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Engineered hydrogels for peripheral nerve repair

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ABSTRACT

Peripheral nerve injury (PNI) is a complex disease that often appears in young adults. It is characterized by a high incidence, limited treatment options, and poor clinical outcomes. This disease not only causes dysfunction and psychological disorders in patients but also brings a heavy burden to the society. Currently, autologous nerve grafting is the gold standard in clinical treatment, but complications, such as the limited source of donor tissue and scar tissue formation, often further limit the therapeutic effect. Recently, a growing number of studies have used tissue-engineered materials to create a natural microenvironment similar to the nervous system and thus promote the regeneration of neural tissue and the recovery of impaired neural function with promising results. Hydrogels are often used as materials for the culture and differentiation of neurogenic cells due to their unique physical and chemical properties. Hydrogels can provide three-dimensional hydration networks that can be integrated into a variety of sizes and shapes to suit the morphology of neural tissues. In this review, we discuss the recent advances of engineered hydrogels for peripheral nerve repair and analyze the role of several different therapeutic strategies of hydrogels in PNI through the application characteristics of hydrogels in nerve tissue engineering (NTE). Furthermore, the prospects and challenges of the application of hydrogels in the treatment of PNI are also discussed.

1. Introduction

Millions of people suffer from acute peripheral nerve injury (PNI) every year. Through traumatic, nontraumatic, and iatrogenic events, patients develop painful neuropathy and neuroma, poor sensation, weakness, and paralysis due to motor and sensory axon damage and loss of function [1]. It is estimated that in developed countries such as Europe and the United States, the proportion of people suffering from PNI each year will account for hundreds of thousands of people, while in developing countries, the ratio is considered higher [2]. The mechanism of nerve regeneration is complex. The nervous system is mainly composed of two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The PNS is mainly composed of cranial nerves, spinal nerves, and peripheral nerves, as well as target organs and muscles connected to the nerve [3]. Among them, peripheral nerves act as channels that transmit sensory information to and from the central nervous system to muscles and glands throughout the body [4]. Neuronal cells are the basic cells in the PNS, while Schwann cells (SCs) and macrophages have also been found to be supporting cells in the PNS system and play an important role in axonal regeneration [5,6]. A series of cellular and molecular events known as Wallerian degeneration occurs first after PNI. When injury occurs, SCs undergo dedifferentiation, proliferation and subsequent activation of macrophages, which are recruited to the injury to remove myelin debris and necrotic tissue, ultimately leading to nerve regeneration [7–9]. Although PNS axons can be regenerated, it is still difficult to achieve satisfactory results. Excess macrophages increase the release of pro-inflammatory factors, which can lead to increased levels of local reactive oxygen species (ROS) in tissues and inhibit peripheral nerve growth [10–12]. When the target muscle is denervated for a long time, it will lead to muscle paralysis and atrophy [13,14]. Therefore, it is necessary to adopt aggressive treatments to enhance peripheral nerve regeneration and reconnect with target organs in as short a time as possible to avoid innervation of nerve-induced dysfunction leading to a decline in patient quality of life.

For most PNI caused by trauma, surgery is required to explore and treat the damage. The gold standard treatment for PNI with a large nerve

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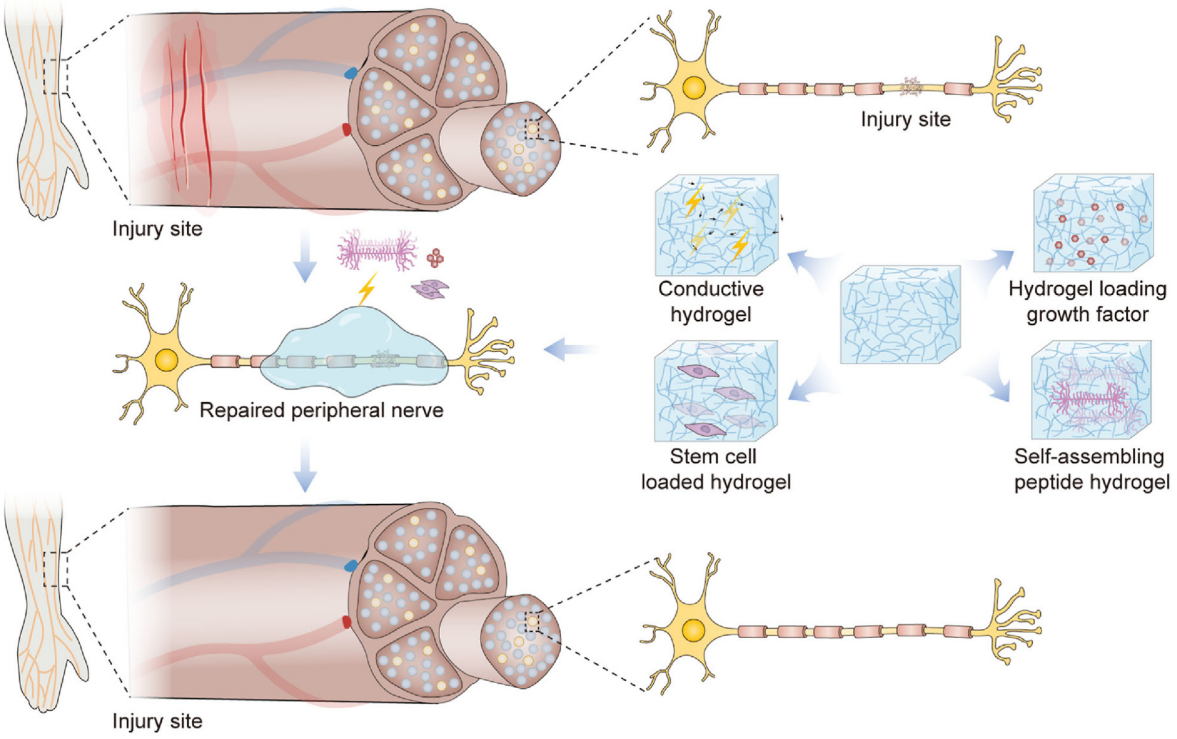
space is autologous nerve transplantation. However, this approach suffers from the need for multiple operations, donor limitation, loss of nerve function, scar formation, etc. [15]. To overcome the limitation of autologous nerve consistency, neural tissue-engineered scaffolds based on biomimetic strategies are emerging as a reliable alternative to clinical nerve transplantation [16]. Traditional tissue engineering strategies have focused on the treatment of injury by implanting natural or synthetic biomaterial-based nerve guide conduits (NGCs) [17,18]. NGC acts as a bridge between the stumps on both sides of the injured nerve, provides structural and nutritional support for both ends and supports the regeneration of surrounding axons along the conduit [19]. However, traditional nerve conduits have a rigid structure and poor flexibility and are incompatible with nerve tissue, resulting in the risk of local cutting of the nerve stump [20,21].

Therefore, because of the lack of current PNI treatment methods and the defects of tissue engineering materials, many researchers are committed to developing new therapeutic strategies as treatment methods for peripheral nerve regeneration. In recent years, based on the inherent physicochemical and biological characteristics of hydrogels, such as high water content, structural similarity to the natural extracellular matrix (ECM), porous structure, low immunogenicity, tunable biodegradability, and biocompatibility, they have become widespread materials for biomedical applications, such as for tissue engineering, drug and gene delivery, wound healing, contact lenses, hemostatic bandages, and biosensors [22]. Nerve tissue is a soft tissue, so the material of choice for promoting nerve cell growth and differentiation should be relatively soft to better mimic the microenvironment surrounding the nerve [23]. This also makes hydrogels a promising candidate for neural tissue engineering [24]. Hydrogels have a three-dimensional (3D) cross-linked network of hydrophilic organic polymers that can absorb large amounts of water, provide a soft and elastic morphology, and minimize irritation to adjacent tissues in vivo [25]. The inherently 3D porous structure of hydrogels can help cells adhere, proliferate and migrate in vivo, and this 3D structure facilitates the transport and retention of nutrients and growth factors [26]. This also makes hydrogels a promising candidate for neural tissue engineering [24]. At present, research on hydrogels for the treatment of PNI mainly includes the following strategies: (I) stimulation of the regeneration of peripheral nerves according to the electrical conductivity of nerves, (II) utilization of the factors that can promote the differentiation of stem cells, (III) the effect of nerve growth factor release on peripheral nerve regeneration, and (IV) recent studies on peptide sequence-based therapy. Several of these therapeutic strategies combine physical, chemical and bioactive clues with hydrogels for the treatment of nerve injuries. In previous studies, each of these strategies has been used individually or in combination to promote nerve regeneration (Scheme 1), so there is an urgent need to systematically summarized work to explore the potential and shortcomings of engineered hydrogels for nerve repair. In this review, we first systematically summarize the design and methods of the hydrogel-based strategies applied to PNI treatment, and then discuss the remaining obstacles and future directions of hydrogel-based materials in the field of PNI treatment.

2. Conductive hydrogels (CHs)

Electrical signals can control the metabolism, adhesion, proliferation, migration, and differentiation of nerve cells [27–29]. Although the mechanism by which electrical stimulation promotes neuronal regeneration is not fully understood, previous studies have shown that the local electric field changes in extracellular matrix molecules [30] and the release of some neurotrophic factors are both dependent on electrical stimulation [31]. This significantly increases the potential for nerve regeneration and myelination by enhancing electrostatic cell-cell and cell-scaffold interactions, resulting in complete overall recovery [20,32]. Therefore, hydrogels with a simulated natural extracellular matrix and conductive properties have attracted increasing attention in the treatment of PNI. CHs not only retain their inherent electrical conductivity but also have excellent properties of hydrogels, such as highwayer content, porosity, softness, plasticity, mechanical properties and large surface area [33,34]. The conductive materials currently used in artificial tissue engineering mainly include conductive polymers and carbon-based conductive materials [35,36].



Scheme 1. Schematic illustration of the application of hydrogels with different therapeutic strategies in the treatment of peripheral injuries.

2.1. Conductive polymer (CP) -based CHs

CPs, such as polypyrrole (PPy), polyaniline (PANI), polythiophene and poly (3,4-dioxoethylene ethionine) (PEDOT), have been widely used in the biomedical field, including bioactuators, sensors, nerve grafts, drug delivery systems and tissue engineering scaffolds [37,38]. Tissue engineering biomaterials based on CPs are now widely used in electrically sensitive tissues and organs such as skeletal muscle, heart muscle, skin, and nerves [39,40]. CPs-based CHs have been reported to enhance the proliferation and adhesion of cardiomyocytes, L929 fibroblasts, mesenchymal stem cells, rat adrenal chromaffin cells (PC-12), and SCs [41].

2.2. PPy-based CHs

PPy can be synthesized chemically or electrochemically, and it has good biocompatibility and a noninflammatory response after long-term implantation in the body [42,43]. **Liu et al**. [44] developed a soft, viscous CH film with good biocompatibility. The hydrogel dressing was constructed by crosslinking PPy and tannic acid (TA) under the action of an oxidation initiator ($FeCl_3$) (Fig. 1A). This hydrogel not only has good electrical conductivity but also good biocompatibility. Cytoskeleton staining images showed that the SCs cells cultured on the conductive hydrogel exhibited good interconnectivity and stretching, demonstrating that this conductive hydrogel dressing can promote the adhesion of SCs (Fig. 1B). Moreover, this hydrogel dressing can self-coil into a tubular shape and easily fit on the surface of a damaged nerve, avoiding more complicated manipulation (Fig. 1C). Recently, Liang et al. constructed exosomes-loaded electroconductive nerve dressing for nerve regeneration and pain relief against diabetic peripheral nerve injury based on the above study [45]. Exosomes carry a variety of signaling molecules, such as proteins, lipids, and miRNAs, that can be transferred to recipient cells and achieve immunomodulatory functions. In recent years, exosomes have emerged as a novel therapeutic strategy for the relief of pain, inflammatory diseases, and damaged tissues [46]. **Xu et al.** [47] mixed N-carboxyethyl chitosan (CEC) with chitosan-modified polypyrene nanoparticles (DCP) by electrostatic action at room temperature and then cross-linked them with unique aldehyde-terminated bifunctional polyurethane (DFPU) to form DCC hydrogels by a dynamic Schiff base reaction (Fig. 1D). The conductive DCC hydrogel is injectable, self-healing, highly absorbent and elastic even after the hydrogel scaffold is deformed. In vivo experiments using zebrafish brain injury models where hydrogel was injected into the damaged site helped restore 80% of function and demonstrated that this conductive hydrogel can initiate nerve regeneration. In another case, **Bu et al**. [48] designed a hydrogel consisting of carboxymethyl chitosan (CMCS) and sodium alginate (SA) by doping PPy to improve the conductivity of the hydrogel, forming a conductive (SA/CMCS/PPy) hydrogel for peripheral nerve regeneration. The SA/CMCS/PPy-CH has good biocompatibility with SCs, PC-12 cells and bone marrow mesenchymal stem cells (BMMSCs).

