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REVIEW

Advances in Conductive Hydrogel for Spinal Cord Injury Repair and Regeneration

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Abstract: Spinal cord injury (SCI) treatment represents a major challenge in clinical practice. In recent years, the rapid development of neural tissue engineering technology has provided a new therapeutic approach for spinal cord injury repair. Implanting functionalized electroconductive hydrogels (ECH) in the injury area has been shown to promote axonal regeneration and facilitate the generation of neuronal circuits by reshaping the microenvironment of SCI. ECH not only facilitate intercellular electrical signaling but, when combined with electrical stimulation, enable the transmission of electrical signals to electroactive tissue and activate bioelectric signaling pathways, thereby promoting neural tissue repair. Therefore, the implantation of ECH into damaged tissues can effectively restore physiological functions related to electrical conduction. This article focuses on the dynamic pathophysiological changes in the SCI microenvironment and discusses the mechanisms of electrical stimulation/signal in the process of SCI repair. By examining electrical activity during nerve repair, we provide insights into the mechanisms behind electrical stimulation and signaling during SCI repair. We classify conductive biomaterials, and offer an overview of the current applications and research progress of conductive hydrogels in spinal cord repair and regeneration, aiming to provide a reference for future explorations and developments in spinal cord regeneration strategies.

Keywords: neural tissue engineering, electrical stimulation, electrical signal, conductive biomaterials, spinal cord injury microenvironment

Introduction

Spinal cord injury (SCI) is a debilitating trauma to the central nervous system (CNS) that results in permanent motor, sensory, and autonomic dysfunctions below the injury site, presenting a significant medical challenge.[1] Globally, it is estimated that there are 250,000 to 500,000 new cases of SCI annually.[2] The clinical management of SCI primarily involves surgical stabilization of the vertebrae and early spinal cord decompression, pharmacological intervention, and rehabilitative treatment.[3] Despite considerable advancements in therapeutic techniques, a cure for SCI remains elusive.[4] Treatment during the early stages primarily aims to stabilize the spinal cord and restore homeostasis immediately following the injury, while long-term management addresses symptoms caused by maladaptive plasticity and other secondary complications.[5] Spinal cord injury can be classified into traumatic and non-traumatic causes. Traumatic spinal cord injuries occur when acute spinal cord injury is caused by an external physical shock, such as a motor vehicle collision, fall, sports-related injury, or direct trauma. In contrast, nontraumatic spinal cord injuries typically occur after an acute or chronic disease process, such as a tumor, an infection, or degenerative disc injury. In traumatic spinal cord injuries, the primary injury damages cells and triggers a complex cascade of secondary injuries involving neuronal and oligodendrocyte death, and leads to the deterioration of the environment surrounding the lesion site, resulting in progressive pathological changes like inflammation, oxidative damage, axonal demyelination, apoptosis, and the formation of irregular cystic cavities and glial fibrosis.[6] It is now understood that glial fibrosis and fluid-filled cysts,[7] along with endogenous remyelination and poor axonal regeneration, impede the electrical signaling and stimulus conduction in spinal cord tissue, thereby hindering neural regeneration.[8] Therefore, the key to treating spinal cord injuries lies in reconnecting the disrupted neural pathways,

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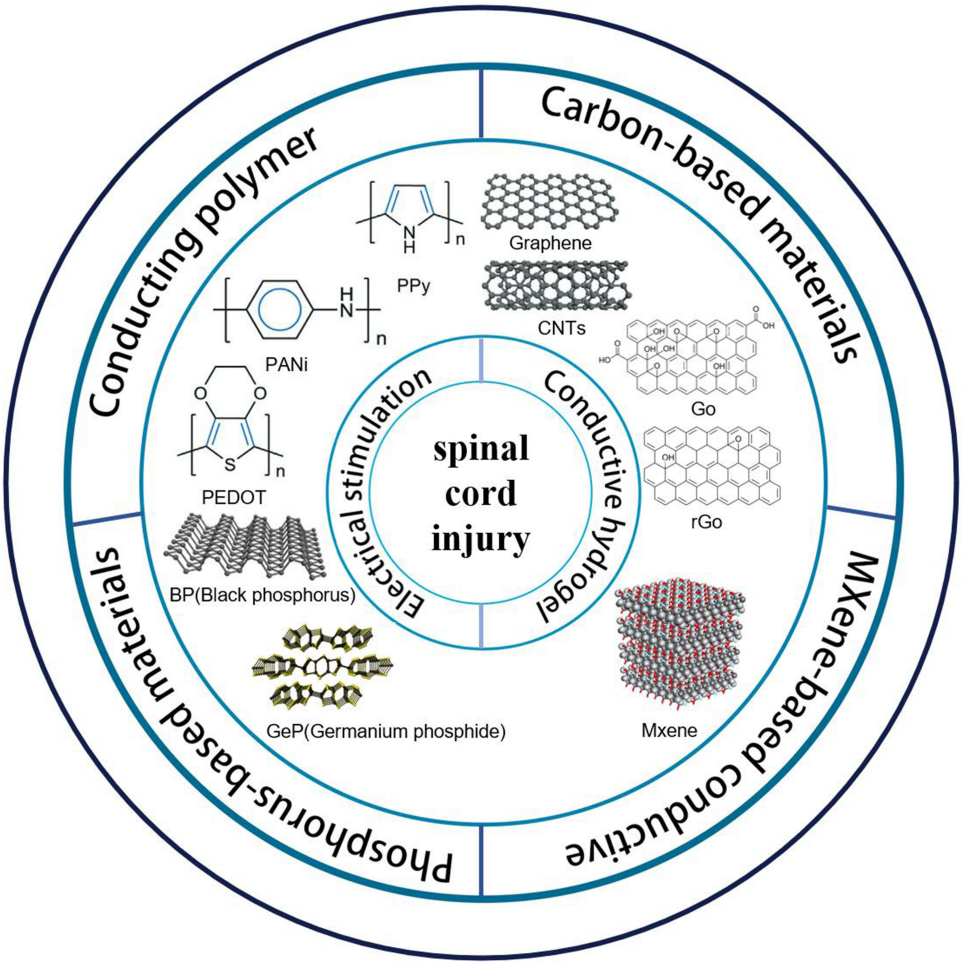
Graphical Abstract



stimulating neuronal differentiation and axonal growth, suppressing inflammation, and providing a regenerative environment and support for damaged neurons.[9] However, current treatment approaches typically target only one aspect of these complex multifactorial causes and have limited efficacy.[10] In recent years, biocompatible materials and tissue engineering approaches have emerged as promising new strategies for treating spinal cord injuries.[11]

Over the past few decades, hydrogels have been widely used as scaffolds in neural tissue engineering due to their exceptional biocompatibility, porosity, and mechanical flexibility.[12–14] Scaffold designs based on hydrogels have been shown to possess similar biochemical and biophysical properties to the natural extracellular matrix of the brain/spinal cord, allowing effective filling of irregular lesions and mimicking the physiological environment of living tissues, thereby promoting the survival and differentiation of neurons.[8,15] Moreover, they can enhance the microenvironment of the injury site and improve cell survival rates and axonal growth by incorporating cells, various neurotrophic factors, or drugs to release bioactive molecules.[5]

Although hydrogels have many desirable properties, they are typically electric insulators, impeding the transmission of intercellular electrical signals. Electrical signals are the foundation of neural system function, as the spinal cord communicates with other types of cells through neural networks and axonal bundles, conducting bioelectric signals.[16] Neural networks not only participate in the differentiation and regeneration of neural stem cells,[17] but also prevent scar tissue formation at injury sites and facilitate the transmission of biological signals to achieve specific biological functions.[18,19] It has been established that the stimulation and transmission of electrical signals are crucial for neuronal function. Therefore,

during the design and preparation of neural tissue regeneration scaffolds, it is imperative to mimic the native extracellular matrix (ECM) of the spinal cord by integrating conductive matrices into the cellular microenvironment to provide an artificial environment that promotes regeneration at injury sites.[20] In neural repair applications, the advantage of conductive hydrogels lies in their ability to simultaneously provide physical and electrical characteristics, with the former being a unique property of hydrogels and the latter achieved through conductive materials.

This review article summarizes recent advances in conductive hydrogels for spinal cord injury repair, providing an overview of the characteristics of these hydrogels (Table 1) and their clinical applications, challenges, and prospects. Furthermore, we expound on the mechanisms underlying electrical stimulation and signaling in spinal cord injury repair.

SCI Microenvironment

This section comprehensively explores the microenvironment following spinal cord injury. Spinal cord injury can be divided into primary and secondary injuries.[33] Temporally, they can be categorized into acute (<48 hours), subacute (48 hours to 14 days), intermediate (14 days to 6 months), and chronic (>6 months) phases 9 (Figure 1). Primary injuries are often irreversible, including compression, stretching, tearing, transection, and bleeding,[34] damaging neurons and oligodendrocytes (a type of glial cell in the central nervous system), disrupting the vascular system, and impairing the blood-spinal cord barrier, thus immediately initiating a cascade of secondary injury reactions. During the acute phase (within 0–48 hours after injury), damage to the microvessels supplying the spinal cord leads to increased cell permeability, infiltration of inflammatory cells, release of cytotoxic molecules, propagation of pro-apoptotic signaling, and ischemic damage.[35] This secondary injury results in the necrosis and/or apoptosis of neurons and glial cells (such as oligodendrocytes), leading to demyelination and loss of neural circuits. During the subacute phase (2–4 days after injury), sustained edema, the formation of blood clots, and vasoconstriction further contribute to ischemia, causing glutamate release,[36] lipid peroxidation,[37] activation of calcium influx and calpain protease,[38] edema, and excitotoxic cell death.[39] The sustained infiltration of inflammatory cells contributes to further cell death,[40,41] and the formation of cystic cavities due to the disruption of extracellular structures of cells and the spinal cord.[42] In addition, astrocyte proliferation occurs and extracellular matrix molecules such as chondroitin sulfate proteoglycans (CSPGs), fibronectin, laminin, and collagen are deposited by astrocytes in the surrounding lesion area, limiting axonal growth.[43,44] It has been shown that certain subtypes of astrocytes yield a neuroprotective effect during the injury process.[45] During the intermediate and chronic phases (2 weeks to 6 months), axonal degeneration continues, and the astroglial scar matures, impeding axonal regeneration and extension.[45,46] The fusion of cystic cavities further restricts axonal regeneration and cell migration.

In addition, inhibitory factors, including Nogo, myelin-associated glycoprotein (Mag), oligodendrocyte myelin glycoprotein (Omgp), Nogo receptor protein, and p75 neurotrophic receptor binding activation of RHOA and Rho-associated protein kinase (ROCK),[48] strongly suppress axonal and myelin sheath regeneration which can result in the collapse of growth cones after SCI.[49–53] The poor axonal growth capability and inhibitory factors hindering axonal regeneration lead to the failure of spinal cord regeneration and neural circuit reconstruction.[54–56]

The Mechanism of Electrical Stimulation/Electric Signal in the Repairing Process of Spinal Cord Injury

Spinal cord injury is a severe traumatic condition affecting the central nervous system, and it is characterized by the limited regenerative potential of neurons following damage. One significant obstacle in this process is the disruption of electrical signaling.[57] In neural tissues, ion channels on the cell membrane of neural cells activate a cellular gap, leading to ion transport across the membrane, resulting in membrane polarization and the generation of an endogenous electric field. Bioelectric signals, stemming from changes in cell membrane potential, represent a primary mode of cellular signaling. These bioelectric signals play a vital role in processes such as neural cell proliferation, differentiation, migration, spreading, and apoptosis via various physiological mechanisms, including cytoskeletal rearrangement, cell membrane depolarization, conformational and positional changes of membrane proteins, and the regulation of transmembrane calcium influx.[58] By facilitating signal transduction between cells and the extracellular matrix, the transmission and delivery of electrical signals regulate the morphology, quantity, location, migration, and differentiation of neural stem

