinal cord injury repair. Polyvinylpyrrolidone (PVP), polyacrylic acid (PA), and MXenes were mixed homogeneously at appropriate concentrations, with a rapid and straightforward gelation process. The PPM hydrogel exhibits excellent shear-thinning and self-healing properties, allowing for non-invasive implantation into irregular injury sites via injection, which fills the lesion cavity. The incorporation of MXenes imparts enhanced electrical conductivity to the hydrogel. In a rat model of complete spinal cord transection, the hydrogel promotes regenerative processes such as angiogenesis, myelin sheath regeneration, axonal growth, and calcium channel activation through the MEK/ERK signaling pathway, significantly facilitating functional recovery.[123]

MoS_2

MoS2 is an inorganic material with the chemical formula MoS2, and it is the primary component of molybdenite. As an emerging two-dimensional nanomaterial, MoS2 demonstrates significant potential for biomedical applications due to its unique layered structure, excellent optical properties, favorable biocompatibility and degradability, high drug-loading

capacity, catalytic activity, and ease of functionalization, among other notable advantages.[100,124] It has become a key material for the development of novel bioimaging probes, efficient tumor therapy platforms, potent antimicrobial agents, highly sensitive biosensors, and advanced tissue engineering scaffolds.[101,125] Liu et al leveraged the acidic microenvironment characteristic of acute spinal cord injury (SCI) to design pH-responsive, injectable conductive hydrogels for SCI repair. The composite hydrogel, synthesized from gelatin methacryloyl, oxidized dextran, and molybdenum disulfide, mimicked the properties of natural spinal cord tissue. The optimized conductive hydrogel effectively bridged the injury gap, facilitated neural connection and signaling, attenuated the inflammatory response, and promoted the recovery of motor function.[126]

Biological Function Regulation of Conductive Hydrogel

The challenges of spinal cord injury repair involve multiple factors, including inflammatory responses, impaired vascularization, and failed axonal regeneration, and a single therapeutic strategy often yields limited results. The unique advantage of conductive hydrogels lies in their ability to function as an electro-biological interface, addressing multiple repair mechanisms either simultaneously or sequentially. Furthermore, they can be combined with external electrical stimulation to enhance functional recovery through the application of controlled electric fields or currents.[127–129] Research efforts have focused on several strategies, including promoting axonal growth to reconnect neural circuits, inhibiting the activation of inflammatory cells and the production of inflammatory factors to protect neurons, neutralizing excess reactive oxygen species (ROS) to prevent neuronal death, preventing scar formation that hinders neural repair, and repairing blood vessels to improve blood flow and support nerve regeneration. Table 2 summarizes the application of conductive hydrogels as an excellent carrier, through functionalization strategies to regulate different pathological changes in spinal cord injuries.

Promotes Neural Regeneration

After spinal cord injury (SCI), primary trauma causes nerve cell death and disrupts neural networks. Damage to neuronal axons impairs nerve signaling, resulting in neurological dysfunction and sensory and motor deficits.[134] The lack of

Table 2 Biological Function Regulation of Conductive Hydrogel

Functionalization	Hydrogel Components	Combined Materials	Highlights	Outcome	Reference
Neural regeneration	GelMA	CNT	Mimic the aligned structure, conductivity and mechanical property combination ES	Enhanced cells proliferation, adhesion, elongation and differentiation	[130]
Anti-inflammation	GelMA	PPy Exosomes TA	NSCs recruitment Release of exosomes on demand	Modulate microglial M2 polarization, significant functional recovery at the early stage	[131]
Antioxidant	GelMA	SDF-1α MXene	ROS scavenging Facilitate the migration of BMSCs Recruitment of endogenous NSC	Promoted neurogenesis and facilitated functional recovery	[34]
Angiogenesis	Chitosan	TA BP Tazarotene	Injectability Good electrical conductivity	Promote vascular regeneration and neural differentiation, motor function recovery	[132]
Inhibit glial scar formation	GelMA PLGA	MXene Au	Combination ES Good electrical conductivity antimicrobial	Decrease neuroglial scar formation and promote motor function recovery	[133]

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effective neuronal axonal regeneration not only hinders spinal cord repair but also accelerates the deterioration of chronic neurological function, significantly affecting patients' quality of life.[135] Conductive hydrogels integrate multiple strategies to promote neuronal axon regeneration in spinal cord injury (SCI), with their structural and functional design playing a crucial role in guiding axon growth. Yao et al developed CNT/GelMA fiber scaffolds with a microscale, axon-like arrangement, suitable electrical conductivity, and mechanical properties by incorporating carbon nanotubes (CNTs) into glycol methacrylate (GelMA) hydrogels via rotating liquid bath electrostatic spinning. This scaffold, in combination with electrical stimulation (ES), significantly promoted neuronal differentiation and axon-like protrusion growth of neural stem cells (NSCs) in vitro. In vivo, it effectively induced nerve fiber regeneration and, when combined with ES, enhanced the recovery of motor function in rats.[130] In addition, the conductive hydrogel serves as a delivery platform capable of targeted neurotrophic factor delivery, effectively promoting axonal regeneration and enhancing nerve repair efficacy. Luo et al developed a hydrogel composed of the natural ECM biopolymer chondroitin sulfate and gelatin, incorporating polypyrrole. The resulting hydrogel exhibited mechanical properties (928 Pa) and electrical conductivity (4.49 mS/cm) similar to those of natural spinal cord tissue. Moreover, the hydrogel is injectable, allowing it to seamlessly fill the injury cavity and accelerate tissue repair in traumatic spinal cord injury. In vitro, the conductive ECM hydrogel promotes neuronal differentiation, enhances axonal growth, and inhibits astrocyte differentiation. In vivo, it activates endogenous neural stem cells and induces myelinated axon regeneration at the injury site through the PI3K/AKT and MEK/ERK pathways, resulting in significant motor function recovery in spinal cord-injured rats.[136] As shown in Figure 3, Liu et al synthesized a double cross-linked conductive hydrogel (BP@Hydrogel) incorporating black phosphorus nanoplates (BP). The material generated stable electrical signals in the presence of a rotating magnetic field (RMF). Under RMF, BP@Hydrogel enhanced anti-inflammatory effects and promoted the differentiation of neural stem cells (NSCs) into neurons in vitro, associated with the activation of the PI3K/AKT pathway. It also significantly improved the behavioral and electrophysiological functions of mice with complete spinal cord injury (SCI) and enabled wireless, non-invasive, distributed electrical stimulation.[137]

