Bioactive Materials 46 (2025) 150–172

Contents lists available at ScienceDirect

Bioactive Materials

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

Review article

Advances in biomaterial-based tissue engineering for peripheral nerve injury repair

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ARTICLE INFO

Keywords:
Peripheral nerve injury
Nerve guidance conduits
Peripheral nerve regeneration
Tissue engineering
Biomaterials

ABSTRACT

Peripheral nerve injury is a common clinical disease. Effective post-injury nerve repair remains a challenge in neurosurgery, and clinical outcomes are often unsatisfactory, resulting in social and economic burden. Particularly, the repair of long-distance nerve defects remains a challenge. The existing nerve transplantation strategies show limitations, including donor site morbidity and immune rejection issues. The multiple studies have revealed the potential of tissue engineering strategies based on biomaterials in the repair of peripheral nerve injuries. We review the events of regeneration after peripheral nerve injury, evaluates the efficacy of existing nerve grafting strategies, and delves into the progress in the construction and application strategies of different nerve guidance conduits. A spotlight is cast on the materials, technologies, seed cells, and microenvironment within these conduits to facilitate optimal nerve regeneration. Further discussion was conducted on the approve of nerve guidance conduits and potential future research directions. This study anticipates and proposes potential avenues for future research, aiming to refine existing strategies and uncover innovative approaches in biomaterial-based nerve repair. This study endeavors to synthesize the collective insights from the fields of neuroscience, materials science, and regenerative medicine, offering a multifaceted perspective on the role of biomaterials in advancing the frontiers of peripheral nerve injury treatment.

1. Introduction

Peripheral nerve injury (PNI) is a challenging clinical common problem. Patients will experience pain, and their sensation, cold resistance, and motor function will be impaired, seriously affecting their daily life. Globally, millions of PNI cases are reported annually [1]. The repair of long-distance nerve defects remains difficult, and autologous nerve transplantation is the gold standard for repairing peripheral nerve injuries. However, this method faces inherent limitations due to limited sources and the risk of scarring [2]. In recent years, artificial nerve guide conduits (NGCs), fabricated from various biomaterials, have become promising therapeutic strategies for promoting peripheral nerve regeneration and restoring function. NGCs can bridge long-distance nerve defects, provide favorable microenvironment and mechanical support for axon regeneration and nerve repair, ultimately aiding in the recovery of sensory and motor functions [3]. At present, variety of NGCs with safety, good degradability and excellent bionic structure have been developed in succession. The improvement of regeneration microenvironment and seed cell implantation provide favorable conditions for promoting nerve regeneration. Despite these advances, full recovery

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https://doi.org/10.1016/j.bioactmat.2024.12.005
Received 4 July 2024; Received in revised form 21 November 2024; Accepted 2 December 2024

from PNI remains elusive, underscoring the need for biomaterial-based tissue engineering strategies to achieve more effective repair.

In this study, we introduce a comprehensive review of the advancements in the repair of peripheral nerve injuries, with an emphasis on the potential of tissue engineering strategies based on biomaterials. It integrates insights from neuroscience, materials science, and regenerative medicine, providing a multifaceted perspective on NGCs. By examining the events of regeneration after peripheral nerve injury and evaluating existing nerve grafting strategies, this study showed advantages and the limitations of current approaches, such as donor site morbidity and immune rejection issues. This research includes a detailed exploration of the progress in the construction and application strategies of different NGCs. These conduits, which are designed to facilitate optimal nerve regeneration, focus on the materials, technologies, seed cells, and microenvironment. This in-depth analysis not only highlights the current state but also identifies potential for future research. Further discussion was conducted on the approve of nerve guidance conduits and potential future research directions. This study proposes potential avenues for future research, aiming to encourage researchers to explore innovative approaches in biomaterial-based nerve repair. By integrating insights from multiple disciplines, this work contributes to the advancement of the frontiers of peripheral nerve injury treatment.

2. Peripheral nerve injury and regeneration

PNI, characterized by the loss of peripheral nerve structure or function due to trauma, surgery or disease, resulting in partial or complete loss of sensory, motor and autonomic nerve functions [4]. Following injury, the distal neuron undergoes a process known as Wallerian degeneration, which is the basis of regeneration after PNI [5] (Fig. 1). In injured neurons, the injury interferes with the retrograde axonal signal from the target innervation sites, leading to axonal swelling, constriction, and eventual rupture. With the axon breakage, the myelin sheaths also degenerate, and disintegrate and form fragments. In this process, Schwann cells (SCs) will undergo a series of changes, such as dedifferentiation, proliferation, migration and secretion. At the same time, local macrophages rapidly proliferate, and peripheral macrophages also be recruited to phagocytize and clear the fragments of axon and myelin, thus providing a favorable environment for nerve regeneration [6]. Denervated SCs exhibit downregulation of proteins such as protein zero, myelin-associated glycoprotein and myelin basic protein. At the same time, when the fragments are removed, SCs collaborate with macrophages, fibroblasts and endothelial cells at the injured site to form "bundles of Büngner", while the cell adhesion molecule (CAM), neural cell adhesion molecule (NCAM) and glial fibrillary acidic protein, along with neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF) and neurotrophin 3 (NT-3) and other related cytokines are up-regulated, forming a favorable environment and axonal regeneration [5].

After injury, the axon ruptures, leading to degeneration and fragmentation of the myelin sheath. SCs rapidly proliferate, and the proliferating and recruited macrophages phagocytize and clear the fragments of axon and myelin. When the fragments are removed, the related cytokines from SCs are up-regulated, forming a favorable environment and axonal regeneration.

The neurons with ruptured axon will have different degrees of degenerative changes, even cell death. If neurons die, axons will not regenerate. Therefore, promoting the survival of neuronal bodies is the premise of axonal regeneration. The timeline of neuronal death offers a window for potential recovery. The adverse consequences of nerve regeneration are related to many factors: growth of axons are slow and insufficient; the growth direction is wrong, but it can be controlled by the nerve growth cone, which will respond to relevant molecular signals, to advance, pause and turn; target organs are atrophy; the cerebral cortex was rapidly reorganized and lasted for a long time; a large number of cells in the innervated neuron pool perish, etc. [7]. These factors significantly influence the functional recovery after proximal nerve injury.

Although researchers have gained insight into the pathophysiology and regenerative mechanism of PNI, patients continue to suffer from the condition. At present, the preferred treatment for nerve injury is surgical repair within 24 h, which can only protect some nerves and obtain a certain degree of structural and functional recovery [8]. In addition, the regenerative capacity of adult neurons in patients is limited, and the regeneration speed of axons after injury is slow, which may result in irreversible atrophy of target organs. Usually, the nerve with >5 mm gap due to injury cannot regenerate naturally and completely [9]. If there is injury gap of nerve and end-to-end suture is not feasible, autologous nerve transplantation remains the gold standard for PNI repair. However, this approach is constrained by the limited availability of autologous nerves and the potential for further damage to healthy nerves and cause other surgical wounds [2]. Therefore, it is crucial to provide suitable support and environment to accelerate axon regeneration for the recovery of PNI.

3. Nerve-grafting

PNI can cause neuropathy and seriously affect the patients' quality of life. When the gap between nerve defects is too long, nerve suture cannot be performed, and autografts remain the gold standard for conventional

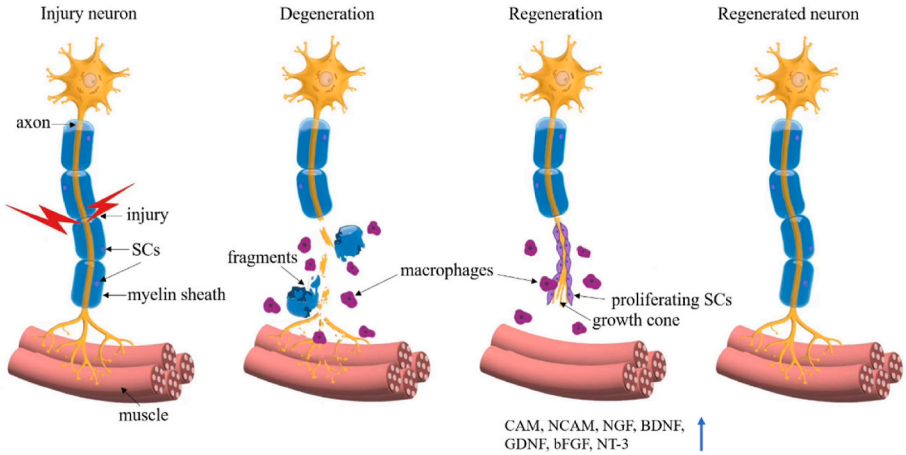

Fig. 1. The schematic illustration of the events after peripheral nerve injury.

treatment [10]. The primary structure, SCs and neurotrophic factors in autologous nerve grafts play important roles in supporting the growth and repair of neurons. Replacing injured peripheral nerve with autologous nerve can provide structural support, guide axonal regeneration, reduce immune response, and mitigates the risk of neuroma and fibrosis formation [11]. However, limitations of autologous transplantation includes: the scarcity of donor tissue, mismatch between donor/recipient nerve, tissue adhesion, the risk of secondary surgery and donor site complications including pain, infection and neuroma [12]. These challenges underscore the need for the development of safe and effective alternatives to autografts.

Allografts are an alternative to autologous nerve transplantation. After appropriate preparation, the donor nerve graft is ready for use. It provides flexible extracellular matrix (ECM), maintains the structure of the primary nerve, allows revascularization, and reshapes the patient's own tissue while supporting the growth of intermittent axons. Allografts has the advantages of sparing the autologous nerve, avoiding secondary surgery, and reducing cost [13]. However, the major drawback remains the risk of host rejection. In order to reduce the immunogenic response, decellularization techniques have achieved satisfactory results. Available acellular allograft such as Avance® (Axogen Inc, USA; human origin), which is ECM made of donated human peripheral nerve tissue treated with mild detergent and chondroitinase, can successfully repair nerve defects up to 7 cm [13,14]. However, allografts also have limitations [15], for example, long grafts with larger diameter must be used cautiously, and lifelong use of immunosuppressive agents.

Xenograft, derived from animal nerves, offers another alternative method [15]. Compared to human grafts, xenografts are more widely available and cost-effective. Faust et al. reported that xenograft from acellular porcine nerves were transplanted into rats, successfully integrated with the proximal and distal nerve segments without obvious proliferation after 8 weeks, although axonal regeneration was limited in the reconstructed nerves, nerve conduction was absent, and the target muscles were significantly atrophied [16]. Jia et al. reported that bone marrow mesenchymal stem cells (BMSCs) were implanted into acellular xenografts to fill the sciatic nerve 10 mm gap of rats, which significantly improved nerve regeneration and functional rehabilitation, providing a promising approach for repairing of peripheral nerve defects [17]. However, as of now, no xenografts have been approved for peripheral nerve repair.

4. Nerve guide conduits

Repairing nerve defects larger than 4 cm after PNI remains a significant challenge. Even with autologous nerve transplantation, the functional recovery is limited [18]. At present, NGCs are alternative and promising strategies to guide the repair and regeneration of impaired peripheral nerve, which have attracted more attention of researchers. Most of the artificial NGCs approved by FDA are hollow tubes constructed from various natural or synthetic biomaterials. However, their use is generally restricted to shorter nerve gaps and have poorer functional recovery, and cannot be comparable with the therapeutic effect of autografts [10]. Recent advances in tissue engineering have changed the concept of simply providing a protective space for nerve regeneration. The researchers are now employing innovative construction techniques, selecting suitable biomaterials, modifying morphology of the conduit lumen, implanting seed cells, and improving regenerative microenvironments to promote nerve growth and accelerating axon regeneration. NGCs need to show good biocompatibility, biodegradability, bionics and mechanical properties, allow the passage of nutrients and oxygen, limit myofibroblast infiltration, reduce scar formation, and improve other properties, such as antibacterial properties and electrical conductivity.

4.1. Material for nerve guide conduits

4.1.1. Synthetic material

A wide variety of materials used to NGCs to promote nerve regeneration. Most NGCs are prepared using synthetic polymer materials. The synthetic materials commonly used in neural tissue engineering include polyvinyl alcohol (PVA), polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), Poly (glycolide-co-lactide) (PGLA), poly (glycerol sebacate) (PGS), polyurethane (PU), poly (L-lactic acid-co-ε-caprolactone) (PLCL), etc. [19] (Fig. 2 and Table 1). In addition, the addition of conductive materials is conducive to the conduit to promote nerve regeneration. The common conductive materials include polypyrrole (Ppy), polyaniline (PANI), polythiophene, etc., but they are not biodegradable and have weak mechanical properties and cannot be manufactured into a three-dimensional structure structures, necessitate their incorporation into composite materials within NGCs [20].

PVA conduit (SaluTunnel) approved by FDA can be used to repair nerve defects, but PVA is not biodegradable, which limits its further application [10]. Oxidized polyvinyl alcohol (OxPVA) is an interesting synthetic polymer. Compared with PVA, the oxidized form shows certain biodegradation characteristics and protein loading capacity, both of which are related to the carbonyl group in molecular skeleton [21] (Fig. 2A). According to the literature, the grooved OxPVA nerve scaffold was obtained by 3D printing, mechanically combined with self-assembly peptide EAK, the scaffold is conducive to the adhesion and proliferation of SH-SY5Y cells. At 21 days, the OxPVA-EAK scaffolds maintained approximately 1.6-fold higher number of cell growth compared to the group without EAK addition [32]. In addition, the oxidized PVA conduit shows mechanical resistance and suture retention ability, has no cytotoxic effect on SH-SY5Y and Schwann cells, and is biodegradable over time [33]. In vivo studies showed that OxPVA conduit containing bioactive EAK-YIGSR could repair 5 mm defect of sciatic nerve in rats, significantly increasing the total number and density of myelin axons [21]. These findings underscore OxPVA's potential for clinical applications in nerve injury repair.

PLA is a synthetic polyester with good mechanical properties, biocompatibility and biodegradability [34]. The degradable PLA non-woven conduit are porous, offering sufficient strength, and have demonstrated efficacy in repairing 7 mm defect of nerve repair in rats, with an increased number of myelinated nerve fibers observed after 13 weeks. There is no significant difference in the diameter of axons between the PLA conduit and the autografts group [22] (Fig. 2B). Compared with hollow NGC, the conduit with PLA multichannel has obvious advantages, and PLA microfiber with a diameter of 10 μm can better guide the growth of axons [35]. PLA microfibers were wrapped by hyaluronic acid (HA) to make a multi module NGC, which was implanted with schwann cells. In the study of 15 mm defect of sciatic nerve in rabbit, the nerve was regenerated after 6 months of bridge, accompanied by higher vascularization. The proportion of myelinated nerve fibers reaching the central parts (69 ± 9 %) and distal parts (65 ± 5 %) of the NGC was higher, and the multi module repair opened up new possibilities for the treatment of long-distance nerve defects [18].

PCL, which is metabolized and excreted by the body, has also shown great potential in nerve repair. The 3D engineered PCL conduit was filled with mg^{2+} releasing hydrogel and implanted into the 10 mm nerve defect in rats. After 12 weeks, axon regeneration and myelin regeneration were significantly enhanced, and functional recovery was enhanced [23]. Additionally, the NGC were prepared by electrospinning technology based on PCL and gelatin, and filled with platelet rich plasma (PRP), to treat 10 mm sciatic nerve defect in rats. The results showed that NGC implantation induced nerve regeneration and restored motor and sensory functions [24] (Fig. 2C).