Table 1 Conductive Hydrogels Applied in Spinal Cord Injuries in Recent Years

Conductive Components	Hydrogel Matrix	Conductivity	Electrical Stimulation	Hydrogel Properties	Outcomes	Reference
PPy	Collagen	0.176±0.07 S/cm	200 mV	Most optimized mechanical strength, electrical conductivity, degradation, and swelling properties	Cell study: promote NSCs differentiation into neurons and inhibit the differentiation of NSCs into astrocytes	[125]
PPy	Bioactive collagen/hyaluronan	0.189 S/ m	100 mV /cm	Reduced the ROS level and inhibited secondary oxidative damage, restored the transmission of endogenous electrical signals, inducing the neuronal differentiation of both implanted BMSCs and recruited endogenous NSCs	In vitro study: promote neuronal differentiation of BMSCs, protect the cells from ROS in the oxidative microenvironment In vivo study: reduce the cavity area, inhibiting the formation of glial scar, and promoting synaptic regeneration, remyelination, and motor function recovery	[127]
Chitosan-modified polypyrrole (DCP) nanoparticle (~;40 nm)	N-carboxyethyl chitosan (CEC)	3–6 mS/cm	100mV	Self-healing, injectability and conductivity, strain/motion-sensing properties, biodegradability and biocompatibility	In vitro study: promote the attachment, proliferation, and differentiation of neural stem cells (NSCs), In vivo study: rescue the motor function in brain-injured zebrafish	[124]
PPy	Agarose+gelatin (Aga/Gel)	0.2×10^{-2}S /cm	-	Injectable, excellent biocompatibility, the thermal stability of the hydrogel at body temperature, similar conductivity and modulus as the spinal cord	In vitro study: promote differentiation of NSCs toward neurons whereas it inhibited over-proliferation of astrocytes In vivo study: completely covered the tissue defects and reduced injured cavity areas, provided a biocompatible microenvironment for promoting endogenous neurogenesis rather than glial fibrosis formation, resulting in significant functional recovery	[21]
PPy	Gelatin+Tannic acid (TA)	3.75×10^{-4} S cm^{-1}	-	Release bFGF on-demand in response to the SCI microenvironment, provide a favorable biophysical microenvironment with comparable mechanical and electrical properties to native spinal cords	In vitro study: allow the delivery of growth factors according to needs after varying degrees of MMP expression In vivo study: inhibit MMPs levels, promote axon regeneration and angiogenesis, increase blood vessel density and improve locomotion function recovery after SCI	[126]

PANI	Poly(amino acid)	-	Square wave, 10 Hz, 3 mA	Good biocompatibility, biodegradability, and conductivity, effectively stimulated SC tissue repair through continuous slow release of NGF and in response to external ES	In vitro study: induce the differentiation of NSCs into neurons in the injured SC while inhibiting the proliferation of astrocytes In vivo study: stimulate endogenous neurogenesis and promoted the restoration of motor function	[130]
PEDOT	Gelatin and hyaluronic acid	$8.3\times10^{-4}\pm 8.1\times10^{-5}$S/cm	-	Optimal porosity, with biomimetic mechanical performance and high conductivity to simulate axons	In vitro study: the scaffolds are cytocompatible In vivo study: diminish astrocyte reactivity. Decreased levels of macrophage and microglia reactivity at the implant site. Provides a more stimulating regenerative environment, allowing relatively larger axons to migrate and grow toward the target implantation site	[131]
Poly(3,4-ethylenedioxythiophene): sulfonated lignin (PEDOT:LS)	Gelatin methacrylate (GelMA), hyaluronic acid methacrylate (HAMA)	0.60 S/m	-	Mechanical property and conductivity similar to native spinal cord tissues	In vitro study: promote the neuronal differentiation of NSCs In vivo study: promote the recovery of hindlimb motor function, effectively promoted the regeneration of neurons at the injury site, reduced the deposition of glial scar, and promoted nerve axon regeneration and myelination	[104]
PEDOT:CSMA, TA	Gelatin/ polyethylene glycol	$(1.61\pm0.11)\times 10^{-5}$ S/cm	-	3D bioprinting 3D topography, technologywell shear-thinning and self- healing properties, Physical and chemical properties similar to natural spinal cord tissue	In vivo study: physical contact for the NSCs with adjacent cells and surrounding matrix was improved to accelerate their signal communication, and in vivo astrocytic production for the NSC-laden conductive composite scaffold was significantly inhibited, facilitating hindlimb function recovery in the rats suffered from the complete- transection SCI	[132]

(*Continued*)

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Table 1 (Continued).

Conductive Components	Hydrogel Matrix	Conductivity	Electrical Stimulation	Hydrogel Properties	Outcomes	Reference
Amine functionalized graphene	Collagen	3.8±0.2 mS/cm	100 mV/mm	Sufficiently high porosity with interconnectivity between the pores, appropriate electric and mechanical cues	Ex vivo study: promote the proliferation of cells from proximal to distal end, thereby aiding in establishment of neural connections, In vitro study: increase the immune-modulatory secretions that may prevent the occurrence of neuro-inflammation, suppressing the neuro-inflammation and promoting the neuronal cellular migration and proliferation	[103]
Graphene oxide	Polyethylene glycol	7.4 S m^{-1}	-	Suitable mechanical strength electric conductivity, and biochemical properties for creating an ideal microenvironment for axon regeneration, three-dimensional architecture, injectability and fast self-recovery	In vitro study: inhibit the astrocytes hyperactivation and inflammation reaction In vivo study: promote the SCI repairing	[141]
Molybdenum sulfide/graphene oxide (MoS_2/GO)	Polyvinyl alcohol (PVA)	0.220 S/m	-	Highly conductive, soft, excellent biocompatible, and anti-inflammatory, appropriate mechanical property	Cell study: promoted the NE-4C cells to differentiate into nerve cells and inhibited glial cell differentiation, inhibit the production of ROS In vivo study: quickly restore the continuity and electrical conductivity after SCI, excellent anti-oxidative property, inhibit the development of astrocytes, promote the repair of spinal cord tissue and improve the locomotor function of SCI mice	[106]
Reduced graphene oxide (rGO)	Xanthan gum	2.07±0.16 S/m	-	High electrical conductivity that transmits electrical signals, soft mechanical properties that match the spinal cord tissue, and porous internal structure that provide enough space for cell growth	In vitro study: good biocompatibility In vivo study: fill the cavity, guide the orderly growth of regenerated nerve fibers and inhibit the formation of glial scar, restore the locomotor function of rats	[146]

Single-walled carbon nanotubes	Polyethylene glycol diacrylate	0.01 S/m	20Hz, 100mV	Stable, injectable, conductive	In vitro study: promote the growth of SH-SY5Y cells, with significant neurite outgrowth while electrical stimulation was given In vivo study: promote nerve tissue regeneration and reduced the formation of scar tissue	[153]
Single-walled carbon nanotubes	Collagen	1723 mS/m	50 mV/mm	Minimize signal attenuation and allow for a reproducible electrical stimulus to be applied across a wide range of injury geometries and model systems, provide some inherent benefit to electrically active cells in the absence of electrical stimulation	Ex vivo study: enhance neurite outgrowth	[154]
Polydopamine modified GeP nanosheets (GeP@PDA)	Hyaluronic acid-graft-dopamine (HA-DA)	0.365 S/m	-	Injectable, good tissue adhesion properties, conductive and biodegradable	In vitro study: accelerate the neuron-oriented differentiation of neural stem cells (NSCs) In vivo study: promote immune regulation, endogenous angiogenesis, and NSCs neurogenesis, and improve the recovery of motor function significantly	[30]
Mxenes	Polyvinylpyrrolidone (PVP)	2.6 mS/cm	-	Injectable, electroconductive, adhesive, and self-healing and biocompatibility	In vitro study: good biocompatibility In vivo study: significantly accelerate spinal cord regeneration by accelerating angiogenesis, remyelination, axon regeneration and calcium channel activation	[105]
Mxenes	Methylacrylylated gelatin	6.2μS/cm	-	Excellent biocompatibility, microgroove structure could induce nerve cells to grow directionally and further promote impaired nerve gaps bridge, excellent conductivity	In vitro study: improve the adhesion, proliferation and differentiation of NSCs In vivo study: promote the regeneration of the spinal cord and recovery of hind limb motor function in rats	[175]
Mxenes-Au	Gelatin methacrylate (GelMA), poly(lactic-co-glycolic acid) (PLGA)	0.57 S/m	100 mV,100 Hz	Containing a patterned nanofiber skeleton, good ROS- scavenging ability, electrical conductivity and antibacterial ability	In vitro study: reduce the formation of ROS, inflammation, and promoting the differentiation and growth of NSCs into neurons In vivo study: reduce the generation of glial scars, enhancing the establishment of synaptic connections between cells, and fostering the functional recovery of SCI, improve the recovery of motor function after SCI in rats	[177]

Notes: In the above table "-" indicates that it is not mentioned in the relevant article.

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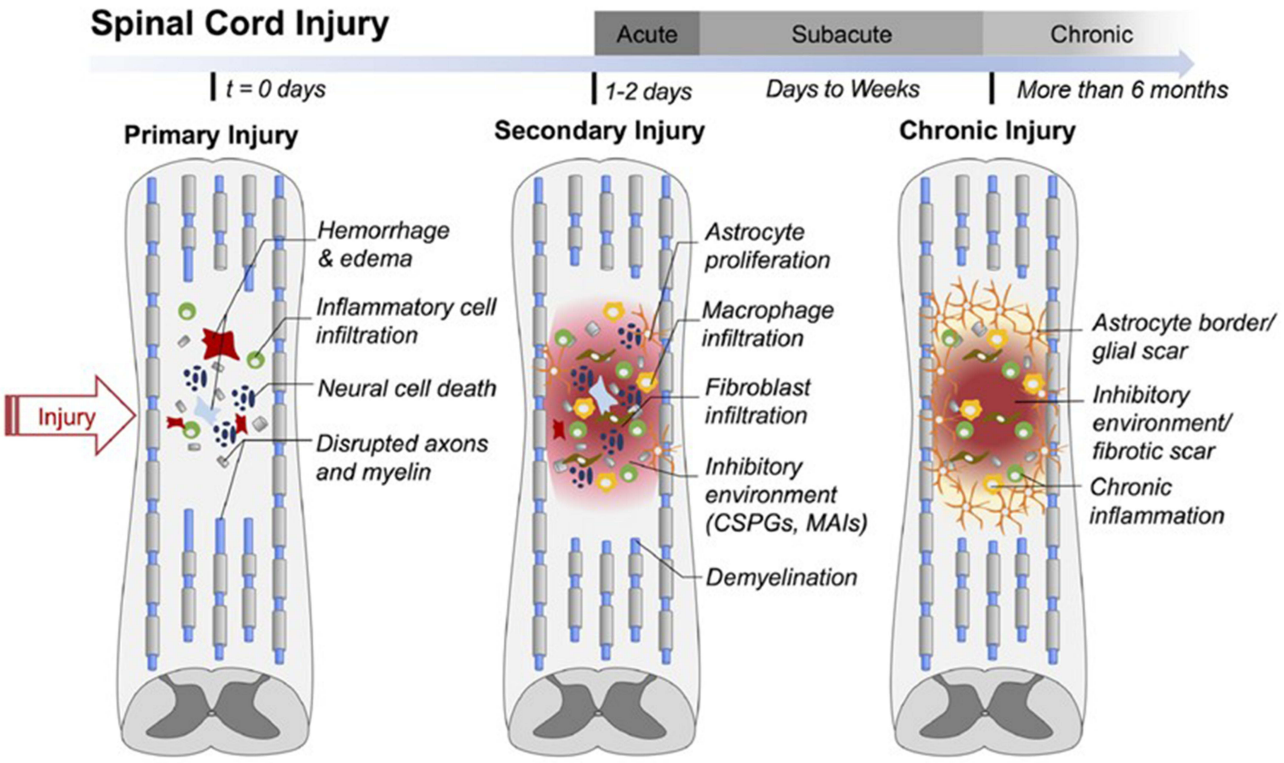


Figure 1 Pathophysiologic mechanisms of spinal cord injury.
Notes: Reprinted from *Acta Biomaterialia*, 139, Kiyotake EA, Martin MD, Detamore MS. Regenerative rehabilitation with conductive biomaterials for spinal cord injury. 43–64. Copyright 2020, with permission from Elsevier.[47]

cells (NSCs), ultimately promoting the maturation of neuronal electrophysiological characteristics.[59] Therefore, the transmission and delivery of electrical signals are essential for neuronal survival, regenerative differentiation, and the activation of neural circuits.

