International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Research Progress on Biomaterials for Spinal Cord Repair

Zhenglie Liao[1,*], Qianyi Bao[1,*], Saijilahu[2], Chimedragchaa Chimedtseren[3], Khaliunaa Tumurbaatar[3], Saijilafu[1]

[1]Key Laboratory of Novel Targets and Drug Study for Neural Repair of Zhejiang Province, School of Medicine, Hangzhou City University, Hangzhou, People's Republic of China; [2]Tongliao Centers for Disease Control and Prevention, Tongliao, Inner Mongolia, People's Republic of China; [3]Institute of Traditional Medicine and Technology of Mongolia, Ulaanbaatar city, Mongolia

*These authors contributed equally to this work

Correspondence: Saijilafu, Email saijlf@hzcu.edu.cn

Abstract: Spinal cord injury (SCI) is a very destructive disease of the central nervous system that often causes irreversible nerve damage. Unfortunately, the adult mammalian spinal cord displays little regenerative capacity after injury. In addition, the glial scars and inflammatory responses around the lesion site are another major obstacle for successful axon regeneration after SCI. However, biomaterials are highly biocompatible, and they could provide physical guidance to allow regenerating axon growth over the lesion site and restore functional neural circuits. In addition, combined or synergistic effects of spinal cord repair can be achieved by integrating different strategies, including the use of various biomaterials and microstructures, as well as combining bioactive molecules and living cells. Therefore, it is possible to use tissue engineering scaffolds to regulate the local microenvironment of the injured spinal cord, which may achieve better functional recovery in spinal cord injury repair. In this review, we summarize the latest progress in the treatment of SCI by biomaterials, and discussed its potential mechanism.

Keywords: biomaterials, spinal cord injury, neural regeneration

The Current State of Spinal Cord Injury

Epidemiology of Spinal Cord Injury

Spinal cord injury (SCI) is a common traumatic disorder. With the development of transportation and construction industries, the number of SCI cases is escalating rapidly. The incidence ratio of SCI ranges from 14.6–60.6 per million, and the average age of onset is 34–55 years old.[1] SCI causes serious dysfunction below the injury site and reduces the life quality of patients, creating a heavy familial and societal economic burden. However, there is no effective treatment for SCI in clinics, and more detailed research is urgently needed in the medical field.

Pathophysiological Mechanism of Spinal Cord Injury

The pathophysiological change of SCI comprises two stages: primary and secondary[2,3] (Figure 1). In clinics, primary SCI is usually caused by vertebral fracture or dislocation from violent injury. The displacement of bone fragments and the tearing of ligaments often causes spinal cord compression[3] and bleeding and blood supply interruption which lead to hypoxia and ischemic infarction. Furthermore, the damaged area contains neurons that are physically broken with reduced myelin thickness, and the damaged tissue forms edemas in which macrophages accumulate[4] to cause irreversible neurological defects. Secondary injury develops from primary injury[5] with a time progression that can be divided into acute, subacute, and chronic stages.[6,7] The acute phase commences approximately 2 hours after injury with increased cell permeability, ischemia, vascular damage, edema, neurotransmitter accumulation, calcium influx, inflammation, lipid peroxidation, and free radical formation. In addition, severe bleeding resulting from vascular injury exposes the spinal cord to a substantial influx of inflammatory cells, cytokines, and vasoactive peptides. Previous research has demonstrated that pro-inflammatory cytokines,

Received: 24 October 2024
Accepted: 22 January 2025
Published: 11 February 2025

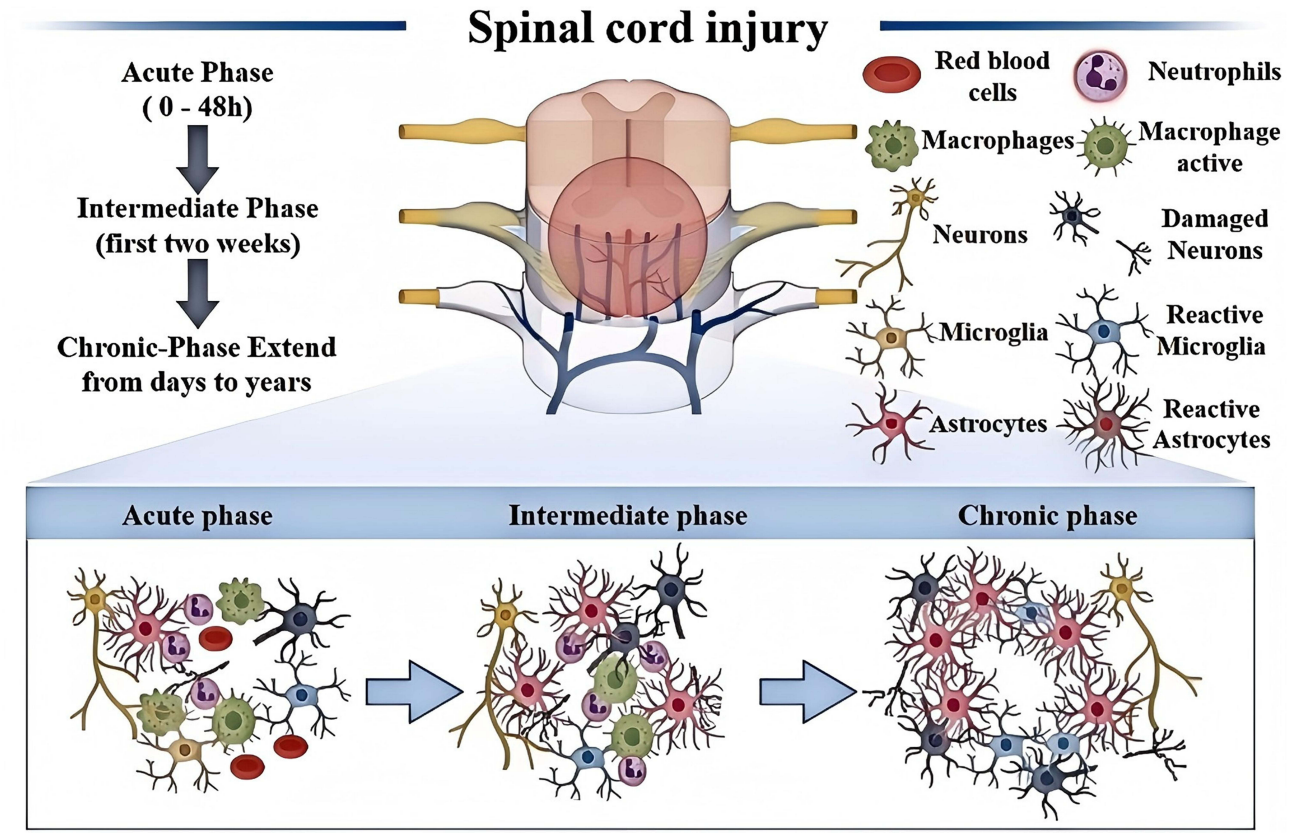

Figure 1 The pathophysiological mechanism of spinal cord injury: In the acute stage of SCI, severing of axon, hemorrhage of blood vessels, death of neuron and glia, ischemia and swelling of spinal cord, astrocytes are started to be activated. In the intermediate stage, macrophages infiltrate and activated, astrocytes proliferate, and glial scars form. In the chronic stage, continued glial scars formation, development of cyst and Wallerian degeneration. By Figdraw.

such as tumor necrosis factor (TNF) and interleukin-1β (IL-1β), exhibit marked increases within minutes following SCI. Concurrently, a significant number of immune cells including macrophages, neutrophils, and lymphocytes migrate into the spinal cord via the bloodstream and persist in this region. The extensive inflammatory response that occurs during both acute and subacute phases of injury. Two weeks later, the injury develops to a subacute stage characterized by demyelination, Wallerian degeneration, matrix remodeling, and fibroglial scar formation.[3] The chronic phase often begins 6 months after injury and is characterized by cyst formation, axon retraction, and glial scar maturation.[7,8] Thus, after SCI, the activated microglia, astrocytes, and macrophages trigger the secretion of extracellular matrix (ECM) proteins, such as chondroitin sulfate proteoglycans (CSPG), tenascin, and NG2 proteoglycans. These proteins interact with reactive astrocytes to form glial scars. Subsequently, these scar tissue creates an impenetrable barrier to nerve regeneration. Therefore, targeting these inhibitory microenvironments might be the most effective approach to promoting axon regeneration in the injured spinal cord. With advances in tissue engineering, it is feasible to utilize biomaterials to regulate the local microenvironment of the injured spinal cord, which may achieve better functional recovery in spinal cord injury repair.