PGA provides essential support for nerve repair and has proven effective in bridging long nerve defects. An artificial NGC composed of an outer microporous chitosan conduit and an inner PGA oriented filament is used to bridge the 30 mm sciatic nerve defect in beagle dogs and

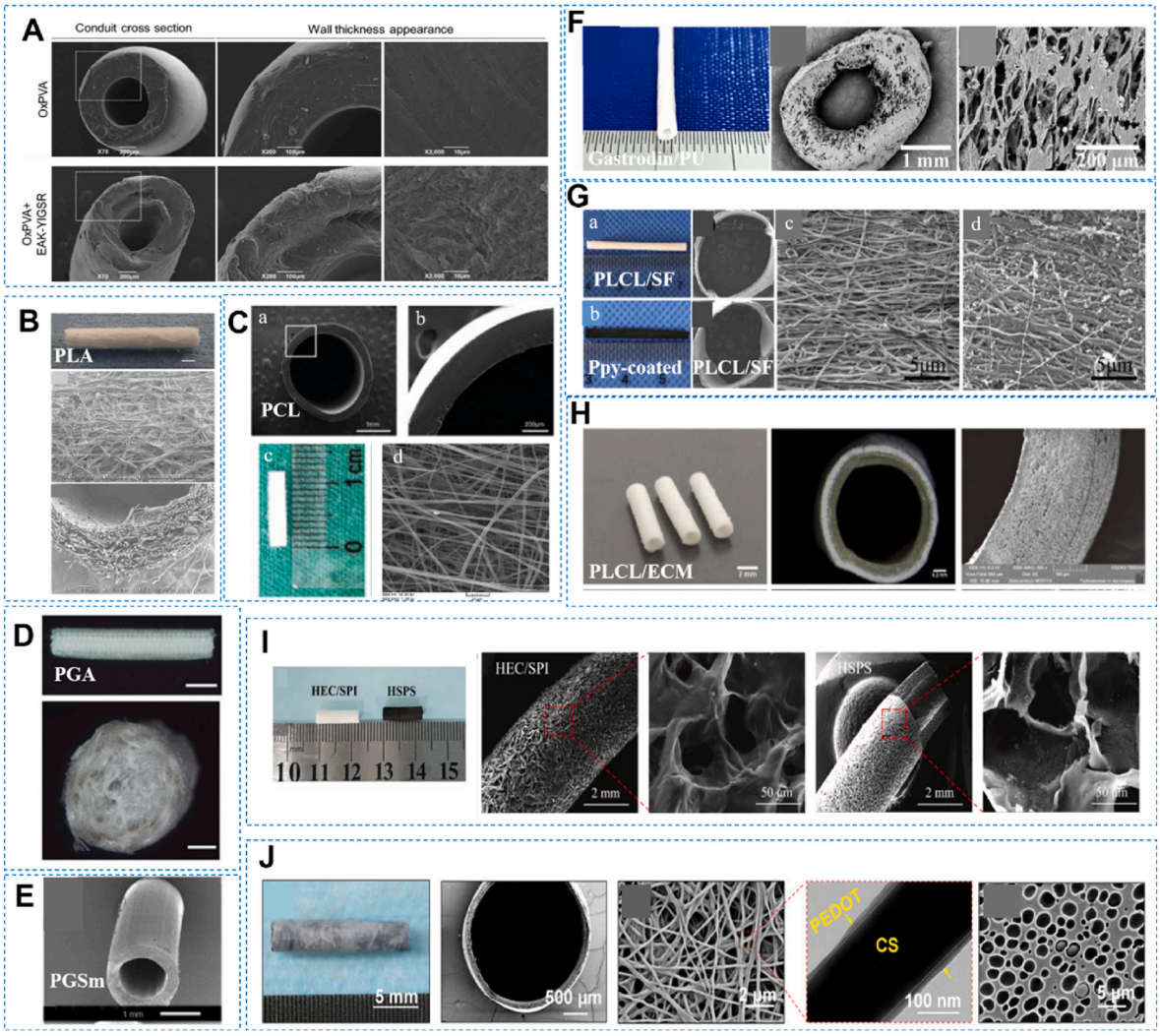

Fig. 2. Synthetic materials for NGCs. (A) OxPVA-based NGCs ultrastructure. SEM photomicrographs showing the NGCs cross section and focusing on wall-thickness appearance [21]. This is an open access article distributed under the terms of the Creative Commons CC-BY license. (B) A non-woven PLA NGC; SEM photographs of the inner surface and cross-section of the PLA NGC [22] with permission of John Wiley & Sons, © 2012. (C) a-b, SEM analysis of the PCL NGCs; c, PCL NGC with a diameter of 2 mm and a length of 12 mm [23]; This article is licensed under a Creative Commons Attribution 4.0 International License. d, SEM micrograph of PCL/Gel nanofibers [24] with permission of Elsevier, © 2020. (D) The PGA NGC filled with collagen sponge [25] with permission of Wolters Kluwer Health, © 2019. (E) SEM images of PGSm NGC with methacrylation after laser cutting [26]. This is an open access article distributed under the terms of the Creative Commons CC-BY license. (F) The characteristics of Gastrodin/PU NGCs (digital photos, cross-section and longitudinal section) [27]. This is an open access article under the CC BY-NC-ND license. (G) Digital photos and cross-sections of (a) PLCL/SF NGC and (c) Ppy-coated NGC. SEM images of (b) the nanofiber surface of PLCL/SF NGC and (d) the nanofiber surface of Ppy-coated NGC [28] with permission of Elsevier, © 2019. (H) The SEM and the stereoscope images of double-layer NGC (outer PLCL and inner ECM) [29]. This is an open-access article distributed under the terms of the Creative Commons Attribution License. (I) The images and SEM images of HEC/SPI and HSPS conduits [30]. This is an open access article under the CC BY-NC-ND license. (J) Macro and micromorphology of NP-NGC. (Optical photo, SEM and TEM images of CS/PEDOT core/shell NF, SEM image of nanoporous PLLA film and nanopore size distribution of the NP-NGC) [31] with permission of John Wiley and Sons, © 2021. SEM: scanning electron microscope. TEM: transmission electron microscope.

the 35 mm median nerve defect of elbow in patient. The nerve continuity and function are restored [36,37]. Moreover, the electrospun nanofiber sheets incorporating methylcobalamin (MeCbl sheets) combined with PGA tube filled with collagen sponge (PGA-c) conduit significantly promoted the recoveries of sensory function, electrophysiology and morphology of sciatic nerve with 10 mm defect in rats [25] (Fig. 2D). Currently, the biodegradable PGA-c conduit has been commercialized for the reconstruction of peripheral nerve and has achieved successful clinical results. In the clinical trial involving the average nerve gap of 16.7 mm, 90 % of the cases have obvious recovery, and PGA-c conduit is suitable for repairing the short gap of human digital nerve [38]. Additionally, human amniotic membrane (HAM) wrapping can promote peripheral nerve regeneration. For example, the effect of HAM wrapped PGA-c conduit in repairing 8 mm sciatic nerve defect in rats is better than that of a single PGA-c conduit [39].

PGLA conduit has biocompatibility and has been proved to be used for the repair of injured nerves. A clinical study showed that PGLA conduit had obvious effect on functional recovery of regenerated nerve after 3–6 months repair, the regenerated superficial radial nerve and digital nerve were close to the area of the normal nerve at postoperative 6 months [40]. Another clinical study used chitosan-PGLA conduit containing bone marrow mononuclear cells (BMMCs) to repair peripheral nerve defects at the distal end of the upper arm, and achieved good clinical results. Five months after operation, the function began to recover, the blood perfusion increased significantly, and the nerve structure could be detected by ultrasound [41].

PGS, a biodegradable elastic polymer, has no adverse effects on the metabolic activity, adhesion and proliferation of Schwann cells, and

Table 1
Synthetic material for NGC.

Synthetic material	NGC	Application	Effects	References
OxPVA	OxPVA conduit containing bioactive EAK-YIGSR	5 mm defect of sciatic nerve in rats	It could repair defect of sciatic nerve, significantly increasing the total number and density of myelin axons	[21]
PLA	degradable PLA non-woven conduit	7 mm defect of nerve repair in rats	There is no significant difference in the diameter of axons between the PLA conduit and the autografts group	[22]
	PLA microfibers wrapped by HA to make a multi module NGC, which was implanted with SCs	15 mm defect of sciatic nerve in rabbit	The nerve was regenerated after 6 months of bridge, accompanied by higher vascularization.	[18]
PCL	PCL conduit was filled with mg^{2+} releasing hydrogel	10 mm nerve defect in rats	After 12 weeks, axon regeneration and myelin regeneration were significantly enhanced, and functional recovery was enhanced	[23]
PGA	NGC composed of an outer microporous chitosan conduit and an inner PGA oriented filament	30 mm sciatic nerve defect in beagle dogs and the 35 mm median nerve defect of elbow in patient	The nerve continuity and function are restored	[36,37]
	PGA tube filled with collagen sponge (PGA-c) NGC	clinical trial of repairing the average nerve gap of 16.7 mm of patient	90 % of the cases have obvious recovery, and PGA-c conduit is suitable for repairing the short gap of human digital nerve	[38]
PGLA	PGLA NGC	27-mm defects of superficial radial nerve of patient	The regenerated superficial radial nerve and digital nerve were close to the area of the normal nerve at postoperative 6 months	[40]
	chitosan-PGLA conduit containing bone marrow mononuclear cells (BMMCs)	50-mm long median nerve defect, 80-mm long ulnar nerve defect of patient	Five months after operation, the function began to recover, the blood perfusion increased significantly, and the nerve structure could be detected by ultrasound	[41]
PGSm	PGSm NGC	nervus peroneus communis defect in mouse	after 21 days implanted of nervus peroneus communis defect in mouse	[26]
PU	5 % gastrodin/PU conduit	10 mm sciatic nerve defect in rats	The conduit not only promote the regeneration of nerve and microvascular network, but also promote the growth of axons and myelin regeneration, thus greatly improving the functional recovery	[27]
PLCL	nanofiber composed of silk fibroin (SF) and PLCL wound into directional NGC	10 mm defect of rat sciatic nerve	It significantly promoted peripheral nerve regeneration	[48]
PPy	PPy/SF NGC	10 mm sciatic nerve defect in rats	It can effectively promote axonal regeneration and myelin regeneration	[52]
PEDOT	NP-NGC with external nanoporous PLLA membrane and internal synthetic CS/PEDOT nanofibers	15 mm defect of rat sciatic nerve	The repairing is obviously close to that of autograft	[31]
GO	Chitosan/GO NGC containing 0.25 % GO	10 mm defect of sciatic nerve in rats	The histology and function of sciatic nerve and target muscle were improved, and the results were similar to those of autografts	[57]

shows good histocompatibility. It is an excellent candidate material for nerve reconstruction [42]. Conventionally polymerized by a two-step polycondensation of glycerol and sebacic acid, variations of synthesis parameters, reactant concentrations or by specific chemical modifications, PGS materials can be obtained exhibiting a wide range of physicochemical, mechanical, and morphological properties. Conventionally, PGS follows a two-step synthesis route via prepolycondensation at 120 °C under a nitrogen or argon atmosphere for 24 h and cross-linking in a vacuum at 120 °C for at least 48 h. However, due to the harsh cross-linking conditions and long reaction times required for its curing, single PGS-based materials show a lack of processability. Alternative processing strategies are required to address these limitations [43]. Modified PGS prepared with methyl methacrylate (MMA) and electrospun into PGS-PMMA nanofibers, mixed with gelatin to improve its hydrophilicity and biocompatibility. It was found that PGS-PMMA/gelatin nanofibers can promote the proliferation of PC12 cells and induce axonal growth [44]. Additionally, biodegradable PGS/calcium titanate (CaTiO3) nanocomposites are used as NGC for peripheral nerve regeneration. The NGC is close to the elasticity and tensile strength of natural nerves, can promote the adhesion and proliferation of PC12 cells, and improve the growth and extension of axons. PGS/CaTiO3 nanocomposites can be used as ideal materials for peripheral nerve regeneration [45].The poly(glycerol sebacate methacrylate) (PGSm) is obtained by functionalizing PGS prepolymer with

methacrylate. This formula allows the instant solidification of PGS prepolymer to prepare NGC. The results show that axons enter the distal stump through PGSm conduit after 21 days implanted of nervus peroneus communis defect in mouse [26] (Fig. 2E). PGSm opens the way for the manufacture of personalized NGC for nerve injury repair.

PU, as a multifunctional biomaterial, shows excellent effect in axonal regeneration and muscle function recovery in injured nerve tissue. The gastrodin/PU scaffold significantly enhanced the proliferation, migration and myelin formation of SCs, while upregulating the expression of neurotrophic factors, and inducing the differentiation of PC12 cells. In vivo studies showed that the 5 % gastrodin/PU conduit had anti-inflammatory effect, and the effect of repairing was similar to that of autograft in 10 mm sciatic nerve defect at 16 weeks postoperatively in rats. The gastrodin/PU conduit not only promote the regeneration of nerve and microvascular network, but also promote the growth of axons and myelin regeneration, thus greatly improving the functional recovery [27] (Fig. 2F). Additionally, the PU/Gel/VEGF NGC containing vascular endothelial growth factor (VEGF) and hydrogel could promote the proliferation and migration of RSC96 cells, and the expression of S100 β; In vivo, PU/Gel/VEGF NGC promotes the recovery of target muscle function with a SFI value of around −70 and effectively improves nerve regeneration and angiogenesis [46]. Moreover, it was also found that the polyurethane/collagen/nano-bio glass (PU/Col/NBG) NGC prepared by electrospinning technology is biocompatible and a favorable conduit for peripheral nerve regeneration and axon growth [47].

PLCL is another material commonly used in NGC construction. The directional composite nanofiber composed of silk fibroin (SF) and PLCL were prepared by electrospinning and wound into directional NGC, which was implanted into 10 mm defect of rat sciatic nerve to significantly promote peripheral nerve regeneration [48]. In addition, the arrangement of PLCL nanofibers has different regulatory effects on the activation of macrophages during the repair process. The NGC constructed by neatly arranged nanofibers significantly promotes the regeneration of peripheral nerves by promoting healing phenotype of macrophages at a certain extent [49]. Furthermore, PPy, which possesses excellent conductivity and is non-toxic, was used to coat a PLCL/SF NGC, resulting in nerve regeneration and functional recovery comparable to autografts and superior to the uncoated PLCL/SF NGC [28] (Fig. 2G). A novel electrospun double-layer NGC with external layer of PLCL and internal layer of ECM was used to bridge 10 mm defects of rat sciatic nerve, which not only retained the good biocompatibility and biological activity of ECM, but also obtained the appropriate mechanical strength from the PLCL [29] (Fig. 2H). The combination of PLCL with biologically active natural materials holds great potential in clinical applications in nerve defect repair.