Neurons inherently possess the ability to transmit electrochemical signals throughout the nervous system and are significantly influenced by external electrical stimulation.[60,61] Electrical stimulation has been shown to promote axon extension in vitro and nerve regeneration in vivo.[62] Studies have shown that electrical stimulation accelerates axonal regeneration and promotes functional recovery when an electric field is established between nerve defects.[63] Although the mechanisms by which electrical stimulation promotes neuronal growth are not fully understood, it is widely thought that multiple mechanisms exist[64](Figure 2):

(a) Calcium ion influx and calcium signaling. ES can increase intracellular calcium levels by activating calcium channels (VGCC) to promote more calcium ions into cells or activating GPCRs to release Ca^{2+} from storage in the endoplasmic reticulum.[65,66] Calcium signaling can negatively regulate the PTEN protein, a major intrinsic barrier to axon regeneration.[67,68] After inhibiting PTEN expression, it promotes axon regeneration in corticospinal neurons by upregulating mTOR activity.[69,70] As a second messenger, intracellular calcium ions are the key factors affecting functional activities such as migration, proliferation, and differentiation of neural stem cells.[71,72] In addition, calcium influx induces phosphorylation of the transcription factor cAMP response element binding protein (CREB), which can regulate the initiation of transcriptional programs and promote the expression of neuronal genes (i.e.NeuroD1 and Neurogenin1), thus exerting important effects on neurogenesis.[73]
(b) Activation of intracellular signaling pathways, such as FAK and p38 ion channels and ERK, MAPK, PI3K/AKT, and ROCK, and reactive oxygen species (ROS) pathways.[74–76] Phosphorylation of FAK (a junction that bridges integrins and the cytoskeleton) by electrical stimulation further stimulates actin remodeling and downstream

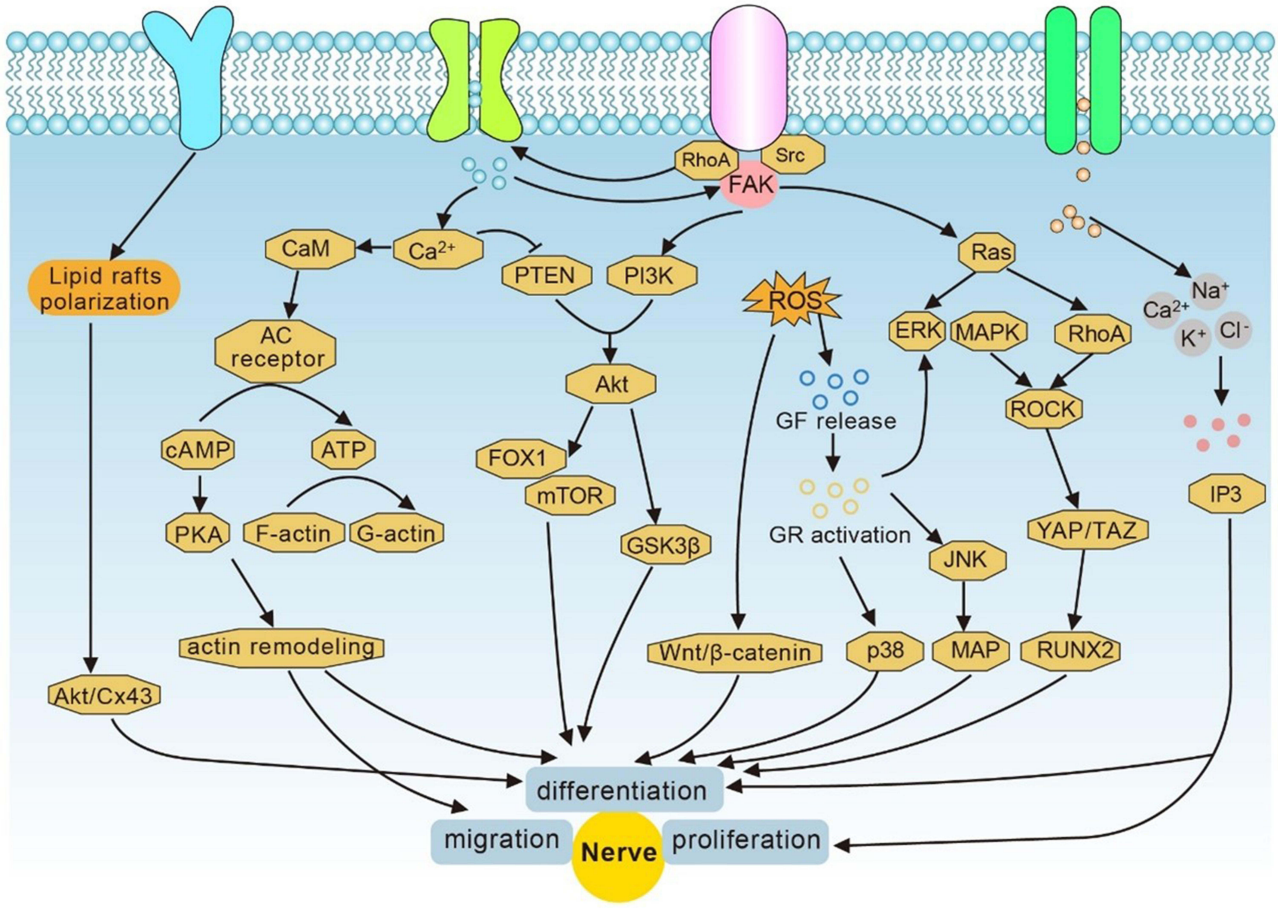


Figure 2 Electrical stimulation acts through intracellular calcium ions, membrane receptors, ATP, ROS, gap junctions, and ECM components, thereby triggering important signaling pathways that regulate nerve cell proliferation, migration, and differentiation.

Abbreviations: gf, growth factor; GR, growth receptor; CaM, calmodulin; AC, adenylate cyclase; cAMP, cyclic AMP; PKA, protein kinase A; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol-3 kinase; PTEN, phospho and tensin homologous protein; Src, steroid receptor coactivator; YAP, yes-associated protein; TAZ, transcriptional coactivator with a PDZ binding motif; ROCK, Rho-associated protein kinase; MAP, microtubule-associated protein; mTOR, mammalian target of rapamycin; FOX1: FOX1: forkhead box protein 1; GSK3β: glycogen synthase kinase-3.

mechanical signaling, such as the MAPK and ERK pathways closely related to neural cell proliferation and differentiation. The subsequent activation of JNK, which is required for neurogenesis, affects neuronal differentiation.[77,78]

(c) Gap junctions: Gap junctions enable neighboring cells to exchange small molecules, and create electrical and metabolic couplings between these cells.[79,80] Electrical stimulation can alter cell gap junctions, affecting the exchange of signaling molecules such as calcium, potassium, cyclic nucleotides, and inositol phosphates, and promote the development and communication of electroactive cells.[81,82]

(d) Extracellular matrix composition: Electrical stimulation can alter ECM composition by affecting proteins, soluble ions, or charged groups, which cause electrophoretic redistribution of cell surface receptors and altered adhesion of adhesion proteins, thereby affecting neurite outgrowth.[83,84]

(e) Electric fields are introduced at the injury site to promote axonal growth and plasticity.[85–87] The use of spinal cord electrical stimulation (ES) to activate or increase the excitability of neuronal networks below the injury directly promotes axon regeneration in the environment by mimicking the action potential of the central nervous system, maintaining the ability of the spinal cord to respond to peripheral stimuli,[88–90] which increases the local synthesis of major proteins in myelin, thereby stimulating myelin induction.[91–94] At the same time, electrical stimulation enhances the expression of neurotrophic factors, such as GDNF, ENO2, and BDNF.[95,96]

Research Progress of Conductive Hydrogel

Hydrogels are three-dimensional structures consisting of a porous polymer network. These materials mimic the extracellular matrix environment, allowing the exchange of nutrients with surrounding tissues, cell migration, and the diffusion of molecules. Hydrogels are characterized by their high water content and controlled release capabilities, making them ideal for implantation.[97] They offer suitable pore sizes, porosity, biocompatibility, low toxicity, adjustable biodegradability, and mechanical properties. Injectable hydrogels, which can be filled into spinal cord injury sites through in-situ gelation, are advantageous for avoiding additional surgical damage.[98,99] Therefore, hydrogels are considered the most suitable scaffold for spinal cord regeneration and neural tissue repair.[100]

Although hydrogels can generate ionic currents through ions dissolved in water, they typically act as electronic insulators, meaning they do not conduct electrons. Under physiological conditions, the electrical properties of hydrogels are generally similar to those of the surrounding tissue medium, and they are far inferior to conventional electronic conductors.[101] One viable approach to enhance the electrical properties of hydrogels is to introduce electronic conductivity alongside their ionic conductivity achieved by incorporating conductive nanomaterials into the polymeric matrix of hydrogels. Consequently, resulting hydrogel composite materials possess both ionic and electronic conductivity while preserving the unique biomechanical advantages of hydrogels. Charge carriers migrate within conductive hydrogels through electronic/hole transport in the polymer network and ionic flow in the porous electrolyte. This movement of electronic/hole carriers induces changes in the polarization of the polymer network, which, in turn, triggers the orientation, migration, and rearrangement of ions in the pore electrolyte of hydrogels. This leads to alterations in the extracellular potential of cell membranes, activating ion channels and initiating the transmembrane flow of ions. Additionally, this process alters the polarization state of neuron cell membranes, initiating a cascade of intracellular signaling pathways.[102] Additionally, hydrogel matrices play a regulatory role in the fate and behavior of neural cells within them, providing favorable conditions for neuroregeneration in treating spinal cord injuries.

To facilitate the repair and regeneration of SCI, researchers have extensively explored other properties of conductive hydrogels besides electrical conductivity. In this respect, Liu et al developed conductive hydrogels with a specific elastic modulus and mechanical strength, enabling them to prevent damage to surrounding residual tissues and maintain the local structure. Moreover, an appropriate elastic modulus (approximately 0.11–1 kPa) can enhance neural stem cell differentiation into neurons and reduce neurogliogenesis.[99] Adequate porosity, permeability, and surface morphology have been found to facilitate material exchange and cell loading, ensuring good swelling properties and the overall stability of the hydrogel.[103] Luo et al grafted dopamine (DA) molecules onto hyaluronic acid (HA) biomolecules to form HA-DA hydrogels, which resulted in HA-based hydrogels with good adhesion properties and stable adhesion to surrounding tissues.[30] Zhang et al designed and prepared conductive hydrogels with good biocompatibility and degradation rates that align with axonal and tissue regeneration. These hydrogels could efficiently degrade in vivo as neural tissues regenerate, preventing long-term presence in the spinal cord tissues, which could impede neural tissue regeneration or cause chronic inflammation or toxicity.[104] Zhao et al prepared PPM hydrogels with significant shear-thinning properties. By adjusting the angular frequency, these hydrogels could be easily injected with a syringe and spontaneously penetrated and filled irregularly shaped areas, owing to their shape memory properties. The reversible non-covalent crosslinking in PPM hydrogels provided remarkable self-healing properties, ensuring structural integrity and prolonging their lifespan.[105] These properties facilitated the rapid injection of hydrogels into the target site, offering the possibility of minimally invasive treatment. Additionally, Chen et al developed a hydrogel based on polyvinyl alcohol (PVA), molybdenum sulfide, and graphene oxide, which exhibited excellent anti-oxidative properties and effectively attenuated ROS, inhibiting the destructive inflammatory response.[106]

The selection of appropriate manufacturing methods and materials plays a critical role in controlling and manipulating the characteristics of hydrogels. Depending on their origin, the most commonly used biopolymer-based hydrogels for SCI scaffolds in current research include natural polymers, synthetic polymers and self-assembled peptides. Natural polymers can be divided into two main categories: protein-based (collagen, gelatin, and matrix gel) and polysaccharide-based (chitosan, alginate, agarose, hyaluronic acid, and methylcellulose).[107] Synthetic polymers are categorized into artificial materials such as methacrylic anhydride and polyethylene glycol.[108] The synthesis of hydrogels can be achieved through

physical and chemical crosslinking methods. Physical crosslinking methods encompass techniques like ion-pairing, complex coacervation, hydrogen bonding, phase transition (either thermal-responsive, involving heating or cooling a polymer solution or crystallization), and hydrophobic interactions. Chemical crosslinking methods involve processes like Michael addition reactions, Schiff base reactions, click chemistry, condensation reactions, crosslinking with aldehydes, thiol-disulfide exchange, radiation crosslinking, free-radical polymerization, photo-induced crosslinking, and enzyme-mediated crosslinking.[109] In terms of design approaches, various hydrogel scaffold designs have been applied and studied in SCI tissue engineering, such as electrospun scaffolds,[110] 3D bioprinted scaffolds,[111] patterned scaffolds, in-situ injectable scaffolds,[98] microfluidic fabrication,[112] and directed microstructures.[113] For injectable conductive hydrogels, the rate of gelation of the material is critical . It is now understood that gelation should neither be too fast, allowing adequate time for injection and filling of the defect site, nor too slow, preventing the hydrogel from flowing out of the lesion. The gelation rate is typically adjusted through chemical or physical cross-linking methods, depending on the type of polymer, its relative molecular mass, concentration, and the type of cross-linking, such as ultraviolet light, pH, and temperature changes.