Clinical Treatment

The current clinical treatment of SCI is a cooperative multidisciplinary approach aimed at minimizing the symptoms and sequelae after injury and helping patients recover function and improve life quality. At present, the clinical treatment methods for SCI mainly include:

First Aid and Initial Care

For patients with acute SCI, first aid is critical. This includes stabilizing the spine and protecting the spinal cord to prevent further injury. Timely emergency management can reduce the extent of injury and reduce the risk of complications.[9]

Surgery

Surgical decompression can effectively reduce bone fragment compression on the spinal cord and prevent further expansion of the injury. Timely surgical operations after severe SCI also can improve patient prognosis.[10]

Pharmacologic Therapy

Pharmacologic therapies include the use of anti-inflammatory drugs, antispasmodic drugs, and analgesics to reduce inflammation and pain. Glucocorticoid hormone shock therapy is used extensively,[9] and neuroprotectants or other drugs may also be used to promote nerve regeneration.[11]

Physical Therapy and Rehabilitation Training

Physical therapy and rehabilitation training are the core of SCI patients to recover muscle strength, balance, and motor function, and further improve patients' self-care abilities.[12–14]

Moral Support

SCI can impact patients and their families psychologically and spiritually, and psychological support and counseling is also important for rehabilitation and the reconstruction of an adapted life.[15]

Neuroprosthetics

The neuroprosthetic technology directly acts on the muscular system or an external device by analyzing electroencephalogram signals to obtain motor commands from brain signals, thereby compensating the brain-spinal-muscle fundamental efferent pathway and restoring the motor function of SCI patients. Recently, artificial intelligence technology and brain-computer interface (BCIs) have emerged as an alternative to drug therapy, opening a new era of SCI rehabilitation treatment.[16] There are two main therapeutic strategies based on BCIs technology applied to SCI treatments, one is BCI-controlled rehabilitation robot, and the other is BCI-controlled functional electrical stimulation of neuromuscular system. It is worth mentioning that most patients with upper limb motor dysfunction caused by cervical SCI can recover and compensate the upper limb motor function through neuroprosthetic approach in clinic. With the improvement of technologies, it is believed that using the functional electrical stimulation of BSI to control the denervated muscles in SCI patients, so that they can restore motor function will be achieved.

However, these strategies cannot fully repair SCIs but can improve symptoms and reduce some complications. Some pharmacological interventions may play a crucial role in mitigating secondary injury when administered promptly, whereas rehabilitation therapies are likely to be effective during the later stages of recovery to facilitate functional improvement.

The Current State of SCI Research

SCI treatment research is currently very active; neuroscientists and medical experts are actively exploring new treatment methods to improve functional recovery and life quality in SCI patients. Current animal studies for SCI include genetic manipulations, biomaterial transplantation, pharmacological interventions, and stem cell therapies (Figure 2).

Traditional pharmacological therapy for SCI is still being improved, and includes the use of glucocorticoid hormone therapy, nerve growth factor, ganglioside, and traditional Chinese medicine. Glucocorticoids are very common in clinical SCI treatment. The administration of methylprednisolone to patients within 8 hours of acute SCI can inhibit local inflammatory responses and lipid peroxidation.[17] However, glucocorticoid hormone therapy is controversial for acute SCI regarding dosage regimens, as large doses of glucocorticoid hormones have many systemic side effects.[18] Many neurotrophic factors regulate neuronal survival and synaptic function in the adult central and peripheral nervous systems.[11] Rosich et al found that glial cell line-derived neurotrophic factor (GDNF) is more effective for SCI when used in combination with other neurotrophic factors than when used alone. Other neurotrophic factors such as brain-

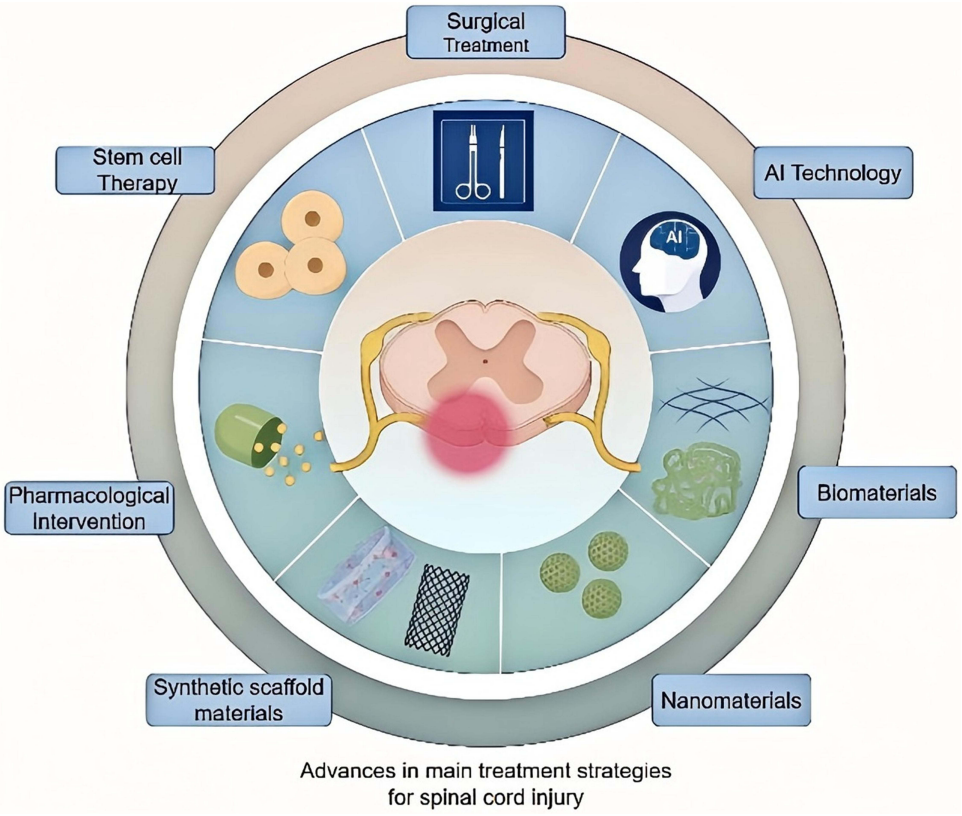

Figure 2 Current major strategies for SCI treatment research. It mainly includes surgical treatment, biomaterial transplantation, pharmacological interventions, and stem cell therapies. By Figdraw.

derived neurotrophic factor (BDNF), neurotrophic factor-3 (NT-3), neurotrophic factor-4/5 (NT-4/5), and neuroproliferative acid (NAP) also substantially improve SCI functional recovery.[19] However, neurotrophic factors are unstable in vivo and cannot penetrate the blood-brain barrier to achieve the desired therapeutic effects. Therefore, ideal carriers are needed to load them and increase their local effects.

Stem cell transplantation is another promising treatment method for SCI. Stem cells can be replenished to differentiate into neurons and restore neurological function. Curtis et al's Phase I clinical trial showed that chronic SCI patients can recover motor function with reduced spasticity after NSI-566 cell transplantation, without side effects for at least 27 months after transplantation.[20] Despite the many potential advantages of stem cell therapy for SCI, there are still some shortcomings and challenges, including its safety, cost, and a lack of long-term follow-up data. Nevertheless, the approach remains cutting-edge and highly anticipated, and these challenges will be overcome with advances in science and technology and more clinical trial data.

In addition to the above methods, new therapeutics are being studied and explored, including biomaterial scaffold[21,22] that are expected to bring new breakthroughs in SCI treatment. Early diagnosis and timely treatment can improve therapeutic effects and recovery potential. Though SCI treatment has made great progress in recent years, neurological functions still cannot be restored to patients, and each treatment has strict restrictions with limited functional recovery. Due to the complex pathological process of SCI, using a single target or a single strategy alone is not sufficient to promote spinal cord repair in clinic. Therefore, the future research on SCI should shift towards multi-target, multi-phase treatment strategies.

Application of Biomaterials for SCI Treatment

With advances in tissue engineering, biomaterials have become very attractive for repairing damaged nerve tissues. Biomaterial scaffolds can be used for drug delivery, cell load, and tissue engineering to facilitate the repair of SCIs, while

acting as a scaffold and microenvironment for tissue growth with reduced inflammatory responses (Figure 3). In this review, we discuss the properties of various biomaterials and their applications in SCI to guide future research direction.

Natural Biomaterial Scaffold

Natural biological materials are easily obtained and have good biocompatibility and degradability, with strong biological activity in vivo and minimal immune responses. Most natural biomaterials are soft and easily prepared as hydrogels that effectively fill the SCI lesion cavity. In addition, they mostly have good adhesion properties and are ideal carriers for seed cells. These materials include collagen, gelatin, acellular matrix, and polysaccharide (Table 1).