Electrical stimulation provided by electroactive materials is an effective tool for nerve formation. Electrical stimulation can guide regenerated axons across the nerve gap and connect with the distal stump of injured nerve via biological signal transduction, which is particularly important for the nervous system [50]. The common strategy for manufacturing NGC is to doping conductive polymers (such as PPy, PANI, polythiophene, etc.) into biodegradable biomaterials [28,51]. PPy has good electrical behavior, but it shows poor solubility and degradation. Studies have shown that conductive PPy/SF NGC can effectively promote axonal regeneration and myelin regeneration of 10 mm sciatic nerve defect in rats, and MAPKs signal transduction pathway is activated at the conductive NGC [52]. PANI also has an excellent conductive ability. However, low solubility and toxic solvents limited its use. The PANI-based composites NGC can effectively promote nerve regeneration and reduce muscle atrophy. For example, NGC containing hydroxyethyl cellulose (HEC)/soy protein isolate (SPI)/PANI sponge (HSPS) and combined with VEGF-A over-expressed Schwann cells or poly (L-lactic acid)-co-poly(ε-caprolactone) (P(LLA-CL)), collagen, PANI, and enriched with adipose-derived stem cells (ASCs) as a P (LLA-CL)-COL-PANI NGC combined with ADSCs have shown good effects in repairing peripheral nerves [30,53] (Fig. 2I). The poly (3, 4-ethylenedioxythiophene) (PEDOT) shows electrochemical stability and stronger conductivity. PEDOT doped with polystyrene sulfonate (PSS) can be easily dispersed in aqueous solution while maintaining good conductivity. But it has limited processability and is unstable in aqueous solutions in the long-term [54]. The effect of implantable nerve electrical stimulation (FI-NES) system in repairing 15 mm defect of rat sciatic nerve is obviously close to that of autograft. The NP-NGC is external nanoporous poly(L-lactic acid) (PLLA) membrane and internal synthetic chitosan (CS)/PEDOT nanofibers with core/shell structure, PEDOT as a conductive layer tightly wraps CS nanofibers, significantly improving the conductivity [31] (Fig. 2J). Graphene is a two-dimensional carbon nanomaterial with good optical, electrical and mechanical properties, which has attracted more and more attention [55]. A conductive 3D graphene NGC wrapped with PCL has been developed, with enhanced mechanical properties, and enhanced proliferation and extension ability of PC12 cells, which can be used in peripheral nerve tissue engineering [56]. Graphene oxide (GO) is rich in oxygen-containing groups, which has been proved to promote the proliferation and adhesion of SCs. Chitosan/GO NGC containing 0.25 % GO was implanted into 10 mm defect of sciatic nerve in rats. The histology and function of sciatic nerve and target muscle were improved, and the results were similar to those of autografts [57]. However, the safety of long-term exposure to graphene still needs to be carefully considered, and GO blends have limited electroconductivity [55]. Moreover, piezoelectric biomaterials have attracted attention in neural tissue engineering due to their biocompatibility and the ability to generate piezoelectric surface charges [58].

The piezoelectric nanofiber hydrogel NGCs with electrical stimulation (ES) triggered by ultrasound (US) and controlled drug release also has a positive role in promoting the functional recovery and nerve axon regeneration in long sciatic nerve defect of rat. The inner layer of NGCs is barium titanate piezoelectric nanoparticles (BTNPs)-doped polyvinylidene fluoride-trifluoroethylene (BTNPs/P(VDF-TrFE)) nanofibers, which has improved piezoelectricity and alignment. The outer layer is a biologically active drug encapsulated thermal responsive poly (N-isopropylacrylamide) hybrid hydrogel. The NGC can not only induce the directional extension of neurons and promote the growth of neurites by US triggered electrical stimulation, but also realize the controlled release of nerve growth factor by hydrogel under the heating triggered by US [59]. Therefore, conductive NGCs can transmit electrical impulses from the proximal nerve stump to the distal nerve stump through electrical stimulation, providing directed nerve regeneration and promoting functional and sensory recovery after regeneration. However, it is great challenges to deliver effective and controllable bioelectronic implantable device. It is necessary to comprehensively consider according to the specific needs and experimental conditions to give full play to its advantages and try to avoid its disadvantages, such as the biodegradability, in vivo safety, and the quantitative control of electrical stimulation.

4.1.2. Natural materials

Natural biomaterials are rich in resources, easy to obtain, with good biocompatibility and biodegradability, and easy to be absorbed by the body. However, the poor mechanical properties and other factors limit its application. These drawbacks can be mitigated through chemical modifications and by combining them with synthetic materials. Examples of natural biomaterials commonly used in nerve tissue engineering include collagen (Col), silk fibroin (SF), spider silk, chitosan, gelatin (Gel), sodium alginate (SA), HA, ECM, etc. (Fig. 3 and Table 2).

Collagen is a natural polymer expressed in the extracellular matrix of the peripheral nervous system, has been widely used in nerve tissue engineering. Recently, marine animals are an emerging source of collagen extraction, which has easy availability and low cost [68]. Various types of collagen also could be produced in mammalian cells, insect cells, and bacteria and yeast. Extensive sources of collagen ensure the great demand for collagen in NGC. In vitro studies showed that the

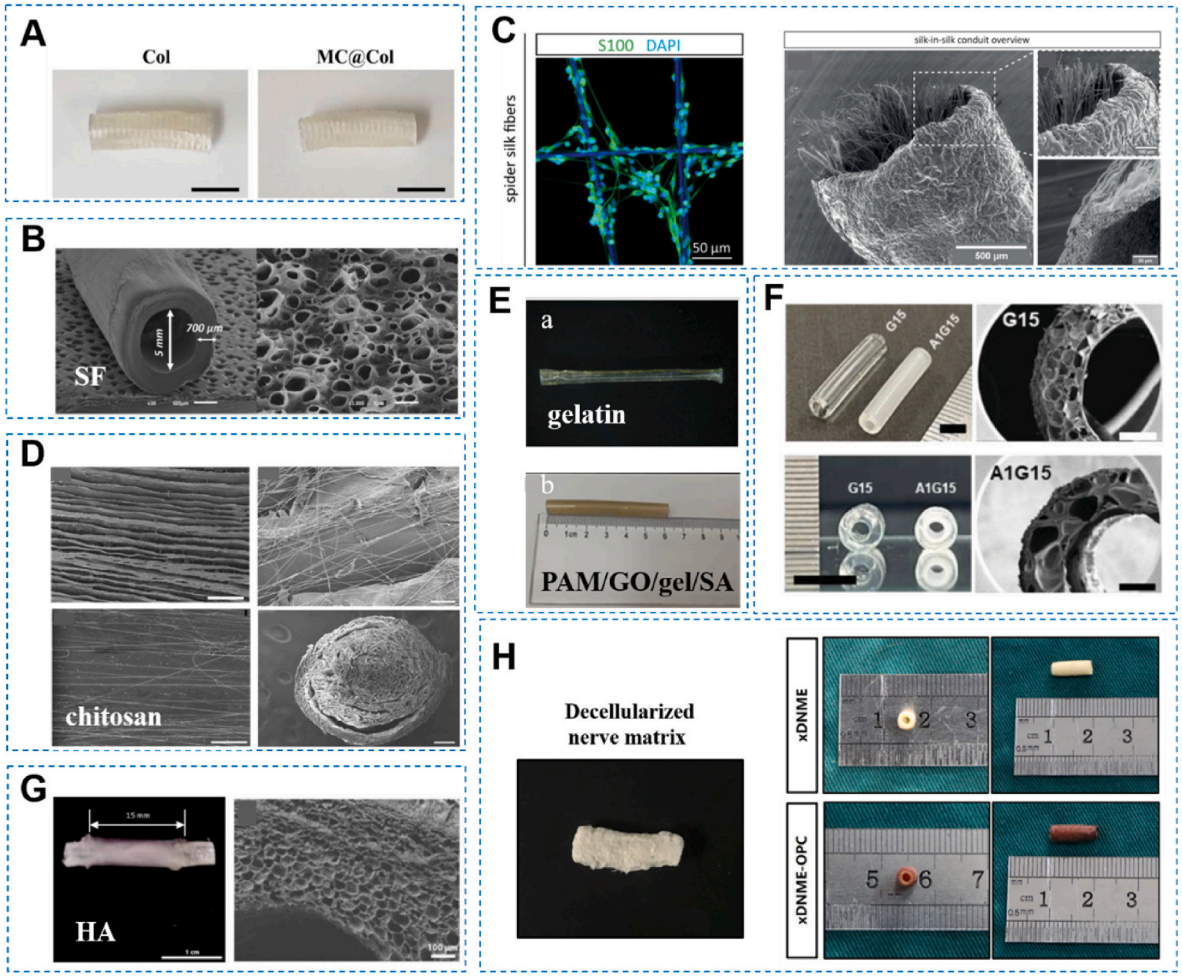

Fig. 3. Natural materials for NGCs. (A) Representative gross morphologies of collagen NGC (Col) and collagen mineralized collagen NGC (MC@Col) [60]. This is an Open Access article distributed under the terms of the Creative Commons Attribution License. (B) SEM microphotographs of the SF conduits incorporating NTFs, by the crosslinking and the absorption method, respectively [61] with permission of John Wiley and Sons, © 2020. (C) Representative immunofluorescence images of rat Schwann cells grown on spider dragline silk; Representative micrograph of the silk fibroin NGC containing longitudinally aligned spider dragline silk, magnification of the marked area, and micrograph of the silk fibroin conduit [62]. This article is licensed under a Creative Commons Attribution 4.0 International License. (D) The morphology of chitosan NGCs (microchannels, aligned chitosan nanofibers, the nanofibers deposited into the microchannels and the complete chitosan NGC) [63] with permission of Elsevier, © 2023. (E) a, the dry gelatin tube was shaped into a conduit-like structure [64] with permission of Wolters Kluwer Health, © 2016. b, PAM/GO/Gel/SA composite hydrogel conduit [65] with permission of John Wiley and Sons, © 2019. (F) Side- and cross-sectional photographic images and scanning electron micrographs of G15 and A1G15 NGCs [66]. This article is available under the Creative Commons CC-BY-NC-ND license. (G) Macroscopic image and field emission scanning electron microscope image with porous structure of the HA conduit [18]. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license. (H) Macroscopic observation of decellularized nerves; The external dimensions of xDNME and xDNME-OPC conduits (xDNME: the porcine decellularized nerve matrix NGC, xDNME-OPC: the porcine decellularized nerve matrix NGC cross-linked to use proanthocyanidins) [67] with permission of Elsevier, © 2022.

secretion of angiogenic factors, ECM deposition, fiber arrangement and the growth of dorsal root ganglion (DRG) axis were increased under the appropriate concentration of collagen I hydrogel [69]. Heparin and collagen are assembled layer by layer to simulate the extracellular environment of NGC. Six-layer heparin and collagen are stable and can enhance the adhesion and repair ability of Schwann cells [70]. In addition, in the clinical study, the NeuraGen (collagen, Integra, USA) NGC was used to repair the median and ulnar neuropathy in patients, and the maximum gap between the stumps was 6 mm. It was found that the NeuraGen can well support the recovery of electrophysiological function. The hand touch sensation quotient of patient recovered partially, rapidly at first, and then more slowly to 81 ± 3 % of control at 24 months, whereas tactile gnosis recovered to 20 ± 4 % [71]. However, the collagen has some undesirable characteristics that affect the clinical applications, including poor mechanical strength, too fast degradation and high swelling ratio [60,72]. The relatively low mechanical strength of collagen means that it may not be able to withstand large external forces. Collagen is easily digested enzymatically in vivo and degrades relatively quickly. This may result in a shorter duration in vivo and an inability to maintain the repair effect in the long term. Especially in long-distance nerve defect repair, the rapid degradation of collagen may become a disadvantage. Based on these, the mineralized collagen (MC) was developed. The modified collagen conduit can deliver the synergistic GDNF and NGF, which may be a promising NGC for repairing peripheral nerve defects. The MC@Col NGC contains Col and MC, with enhanced mechanical and degradation properties. After 12 weeks of implantation and repair of 10 mm sciatic nerve defect in SD rats, the regeneration effect is similar to that of autograft in some aspects, which is superior to Col NGC, chitosan NGC or PCL NGC [60]. MC@Col NGC has great potential in clinical application (Fig. 3A).

SF is the main component of silk fiber secreted by silkworm. SF is a biodegradable and cost-effective natural fibrin, known for its excellent biocompatibility and ability to self-assemble in solution. After nerve injury, the lack of neurotrophic factor in the proximal nerve lead to

Table 2
Natural materials for NGC.

Natural materials	NGC	Application	Effects	References
collagen	collagen NGC (NeuraGen)	maximum 6 mm gap of median and ulnar neuropathy	NeuraGen can well support the recovery of electrophysiological function	[71]
	MC@Col NGC containing Col and mineralized collagen	10 mm sciatic nerve defect in rats	the regeneration effect is similar to that of autograft in some aspects	[60]
SF	SF NGC filled with 300 degummed SF fibers	30 mm sciatic nerve gap of dog	satisfactory regeneration results close to autograft were obtained	[73]
	SF NGC loaded with GDNF	10 mm defect of the sciatic nerve in rats	he role of retrograde transport, neuron protection and motor nerve regeneration has been substantially improved	[61]
	double-layer SF/PLLA NGC containing exosomes of human endometrial stem cell (EnSC)	10 mm sciatic nerve defect in rats	It significantly promoted nerve regeneration and functional recovery	[75]
Spider silk	decellularized blood vessels filled with the spider silk of Trichonephila edulis	60 mm defect of nerve in black headed sheep	The effect of the spider silk conduit was equivalent to that of the autograft, which may be an important way to repair the long nerve defect	[76]
	spider silk NGC based silk fibroin	10 mm sciatic nerve defect in rats	the silk in silk NGC obtained similar regeneration performance to the autograft	[62]
Chitosan	multi-channel chitosan NGC	10 mm nerve defect in rats	The peripheral nerve was successfully reconstructed in terms of tissue and function, and its regeneration effect was equivalent to that of autograft.	[82]
	chitosan NGC combined with microgels containing VEGF and BDNF	5 mm nerve defect in rats	It significantly promoted nerve fiber regeneration and myelination, neuron recovery, muscle function, nerve conduction recovery	[84]
Gelatin	PCL and gelatin NGC filled with platelet rich plasma (PRP)	10 mm sciatic nerve defect in rats	NGC implantation induced nerve regeneration and restored motor and sensory functions.	[24]
SA	novel double network hydrogel NGC with crosslinking of SA and gelatin	10 mm sciatic nerve defect of rats	It significantly improved the recovery of nerve function and nerve regeneration, and reduced fibrotic scar	[66]
HA	HA granular hydrogel NGC	10 mm sciatic nerve gap in rats	NGC could effectively promote regeneration of sciatic nerve axon and myelin sheath, and promote the recovery of morphology and function of injured sciatic nerve	[93]
	porcine decellularized nerve matrix NGC	8 mm nerve defect of rat	the regenerated nerve fibers were completely connected to the two ends of the nerve defect	[67]
ECM	double-layer NGC with internal ECM and external PLCL	10 mm rat sciatic nerve defect	It showed good nerve regeneration	[29]

incomplete nerve regeneration. Owing to its unique properties, SF can slowly and long-term release neurotrophic factors and promote the effective regeneration of injured nerves (Fig. 3B) [61]. The SF conduit with an inner diameter of about 5 mm prepared by electrospinning was filled with 300 degummed SF fibers. The SF NGC is implanted into the 30 mm sciatic nerve gap of dog. After 12 months, satisfactory regeneration results close to autograft were obtained [73]. Moreover, when a GDNF-loaded SF NGC was implanted to 10 mm defect of the sciatic nerve in rats, the conduit significantly enhanced retrograde transport, neuron protection and motor nerve regeneration, compared to both autografts and standard SF NGCs [61]. Studies have showed that FIBL-Linker-NT3 is composed of silk fibroin light chain (FIBL) and NT-3 via polypeptide connection, can promote the growth and regeneration of axons in vivo and in vitro. Chitosan/SF-FIBL-Linker-NT3 NGC is constructed through self-assembly of FIBL-Linker-NT3 and SF heavy chain (SFH), and chitosan scaffolds provide a suitable microenvironment. Chitosan/SF-FIBL-Linker-NT3 is implanted into the 8 mm defect of rat sciatic nerve. It has superior nerve regeneration ability, and has good recovery in neurite length, sciatic function index, thermal sensitivity, target muscle function, myelin sheath [74]. In addition, the double-layer SF/PLLA NGC containing exosomes of human endometrial stem cell (EnSC) significantly promoted nerve regeneration and functional recovery in 10 mm sciatic nerve defect in rats [75]. For effective peripheral nerve regeneration, NGCs must exhibit a neutral modulus of elasticity and high elongation at break. However, the treatment efficacy of silk fibroin-based NGCs is unsatisfactory due to their unmatched mechanical properties and the strategies to improve its mechanical properties are needed to promote nerve regeneration.