Anti-Inflammation

Neuroinflammation is a major secondary consequence of spinal cord injury (SCI), primarily mediated by macrophages and microglia. The polarization state of these cells determines the extent of tissue recovery.[4] Microglia exist in two distinct states: M1 and M2. M1 macrophages secrete pro-inflammatory factors, such as TNF-α and IL-6, which exacerbate

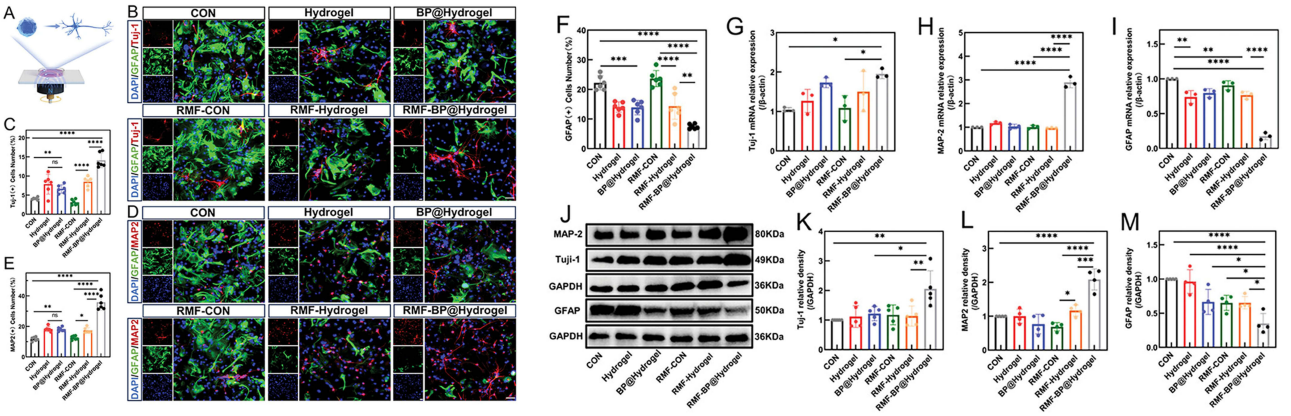

Figure 3 RMF-BP@Hydrogel induced NSCs to differentiate into neurons in vitro. (**A**) The schematic diagram of NSCs' differentiation into neurons induced by the RMF-BP @Hydrogel strategy. (**B**) Immunofluorescence staining of NSCs cultured on different groups. Tuj1 was stained red. GFAP was stained green. 4′,6-diamidino-2-phenylindole (DAPI) was stained blue. Scale bar: 50 μm. (**C**) Statistical analysis of the percentage of Tuj-1 (+) cells to total cell number (n = 6). (**D**) Immunofluorescence staining of NSCs cultured on different groups. MAP2 was stained red. Scale bar: 50 μm. (**E** and **F**) Statistical analysis of MAP2 (+) cell percentage to total cell number. Statistical analysis of GFAP (+) cell percentage to total cell number (n = 6). (**G**–**I**) The RT-qPCR analysis of the gene expression of Tuj1, GFAP, and MAP2 (n = 3). (**J**) Western blot images showed the changes in protein expression of Tuj-1, GFAP, and MAP2. (**K**) Quantitative analysis of Tuj-1/Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) ratio in Western blot images (n = 5), (**L**) Quantitative analysis of MAP2/GAPDH ratio in Western blot images (n = 4). (**M**) Quantitative analysis of GFAP/GAPDH ratio in Western blot images (n = 4). Significance: ns-not significant, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Adapted with permission from [Ref.[137]]. Copyright 2024, Wiley.