Collagen

Collagen is a mechanically strong triple-helical structure comprising three alpha-chain polypeptides.[46] There are several subtypes; the primary types in the human body are types I, II, and III;[47,48] type I is the most widely used in biomedicine. Collagen is a major component of the extracellular matrix (ECM) of connective tissue and a highly dynamic material that can be constantly reshaped to maintain original physiological functions.[49] Although collagen scaffolds are limited by rapid degradation rate and poor mechanical strength, mammalian cells have cell-surface integrins with a high affinity for specific collagen sequences,[46] making collagen superior for promoting cell adhesion and growth. Therefore, collagen-based three-dimensional (3D) porous scaffolds are advantageous and can be made into hydrogels, sponges, and microspheres[16] that can guide axon regeneration, deliver drugs, and promote tissue healing in SCI repair. Yeh et al inserted collagen scaffold into the T8 spinal cord defect area of rats and observed that collagen scaffolds were effective in

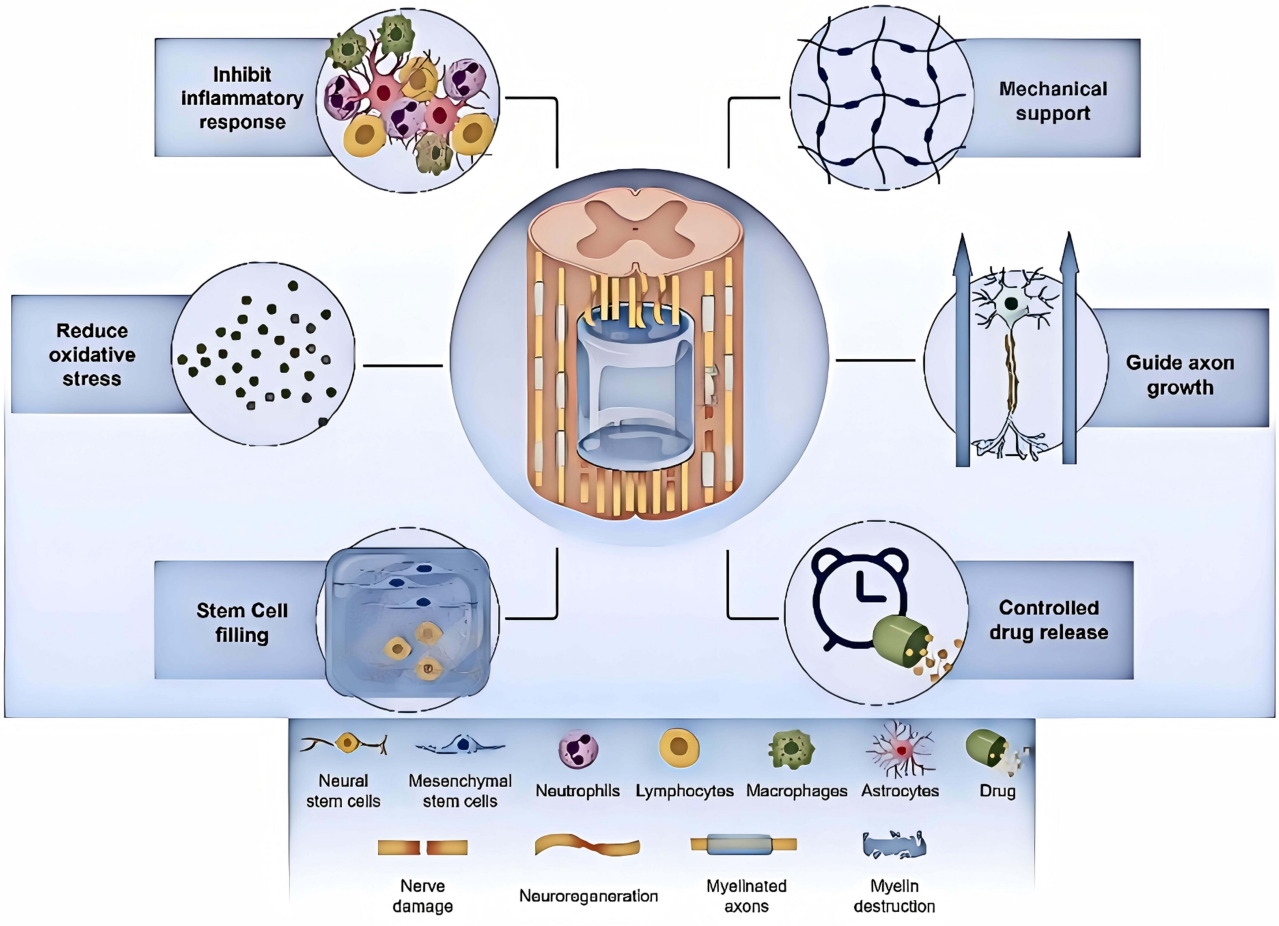

Figure 3 The main strategies of SCI treatment using biomaterials. (1) Inhibit inflammatory responses.(2) Reduces oxidative stress. (3) Stem cell filling. (4) Mechanical support. (5) guide axon growth. (6) Controlled drug release. By Figdraw.

https://doi.org/10.2147/IJN.S501121

Table 1 Application of Natural Biomaterials in Spinal Cord Injury

Material	Application	References
Collagen	Loaded with drugs, NSCs, neurotrophic factors. Protect neurons, guide axon regeneration, and provide a good microenvironment. Inhibition of glial scars and apoptosis (Col-I-mir21)	[23–25]
Gelatin	Loaded drugs (GNS), neural stem cells. Provides a favorable microenvironment for cell survival. Anti-inflammatory, inhibits glial scars, supports axon regeneration	[26–28]
Acellular matrix	Loads cells, neurotrophic factor (bFGF-ASC-HP), and vascular endothelial growth factor. Excellent carrier of BMSCs. Promotes long-term nerve regeneration.	[29–32]
Hyaluronic acid	Carrier of neural stem cells. Creates a good microenvironment, inhibits glial scars, anti-inflammatory, anti-tissue adhesion, stabilizes synaptic connections, and promotes neuronal maturation.	[33–35]
Chitosan	Delivers drugs (CMC/CS/CBD), neurotrophic factors. Good bridging and supporting functions, promotes nerve fiber growth.	[36–38]
Agarose	Carries BMSCs and neurotrophic factors. Anti-inflammatory; increases axon length.	[39–42]
Alginate	Drug delivery (GelMA. PTX). Promote axon regeneration. Anti-apoptosis, anti-infection, improve tissue repair (EPO-CH/AL)	[43–45]

maintaining astrocyte production and inhibiting glial scarring.[50] Breen et al injected NT-3-loaded collagen hydrogel into the SCI lesion site and found enhanced nerve regeneration.[51]

Neural stem cells (NSC) are the most ideal seed cells for SCI repair, but the harmful microenvironment of SCI promotes their differentiation into astrocytes.[52] However, collagen scaffolds can create a favorable microenvironment for NSCs and enhance their differentiation into neurons. A collagen scaffold loaded with paclitaxel liposomes can activate the Wnt/β-catenin signaling pathway and promote NSC differentiation into neurons.[53] A collagen sponge with basic fibroblast growth factor (bFGF) can enhance NSCs to proliferate efficiently.[54] In addition, collagen hydrogels are well-suited for the delivery of immunosuppressive drugs; a tacrolimus-coated collagen hydrogel implanted into the spinal cord provides sustained drug release with reduced immune rejection and promotes nerve regeneration.[55]

Gelatin

Gelatin is a water-soluble protein obtained from the partial hydrolysis of collagen and like to collagen, is renewable, biodegradable, and hydrophilic, with good biocompatibility and low antigenicity[56,57] and a 3D gelatin sponge (3D-GS) scaffold can induce strong axon growth.[58] Typically, a GFAP-positive glial scar barrier forms around the SCI lesion site and inhibits axon growth. However, after 3D-GS scaffold transplantation, the $GFAP^+$ astrocytes become axon conductive, and numerous regenerated axon fibers are detected behind the lesion site. In addition, 3D-GS scaffolds can destroy the $GFAP^+/\alpha SMA^+$ cell interface and promote the migration of astrocytes and stromal cells. Those migrating cells can secrete ECM components, such as collagen, to improve the local microenvironment of the SCI.[59] Furthermore, a gelatin microsphere scaffold made by 3D-printing technology can support the survival of severed axons and promote its regeneration.[26] Although gelatin have many advantages, however, its biomedical applications is still limited because of poor mechanical strength and rapid degradation.[60]

GelMA gel is a photosensitive hydrogel obtained by the reaction of methacrylate anhydride with natural gelatin.[61] Because of its good histocompatibility, biodegradability, and controllable mechanical properties, GelMA gel widely used in tissue engineering field.[62] Furthermore, its good mechanical properties are well suited for combining with seed cells for SCI treatment. Fan et al implanted 3D GelMA hydrogel loaded with IPSC-derived NSCs into a spinal cord

transection model and found that the astrocyte scar was significantly reduced and showed better motor recovery.[28] 3D GelMA hydrogel scaffolds loaded with BMSCs also promote cell survival and differentiation into neurons.[63] Therefore, a 3D composite scaffold of GelMA hydrogel can provide a more favorable microenvironment for the cell adhesion, proliferation, and differentiation of NSCs into neurons, and promotes axon regeneration.[64,65]

Acellular Scaffolds

Acellular scaffolds (ASCs) have no cellular structure and retain ECM components including collagen IV, fibronectin, and laminin that are conducive to neuron attachment and axon growth.[66,67] ASCs are non-toxic and soft texture with low immunogenicity and good biocompatibility.[32,68,69] ASCs have a 3D network structure with abundant spaces that is conducive to cell proliferation.[31] Zhu et al implanted ASCs into the spinal cord lesion site in rats and observed many GAP-43 and NF200-positive axon fibers in the scaffold, and the expression of Nestin and GAP-43 was maintained for 12 weeks after injury, showing that ASCs can promote long-term nerve regeneration.[29] It has been reported that BMSCs can adhere, proliferate, and migrate well on ASCs surface, and maintain its stemness to continuously express stem cell markers CD44 and CD90.[31] A composite scaffold crosslinked with a NT-3 and ASCs can promote the differentiation of BMSCs into neuron-like cells. In addition, ASCs can be implanted with adipose-derived stem cells in SCI lesion site that promote axon regeneration and reduce reactive glial cell formation.[70] However, it has been reported that ASCs are mechanically weak, but it can be improved by modifying the many free amino acid residues.