2.3. PEDOT-based CHs

PEDOT is a further prepared polymer based on polythiophene (PTH), which has excellent electrical activity and chemical stability [35]. The higher conductivity of PEDOT is related to the lack of α-β and β-β′ coupling under biological conditions [50,51]. Studies have shown that PEDOT, as a commonly used biomedical material, is resistant to oxygen and water degradation [52]. In recent years, PEDOT has been increasingly introduced into biopolymer (chitosan [36], cellulose [53], gelatin [54], hyaluronic acid, etc.)-based hydrogels, as an effective method to promote nerve regeneration. For instance, **Huang et al**. [55] prepared a new type of conductive hydrogel film of chitin/PEDOT (ChT-PEDOT-p) by using the electrostatic interaction between partially deacetylated chitin and PEDOT NPs. The ChT-PEDOT-p hydrogel was modified with Cys-Arg-Gly-Asp (CRGD) and implanted into a 10-mm rat model of sciatic nerve defects for treatment and induction of nerve regeneration (Fig. 2A). The ChT-PEDOT-p hydrogel can effectively enhance the proliferation of

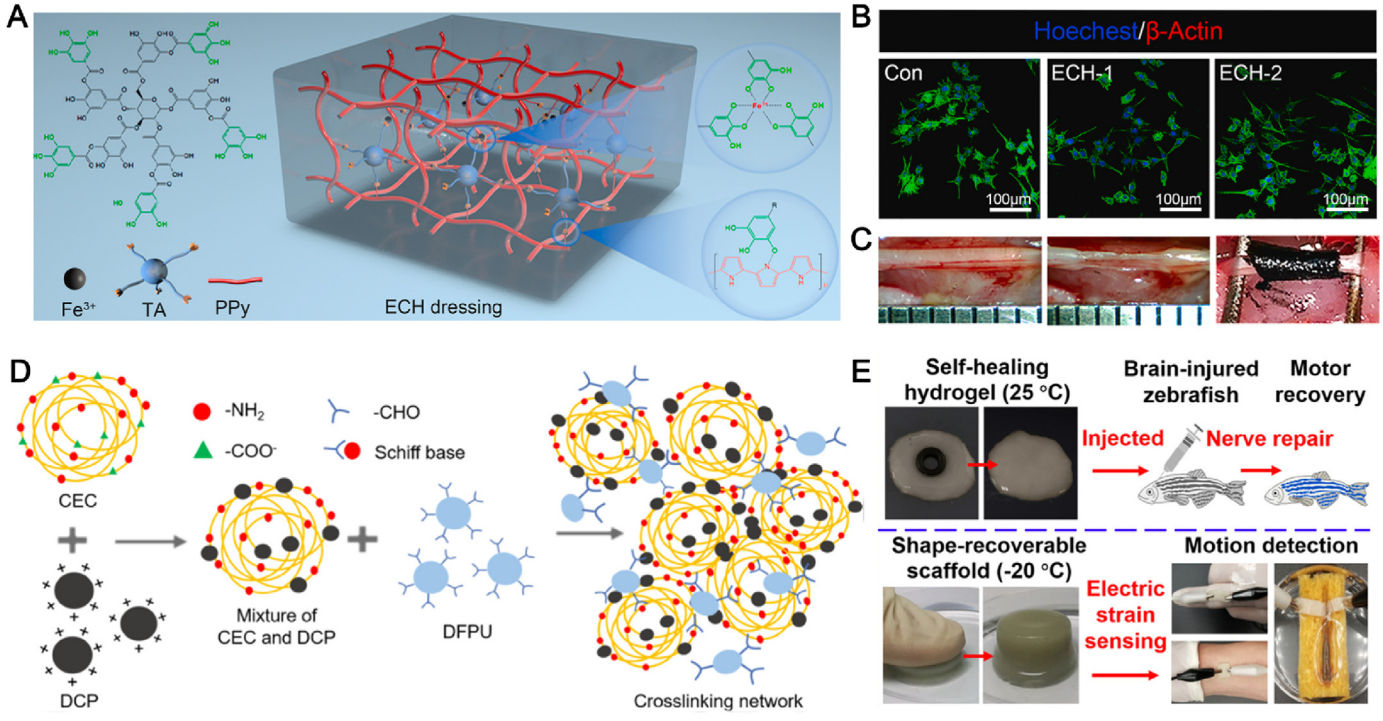


Fig. 1. Conductive hydrogels based on PPy. (A) Schematic representation of the chemical structure of ECH formation. (B) ECH promotes adhesion of SCs. (C) The electrically conductive hydrogel dressing, when implanted in the body, self-curling around the injured nerve to form a tubular wrap around the nerve. (D) Synthesis process of CDD hydrogel. (E) Morphology and self-healing properties of hydrogels at different temperatures and application to zebrafish brain injury for treatment. Reused with permission [44]. Copyright, Elsevier Ltd. (2021). Reused with permission [49], Copyright, American Chemical Society (2020).

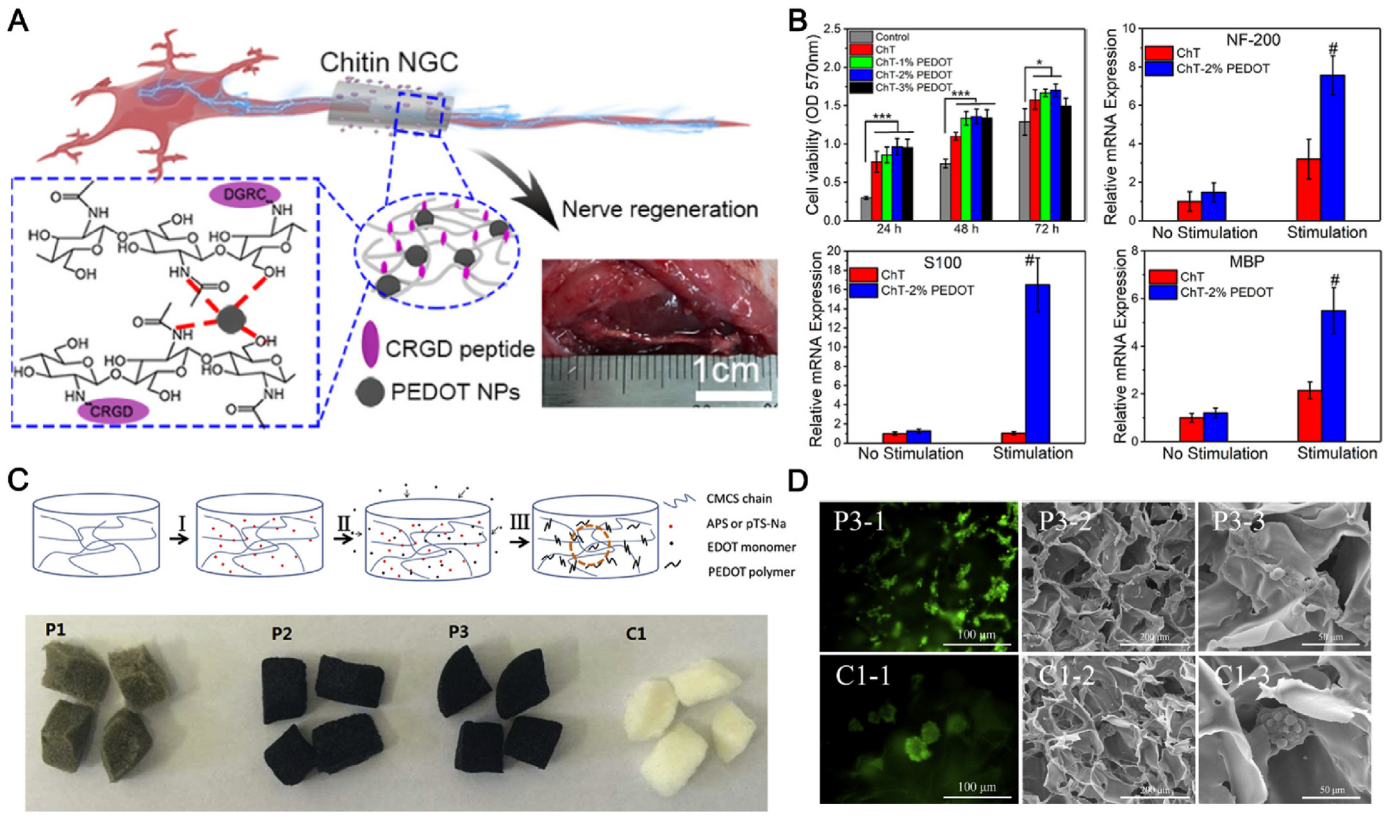


Fig. 2. (A) Schematic representation of the synthesis of ChT-PEDOT-p hydrogel modified with the tetrapeptide Cys-Arg-Gly-Asp (CRGD) and used to repair sciatic nerve defect in rats. (B) Cellular experiments demonstrate that this conductive hydrogel promotes the proliferation of SCs and the expression of neuroregeneration-related proteins. (C) The synthesis process of PEDOT/CMCS hydrogels and the external phase of hydrogels with different concentrations of PEDOT content. (D) Immunofluorescence and SEM images of PC-12 cell conducting hydrogel and pure CMCS hydrogel. Reused with permission [55], Copyright, American Chemical Society (2021). Reused with permission [56], Copyright, Elsevier B.V. All rights reserved (2018).

SCs in vitro, and enhance the expression of SC cell-activated proteins S100 and NF-200 and myelin fundamental protein (MBP) with the help of electrical incitement (Fig. 2B).

Agarose can also promote the adhesion, survival, and synaptic growth of nerve cells [57]. **Abidian et al.** [58] electrodeposited PEDOT in the lumen of agarose hydrogel nerve conduits by electrodeposition to form hydrogel nerve conduits with PEDOT coating. The mechanical strength and electrical conductivity of the PEDOT-modified agarose conduit were further improved. In experimental assessments of the number of innervated muscles, the number of myelinated axons, nerve fiber diameter, axon diameter, and myelin thickness, the PEDOT-modified agarose catheter recovered better than the control group.

Moreover, CMCS can be easily modified due to its –OH, $–NH_2$, and –COOH groups [59]. Based on these advantages, **Xu et al.** [56] developed a conductive composite hydrogel (PEDOT/CMCS) using CMCS as a biodegradable polymer network with the introduction of PEDOT by in situ chemical polymerization. Compared to the pure CMCS hydrogel with white color, the conductive hydrogel deepened in color and increased in conductivity with increasing PEDOT content (Fig. 2C). The expansion and growth morphology of PC-12 cells on the conductive hydrogels were significantly better than those on the pure CMCS hydrogels as observed by fluorescence staining and SEM (Fig. 2D).

2.4. PANI-based CHs

PANI has been widely studied due to its low cost and availability of raw materials, easy synthetic route, good environmental stability, electrical conductivity, and better compatibility compared to other biopolymers [60].

In recent years, in addition to the properties of polymer materials used to tune the properties of hydrogel synthesis, numerous studies have pointed out that acousto-optic stimulation to the synthesis of hydrogels. **Dong et al.** [61] developed a conductive hydrogel similar to native nerve tissue by polymerizing polyacrylamide (PAM) and PANI (Fig. 3A). Following irradiation using near-infrared light, PANI enhanced the bioelectrical signal and used this conductive hydrogel as a replacement for peripheral nerve defects. When this conductive hydrogel was applied to the damaged sciatic nerve of a toad and electrically stimulated, the action potential emitted resulted in the contraction of the gastrocnemius muscle when above the resting potential threshold. This hydrogel was shown to have good electrical conductivity (Fig. 3B).