inflammatory injury, while M2 macrophages release anti-inflammatory cytokines, such as IL-10 and TGF-β, that promote tissue repair.[138] Excessive or prolonged neuroinflammation severely damages the central nervous system, induces neuronal apoptosis, and disrupts neural circuits, thereby impeding spinal cord recovery after SCI.[139] Conductive hydrogels play a multidimensional role in regulating the SCI microenvironment. Their primary functions include the sustained release of anti-inflammatory factors, modulation of immune cell behavior, and inhibition of excessive inflammatory responses, thereby creating a favorable environment for nerve regeneration. As shown in Figure 4, Fan et al developed a neural tissue-like conductive hydrogel loaded with BMSC-exosomes, which regulates the M2 polarization of microglial cells through the NF-κB pathway and synergistically enhances the transition of neural stem cells (NSCs) into neurons and oligodendrocytes. Additionally, it inhibits astrocyte differentiation and promotes axon growth through the PTEN/PI3K/AKT/mTOR pathway. In the SCI mouse model, the combination of exosomes and conductive hydrogel significantly reduced the number of CD68-positive microglia, enhanced the recruitment of local NSCs, and facilitated neuron and axon regeneration, leading to significant functional recovery at an early stage.[131] Liu et al developed a biomimetic magneto-electric hydrogel that combines Fe3O4@BaTiO3 core-shell nanoparticles and human umbilical cord mesenchymal stem cell exosomes (HUMSC-Exos), based on the concept of synergistically enhancing the treatment of spinal cord injury (SCI) with remote non-invasive electrical stimulation. The activation of Fe3O4@BaTiO3 by a peripheral magnetic field generates electrical stimulation, which, in combination with the synergistic effects of HUMSC-Exos, significantly alleviates the early inflammatory response associated with SCI, promotes the regeneration of newborn neurons and axons, and creates favorable conditions for functional recovery.[140]

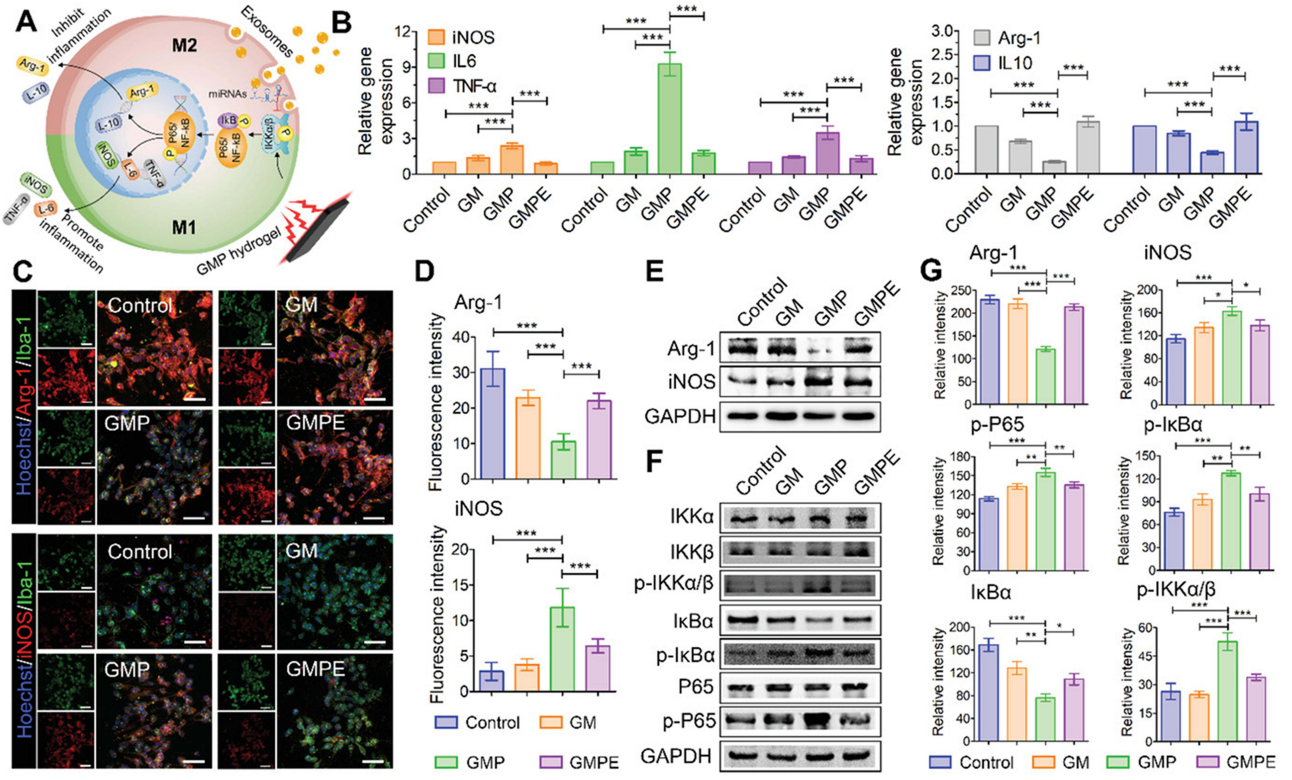

Figure 4 GMPE hydrogels promote microglia M1 to M2 switch by activating the NF-κB pathway. (**A**) An illustration of microglia switching from an M1- to M2-dominant phenotype through NF-κB pathway activity. (**B**) RT-qPCR results of the level gene expression of anti-inflammatory factors Arg-1 and IL-10 and the proinflammatory factors iNOS, IL-6, and TNF-α in BV2 cells cultured on hydrogels (n = 3). (**C**) IF imaging showing the proportion of Arg-1 positive and iNOS positive BV2 cells cultured in each hydrogel treatment group. Green IF represents the microglia/macrophage specific protein marker Iba-1, red fluorescence represents the M1/M2 microglia/macrophage phenotype marker iNOS or Arg-1, blue fluorescence represents the nuclear marker Hoechst 33342. Scale bars: 200 μm. (**D**) Quantification of fluorescence intensity of iNOS and Arg-1 level in each hydrogel treatment group (n = 5). (**E**) GMPE hydrogel promoted BV2 cell M2 polarization. (**F**) GMPE hydrogel regulated the expression of the relative proteins of NF-κB pathway, further indicating that the GMPE hydrogel promotes BV2 cell M2 polarization through NF-κB pathway activation. (**G**) Protein band intensity was quantified using ImageJ (n = 3). Statistical differences were determined using an ANOVA with Bonferroni's multiple comparison test (*p < 0.05, **p < 0.01, ***p < 0.001). Reprinted with permission from [Ref.[131]]. Copyright 2022, Wiley.