Polysaccharose

Hyaluronic acid (HA), one of the main polysaccharide components of ECM, is a biopolymer composed of D-glucuronic acid and n-acetylglucosamine disaccharide units that form a biocompatible network structure.[71,72] HA is highly expressed in perineural networks; therefore, HA-based hydrogels are widely used as biocompatible scaffolds. HA can interact with surface receptors of CD44-positive cells to down-regulate inflammatory signaling pathways, thereby indirectly inhibiting astrocyte proliferation and migration. Moreover, HA can reduce the density of $GAFP^{+}$ cells and inhibit glial scar formation.[34] However, the non-adhesion of HA hydrogels limits cell penetration and inflammatory cell migration. Khaing et al implanted high-molecular-weight HA hydrogels into an SCI model and found that the number of immune cells decreased in the acute stage of injury, while CSPG deposition was significantly reduced 10 days after injury and astrocyte proliferation was inhibited 9 weeks after injury.[73] HA scaffolds can also preserve intact axons at the injured site and are neuroprotective.[74,75] Chitosan is a linear polysaccharide, which has been found to reduce fiber scarring, promote axon regeneration and myelin formation in SCI treatment.[36,76] Agarose is another water-soluble linear polysaccharide extracted from seaweed, it has been reported that agarose-loaded scaffolds containing multiple linear channels can promote axon regeneration at the injured site and reestablish motor circuits.[77] Agarose scaffolds can also serve as vectors for BMSCs, supporting secretion of BDNF and guiding regenerating axon grow over the lesion site.[42] Alginate is a natural biopolymer extracted from brown algae, and alginate-based hydrogels are also widely used in SCI treatment.[78,79] Huang et al constructed an alginate gel containing anisotropic capillaries and found that the scaffold supported regeneration of descending motor axons and ascending sensory axons without neurotrophic factors.[44] Furthermore, sodium alginate/gelatin scaffolds loaded with NSCs, can promote re-myelination, axon regeneration, and motor function recovery.[80]

Synthetic Biomaterial Scaffolds

Compared with natural biomaterials, synthetic biomaterials are more easily available and have adjustable strength and degradation rates. As biomaterials for tissue regeneration, synthetic scaffolds should be histocompatible and provide a favorable microenvironment for stem cell differentiation and proliferation (Table 2).

Synthetic Peptides

Synthetic peptides are composed of small natural amino acids and can be safely metabolized in the human body. In recent years, synthetic peptide scaffolds have been widely used as drug delivery systems to promote neural tissue regeneration. Alvarez et al constructed a scaffold that integrates the laminin IKVAV and fibroblast growth factor 2 (FGF-2) with the diphilic polypeptide (PA). This scaffold improve axon regeneration and functional recovery after transplantation into SCI

Table 2 Application of Various Synthetic Materials in Spinal Cord Injury

Material	Application	References
Synthetic Peptide	Promote neurological function recovery. Reduce glial scarring. Supports neuronal adhesion and promotes axon growth. Enhanced loaded stem cell survival and differentiation.	[81–84]
PCL	Enhance neuronal differentiation of spermatogonial stem cells. Inhibit secondary injury and restore sensory and motor function. Promotes nerve regeneration.	[85–88]
PEG	Rapid neuroprotective effect.	[89,90]
PLA	Decreased apoptosis of nerve cells and increased axon regeneration.	[91,92]
PLGA	Inhibits inflammation and glial cell proliferation. Improve motor function. Promote nerve regeneration. Promote the proliferation and differentiation of NSCs.	[93–95]
Nanomaterials	Provides mechanical support. Promotes nerve regeneration. Improve nerve conduction function. Regulate inflammation.	[96–98]

by enhances the supramolecular motion within the scaffold fibers.[99] Zahra et al also found that IKVAV-PA hydrogel scaffold carrying BDNF could continuously release BDNF for more than three weeks and reduce the astrocytes proliferation.[100]

Synthetic Polymer Scaffolds

Synthetic polymer scaffolds are mainly divided into polycaprolactones (PCL), polylactic acid (PLA), polylactic acid-glycolic acid copolymer (PLGA), and polyethylene glycol (PEG). Among them, PCL is a degradable polymer that has recently emerged as a tissue engineering scaffold material for 3D printing because of its low melting point and ductility. In addition, PCL is a partially crystalline hydrophobic polymer, complete degradation takes 2 to 4 years, thus, it also used as a drug delivery system.[88] PCL is also suitable for electrospinning, which can generate parallel or randomly oriented nanofibers,[101–103] and this PCL nanofiber scaffolds are biocompatible and mechanically strong to support the adhesion and proliferation of BMSCs.[104] The polysialic acid (PSA)-based polyPCL hybrid nanofiber scaffold can inhibit the release of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This scaffold can promote SCI repair by enhancing axon growth and inhibiting the GFAP and apoptosis-related Caspase-3 protein expression.[105]

Polyethylene glycol (PEG) is an attractive and structurally flexible, biocompatible, diphilic molecule with no steric hindrance and good hydration and loading capacity.[106] PEG is a good cell membrane sealant and inhibits apoptosis and oxidative stress while reducing cell membrane permeability.[107] After SCI, cell membrane rupture and uncontrolled ion exchange lead to progressive cell death, and PEG can be applied for SCI treatment by sealing these cell membrane ruptures.[108] In addition, PEG scaffolds promote the migration of glia cells into the lesion area, where they promote remyelination and axon growth. Therefore, PEG scaffolds may be ideal biomaterial for the repair of large nerve defects.[109] However, Cole et al found that prolonged exposure to PEG may inhibit nerve conduction velocity. In general, PEG is widely used in the biomedical field as a sealant for cell membrane fusion and repair in short-term. The therapeutic effects of PEG for SCI treatment can be enhanced with auxiliary materials. Cheng et al explored the effect of combined treatment with electric stimulation and PEG and found that the combined treatment can inhibit cation inflow and promote SCI repair.[110]

Polylactic acid (PLA) is a biodegradable thermoplastic polymer formed by the lactic acid (LA) molecules polymerization. Since LA is a chiral molecule, three forms of polylactic acid can be formed that differ in their characteristics:

poly-L-lactic acid (PLLA), poly-D-lactic acid (PDLA), and poly-D, L-lactic acid-lactic acid (PDLLA). PDLLA biodegrades more quickly degrades than PDLA and PLLA. This makes PDLLA more suited for medical applications requiring rapid degradation, while PLLA is suited for applications requiring long-term support.[111] PLA is very hydrophobic, making it unsuitable for drug delivery. Fasolino et al investigated the possibility of an electrospun PLA fiber scaffold coated with eumelanin for SCI repair. The melanin in the scaffold can reduce ROS and regulate the inflammatory response of SCI.[112] Raynald et al used polypyrrole (PPy) and PLA composite nanofiber scaffolds combined with BMSCs to promote functional recovery of SCI in rats. Both electrophysiological and behavioral evaluation showed that the Ppy/PLA/BMSCs treatment showed the significant functional recovery.[113] Overall, PLA and its degradation products are biocompatible with spinal cord tissue and have the potential to become scaffolds and drug carriers for SCI repair.

Polylactic acid-glycolic acid copolymer (PLGA) forms a blocky structure or random aggregate with good pore structure, hydrophilicity, and rapid biodegradation.[114,115] During the hydrolysis of PLGA, two monomers are produced: lactic acid and glycolic acid, both of which are common non-toxic cell metabolites. Schwann cells proliferated well on the PLGA scaffold surface and promoted axonal regeneration in the lesioned spinal cord. However, motor function recovery is limited.[116,117] Furthermore, PLGA nanoparticle-based drug delivery systems enable the controlled release of drugs when applied locally. FTY720 was incorporated into PLGA nanoparticles, transplanted with NSCs into an acute SCI model, and significantly promoted nerve function recovery and stem cell differentiation into oligodendrocytes.[118] PLGA nanoparticle-loaded chondroitin enzyme ABC (ChABC) can markedly promote motor function and digest local scar tissue.[119] Therefore, PLGA can provide a favorable microenvironment for local cells, and can act as a controlled drug delivery system in SCI treatment.

Its degradability and mechanical strength are critical factors that significantly influence the clinical applicability of biomaterials. The advantages of using natural biomaterials for SCI repair are its good biocompatibility, biodegradability, and facilitation of cell adhesion and growth. However, some natural materials may cause inflammatory reactions. Synthetic biomaterials have controlled physical and chemical properties and degradation rate, which can meet different application needs. The major disadvantage of synthetic biomaterials is the potential cell toxicity of their degradation products. Due to the complex biological mechanisms of SCI and nerve regeneration process, a single-function scaffold may not be able to meet the needs. By combining two or more biological materials of different properties, a scaffold with complementary properties can be designed to meet the needs of SCI.

Nanomaterials

Nanomaterials are novel materials ranging in size from 1–100 nm that are lightweight and pH sensitive with diverse compositions including metals (eg, gold, silver, iron oxide, cadmium, zinc, and cerium) and ceramics, carbon-based nanomaterials, and other organic, inorganic, and composite materials. Furthermore, nanomaterials can be combined with each other to achieve new synergetic effects.