Currently, conductive hydrogels often employ electrical stimulation to promote neuroplasticity by providing a matrix that guides axonal growth in specific directions, aligning neural cells with fiber axons, and effectively promoting neurogenesis.[114,115] Moreover, they can regenerate damaged tissues by delivering cells, drugs, and/or bioactive molecules, thus bridging these two distinct features.[116] In the following sections, we will discuss recently used conductive biomaterials for constructing conductive hydrogels and their advantages and disadvantages in SCI treatment.

Conductive Hydrogel for Spinal Cord Injury Repair

Over the years, the application of conductive hydrogels for spinal cord injury treatment has gained significant momentum. The conductive nanomaterials used to construct these hydrogels include conductive polymers, carbon-based nanomaterials, phosphorus-based nanomaterials, MXene, and various combinations of these materials. Conductive polymers, such as polypyrrole (ppy), polyaniline, and poly 3,4-ethyl-dioxothiophene, are the most commonly used conductive polymers in the field of biomedical research. They offer good electrical properties and biocompatibility.[117,118] Carbon-based materials, including graphene, reduced graphene oxide (rGO), and carbon nanotubes, are also utilized in the development of conductive biomaterials due to their high electrical conductivity (ranging from 10^3 to 10^4 S/cm) and large surface area, which allows for functionalizing biomolecules and modulating cellular responses.[25] GeP, as an emerging material in the phosphorus-based family, is known for its excellent biocompatibility, degradability, and electrical conductivity, making it a multifunctional nanomaterial suitable for various applications.[119,120]

MXene is, a class of two-dimensional transition metal carbide and nitride materials, combines the electrical conductivity of a transition metal with the physicochemical characteristics of carbon- nitride. Its surface is rich in functional groups, making MXene hydrophilic and highly modifiable for various bioengineering applications. The functionalization of MXene materials has become a research hotspot in recent years.[121,122]

Table 2 provides a comprehensive list of the advantages and disadvantages associated with each of these materials.

Conductive Hydrogels Based on Conductive Polymers

Conductive polymers (CPs) are a class of organic materials that exhibit unique electrical and optical properties similar to inorganic semiconductors and metals. Typically, conductive polymers have conjugated chains with alternating single and double bonds. Due to the highly delocalized and polarizable nature of the π electrons, they can form pathways for charge carriers, allowing electrons to move along the polymer chains.

In recent years, conductive polymers have attracted significant interest as biomaterials in tissue engineering applications because of their physical and chemical properties, ability to transmit electrical signals to cells, and capacity to offer a conducive platform for specific cell responses like cell adhesion, growth, and proliferation. Among the conductive polymers frequently used in spinal cord injury repair are polypyrrole (PPy), polyaniline (PANi), polythiophene(PT), and its derivative, poly(3,4-ethylenedioxythiophene) (PEDOT). These conductive polymers have been widely employed in the development of conductive hydrogel. While these conductive polymers have relatively low intrinsic conductivity, their conductivity can be substantially enhanced through processes such as oxidation (p-doping) or reduction (n-doping),

Table 2 Conductive Biomaterials for Use as Conductive Hydrogels

Conductive Biomaterials		Advantages	Disadvantages	Reference
Conductive polymer	Polypyrrole (PPy)	Easily chemically synthesized, highly stable, adjustable mechanical, high conductivity, highly cellular biocompatible	Irreversible oxidation, may reduce conductivity over time, Insoluble monomer and polymer in water	[21,22]
	Polyaniline(PANI)	Low cost, easy to synthesize, good chemical stability, low toxicity	Poor flexibility, poor degradability, poor processability, low solubility, Poor biodegradability	[23,24]
	Poly (3,4-ethylenedioxythiophene) (PEDOT)	High conductivity when doped, Good biocompatibility/cell adhesion, High stability when doped with PSS	Stability and conductivity require additives or post-processing	[21]
Carbon-based nanomaterials	Reduced graphene oxide (rGO)	High conductivity, good mechanical properties, Good stability, High surface area and good biocompatibility	Less hydrophilic, can aggregate	[25,26]
	Go	Excellent mechanical properties, good chemical stability, large specific surface area, better hydrophilicity, lower toxicity, lower toxicity, easy to functionalize	Low to moderate conductivity, dependent on oxidation, Toxicity not well-known, but dependent on method of synthesis, size, and dose,	
	Single-walled carbon nanotubes	High conductivity, good stability, large surface area and easy to functionalize, functionalized CNTs are easy to blend with other materials	Easy hydrophobic aggregation and difficult uniform dispersal, high hydrophobicity leads to aggregation, inflammation, and toxicity, invasive tubular	[27]
Phosphorus-based nanomaterials	Black phosphorus nanosheets (BP)	High conductivity, excellent biocompatibility, Naturally degradable	Lower stability	[28,29]
	GeP	Highly conductive, Biodegradable, reducing residual and cytotoxicity of biomaterials, Scavenge oxygen free radicals and promotes angiogenesis	As a heavy metal element, germanium needs to be further studied for its metabolism and fate after implantation in the body	[30]
MXene		High conductivity, hydrophilicity, rich modifiability, high biocompatibility, high mechanical properties, giving the hydrogel a rougher surface morphology, promoting cell migration, and reducing ROS production	Poor natural degradability	[31,32]

with dopant ions serving to maintain electrical neutrality. This enhancement enables them to reach the conductivity, range of semiconductors and metals.

PPY

PPy is one of the most commonly used conductive polymers in the treatment of spinal cord injuries. Doped PPy exhibits high conductivity, excellent environmental stability, ease of preparation, and easy modification. Its electrical conductivity can reach up to approximately 10^3 S cm^{-1}, and PPy can be easily synthesized in large quantities using various common organic solvents and water at room temperature. Furthermore, its good biocompatibility can significantly promote the

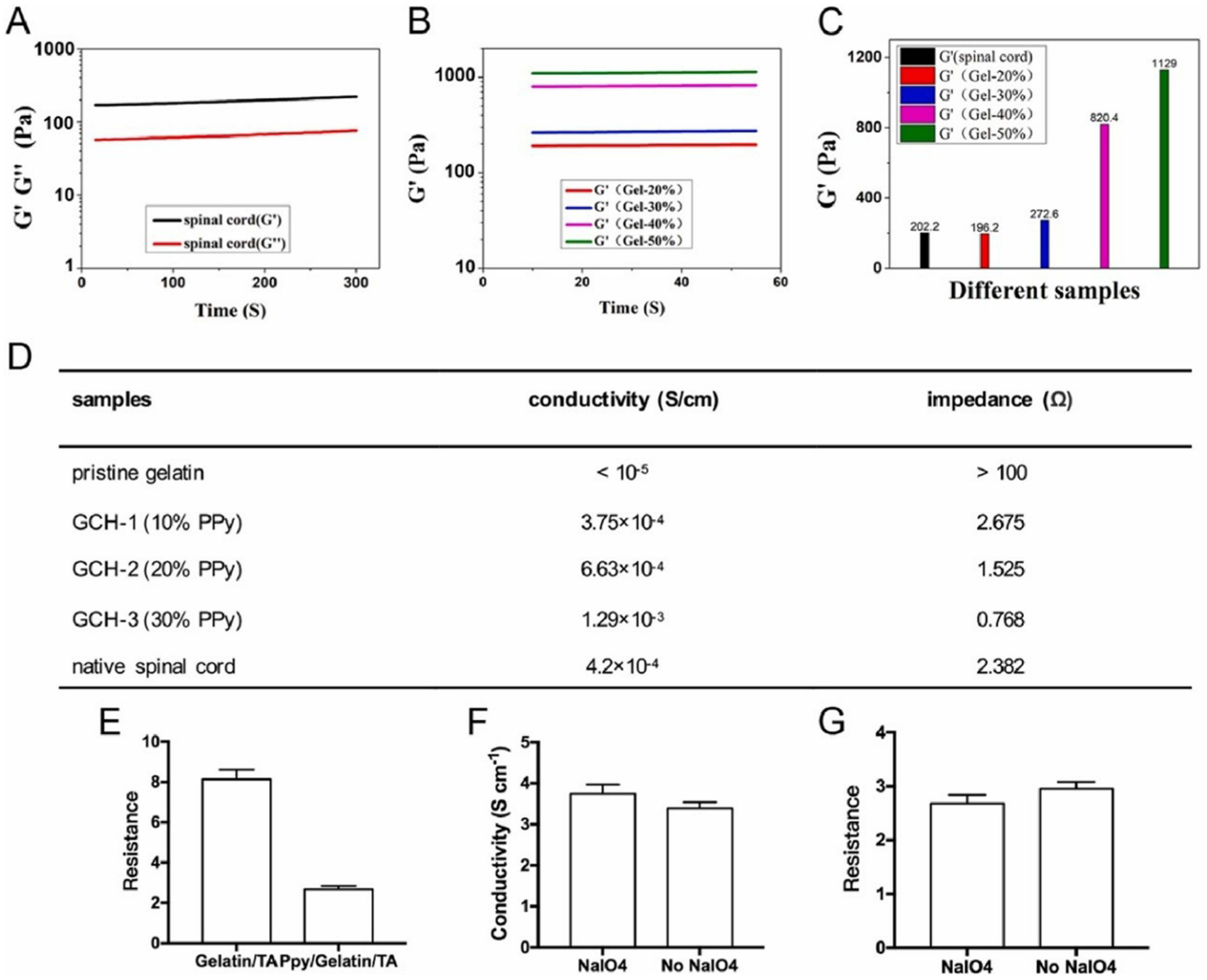
adhesion, proliferation, and differentiation of different types of cells in vitro.[123] At the same time, it can be integrated into materials with large surface areas and different porosity, and can be easily modified by incorporating bioactive molecules, making it suitable for biomedical applications.

Despite the above-mentioned advantages of PPy, it still has some limitations. Previous studies have shown that PPy can be challenging to further process due to its crystalline, mechanically rigid, brittle, and insoluble, nature, which makes it unsuitable for soft natural spinal cord tissue. It can readily trigger stress and induce inflammatory reactions, significantly limiting its application in the field of central nervous system regeneration. To address these issues, researchers have found that PPy's limitations can be mitigated by carefully selecting dopants and optimizing synthesis methods and conditions. A common strategy involves blending PPy with other degradable synthetic or natural polymers, such as PLA, PLGA, PCL, chitosan, and silk fibroin, to create conductive hydrogels. For instance, Xu et al synthesized a shape-recoverable, self-healing conductive hydrogel by utilizing Schiff base reactions, incorporating N-carboxyethyl chitosan (CEC), chitosan-modified polypyrrole (DCP) nanoparticles, and a unique aldehyde-terminated difunctional polyurethane (DFPU) crosslinker. This hydrogel was found to promote the attachment, proliferation, and differentiation of neural stem cells, resulting in remarkable recovery of motor function in brain-injured zebrafish.[124] Huang et al developed a conductive hydrogel by blending collagen with PPy, achieving the most suitable Young's modulus and electrical conductivity similar to spinal cord tissue. Combined with electrical stimulation, this hydrogel led to increased cell proliferation and differentiation into neurons, inhibiting differentiation into astrocytes.[125] It has been established that the electrical signal transmission level in the natural spinal cord is 4.2×10^{-4} S cm^{-1}, and the elastic modulus is 202.2 Pa. Dai et al harnessed PPy's conductivity, gelatin's tissue affinity, and tannic acid's (TA) supramolecular interaction to create a gelatin-based conductive hydrogel (GCH) with mechanical properties and electrical conductivity comparable to the natural spinal cord by controlling the concentrations of gelatin and PPy (Figure 3). By utilizing glutathione (GSH) conjugation, this hydrogel allowed the on-demand release of bFGF in response to the SCI microenvironment. In vivo results showed significant attenuation of matrix metalloproteinases (MMPs) expression, creating a conductive microenvironment that promoted axon regeneration at the injury site, increasing vessel density.[126]