Some studies have used cellulose hydrogels as a template and in situ-synthesized PANI through finite interface polymerization to produce PANI/cellulose composite hydrogels with conductive interfaces. This hydrogel can significantly induce the adhesion and extension of neurons. **Xu et al.** [62] designed a high-strength conductive hydrogel coated with PANI. This conductive hydrogel supports the adhesion and proliferation of neural stem cells (NSCs) and modulates the specific differentiation of NSCs under electrical stimulation (Fig. 3C)

2.5. Graphene-based CHs

Graphene is known for its high specific surface area, high chemical stability and good electrical conductivity [63]. The edges of graphene have multiple functional groups, such as phenolic hydroxyl groups, carboxylic acid, and epoxide groups. These radicals can incorporate other materials into the framework through electrostatic and π-π interactions, hydrogen bonding, etc [64,65]. Graphene-based materials can be used to

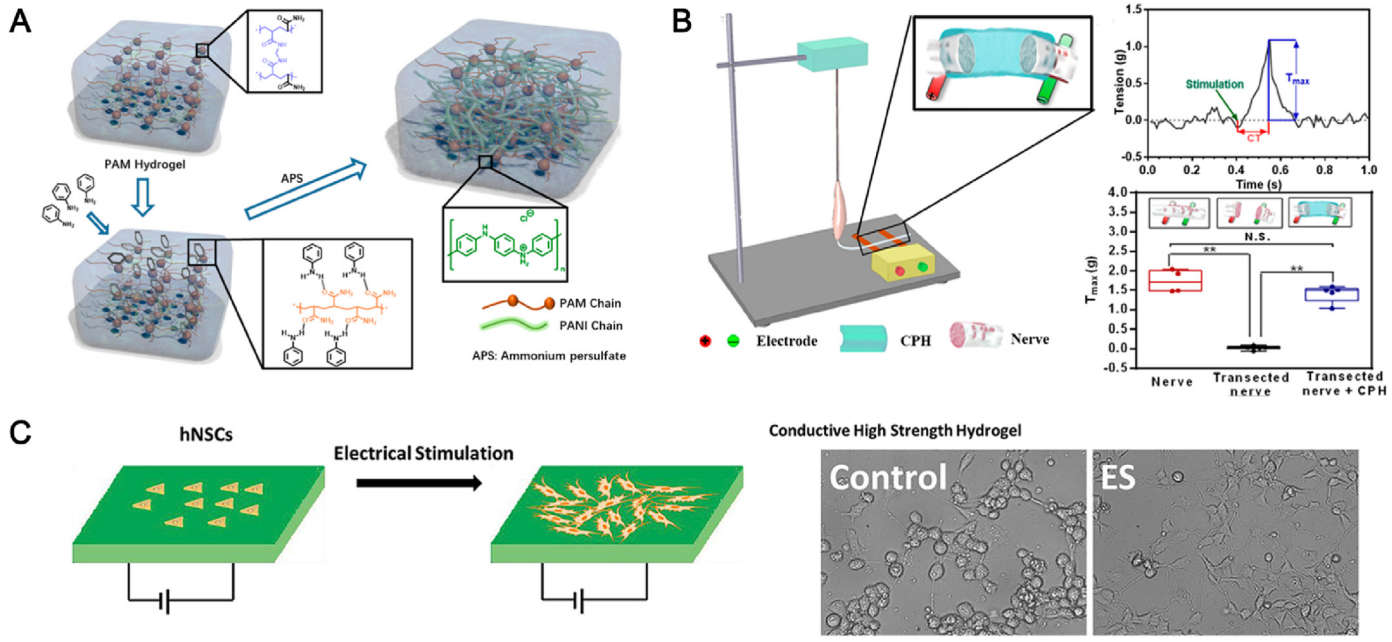


Fig. 3. (A) Diagram of crosslinking PAM and PANI to make a conductive hydrogel. (B) Application of a conductive hydrogel to the damaged sciatic nerve of the toad, with the aid of electrical stimulation to test the contraction of the gastrocnemius muscle and record the contraction curve. (C) Conductive high-strength hydrogels doped with PANI support the attachment and proliferation of NSCs and promote neuronal differentiation through electrical stimulation. Reused with permission [62], 2016 Elsevier Ltd. All rights reserved. Reused with permission [61], Copyright, American Chemical Society (2020).

fabricate conductive materials with good biocompatibility and chemical-physical interactions to promote cell attachment and proliferation [66]. **Zhao et al.** [67] prepared polyacrylamide/graphene oxide/gelatin/sodium alginate (PAM/GO/Gel/SA) composite hydrogels by incorporating graphene oxide, gelatin, and sodium alginate into polyacrylamide hydrogels. In addition to the excellent electrical and mechanical properties, PAM/GO/Gel/SA hydrogels can promote the growth of Schwann cells. At the same time, the expression of the neural-specific proteins GAP43 and MBP was superior to that of the nerve conduit group in the PAM/GO/Gel/SA hydrogels. Therefore, based on this, a PAM/GO/Gel/SA hydrogel conduit was further constructed to repair an 8-mm sciatic nerve defect, and positive neuro repair results were obtained [68]. Graphene also has some limitations, such as few active sites, poor chemical stability, and direct application of graphene in vivo where its biocompatibility remains controversial [69]. Owing to the long-term retention of biomaterials that require adjuvant therapy after nerve injury, to avoid unnecessary in vivo toxicity, researchers have gradually shifted their attention to graphene derivatives with better biocompatibility for the design and development of biomedical materials [70]. For example, graphene oxide (GO) is a simple graphene derivative with high biomolecular uptake due to the presence of carboxyl (-OOH) epoxy (-O) and hydroxyl (-OH) groups on the edges and planes of its structure. Reduced graphene oxide (rGO) is another important member of the graphene family and is produced by reducing the oxygen content in graphene oxide through exposure to high temperatures, chemical methods, or ultraviolet (UV) radiation [71]. **Park et al.** [19] used graphene oxide and methacrylate gelatin (GelMA) to form a reduction (r(GO/GelMA)). A hydrogel NGC with good electrical conductivity, flexibility, mechanical stability, and permeability was designed. Compared with GelMA without GO, r(GO/GelMA) can make PC-12 neural cells more differentiated. This may be caused by the electroactivity and molecular interaction of rGO in the hydrogel.

The good mechanical strength of graphene also means that it can be used as a biomaterial for the preparation of NGCs. **Huang et al.** [72] fabricated 3D graphene mesh tubes (GMTs) using nickel mesh as a template. Subsequently, Netrin-1 was filled into the gel and used to treat a 10-mm defect in the sciatic nerve of rats (Fig. 4A). Immunofluorescence staining of sciatic nerve S100 showed that the immunofluorescence expression of S100 in the hydrogel scaffold containing Netrin-1 was significantly better than that in the autologous nerve graft and hydrogel scaffold alone groups, demonstrating that the hydrogel scaffold containing Netrin-1 could better promote the secretion of trophic factors to aid peripheral nerve recovery (Fig. 4 B).

Other materials, such as silk fibroin (SF) [73] and carbon nanotubes (CNT) [74] are also frequently involved in the fabrication of conducting hydrogels and stimulate the growth of SCs and the secretion of trophic factors through electrical conductivity. Neural repair achieved desirable results. In addition, combining the electrophysiological environment of neural tissue with various conductive polymers, carbon-based materials, metal nanoparticles, and other conductive materials to form a conductive hydrogel can provide an electrophysiological environment suitable for neural tissue [75,76]. **Zhao et al.** [73] prepared silk protein (SF)/GO biocomposite hydrogels with conductive properties by combining SF and GO nanosheets in different proportions (Fig. 4C). By observing the morphology of SCs through a bright field and fluorescence images of f-actin, it was found that the conductivity of the hydrogels facilitated the adhesion and diffusion of SCs, and the results showed that a relatively soft hydrogel matrix would give a good morphology of SCs (Fig. 4D).

Carbon nanotubes (CNTs), such as graphene, are also commonly used carbon-based conductive materials (CBCMs), which have excellent electrical and thermal conductivity [77]. When carbon-based materials are added to hydrogels, their electrical conductivity can significantly stimulate the response of nerve cells [78]. **He et al.** [74] prepared nanofibrous hydrogels with good electrical conductivity and injectability by homogeneously mixing carbon nanotubes with functional self-assembled peptides (SAPs). Experiments on the surface and inside the hydrogel showed that the conductive hydrogel can promote axonal growth and SC migration from the dorsal root ganglion (DRG).

3. Hydrogels combined with stem cells for peripheral nerve injury

After PNI, SCs play a key role in nerve repair, and SCs develop a microenvironment conducive to axon regeneration by secreting various

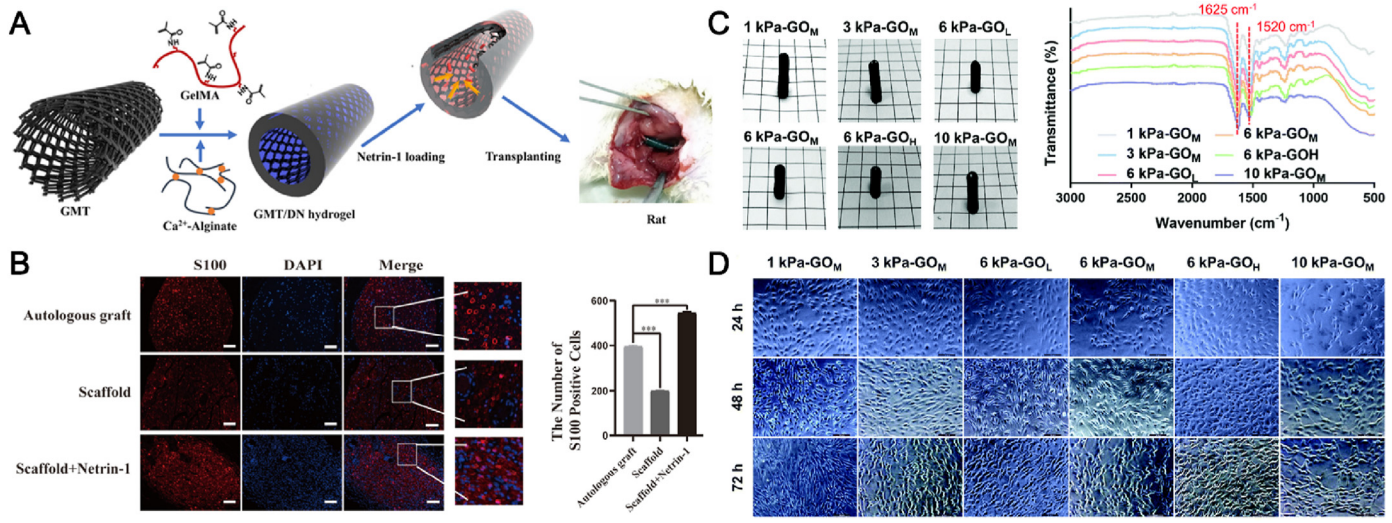


Fig. 4. (A) Schematic representation of the synthesis of a 3D graphene hydrogel scaffold containing Netrin-1 with the treatment of a 10 mm sciatic nerve defect. (B) S100 immunofluorescence expression results (Scale bar: 100 μm). (C) Optical images and FTIR spectra of SF/GO hydrogels with different GO contents. (D) Optical images of SC incubated on SF/GO biocomposite hydrogels for 24, 48, and 72 h respectively (Scale bar: 100 μm). Reused with permission [72], Copyright, American Chemical Society (2021). Reused with permission [73], Copyright, Royal Society of Chemistry (2022).

neurotrophins and neurophilic factors [79]. SC also showed an enhanced response when binding to other cells. It has been proven that these cells cooperate to promote myelin formation and repair of sciatic nerve axon injury [80,81]. However, SC has some obvious disadvantages in nerve repair, such as being difficult to culture [82] and obtain [83]. Stem cells as the source of SCs have attracted much attention from researchers. Multiple stem cells can be used to replace SC in peripheral nerve regeneration [84–86]. Recently, many studies have elaborated on the viability of using hydrogels as a vehicle to load and stimulate the differentiation of neural progenitor cells into various cell types. The hydrogel can be used as a medium to make stem cells have better viability and promote cell proliferation and preservation [87,88]. An important application of hydrogels as bioactive materials is their use and role in stem cell therapy [89].

3.1. Hydrogel combined with embryonic stem cells (ESCs)

ESCs are pluripotent stem cells derived from the blastocyst stage of embryonic development [90]. This method of isolating pluripotent cell lines from human blastocysts was proposed by Thomson et al., in 1998 [91]. ESCs can separate into cells with the morphological and atomic characteristics of SCs and physically associate with axons to supplant SCs fundamental for nerve recovery. **Ziegler et al.** [79] invented a method to differentiate SCs from hESCs with an efficiency of 60%. Differentiated SCs from human ESCs express Schwann cell markers, such as p75 glial fibrillary acidic protein and S100, while also stimulating the myelination of dorsal root ganglion neurons [92]. Studies have used mouse ESCs directly microinjected into an injured peripheral epineurium to achieve significantly improved regeneration of the sciatic nerve. The transplanted stem cells survived in the body for up to three months and differentiated into myelin cells [93].

However, ESC also has obvious drawbacks. It has been reported that ESCs can lead to teratoma formation, mainly because of their inherent tumorigenic nature [94]. However, this source of stem cells has the risk of immunogenicity and various ethical barriers [95].

3.2. Hydrogel combined with adipose-derived mesenchymal stem cells (ADSCs)

Compared with the invasive and painful procedure of obtaining BMSCs, ADSCs can be obtained in a minimally invasive manner [96]. The proliferation and differentiation ability of ADSCs is also much higher than that of bone mesenchymal stem cells (BMSCs) [97]. ADSCs proliferated faster in culture than BMSCs. The quantitative differentiation of SCs by immunocytochemical staining showed that although the difference was not significant, the S100-positive ADSCs (88.6 ± 4.0%) were higher than the S100-positive BMSCs (84.23 ± 5.65%). Therefore, ADSCs show the same positive function as BMSCs in nerve regeneration [98]. While ADSCs are easier to harvest and expand than BMSCs [99].

In tissue engineering, various synthetic nerve conduits are commonly used to study peripheral nerve repair. **Klein et al.** [100] used a commercially available absorbable collagen nerve conduit (NeuraGen) loaded with **ADSCs** from different sources to treat 10-mm peripheral nerve defects. Increased S100 immunoreactivity was detectable in the ADSCs-inoculated conduit group at 6 months postinjury, but not in the ADSCs-free control group. The conduits preseeded with ADSCs showed a more ordered axonal arrangement inside compared to the control nerve conduits without ADSCs. Similar studies have shown that ADSCs-filled conduits have the same regenerative effect on rat sciatic nerve injury as SCs-filled conduits [101].