After SCI, neuroinflammation is a prominent characteristic of its acute phase. The rupture and bleeding of small blood vessels often triggers the infiltration of inflammatory cells into the injured area of SCI. In addition, a few hours later, relevant inflammatory factors, such as interleukin and Tumor necrosis factor (TNF) began to be released successively. Thus, these inflammatory factors enhance the inflammatory response of neurons, and oxidative stress caused by reactive oxygen species (ROS) often leads to prolonged neuroinflammation response, which in turn triggers furthermore serious spinal tissue damage. In addition, because of the generation and accumulation of ROS in SCI, the efficacy of stem cell transplantation in SCI is seriously reduced by severe inflammation and ROS accumulation that cause a good deal of cell death.[120] However, antioxidants based on nano-metal oxides can inhibit ROS accumulation. Thus, Liming et al employ HA-peptide-modified MnO2 nanoparticles to mitigate the oxidative environment by regulating reactive oxygen species (ROS) during the acute phase of SCI. In addition, significant motor function recovery was observed in the rat SCI model after implantation of HA-peptide-modified MnO_2 nanoparticles.[121] Dezun et al constructed a ROS-responsive mesoporous silica nanoparticle (rMSN) loaded with an interferon regulatory factor (IRF5)-targeted siRNA. This nanomaterial-mediated delivery of siRNA-IRF5 transforms M1 macrophages into an M2 phenotype that reduced pro-inflammatory cytokines production[122] and cleavage the ROS to inhibit the inflammatory response.[123]

At the subacute phase of SCI, the fibroglial scar formation is a major problem of spinal cord repair. For solve this problem, Chen et al developed a composite hydrogel based on polyvinyl alcohol (PVA) and molybdenum sulfide/graphene oxide (MoS_2/GO) nanomaterials for SCI treatment. As in the mouse SCI model, the implantation of MoS_2/GO/PVA hydrogel scaffold promotes the motor function via inhibits glial cell activation and scar tissue formation. In addition, this kind of composite hydrogel also promoted the differentiation of NSCs into neurons and inhibiting the astrocytes proliferation.[120]

In the chronic phase, promoting neuronal regeneration might be the focus of treatment. Thus, multiple strategies may be used to achieve ideal results. The microstructure and high surface area of nanomaterials also can be used for the loading and delivery of drugs during tissue engineering applications. The drug delivery system based on nanomaterials has good drug loading ability and can significantly improve the pharmacokinetic characteristics of the loaded drugs, which effectively increase the local concentration of drugs at the lesion site (Figure 3). It has been found that MnO_2 nanoparticles, cerium oxide nanoparticles, and selenium-doped carbon quantum dots, can effectively alleviate oxidative stress after traumatic SCI, thereby promoting neuronal survival and regeneration.[124,125]

Problems and Challenges

Although biomaterials have made significant progress toward clinical applications for SCI treatment, many challenges remain to be solved. First, the detailed molecular mechanisms of SCI treatment by different biomaterials must be elucidated. Second, treatments method must be optimized regarding duration and implantation method, timing, and location, while also considering biocompatibility, degradability, mechanical strength, and toxicity. For example, although natural biomaterials are biocompatible, they have inherent shortcomings. Synthetic materials have high scaffold strength but lack inherent biological activities, thus requiring combination with other biomaterials to trigger the expected biological reaction in vivo. Thus, further investigation is needed to understand their safety and efficacy, and additional clinical studies should be undertaken to promote biomaterials in the SCI treatment. In addition, future research should prioritize enhancing the degradation resistance of biomaterials and their ability to positively interact with the host biological environment. A comprehensive exploration of the physicochemical properties of the scaffold, not only to ensure structural integrity but also to improve the delivery efficiency of bioactive molecules, thereby achieving a synergistic effect between mechanical properties and therapeutic functionality.

Summary

This review summarizes the current research status of the application of biomaterials to the SCI treatment, in recent years, to provide some comprehensive information and reference value for future exploration of new SCI repair strategies. Although biomaterials have great potential for SCI treatment, we should also be aware of the complexity of SCI pathological changes. The complex mechanism of SCI injury cascade and the limitations of translation from animal experiments to clinical trials need to be solved. A single treatment method may be difficult to achieve ideal results. To promote the neural circuits remodeling to achieve functional recovery is the goal of SCI treatment. Thus, the ideal biomaterials should have properties to include activating the intrinsic growth capacity of neurons, creating a favorable local environment conducive to nerve regeneration and axon growth.

Data Sharing Statement

All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Approval

This is a review study. The Hangzhou City University Research Ethics Committee has confirmed that no ethical approval is required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the start-up funding from Hangzhou city university to Saijilafu.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Chen C, Qiao X, Liu W, Fekete C, Reinhardt JD. Epidemiology of spinal cord injury in China: a systematic review of the Chinese and English literature. *Spinal Cord*. 2022;60:1050–1061. doi:10.1038/s41393-022-00826-6
2. Shao A, Tu S, Lu J, Zhang J. Crosstalk between stem cell and spinal cord injury: pathophysiology and treatment strategies. *Stem Cell Res Ther*. 2019;10:238. doi:10.1186/s13287-019-1357-z
3. Anjum A, Yazid MDI, Fauzi Daud M, et al. Spinal cord injury: pathophysiology, multimolecular interactions, and underlying recovery mechanisms. *Int J Mol Sci*. 2020;21:7533. doi:10.3390/ijms21207533
4. Zhang Y, Al MA, Yuan Y, et al. Acute spinal cord injury: pathophysiology and pharmacological intervention. *Mol Med Rep*. 2021;23. doi:10.3892/mmr.2021.12056
5. Quadri SA, Farooqui M, Ikram A, et al. Recent update on basic mechanisms of spinal cord injury. *Neurosurg Rev*. 2020;43:425–441. doi:10.1007/s10143-018-1008-3
6. Kim Y, Ha K, Kim S. Spinal cord injury and related clinical trials. *Clin Orthop Surg*. 2017;9:1. doi:10.4055/cios.2017.9.1.1
7. Feng C, Deng L, Yong Y, et al. The application of biomaterials in spinal cord injury. *Int J Mol Sci*. 2023;25:24. doi:10.3390/ijms25010024
8. Prins C, Oliveira F, Coelho V, et al. Galectin-3 absence alters lymphocytes populations dynamics behavior and promotes functional recovery after spinal cord injury in mice. *Exp Neurol*. 2024;377:114785. doi:10.1016/j.expneurol.2024.114785
9. Yin Y, Yang X, Tian Y, et al. Synchronized and integrated prehospital treatment for acute cervical spinal cord injury. *Am J Transl Res*. 2021;13:7008–7014.
10. Huang H, Young W, Skaper S, et al. Clinical neurorestorative therapeutic guidelines for spinal cord injury (IANR/CANR version 2019). *J Orthop Transl*. 2020;20:14–24.
11. Keefe KM, Sheikh IS, Smith GM. Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. *Int J Mol Sci*. 2017;18:548. doi:10.3390/ijms18030548
12. Barra B, Conti S, Perich MG, et al. Epidural electrical stimulation of the cervical dorsal roots restores voluntary upper limb control in paralyzed monkeys. *Nat Neurosci*. 2022;25:924–934. doi:10.1038/s41593-022-01106-5
13. Sutor TW, Kura J, Mattingly AJ, Otzel DM, Yarrow JF. The effects of exercise and activity-based physical therapy on bone after spinal cord injury. *Int J Mol Sci*. 2022;23:608. doi:10.3390/ijms23020608
14. Harvey LA. Physiotherapy rehabilitation for people with spinal cord injuries. *J. Physiother*. 2016;62:4–11. doi:10.1016/j.jphys.2015.11.004
15. Mercier LJ, Grant C, Langelier DM, Plamondon S. Scoping review of music therapy and music interventions in spinal cord injury. *Disabil Rehabil*. 2023;45:1736–1749. doi:10.1080/09638288.2022.2073391
16. Lorach H, Galvez A, Spagnolo V, et al. Walking naturally after spinal cord injury using a brain-spine interface. *Nature*. 2023;618:126–133. doi:10.1038/s41586-023-06094-5
17. Samano C, Nistri A. Mechanism of neuroprotection against experimental spinal cord injury by riluzole or methylprednisolone. *Neurochem Res*. 2019;44:200–213. doi:10.1007/s11064-017-2459-6
18. Canseco JA, Karamian BA, Bowles DR, et al. Updated review: the steroid controversy for management of spinal cord injury. *World Neurosurg*. 2021;150:1–8. doi:10.1016/j.wneu.2021.02.116
19. Rosich K, Hanna BF, Ibrahim RK, Hellenbrand DJ, Hanna A. The effects of glial cell line-derived neurotrophic factor after spinal cord injury. *J Neurotrauma*. 2017;34:3311–3325. doi:10.1089/neu.2017.5175
20. Curtis E, Martin JR, Gabel B, et al. A first-in-human, phase i study of neural stem cell transplantation for chronic spinal cord injury. *Cell Stem Cell*. 2018;22:941–950. doi:10.1016/j.stem.2018.05.014
21. Karsy M, Hawryluk G. Modern medical management of spinal cord injury. *Curr Neurol Neurosci Rep*. 2019;19:65. doi:10.1007/s11910-019-0984-1
22. Yin W, Yang C, Liu D, et al. Mussel shell-derived pro-regenerative scaffold with conductive porous multi-scale-patterned microenvironment for spinal cord injury repair. *Biomed Mater*. 2024;19(3):035041. doi:10.1088/1748-605X/ad3f63
23. Zhang L, Fan C, Hao W, et al. NSCs migration promoted and drug delivered exosomes-collagen Scaffold via a bio-specific peptide for one-step spinal cord injury repair. *Adv Healthc Mater*. 2021;10:2001896.
24. Asadi-Golshan R, Razban V, Mirzaei E, et al. Efficacy of dental pulp-derived stem cells conditioned medium loaded in collagen hydrogel in spinal cord injury in rats: stereological evidence. *J Chem Neuroanat*. 2021;116:101978. doi:10.1016/j.jchemneu.2021.101978
25. Liu X, Zhang L, Xu Z, et al. A functionalized collagen-I scaffold delivers microRNA 21-loaded exosomes for spinal cord injury repair. *Acta Biomater*. 2022;154:385–400. doi:10.1016/j.actbio.2022.10.027

