Evolution of natural polymer nerve conduit technology in peripheral nerve repair: a narrative review

Evolution of natural polymer nerve conduit technology in peripheral nerve repair: a narrative review

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Abstract

Peripheral nerve injury is a worldwide challenge in the clinic. Although autologous nerve is considered the gold standard for bridging large nerve defects (> 5 mm), donor-site morbidity, limited sources of donor nerves and other potential side effects restrict its application in nerve regeneration. Nerve guidance conduits have become increasingly popular as a promising alternative to autologous nerve repair and regeneration. The evolution of nerve guidance conduits from nondegradable materials to various biodegradable materials subsequently results in enhanced properties, such as superior biodegradability, a mimetic extracellular matrix and an optimal structure. This review describes current therapies for nerve repair and the mechanism and evolution of nerve guidance conduits with advantages and limitations; proposes the detailed requirements of ideal nerve guidance conduits; and emphasizes the applications of natural polymers, including collagen, chitosan, alginate, gelatin, silk fibroin and hyaluronic acid, in nerve regeneration with the incorporation of various functional materials, chemical modifications and feasible techniques to promote cell proliferation and axon regeneration. Compared with natural polymers, advanced nerve guidance conduits have considerable potential for nerve regeneration in the clinic.

Key words: chemical modification; natural polymers; nerve guidance conduits; nerve regeneration; peripheral nerve injury; technique; technology

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INTRODUCTION

Peripheral nerve injury (PNI) is a global clinical challenge that affects 13 to 23 per 100,000 people annually and significantly impairs patients' quality of life by causing painful neuropathies, loss of mobility and sensory functions and even paralysis.[1] PNI commonly results from traffic accidents, industrial accidents, and penetrating trauma, leading to compression, stretching, laceration and/or trauma to peripheral nerves. Upon the onset of nerve injury, the body initiates an intrinsic healing response characterized as Wallerian degeneration, which involves changes in morphology and biochemical substrates to facilitate axonal growth.[2] Briefly, the process of nerve regeneration starts at the proximal nerve stump within the first 48 hours, as the growing axons attempt to bridge the distal nerve stump and reinnervate the targeted cells and tissues.[3] However, the natural repair mechanism is too slow to achieve timely nerve repair, as the average rate of axonal growth is approximately 1 mm per day, especially considering that endogenous nerve regeneration is unfeasible over 1 year.[4, 5]

Therapies for treating PNI are classified as pharmacotherapy to mitigate inflammation and pain, physiotherapy for functional recovery, and surgical interventions such as nerve suturing or grafting.[6-8] Advanced therapies such as cell and gene therapies, along with rehabilitation training and assistive devices, are also employed.[9-11] Although versatile treatments are available for nerve repair, there are limitations such as side effects, postoperative infection, ongoing rehabilitation training and poor therapeutic efficiency.

Severe PNIs can lead to nerve rupture, and short defects (< 5 mm) are preferable to end-to-end suture,[9] while autologous nerve grafting is currently the gold standard for larger defects.[12, 13] However, the use of autologous nerve grafting is impeded by its limited sources of donor nerves, scarring, additional surgery,

potential neuroma formation, donor-site morbidity and mismatch in structure and size.[14] Therefore, increasing interest in nerve guidance conduits (NGCs) fabricated from various biomaterials is presented as promising solutions for PNI to bridge nerve gaps and facilitate regeneration of large peripheral nerve defects. NGCs are designed to address donor-site morbidity and immunological rejection attributed to autografts or allografts.[15, 16] The regeneration of axons from the proximal nerve stump to the distal nerve stump is realized via surgical implantation of NGCs (**Figure 1**). Initially, neurotrophins and the extracellular matrix (ECM) are released from the nerve stump to form fibrin cables.[17] Subsequently, dedifferentiated Schwann cells (SCs) move along the fibrin cable to form Büngner bands, providing basal guidance for axon outgrowth.[18] The myelin sheath is constructed of cell adhesion molecules, integrins, and neurotrophins secreted by SCs during the axon remyelination process.[19] The last and most important step is the reestablishment of nerve–muscle connections and the targeting of muscle reinnervation to promote functional recovery.