Spider silk harvested directly from spiders are attractive biomaterials that support and guide nerve growth due to its excellent significant biocompatibility, toughness and biodegradability. Spider silk is produced by specific silk glands to condense the protein mucus in the air into firm spider silk. Studies show that the spider silk conduit was constructed by longitudinal filling in decellularized blood vessels with the spider silk of Trichonephila edulis, which was used to repair the 6 cm defect of nerve in black headed sheep. The effect of the spider silk conduit was equivalent to that of the autograft, offering a promising approach for repairing long nerve defect [76]. In vitro studies suggests that the synergy between the hardness and composition of Trichonephila spider silk significantly influences SC migration [77]. The spider silk NGC based silk fibroin was prepared by combining the excellent processability of silk fibroin with the excellent cell adhesion performance of spider silk, to repair 10 mm sciatic nerve defect in rats. Due to the good guiding properties of spider silk, the NGC achieved nerve regeneration outcomes similar to those of autografts (Fig. 3C) [62]. The effects of the silks of two kinds of spiders (Trichonephila inaurata and Nuctenea umbratica) and jumping spider (*Phidippus regius*) on the

regeneration potential of SC were further compared. The silk of *Phidippus regius* was minor ampullate. Due to the interaction between the primary protein structure and mechanical properties of the silk, the regeneration speed of SCs on the silk of *Phidippus regius* was stronger and SCs changed to the myelinated phenotype [78]. As a novel material, spider silk holds significant potential for advancing NGC strategies.

Chitosan is mainly derived from the shells such as shrimp and crabs, as well as some plants and the cell walls of fungi. Chitosan is formed by deacetylation of chitin, which has good biodegradability, biocompatibility and bioabsorbability [79]. It supports axonal regeneration and functional recovery, and prevents extensive scarring and neuroma formation, making it a promising candidate for NGC development [80,81]. Microchannels and nanofibers are beneficial to promote neurite elongation. By combining unidirectional freezing with electrospinning, the unique chitosan NGC with longitudinal microchannels and parallel nanofibers is prepared, which can promote growth, migration of SCs and neurite elongation of PC-12 cells, and provide good support and guidance for peripheral nerve regeneration (Fig. 3D) [63]. The composite multi-channel chitosan NGC, composed of chitosan scaffold by warp knitting and internal guiding N-succinyl-chitosan fibers, was used to bridge the 10 mm nerve defect in rats. The peripheral nerve was successfully reconstructed in terms of tissue and function, and its regeneration effect was equivalent to that of autograft. At 20 weeks after sciatic nerve trauma, a similar degree of gastrocnemius muscle atrophy was observed in the conduit and autologous groups. There was no significant difference in the wet weight ratio (around 70 %) or fiber cross-sectional area (close to 100 %) of the gastrocnemius muscle between the autograft and multi-channel chitosan NGC groups [82]. The chitosan/propylene NGC, which is easy to be implanted, has also been developed. The NGC combines acrylic acid and N-hydroxysuccinimide to reduce nerve damage in the repair process, and adhesive repair can significantly reduce the local inflammation caused by traditional suture. The positive charge of chitosan can destroy the bacterial cell and reduce implant related infection [83]. In addition, chitosan NGC combined with microgels containing VEGF and BDNF to treat injured nerve in rats, and significant promoted nerve fiber regeneration and myelination, neuron recovery, muscle function, nerve conduction recovery [84]. The peripheral nerve repair graft (No. 20203130898), containing chitosan material and developed by the Xiaosong Gu' team at Nantong University, was approved for clinical use.

Gelatin, derived from collagen by acid or base treatment, supports neural and glial cell growth and differentiation and can be used to repair PNI. Studies have shown that gelatin hydrogel NGC, containing adipose derived stem cells, repair the injured site of sciatic nerve in mice. While adipose derived stem cells do not differentiate into SCs, they significantly promote the regeneration of peripheral nerve (Fig. 3E, top) [64]. Another study showed that a gelatin conduit containing fetal neocortex can bridge the severed sciatic nerve in mice, which can significantly promote the regeneration and functional recovery after nerve injury [85]. The PCL/Gel NGC containing PRP was implanted into the 10 mm sciatic nerve defect in rats, which promoted the regeneration of nerve tissue [24]. In addition, in the study of composite materials, the gelatin coated multi-channel PLLA NGC has good degradation rate, flexibility and nano-effect, which is a good choice for future research on nerve injury repair [86]. It has also been reported that the hydrophilicity of poly (lactic-co-glycolic acid) (PLGA) scaffold after gelatin treatment is enhanced. In vitro studies have shown that the NGC composed of PLGA-gelatin nanofibers is a promising biomaterial for nerve tissue regeneration. However, in vivo studies using the NGC to implant the rat sciatic neuropathy model have no significant improvement in nerve regeneration [87]. Thus, gelatin, as a hydrophilic material, and the combination of different synthetic materials to construct NGC, may have different effects on peripheral nerve injury repair.

SA, as an anionic linear polysaccharide, has been widely used in nerve tissue engineering. In the study of composite materials, N,N′-disuccinimidyl carbonate (DSC) was used as covalent crosslinking agent to extend the degradation time of SA hydrogel to 2 months. In the double-layer NGC, the inner layer of DSC crosslinked SA promoted the adhesion and proliferation of nerve cells, while the outer layer of electrospun PCL nanofibers provided the maximum tensile strength for the NGC. The double-layer NGC promoted Schwann cells' migration along the axon in the rat model and is an ideal material for repairing the sciatic nerve [88]. A bioactive PGGS composite hydrogel NGC, incorporating polyacrylamide (PAM), GO, Gel and SA, was blended and injected into a mold with an inner diameter of 2 mm and an outer diameter of 6 mm to prepare the composite hydrogel NGC (Fig. 3E, bottom). Then the NGC was further modified with YIGSR peptide and implanted into the sciatic nerve gap of rats, which can effectively promote the regeneration of sciatic nerve in rats [65]. The novel double network hydrogel (DN) was constructed by two-step crosslinking of SA and gelatin (1 % SA and 15 % gelatin) through gamma radiation and ion crosslinking, showing significantly improved mechanical properties. The DN hydrogel NGC significantly improved the recovery of nerve function and nerve regeneration, and reduced fibrotic scar in sciatic nerve defect of rat (Fig. 3F) [66]. SA has good biocompatibility and non-toxicity. However, its application is limited by poor mechanical strength, easy degradation and difficult processing. SA can be used in composite materials of NGCs.

HA, a naturally occurring component in the human body, is widely found in various tissues and organs. HA hydrogel can promote the colony formation and axon extension of neurons and astrocytes in vitro. The cell viability of clinically relevant hiPSC-derived neuronal populations in the HA hydrogel scaffolds remained significantly higher (63 $\pm$ 7 % VS 36 $\pm$ 6 %) after 7 days in culture and the average neurite length has increased nearly 3 fold on day 7 [89]. However, HA often show strong water absorption ability and easy degradation by enzymes. Therefore, it is usually modified or used in combination with other materials to overcome these shortcomings. HA was chemically altered with cysteamine HCl and methacrylic anhydride to create thiolated HA (HA-SH) and methacrylated HA (HA-MA). The 3D printed HA system demonstrated proficiency in loading and releasing Tyrosol, a neurotrophic compound, at physiological pH. In vitro study showed the promising role of HA system in the nerve tissue engineering [90]. Shi et al. prepared phenylboronic acid modified hyaluronic acid (HA-PBA)/PVA dynamic hydrogel-coated neural precursor cells that showed good viability in vitro [91]. In fact, there are relatively few reports of the use of HA in the design of nerve conduits in vivo studies. Li et al. showed the HA combined with chitosan conduit inhibited sciatic nerve extraneural scaring and adhesion, and promoted neural regeneration and recovery in a rat model of peripheral nerve crush injury [92]. Another study showed that HA granular hydrogel NGC was transplanted to repair 10 mm sciatic nerve gap in rats. The results showed that the NGC could effectively promote regeneration of sciatic nerve axon and myelin sheath, and promote the recovery of morphology and function of injured sciatic nerve [93]. In addition, the multi-module NGC composed of PLA microfibers inserted into the HA conduit is used to treat large gap nerve injury. The conduit plays the role of nerve adventitia and retains the pre-implanted SCs. After 6 months of implantation into the 15 mm sciatic nerve defect of rabbit, good nerve regeneration is observed (Fig. 3G) [18]. This demonstrates that HA-based NGCs hold significant potential for treating large-gap nerve injuries.

ECM is rich in essential components such as collagen I, collagen IV, laminin, fibronectin, glycosaminoglycan, NGF and BDNF. It is an ideal nerve repair material. Without adding any other additives, the porcine decellularized nerve matrix NGC (xDNME) prepared by electrospinning significantly promoted the regeneration of rat sciatic nerve, and the regenerated nerve fibers were completely connected to the two ends of the about 8 mm nerve defect (Fig. 3H) [67]. However, as a conduit for bridging nerve defects, ECM lacks sufficient mechanical strength and is usually combined with natural or artificial polymer to construct NGC [94]. For instance, adding ECM to PLCL/ECM NGCs has been shown to improve biocompatibility and biological activity, enhancing SC functional protein expression and promoting nerve regeneration [95]. The

electrospun double-layer NGC with internal ECM and external PLCL bridged 10 mm rat sciatic nerve defect, showing good nerve regeneration [29]. In cases of large-gap nerve defect, collagen-chondroitin sulfate (Coll-CS) material was functionalized with ECM. The ratio of fibronectin, laminin 1 and laminin 2 was 1:4:1, and components were rapidly freeze-dried to form NGC. The NGC was implanted into 15 mm sciatic nerve defect in rats, significantly improving axon density and angiogenesis [96]. While ECM provides a favorable biological environment, its mechanical strength is insufficient. Therefore, combining ECM with synthetic materials is a promising strategy for better mimicking a native microenvironment for NGCs and enhance their structural stability.

4.2. Technique for nerve guide conduits

With the ongoing advancements in artificial NGC technology, a variety of innovative methods have emerged. Beyond the selection of suitable biomaterials, the construction techniques used in tissue-engineered NGCs play a critical role in determining their properties and efficacy. Even when using the same material, different manufacturing techniques can result in varying characteristics. Common NGC fabrication technologies include solution casting, salt immersion, freeze-drying, gas foaming, phase separation, electrospinning, 3D printing, microfluidics, inkjet printing, and fused deposition modeling (Fig. 4 and Table 3). Among these, rapid prototyping methods, which utilize computer-aided design, are capable of creating complex support structures that are otherwise difficult to produce using traditional methods. Despite the diversity of NGC fabrication technologies, establishing specific standards or strategies to ensure their reliable application in nerve tissue remains crucial. It is essential to address challenges such as construction complexity, high costs, low reproducibility, and solvent-related issues, to improve the practical functionality of NGCs in clinical settings [97].

Solvent casting is a relatively simple method that allows for the control of conduit morphology based on mold shape. However, it is limited to creating simple conduit structures and often results in poor geometric accuracy and size control [4,103]. This process has several disadvantages, including the use of toxic solvents and poor pore connectivity (Fig. 4A) [98,104]. Combined with salt leaching, pore

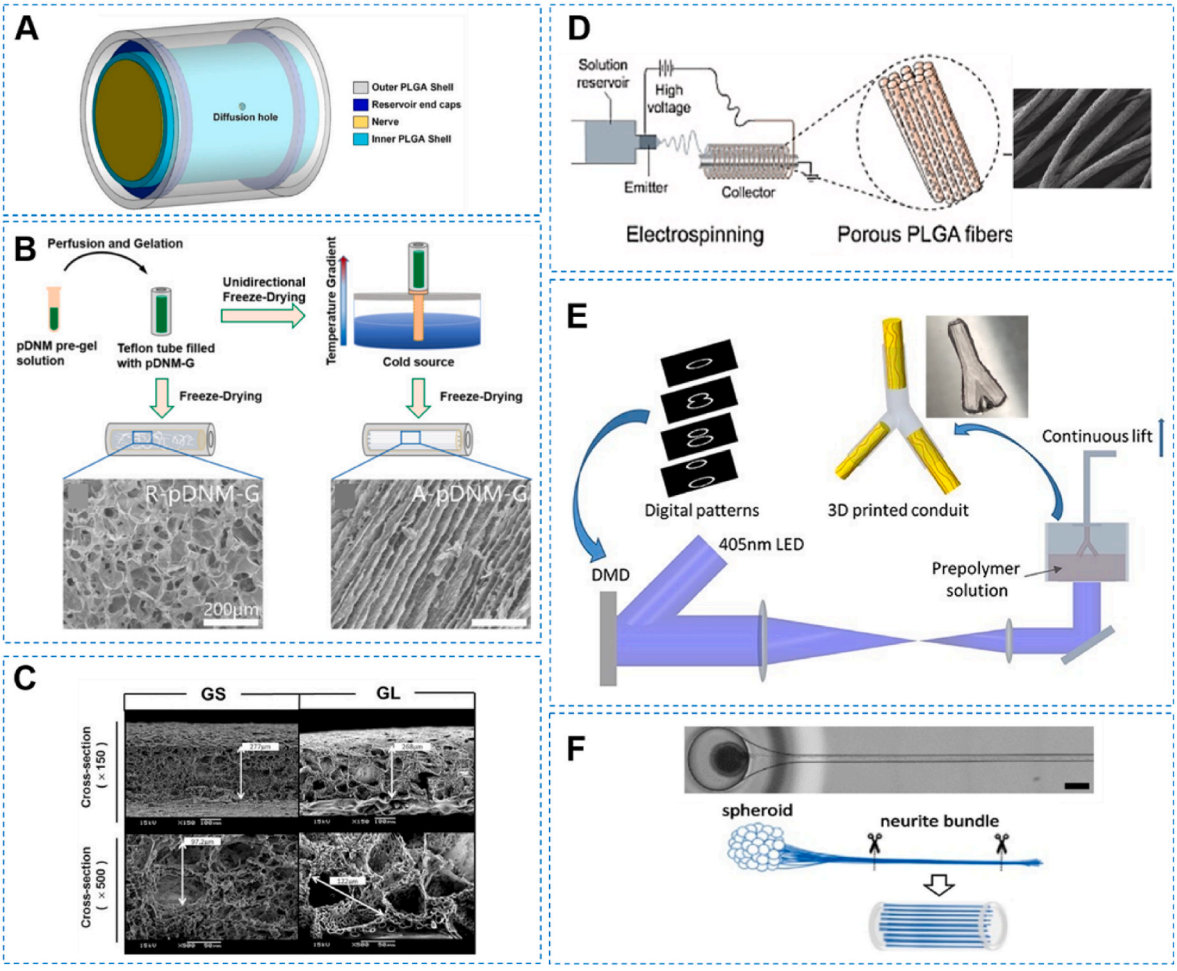

Fig. 4. Technique for nerve guide conduits (A) Schematic illustrating a device related to solvent casting, highlighting structural characteristics including: Inner (light blue) and outer (grey) PLGA conduit, drug reservoir (space between the conduits), and end caps defining boundary of reservoir (dark blue) [98] with permission of IOP Publishing, © 2017. (B) Schematic of the fabrication process related to freeze-drying of pDNM-G conduit with distinct microstructures [99] with permission of Elsevier, © 2021. (C) SEM images showing the microstructure of the PLA substrates (GL and GS) related to gas foaming and solvent nonsolvent phase transformation. The substrates GS and GL represent those fabricated by the use of smaller salt particles and larger salt particles, respectively [100] with permission of SAGE Publications, © 2016. (D) Schematic and image of porous PLGA fibers by electrospinning [54]. This is an open access article under the CC BY-NC license. (E) Schematic illustration of the fabrication of customizable 3D-printed two-branch nerve conduits by a rapid continuous 3D printing system. DMD: digital micromirror device; LED: light emitting diode [101]. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License. (F) Whole image of the nerve organoid cultured in the microfluidic device. Scale bar = 300 μm. Schematic explanation of the procedure for neurite bundle-derived artificial nerve creation by removing spheroids that contained cell bodies from the nerve organoids [102]. This article is licensed under a Creative Commons Attribution 4.0 International License.