26. Ke H, Yang H, Zhao Y, et al. 3D gelatin microsphere Scaffolds promote functional recovery after spinal cord hemisection in rats. *Adv Sci*. 2023;10:e2204528. doi:10.1002/advs.202204528
27. Zhang B, Ding Z, Dong J, Lin F, Xue Z, Xu J. Macrophage-mediated degradable gelatin-coated mesoporous silica nanoparticles carrying pirfenidone for the treatment of rat spinal cord injury. *Nanomedicine*. 2021;37:102420. doi:10.1016/j.nano.2021.102420
28. Fan L, Liu C, Chen X, et al. Directing induced pluripotent stem cell derived neural stem cell fate with a three-dimensional biomimetic hydrogel for spinal cord injury repair. *ACS Appl Mater Interfaces*. 2018;10:17742–17755. doi:10.1021/acsami.8b05293
29. Zhu J, Lu Y, Yu F, et al. Effect of decellularized spinal scaffolds on spinal axon regeneration in rats. *J Biomed Mater Res Part A*. 2018;106:698–705. doi:10.1002/jbm.a.36266
30. Xu Z, Zhang L, Wang C, et al. Acellular spinal cord Scaffold implantation promotes vascular remodeling with sustained delivery of VEGF in a rat spinal cord hemisection model. *Curr Neurovasc Res*. 2017;14:274. doi:10.2174/1567202614666170718093508
31. Li C, Song J, Wang Y, et al. Adhesion and proliferation of bone marrow stromal cells on acellular spinal cord scaffolds. *Int J Neurosci*. 2022; ahead–of–print, 1–10.
32. Xu HL, Tian FR, Lu CT, et al. Thermo-sensitive hydrogels combined with decellularized matrix deliver bFGF for the functional recovery of rats after a spinal cord injury. *Sci Rep*. 2016;6:38332. doi:10.1038/srep38332
33. Khaing ZZ, Seidlits SK. Hyaluronic acid and neural stem cells: implications for biomaterial design. *J Mat Chem*. 2015;3:785–7866.
34. Xu GY, Xu S, Zhang YX, et al. Cell-free extracts from human fat tissue with a Hyaluronan-based hydrogel attenuate inflammation in a spinal cord injury model through M2 microglia/microphage polarization. *Small*. 2022;18:2107838.
35. Zheng C, Zhang H, Cui Y, et al. Bio-C (Modified hyaluronic acid-coated-collagen tube) implants enable functional recovery after complete spinal cord injury. *Pharmaceutics*. 2022;14:596. doi:10.3390/pharmaceutics14030596
36. Yao Z, Chen F, Cui H, Lin T, Guo N, Wu H. Efficacy of chitosan and sodium alginate scaffolds for repair of spinal cord injury in rats. *Neural Regen Res*. 2018;13:502–509. doi:10.4103/1673-5374.228756
37. Rao JS, Zhao C, Zhang A, et al. NT3-chitosan enables de novo regeneration and functional recovery in monkeys after spinal cord injury. *Proc Natl Acad Sci U S A*. 2018;115:E5595–E5604. doi:10.1073/pnas.1804735115
38. Zhang H, Hu T, Xiong M, et al. Cannabidiol-loaded injectable chitosan-based hydrogels promote spinal cord injury repair by enhancing mitochondrial biogenesis. *Int J Biol Macromol*. 2022;221:1259–1270. doi:10.1016/j.ijbiomac.2022.09.013
39. An H, Li Q, Wen J. Bone marrow mesenchymal stem cells encapsulated thermal-responsive hydrogel network bridges combined photo-plasmonic nanoparticulate system for the treatment of urinary bladder dysfunction after spinal cord injury. *J Photochem Photobiol B*. 2020;203:111741. doi:10.1016/j.jphotobiol.2019.111741
40. Stokols S, Sakamoto J, Breckon C, Holt T, Weiss J, Tuszynski MH. Templated agarose scaffolds support linear axonal regeneration. *Tissue Eng*. 2006;12:2777–2787. doi:10.1089/ten.2006.12.2777
41. Gros T, Sakamoto JS, Blesch A, Havton LA, Tuszynski MH. Regeneration of long-tract axons through sites of spinal cord injury using templated agarose scaffolds. *Biomaterials*. 2010;31:6719–6729. doi:10.1016/j.biomaterials.2010.04.035
42. Gao M, Lu P, Bednark B, et al. Templated agarose scaffolds for the support of motor axon regeneration into sites of complete spinal cord transection. *Biomaterials*. 2013;34:1529–1536. doi:10.1016/j.biomaterials.2012.10.070
43. Nazemi Z, Nourbakhsh MS, Kiani S, et al. Co-delivery of minocycline and paclitaxel from injectable hydrogel for treatment of spinal cord injury. *J. Control. Release*. 2020;321:145–158. doi:10.1016/j.jconrel.2020.02.009
44. Huang L, Wang Y, Zhu M, et al. Anisotropic alginate hydrogels promote axonal growth across chronic spinal cord transections after scar removal. *ACS Biomater Sci Eng*. 2020;6:2274–2286. doi:10.1021/acsbiomaterials.9b01802
45. Gholami M, Gilanpour H, Sadeghinezhad J, Asghari A. Facile fabrication of an erythropoietin-alginate/chitosan hydrogel and evaluation of its local therapeutic effects on spinal cord injury in rats. *Daru*. 2021;29:255–265. doi:10.1007/s40199-021-00399-4
46. Heino J, Huhtala M, Kapyla J, Johnson MS. Evolution of collagen-based adhesion systems. *Int J Biochem Cell Biol*. 2009;41:341–348. doi:10.1016/j.biocel.2008.08.021
47. Olsen D, Yang C, Bodo M, et al. Recombinant collagen and gelatin for drug delivery. *Adv Drug Deliv Rev*. 2003;55:1547–1567. doi:10.1016/j.addr.2003.08.008
48. Mienaltowski MJ, Birk DE. Structure, physiology, and biochemistry of collagens. *Progress Heritable Soft Connective Tissue Dis*. 2014;802:5–29.
49. Song R, Murphy M, Li C, Ting K, Soo C, Zheng Z. Current development of biodegradable polymeric materials for biomedical applications. *Drug Design Develop Therapy*. 2018;12:3117–3145. doi:10.2147/DDDT.S165440
50. Yeh J, Wang D, Cherng J, et al. A collagen-based Scaffold for promoting neural plasticity in a rat model of spinal cord injury. *Polymers*. 2020;12:2245. doi:10.3390/polym12102245
51. Breen BA, Kraskiewicz H, Ronan R, et al. Therapeutic effect of neurotrophin-3 treatment in an injectable collagen scaffold following rat spinal cord hemisection injury. *ACS Biomater Sci Eng*. 2017;3:1287–1295. doi:10.1021/acsbiomaterials.6b00167
52. Yang Y, Fan Y, Zhang H, et al. Small molecules combined with collagen hydrogel direct neurogenesis and migration of neural stem cells after spinal cord injury. *Biomaterials*. 2021;269:120479. doi:10.1016/j.biomaterials.2020.120479
53. Li X, Fan C, Xiao Z, et al. A collagen microchannel scaffold carrying paclitaxel-liposomes induces neuronal differentiation of neural stem cells through Wnt/beta-catenin signaling for spinal cord injury repair. *Biomaterials*. 2018;183:114–127. doi:10.1016/j.biomaterials.2018.08.037
54. Ma F, Xiao Z, Chen B, et al. Accelerating proliferation of neural stem/progenitor cells in collagen sponges immobilized with engineered basic fibroblast growth factor for nervous system tissue engineering. *Biomacromolecules*. 2014;15:1062–1068. doi:10.1021/bm500062n
55. Zhao X, Gu R, Zhao Y, et al. Adult spinal cord tissue transplantation combined with local tacrolimus sustained-release collagen hydrogel promotes complete spinal cord injury repair. *Cell Prolif*. 2023;56. doi:10.1111/cpr.13451
56. Roy S, Rhim J. Preparation of antimicrobial and antioxidant gelatin/curcumin composite films for active food packaging application. *Colloids Surfaces B*. 2020;188:110761. doi:10.1016/j.colsurfb.2019.110761
57. Zhang Y, Yao A, Wu J, et al. Conductive hydrogel restores electrical conduction to promote neurological recovery in a rat model. *Tissue Eng Part A*. 2024;30:577–587. doi:10.1089/ten.TEA.2023.0372