One major challenge in spinal cord injury repair is the secondary injury cascade reactions, including elevated ROS levels, lipid peroxidation, and other oxidative pathological microenvironments.[40] Wu et al developed a conductive hydrogel composed of PPy and methacrylic anhydride (MA)-modified hyaluronic acid and collagen. The incorporated PPy within the matrix demonstrated antioxidant properties, helping to regulate the oxidative pathological microenvironment, protect exogenous cells from oxidative damage, and maintain electrical signals. The hydrogel also facilitated the delivery of exogenous stem cells to the lesion site, restoring the transmission of endogenous electrical signals.[127]

Importantly, the spinal cord transmits information in the form of electrical impulses along highly conductive nerve fibers. Endogenous bioelectrical signals are essential for maintaining neuronal function and axonal growth. Therefore, the design and fabrication of scaffolds for spinal cord regeneration should mimic the highly conductive properties of the spinal cord. Zhou et al used tannic acid (TA) as a dopant and crosslinking agent to prepare a conductive hydrogel with polypyrrole as the backbone. Compared with the traditional conductive hydrogel, this hydrogel synthesized a polymer without insulation due to PPy's natural crosslinking with tannic acid through intermolecular interactions, resulting in good conductivity. Implanted highly conductive hydrogel bridges in a severe mouse spinal cord injury model promoted neuronal differentiation, inhibited astrogliogenesis and promoted endogenous neurogenesis, leading to functional recovery by restoring disrupted spinal cord circuits.[128]

The pathological microenvironment after spinal cord injury can impair the electrical signal transmission of living nerve cells in the lesion, disrupt the electrical connection of the injured spinal cord, and ultimately destroy the neural circuit. To address this issue, Yang et al developed an agarose/gelatin/poly pyrrole (Aga/Gel/PPy, AGP3) hydrogel with similar electrical conductivity and modulus to those of the spinal cord. The physical crosslinking method employed makes it suitable for injection. In vivo studies have shown that AGP3 hydrogels could provide a suitable microenvironment for the migration and differentiation of neural stem cells, which could significantly promote endogenous neurogenesis and reduce the formation of glial fibrosis. SCI mice exhibited significant functional recovery based on functional assessments of Basso-Beattie-Bresnahan (BBB) scores, footprint tests, and inclined plane test (IPT) scores. Further



D

samples	conductivity (S/cm)	impedance (Ω)
pristine gelatin	$< 10^{-5}$	> 100
GCH-1 (10% PPy)	3.75×10^{-4}	2.675
GCH-2 (20% PPy)	6.63×10^{-4}	1.525
GCH-3 (30% PPy)	1.29×10^{-3}	0.768
native spinal cord	4.2×10^{-4}	2.382

Figure 3 Optimizing GCHs with spinal cord-like mechanical property and conductivity. (**A**) Time sweep of the native spinal cord (frequency = 1 Hz, temperature = 37°C). (**B**) Time-dependent G' of hydrogels with different gelatin concentrations. (**C**) G' comparison of the natural spinal cord and different hydrogels. (**D**) Electrical conductivity and impedance of pure gelatin, three GCHs, and the native spinal cord. (**E**) Resistance of conductive and non-conductive hydrogels. (**F**) Conductivity of GCHs with or without 50 mM $NaIO_4$. (**G**) Resistance of GCHs with or without 50 mM $NaIO_4$.

Notes: Reprinted from *Biomaterials*, 288, Fan CX, Yang W, Zhang LL, et al Restoration of spinal cord biophysical microenvironment for enhancing tissue repair by injury-responsive smart hydrogel. Copyright 2022, with permission from Elsevier.[126]

analysis using RNA-sequencing revealed that the AGP3 hydrogel significantly notably regulated the expression of genes related to neurogenesis through an intracellular Ca^{2+} signaling cascade. Moreover, the incorporation of electroactive materials amplifies the weak local electric field generated by the cell membrane, thus creating a transmembrane voltage gradient that influences the inflow of ions across the cell membrane. Consequently, intracellular signaling significantly impacts the proliferation and differentiation of neural stem cells (Figure 4).[21]

PANI

Polyaniline is another commonly used conducting polymer, which can be synthesized chemically or electrochemically from the monomeric aniline. Similar to PPy, PANI boasts high environmental stability, cost-effectiveness in synthesis, and the ability to transition between conductive and resistive states, as well as various structural forms. However, the drawbacks of polyaniline and its derivatives in the field of biological tissue engineering primarily pertain to their limited cytocompatibility, processability, flexibility, and non-biodegradability, which can result in chronic inflammation and pain.[129] Furthermore, as hydrogels swell under physiological conditions, ionic or physically loaded PANI may leach out, resulting in decreased conductivity and toxicity.

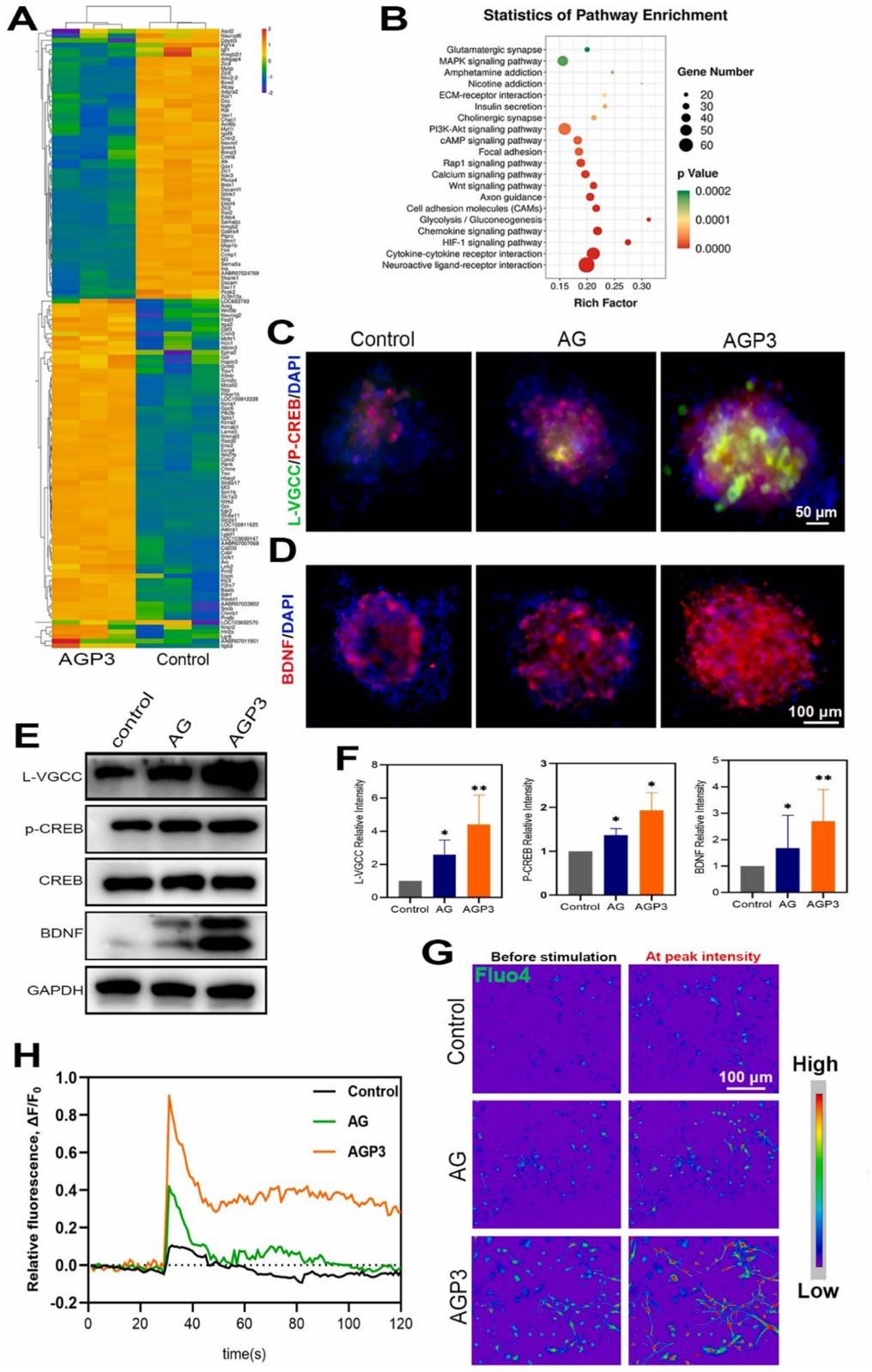


Figure 4 Investigations of RNA-seq and assessments of intracellular calcium involved in neurogenesis. (**A**) Heat map of neurogenesis-related gene expression. (**B**) The gene enrichment KEGG pathway analysis. (**C** and **D**) Immunofluorescence images of L-VGCC, p-CREB and BDNF in each group on day 7. (**E**) WB analysis of L-VGCC, p-CREB and BDNF. (**F**) Quantitative analysis of L-VGCC, p-CREB and BDNF. (**G**) Pseudo-color pictures of representative calcium images before and after glutamate stimulation. (**H**) Image-derived fluo-4 intensity measurements over time in NSCs.

Notes: Reprinted from *Acta Biomaterialia*, 15, Yang B, Liang C, Chen D, et al A conductive supramolecular hydrogel creates ideal endogenous niches to promote spinal cord injury repair. 103–119. Copyright 2022, with permission from Elsevier.[21]

Liu et al addressed these issues by creating an electroactive hydrogel based on poly amino acid and electroresponsive polyaniline. It has been established that polyamino acid possesses excellent characteristics such as biocompatibility, safety after degradation, non-toxicity, and ease of modification, which mitigates the challenges associated with using PANI in neural tissue engineering. Implanting this hydrogel into a rat model of spinal cord injury and applying electrical stimulation, led to the inhibition of astrocyte proliferation, prompting damaged neural stem cells in the spinal cord to differentiate into neurons and stimulating endogenous neurogenesis. Evaluations through footprint tests and the BBB score demonstrated that the electroactive hydrogel, when combined with electrical stimulation, significantly enhanced the recovery of motor function in spinal cord injury rats. Histological and ultrastructural observations confirmed that the damaged area predominantly comprised newly generated neuronal cells, regenerated myelin, and axons.[130]

PEDOT

A third common conjugated polymer is poly(3,4-ethylenedioxythiophene) (PEDOT), a polythiophene (PTh) derivative. Compared to PPy, PEDOT offers superior electrical conductivity and chemical stability. However, its low solubility makes it challenging to uniformly disperse in water. Typically, polystyrene sulfonate (PSS) is used as a dopant and templating agent to enhance the water solubility and stability of PEDOT. Nonetheless, the disadvantages of PSS, such as its insulating properties, hydrophilicity, and strong acidity, limit its applicability in tissue engineering. To overcome these limitations, researchers synthesized PEDOT nanoparticles (NPs) through chemical oxidative polymerization within microemulsions. These NPs can be uniformly integrated into hydrogel-based scaffolds, substantially increasing the electrical conductivity of the scaffolds to $8.3\times10^{-4} \pm 8.1\times10^{-5}$ S/cm without biocompatibility issues.[131] Gao et al introduced sulfonated lignin (LS) as a dopant, which not only improved the dispersion and conductivity of PEDOT but also demonstrated the excellent biocompatibility of the synthesized PEDOT: LS. The conductive hydrogel prepared by 3D bioprinting simulated the composition of spinal cord ECM with gelatin and hyaluronic acid, promoted the growth and adhesion of nerve cells, and its conductivity was comparable to that of spinal cord white matter (0.60 S m−1). At the same time, it simulated the structure of the parallel arrangement of the white matter of the spinal cord, facilitating the orderly parallel growth of new neurofilaments along the bioprinted scaffold, thus enabling efficient spinal cord injury repair.[104] Moreover, Song et al advanced the bioinks for 3D bioprinted conductive hydrogel scaffolds. By integrating PECT (PEDOT: CSMA, TA) with a photocrosslinked gelatin/polyethylene glycol physical gel (GP) matrix, followed by a cooling process, they achieved optimal shear-thinning behavior and suitable rheological properties. This design bolstered cell-cell and cell-matrix interactions within a conductive microenvironment, enhancing the therapeutic effect of neural stem cells and promoting nerve regeneration in spinal cord injury repair.[132]

Hydrogels formed with conductive polymers have attracted significant interest in recent years. Through the modification and amalgamation of various substances, they offer an appropriate microenvironment conducive to the healing and rejuvenation of spinal cord injuries. Importantly, as biomaterials degrade over time, ensuring enduring electrical stability poses a crucial challenge that demands further exploration in the future.