Also, ADSCs-filled hydrogels are proven to be promising for nerve tissue engineering. **Allbright et al.** [102] used ADSC-containing poloxamer hydrogels filled in polycaprolactone conduits for bridging 15-mm gaps in rat sciatic nerves and obtained better results in neurofilament protein and S100β expression. In addition, the conduits loaded with ADSCs showed a significantly higher number of myelinated nerve fibers than in the control group. Furthermore, the qPCR results confirmed that the addition of ADSCs promoted the expression of nerve regeneration-related factors in muscle tissue. The current gold standard for nerve repair in larger gaps is still autologous nerve transplantation (ANT). Compared with ANT, **Hu et al.** [103] used 3D printing technology to model a 'lock and key' mold to design a biodegradable scaffold made of low-temperature polymerized methacrylate-based gels that were loaded with ADSCs for attachment to a 10-mm sciatic nerve gap (Fig. 5A). The 3D-printed hydrogel conduit has a highly porous microstructure under SEM observation, which is favorable for cell attachment, proliferation, and survival (Fig. 5B). Postoperative electrophysiological tests also revealed that the results of this hydrogel scaffold loaded with ADSCs were closer to those of the autograft group in terms of nerve conduction velocity and latency, suggesting that this 3D-printed hydrogel conduit could facilitate functional recovery of the peripheral nerve (Fig. 5C). A similar study used differentiated rat ADSCs in combination with collagen

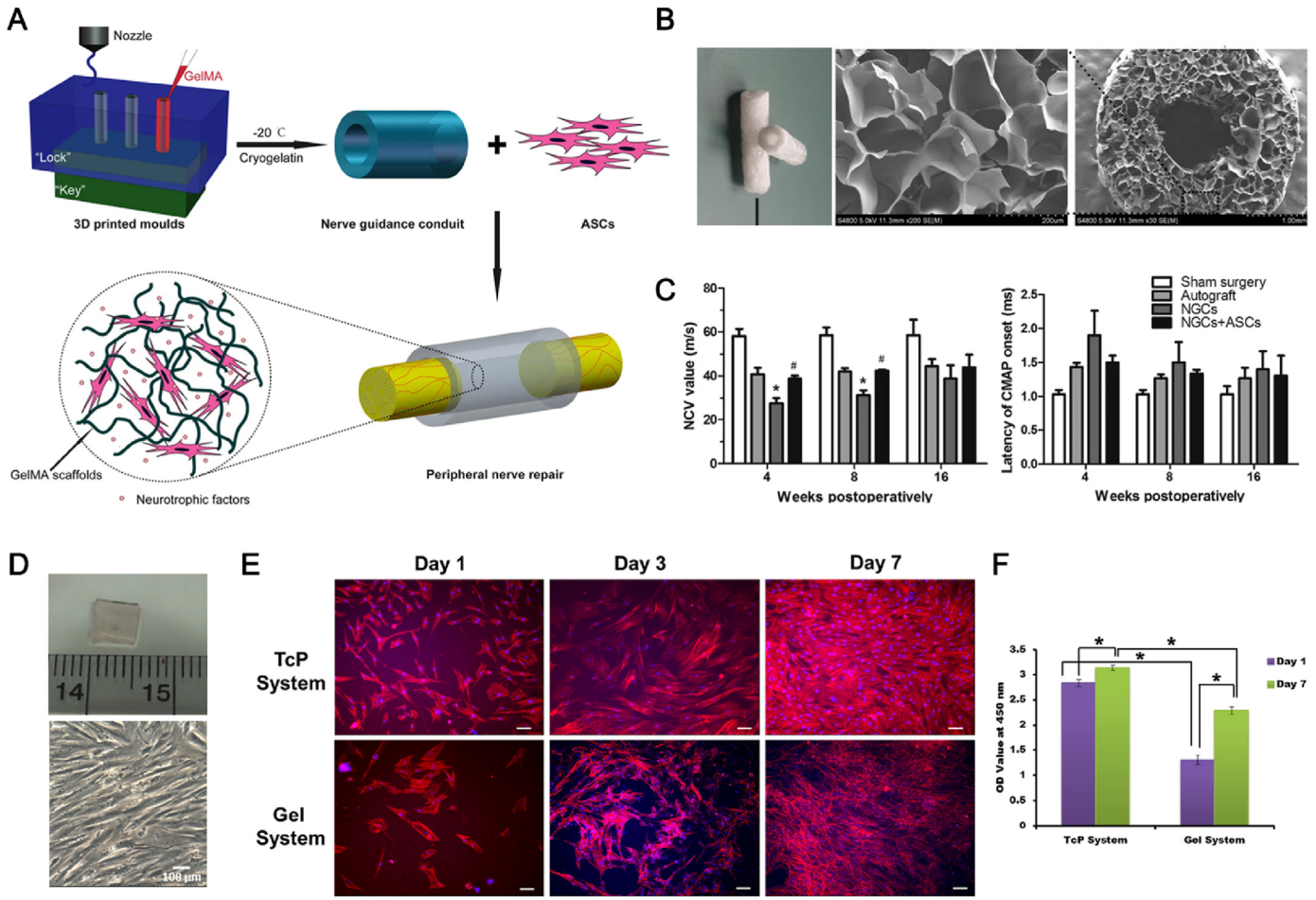


Fig. 5. (A) Schematic diagram of a 3D hydrogel conduit for peripheral nerve injury. (B) SEM images of 3D hydrogel conduit and (C) results of postoperative electrophysiological tests. (D) Image of PAAm/Algi hydrogel substrate. (E–F) Results of Alexa fluor 546 Phalloidin cytoskeleton staining and CCK8 assay for cell proliferation. Reused with permission [103], Copyright, Elsevier B.V. All rights reserved (2017). Reused with permission [105], Copyright, scientific reports (2016).

hydrogels to repair sciatic nerve defects in rats with a length gap of 15 mm. This showed that when differentiated ADSCs were transferred to a three-dimensional collagen environment, there was a significant increase in the expression of key growth factors associated with neural regeneration and an altered cellular phenotype [104].

When ADSCs act on the local release of nerve injury, the sustained release ability of the surrounding environment and drug delivery system is very important for the recovery of nerve injury. Moreover, researchers are gradually paying attention to the low survival rate of transplanted stem cells due to immune rejection, and are trying to use immunosuppressive agents in synergy with delivery platforms to improve the survival rate of transplanted stem cells and achieve therapeutic effects. **Saffari** and colleagues [106] designed a fibrin gel-based drug delivery platform. Tacrolimus was packed into poly (lactic-co-glycolic acid) (PLGA) microspheres and co-delivered with ADSCs in a hydrogel to the site of peripheral nerve injury for synergistic treatment. Tacrolimus microspheres (100 ng/mL) were released continuously in the hydrogel for 35 days. In combination with the results of cellular experiments on rat ADSCs, the combination of tacrolimus and ADSCs in the hydrogel not only had no cytotoxic effect on the transplanted ADSCs but also increased the survival rate for therapeutic purposes. In a similar study, a chitosan-AAD terpolymer hydrogel loaded with tacrolimus (FK506) was designed for PNI treatment. The polarizing effect of FK506 on M2 caused the formation of an anti-inflammatory microenvironment near the injury, which was conducive to the reconstruction of myelin structure [107]. Although ADSCs play a positive role in peripheral nerve repair, some obstacles can limit the growth of ADSCs such as donor age and cell collection sites [108,109].

3.3. Hydrogels combined with bone mesenchymal stem cells (BMSCs)

BMSCs can differentiate into neurons, astrocytes, and SCs under appropriate conditions [110]. BMSCs can facilitate nerve regeneration by releasing nerve growth factors [111]. In a rat model of sciatic nerve injury, intramuscular implantation of BMSCs in autologous vein grafts resulted in an early increase in nerve growth factor and S100-positive Schwann-like cells compared with autologous vein grafts alone [112]. One study using a nerve scaffold containing BMSCs for a 10-mm sciatic nerve defect showed better repair outcomes in terms of axonal growth, targeted muscle retention, and walking trajectory compared to a normal nerve graft [113].

The promotion of peripheral nerve regeneration by BMSCs is complex. It has been reported that BMSCs can not only induce the differentiation of SCs but also contribute to the promotion of angiogenesis [114]. Netrin-1 is a key molecule in nerve and axon growth. At the same time, it affects the formation of the vascular network. Netrin-1 is a key molecule in nerve and axon growth. After sciatic nerve crush injury, BMSCs or culture media infected with a recombinant adenovirus expressing Ad5-Netrin-1-EGFP (epidermal growth factor) were injected into the injury site. The results showed that sciatic nerve function significantly improved after BMSCs were infected with Ad5-Netrin-1-EGFP. At 28 days after injury, the number of SCs in BMSCs infected with

Ad5-Netrin-1-EGFP was significantly higher than that in the control group [115].

Although BMSCs are easier to obtain than NSCs and ESCs, the proliferation and differentiation capacity of BMSCs are poor, and the process of obtaining them is invasive and often requires anesthetic support, so these impediments often lead to a reduction in the expected outcome of treatment with BMSCs [116]. For many years, the main barrier to the clinical application of stem cell technology has been the limited survival time of stem cells after transplantation. **Rana et al.** [105] designed a polyacrylamide/alginate (PAAM/ALgi)-based biomimetic hydrogel for the culture and amplification of human BMSCs (hBMSCs) (Fig. 5D). Cytoskeleton staining of hBMSCs cultured on hydrogel substrates and conventional polystyrene-based tissue culture plates (TcP) was performed by using Alexa fluor 546 Phalloidin, and it was observed that BMSCs had higher cell densities at Days 3 and 7 of the hydrogel substrates than the TcP system (Fig. 5E). Therefore, the PAAM/ALgi hydrogel was able to accelerate the growth of hBMSC (Fig. 5F).

3.4. Hydrogels combined with olfactory stem cells (OSC)

OSCs are present in the nasal mucosa and are readily available, providing an ideal source of stem cells for peripheral nerve repair. They have better clonogenicity than other neural stem cells, with higher proliferation rates and a more natural tendency to differentiate into neural and glial cells [117]. OSCs share a highly similar gene expression profile with bone marrow stem cells but have some unique features, such as extensive overexpression of neuronal gene markers [118]. OSCs can secrete a variety of neurotrophic factors (NT), such as ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF), which are used to enhance the regeneration of damaged peripheral nerves [119]. Moreover, OSCs exhibit high levels of peripheral proteins, which are thought to play an important role in axonal growth [120].

OSC has been extensively studied in models of the central nervous system, and the olfactory mucosa contains olfactory cells and OSCs, both of which support axonal growth following SCI [116]. At present, the application of OSCs in long-gap peripheral nerve defects is rare. **Roche et al.** [121] designed biphasic collagen and laminin-functionalized hyaluronate-based NGC and loaded with OSCs and NGF to treat sciatic nerve defects. The results confirmed that the number of axons in the OSCs group was higher than that in the control group. To test the effect of OSC transplantation in vivo, **Esaki et al.** [122] used commercialized Medgel (a biodegradable hydrogel sponge) to study facial nerve palsy in rats. Histopathological results showed that greater remyelination was observed on days 7 and 14 in the OSC/Medgel group than in the control group, indicating the best recovery from this treatment. Meanwhile, the OSC/Medgel group underwent electrophysiological testing after 14 days of treatment, the CMAP amplitude was significantly larger than that of the control group, and the amplitude curve was consistent with the normal amplitude curve. Therefore, these results also confirmed that OSCs/Medgel has a positive effect on nerve recovery.

Based on this, **Salehi et al**. [118] used a sodium alginate/chitosan (alg/chit) hydrogel to transplant OSCs into a crushed 3-mm rat sciatic nerve to study peripheral nerve regeneration. The sciatic nerve function index, hot plate latency, electrophysiological assessment, and gastrocnemius wet weight rate all showed positive effects compared with controls.

3.5. Hydrogels combined with dental pulp stem cells (DPSCs)

The formation of new odontoblasts and the production of dentin after severe tooth injury suggest the presence of mesenchymal stem cells in the dental pulp tissue. **Gronthos et al.** [123] first discovered and isolated DPSCs in 2000. Studies have shown that DPSCs coexpress a variety of early neuronal markers, such as Nestin, recombinant doublecortin (DCX), β-tubulin III, NeuN, GFAP, and S100 calcium-binding protein [124]. DPSCs can be obtained from the third molars and premolars without additional procedures, which can avoid causing additional injuries or ethical issues [125].

Similar to other mesenchymal stem cells, DPSCs secrete various trophic factors to assist in neural repair [126]. Sanen et al. [127] investigated the transplantation of differentiated DPSCs to repair 15-mm sciatic nerve defects in rats. DPSC can produce trophic factors in injured nerves after transplantation and promote peripheral nerve regeneration. Immunohistochemical results also showed regenerated myelinated nerve fibers and ingrowth of nerve axons. DPSCs can also differentiate into SCs to enhance remyelination and axon regeneration in PNI. **Al-zer et al.** [128] induced DPSC differentiation and high expression of the SC marker S100β, indicating that DPSCs can be used as a source of SCs. Luo and coworkers designed a novel cellulose/soy protein isolate composite membrane (CSM) conduit combined with a GelMA hydrogel loaded with bFGF and DPSCs to constructed to construct a novel nerve conduit (CSM-GFD) for the treatment of 15-mm sciatic nerve defects in rats. The nerve-specific markers GFAP, S-100, and MBP stained the neonatal nerve tissue and found that the new conduit group could positively express three neural markers. A comparable number of nerve fibers and Schwann-like cells were observed with autologous nerves. Therefore, this novel hydrogel-filled conduit is considered to be an alternative to traditional ANT methods [129].