Table 3
Technique for NGC.

Technique	Advantage	Disadvantage	Important factors for improvement
solvent casting	Controlled morphology, simple to construct	the use of toxic solvents, poor pore connectivity	The more refined mold facilitates the application of solvent casting technology to NGCs.
Freeze-drying	bioactive factors do not produce denaturation or lose biological activity, less risk of solvent residue	size and shape of micropores are relatively irregular	The process parameters such as temperature, freezing rate, freeze-drying temperature and time play important roles in NGCs.
Electrospinning	simple, convenient and fast	fibers are random and highly disordered, with poor repeatability, and uncontrollable diameter	The properties of the solution, the processing process, and the environment are key factors
Additive manufacturing	high degree of freedom in the construction of materials, manufacturing complex structures, high reproducibility	limited materials used and the low shape resolution	Optimization of printing parameters: the geometry of the nozzle hole, the printing speed, the extrusion speed, the printing temperature, the curing method or time, the properties of the interaction between the bioink and the substrate
Stereolithography	very rapid and highly accurate	High material cost, material limitation, complex equipment, and cumbersome post-processing	Equipment performance, material properties, printing parameters, environmental conditions, and design factors
Microfluidic	High throughput analysis, integration and automation, controllable reaction conditions	difficult to process, integration is limited, cost is difficult to reduce and flow control accuracy is insufficient	Microfluidic chip design, fabrication, and experimental operation
Blow spinning	produce superfine fibers, fast generation of fibers, the simplicity of the experimental setup	relatively large number of experimentations are required to obtain suitable fibers	concentration and viscosity of solution, Flow rate, Gas pressur, Nozzle diameter, Nozzle-collector distance

connectivity and porosity can be improved. For instance, this technique has been used to introduce interconnected pores into PCL conduit, enhancing adjustment of mechanical properties such as elastic modulus and tensile strength. Without the use of growth factors, axon entry and SCs infiltration can be observed in the microchannel PCL conduit, but salt leaching may lead to particle residue [105]. Refining the mold design can enhance the application of solvent casting in the construction of NGCs.

Freeze-drying is another technique that involves forming ice crystals from the solvent, where polymer molecules gather in the voids. Upon sublimation of the frozen solvent under low pressure, a highly interconnected porous polymer structure is produced. However, the micropores generated are often irregular in size and shape (Fig. 4B) [99,106]. The dual freeze-drying technology can be further used to prepare the dual phase NGCs (wall thickness 0.84 mm, lumen diameter 2 mm), that is, the outer collagen conduit is prepared and mechanically optimized, and then the inner HA filler is seamlessly integrated into the conduit to form a longitudinal pore microstructure [107]. In order to obtain highly aligned microchannels, the thermoelectric effect can also be used to replace the traditional freezing solvent. The collagen/chitosan scaffold with a length of 35 mm and a diameter of 5 mm can be obtained by using the freeze casting technology, which can be used for peripheral nerve repair in the future [108]. Gas foaming, combined with solvent-nonsolvent phase separation, can create asymmetric porous structures in PLA NGCs. In these conduits, ADSCs can be seeded on the outer wall, promoting nerve regeneration (Fig. 4C) [100]. The disadvantage of gas foaming is poor pore connectivity. Although the phase separation technology has high interconnection and high porosity, it is limited to specific polymers such as PLLA [4,109]. When using these methods to construct NGCs, the challenge of irregular pore structures should be carefully considered.

Electrospinning is a widely used technology for fabricating randomly or longitudinally arranged nanofibers or microfibers, making it a valuable tool in nerve tissue engineering. By applying a high voltage between the nozzle tip and the substrate, continuous polymer nanofibers can be obtained efficiently and rapidly. In NGC fabrication, electrospun fibers can serve as internal fillers or be braided into conduits, offering topographical cues that guide axonal regeneration [4,104]. For example, SF/P(LLA-CL) scaffolds are prepared by electrospinning technology, the scaffolds are wound on stainless steel rods with a diameter of 1.4 mm and sutured into NGC, which can promote peripheral nerve regeneration by improving angiogenesis in the conduit [110]. Similarly, electrospun PLGA fiber-based NGCs, optimized with conductive PEDOT: polystyrene sodium sulfonate (PSS) coatings and fiber alignment, have shown to effectively support nerve regeneration (Fig. 4D) [54]. In addition, a novel aligned piezoelectric nanofiber hydrogel NGCs with ultrasound triggered electrical stimulation and controllable drug release was developed to repair peripheral nerve injury. The inner layer is BTNPs/P(VDF-TrFE) nanofibers, which improves piezoelectric properties and alignment orientation. The outer layer is wrapped with biologically active drug encapsulated thermal responsive poly (N-isopropylacrylamide) hybrid hydrogel. The NGC has a positive effect on the functional recovery and axonal regeneration in long sciatic nerve defect of rat [59]. Using polyurethane copolymer containing conductive aniline trimer and degradable lysine (PUAT) to prepare directional electrospun nanofiber NGCs, which increased the proportion of healing promoting macrophages in sciatic nerve injury of rat, regulated the immune microenvironment and improved peripheral nerve regeneration [111]. Despite its many advantages, electrospinning also has drawbacks, such as the random and disordered arrangement of fibers, poor reproducibility, and an uncontrollable fiber diameter [4]. There is a need for further development of more stable and consistently aligned electrospun fibers to enhance the efficacy of NGCs in nerve repair.

Additive manufacturing (AM), also known as 3D printing, refers to the process of building 3D structural materials by adding materials layer by layer [104]. Given the complexity of neural structures, AM has emerged as a promising and efficient approach for fabricating intricate designs in neural tissue engineering. For example, a silk fibroin-sodium alginate-gelatin hydrogel scaffold was constructed using biological 3D printing, with reduced graphene oxide (rGO) incorporated as a conductive material. Pulsed electromagnetic fields (PEMF) were used to stimulate microcurrent, effectively promoting nerve regeneration, and the resulting NGC showed outcomes comparable to autografts [112]. In 3D bioprinting, gelatin methacrylate/poly(ethylene glycol) diacrylate/carbon nanofiber/gellan gum (GelMA/PEGDA/CNF/GG) hydrogel was used as a four-component electroactive biomaterial ink.

PEGDA as a secondary crosslinking agent significantly improved the strength and elastic modulus. The prepared NGC was conducive to improving the viability of nerve cells, providing the possibility for the development of functional clinical size NGC (length: 20 mm; diameter: 2–8 mm) [113]. The GelMA/silk fibroin glycidyl methacrylate (SF-MA) elastic hydrogel NGCs prepared by continuous 3D printing technology and coated with 7,8-dihydroxyflavone (7,8-DHF) nano-components can effectively promote axon regeneration, myelin sheath regeneration and functional recovery when implanted into the 12 mm sciatic nerve defect of rats [114]. Another innovation involves 3D-printed hydrogels coated with gelatin-rich nanofibers, which can undergo programmable shape changes that help tightly clamp the nerve ends, simplifying surgical procedures [115]. 3D printed layered fiber multi-scale conductive NGC is constructed with electrospun PCL/collagen nanofibers as sheath, reduced graphene oxide/PCL microfibers as skeleton, and PCL microfibers as internal structure. It has good permeability, mechanical stability and conductivity, and significantly promotes peripheral nerve regeneration, such as improving axon myelination, muscle weight and sciatic nerve function index [116]. 3D printing can also customize the branch NGC of gelatin methacrylate material, which provides a potential method for nerve transplantion (Fig. 4E) [101]. In addition, the NGC prepared by inkjet 3D printing technology is constructed with nano-membrane nanoceria (NC)/PCL mixed innermost layer, the collagen outermost layer, and the PCL middle layer. The Col/NC/PCL NGC improves the proliferation and adhesion of Schwann cells, is implanted in the 15 mm sciatic nerve defect of rat can significantly alleviate inflammation and oxidative stress, promote the growth of microvessels, and contribute to the long-term nerve recovery of function, electrophysiology and morphology [117]. The good tensile properties of polyhydroxyalkanoates (PHAs) and PLLA filaments prepared by melt deposition modeling (FDM) also make them promising candidates for NGC fabrication [118]. Moreover, a proof-of-concept intelligent NGC based on stereolithography and multi-response four-dimensional (4D) technology, featuring a graphene-infused 4D structure, demonstrated exceptional multifunctional properties for nerve regeneration [119]. The light curable and biodegradable PGSm NGC constructed by stereolithography technology is conducive to the repair of common peroneal nerve injury in mice, opening the way for personalized NGC manufacturing [26]. Although these methods offer high flexibility in material construction and enable the fabrication of complex, biomimetic scaffolds with high reproducibility, they are still constrained by a limited range of useable materials and low shape resolution.

Microfluidics is emerging as a promising technique for the preparation of functional materials, owing to its precise flow control capabilities. However, its application in NGC research remains limited. A microfluidic nozzle with multi-axis extrusion can rapidly print multilayer concentric conduit structures. By adjusting flow rate, printing speed, and material concentration, complex heterogeneous and layered conduits can be produced in seconds. These conduits, initially designed for vascular tissue, hold significant potential for NGC applications as well [120]. The collagen fibers produced by microfluidics are filled into the conduit made of recombinant spider silk. The conduit is used for guiding neurites, promoting the differentiation of NG108-15 cells into functional neurons, forming neuronal networks and synapses, and is suitable for peripheral nerve repair [121]. Moreover, a silicon-based nerve sleeve lead and hydrogel microfluidic conduit were developed in implantable nerve regulation device. The microfluidic nerve sleeve provides a larger space between the metal electrode and the target nerve as thin, soft and flexible connection [122]. In addition, microfluidic is used to form straight unidirectional neurites from nerve like organs differentiated from the human induced pluripotent stem cells (hiPSCs). After the organoid cell body and neurites are separated to obtain parallel arrangement of acellular neurite bundles, six neurite bundles are longitudinally placed in a 15 mm silicone tube, and collagen gel is added to assemble a new artificial NGC for transplantation. It is found that the implantation of NGC in rats has significant therapeutic effect in function and histology, and has no immunosuppression, which provides the possibility for the treatment of patients with peripheral nerve injury in the future (Fig. 4F) [102]. As an advanced fabrication technology, microfluidics is expected to play an increasingly important role in future NGC development.

Numerous technologies are being applied to the research and development of NGCs. Blow spinning, a technique that uses high-speed airflow instead of an electric field to produce superfine fibers, offers a simpler alternative to electrospinning. Using multi-needle blow spinning, a novel NGC was developed by spinning collagen nanofibers into a double-layered conduit. The outer layer, composed of random fibers, enhances mechanical strength, while the inner layer, with aligned fibers, guides axonal regeneration. The porosity of this NGC facilitated nutrient delivery and metabolism. In a 15 mm sciatic nerve defect model in rats, this NGC promoted SC growth, neurotrophic factor secretion, axonal regeneration, and motor function recovery [123]. In addition, the NGCs with complex structures and synergistic effects have also been developed. Biomimetic microneedles that mimic the structure and piezoelectric function of sea cucumbers are integrated into NGCs. On the outer surface, there are outward pointing needles that apply electrical stimulation to denervated muscles. Inside, there are microchannels to guide the migration of SCs. Conductive rGO and piezoelectric zinc oxide nanoparticles are incorporated into the polylactone scaffold to enhance the conductivity and piezoelectric properties, and promote the migration of SCs, myelin regeneration, axon growth and the recovery of neuromuscular function [124]. Auxiliary technologies, such as pulsed electromagnetic fields and electrical stimulation, have also proven effective in accelerating the regeneration of sensory and motor nerve axons with greater precision [125]. Additionally, nerve US imaging is an important tool for monitoring the progress of nerve injury repair, offering valuable insights for artificial NGC research [19]. Since different technologies yield NGCs with varying structural and functional properties, careful selection of the appropriate fabrication technique is essential for ensuring the controlled preparation and successful clinical application of NGCs.

4.3. Structure for nerve guide conduits

Topographic cues on biomaterials have a profound impact on cell behavior, particularly for nerve cells, which are highly responsive to such cues. These surface features influence a range of cellular activities, including adhesion, migration, differentiation, and intercellular interactions (Fig. 5). The use of biomaterials with topographic features can effectively affect the differentiation of neurons and promote the growth of neurites [126]. The interaction between cells and micro/nano-patterns topological features, significantly influences cell behavior, including adhesion, orientation, and network formation. The micropattern membranes with various topographic features, like channels, columns, and pits, have been shown to promote specific neuronal morphologies and growth patterns. In particular, grooves of 30/30 μm optimal sizes can effectively guide the migration and orientation of SCs, enhancing neural network formation and repair. Multichannel or aligned fibers conduits, mimicking the microstructure of fascicular connective tissue, further promote directional neurite growth and increase the likelihood of successful nerve reconnection. Moreover, anisotropic microfiber-grids, as a specific NGC structure, provide an instructive microenvironment for nerve regeneration and repair, demonstrating positive effects on long-distance defects in animal models. Changing the topological microstructure of NGCs is conducive to the proliferation and migration of SCs [97], which is very important for the repair of nerve defects.