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Antioxidant

Under physiological conditions, reactive oxygen species (ROS) act as key signaling molecules that precisely regulate important physiological functions, including cell proliferation, differentiation, gene expression, and immune defense.[141,142] However, in severe pathological conditions such as spinal cord injury (SCI), this balance is completely disrupted. The massive infiltration of immune cells at the injury site becomes over-activated, leading to the production of excessive reactive oxygen species (ROS), such as superoxide anion (O2•−), hydrogen peroxide (H2O2), and hydroxyl radicals (•OH), which far exceed the body's ability to scavenge them. Instead of acting as signaling molecules, these ROS transform into potent mediators of damage, activating downstream pathways that induce lipid peroxidation, protein oxidation, DNA damage, and the activation of inflammatory agents.[58,143] These excess ROS, rather than functioning as signaling agents, become powerful damage mediators that activate inflammatory signaling cascade. The oxidative damage and persistent inflammatory signals form a vicious cycle, which constitutes the core pathological mechanism of secondary spinal cord injury, leading to neuronal death, axonal degeneration, and glial scar formation, all of which severely impede nerve repair and functional recovery.[144,145] Therefore, targeting and removing excessive ROS at the injury site to break the vicious cycle of oxidative stress and neuroinflammation, and improve redox balance, is a promising strategy for SCI treatment. Conductive hydrogels can modulate intracellular antioxidant signaling pathways through their intrinsic electrical activity. Previous studies have shown that electrically conductive environments or exogenous electrical stimulation facilitate the dissociation of Nrf2 from its repressor Keap1 and promote its nuclear translocation. This, in turn, activates the antioxidant response element (ARE), thereby upregulating the transcription of downstream antioxidant enzymes, including HO-1, NQO1, SOD, and CAT. Such activation contributes to the restoration of cellular redox homeostasis and the attenuation of oxidative stress-induced damage.[146,147] In addition, conductive hydrogels may further regulate cellular responses to oxidative stress through multiple signaling pathways, such as PI3K/Akt, MAPK, and Ca^{2+}, with emerging evidence reported in models of myocardial protection, neural repair, and cartilage regeneration.[148,149] Functioning as "electro-biointerfaces", conductive hydrogels can exert a dual effect of "direct ROS scavenging + endogenous antioxidant amplification" when combined with external electrical stimulation or local microelectrical fields. In recent years, a variety of conductive hydrogels have demonstrated remarkable ROS-scavenging capacity, either through their inherent antioxidant properties or via the incorporation of exogenous antioxidant factors. Zhu et al designed a conductive hydrogel for SCI therapy by combining stromal cell-derived factor-1 α (SDF-1α) and MXene nanosheets, which enhanced neural stem cell (NSC) survival and differentiation by scavenging ROS and reprogramming macrophages to the M2 phenotype.[34] You et al synthesized a particulate nanocomposite with a Schottky heterojunction (Au@BT) by in situ growth of gold nanoparticles (AuNPs) on piezoelectric BaTiO3. This nanocomposite can continuously generate H2 through piezoelectric-catalyzed H+ reduction and achieve an anti-inflammatory effect by scavenging intracellular reactive oxygen species (ROS).[150] As shown in Figure 5, Li et al constructed a conductive piezoelectric hydrogel (SFBP/PER) with ultrasound-triggered wireless electrical stimulation (ES) capability, fulfilling the electrical conductivity requirements for spinal cord injury (SCI) regeneration. The SFBP/PER hydrogel significantly promotes recovery in spinal cord-injured rats by attenuating oxidative stress, apoptosis, and inflammation, reducing the lesion cavity, facilitating the regeneration of myelin sheaths, and promoting the regeneration of functional neurons.[84]

Inhibit Glial Scar Formation

Glial scar formation is an exaggerated tissue response to injury, typically involving the formation of neuroglial and fibrotic scars. While these scars offer protection by containing the injury and limiting the spread of acute-phase inflammation, they also impede axonal regeneration and the recovery of nerve function.[151,152] Scar formation results from three main factors. The first is the overactivation of glial cells and fibroblasts. After spinal cord injury (SCI), astrocytes, microglia, and perivascular fibroblast-like cells rapidly accumulate at the injury site, releasing large amounts of proinflammatory cytokines and extracellular matrix (ECM) molecules. These actions contribute to the development of barrier-like structures. The second factor is the prolonged release of proinflammatory cytokines. Continued inflammation following SCI, driven by elevated levels of mediators such as IL-1β and TNF-α, exacerbates scar formation and perpetuates a vicious cycle of tissue damage. The third factor is the excessive accumulation of ECM components. Overproduction of ECM molecules, particularly