Conductive Hydrogels Based on Carbon-Based Materials

Numerous studies have demonstrated the excellent physicochemical and mechanical properties, as well as substantial electrical conductivity (ranging from 10^3 to 10^4 S/cm), of carbon-based nanomaterials. These properties enable these materials to facilitate axon regeneration and encourage stem cell differentiation via neural electrical signals within spinal cord tissue. Their large surface area is advantageous for functionalizing biomolecules and modulating cellular responses. However, the presence of peripheral hydrophobic groups limits their interaction with hydrophilic polymers. To address these limitations, researchers have either modified the surface of nanomaterials with various polar functional groups, such as -OH, -NH_2, and carboxyl (-COOH), or enhanced their dispersion by grafting different polymer chains. Conjugated and modified carbon-based nanomaterials, including graphene and its derivatives and carbon nanotubes (CNTs), have shown significant potential in the context of nerve regeneration.

Graphene

Graphene is a two-dimensional material composed of a single layer of carbon atoms arranged in a hexagonal honeycomb lattice. Its distinct structure and geometry account for its exceptional physicochemical properties, including high fracture strength, a high Young's modulus, excellent thermal and electrical conductivity, a large specific surface area, and

biocompatibility.[133] While graphene exhibits biocompatibility as an immobilizing surface for neuronal growth and can induce human neural stem cells (hNSCs) to differentiate more towards neurons while preventing their differentiation into glial cells,[134–136] its smoothness, chemical inertness, and lack of biological cues hinder its use as a conductive material for synthesizing conductive hydrogels. To address these limitations, researchers have modified graphene and its derivatives to form nanocomposites. For example, Agarwal et al developed collagen-based cryogels utilizing amino-functionalized graphene nanocrosslinkers. The addition of amino-functionalized graphene improved the order and crosslinking degree of collagen molecules in the cryogel, resulting in sufficient porosity and interconnectivity that facilitated cell penetration and unimpeded nutrient transfer, necessary for accelerated axon regeneration.[137] The implantation of 0.5% w/v graphene collagen cryogel into the injured spinal cord promoted cell proliferation from proximal to distal, enhanced the secretion of immune regulators, established neural connections, and facilitated spinal cord regeneration and repair of injuries.[103]

Graphene oxide (GO), the main derivative of graphene,[138] contains carboxyl groups (-OOH) on the edges of its structure, with epoxy groups (-O) and hydroxyl groups (-OH) on the basal plane. The negatively charged carboxylate groups increase colloidal stability and hydrophilicity, rendering them more conducive to nerve cell surface attachment, proliferation, and differentiation. Over the years, graphene oxide GO has been extensively used in neural engineering due to its outstanding electrical properties and affinity for neural cells.[139] Studies have shown that GO can promote the differentiation of neural stem cells, sustain the survival of neurons, accelerate the growth of neurons, and enhance neuroelectric properties.[140] Zhang et al developed a supramolecular conductive hydrogel by crosslinking graphene oxide and diacerein-functionalized four-arm polyethylene glycol. The presence of GO imparted high electrical conductivity to the hydrogel, which facilitated neuron growth and axon myelination. The incorporation of the anti-inflammatory drug diacerene provided a sustainable anti-inflammatory environment for spinal cord injury repair. In vivo experiments in rat models confirmed evident spinal cord regeneration.[141] However, the electrical conductivity and mechanical strength of graphene oxide were reduced due to high vacancy defects and hole defects caused by the presence of functional groups. In response, Chen et al developed a composite hydrogel using polyvinyl alcohol (PVA) and molybdenum sulfide/graphene oxide (MoS_2/GO) nanomaterials (Figure 5). The defects in GO were leveraged to enhance fast electron transfer and high

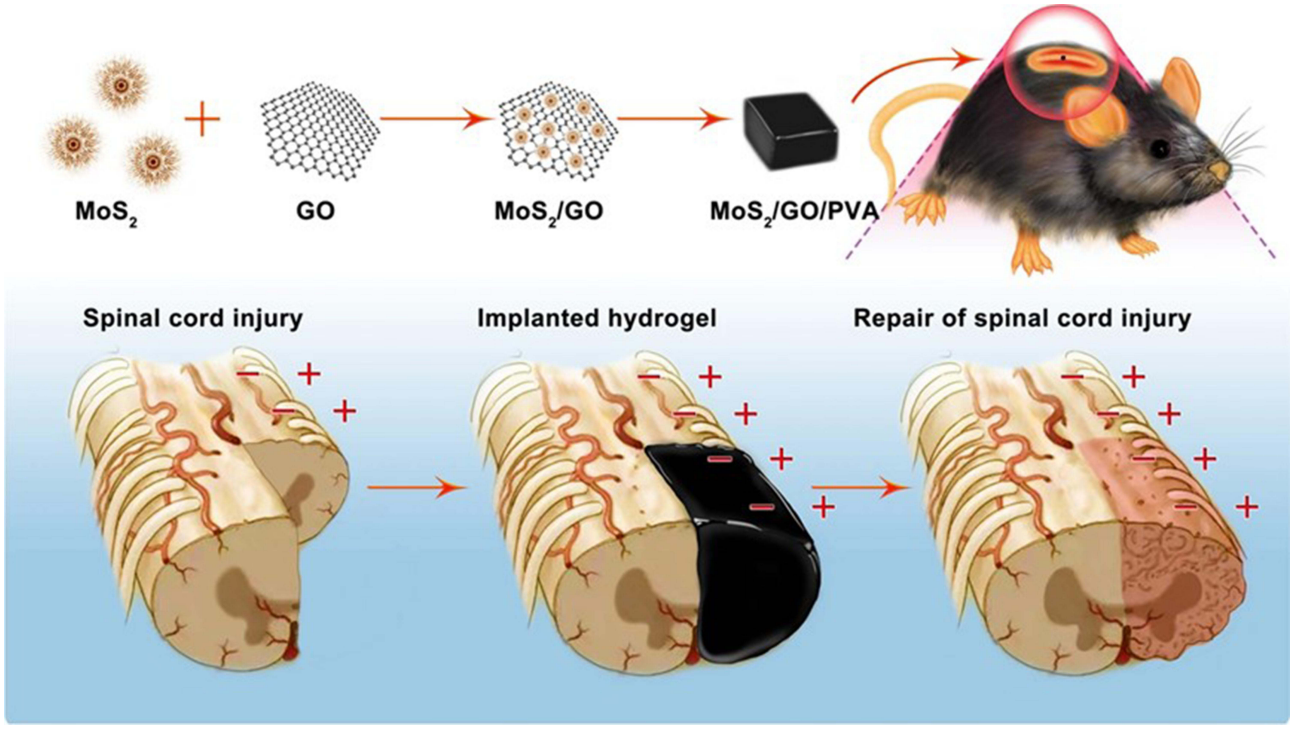


Figure 5 The schematic diagram shows the preparation steps of MoS2/GO/PVA nanocomposite hydrogel and the treatment process of mouse SCI.
Notes: Reprinted from *Journal of Nanobiotechnology*, 20, Chen LL, Wang WS, Lin ZF, et al Conducting molybdenum sulfide/graphene oxide/polyvinyl alcohol nanocomposite hydrogel for repairing spinal cord injury. Copyright 2022, with permission from Spring Nature. Creative Commons.[106]

electrical conductivity after reacting with MoS_2. This combination effectively promoted the differentiation of neural stem cells into neural cells. Additionally, the mechanical properties of PVA were improved by the addition of MoS_2 and GO conductive nanoparticles, resulting in a lower elastic modulus that reduced growth resistance after spinal cord injury and significantly increased the proliferation rate of neural stem cells. The results demonstrated that implantation of the composite hydrogel promoted the repair of spinal cord tissue and enhanced the motor function of injured mice.

rGO is a structural intermediate between graphene and GO that can be synthesized in large quantities from GO through various reduction conditions. Compared with GO, the reduction of oxygen-containing functional groups and the restoration of π-π bonds in rGO result in increased conductivity. The remaining oxygenated groups can also be further modified or functionalized, enhancing rGO's performance in both organic and aqueous environments. In the realm of neural tissue engineering, rGO boasts several advantageous attributes, including electrical conductivity, biocompatibility, biodegradability, antibacterial properties,[142] and pro-angiogenic characteristics.[143] Ankor et al demonstrated that rGO is biocompatible with neurons and glial cells in vivo. Reduced graphene oxide could adhere to cells and induce cell migration based on the π-π interaction between reduced graphene oxide and cells.[144] Serrano et al explored microfiber-shaped rGO materials (rGO-MF), revealing their potential in promoting nerve cell regeneration and the possibility of aiding axon and blood vessel regeneration in injured spinal cords.[145] Xue et al prepared a conductive, porous, soft gel scaffold for spinal cord injury repair using xanthan gum and rGO. The gel scaffold exhibited an elastic modulus and high electrical conductivity similar to spinal cord tissue, as well as a 3D porous structure mimicking extracellular matrix, providing growth space and nutrient transport channels for spinal cord tissue regeneration. The endogenous bioelectrical signals generated by this scaffold, along with the required electric field for nerve cell growth, enhance nerve differentiation into neurons. Additionally, the π-π interaction between rGO and amino acids on cell membranes facilitates nerve cell adhesion within the scaffold. Both in vitro and in vivo experiments confirm the ability of the conductive hydrogel to inhibit astrocyte proliferation around the spinal cord injury area and promote motor function recovery in rats with spinal cord injuries.[146]

Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical nanostructures arranged in single-walled or multi-walled nanotubes composed of a lattice of carbon atoms. Carbon nanotubes exhibit unique properties such as flexibility, electrical conductivity, mechanical strength, and ease of functionalization, making them well-suited for interaction with electrically active tissues. Current studies suggest that carbon nanotube substrates can support neuron survival and promote the growth of neuronal processes,[147–149] and the high conductivity of carbon nanotubes improves the transmission efficiency of neuronal electrical signals. For example, hippocampal neurons grown on CNT substrates showed increased spontaneous synaptic activity and firing frequency.[150] CNTs can also facilitate synaptogenesis and, thus, neural connectivity of neural circuits.[151,152] However, a significant drawback of carbon nanotubes is their insolubility in water, leading to aggregation and cytotoxicity in the central nervous system. This aggregation can trigger inflammation, excessive production of ROS, mitochondrial dysfunction, and impaired synaptic plasticity. To address this issue, Sang and colleagues used a multifunctional crosslinking agent to polymerize single-walled carbon nanotubes, forming a thermosensitive hydrogel. The inclusion of dodecylamine, an amphiphilic coupling agent, and long hydrophobic alkyl chains stabilizes carbon nanotubes and promotes SH-SY5Y cell and neurite outgrowth when coupled with in vitro electrical stimulation. This SWNT-PNIPAAM hydrogel enhances neural tissue regeneration and reduces scar formation in a spinal cord injury model.[153] In addition, Koppes and colleagues investigated the synergistic effects of electrical stimulation when combined with conductive 3D hydrogels. They found that SWCNTs loaded at various concentrations promoted neurite outgrowth. Interestingly, 20 μg/mL displayed the most significant advantages, particularly regarding total neurite outgrowth and the longest neurite length. Lower concentrations of more dispersed SWNTs increased electrical conductivity and did not significantly impact the elastic modulus, highlighting the dose-independent advantages (Figure 6). Combining these nanomaterial-loaded hydrogels with electrical stimulation further enhanced neurite length.[154]

The low solubility of carbon nanotubes makes it challenging for non-functionalized carbon nanotubes with high conductivity to disperse in aqueous polymer solutions. Existing studies have attempted to modify carbon nanotubes with various functional groups, including hydroxyl, carboxyl, and amino groups. However, traditional carbon nanotube functionalization processes often resulted in the destruction of the sample, causing defects and reducing electrical