Micro/nano-patterns like porous pits can generate numerous focal adhesion points when interacting with cells. As cells migrate across three-dimensional surfaces, they tend to settle in concave areas and avoid convex ones [127]. The PLGA micropattern membrane showed the topographic features of channels, circular columns, rectangular

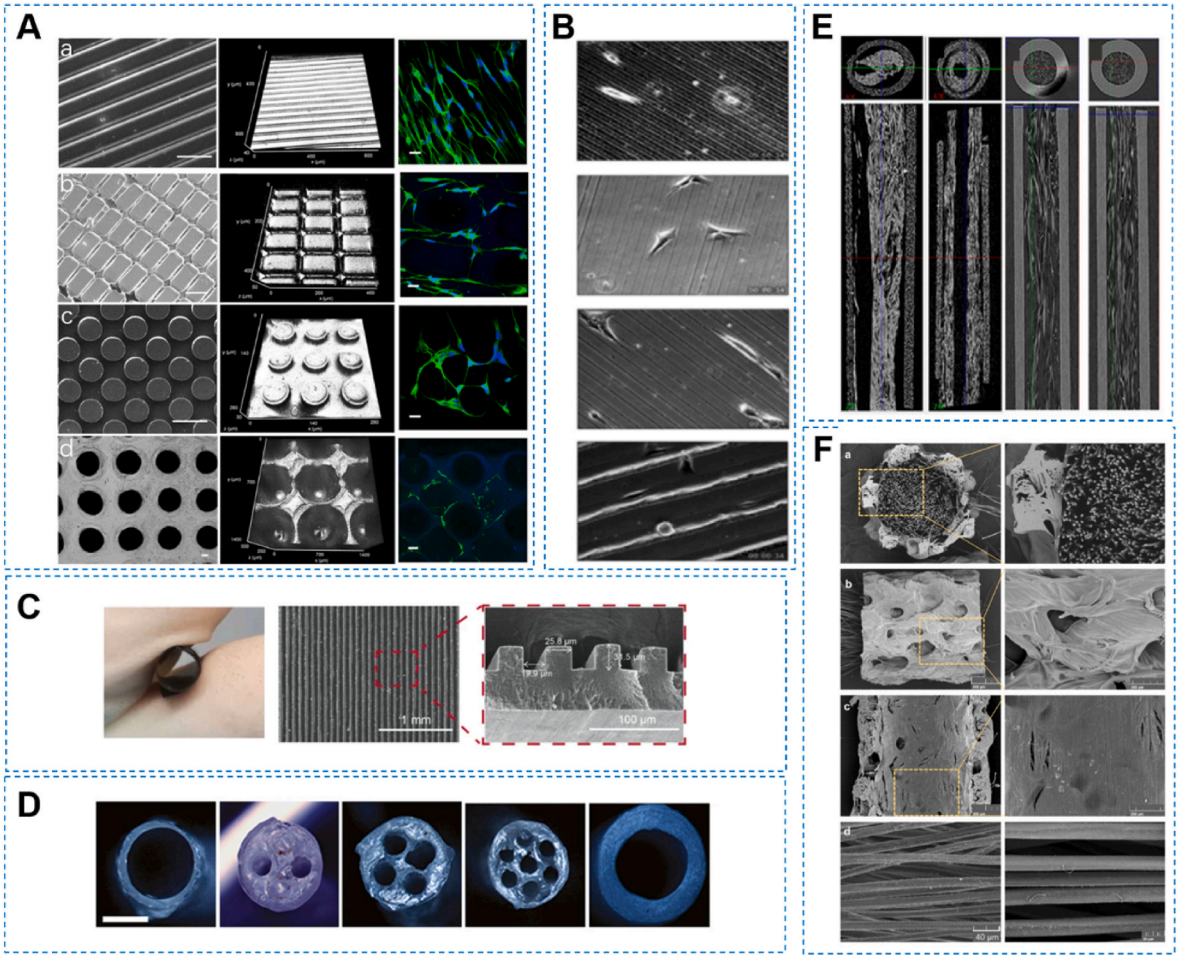

Fig. 5. Structure for nerve guide conduits (A) Topographical cues of PLGA membranes and neuronal cells on PLGA flat with: a, channels; b, pillars of rectangular; c, circular shapes; d, pits [128] with permission of Elsevier, © 2023. Scale bar: 100 μm. (B) Anisotropic ridge/groove microstructure for regulating morphology of Schwann cells. 10/10 μm, 20/20 μm, 30/30 μm, 50/50 μm [133] with permission of Elsevier, © 2020. (C) Microtopography and 20 μm width of micropatterns for both ridges and grooves about PLCL/PDA/GN films [134] with permission of John Wiley and Sons, © 2023. (D) The transverse images of multichannel conduits [138] with permission of Elsevier, © 2010. Scale bar, 1 mm. (E) Microcomputed tomography (microCT) analysis of transversal and longitudinal sections of P(3HO)/P(3HB) (50:50) 5 μm fibers, P(3HO)/P(3HB) (50:50) 8 μm fibers, PCL 5 μm fibers, and PCL 8 μm fibers threaded into 3D nerve guide conduits. Tubular structures are 1.1 mm in diameter and 5 mm in length and have a wall thickness of 250 μm [140]. This article is licensed under a Creative Commons Attribution 4.0 International License. (F) SEM images of the novel multichannel chitosan/NS-chitosan NGCs. A, Transverse section; b, Outer surface; c, Inner surface; d, NS-chitosan fibers [82] with permission of Elsevier, © 2023.

columns and pits. The nerve cells seeded on linear channels promoted the slender morphology. Rectangular and circular columns acted as discontinuous cues at the cell membrane interface, encouraging multi-directional growth. On pit-patterned membranes, cells exhibited precise spatiotemporal regulation, growing between interconnected pit spaces and bypassing the pits, which significantly influenced adhesion, orientation, and network expansion (Fig. 5A) [128]. The nerve cells grow in one or two directions, form a neural network, and promote the connection of nerve cells on the conductive anti-opal membrane with anisotropic elliptical porous pattern [129]. In addition, the reticular NGC has the characteristics of high porosity, stable structure, excellent flexibility, good mechanical properties [130,131]. For instance, chitosan warp conduits have porous structure, which is conducive to nutrient exchange with the external microenvironment [82]. Reticular structures containing >75 μm pores allow better penetration of macrophages, fibroblasts and collagen [132]. Although better results have been achieved in nerve cells, it would be more significative if DRG cells can be adopted.

Groove patterns resembling normal nerve tissue significantly influence nerve cell behavior. Li et al. used micro-injection molding to produce groove patterns of varying sizes on chitosan film and found that a groove width of 10 μm caused SCs to diffuse randomly across the surface. In contrast, when the groove width was 20–30 μm, matching the cell size, SCs migrated along the grooves (Fig. 5B) [133]. The conductive PLCL/graphene composite conduit by micro imprinting technology and self-assembled polydopamine (PDA) to prepare 20 μm micro-pattern grooves on the surface. By providing the functional integration of physical guidance, bionic biological regulation and bioelectrical stimulation, PLCL (G)/PDA/graphene composite conductive NGC promotes the growth of myelin sheath, accelerates nerve regeneration, and restores the function in vivo (Fig. 5C) [134]. In addition, human neural stem cells (hNSCs) can sense nanometer deep grooves on PCL materials with different aspect ratios, and show different morphology and differentiation fate. When the groove width, nanometer height and spacing ratio are 1 μm/80 nm/80, 5 μm/210 nm/42 and 10 μm/280 nm/30, respectively, the smaller groove pattern leads to longer neurites and more effective neuronal differentiation, while the larger groove pattern promotes the multidimensional differentiation of neurons and glial cells [126]. Photolithography and micro-molding were used to define various combinations of ridge/groove dimensions on PLGA films. The DRG cells obtained from chicken embryos were cultured on micropatterned PLGA films for cell orientation and migration evaluation. The migration rate

and neurite extension of DRG neurons were greatest on 10 μm/10 μm and 30 μm/30 μm micropatterned PLGA films [135]. In addition, the regulation of Schwann cells behavior by chitosan micropatterning was evaluated. Schwann cells on chitosan micropatterning showed orientation adhesion and began to grow along a certain direction after culture for 2 h, and displayed the minimal orientation angle and the largest length/width ratio on 30/30 μm micropatterning after further culture for 3 d and 5 d, indicating the most obvious cell orientation [136]. Another study aimed to illuminate the micropatterned chitosan-film action on the rat skin precursor-derived Schwann cells (SKP-SCs). Chitosan-film with different ridge/groove size was fabricated and applied for the SKP-SCs induction. Results indicated that SKP-SCs cultured on 30 μm size microgroove surface showed better oriented alignment phenotype. Induced SKP-SCs presented similar genic phenotype as repair Schwann cells [137]. Therefore, the optimal size of the groove seems to be 30/30 μm. But, the molecular mechanism affecting cell behavior is unclear, and more studies are needed to reveal its mechanism of action.

Multichannel conduits, designed to mimic the microstructure of fascicular connective tissue, promote directional neurite growth and increase the likelihood of successful reconnection between two nerve ends. Single-channel conduits can lead to dispersed axon regeneration, which may result in misaligned or inappropriate nerve regrowth-an issue mitigated by multichannel conduits (Fig. 5D) [138]. Studies have shown that 1-channel and 4-channel PLGA conduits are superior to other types of conduits in axonal regeneration, possibly because multi-channel will affect dispersion [138]. Reducing the channel diameter to prevent nerve winding may lead to channel blockage, while increasing the channel diameter may lead to irregular nerve arrangement and nerve curl [139]. Thus, determining the optimal channel diameter remains a key area of study, as multichannel conduits may also help prevent the misconnection of nerves.

The NGC with aligned fibers accelerates the healing process by promoting the directional growth of neurons. The damaged peripheral nerve is usually difficult to repair correctly, because of the wrong migration direction of SCs or the incorrect connection of two nerve endings. The intracavitary aligned fibers of conduit has been proved to increase the neurite growth of nerve cells and the migration distance of Schwann cells [140]. Compared with PCL fibers, poly (3-hydroxyoctanoate)/poly(3-hydroxybutyrate) (P(3HO)/P(3HB)) (50:50) blend fibers produced via electrospinning demonstrated superior adhesion for neurons and SCs compared to PCL fibers. In a 3D in vitro nerve injury model, 5 μm blend fibers notably improved DRG neurite growth and SC migration (Fig. 5E) [140]. The composite chitosan multichannel NGC composed of inner directional NS-chitosan fibers was successfully used to histologically and functionally reconstruct the 10 mm peripheral nerve defect in rats (Fig. 5F) [82]. The conduit of core-shell multi-walled carbon nanofibers (MWCNT) significantly enhanced the function of NGCs, which effectively promote adhesion and proliferation of RSC96 cells along the directional fibers, showing a good response to its unique structure and characteristics. MWCNT has significant effects on promoting peripheral nerve regeneration, growth of mature axons, muscle recovery and higher density of myelinated axons in the repair of 10 mm sciatic nerve injury of rats [141]. However, the aligned fibers may have an adverse effect on the correct connection of nerve endings [97]. Further optimization of the compositions and structures is deserved to promote the NGCs application.

Anisotropic microfiber-grids are a kind of structure of NGC, which demonstrated the capacity to directionally guide Schwann cells and neurites. The anisotropic structure provided an instructive microenvironment for nerve regeneration and repair. The melt electrowriting (MEW) was used to print anisotropic, microfibrous PCL architectures, and preferential neurite extension of PC12 cells along the long arm direction was achieved. Such anisotropic neurites guidance was further strengthened when the intersection angles were reduced from 90° to 30° [142]. The rGO/PCL scaffold characterized with anisotropic microfibers and oriented nanogrooves by electrospinning technique was fabricated. Adipose-derived stem cells (ADSCs) are seeded on the scaffolds in vitro. RGO/PCL conduits reprogram the phenotype of seeded cells and efficiently repair 15 mm sciatic nerve defect in rats [143]. In addition, the NGC composed of high-resolution anisotropic microfiber grid-cordes with randomly organized nanofiber sheaths showed the positive effects of these biomimetic structures on peripheral nerve regeneration. At 12 months post-implant, the composite NGC bridged 30-mm long sciatic nerve defects showed restored neurological functions in canine models [144]. Therefore, the NGCs with anisotropic guidance structures would be beneficial to nerve regeneration and repair across long-distance defects.

5. Strategies to stimulate rapid nerve regeneration in nerve guide conduits

5.1. Seed cells

SCs play very important roles in nerve regeneration following nerve injury, making cell therapy a promising approach in the field of nerve regenerative engineering, especially for long defects of nerve. After peripheral nerve injury, SCs promotes nerve repair through activation, dedifferentiation, division and distal proliferation. However, the proliferation of autologous SCs is limited, requiring nerve biopsy and prolonging the culture time, so stem cells are a feasible improvement strategy in clinic. With the development of a large number of studies, embryonic stem cells (ESCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs) and skin-derived precursor-induced Schwann cells (SKP-SCs) have expanded the use of seed cells implanted into artificial NGCs (Table 4) [19,72]. While SC delivery through NGCs stimulates nerve regeneration, live cell delivery presents challenges in terms of cost and complexity [145]. These various seed cells play distinct roles in neuronal repair, and ensuring their viability and providing an optimal extracellular environment are essential for successful nerve regeneration.

SCs are glial cells in the peripheral nervous system. The transplantation of SCs has good potential in promoting nerve regeneration. The chitosan (outer layer)-collagen (inner layer) hydrogel NGC encapsulated SCs was transplanted into 10 mm sciatic nerve defect of rat. In the early stage after transplantation, SCs encapsulation had a positive effect on nerve recovery and peripheral nerve regeneration, especially the axon regeneration and myelin sheath regeneration of host SCs [146]. Another study demonstrated that co-culturing SCs and NSCs in laminin-chitosan-PLGA NGCs promoted regeneration of a 5 mm recurrent laryngeal nerve defect, with outcomes comparable to autografts [147]. In addition, SCs with overexpressed GDNF were filled into silicone conduit to bridge 10 mm sciatic nerve defect of rats, and nerve regeneration was better than that in empty conduit [148]. The healing process of PNI is usually accompanied by not only axonal and myelin regeneration, but also angiogenesis. PLGA/GelMA-SC composite NGC containing SCs with vascular endothelial growth factor-A (VEGF-A) overexpressing promotes peripheral nerve regeneration through angiogenesis [149]. These findings suggest that further development of engineered SCs may offer even greater potential in future NGC applications.

ESCs have strong proliferation and differentiation ability, which is conducive to promoting peripheral nerve repair. The 1 cm sciatic nerve defect model of rat was used to test the ability of ESCs-derived neural progenitor cells (ES-NPCs) to promote the repair of severely injured peripheral nerves. The peripheral nerve adventitia was used as a natural conduit, and ES-NPCs were implanted into the nerve gap and differentiated into myelin-forming cells, providing a potential treatment for severely injured peripheral nerves [150]. However, other studies have shown that while PLGA nanofibers treated with gelatin improved hydrophilicity and supported the adhesion and proliferation of mouse ESCs (mESCs) and human MSCs, in vivo transplantation did not significantly

Table 4
Seed cells for NGC.