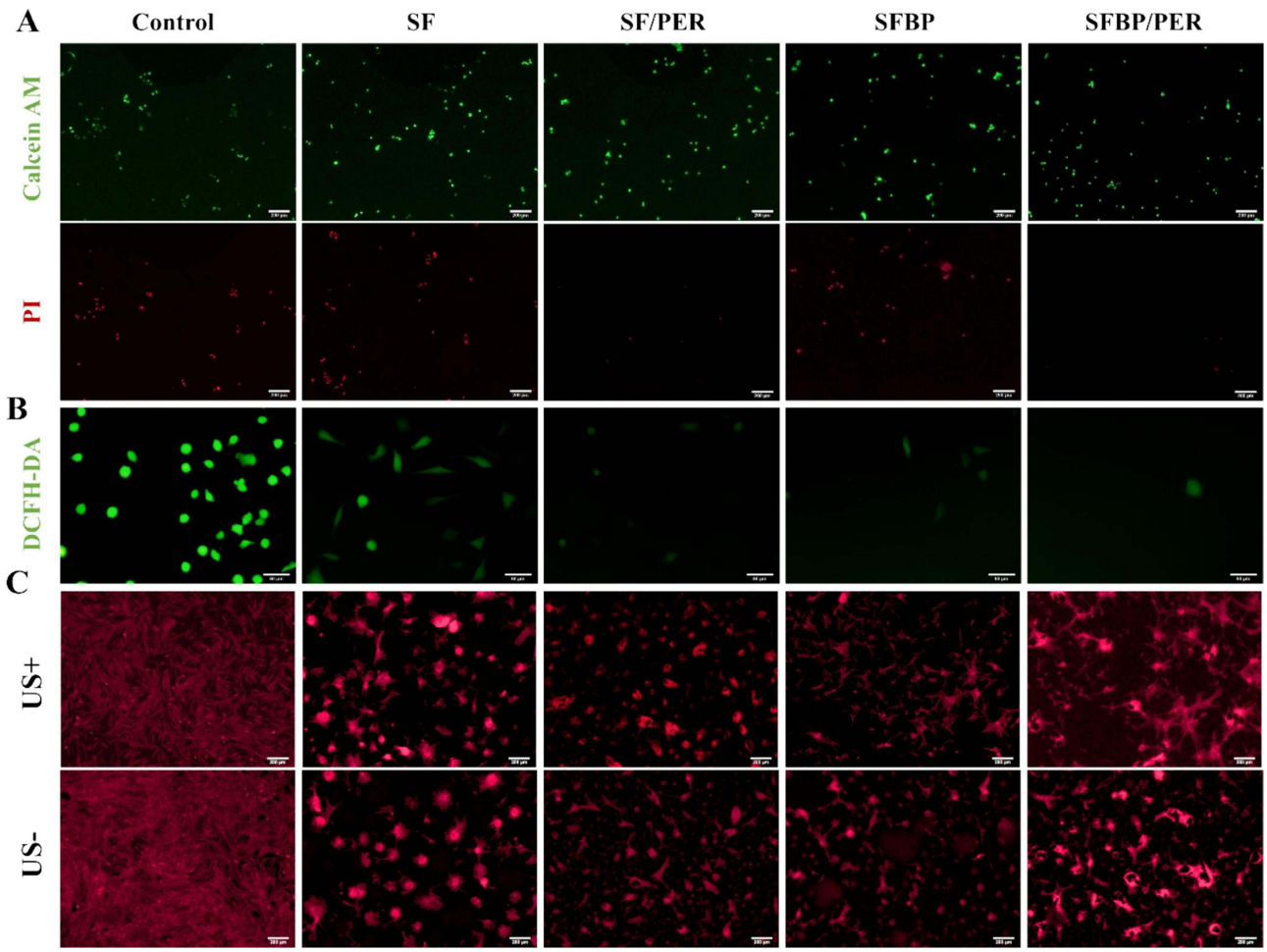

Figure 5 In vitro neuron-protective capability of the SFBP/PER hydrogels. (**A**) In vitro anti-glutamate excitotoxicity ability of the SFBP/PER hydrogels. All groups were treated with glutamate (500 μM) for 6 h. Live cells are stained in green, and dead cells are stained in red. (**B**) In vitro antioxidative ability of SFBP/PER hydrogels. All groups were treated with H2O2 (1 mM) for 2 h. Fluorescent images of ROS detected in HT-22 cells using 2′,7′-dichlorofluorescein diacetate (DCFH-DA) probe. Scale bar = 50 μm. (**C**) F-actin staining of HT-22 cells after 3 days of culturing on the hydrogels with or without US. Reprinted with permission from [Ref.[84]]. Copyright 2024, Elsevier.

chondroitin sulfate proteoglycans (CSPG), significantly enhances the inhibitory microenvironment at the injury site, hindering axon elongation and the re-establishment of functional neural connections. Conductive hydrogels can effectively prevent scar formation after SCI by attenuating the activation of glial cells and fibroblasts, and limiting the deposition of inhibitory ECM molecules, including CSPG. Yang et al developed an easy-to-prepare agarose/gelatin/polypyrrole hydrogel (Aga/Gel/PPy, AGP3) with conductivity and modulus similar to that of the spinal cord by varying the concentrations of agarose (Aga) and polypyrrole (PPy). The AGP3 hydrogel exhibited good biocompatibility and promoted the differentiation of neural stem cells (NSCs) into neurons, while inhibiting the overproliferation of astrocytes. In vivo, the AGP3 hydrogel completely covered the tissue defect and reduced the injury cavity area.[153] As shown in Figure 6, Kong et al developed a novel multifunctional hydrogel containing an MXene-Au complex and loaded neural stem cells (NSCs) into the hydrogel, combining it with electrical stimulation to promote motor function recovery after SCI in rats. The hydrogel exhibited excellent reactive oxygen species (ROS) scavenging ability, electrical conductivity, and antibacterial properties. Additionally, electrical stimulation promoted the proliferation and differentiation of NSCs into neuronal cells and the establishment of synaptic connections between neurons. In the rat SCI model, the hydrogel carrying NSCs, in combination with electrical stimulation, reduced the formation of vacuoles and glial scars in the injury site, enhanced neuronal differentiation and myelin regeneration of NSCs, and facilitated the recovery of motor function after SCI.[133]