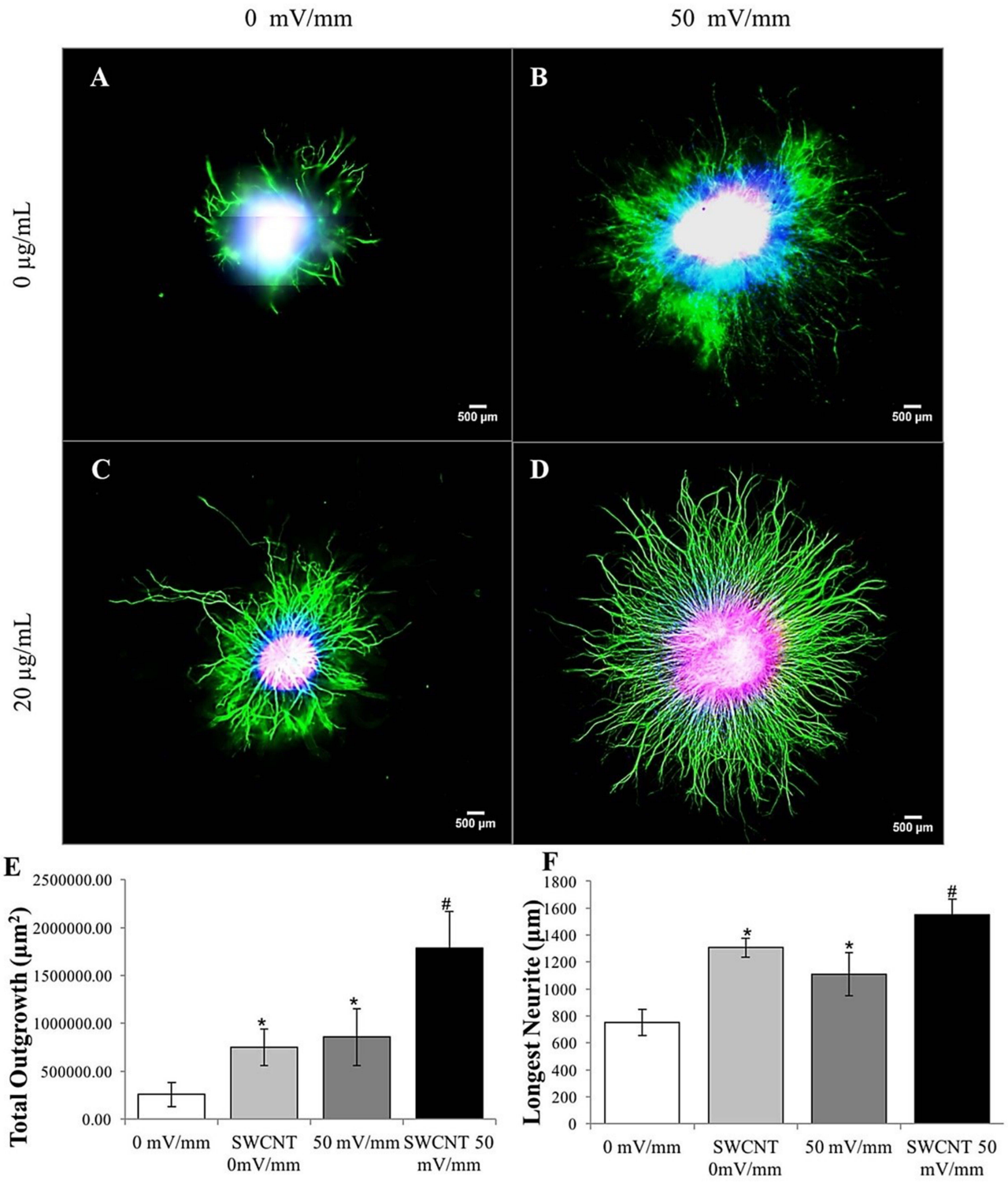


Figure 6 Electrical stimulation enhances neurite outgrowth in SWCNT composite hydrogels. (**A**) DRG cultured in nanomaterial-free hydrogel and without electrical stimulation. (**B**) DRG cultured in nanomaterial-free hydrogel but using electrical stimulation (50 mV/mm, 8h, 1mA). (**C**) DRG cultured in hydrogels with 20 µg/mL SWCT without electrical stimulation. (**D**) DRG cultured in hydrogels containing 20 µg/mL SWCNTs and using electrical stimulation (50 mV/mm, 8h, 1mA). (**E**) DRG using electrical stimulation (50 mV/mm, 8h, 1mA) and cultured in hydrogels containing 20 µg/mL SWCNT had the largest total neurite outgrowth compared with the other three control groups. (**F**) DRG using electrical stimulation (50 mV/mm, 8h, 1mA) and cultured in hydrogels containing 20 µg/mL SWCNT had the longest neurite length compared with the other three control groups. Green = β-III-Tubulin neurites, Red = Phalloidin actin, Blue = DAPI nuclei, Bar = 500 µm, 20x. * = $p < 0.05$ compared to all conditions, # = $p < 0.05$ compared to all conditions, n = 3, standard error shown.

Notes: Reprinted with permission from *Acta biomaterialia*, 39, Koppes AN, Keating KW, McGregor AL, et al Robust neurite extension following exogenous electrical stimulation within single walled carbon nanotube-composite hydrogels. 34–43. Copyright 2016, with permission from Elsevier.[154]

conductivity. Inspired by mussel foot proteins.[155] Inspired by mussel podiacin, Shin et al combined and efficiently dispersed single-walled carbon nanotubes and PPy into catechol-functionalized HA hydrogels via oxidative catechol chemistry. This approach created a biocompatible, dynamic, and conductive 3D extracellular matrix for neuronal regeneration. The formation of HA-CA hydrogels overcame the difficulties in uniformly dispersing non-functionalized conductive materials, such as oxidized PPy and/or CNTs, within 3D HA hydrogels.[156,157] Experimental results indicated that the conductive 3D environment provided by the CNT/PPy-containing HA-CA hydrogel promoted neurogenesis in human stem cells by increasing the expression of functional calcium channels (Cav1.2) and intracellular calcium levels.[158]

While conductive hydrogels based on carbon-based materials hold promise for spinal cord injury repair and regeneration, more extensive safety assessments are essential for their future clinical application. These assessments should explore long-term toxicity, genotoxicity, biodegradation, distribution, metabolism, and organ accumulation.

Conductive Hydrogels Based on Phosphorus-Based Materials

Conductive hydrogels based on phosphorus-based materials offer significant advantages in the context of spinal cord injury repair. Unlike conventional conductive materials such as conductive polymers and carbon nanomaterials, phosphorus-based conductive hydrogels provide the high conductivity required for nerve tissue regeneration while gradually degrading alongside the regeneration of new nerve tissue, leaving no foreign body residues.[159] In recent years, phosphorus-based 2D nanomaterials, such as black phosphorus(BP), silicon phosphide, and germanium phosphide (GeP), have attracted significant attention for applications in nerve repair and regeneration.[160,161] Black phosphorus, which has a similar structure and properties to graphene, boasts a high conductivity of up to 300S/M and offers both conductivity and degradation characteristics.[162] Moreover, being an allotrope of phosphorus, a basic element of the human body, it can naturally degrade into non-toxic phosphorous acid, phosphate, and other PxOy substances under physiological conditions, ensuring good biocompatibility.[163] Silicon Phosphorus (Si P) introduces biologically active silicon elements; in addition to providing conductivity and degradability, it promotes angiogenesis. Germanium phosphorus has a narrower band gap, larger charge carrier mobility, and higher conductivity.[164] The inclusion of silicon and germanium effectively slows down the oxidation process. To enhance the biostability and biocompatibility of GeP nanosheets, Xu and colleagues doped polydopamine (PDA)-modified GeP nanosheets into a hyaluronic acid hydrogel matrix. In this system, PDA improved the stability of GeP nanosheets, while dopamine molecules grafted onto HA biomolecules endowed the hydrogel with excellent tissue adhesion properties. This injectable hydrogel, crosslinked using horseradish peroxidase (HRP)/H_2O_2 as an initiator system, enhanced neuron-directed differentiation of neural stem cells in vitro. In a rat model of complete spinal cord injury, the implantation of this hydrogel promoted immune regulation, reduced local inflammatory responses, facilitated endogenous angiogenesis and NSC neurogenesis, and significantly improved motor function recovery.[30] The unique advantages of phosphorus-based materials, such as their biocompatibility, conductivity, and degradability, position them as promising candidates in the field of spinal cord injury repair. Given that phosphorus-based conductive materials are natural constituents of the human body, they offer inherent degradation properties. However, long-term studies are warranted to assess whether excessive phosphate ions in the body could lead to phosphate poisoning and the loss of other essential metal ions, such as calcium and magnesium.

MXene-Based Conductive Hydrogels

MXenes represent a new class of 2D materials consisting of nitrides, carbides, and carbonitrides of transition metals,[165] with the general formula Mn+1Xn (n=1–3), where M is an early transition metal (eg Sc, Ti, Zr, Hf, V, Nb, Ta, Cr, Mo) and X is carbon or nitrogen.[166] These materials offer rich physical and chemical properties and functionalities, owing to the various types and quantities of transition elements and the diverse functionalizations they undergo. MXenes combine the metallic conductivity of transition metal carbides/nitrides with the hydrophilicity of their hydroxyl/oxygen/fluorine-terminated surfaces in the presence of intact metal atomic layers and abundant surface functional groups.[167] This endows MXenes with fascinating properties such as good electrical conductivity,[168] antibacterial properties,[169] hydrophilicity,[170] degradability[171] and biocompatibility.[172] Notably, MXene's increased hydrophilic groups make it more amenable to surface modifications,[173,174] rendering it well-suited for diverse applications in spinal cord injury repair. Yu et al successfully developed hydrogels using phytic acid (PA), polyvinylpyrrolidone (PVP), and MXenes, offering properties like

injectability, conductivity, adhesion, and self-healing capabilities. The electrically stimulating microenvironment enabled by MXenes triggers the MEK/ERK signaling pathway, leading to increased secretion of nerve regeneration-related cytokines and eventual promotion of spinal nerve regeneration (Figure 7). In vivo experiments have further verified that hydrogels containing MXene groups create an optimal microenvironment that accelerates nerve regeneration, angiogenesis, remyelination, axon regeneration, and calcium channel activation.[105] To achieve targeted neuronal growth, Cai et al designed a composite hydrogel of gelatin methacrylate (GelMA) and MXene with a microgroove structure, which effectively promoted the adhesion, proliferation, and targeted differentiation of NSCs, attributed to MXene's excellent electrical conductivity.[175] In addition, MXenes and their derivatives can be effectively integrated or hybridized with various materials, including metals, graphene and its derivatives, carbon dots, MOFs, and CNTs, to enhance their overall performance and functionality.[176] Kong et al combined gold nanoparticles (AuNPs) and MXene, harnessing the good electrical conductivity and biocompatibility of metal nanoparticles (AuNPs), as well as the characteristics of promoting the differentiation of NSCs and the growth of neurons. Coupled with the anti-oxidative ability of MXene to reduce the inflammatory response in the spinal cord injury area, an MAu-GelMA hydrogel loaded with NSCs combined with ES was constructed (Figure 8). The experimental results showed that MAu-GelMA hydrogel could reduce the accumulation of inflammatory cells by scavenging ROS, creating a more suitable microenvironment for NSC growth in the injured area compared to the MXene-GelMA control group. Combined with electrical stimulation, it further promoted the differentiation of NSCs into neural cells and reduced the generation of glial scars, thereby improving the establishment of intercellular synaptic connections and promoting the functional recovery of SCI.[177]