58. Zeng X, Zeng Y, Ma Y, et al. Bone marrow mesenchymal stem cells in a three-dimensional gelatin sponge Scaffold attenuate inflammation, promote angiogenesis, and reduce cavity formation in experimental spinal cord injury. *Cell Transplant*. 2011;20:1881–1899. doi:10.3727/096368911X566181
59. Zeng X, Wei Q, Ye J, et al. A biocompatible gelatin sponge scaffold confers robust tissue remodeling after spinal cord injury in a non-human primate model. *Biomaterials*. 2023;299:122161. doi:10.1016/j.biomaterials.2023.122161
60. Liu Y, Cheong NG,S, Yu J, Tsai W. Modification and crosslinking of gelatin-based biomaterials as tissue adhesives. *Colloids Surfaces B*. 2019;174:316–323. doi:10.1016/j.colsurfb.2018.10.077
61. Ramis JM, Blasco Ferrer M, Calvo J, et al. Improved physical and osteoinductive properties of demineralized bone matrix by gelatin methacryloyl formulation. *J Tissue Eng Regen Med*. 2020;14:475–485. doi:10.1002/term.3012
62. Chen S, Wang Y, Lai J, Tan S, Wang M. Structure and properties of Gelatin Methacryloyl (GelMA) synthesized in different reaction systems. *Biomacromolecules*. 2023;24:2928–2941. doi:10.1021/acs.biomac.3c00302
63. Zhou P, Xu P, Guan J, et al. Promoting 3D neuronal differentiation in hydrogel for spinal cord regeneration. *Colloids Surfaces B*. 2020;194:111214. doi:10.1016/j.colsurfb.2020.111214
64. He W, Zhang X, Li X, et al. A decellularized spinal cord extracellular matrix-gel/GelMA hydrogel three-dimensional composite scaffold promotes recovery from spinal cord injury via synergism with human menstrual blood-derived stem cells. *J Mater Chem B Mater Biol Med*. 2022;10:5753–5764. doi:10.1039/D2TB00792D
65. He W, Wang H, Zhang X, et al. Construction of a decellularized spinal cord matrix/GelMA composite scaffold and its effects on neuronal differentiation of neural stem cells. *J Biomater Sci*. 2022;33:2124–2144. doi:10.1080/09205063.2022.2102275
66. Kalotra S, Saini V, Singh H, Sharma A, Kaur G. 5-Nonyloxytryptamine oxalate–embedded collagen–laminin scaffolds augment functional recovery after spinal cord injury in mice. *Ann NY Acad Sci*. 2020;1465:99–116. doi:10.1111/nyas.14279
67. Siddiqui AM, Brunner R, Harris GM, et al. Promoting neuronal outgrowth using ridged Scaffolds coated with extracellular matrix proteins. *Biomedicines*. 2021;10:9. doi:10.3390/biomedicines10010009
68. Xing H, Yin H, Sun C, et al. Preparation of an acellular spinal cord scaffold to improve its biological properties. *Mol Med Rep*. 2019;20:1075–1084. doi:10.3892/mmr.2019.10364
69. Wang Q, Zhang C, Zhang L, et al. The preparation and comparison of decellularized nerve scaffold of tissue engineering. *J Biomed Mater Res Part A*. 2014. doi:10.1002/jbm.a.35103
70. Yin H, Jiang T, Deng X, Yu M, Xing H, Ren X. A cellular spinal cord scaffold seeded with rat adipose-derived stem cells facilitates functional recovery via enhancing axon regeneration in spinal cord injured rats. *Mol Med Rep*. 2018;17:2998–3004. doi:10.3892/mmr.2017.8238
71. Kobayashi T, Chanmee T, Itano N. Hyaluronan: metabolism and Function. *Biomolecules*. 2020;10:1525. doi:10.3390/biom10111525
72. Serban MA, Skardal A. Hyaluronan chemistries for three-dimensional matrix applications. *Matrix Biol*. 2019;78–79:337–345.
73. Khaing ZZ, Milman BD, Vanscoy JE, Seidlits SK, Grill RJ, Schmidt CE. High molecular weight hyaluronic acid limits astrocyte activation and scar formation after spinal cord injury. *J Neural Eng*. 2011;8:46031–46033. doi:10.1088/1741-2560/8/4/046033
74. Kushchayev SV, Giers MB, Hom Eng D, et al. Hyaluronic acid scaffold has a neuroprotective effect in hemisection spinal cord injury. *J Neurosurg Spine*. 2016;25:114. doi:10.3171/2015.9.SPINE15628
75. Ma C, Zhang P, Shen Y. Progress in research into spinal cord injury repair: tissue engineering scaffolds and cell transdifferentiation. *J Neurorestoratology*. 2019;7(4):196–206. doi:10.26599/JNR.2019.9040024
76. Chen Q, Qi Y, Jiang Y, et al. Progress in research of Chitosan chemical modification technologies and their applications. *Mar Drugs*. 2022;20:536. doi:10.3390/md20080536
77. Han S, Lee JY, Heo EY, Kwon IK, Yune TY, Youn I. Implantation of a Matrigel-loaded agarose scaffold promotes functional regeneration of axons after spinal cord injury in rat. *Biochem Biophys Res Commun*. 2018;496:785–791. doi:10.1016/j.bbrc.2018.01.157
78. Tang G, Zhou B, Li F, et al. Advances of naturally derived and synthetic hydrogels for intervertebral disk regeneration. *Front Bioeng Biotechnol*. 2020;8:745. doi:10.3389/fbioe.2020.00745
79. Zhou J, Wu Y, Tang Z, et al. Alginate hydrogel cross-linked by Ca2+ to promote spinal cord neural stem/progenitor cell differentiation and functional recovery after a spinal cord injuryhh. *Regen Biomater*. 2022;9:rbac057.
80. Liu S, Yang H, Chen D, et al. Three-dimensional bioprinting sodium alginate/gelatin scaffold combined with neural stem cells and oligodendrocytes markedly promoting nerve regeneration after spinal cord injury. *Regen Biomater*. 2022;9:rbac038. doi:10.1093/rb/rbac038
81. Zhao J, Pang A, Yin S, et al. Peptide OM-LV20 promotes structural and functional recovery of spinal cord injury in rats. *Biochem Biophys Res Commun*. 2022;598:124–130. doi:10.1016/j.bbrc.2022.02.017
82. Yin S, Yang M, Li Y, et al. Peptide OM-LV20 exerts neuroprotective effects against cerebral ischemia/reperfusion injury in rats. *Biochem Biophys Res Commun*. 2021;537:36–42. doi:10.1016/j.bbrc.2020.12.053
83. Abdolahi S, Aligholi H, Khodakaram-Tafti A, Khaleghi GM, Stummer W, Gorji A. Improvement of rat spinal cord injury following lentiviral vector-transduced neural stem/progenitor cells derived from human epileptic brain tissue transplantation with a self-assembling peptide Scaffold. *Mol Neurobiol*. 2021;58:2481–2493. doi:10.1007/s12035-020-02279-5
84. Álvarez Z, Ortega JA, Sato K, et al. Artificial extracellular matrix scaffolds of mobile molecules enhance maturation of human stem cell-derived neurons. *Cell Stem Cell*. 2023;30:219–238. doi:10.1016/j.stem.2022.12.010
85. Wang Z, Jia S, Xu H, et al. A functionalized self-assembling peptide containing E7 and YIGSR sequences enhances neuronal differentiation of spermatogonial stem cells on aligned PCL fibers for spinal cord injury repair. *Theranostics*. 2022;12:7567–7585. doi:10.7150/thno.78448
86. Babaloo H, Ebrahimi-Barough S, Derakhshan MA, et al. PCL/gelatin nanofibrous scaffolds with human endometrial stem cells/Schwann cells facilitate axon regeneration in spinal cord injury. *J Cell Physiol*. 2019;234:11060–11069. doi:10.1002/jcp.27936
87. Golland B, Tipper JL, Hall RM, Tronci G, Russell SJ. A biomimetic nonwoven-reinforced hydrogel for spinal cord injury repair. *Polymers*. 2022;15:14. doi:10.3390/polym15010014
88. Woodruff MA, Hutmacher DW. The return of a forgotten polymer—Polycaprolactone in the 21st century. *Prog Polym Sci*. 2010;35:1217–1256. doi:10.1016/j.progpolymsci.2010.04.002
89. Rodemer W, Selzer ME. Role of axon resealing in retrograde neuronal death and regeneration after spinal cord injury. *Neural Regen Res*. 2019;14:399–404. doi:10.4103/1673-5374.245330