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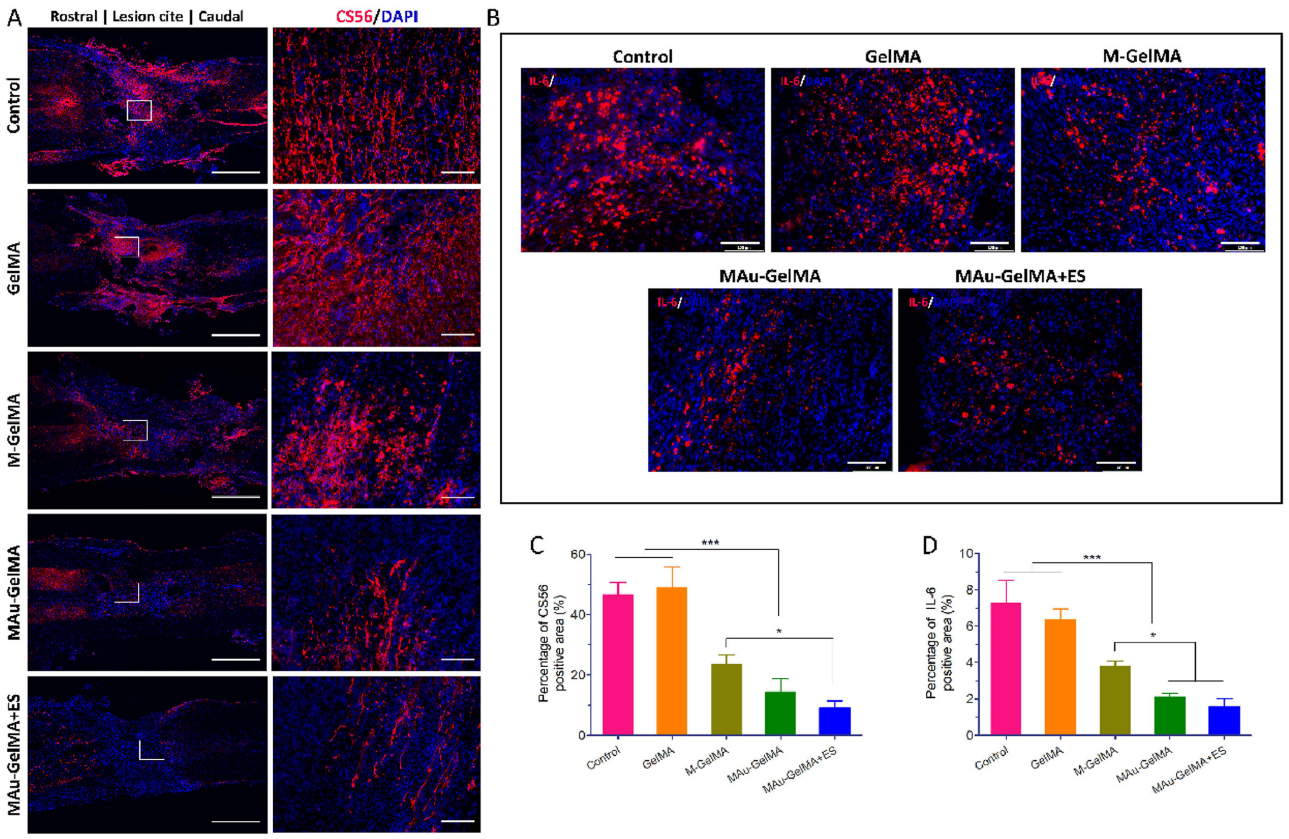

Figure 6 MAu-GelMA + ES reduced inflammatory cell aggregation and glial scar formation. (**A**) CS56 positive glial scar (red) in each group. The enlarged images of white dashed rectangular are shown on the right panel. Scale bar: left = 1000 μm; right = 100 μm. (**B**) The inflammatory cells in the lesion area of different groups. Inflammatory cells are labeled in red, scale bar = 100 μm. (**C**) Percentage of CS56 positive area in each group. (**D**) Percentage of IL-6 positive area in each group. *, ** and ***indicates $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively. Reprinted with permission from [Ref.[133]]. Copyright 2023, Elsevier.