In general, ideal NGCs possess the following properties: high biocompatibility and histocompatibility to minimize immune rejection and potential inflammation; effective biodegradability to eliminate the possibility of secondary surgery; desirable porosity or permeability to deliver nutrients and waste exchange and support cell migration; a topographical structure to promote cell proliferation and migration; and satisfactory mechanical properties, such as biodegradability, saturability, toughness, moldability, facile use, and perfect matching defect size.[20, 21] The design and material selection of NGCs have undergone significant development. **Figure 2** illustrates the crucial stages in the evolution of NGCs, emphasizing the transition from the initial application of nondegradable materials to the use of biocompatible and biodegradable alternatives.

The first generation of NGCs was composed of nondegradable silicone or polytetrafluoroethylene to provide mechanical support for nerve repair. Silicone tubes were successfully employed in PNI to bridge a 2–3 mm nerve gap,[22] and polytetrafluoroethylene conduits were used to repair a 4 cm nerve defect in humans.[17] Since these conduits need to be removed by secondary surgery, biocompatible and biodegradable materials such as poly(lactic–coglycolic) acid (PLGA) and poly(ε–caprolactone) (PCL) have been introduced to produce nerve conduits. Subsequently, structure, permeability, incorporation with bioactive compounds.[7] Currently, NGCs are based on natural materials, such as collagen, chitosan (CS) and silk fibroin (SF), to mimic the native ECM for nerve regeneration. The developed technology allows patient-specific customization of NGCs. Materials science plays a vital role in designing NGCs by controlling their degradation rate, biocompatibility, and mechanical properties; introducing biomaterials to improve their biodegradability and lower immunogenicity; and fabricating hybrid materials and performing advanced techniques such as 3D printing. These findings provide a promising horizon for promoting nerve regeneration.

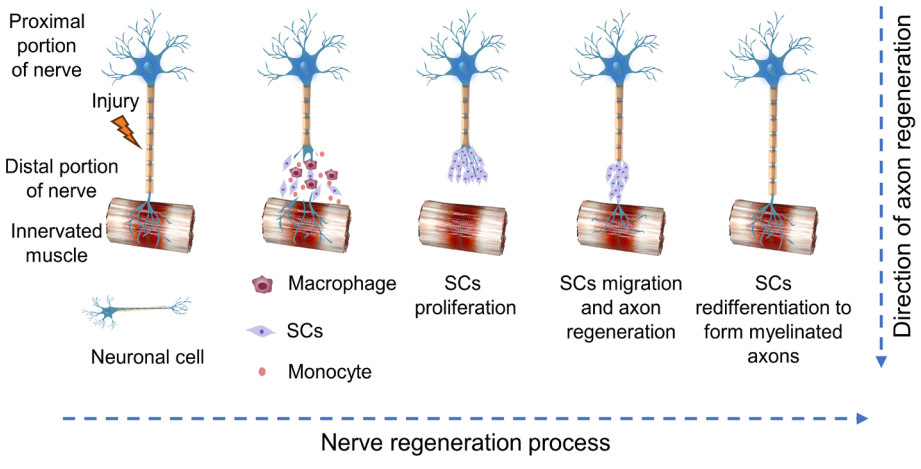

Figure 1: The regeneration mechanism of peripheral nerve injuries.
Note: After peripheral nerve injury, the distal nerve stump undergoes Wallerian degeneration, whereas the proximal stump experiences minimal changes. The injury triggers a bioelectric field that guides macrophages and Schwann cells (SCs) to the injury site. Macrophages clear debris in the later stages of degeneration, facilitating axonal regeneration. SCs form Büngner bands, providing guidance and support for axonal regrowth, and release neurotrophic factors that promote axon growth and functional recovery. Finally, SCs differentiate into myelinated cells, completing the nerve regeneration process. Created with PowerPoint and Cinema 4D software.