3.6. Others

Other stem cells are often used in combination with hydrogels, such as classical NSCs. As the original cells of the nervous system, neural stem cells are an important cell source of neurons and glial cells. Similar to the function of other stem cells, they can also differentiate into SCs and neurons and secrete many key neurotrophic factors that accelerate nerve regrowth and myelin formation [130,131].

Zhao et al. [132] developed a polysaccharide-based self-healing injectable hydrogel carrier that mimics the biomechanical properties of brain tissue. NSCs were loaded into hydrogels, and the hydrogels maintained the normal function of NSC proliferation and differentiation.

In addition to being a carrier for cells, hydrogels with synergistic morphological, physical, chemical, and biological cues have been developed to improve nerve recovery and shown to modulate the directional growth and accelerate the migration of SCs [133]. **Liu et al.** designed a hydrogel conduit with a synergistic effect of morphology and elasticity [134]. The DRG neurite showed good directional growth ability in this synergistic hydrogel injury, and in vivo experimental results showed that the marker protein of axon extension was increased. In addition to traditional hydrogels, in recent years, biological scaffold hydrogels based on the decellularized matrix (dECM) have been found to have the potential to promote the differentiation of DRG cells and promote neurite extension in vitro and axonal regeneration in vivo [135]. Therefore, we believe that hydrogels with multi-angle cue synergy can provide a new choice for peripheral nerve injury in the future.

4. Hydrogels containing neurotrophic factors

With the advancement of medical tissue engineering technology, tissue engineering materials may become an elective strategy for treating severe PNI [136]. However, some unknown factors limit the availability of these tissue engineering materials in clinical use [137]. Therefore, many studies have focused on the use of growth factors (GF) to repair injured peripheral nerves and achieve nerve regeneration and functional recovery [138–140]. These beneficial effects on nerve tissue occur primarily by enhancing intrinsic transduction potentials and modulating interactions with molecular and mechanical signaling cascades [141]. For example, the growth factor family of neuregulin is crucial to the association between regenerated axons and the surrounding SCs. Neuregulin-1 is expressed by regenerated axons and binds to ErbB tyrosine kinase receptors on the surrounding SCs [142]. In SCs, this signaling illustrates different pathways, including the ERK1/2-MAPK

calcineurin-NFAT and PI3K-Akt pathways [142]. Multiple studies have demonstrated that in vitro GF can continue to promote the survival of neurons in vitro, while in vivo GF has a variety of functions, including promoting SC migration, axon regeneration, myelin regeneration, and reconnection of adjacent targets during nerve repair [143]. However, in the early regeneration process after injury, there is not enough GF in the distal damaged nerve stump to support its growth and regeneration [144], and long-term insufficient GF supply will lead to the death of a large number of neurons. Therefore, the application of exogenous GF to support axon and myelin regeneration will provide more options for the treatment of PNI. In addition, NGF can increase electrophysiological parameters and functional recovery after PNI [145]. However, due to their molecular size, relatively short survival time and side effects, such as pain and allergy, direct delivery of neurotrophic factors has proven difficult [146,147]. Thus, hydrogels, which are easy to synthesize and have the ability to transport and load biomolecules, offer a new approach to neurotrophic factor delivery. Various types of hydrogels are widely used because of their biocompatibility, biodegradability and adjustable mechanical properties.

4.1. Hydrogels combined with basic fibroblast growth factor (bFGF)

In the FGF family, bFGF is considered to be the most prominent molecule involved in nerve regeneration [148]. bFGF stimulates the DRG in vitro and accelerates the mitosis and proliferation of neurons and SC [149], angiogenesis, myelination, and synaptic regeneration [150]. Studies have shown that bFGF is also a key factor in promoting the proliferation and differentiation of NSCs [151]. Many studies have been carried out on how bFGF can be better delivered to the body and help nerve regeneration after PNI [152,153]. However, bFGF is susceptible to various proteolytic cleavage events which lead to its inactivation in body fluids [154]. Many hydrogels are mixed with heparin to produce affinity hydrogels because the negatively charged sulfate group on heparin can be used to fix most neurotrophic growth factors [155,156], among which the ion interaction between bFGF and the negatively charged group of heparin will eventually prolong the release time in hydrogels. **Li et al.** [157] based on the high affinity of heparin [158], prepared a new biomaterial for growth factor delivery through charge interactions between polycation-poly(ethylene arginine separated glycerides) (PEAD) and heparin bound to bFGF [159]. This coacervate can not only control the release of bFGF, but the reduction in endoplasmic reticulum stress signals is also involved in sciatic nerve protection. Another study by **Li** and coworkers [160] developed a new thermosensitive heparin-polysaccharide (HP) hydrogel in combination with bFGF and NGF for use in a diabetic rat sciatic nerve crush injury model. HP was liquid at 4 °C and formed a gel when heated to 37 °C, with or without bFGF and NGF, and rheological results showed a rapid increase in strain values at approximately 19 °C (Fig. 6A). The results of the animal studies showed that the extension of the toes of the footprint of the rats in the GF-HP group was significantly better than that in the other treatment groups. Similarly, the gastrocnemius atrophy in the GF-HP group was better than that in the other treatment groups, suggesting that this GF-HP hydrogel could minimize muscle atrophy and promote recovery of motor function (Fig. 6B). The proliferation of SCs was assessed by double immunofluorescence staining of Ki67 (green) and GFAP (red), and the GF-HP group showed the greatest fluorescence intensity and more Ki67-positive cells, indicating that the GF-HP hydrogel was beneficial for improving the proliferative function of SCs (Fig. 6C).

bFGF also interacts with other GFs to produce synergistic effects. **Cui** et al. [161] developed a functional nerve scaffold that combines ciliary

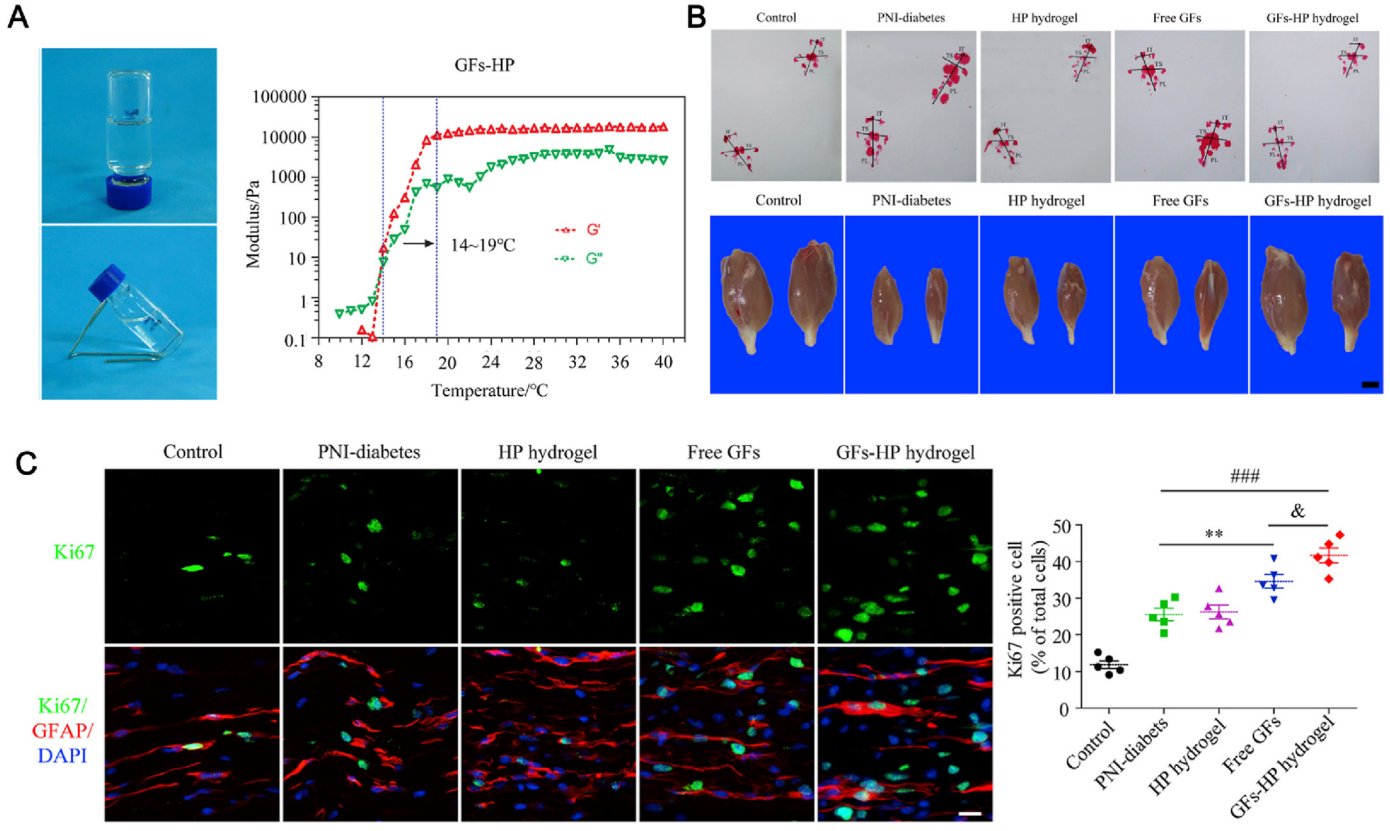


Fig. 6. (A) Image and rheological test of HP hydrogel. (B) Footprints and gastrocnemius images of rats (C) Double immunofluorescence staining of Ki67 (green) and GFAP (red) were used to mark proliferating SC, with a scale of 50 μm, and percentage of KI67 and GFAP double-positive cells in total DAPI positive cells (representing the proliferation rate of SCs). Reused with permission [160], Copyright, Elsevier Ltd (2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

neurotrophic factor (CNTF) and bFGF. In the mini pig facial nerve injury model, through electrophysiological evaluation and histological examination, collagen scaffolds modified with bFGF and CNTF could improve peripheral nerve reconstruction. Although CNTF and bFGF adopt different mechanisms, the experimental results show that it is feasible to let them work together.

4.2. Hydrogel combined with glial cell-derived neurotrophic factor (GDNF)

GDNF is considered the most protective factor of motor neurons [162]. Meanwhile, this factor can effectively support the survival and growth of neurons [163]. GDNF is a transforming growth factor-β, a member of the superfamily, and it acts as a powerful neurotrophic factor (NTF) supporting the survival and growth of motor neurons and primary sensory neurons [164]. Recently, many reports have noted that the co-delivery of NGF and GDNF can also provide a synergistic biological effect on axonal growth [165]. **Madduri et al.** [166] showed that collagen nerve ducts loaded with GDNF and NGF were used to treat sciatic nerve injury in rats. GDNF and NGF have synergistic effects. The number of new axons and the SC state of proliferation showed that GDNF and NGF jointly promoted the speed and quality of early nerve structure regeneration, and the experiment showed that GDNF and NGF could be released continuously in the nerve duct for 28 days.

Other innovative methods to control the release of nutritional factors include the addition of microspheres/nanoparticles loaded with nutritional factors to the hydrogel matrix. **Zhuang et al.** [167] prepared microspheres loaded with a GDNF and then implanted them into a gelatin methacrylamide hydrogel. Finally, they were mixed with a commercial double-layer collagen membrane (Bio-Gide®). As a result, a novel nerve guide was formed to bridge a 10-mm-long sciatic nerve defect in rats. The results proved that axon regeneration and collagen conduit function recovery in the GDNF microspheres group were similar to those in the autograft group.