Promotes Angiogenesis

After spinal cord injury (SCI), the primary mechanical injury and subsequent secondary injury response lead to severe vascular damage. Direct mechanical injury disrupts vascular integrity, causing hemorrhage and local ischemia, which interrupt the delivery of oxygen and nutrients to the injury site, exacerbating neuronal apoptosis and worsening the spinal cord microenvironment.[26] During secondary injury, the inflammatory response, oxidative stress, and release of pro-inflammatory factors severely impair vascular endothelial cell function, disrupt the blood-brain barrier (BBB), and promote the infiltration of peripheral immune cells. This creates a vicious cycle that hinders angiogenesis, reduces waste removal, and further impedes axonal elongation, functional recovery, and overall spinal cord repair.[154] Liu et al developed a lipoic acid-modified chitosan hydrogel matrix (LAMC). The injectable LAMC/BP@TA, constructed by incorporating tannic acid (TA)-modified BP nanosheets (BP@TA) into the LAMC hydrogel matrix and loading tazarotene, significantly promoted motor function recovery, endogenous angiogenesis, and neurogenesis at the injury site in a rat spinal cord injury model.[132] As shown in Figure 7, Fan et al developed a novel hydrogel by controlling the concentrations of gelatin and polypyrrole (PPy) and prepared matrix metalloproteinase (MMP)-responsive hydrogels with recombinant proteins GST-TIMP-bFGF. This was achieved by coupling glutathione (GSH) to the hydrogel via gelatin-derived amine groups and glutathione-derived sulfhydryl groups. The MMP-responsive conductive hydrogels release bFGF in response to the spinal cord injury microenvironment, providing a favorable biophysical microenvironment. In a rat spinal cord injury model, the MMP-responsive bionic machinery and conductive hydrogel inhibited MMP levels, promoted axonal regeneration and angiogenesis, and improved motor function recovery after spinal cord injury.[155]

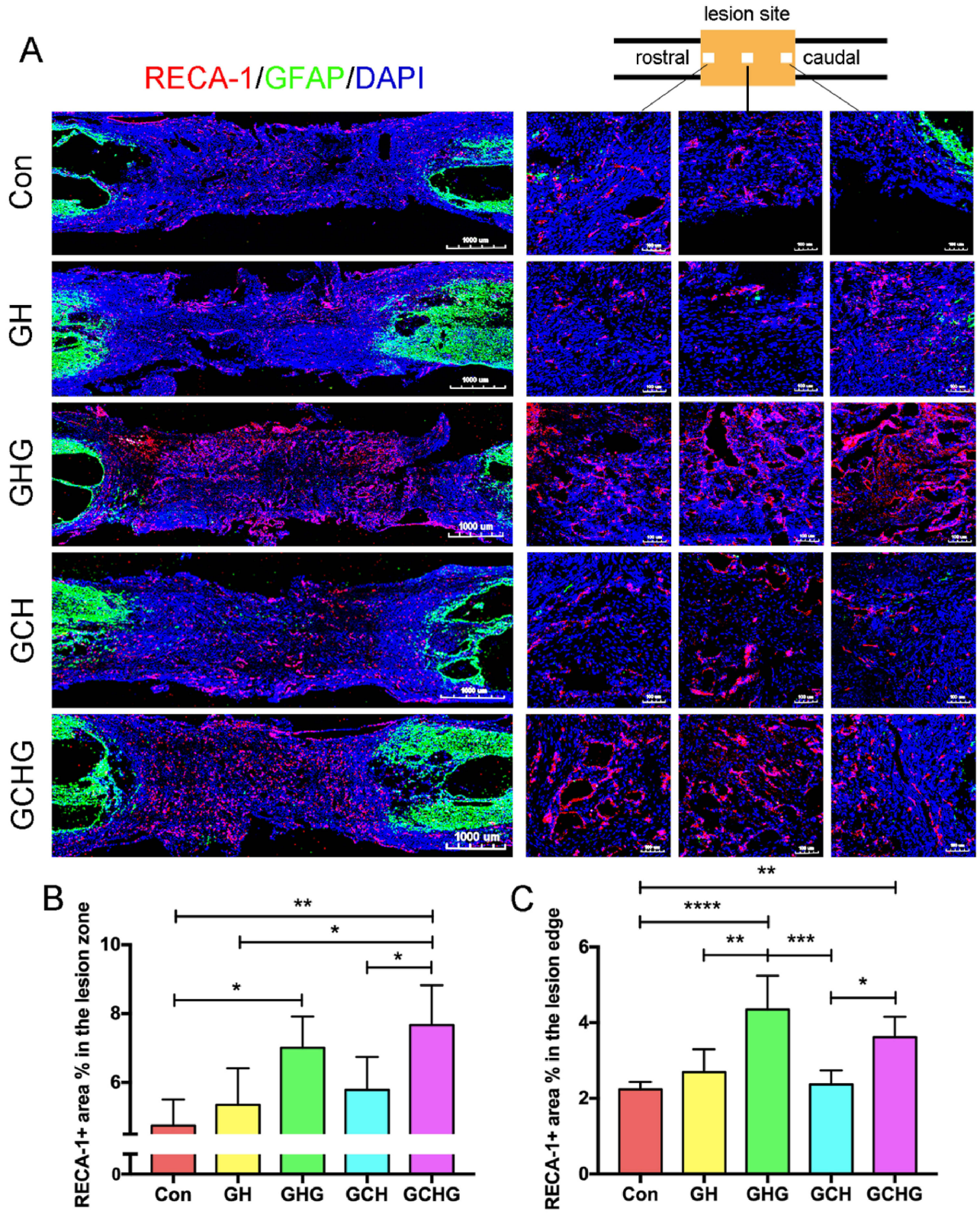

Figure 7 Blood vessels at the injured area. (**A**) At 8 weeks after injury, RECA+ blood vessels were observed at the injury sites of rats in different treatment groups. (**B**) Quantification of RECA+ blood vessels in SCI zone. (**C**) Quantification of RECA+ blood vessels in SCI edge. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. Reprinted with permission from [Ref.[155]]. Copyright 2022, Elsevier.