Seed cells	NGC	Application	Effects	References
SCs	chitosan (outer layer)-collagen (inner layer) hydrogel NGC encapsulated SCs	10 mm sciatic nerve defect of rat	In the early stage after transplantation, SCs encapsulation had a positive effect on nerve recovery and peripheral nerve regeneration.	[146]
	the co-culture of SCs and NSCs in laminin-chitosan-PLGA NGC	5 mm defect of recurrent laryngeal nerve	It promotes the regeneration of defect of recurrent laryngeal nerve, which is similar to autograft.	[147]
	SCs with overexpressed GDNF were filled into silicone NGC	10 mm sciatic nerve defect of rats	The nerve regeneration was better than that in empty conduit.	[148]
	PLGA/GelMA-SC composite NGC containing SCs with VEGF-A overexpressing	10 mm sciatic nerve defect of rats	It promotes peripheral nerve regeneration through angiogenesis.	[149]
ESCs	peripheral nerve adventitia encapsulated ESCs-derived neural progenitor cells (ES-NPCs)	10 mm sciatic nerve defect model of rat	ES-NPCs were differentiated into myelin-forming cells.	[150]
	PLGA NGC seeded with mouse ESCs or human MSCs	1 mm sciatic nerve defect in rats	Nerve regeneration has not been significantly improved by transplantation in vivo.	[87]
NSCs	chitosan/PGA NGC filled with NSCs	10 mm sciatic nerve defect in rats	The introduction of NSCs seemed to have no significant benefit on the regeneration results.	[153]
	silicone conduit filled with brain derived NSCs	10 mm gap of sciatic nerve injury in rats	It significantly promoted the recovery of nerve function and the myelination of regenerated nerve axons	[154]
iPSCs	functional neural crest stem cells (NCSCs) induced by iPSCs were implanted into PLCL composite nanofiber NGC	10 mm sciatic nerve defect of rat	NGC accelerated the regeneration of sciatic nerve and differentiation into SCs, promoted the formation of axon myelin sheath, and avoided teratoma.	[155]
	LA/PCL NGC coated with iPSC-derived neurospheres	5 mm sciatic nerve defect in mice	It promoted axon growth and increased the expression of neurotrophic factors related to nerve regeneration.	[156,157]
MSCs	P-LA-CL NGC loaded with undifferentiated BMSCs	30 mm nerve defect in beagle dogs	Nerve regeneration was not as good as that of reverse autograft, but there was no significant difference in the electrophysiology, morphology or wet weight of reinnervated muscles	[159]
	chitosan/SF NGC filled with ECM of BMSCs	10 mm sciatic nerve defect in rats	It has good promoting effect on nerve regeneration.	[160]
	biological NGC composed of adipocyte derived mesenchymal stem cells (ADMSCs) and amniotic membrane	10 mm sciatic nerve defect of rats	It significantly promoted nerve regeneration, and can be used as an alternative treatment for autograft	[161]
	exosomes of gingival mesenchymal stem cells (GMSCs) combined with biodegradable chitin NGC	10 mm sciatic nerve defect of rats	significantly increased the number and diameter of nerve fibers, promoted the formation of myelin, and significantly restored muscle function, nerve conduction function and motor function	[165]
	3D collagen/HA/PLGA composite NGC and human umbilical cord MSC-derived exosomes	10 mm gap of peripheral nerve injury	It promoted nerve regeneration and motor function recovery, which is similar to autograft	[166]
SKP-SCs	SKP-SC-mediated chitosan/silk fibroin-fabricated NGC	10 mm sciatic nerve defect in rats	It can promote sciatic nerve regeneration and functional restoration nearly to autografting according to behavioral, histological, and electrophysiological evidence	[168]
	chitosan/PLGA NGC containing SKP-SC-EVs	40-mm long sciatic nerve defect in dogs	The NGC significantly accelerated the recovery of hindlimb motor and electrophysiological functions, supported the outgrowth and myelination of regenerated axons, and alleviated the atrophy of target muscles	[170]

enhance nerve regeneration [87]. Moreover, the use of ESCs, especially for clinical use, requires several considerations, including their inherent properties of tumorigenicity, immunogenicity, and heterogeneity [151]. The infinite proliferation property of ESCs is a double-edged sword, because if cells keep proliferating even after transplantation, they may result in tumors. Immune rejection is another critical issue. Traditionally, rejection has been overcome by the use of immunosuppressants.

NSCs are primitive cells with multiple differentiation potentials with low immunogenicity during the development of the nervous system. NSCs obtained from embryonic cerebral cortex of rat cultured in DMEM/F12 medium supplemented with fibronectin and epidermal growth factor (EGF), proliferated widely and differentiated into MAP2 positive neurons, which is conducive to the application in NGCs [152]. For example, chitosan/PGA NGCs filled with NSCs were used to repair a 10 mm sciatic nerve defect in rats, though the regeneration outcomes were not significantly different compared to NGCs without NSCs or autografts, suggesting limited benefit from NSC introduction [153]. The silicone conduit filled with brain derived NSCs bridged the 10 mm gap of sciatic nerve injury in rats, significantly promoted the recovery of nerve function and the myelination of regenerated nerve axons [154]. Although NSCs may partially replace the role of SCs and have promising clinical potential, their limited availability remains a challenge for broader application in NGCs.

The iPSCs, reprogrammed from somatic cells, offer the possibility of patient-specific cell therapies in tissue engineering. iPSCs can be effectively induced to form functional neural crest stem cells (NCSCs). When NCSCs were implanted into electrospun PLCL composite nanofiber NGCs to bridge a 1 cm sciatic nerve defect in rats, they accelerated nerve regeneration, differentiated into SCs, promoted axonal myelination, and avoided teratoma formation [155]. PLA/PCL NGC coated with iPSC-derived neurospheres was transplanted to treat 5 mm sciatic nerve defect in mice. The neurospheres migrated to regenerated axons and survived as Schwann-like cells, promoting axon growth and increasing the expression of neurotrophic factors related to nerve regeneration [156,157]. Neural tracts isolated from human iPSC-derived motor and sensory nerve organs prepared by microfluidic technology are implanted into silicone tubes, which have significant therapeutic effects in nerve repair [147]. However, there are still many important problems to be solved, such as the differences in differentiation and amplification of different iPSC lines.

MSCs derived from the early mesoderm are multipotent stem cells, which can be easily separated from bone marrow, umbilical cord, placenta and other tissues [158]. Strategies to promote peripheral nerve regeneration include the uses of NGCs containing MSCs, exosomes and ECM related to MSCs. The P-LA-CL NGC that consisted of l-lactide and ε-caprolactone loaded with undifferentiated BMSCs was transplanted to treat the 30 mm nerve defect in beagle dogs. Nerve regeneration was not as good as that of reverse autograft, but there was no significant difference in the electrophysiology, morphology or wet weight of reinnervated muscles [159]. In addition, the ECM of BMSCs in chitosan/SF

NGC has good promoting effect on nerve regeneration of 10 mm sciatic nerve defect in rats [160]. Biological NGCs composed of adipose-derived mesenchymal stem cells (ADMSCs) and amniotic membrane have also shown potential in reconstructing a 10 mm sciatic nerve defect in rats, significantly promoting nerve regeneration and offering a viable alternative to autografting [161]. The ADSCs with similar differentiation potential to ADMSCs are also used in neural tissue engineering [162]. ADSCs have multilineage differentiation capacity and can be differentiated to a SC phenotype or be induced to form glia-like cells when cultured with neural induction medium. Moreover, ADSCs shows immunomodulatory effects, which are important in peripheral nerve regeneration and benefit to prevent excessive inflammation [163]. ADSCs were delivered to a 15 mm sciatic nerve defect of rats by a filling functionalized hydrogel (Biogelx-IKVAV) PCL NGC, and strong nerve regeneration was observed through axon elongation and SCs proliferation [164]. The exosomes of gingival mesenchymal stem cells (GMSCs) combined with biodegradable chitin NGC were implanted into the sciatic nerve defect of rats, which significantly increased the number and diameter of nerve fibers, promoted the formation of myelin, and significantly restored muscle function, nerve conduction function and motor function [165]. 3D collagen/HA/PLGA composite NGC and human umbilical cord MSC-derived exosomes have synergistic effects in repairing 10 mm gap of peripheral nerve injury, promoting nerve regeneration and motor function recovery, which is similar to autograft [166]. Compared to ESCs and iPSCs, MSCs offer the advantage of fewer ethical concerns and a lower risk of teratoma formation, making them an attractive option for nerve repair therapies.

The SKP-SCs are also the seed cells that promote nerve growth. The advantage of SKP-SCs was their identical neural crest cell developmental origin with native SCs and high purity [167]. The SKP-SCs displayed the oriented parallel growth on anisotropic topography surface of chitosan-film, the transition towards repair SC phenotype, and the enhanced paracrine effect on neural regeneration [137]. The SKP-SC-mediated chitosan/silk fibroin-fabricated NGC that can promote sciatic nerve regeneration and functional restoration nearly to autografting according to behavioral, histological, and electrophysiological evidence [168]. Moreover, extracellular vesicles (EVs) from seed cells on scaffolds could exert further pro-regeneration effect through paracrine signals. The EVs from SKP-SC promote neurite outgrowth of sensory and motor neurons in vitro. The NGC incorporated with SKP-SC-EVs significantly accelerated the recovery of motor, sensory, and electrophysiological functions of rats, facilitated outgrowth and myelination of regenerated axons, and alleviated atrophy of target muscles [169]. In addition, the chitosan/PLGA NGC containing SKP-SC-EVs bridged a 40-mm long sciatic nerve defect in dogs. The NGC significantly accelerated the recovery of hindlimb motor and electrophysiological functions, supported the outgrowth and myelination of regenerated axons, and alleviated the atrophy of target muscles. Further study showed that miR-30b-5p contained within SKP-SC-EVs exerted nerve regeneration-promoting effects by targeting the Sin3a/HDAC complex and activating the phosphorylation of ERK, STAT3 or CREB [170]. These studies can provide inspiration in the design of clinical scaffolds for bridging the PNI.

5.2. Bioactive factors and small molecules

As research into engineered NGCs deepens, peptides, hormones, growth factors, and small-molecule compounds have emerged as powerful agents to further promote nerve regeneration and repair (Table 5). These compounds may play pivotal roles in reducing neuron death, promoting axon regeneration, and facilitating recovery after injury.

Self-assembled peptides (SAPs), known for their ability to spontaneously form well-organized nanostructures, can serve as biocompatible carriers and provide microenvironment conducive to the reconstruction of neural networks and the recovery of injured neural functions. The common peptides for self-assembly are RAD, IKVAV, RGI, RGD, YIGSR, etc. RAD, a typical SAP, offers high biocompatibility and low cytotoxicity, making it useful in nerve tissue engineering. Studies have shown that RAD/IKV/RGI and RAD/IKV-GG-RGI hydrogels are injected into chitosan NGC to bridge 10 mm sciatic nerve defects in rats. IKVAV, which promotes adhesion and migration of SCs, and neurotrophic RGI have a synergistic effect on axonal regeneration and functional recovery after peripheral nerve injury [171]. Similarly, the cell adhesion-promoting peptide RGD and laminin-derived peptide YIGSR, when non-covalently bound to PCL NGCs, synergistically promoted the regeneration of 15 mm sciatic nerve defects in rats [172]. In addition, hormone is a promising bioactive factor for the treatment of nerve injury. The neuroprotective ghrelin and adipose-derived mesenchymal stromal cells improve nerve regeneration through epsilon-caprolactone NGC in a 10 mm sciatic nerve gap of rats [173]. Similarly, melatonin/PCL NGC can promote the regeneration of nerve function, electrophysiology and morphology of 15 mm sciatic nerve defect in rats, reduce oxidative stress, inflammation and mitochondrial dysfunction, restore the regeneration microenvironment, reduce nerve cell apoptosis, promote the removal of nerve fragment [174]. Additionally, 17-β-estradiol also promotes the regeneration of sciatic nerve and reduces inflammatory reaction in the repair of 7 mm gap through chitosan NGC in ovariectomized female rats [175]. These studies show that nutritional and developmental regulatory factors can promote peripheral nerve regeneration.

A regenerative environment enriched with nutritional factors plays a critical role in facilitating nerve recovery post-injury. However, the short half-lives of neurotrophic factors like NGF and BDNF limit their therapeutic applications. To address this, NGCs with sustained NGF release have been developed, bridging facial nerve defects or 10 mm sciatic nerve gaps in rats, and yielding nerve regeneration outcomes comparable to autografts [176,177]. Similarly, BDNF and PLA were mixed to prepare a composite NGC with sustained-release BDNF, which maintained biological activity of BDNF for at least 3 months and promoted the regeneration of 10 mm gap of sciatic nerve in rats [178]. GelMA-CNTF/IGF-1 composite hydrogel can provide continuous release of CNTF and IGF-1, load into PCL NGC to repair 15 mm sciatic nerve defect in rats, accelerate nerve regeneration, promote the formation of new axon myelin sheath and nerve electrophysiological function, and promote the recovery of motor function [179]. GDNF-Gel/HA-Mg conduit can release GDNF to enhance the nutritional support required for peripheral nerve regeneration. Mg^{2+} produced in the degradation process can also effectively promote the regeneration. The conduit may participate in the repair of peripheral nerve defects by regulating PPAR-γ/RhoA/ROCK signaling pathway [180]. Wnt5a can promote the proliferation of SC, the expression and secretion of vascular endothelial growth factor (VEGF), NGF, cholinergic neurotrophic factor (CNTF). Wnt5a loaded hydrogel NGC can promote the nerve regeneration for repairing 10 mm sciatic nerve defect in rats [181]. Despite these promising advancements, attention is still required to determine safe and effective dosages of nutritional factors and to elucidate the precise mechanisms underlying their effects on nerve regeneration. This will be essential for translating these strategies into safe, reliable clinical therapies.

Extensive research has been conducted on small molecule therapies for PNI, demonstrating significant potential for their integration into NGCs. The FDA has approved several drugs for the treatment of PNI by systemic administration or local injection, including Tacrolimus, CsA, nimodipine and acetyl-L carnitine. However, there is no effective delivery method to improve its efficacy by prolonging its release time [182]. Nanocomposite conduit can be used as a common carrier of valproic acid (VPA) similar to the effect of neurotrophic factors. A new bioabsorbable NGC of slow-release VPA based on PDLLA/PRGD has been developed to repair the 10 mm gap of sciatic nerve in rats, and its promoting effects on peripheral nerve regeneration is equivalent to that of autograft [183]. In addition, the 4-aminopyridine (4-AP), a potassium

Table 5
Bioactive factors for NGC.

Bioactive factors		NGC	Application	Effects	References
SAPs	RAD, IKVAV, RGI	RAD/IKV/RGI and RAD/IKV-GG-RGI hydrogels are injected into chitosan NGC	10 mm sciatic nerve defects in rats	It promoted axonal regeneration and functional recovery after peripheral nerve injury	[171]
	RGD, YIGSR	RGD and YIGSR non-covalent binding with PCL NGC	15 mm sciatic nerve defects in rats	It promoted the regeneration of nerve.	[172]
nutritional factors	NGF	NGC with sustained release of NGF	10 mm sciatic nerve defect in rats	It significantly promoted nerve regeneration, and the recovery effect is similar to that of autograft	[176,177]
	BDNF	a composite NGC with sustained-release BDNF	10 mm gap of sciatic nerve in rats	It maintained biological activity of BDNF for at least 3 months and promoted the regeneration of nerve.	[178]
	CNTF/IGF-1	GelMA-CNTF/IGF-1 composite hydrogel load into PCL NGC	15 mm sciatic nerve defect in rats	It accelerated nerve regeneration, promoted the formation of new axon myelin sheath and nerve electrophysiological function, and promoted the recovery of motor function	[179]
small molecule	VPA	bioabsorbable NGC of slow-release VPA based on PDLLA/PRGD	10 mm gap of sciatic nerve in rats	its promoting effects on peripheral nerve regeneration is equivalent to that of autograft	[183]
	4-AP	NGC with arranged microchannel pores provides continuous release of 4-AP	15 mm defect of the sciatic nerve in rats	peripheral nerve regeneration is equivalent to autograft	[145]
	curcumin	NGC prepared by PLLA and surface modified multi-walled carbon nanotubes (mMWCNT) was filled with nanocurcumin and SCs	10 mm nerve defect in rats	The curcumin added significantly increased the number of axons, and there was no significant difference in response time and sciatic function index between the NGC and autograft	[186]

channel blocking agent, applied to nerve crush injury with damaged myelin sheath can increase myelin regeneration and nerve conduction, leading to functional recovery. The NGC with arranged microchannel pores provides continuous release of 4-AP at the 15 mm defect of the sciatic nerve in rats, and peripheral nerve regeneration is equivalent to autograft [145]. Curcumin can also promote regeneration of PNI [184]. The nanoscale delivery platform of curcumin encapsulated tannic acid (TA) and polyvinylpyrrolidone (PVP) has been developed as bioactive agents suitable for NGC [185]. In another approach, an NGC prepared by PLLA and surface modified multi-walled carbon nanotubes (mMWCNT) was filled with nanocurcumin and SCs to repair 10 mm nerve defect in rats. The curcumin added significantly increased the number of axons, and there was no significant difference in response time and sciatic function index between the NGC and autograft [186]. Despite these promising results, the precise mechanisms of action of these small molecules remain unclear and require further investigation.