It is found that GDNF can play an important role in labor when applied to a model of neuropathic pain [168]. Kong et al. [169] prepared an HA-PBA conjugate with phenylboronic acid (PBA) and hyaluronic acid (HA), mixed the HA-PBA conjugate with polyvinyl alcohol (PVA) to form a multifunctional HA-PVA hydrogel, and added heparin into the HA-PVA hydrogel to prepare an HA-PVA-Hep injectable hydrogel. After adding heparin, GDNF can be more ideally controlled release to treat peripheral nerve crush injury (Fig. 7A). This hydrogel not only maintained the release of the neurotrophic factor GDNF but also had anti-inflammatory effects. After 28 days of crush injury, the HA-PVA-Hep hydrogel group showed good levels of anti-inflammation with TNF-α expression close to that of the Sham group. However, the higher TNF-α expression in the added GDNF group was due to GDNF counteracting the

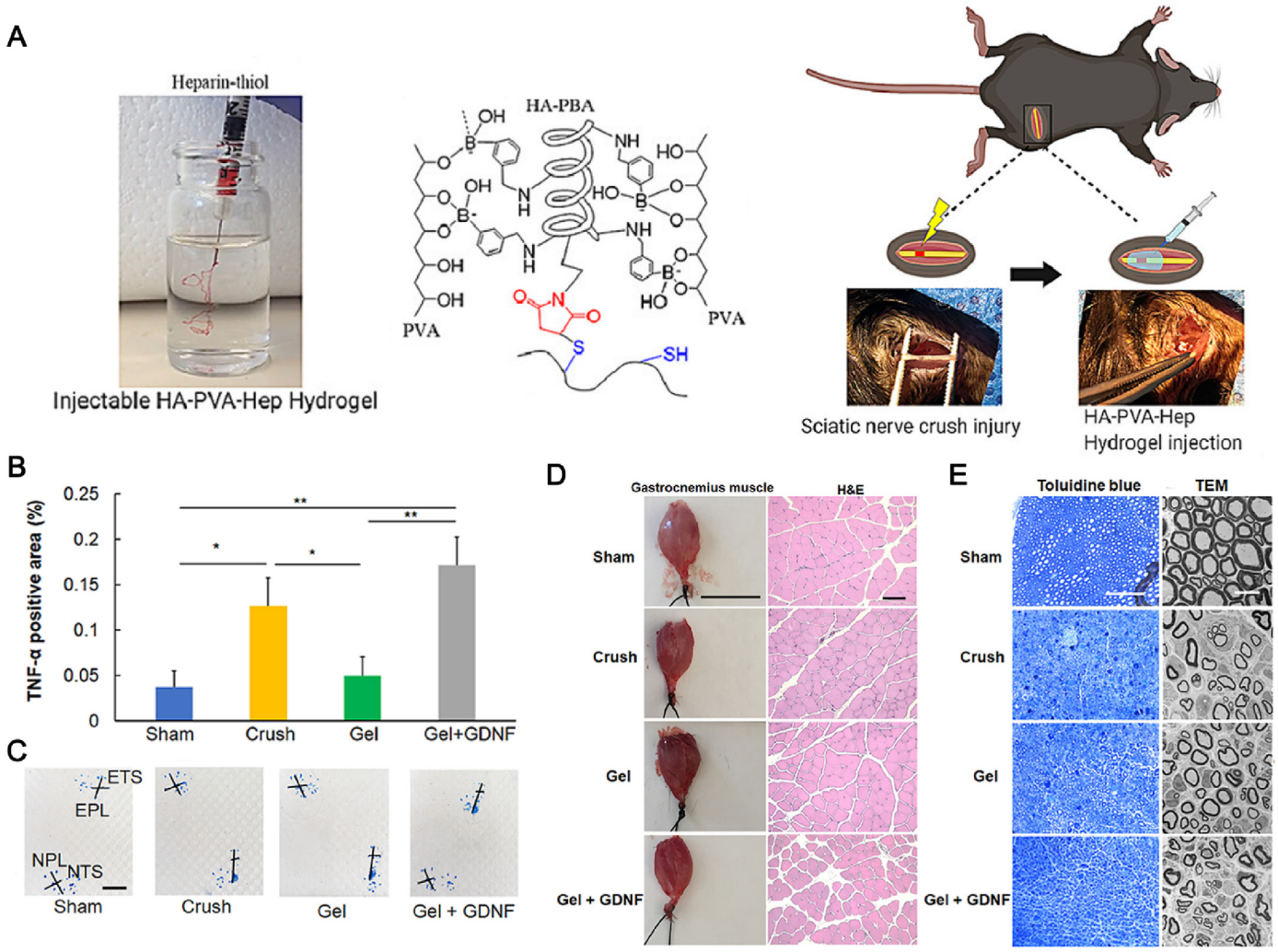


Fig. 7. (A) Synthesis of injectable HA-PVA-Hep hydrogel and schematic diagram of animal experiment. (B) TNF-α antibody staining was used to detect the anti-inflammatory properties of hydrogels. (C–E) Postoperative gait analysis, muscle HE staining, wet weight of gastrocnemius, cross section toluidine blue staining (scale: 100 μm), and TEM (scale: 10 μm) were performed. Reused with permission [169], Copyright, Elsevier Ltd (2021). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

anti-inflammatory effect of the HA-PVA-Hep hydrogel itself (Fig. 7B). Gait analysis, HE staining of the gastrocnemius muscle, and TEM of nerve axons in rats showed that HA-PVA-Hep hydrogel supplemented with GDNF could help improve motor function and promote the growth of myelinated axons (Fig. 7C–E).

4.3. Hydrogels combined with brain-derived neurotrophic factor (BDNF)

BDNF is important in NSC proliferation, differentiation, and directed migration [170, 171]. Few studies have systematically compared the effects of different doses of neurotrophic factors, but many have proposed avoiding nonnormal repair caused by excessive use. In some studies, BDNF was used for experiments, and a low dose (0.5–2 μg/d, 28 days) promoted motor neuron axon regeneration, while a high dose (12–20 μg/d, 28 days) significantly inhibited axonal regeneration [172].

Using an adaptable delivery carrier to maintain the biological activity and controlled release of BDNF in a stable manner is promising for nerve regeneration. **Madduri et al.** [173] concluded that loading BDNF into collagen ducts could provide a microenvironment for the regeneration of damaged peripheral nerves, and local slow release reduced the early rapid release of BDNF and provided continuous support for the treatment of nerve injury. Controlled release of bioactive BDNF through a drug delivery system can promote nerve regeneration after injury. In some studies [174], recombinant rat BDNF was encapsulated into chitosan/sodium tripolyphosphate (STPP) microspheres by the lotion ion crosslinking method. The biological activity of BDNF released from microspheres can be demonstrated by stimulating the phenotypic transformation of PC-12 cells into neurons in vitro.

Anjana et al. [175] used agarose hydrogel gel scaffolds to conformally fill irregular dorsal spinal cord defects in adult rats. Quantitative analysis of GFAP-positive astrocytes, nf-160 kDa neurons and axons and CS-56 chondroitin sulfate proteoglysaccharides at the interface between the scaffolders and host spinal cord proved that BDNF promoted the growth of neurites in the 3D scaffold and released anti-scar enzymes to further reduce the obstacle of regeneration after spinal cord injury.

When treating peripheral nerve injury, the efficacy is often lower than expected due to the absence of growth factors in simple nerve ducts, insufficient cell activity, and the absence of an extracellular matrix (ECM)-like microenvironment. To improve functional recovery and optimize peripheral nerve regeneration, **Chang et al.** [176] designed a gelatin-based multichannel nerve conduit. Aligned nanofibers were created by electrospinning to induce axonal growth in one direction. The two growth factors were loaded into gelatin tubes or embedded with nanoparticles for local slow release. Early on, NGF protects injured axons and promotes axon regeneration. Later, BDNF increases myelin protein expression.

4.4. Hydrogels combined with vascular endothelial growth factor (VEGF)

The key role of VEGF is to induce neovascularization and increase the proliferation rate of vascular endothelial cells (ECs). VEGF strengthens neurites and protects the survival of neurons. Therefore, it plays a nourishing and protective role in the nervous system [177]. As mentioned above, to achieve the continuous transmission of biochemical clues, the use of biologically active hydrogels is a promising strategy. **Xu et al.** [178] used the biomaterial polyurethane (PU) to make the conduit and then injected the GelMA hydrogel loaded with VEGF into the PU conduit to construct the (PU/Gel/VEGF) conduit. The results showed that the number of blood vessels formed in the GelMA hydrogel conduit containing VEGF (PU/Gel/VEGF) was higher than that in the PU/Gel conduit alone, and the percentage and area of myelin axons regenerated in the PU/Gel/VEGF conduit group were higher than those in the PU/Gel conduit group. On this basis, **Xu** and his colleagues [179] cross-linked a 5% (w/v) uncross-linked GelMA solution by performing UV light irradiation for 20 s to form a GelMA hydrogel, and VEGF was incorporated to treat peripheral nerve crush injury in rats (Fig. 8A and B). Postoperative results by nerve TEM images (Fig. 8C), and quantification of myelinated axons (Fig. 8E) illustrate that the VEGF@GelMA hydrogel group was significantly better than the other treatment groups and closer to the Sham group. Similarly, the results of staining the tissue with a vascular indicator (Fig. 8D) and quantification of mature vessel density after staining (Fig. 8F) indicated that the VEGF@GelMA hydrogel group was significantly denser than those in the other treatment groups. The above experimental results prove that the application of VEGF@GelMA hydrogel treatment not only accelerates the repair of damaged nerves but also controls the release of VEGF and promotes the formation of blood vessels in damaged nerves, thus increasing material exchange, providing nutrition and helping nerve regeneration.

It has been reported that BDNF and VEGF may have the same origin of receptors on nerve cells and vascular endothelial cells (ECs), so they can synergize in vitro and in vivo to mediate complex crosstalk of neurotic cells and vascular endothelial cells (ECs) [172,180]. BDNF has dual roles in the nervous and vascular systems; it not only regulates neuronal survival and differentiation but also promotes vascular ECs survival and vascular stability [181]. **Lu et al.** [182] found that BDNF and VEGF simulated peptides synergistically promote the nerve regeneration process. Similar studies [183] found that transplantation of aligned chitosan fiber hydrogel with RGI (a BDNF simulated peptide)/KLT (a VEGF simulated peptide) to the site of nerve injury could effectively promote sciatic nerve regeneration. Many commonly used neurotrophic factors play an important role in the treatment of the nervous system, such as the classic NGF. It was first described as a neurotrophic factor in 1951 [184]. As mentioned above, hydrogels can be used as a suitable delivery platform for NGF. **Xu et al.** [185] prepared injectable CS-HA/NGF hydrogel fillers loaded with NGF as fillers for nerve conduits. The NGF release curve proved that these hydrogels could maintain the activity of NGF and realize the sustained release of NGF. Recently, the use of multifunctional scaffolds combined with physical and chemical cues to support and promote axonal regeneration after nerve injury has been proven effective and a promising method to overcome the current treatment obstacles. **Qian et al.** designed a multilayered and mechanically stable gradient-magnetized scaffold based on iron oxide nanoparticles [186]. This gradient-magnetized scaffold not only induced the directional growth of neurons but also immunoregulation of the polarization of macrophages. The results of animal experiments also showed that the application of magnetization gradient scaffolds in vivo significantly improved the regeneration of myelin sheath and axons at the injured site. **Shefi** and colleagues have previously demonstrated that the combination of NGF and magnetic nanoparticles (MNPs) can improve bioavailability and stability. Based on this, **Shefi et al.** [187] developed a bionic-regenerated gel as a filler for NGC, integrating physical and chemical clues into the biocompatible “one-pot reaction” strategy. NGF-coated MNP were embedded in collagen gel, and the collagen fiber arrangement and anisotropic particle distribution were induced by a gradient magnetic field for remote application. The same neurotrophic factor 3 (NT-3) has a similar effect, and its main role is to promote the regeneration of glia. In some studies, hyaluronic acid and methylcellulose (HAMC) hydrogels have been combined with polymer PLGA nanoparticles loaded with NT3. The results showed that NT3 could be released for up to 28 days [188].