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Challenges and Perspectives

Regarding spinal cord injury (SCI) repair, most existing approaches address only one of the multiple inhibitory factors. However, a comprehensive therapeutic intervention is required to address the pathological changes associated with SCI. Systematic strategies for SCI repair can be divided into two main components. The first strategy focuses on building bridges at the injury site to provide physical support for axonal regeneration, directing axonal growth to distal nerves for proper reconnection of neural pathways. The second strategy involves creating an environment that promotes recovery through specific functionalization, such as physicochemical surfaces that attract targeted nerve cells and enable drug or cell-based delivery. Conductive hydrogel electrodes can effectively combine these two strategies by first mimicking the cellular electrophysiological environment, replacing the lost neural extracellular matrix (ECM), and second, multi-facetedly addressing pathological changes after injury through functionalization. In this paper, we describe strategies for the development of conductive hydrogels designed as an integrative therapeutic intervention for simultaneous multifaceted regeneration in a systematic manner.

Despite the promising potential of hydrogels for spinal cord rehabilitation, significant challenges remain in their clinical translation and application. First, the long-term biocompatibility of conductive polymers or their complexes must be thoroughly evaluated, including their degradation rate, compatibility with nerve regeneration, and the potential toxicity of degradation products, all of which require intensive evaluation over an extended period. When combined with electrical stimulation, maintaining stable, long-term contact between electrodes and tissue while avoiding deformation or compression of spinal tissue remains a critical issue. Moreover, the spinal cord's intricate anatomical and functional heterogeneity poses additional challenges. Designing conductive hydrogels with spatially tailored properties to meet the distinct requirements of gray matter and white matter necessitates precise control over electrical, mechanical, and biological characteristics. Given that spinal cord tissue exhibits an elastic modulus of only ~0.1–1 kPa, repair materials must be sufficiently soft to avoid secondary injury, yet mechanically robust enough to maintain structural integrity and preserve neural pathways. Currently, most studies rely on acute injury models in mice or rats. Although conductive hydrogels have demonstrated encouraging outcomes in these standardized models, a substantial gap remains between small-animal experiments and the heterogeneous reality of human spinal cord injuries, which vary widely in location, severity, mechanism, and timing. This disparity highlights the limitations of universal hydrogel formulations and underscores the necessity of personalized designs tailored to specific injury types. Beyond technical hurdles, conductive hydrogel products face stringent regulatory requirements as implantable devices. Their clinical approval demands validation in large-animal models, stringent quality control in scalable manufacturing, and ultimately, multi-center randomized controlled trials to establish safety and efficacy.

Future research will focus on developing smarter and multifunctional conductive hydrogel materials to achieve spatiotemporally accurate and controllable, individually adaptive smart electrical stimulation. For long-term biological safety testing of materials, the integration of organoids and microfluidic technologies provides innovative platforms. Organoids are three-dimensional cellular structures cultivated from stem cells or organ-specific progenitor cells, capable of mimicking the key functions and structures of corresponding organs. Meanwhile, organ-on-a-chip utilizes microfluidic technology to construct three-dimensional cellular models on a chip, simulating the physiological activities of human organs. The integration of these two technologies creates a multi-level, controllable validation platform. It enables high-throughput screening of the electrical and mechanical properties of conductive hydrogels in the early stages, followed by assessment of their long-term stability and biosafety under simulated chronic injury conditions in later phases.

To overcome the limitations of conventional electrodes and accommodate the dynamic environment of spinal cord injury, dynamic crosslinking strategies can be applied. These leverage reversible physical interactions (eg, hydrogen bonding, π–π stacking, ionic bonding) or dynamic covalent chemistry (eg, Schiff base bonds, borate bonds, Diels–Alder reactions) to construct adaptable hydrogel networks. Such designs confer viscoelasticity and tissue-like adaptability. By tuning crosslinking rates and strengths, hydrogels can dynamically respond to implantation conditions: during acute injury, greater flexibility mitigates inflammatory responses, while enhanced mechanical support in later stages promotes axonal extension. This "programmable" adaptability positions conductive hydrogels as superior alternatives to traditional metallic electrodes, offering both functional and biocompatible advantages for intelligent neural interfaces.

Given the marked heterogeneity of spinal cord injuries—including differences in location, severity, and progression—personalized design will be critical. Advanced imaging modalities such as magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) provide foundational data for individualized implants. Deep learning and artificial intelligence algorithms can process and model these datasets, refining design precision. Concurrently, high-resolution 3D printing techniques—including stereolithography, digital light processing, and inkjet printing—allow precise control over pore size, porosity, and conductive network distribution. This structural tuning optimizes electrical pathways and supports neural cell growth. As printing resolution improves and bioink systems mature, 3D printing will enable integrated control over macroscopic architecture, microscopic structure, and multimaterial functionality, facilitating the transition from "customized implants" to "precision repair". Extending this concept, 4D printing introduces dynamic programmability, enabling hydrogels to adaptively respond to evolving microenvironmental cues, thereby opening new avenues for personalized therapy.

Clinical translation will require interdisciplinary, multicenter collaboration, as no single discipline can independently advance conductive hydrogels from bench to bedside. Large-animal spinal cord injury models must be established for systematic evaluation. Integration with stem cell technologies, genetic engineering, and advanced biosensing systems will enable the development of highly integrated therapeutic platforms. Parallel efforts must focus on building standardized quality control systems and regulatory pathways, ensuring reproducibility and compliance for classification as medical devices or tissue-engineered products. Through coordinated scientific validation, engineering scale-up, and clinical standardization, conductive hydrogels hold the potential to accelerate toward clinical adoption and ultimately deliver meaningful functional recovery for patients with spinal cord injuries.

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Disclosure

The authors report no conflicts of interest in this work.

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