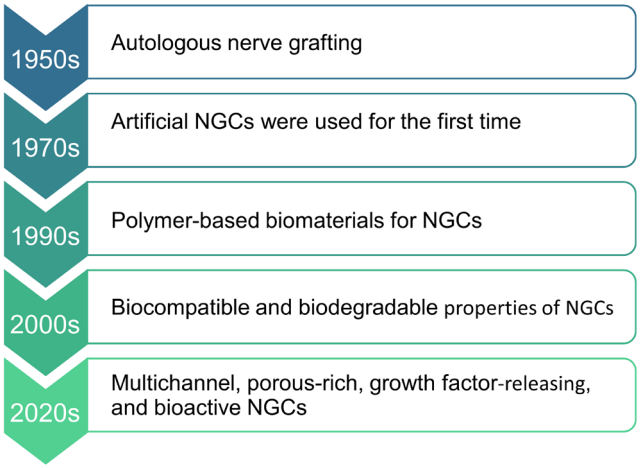

Figure 2: Important time milestones in the development of nerve guidance conduits (NGCs).
Note: Created with Microsoft PowerPoint.

Search Strategy

A comprehensive literature search was conducted in the following electronic databases, without regard to language: the PubMed and Web of Science databases were also consulted. The search terms included "neural guidance conduit," "nerve regeneration," "biomaterials," and "peripheral nerve injury." A combination of keywords was employed to optimize the search results. The search was last updated on July 30, 2024, and all studies published prior to this date were considered for inclusion. Two independent reviewers conducted title and abstract screening, followed by a full-text review of potentially eligible studies.

Properties of Nerve Guidance Conduits

The ideal NGCs display a synergistic combination of physical, chemical, and mechanical properties to facilitate the complex process of nerve repair and regeneration (**Figure 3**).[23] The physical attributes of NGCs, such as biodegradability and biocompatibility, along with their topographic structure, are essential for integration with host tissues, offering a negligible thrombogenic and immunological interface. Owing to their chemical properties, due to the presence of functional groups, neurotrophic factors, and cellular receptors, therapeutic agents are able to bind with NGCs to promote cell proliferation and axon outgrowth.[24] Mechanical properties, such as tensile strength and elasticity, must match those of native tissue to withstand physiological stresses and strains during the healing process. The mechanical properties include tensile strength and stiffness, ensuring that the designed NGCs maintain their structural integrity throughout the regeneration process. Moreover, the biodegradability of NGCs and their drug delivery efficacy enhance their therapeutic effects, and precise manufacturing techniques ensure the accurate realization of their design. Consequently, a holistic design philosophy that integrates these multifaceted considerations is essential for achieving the optimal performance of NGCs in neural repair.