In nerve regenerative engineering, SCs have emerged as pivotal players in facilitating nerve regeneration after injury, particularly in cases of long-distance nerve defects. However, the limited proliferative capacity of autologous SCs necessitates the utilization of other seed cells, such as ESCs, NSCs, iPSCs, MSCs and SKP-SCs. While the delivery of seed cell via NGCs holds promise for stimulating nerve regeneration, it entails challenges related to cost and complexity. Furthermore, the creation of an optimal extracellular environment and the maintenance of cell viability are crucial for the successful repair of injured nerves. In parallel, engineered NGCs, enhanced with SAPs, hormones, nutritional factors, and small molecule compounds, have demonstrated potential in further promoting nerve regeneration and repair.

The exploration of SCs and various stem cell populations as therapeutic strategies to stimulate rapid nerve regeneration in NGC represents a significant progress facing the challenges associated with long-distance nerve repair. The abilities of SCs to promote nerve regeneration, combined with their plasticity and responsiveness to injury, make them highly attractive as seed cells. However, the limited proliferative capacity of autologous SCs need to develop alternative cell sources. The stem cells, particularly those derived from embryonic and neural offers a promising solution. More importantly, seed cells with more abundant sources, such as iPSC, different tissue-derived MSC and SKP-SCs, also showed significant effects on promoting nerve regeneration. These cells possess the capacity for self-renewal and differentiation into multiple cell types, including those of the neuronal lineage. Moreover, EVs from seed cells in NGC could exert further pro-regeneration effect. Therefore, these provide a variety of options to replace autologous SCs to be applicable to patients with different needs. The construction of beneficial intraluminal microenvironment of NGCs provids an effective method to bridge the gap in nerve regeneration. In the process of nerve injury repair, the up-regulation of neurotrophic factors promotes nerve regeneration and repair. NGF, BDNF, CNTF and so on are well-known for their neuroprotective and neurotrophic effects, which can enhance peripheral nerve regeneration. The self-assembling peptides, such as RAD, IKVAV (fragments of the LN secreted by SCs) and RGI (derived from BDNF) in NGC, similarly mimics the microenvironment of nerve repair after injure, further enhances the nerve regenerative potential of these conduits. In addition to cellular therapies and nutritional factors, the role of small molecule compounds in promoting nerve regeneration cannot be overlooked. Tacrolimus, CsA, nimodipine, and acetyl-L carnitine have demonstrated potential in reducing inflammation, modulating immune responses, and promoting axon regeneration.

The synergistic effects of biological and pharmacological agents, combined with the regenerative capacity of seed cells and the supportive role of NGCs, create a holistic therapeutic approach that holds promise for significantly improving outcomes in nerve regenerative engineering. However, there remain several challenges, including optimized cell delivery strategies and NGC design to better mimic the native nerve microenvironment, and the identification of the optimal combination of therapeutic agents. Ongoing research is essential to translate these promising strategies into clinically therapies that can improve the lives of patients with defect of nerve.

6. Approved nerve guide conduits

Clinical research on peripheral nerve repair using NGC has been ongoing for many years. In China, five kinds of NGCs for the treatment of PNI have been approved by the National Medical Products Administration (NMPA, https://www.nmpa.gov.cn/), including acellular allogeneic nerve repair material, artificial nerve sheath, acellular matrix peripheral nerve repair membrane, peripheral nerve repair graft and peripheral nerve cuff (Table 6) [3,15]. Acellular allogeneic nerve repair material is obtained from peripheral nerves collected from human body after acellular treatment. It is mainly composed of collagen fibers and extracellular matrix. It is suitable for repairing 1–5 cm traumatic sensory nerve defects caused by various reasons. The artificial nerve sheath is mainly derived from bovine tendon and processed into spongy collagen sheath for the repair of peripheral nerve defects with the length of the $\leq$ 2 cm. Acellular matrix peripheral nerve repair membrane is mainly composed of porcine peripheral nerve extracellular matrix, which is

suitable for auxiliary repair of peripheral nerve injury without parenchymal defect or after anastomosis. The peripheral nerve repair graft, is composed of the conduit made of chitosan, chitin and medicinal gelatin by freeze-drying and inner PGLA fibers, which is used to repair the ≤ 3 cm defects of the digital nerve, the superficial branch of radial nerve and the median forearm nerve. The peripheral nerve cuff is made of chitosan material by acetylation. It is used to repair the median nerve, ulnar nerve and radial nerve of the upper limb with end-to-end tension-free cuff suture.

Currently, 33 NGCs have been approved by FDA (https://www.accessdata.fda.gov/scripts/cdrh/Cfdocs/cfpmn/pmn.cfm) for the treatment of PNI, and the NGCs approved before 2020 have been well reported by Parker BJ et al. [15]. We summarize 8 NGCs approved by FDA from 2020 to 2024 (Table 7). Among them, several NGCs can repair nerve gap. The Rebuilder (k230794/2024) made of poly (lactide-co--caprolactone) is suitable for the reconstruction of patients with peripheral nerve gaps up to 20 mm; The Neurolac (k112267/2011, k050573/2005, k032115/2003) made of poly (DL-lactide--co-ε-caprolactone) is also suitable for the reconstruction of patients with peripheral nerve gaps up to 20 mm; Moreover, the Neurotube (k983007/1999) made of PGA is suitable for patients with peripheral nerve gaps of 8–30 mm. However, autografts and processed allografts are still needed for large gap repair of nerve [97]. It is expected that new NGCs will be approved to make up for the regrets.

Compared to FDA-approved NGCs and nerve cuffs, such as NerveTape, Axoguard HA + Nerve Protector and NervAlign, made of natural materials, but they are more suitable for repairing peripheral nerve injuries in which there is no gap or where a gap closure is achieved by flexion of the extremity. The NGCs, including acellular allogeneic nerve repair material and artificial nerve sheath, made of natural materials, approved by the National Medical Products Administration of China, showed good effects on the repair of peripheral nerve defects with gaps. But there may be the risks of immune rejection or cross-species disease transmission due to allogeneic or animal origin. Peripheral nerve repair graft and peripheral nerve cuff may require further research and clinical data to demonstrate long-term efficacy and safety.

7. Prospectives

Artificial NGCs offer promising alternative strategies for treating peripheral nerve injuries by promoting the directional growth of neurites within the conduit, simulating the natural nerve microenvironment, and supporting the repair and regeneration of damaged nerves. Advances in tissue engineering have introduced new approaches for designing NGCs, including the selection and combination of materials, manufacturing techniques, micro-/nano-structures, bioactive factors, and small molecules. Beyond material selection and technological innovations, NGCs with engineered surface morphologies play critical roles in guiding axonal growth, promoting cell proliferation and differentiation, and inhibiting fibrous infiltration during peripheral nerve regeneration. However, the regulatory mechanisms governing peripheral nerve regeneration remain unclear.

Existing studies have shown that electrical stimulation and conductive polymers help to promote peripheral nerve regeneration. The application of electrical stimulation can enhance the proliferation and differentiation of nerve cells by simulating the electrophysiological environment in vivo. Non-invasive electrical stimulation can modulate nerve cell behavior by wearing electronic devices, which can trigger the cells to transmit signals, leading to the enhancement of cell migration, differentiation, proliferation and other activities. However, it also faces some challenges, including contact of the electrode may result in temperature increases and pH changes that may adversely affect the cells; In some cases, electrical stimulation may produce harmful products, such as reactive oxygen species, which can cause damage to cells. The different parameters of electrical stimulation have a considerable impact on regulating cell behavior, as well as effective electrical stimulation controllability issues. Invasive electrical stimulation includes wearing the implantable device and implanting NGCs containing conductive polymer materials, in which conductive materials have the ability to be easily biofunctionalized and good compatibility, and can be prepared into different shapes and sizes to meet the different needs of NGCs. However, implantable electrical stimulation also has some disadvantages. The insufficient biocompatibility of the electrode of implantable device may lead to cell damage or inflammatory response; The lack of stability of conductive polymers still limits their clinical applications, especially in the case of long-term stimulation. The non-biodegradability, in vivo toxicity and the mechanism of some conductive polymers remain uncertain. Specifically, GO blends have limited electroconductivity, PANI:CSA requires toxic solvents to yield satisfactory electroconductivity/processability, PEDOT:PSS has limited processability and is unstable in aqueous solutions in the long-term. The mechanism by which electrical stimulation promotes nerve regeneration may involve the increase of neurotrophic factors and receptors, such as BDNF and NGF, followed by the increase of intracellular cAMP level and the activation of downstream pathways to promote the expression of growth-associated protein 43 and other proteins, further promoting axonal and myelin regeneration [187]. However, the mechanisms regulated by electrical stimulation have not been fully elucidated. All of which limit their clinical translation and require further investigation. In the selection of applications, it is necessary to comprehensively consider according to the specific needs and experimental conditions to give full play to its advantages and try to avoid its disadvantages.

Table 6
NGCs for the treatment of PNI have been approved by the National Medical Products Administration of China.

Product name	Company	Number	Date	Material	Indications for Use
Acellular allogeneic nerve repair material	Guangzhou ZHONGDA Medical Instrument Co. LTD	20163131598	08/26/2021	peripheral nerves collected from human body after acellular treatment, mainly composed of collagen fibers and extracellular matrix	repairing 1–5 cm traumatic sensory nerve defects caused by various reasons
Artificial nerve sheath	Tianxinfu (Beijing) MEDICAL Equipment Co., LTD	20163132399	09/08/2021	bovine tendon and processed into spongy collagen sheath	the repair of peripheral nerve defects with the length of the ≤ 2 cm
Acellular matrix peripheral nerve repair membrane	Shandong Juanxiu Biotechnology Co., LTD	20193130355	01/04/2024	composed of porcine peripheral nerve extracellular matrix	auxiliary repair of peripheral nerve injury without parenchymal defect or after anastomosis
Peripheral nerve repair graft	Jiangsu Yitong Biotechnology Co. LTD	20203130898	11/17/2020	the conduit made of chitosan, chitin and medicinal gelatin by freeze-drying and inner PGLA fibers	repair the ≤ 3 cm defects of the digital nerve, the superficial branch of radial nerve and the median forearm nerve
Peripheral nerve cuff	Beijing Huifukang Technology Co., LTD	20213130298	04/30/2021	chitosan material by acetylation	repair the median nerve, ulnar nerve and radial nerve of the upper limb (the length of nerve defect is not more than 2 cm) with end-to-end tension-free cuff suture

Table 7
FDA Cleared NGCs and Nerve Cuffs under the product code 'JXI', (510(k) FDA database, 2020–2024).

Product name	Company	510(k) Number	Date	Material	Indications for Use
Rebuilder Nerve Guidance Conduit	CelestRay Biotech Company, LLC.	K230794	01/29/2024	Poly (lactide-co-caprolactone), poly (lactide-co-glycolic acid) and Polylactic acid-b-Polyethylene glycol	the reconstruction of a peripheral nerve discontinuity up to 20 mm in patients who have sustained a complete division of a nerve
NerveTape	BioCircuit Technologies Inc	K233533	02/12/2024	Porcine small intestinal submucosa: primarily collagen types I, III, IV, and VI	the repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity
VersaWrap	Alafair Biosciences Inc	K232029	11/02/2023	Calcium alginate and hyaluronic acid	the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue
Axoguard HA + Nerve Protector	AxoGen Corporation	K231708	10/12/2023	Porcine SIS 2.0 decellularized extracellular matrix, sodium hyaluronate and sodium alginate	The management and protection of peripheral nerve injuries where there is no gap, or following closure of the gap
Axoguard HA + Nerve Protector	AxoGen Corporation	K223640	04/07/2023	Porcine SIS 2.0 decellularized extracellular matrix sodium hyaluronate and sodium alginate	the management of peripheral nerve injuries where there is no gap
Nerve Tape	BioCircuit Technologies Incorporated	K210665	07/15/2022	Porcine small intestinal submucosa; primarily collagen types I, III, IV, & VI	the repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity
NervAlign	Renerve Ltd	K202234	02/10/2022	Collagen Matrix–Porcine Pericardium	the repair of peripheral nerve injuries in which there is no gap or where a gap closure is achieved by flexion of the extremity
VersaWrap	Alafair Biosciences Inc	K201631	09/14/2020	Calcium alginate and hyaluronic acid	the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue

The design of NGCs is a complex and critical process, which involves a variety of factors, including materials, structure, function, and clinical application requirements. For materials, the following characteristics should be considered: (1) Biocompatibility: It will not cause adverse reactions in vivo, such as allergic reactions, toxicity or immune rejection. (2) Degradability: The rate of degradation should match the rate of nerve growth and the degradation products should eventually be removed. (3) Mechanical properties: The conduit needs to have a certain strength and flexibility. (4) Permeability or porosity: promotes cell adhesion and nerve regeneration. (5) Cell adhesion and growth: The surface allows cell adhesion and promotes cell growth [188]. Based on the above requirements, the relevant studies of the material section and approved NGCs, the authors believe that according to the needs of different patients, the best materials can be selected. For example, for the repair of nerve defects ≤ 2 cm, the choice of natural materials can be favored. Among the approved NGCs, natural materials such as ECM, type I collagen, and chitosan all seem to be the good choices. For the repair of longer distance nerve defects, ECM is the good material choice when the mechanical strength is not demanding. When mechanical strength is required, synthetic materials are preferred, and among approved NGCs, synthetic materials such as PGA and PGLA seem to be the good choice. Moreover, when necessary, composite materials are more conducive to promoting nerve regeneration. In addition, according to feedback on the clinical application of NGCs approved by the US Food and Drug Administration (FDA), in recent years, the failure of NGCs has been attributed to lumen volume reduction, traction suture pull-out during mobility, and swelling due to material-dependent immunogenicity [144]. In future studies, materials with stable mechanical properties and low immunogenicity will be more important for clinical research.

To further improve the performance of the NGCs, researchers are exploring the integration of active factors into the conduit to promote nerve regeneration. Computational and mathematical modeling also serve as powerful tools in the design of novel NGCs, allowing simulation of nerve anatomy and physiology, testing conduit performance, and optimizing designs. Despite the considerable progress in NGC research, challenges remain, particularly in addressing long-distance nerve defects. Many NGC strategies are still in the experimental stage. Further evaluation and validation of NGCs in the repair of long nerve defects can provide data support for clinical application. In addition, it is still necessary to solve the problems, such as manufacturing complexity, cost, repeatability and safety, so as to promote the clinical application of the NGCs. Meanwhile, future researches will continue to explore new materials, manufacturing technologies and treatment strategies to achieve better repair and functional recovery after nerve injury. With the further development of materials science, tissue engineering, cell science and biomedical engineering, more effective, safer and more economical artificial NGCs are expected to be developed.

CRediT authorship contribution statement

Xinlei Yao: Writing – original draft, Visualization, Methodology, Investigation. **Tong Xue:** Writing – original draft, Methodology, Investigation. **Bingqian Chen:** Writing – original draft, Methodology, Investigation. **Xinyang Zhou:** Visualization, Software, Methodology, Investigation. **Yanan Ji:** Validation, Methodology, Investigation. **Zihui Gao:** Validation, Software, Methodology. **Boya Liu:** Validation, Software, Methodology. **Jiawen Yang:** Validation, Methodology. **Yuntian Shen:** Project administration, Funding acquisition. **Hualin Sun:** Writing – review & editing, Funding acquisition, Conceptualization. **Xiaosong Gu:** Supervision, Resources, Conceptualization. **Bin Dai:** Writing – review & editing, Resources, Conceptualization.

Ethics approval and consent to participate

Not Applicable.

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 32130060, 82401633, 82072160), the Natural Science Foundation of Jiangsu Province (No. BK20232023), and Natural Science Research Projects in Universities of Jiangsu Province (No. 24KJB310013, 24KJA310007), Suzhou Science and Technology Development Program (No. SYW2024048).

Declaration of Competing interests

The authors declare that they have no competing interests.

Acknowledgments

Not Applicable.

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