5. Self-assembling peptide hydrogels

Polypeptides can be cross-linked in different ways to form nontoxic, adjustable, and biologically functional hydrogels, which could be used as a new alternative treatment for nerve injury in the future [189–191]. Under normal conditions, synthetic peptides are self-assembled into ordered nanostructures called self-assembled peptides (SAPs) [192,193]. The peptide sequences commonly used for nerve injury repair are IKVAV (isoleucine lysine valine alanine valine), RGD (arginine glycine aspartate), YIGSR (tyrosine isoleucine glycine serine arginine) and RADA16 (Ac-RARADADARARADADA-NH_2). Compared with other synthetic

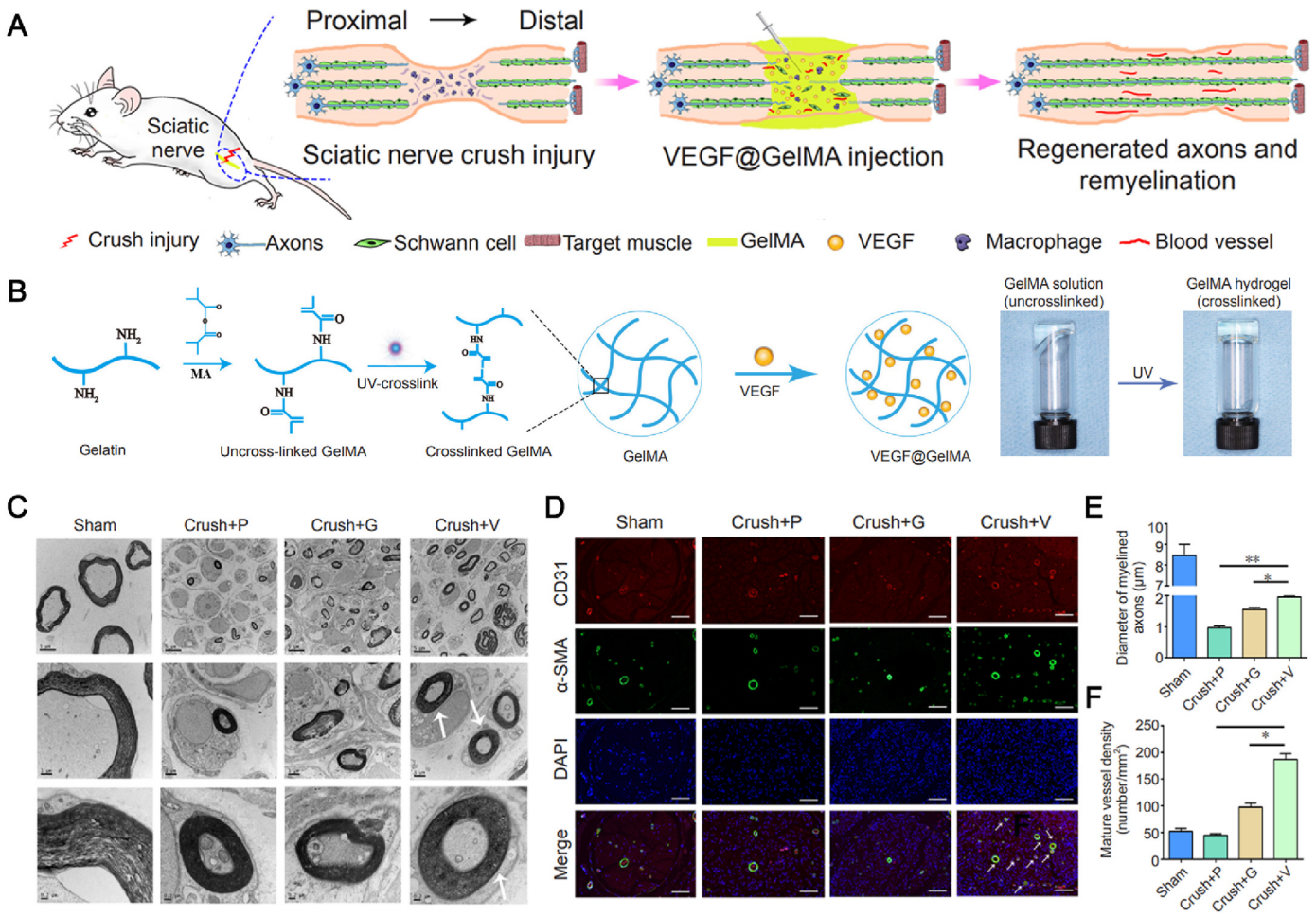


Fig. 8. (A) Schematic representation of VEGF@GelMA hydrogel promoting nerve regeneration after crush injury. (B) Preparation of VEGF@GelMA hydrogels. TEM images of neural tissue (C), and quantitative indicators of myelinated axons (E). Staining of mature blood vessels in regenerating nerves (D), and Quantification of mature vessel density (F). Reused with permission [179], Copyright, Neural Regeneration Research (2022).

hydrogels, SAP has higher biocompatibility and simple functional adhesion molecules [192,194]. It has been reported that SAP hydrogels play an important role in the targeted differentiation of stem cells [195]. When loaded with nerve cells, SAP hydrogels can improve the survival rate of nerve cells, which also confirms that they have better biocompatibility.

RADA16 is a complementary peptide with hydrophilic and lipophilic properties [196]. It can self-assemble into nanofibrous hydrogels, delivering neuronutrients to nerve cells and playing a key role in nerve damage. Researchers prepared an injectable SAP hydrogel from angiogenic peptide (pro-angiogenic) modified RADA16 and used it to study spinal cord injury in rats [197]. Under physiological conditions, the formation of a nanofiber network can increase the number and density of blood vessels around the injured spinal cord and the level of neurofilament.

IKVAV can weaken the adhesion and differentiation function of glial cells, inhibit adverse factors that hinder nerve regeneration, and promote axon growth and neuron adhesion in peripheral nerve injury areas. To provide a suitable microenvironment for nerve repair of injured peripheral nerves [198]. **Wu et al.** [199] designed SAP solutions of IKVAV and RGD-modified RADA16-I functional sequences, and mixing the two neutral solutions resulted in a nanofibrous hydrogel RADA16-Mix that overcame the major drawback of the low pH of RADA16-I as a hydrogel filler in electrostatic spinning conduits to promote nerve regeneration. Longitudinal and lateral full views of the regeneration of axons from proximal to distal directions were observed at 12 weeks postoperatively by observing axons stained with NF-200 red in electrospun silk catheters in which the RADA16-Mix group grew parallel to the direction of the catheter and was uniformly dense (scale bar: 1000 μm) (Fig. 9D). The results of NF-200 and S100 labeling also indicated that axons and SCs grew uniformly and significantly better in the RADA16-Mix group than in the other two groups (scale bar: 200 μm) (Fig. 9E). At 12 weeks, axon quantification was also highest in the RADA16-Mix group at the intermediate and distal positions (Fig. 9F). The above results indicate that the RADA 16-Mix SAP nanofiber hydrogel has a positive effect on nerve axon growth entanglement and provides a better environment for rat sciatic nerve regeneration.

SAP hydrogels can mimic ECM-like structures to provide a water-rich soft microenvironment for damaged nerves. SAP hydrogels can exchange substances in damaged nerves, eliminate metabolic waste and promote the absorption of nutrient factors [201]. As mentioned earlier, SAP hydrogels also help stem cells differentiate [195]. **Kuo et al.** [202] combined the IKVAV peptide with the RADA16 chain to construct SAP that can encapsulate NSCs in an assembly hydrogel matrix, to promote the regeneration and repair of injured nerve tissue.

Epitope peptides can either be linked in a linear modification after synthesis or synthesized directly at any site in the SAP sequence [203–206]. Due to the accurate purification method and controllable chemical structure, the influence of different bioactive epitopes and the epitopes' density on them can be studied [207]. **Yang et al.** [200] prepared dual-function SAP nanofiber hydrogels (RAD/IKV/RGI and RAD/IKV-GG-RGI) by mixing RADA16 with two epitopes for the

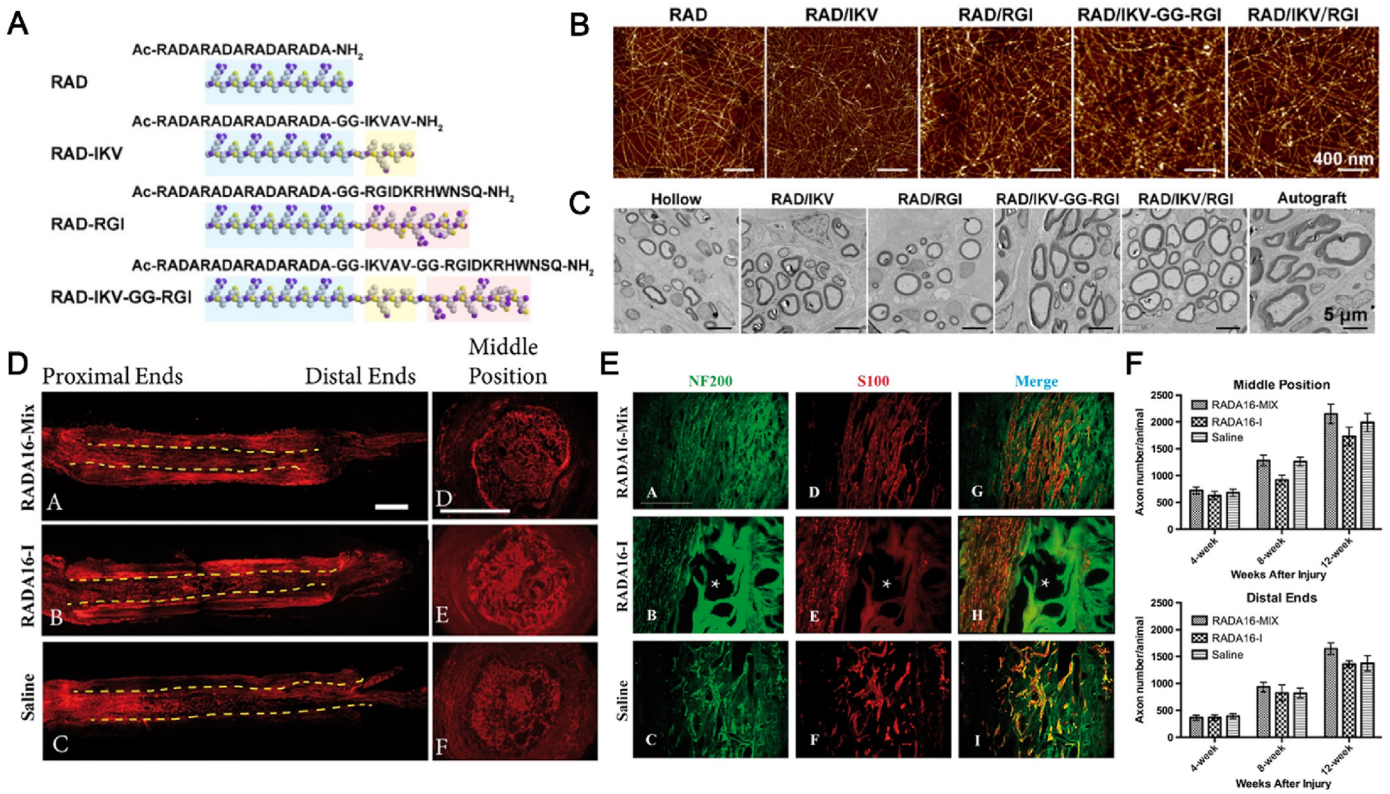


Fig. 9. (A) Sequences of different functionalized self-assembling peptides. (B) Atomic force microscope image of a peptide solution. (C) TEM image of the regenerated nerve. (D) Full longitudinal and transverse views of axon regeneration at 12 weeks after implantation of different fillers in an electrospinning conduit (scale bar: 1000 μm). (E) Observation of axons (NF-200) and SCs (S100) in the middle longitudinal diagram (scale bar: 200 μm), And (F) Axon quantification at intermediate and distal positions. Reused with permission [199], Copyright, Oxford University Press (2016). Reused with permission [200], Copyright, THERANOSTICS (2021).

treatment of peripheral nerve injury (Fig. 9A). Atomic force microscopy (AFM) showed that long interwoven nanofibers with uniform morphology appeared in the mixture of RAD and functional peptides, and the widest nanofibers appeared in RAD/IKV-GG-RGI. The results indicated that the width of the nanofibers was determined by the longer base sequence (Fig. 9B). TEM distal axon morphology showed that the RAD/IKV-GG-RGI and RAD/IKV/RGI groups had denser nerve fibers than the other experimental groups, with axon diameter and myelin sheath thickness also superior to the rest of the treatment groups (Fig. 9C). These assessments indicate that RGI and IKVAV are effective in assisting axon regeneration and functional recovery.

Different concentrations of the same SAP functionalized sequences were mixed with nonphysiological sequences to modify the epitope density of IKVAV. The higher the density of IKVAV epitopes, the more obvious the differentiation of neurons and the less obvious the development of astrocytes. The combination of different functions in the same SAP sequence can realize the synergy of different requirements. For instance, by binding RGD surface sites to specific glycine sites, PA nanofibers were functionalized and proved to affect cell diffusion on 7 scaffold nanostructures [208].

Currently, self-assembled peptide hydrogels that have been successfully transformed into commodities have been gradually put into clinical application. **Faroni et al.** [209] used commercially available (PeptiGel-Alpha1 and PeptiGel-Alpha2) self-assembling peptide hydrogels to form self-assembling peptide hydrogels containing human adipose-derived stem cells (hdASCs) by incubating them in hdASC-containing medium for more than 2 h. Most of the cells in the hydrogels were stained positively by cell activity staining, especially hdASCs cultured on Alpha2 in the classic spindle shape (Fig. 10A). Both hydrogels Alpha 1 and Alpha 2 allowed for DRG neurite attachment and neurite germination with or without a laminin coating (scale bar 100 μm) (Fig. 10B). Neuronal cultures proved viable when stimulated using KCl and were able to induce action potentials and generate calcium inward flow (100 μm in scale) (Fig. 10C). These results suggest that commercial self-assembled peptide hydrogels, particularly Alpha 2, with their cell adhesion, cell growth, and sustained differentiation properties, have great potential as a delivery platform for hdASCs in the environment of peripheral nerve injury.

6. Conclusion and prospects

PNI has a high incidence and poor functional recovery, causing physical and psychological pain in patients. Therefore, how to help peripheral nerves recover more effectively has always been the focus of medical attention. Only approximately 3% of patients who underwent neurosurgery were able to feel normal after five years, and less than 25% had normal motor function [210]. In the 1960s, the detrimental consequences of tension sutures were recognized through innovations in nerve repair microscopy and the technical aspects of nerve repair were improved [211]. For long-distance nerve defects, nerve autologous transplantation is still the preferred treatment [212], but it has limitations due to donor nerve limitations. End-to-end suturing and nerve autologous transplantation of damaged nerves are common options for PNI treatment. In recent years, surgical techniques such as tendon transfer and nerve transfer have been established, and these new methods can replace some functions but are far from the desired recovery results after nerve injury [213]. Therefore, the strategy of repairing PNI by tissue engineering has gradually attracted the attention of researchers [137,214,215]. To date, nerve conduits approved by the U.S. Food and Drug Administration (FDA) have been used for peripheral nerve repair and have achieved some therapeutic results, while transformation products to solve more complex nerve problems are rare.