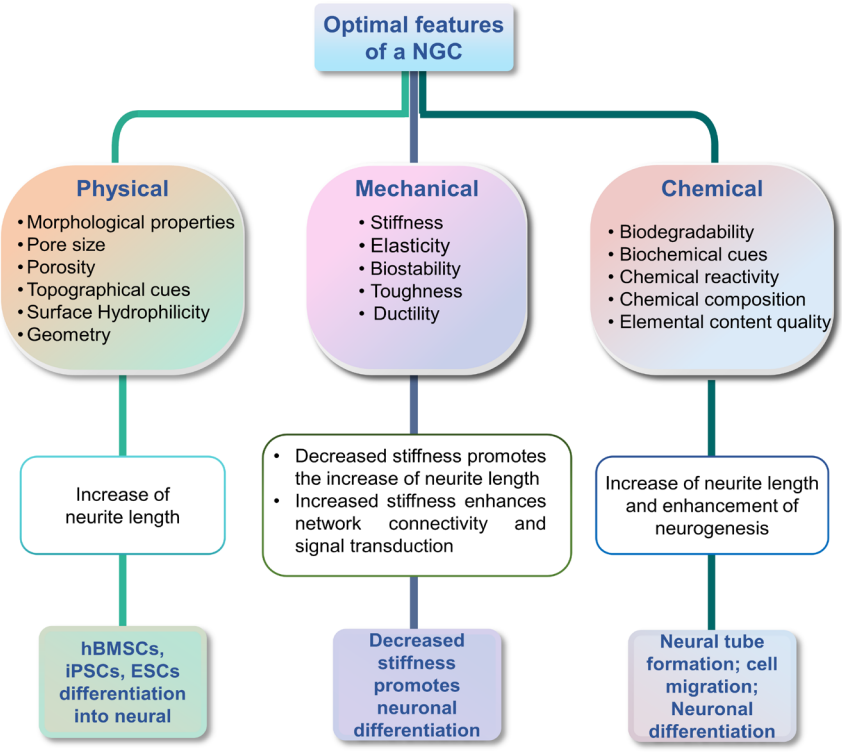

Figure 3: Physical, mechanical and chemical properties of NGCs.
Note: Created with Microsoft PowerPoint. ESCs: Embryonic stem cells; hBMSCs: human bone marrow mesenchymal stem cells; iPSCs: induced pluripotent stem cells; NGCs: nerve guidance conduits.

Physical properties

In the field of neural regeneration, designing an ideal physical scaffold for NGCs is essential for nerve repair. The physical properties of NGCs are optimized to meet several biological functions, including porosity, surface characteristics, and hydrophilicity, which are related to the migration of neural cells, diffusion of nutrients, exchange of oxygen, and removal of waste products, all of which are crucial for promoting cell adhesion and proliferation. These properties have synergistic effects on the integration of NGCs with the biological milieu, thereby enhancing the overall success of neural regeneration.[25, 26]

The pore structure of nerve conduits profoundly influences cell migration and regeneration. The pore size and porosity of NGCs play important roles in the migration of cells and regeneration of nerves. Several studies have demonstrated that the pore size of NGCs ranges from 20–70 μm, and a porosity exceeding 90% could effectively facilitate the transport of nutrients and the migration of cells, which is conducive to the regeneration and repair of nerves.[27, 28] Porosity affects not only cell migration within the conduit but also the interaction between the conduit and the surrounding tissues, as well as the internal environment. A well-designed pore structure could provide a favorable environment for cell migration, allowing the movement of nerve cells and growth factors, which is essential for nerve regeneration. A reduced graphene oxide aerogel neural conduit with axial hollow channels and a radially oriented porous network in the wall exhibited significant structural robustness and an exceptionally high porosity of 98.5% ± 0.24%, facilitating neural growth in the complex *in vivo* environment.[29]

Surface characteristics, such as roughness and topography, also contribute to the properties of NGCs. These characteristics determine the initial interaction between cells and the conduit material, which affects cell adhesion, proliferation, and differentiation. The topological structures of NGCs are designed to mimic the conducive microenvironment for nerve regeneration. This includes providing guidance for the orientation and alignment of axons and neural cells, maintaining the structural integrity of the nerve conduit, and incorporating different secondary physical cues.[30] NGCs facilitate the exchange of molecules, cells, and interstitial fluid. Nerve cells are confined to dense regions while migrating to the topological structure.[31] The risk of neuroma formation is associated with NGC wall thickness.[32] Thinner wall thickness may lead to insufficient support (e.g., NGC collapse or deformation or even structural integrity) that impedes the growth and alignment of nerve regeneration in an organized manner, resulting in misrouting and the formation of neuromas. Furthermore, thinner NGCs create a suboptimal environment, which impairs the diffusion of nutrients and oxygen to regenerative cells, affects the migration of SCs and waster exchange. In contrast, a greater wall thickness of NGCs could prevent external pressure or trauma and impede the formation of fibrous tissue and neuromas. Additionally, the length of NGCs must be adequate to bridge the gap between severed nerves, and their size should correspond to the diameter of the damaged nerves to provide sufficient space for axonal growth and neural cell infiltration.[33] NGCs that are too small can compress nerves and hinder regeneration, whereas those that are too large can disrupt axonal alignment and lead to misrouting. Advanced NGCs feature several internal channels to mimic the fascicular structure of nerves, containing a larger area for cell attachment, providing various pathways for nerve regeneration and minimizing the dispersion of regenerated axonal branches.[6, 32]