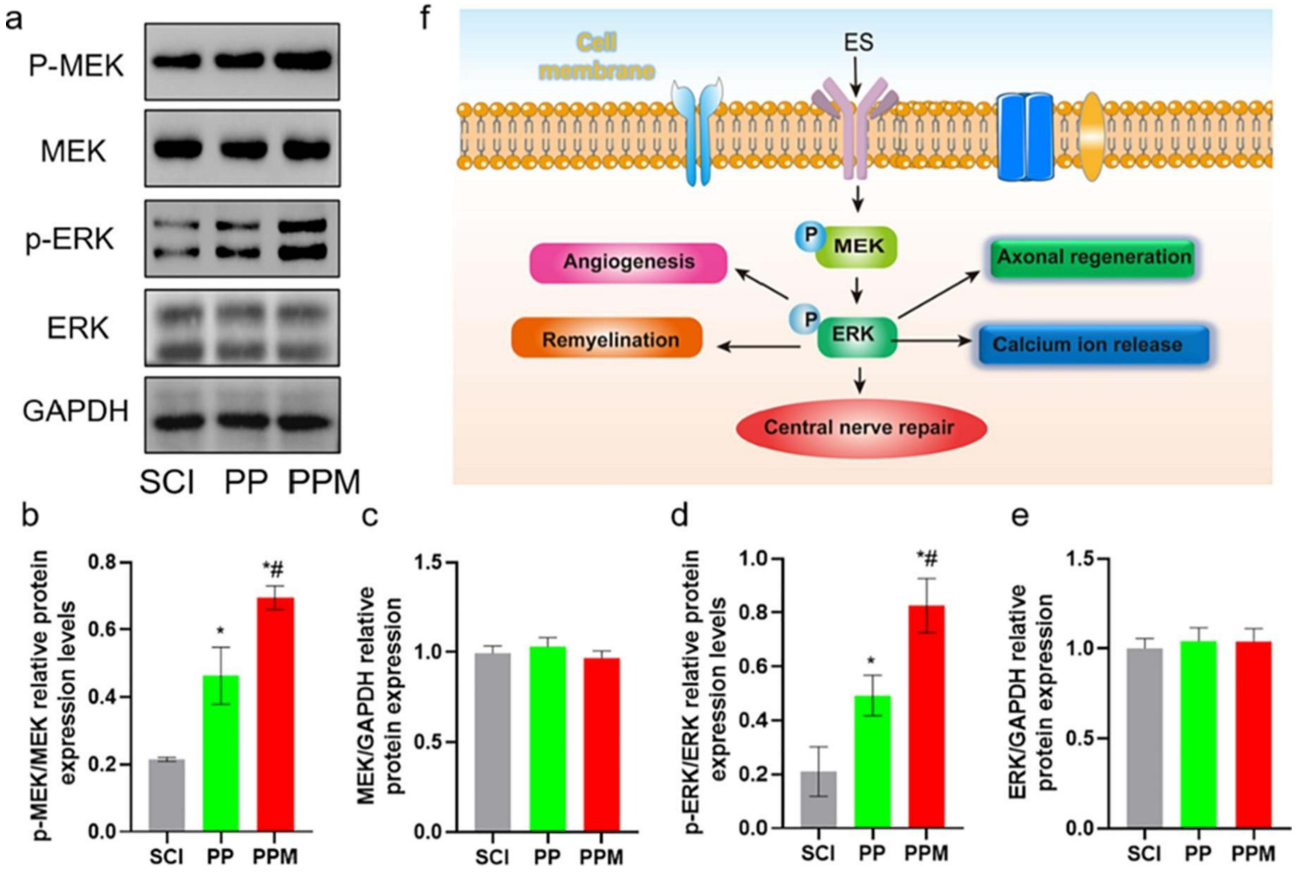


Figure 7 Possible molecular mechanisms of PPM hydrogel promoting spinal cord regeneration. (**a**) Western blot analysis of regenerated nerves in SCI, PP and PPM groups; (**b**) p-MEK/MEK relative protein expression level analysis; (**c**) MEK/GAPDH relative protein expression level analysis; (**d**) p-MEK/MEK relative protein expression level analysis; (**e**) ERK/GAPDH relative protein expression level analysis; (**f**) Possible molecular mechanisms of PPM hydrogel promoting spinal cord regeneration; *: $P < 0.05$ compared with SCI group; #: $P < 0.05$ compared with PP group; n = 5.

Notes: Reprinted with permission from *Chemical Engineering Journal*. Yu QN, Jin SC, Wang SC, Xiao HN, Zhao YT. Injectable, adhesive, self-healing and conductive hydrogels based on MXene nanosheets for spinal cord injury repair. Copyright 2022, with permission from Elsevier.[105]

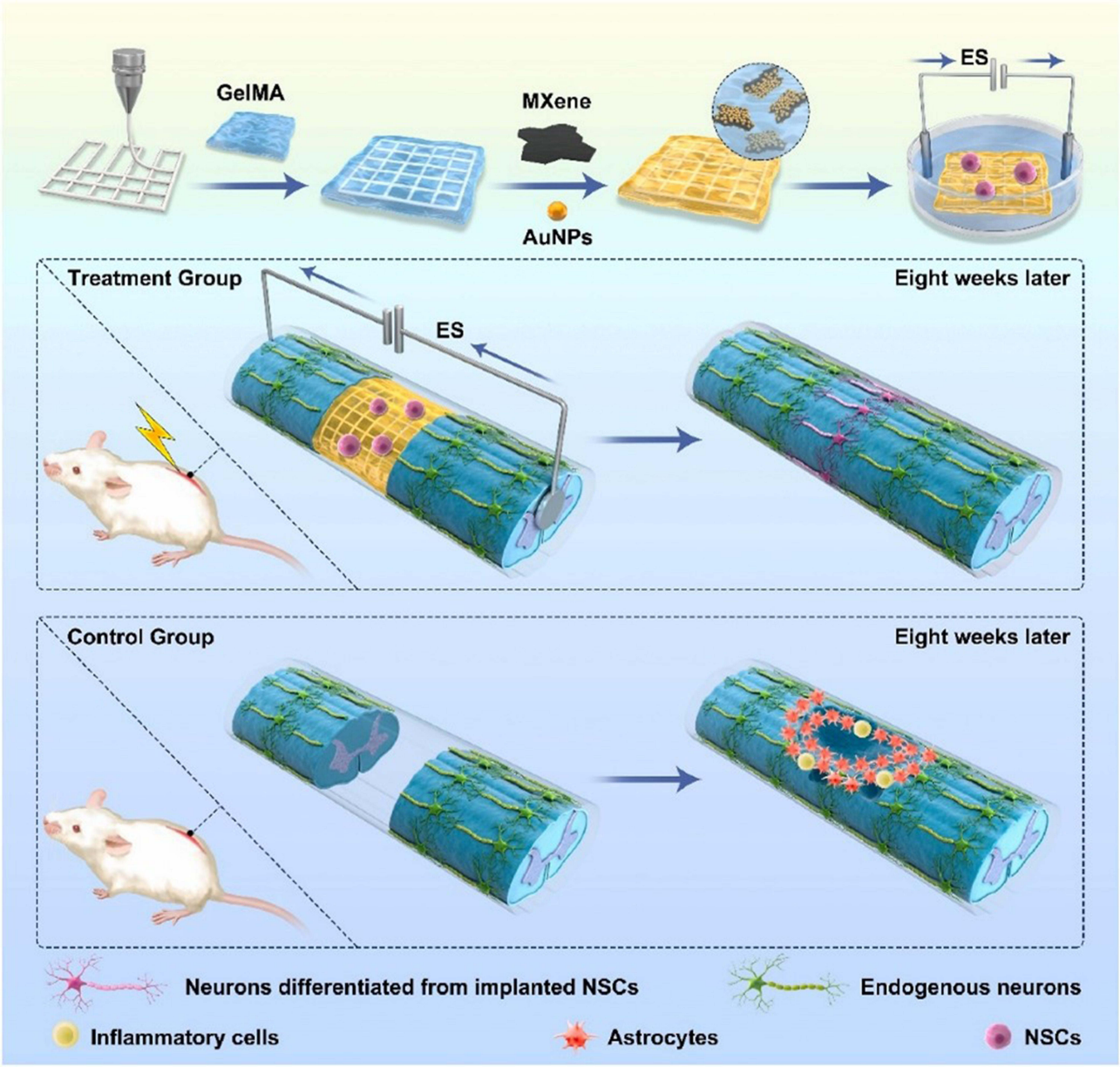


Figure 8 A novel multifunctional hydrogel containing MXene-Au composite and NSCs combined with electrical stimulation therapy was constructed to promote motor function recovery after SCI in rats. The combination of MAu-GelMA with NSCs and ES could promote the proliferation and differentiation of NSCs and stimulate the growth of nerve cell synapses.

Notes: Reprinted from *Ceramics International*, 49, Kong WJ, Zhao YL, Yang XY, et al Combined treatment using novel multifunctional MAu-GelMA hydrogel loaded with neural stem cells and electrical stimulation promotes functional recovery from spinal cord injury. 20623–20,636. Copyright 2023, with permission from Elsevier.[177]

Benefiting from its excellent conductivity and diverse surface functional groups, MXene holds the potential to serve multiple roles within conductive hydrogels. The development of improved design and preparation methods for MXene composite hydrogels, addressing drawbacks such as poor dispersion and rapid oxidation,[178] is expected to pave the way for their application in the repair and regeneration of spinal cord injuries.

Conclusions and Prospects

The process of repairing and regenerating spinal cord injury is a multifaceted one influenced by numerous factors. Despite extensive research in this area, no single therapeutic approach has yet emerged to achieve full motor and sensory

recovery after a spinal cord injury. A promising avenue involves integrating regenerative medicine and rehabilitation approaches to stimulate the regeneration of neural pathways and facilitate functional rehabilitation post-SCI. This comprehensive approach encompasses regenerative medicine[179] (eg, cells, drugs and bioactive molecules, biomaterials) and rehabilitation therapies (eg, motor training, electrical stimulation). While rehabilitation therapies have demonstrated positive results in previous clinical studies, their effectiveness diminishes in cases where the injury is severe and significant neural tissue loss has occurred. On the other hand, regenerative medicine approaches, relying on cells, drugs, and bioactive molecules, face their own set of limitations, such as constraints on cell sources, challenges in cell culturing, and difficulties ensuring cell survival following implantation.[120] While capable of reducing secondary damage at the injury site and promoting regeneration, drugs and bioactive molecules require multiple administrations over extended periods to maintain therapeutic efficacy, rendering clinical treatment challenging. In light of advancements in biomaterials science and research pertaining to the microenvironment following spinal cord injuries, conductive biomaterials have emerged as a promising component of regenerative medicine. These biomaterials offer the potential to promote SCI repair while being compatible with electrical stimulation to enhance neuroplasticity. For instance, preformed catheters and fibrous scaffolds created through electrostatic spinning, multilayer stacking of electrically conductive materials, or nanofibers can guide the directional growth of axons and serve as carriers for cells, drugs, and bioactive molecules.[180,181] However, these scaffolds often lack the mechanical strength required to match spinal cord tissue, presenting challenges in bridging irregular defects caused by contusion or compression-type injuries and potentially leading to secondary damage.

Biomaterials, particularly conductive hydrogels, have proven effective in addressing the limitations of the aforementioned treatment approaches. Currently, these conductive hydrogel scaffolds are designed to closely mimic native spinal cord tissues in terms of properties such as swelling rate, porosity, mechanical strength, electrical conductivity, structural features, and biochemical characteristics. Injectable hydrogels can fill irregular injury gaps and improve the microenvironment at the injury site by providing damaged spinal cord tissue with a matrix for delivering cells, drugs, and bioactive molecules. Leveraging their electroactivity, these conductive hydrogels can reestablish interrupted neuroelectrical signal transmission, deliver electrical stimuli to enhance axonal regeneration and neurogenesis and accelerate the formation of synaptic connections and neurogenesis, ultimately promoting injury repair. Simultaneously, the incorporation of electrical stimulation within the spinal cord injury repair process can lead to more effective functional recovery. While there is limited research on the application of conductive hydrogels in spinal cord injury, the reported results thus far are highly promising and underscore the potential of conductive hydrogels within current tissue engineering and regenerative medicine strategies for enhancing spinal cord injury repair.

Despite the excellent physicochemical properties and applications of conductive hydrogels in spinal cord repair, there is room for improvement when it comes to translating them into clinical practice. The challenge lies in fabricating conductive hydrogels with various combinations of functionalities. Future conductive hydrogels should not only provide spatial and directional support for spinal cord regeneration but should also mimic the electrophysiological microenvironment of neural tissues, transmit endogenous bioelectrical signals, and regulate the microenvironment and endogenous neural stem cells. Further refinement is necessary to ensure these hydrogels possess more appropriate and effective properties, such as maintaining long-term electrical stability, aligning the rate of scaffold degradation with the rate of tissue regeneration, and autonomously responding to changes in the microenvironment to meet the specific repair requirements during different stages of spinal cord injury. Moreover, additional preclinical assessments are required, encompassing long-term toxicity studies, evaluations of cellular uptake, and assessments of effects on metabolic pathways to ensure safe clinical application. Subsequent in vivo studies should include multiple long-term assays examining scaffold components in various body sites, organs, blood, and cells. Furthermore, future research should focus on determining the type and location of electrical stimulation and the parameters of electrical stimulation in synergy with conductive biomaterials. In summary, several challenges exist regarding the development of biomaterials and their clinical application, necessitating further research and development to unlock the full potential of conductive hydrogels as a new direction in spinal cord injury treatment.

Disclosure

The authors report no conflicts of interest in this work.

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