90. Berkovitch Y, Seliktar D. Semi-synthetic hydrogel composition and stiffness regulate neuronal morphogenesis. *Int J Pharm*. 2017;523:545–555. doi:10.1016/j.ijpharm.2016.11.032
91. Shu B, Sun X, Liu R, et al. Restoring electrical connection using a conductive biomaterial provides a new therapeutic strategy for rats with spinal cord injury. *Neurosci Lett*. 2019;692:33–40. doi:10.1016/j.neulet.2018.10.031
92. Wang Y, Zhang Y, Li X, Zhang Q. The progress of biomaterials in peripheral nerve repair and regeneration. *J Neurorestoratology*. 2020;8:252–269. doi:10.26599/JNR.2020.9040022
93. Wen Y, Yu S, Wu Y, et al. Spinal cord injury repair by implantation of structured hyaluronic acid scaffold with PLGA microspheres in the rat. *Cell Tissue Res*. 2016;364:17–28. doi:10.1007/s00441-015-2298-1
94. Kong W, Qi Z, Xia P, et al. Local delivery of FTY720 and NSCs on electrospun PLGA scaffolds improves functional recovery after spinal cord injury. *Rsc Adv*. 2019;9:17801–17811. doi:10.1039/C9RA01717H
95. Pan S, Qi Z, Li Q, et al. Graphene oxide-PLGA hybrid nanofibres for the local delivery of IGF-1 and BDNF in spinal cord repair. *Artif. Cell Nanomed Biotechnol*. 2019;47:651–664.
96. Liu X, Hao M, Chen Z, et al. 3D bioprinted neural tissue constructs for spinal cord injury repair. *Biomaterials*. 2021;272:120771. doi:10.1016/j.biomaterials.2021.120771
97. Wang P, Wang H, Ma K, et al. Novel cytokine-loaded PCL-PEG scaffold composites for spinal cord injury repair. *RSC Adv*. 2020;10:6306–6314. doi:10.1039/C9RA10385F
98. Javed R, Ao Q. Nanoparticles in peripheral nerve regeneration: a mini review. *J Neurorestoratol*. 2022;10:1–12. doi:10.26599/JNR.2022.9040001
99. Alvarez Z, Kolberg-Edelbrock AN, Sasselli IR, et al. Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury. *Science*. 2021;374:848. doi:10.1126/science.abh3602
100. Hassannejad Z, Zadegan SA, Vaccaro AR, Rahimi-Moyaghar V, Sabzeyari O. Biofunctionalized peptide-based hydrogel as an injectable scaffold for BDNF delivery can improve regeneration after spinal cord injury. *Injury-Int J Care Inj*. 2019;50:278–285. doi:10.1016/j.injury.2018.12.027
101. Bechara SL, Judson A, Popat KC. Template synthesized poly(ε-caprolactone) nanowire surfaces for neural tissue engineering. *Biomaterials*. 2010;31:3492–3501. doi:10.1016/j.biomaterials.2010.01.084
102. Abbasi N, Hashemi SM, Salehi M, et al. Influence of oriented nanofibrous PCL scaffolds on quantitative gene expression during neural differentiation of mouse embryonic stem cells. *J Biomed Mater Res Part A*. 2016;104:155–164. doi:10.1002/jbm.a.35551
103. Donoghue PS, Lamond R, Boomkamp SD, et al. The development of an ε-polycaprolactone scaffold for central nervous system repair. *Tissue Eng Part A*. 2013;19:497–507. doi:10.1089/ten.tea.2012.0382
104. Xue R, Qian Y, Li L, Yao G, Yang L, Sun Y. Polycaprolactone nanofiber scaffold enhances the osteogenic differentiation potency of various human tissue-derived mesenchymal stem cells. *Stem Cell Res Ther*. 2017;8:148. doi:10.1186/s13287-017-0588-0
105. Zhang S, Wang XJ, Li WS, et al. Polycaprolactone/polysialic acid hybrid, multifunctional nanofiber scaffolds for treatment of spinal cord injury. *Acta Biomater*. 2018;77:15–27. doi:10.1016/j.actbio.2018.06.038
106. D'Souza AA, Shegokar R. Polyethylene glycol (PEG): a versatile polymer for pharmaceutical applications. *Expert Opin Drug Deliv*. 2016;13:1257–1275. doi:10.1080/17425247.2016.1182485
107. Luo J, Borgens R, Shi R. Polyethylene glycol improves function and reduces oxidative stress in synaptosomal preparations following spinal cord injury. *J Neurotrauma*. 2004;21:994–1007. doi:10.1089/0897715041651097
108. Papastefanaki F, Jakovcevski I, Poulia N, et al. Intraspinal delivery of polyethylene glycol-coated gold nanoparticles promotes functional recovery after spinal cord injury. *Mol Ther*. 2015;23:993–1002. doi:10.1038/mt.2015.50
109. Estrada V, Brazda N, Schmitz C, et al. Long-lasting significant functional improvement in chronic severe spinal cord injury following scar resection and polyethylene glycol implantation. *Neurobiol Dis*. 2014;67:165–179. doi:10.1016/j.nbd.2014.03.018
110. Zhang C, Wang A, Zhang G, Rong W, Wu C, Huo X. Effects of the combination therapy of electric field stimulation and polyethylene glycol in the ex vivo spinal cord of female rats after compression. *J Neurosci Res*. 2021;99:1850–1863. doi:10.1002/jnr.24839
111. Li G, Zhao M, Xu F, et al. Synthesis and biological application of polylactic acid. *Molecules*. 2020;26:25. doi:10.3390/molecules26010025
112. Fasolino I, Carvalho ED, Raucci MG, et al. Eumelanin decorated poly (lactic acid) electrospun substrates as a new strategy for spinal cord injury treatment. *Biomater Adv*. 2023;146:213312. doi:10.1016/j.bioadv.2023.213312
113. Raynald S, Liu B, B. X, et al. Polypyrrole/polylactic acid nanofibrous scaffold cotransplanted with bone marrow stromal cells promotes the functional recovery of spinal cord injury in rats. *CNS Neurosci Ther*. 2019;25:951–964. doi:10.1111/cns.13135
114. Swider E, Koshkina O, Tel J, Cruz LJ, de Vries I, Srinivas M. Customizing poly (lactic-co-glycolic acid) particles for biomedical applications. *Acta Biomater*. 2018;73:38–51. doi:10.1016/j.actbio.2018.04.006
115. Wei G, Jiang D, Hu S, et al. Polydopamine-decorated microcomposites promote functional recovery of an injured spinal cord by inhibiting neuroinflammation. *ACS Appl Mater Interfaces*. 2021;13(40):47341–47353. doi:10.1021/acsami.1c11772
116. Sun F, Shi T, Zhou T, et al. 3D poly (Lactic-co-glycolic acid) Scaffolds for treating spinal cord injury. *J Biomed Nanotechnol*. 2017;13:290–302. doi:10.1166/jbn.2017.2348
117. Xia L, Wan H, Hao SY, et al. Co-transplantation of neural stem cells and Schwann cells within poly (L-lactic-co-glycolic acid) scaffolds facilitates axonal regeneration in hemisected rat spinal cord. *Chin Med J*. 2013;126:909–917. doi:10.3760/cma.j.issn.0366-6999.20120476
118. Zeraatpisheh Z, Mirzaei E, Nami M, et al. Local delivery of fingolimod through PLGA nanoparticles and PuraMatrix-embedded neural precursor cells promote motor function recovery and tissue repair in spinal cord injury. *Eur J Neurosci*. 2021;54:5620–5637. doi:10.1111/ejn.15391
119. Azizi M, Farahmandghavi F, Joghataei MT, et al. ChABC-loaded PLGA nanoparticles: a comprehensive study on biocompatibility, functional recovery, and axonal regeneration in animal model of spinal cord injury. *Int J Pharm*. 2020;577:119037. doi:10.1016/j.ijpharm.2020.119037
120. Chen Z, Zhang H, Fan C, et al. Adhesive, stretchable, and spatiotemporal delivery fibrous hydrogels harness endogenous neural stem/progenitor cells for spinal cord injury repair. *ACS Nano*. 2022;16:1986–1998. doi:10.1021/acsnano.1c06892
121. Li L, Xiao B, Mu J, et al. A MnO_2 nanoparticle-dotted hydrogel promotes spinal cord repair via regulating reactive oxygen species microenvironment and synergizing with mesenchymal stem cells. *ACS Nano*. 2019;13:14283–14293. doi:10.1021/acsnano.9b07598

122. Gao X, Han Z, Huang C, et al. An anti-inflammatory and neuroprotective biomimetic nanoplatform for repairing spinal cord injury. *Bioact Mater*. 2022;18:569–582. doi:10.1016/j.bioactmat.2022.05.026
123. Ma D, Shen H, Chen F, et al. Inflammatory microenvironment-responsive nanomaterials promote spinal cord injury repair by targeting IRF5. *Adv. Healthc. Mater*. 2022;11:e2201319. doi:10.1002/adhm.202201319
124. Xu D, Wu D, Qin M, et al. Efficient delivery of nerve growth factors to the central nervous system for neural regeneration. *Adv Mater*. 2019;31 (33):e1900727. doi:10.1002/adma.201900727
125. Luo W, Wang Y, Lin F, et al. Selenium-doped carbon quantum dots efficiently ameliorate secondary spinal cord injury via scavenging reactive oxygen species. *Int J Nanomed*. 2020;15:1011. doi:10.2147/IJN.S282985