Hydrophilicity represents a pivotal physical attribute of neural conduit materials, influencing their biocompatibility, lubricity, softness, and integration with biological tissues. The high degree of hydrophilicity observed in these materials is attributed to their enhanced flexibility and smoothness, which facilitate their integration with neural tissues and mitigate inflammatory and scarring responses.[23] This property is also crucial for maintaining the internal moisture levels of the conduit, which are primary for cellular survival and functionality. Hydrophilic surfaces promote the initial adhesion of cells, which is a fundamental step in nerve regeneration. This is achieved by promoting enhanced cell spreading and interaction with the extracellular matrix. This resulted in a more effective nerve repair process.[34] Furthermore, hydrophilicity can facilitate the diffusion of water-soluble molecules, such as nutrients and neurotrophic factors, which can contribute to axonal growth and myelination. In summary, the hydrophilicity of materials plays a significant role in the functionality of neural conduits. Moreover, it is an important factor in the selection and design of suitable materials for neural regeneration.

Mechanical properties

The central nervous system is protected by mechanical barriers such as the skull and spine; however, the peripheral nervous system lacks substantial mechanical protection. The mechanical properties of NGCs are

dictated by diverse parameters, including material selection, fabrication technique, wall thickness and lumen filler. It is essential for NGCs to withstand suturing and remain intact after surgery.[35] To simulate the mechanical properties of peripheral nerves, artificial NGCs are designed to endure compression from muscles, bones and surrounding tissues to guide and protect regenerated axons. The mechanical properties of NGCs generally include the Young's modulus, tensile strength, elongation at break and elasticity. The Young's modulus and tensile strength of the rat sciatic nerve were reported as 0.58 MPa and 3 ± 1 MPa,[36, 37] respectively. Artificial NGCs require appropriate performance to match native nerve tissue.

It is important to balance the stiffness and flexibility of nerve conduits. Adequate stiffness allows conduits to resist compression from surrounding tissues and create a supportive environment for nerve regeneration. The increased stiffness of the nerve conduit maintains its shape and structure during limb movements, preventing deformation or collapse of its inner lumen.[38] However, the decreased stiffness of NGCs increases neurite length by providing biochemical cues, promoting cell adhesion and migration, enhancing biosignals for neurite outgrowth and effectively interacting with ECM proteins and growth factors.

Moreover, the mechanical compatibility between the NGC and the host tissue is of paramount importance for successful integration and functional recovery. A conduit that is excessively rigid may impede axonal growth and tissue integration. Conversely, a conduit that lacks sufficient rigidity may fail to provide the structural support necessary for effective nerve regeneration. Therefore, the design of NGCs must consider not only the intrinsic mechanical requirements of the nerve but also the dynamic nature of the healing environment.

Chemical properties

A desired nerve conduit is considered a "bridge" to connect nerve gaps; thus, the degradation of NGCs over time following the rate of nerve regeneration is highly important. The axonal regeneration rate of human nerves is reportedly 1–3 mm per day and slightly faster in rats,[39] which may take several months or years to repair nerve defects. The fast degradation rate may lead to focal inflammation, the formation of scar tissues and reduced mechanical support.[40] The degradation rate of the nerve conduit should be as slow as possible to maintain its integrity and mechanical properties during nerve regeneration to support axonal growth or cell proliferation and attachment. However, a delayed degradation rate also affects the regeneration process since it could result in sustained compression of regenerated nerve tissue or even impair it or the presence of chronic inflammation and sustained activation of glial cells, also known as the foreign body response surrounding focal tissue.[41] Furthermore, Houshyar et al.[40] suggested that the degradation rate of nerve conduits close to the proximal nerve end should be slow and that the degradation rate at the distal end should be lower, especially for long-distance nerve repair.