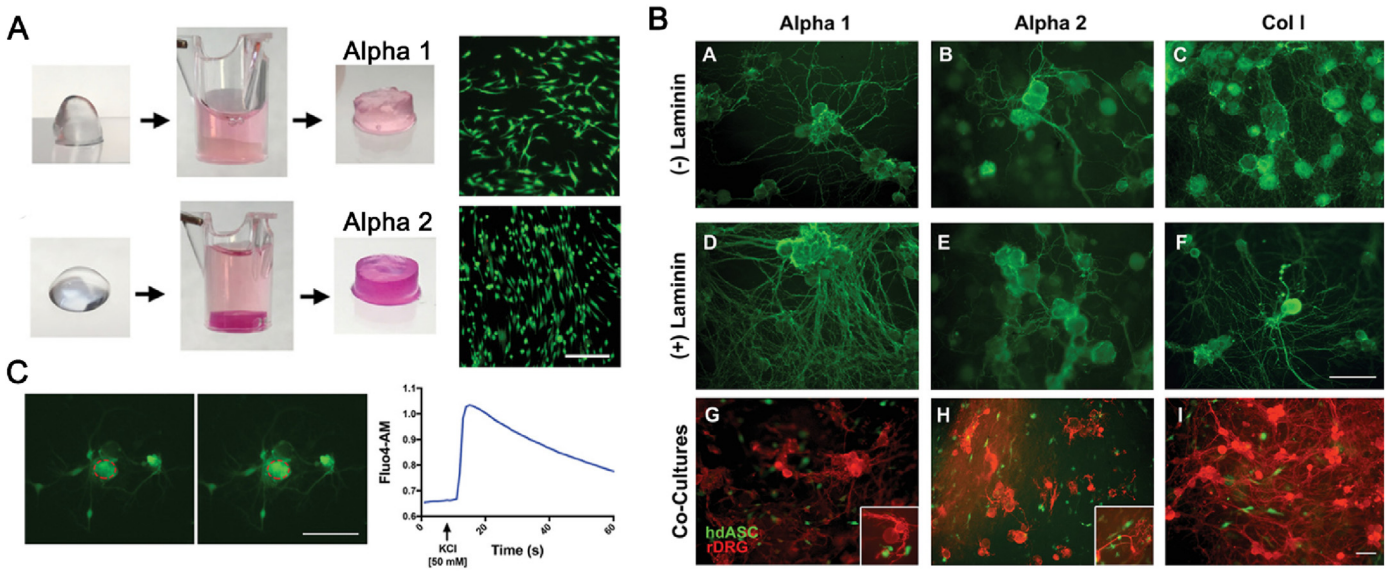


Fig. 10. (A) Hydrogels were co-incubated with media containing hdASCs to form hydrogels containing hdASCs and stained for cell activity. (B) Observe the adhesion of rat DRG neurons on Alpha 1 and Alpha 2 hydrogels (scale 100 μm). (C) Representative high-magnification images and corresponding traces of potassium chloride stimulation of DRG neurons show that Ca^{2+} (100 μm in scale) is measured in the red dotted area. Reused with permission [209], Copyright, John Wiley and Sons, (2019) . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The research and development of hydrogels are encouraging for neural tissue engineering. Hydrogels provide a 3D environment, can well mimic the ECM, and are promising in tissue engineering [216]. The mechanical properties of hydrogels, such as stiffness and viscoelasticity, are similar to those of native neural tissue. Additionally, hydrogels can be used to maintain local drug delivery [217,218], and as intraluminal fillers for nerve-guiding conduits or fiber integration to guide neuron regeneration. Although several types of hydrogel systems have been developed and have achieved ideal results in cell experiments, successful transformation is still a long way off. This review summarizes the recent progress and prospects of CHs, stem cell-loaded hydrogels, growth factor-loaded hydrogels, and self-assembling peptide hydrogels, which have often been used in peripheral nerve repair strategies in recent years.

Conductive hydrogels. CHs, with the characteristics of conventional biomedical hydrogels (3D porous structure, high water content, and good biocompatibility), are well combined with conductive polymer and carbon material characteristics (solid mechanical properties, good electrochemical performance, and multi-stimulus response performance). CHs show tunable physical and chemical properties that can reassemble many properties and functions of native tissues. Several reports have suggested that electric fields play a positive role in paracrine activities of cell arrangement, proliferation, migration, and differentiation, as well as structural and functional restoration after PNI [219,220]. While CHs have achieved satisfactory results in facilitating neurological recovery, there are still some unsolved challenges in future clinical practice. Many medical hydrogel materials are biodegradable, but conductive materials, such as conductive polymers or carbon-based materials in CHs, have relatively low biodegradability. This can lead to the need for secondary surgery to remove CHs, or the prolonged retention of undegraded materials in the body can lead to local inflammation of the tissue or toxic effects [215]. Therefore, current research tends to blend conductive polymers with biocompatible degradable polymers (natural or synthetic) to develop composite hydrogels based on CPs. The mechanical strength of natural polymer hydrogels is enhanced while improving the degradability of CHs. Therefore, in future research on CHs, appropriate materials should be selected to ensure good histocompatibility, degradability, mechanical strength, and electroconductibility of CHs. Currently, the animal models commonly used for neurological experiments are mostly rats and rabbits. While using animal models to simulate experiments, effective human clinical trials should not be neglected to translate more meaningful therapeutic products for the benefit of mankind [221].

Stem cell-loaded hydrogels. Stem cell transplantation is a widely used method in neural tissue engineering (NTE). It is mainly used to introduce specific stem cells to enhance the regeneration of injured nerves by nutritional factors and nerve cells secreted by them in the process of nerve repair. The hydrogel mimics the three-dimensional extracellular matrix and provides a friendly environment for stem cells. Stem cells, on the other hand, can sense their surroundings for the next step, stretch, proliferate, or just linger briefly. Modification of hydrogel material properties is crucial in biomedical applications and has been widely used as a delivery vehicle for drug myocytes [222,223]. At the same time, mechanical forces can cause severe damage to the extracellular membrane during injection [224]. In particular, features, such as shear thinning and self-healing properties provide injectable hydrogel potential in cell transplantation. However, most injectable hydrogels degrade rapidly, and the crosslinking network is not stable. The resulting rapid and uncontrolled collapse of the cell scaffold can lead to explosive cell release. Therefore, how to overcome the adverse effects of local cell injection therapy by hydrogels will be an important research direction in the future [225]. Based on this, Ding et al. [226] through the Knoevenagel condensation reaction (KC) designed a kind of injectable in situ forming double network (DN-I) hydrogel, that can provide mechanical protection for cells. The process of injection by UV light-induced secondary crosslinking network improved the retention of transplanted cells after injection and provided support for cell proliferation and differentiation. This study also provides direction and reference for future exploration of injectable hydrogels for cell transplantation therapy.

Growth factors-loaded hydrogels. The controlled release of neurotrophic factors plays a key role in regulating the proliferation and promoting the survival of nerve cells. However, the vulnerability of neurotrophic factors to changes in their chemical structure, their short half-life, and their tendency to inactivate make direct delivery difficult. Based on the degradation rate, porosity, and other physical properties of their synthetic polymers, hydrogels can release their loaded neurotrophins by controlling their concentration, duration, and release rate [147,173]. Macromolecules, such as neuro factors, are usually encapsulated in hydrogels during gelation and are subsequently released through the diffusion and degradation mechanisms of hydrogels. Hydrogels can

Table 1
Advantages and disadvantages of engineered hydrogels used in peripheral nerve repair.

Category	Component	Advantages	Disadvantages
Conductive Hydrogels	PPy	Intensify bioelectrical signal	Poor degradation and need secondary surgical
	PEDOT	Enhance the mechanical properties of hydrogels	Poor biocompatibility and will cause inflammation in the body for a long time
	PANI	Mimics the structure of neural tissue	
	Carbon-based material	Stimulate cell adhesion, migration and paracrine	The stability of crosslinking based on electrostatic interaction is feeble
		Low cytotoxicity	
		Promote nerve axon regeneration	
Stem cell-loaded Hydrogels	ESC	Differentiate Schwann-like cells	Tumorigenic properties
	ADSC	Secrete neurotrophic factors	Ethical uncertainty
	BMSC	Facilitate nerve axon and myelin regeneration	Immune rejection
	OSC	Promoting angiogenesis	Complex acquisition process
	DPSC		
	NSC		
Growth factor-loaded Hydrogels	bFGF	Good biocompatibility	Prone to protein hydrolysis and degradation
	GDNF	Protect neuronal survival	Short half-life in vivo
	BDNF	Accelerate axon and myelin regeneration	The concentration of GF required for the injury site is insufficient
	VEGF	Promote SCs proliferation and migration	
	NGF	Accelerate angiogenesis	
Self-assembling peptide (SAP) Hydrogels	RADA16	Structure similar to ECM	The treatment effect is poor in severe long gap nerve defect
	IKVAV	Predominant biocompatibility	Less theoretical support for exploring the addition of electroactivity
	YIGSR	Conducive to nerve cell adhesion, proliferation and migration	
	RGD		

support the continuous release and delivery of one or more molecules to the desired location in the body. In the future, how to accurately release drugs and nutritional factors is still the main research direction. We can use the application of stimuli-responsive hydrogels, in which some external stimuli (pH, temperature, light) are used to change the properties of the hydrogel, thus regulating molecular release. Recently, some novel studies have often added microparticles/nanoparticles loaded with neuronutrients into hydrogels for controlled release, which provides a new choice for the future application and exploration of neurotrophic factors.

Self-assembling peptide (SAP) hydrogels. SAP are a material that has been extensively studied in the field of medical tissue engineering in recent years. This peptide-based fibrous network is structurally and compositionally similar to the fibronectin in the ECM and has excellent bioactivity, biodegradability, and biocompatibility, so SAP hydrogels can be used as a suitable substrate for culturing neural cells helping to repair damaged tissues and restore their biological functions. Dynamic changes in different environmental conditions, such as pH, temperature, and enzymes, can alter the structural properties of SAP hydrogels to achieve controllability. Future research directions could enhance peripheral nerve repair by screening novel materials for synthetic hydrogels combined with SAPs used to provide various physical and biochemical cues. Thus far, there have been studies combining electroactive materials with SAP hydrogels to explore, but the stability and degradability of electroactive materials in SAP hydrogels have not yet been determined. Despite current limitations, the application of self-assembly technology in the field of nerve repair illustrates the tunability and feasibility of exploiting 3D conduction self-assembly networks for the treatment of nerve injuries [227,228].

In summary, the core problem of nerve recovery is to restore the functional connection between axons, neural circuits, and nonneuronal cells, which is a well-known challenge because there are various inhibitory parts of the nervous system. Understanding the anatomy of nerve tissue and advances in regenerative biology will contribute to the development of targeted neural scaffolding systems that can more closely simulate the physiological microenvironment of nerve regeneration. Therefore, various types of hydrogels (CHs, loaded stem cell/neurotrophic factor hydrogels, SAP hydrogels) have been designed and developed for neurohistological engineering. And the main advantages and disadvantages of each type of engineered hydrogel for peripheral nerve regeneration discussed in this review are presented in Table 1. As mentioned above, hydrogels can be used as repair materials (e.g., conductive hydrogels) or as delivery vehicles for stem cells, or bioactive factors (such as growth factors) for peripheral nerve repair. The hydrogel used for tissue engineering has good biocompatibility. The modification of different materials can also increase the mechanical properties, electrical conductivity, and bioactivity of hydrogels, and it is advantageous for cell differentiation, adhesion, migration, proliferation, and synapse formation. In conclusion, the application of hydrogels as scaffolds for neural tissue engineering is expected to achieve acceptable anatomical structure and functional recovery. However, there is still a certain gap in clinical translation. The hydrogel-based material for PNI treatment still has some disadvantages, such as low stability and low adhesion, which are not conducive to the long-term nerve repair process. Recently, Du et al. have demonstrated that materials with enhanced bond strength are beneficial in promoting peripheral nerve transection repair [229]. Moreover, **Luo et al.** also showed that conductive hydrogels with high bioadhesive properties can further improve hydrogel's therapeutic effect on PNI [230]. Thus, how to reduce the potential toxicity of conductive polymers as the backbone and how to improve the strength, viscosity, and responsiveness of the hydrogels as delivery vehicles are all key points to be explored in the future development of hydrogel materials for peripheral nerve regeneration. Thus, combining the actual clinical needs (mild, efficient, mass-producible, and cost-effective), targeted solutions to the deficiencies summarized in Table 1 will hopefully overcome the limitations of hydrogel-based materials for peripheral nerve injury repair and facilitate the translation of hydrogel materials for clinical applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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