Biocompatibility refers to the biological compatibility of NGCs interacting with host tissues without inducing any adverse effects. The ideal NGCs are nontoxic, have no immune response and promote cell adhesion, proliferation and differentiation. It is essential to conduct an *in vitro* evaluation of NGCs with specific cells to assess cell viability when they are seeded on the fabricated materials. The viability and reactivity of microglia and astrocytes are generally used as indicators of *in vivo* biocompatibility.[42] Moreover, the biocompatibility of byproducts from NGC degradation is involved, as most of them are bioactive and affect the surrounding environment.[41]

Wettability reflects the behavior of "fluid" across the surface of NGCs, which classify the surface as hydrophilic or hydrophobic according to the chemical properties of the NGCs. NGCs possess greater hydrophilicity, which contributes to nerve regeneration, such as enhancing cell adhesion and attachment, facilitating the transport of nutrients and oxygen and improving protein adsorption.[43] Hydrophobic nerve conduits have poor water affinity and are less attractive for nerve regeneration.[44]

Surface modification is an effective approach to impart superior functionalities to NGCs (e.g., ECM proteins and peptides). Collagen contains a versatile cell-binding domain to guide the oriented outgrowth of axons, which is commonly used to coat NGCs.[45] Laminin has served as a bioactive component of the basal lamina for decades. Laminin demonstrated a pronounced ability for SC adhesion and neurite-oriented growth and showed greater proliferation capacity than collagen I and fibronectin in SCs *in vitro*.[46] Peptides are attractive for improving cell adhesion and proliferation, increasing axon diameter and promoting nerve regeneration *in vivo*.[37] Although peptides have a short half-life and are sensitive to enzymes *in vivo*, numerous strategies, such as the use of pseudopeptides and covalent bonding, have been explored to extend their retention period.[47]

Natural Polymers for Nerve Guidance Conduits Fabrication

Although synthetic polymers can be designed to mimic some functions of natural polymers,[48] natural polymers exhibit greater biocompatibility and bioactivity than synthetic polymers do. In addition, natural polymers can interact with living tissue, which are important for promoting nerve regeneration. Most natural polymers can be degraded in the body and naturally excreted, avoiding the inflammatory reactions associated with long-term implants. Therefore, natural polymers are considered desirable biomaterials for medical applications. In addition, natural polymers are able to mimic the ECM, which increases the attractiveness of manufacturing nerve conduits.[49] Typical natural polymers have been employed in nerve conduit fabrication as described below (**Table 1**).[50-65] The properties required for NGCs and natural polymers for the preparation of NGCs are shown in **Figure 4.**

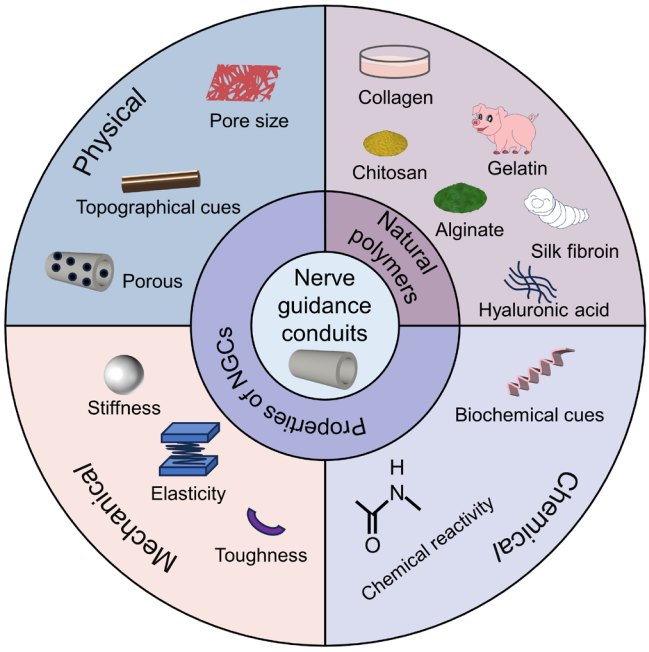

Figure 4: Properties required for nerve guidance conduits and natural polymers for the preparation of nerve guidance conduits (NGCs).

Table 1: Natural polymer NGCs

Natural material	NGC's material	Filler material	Cell/Growth factor	Reference
Collagen	PCL/collagen PCL/rGO	PCL	SCs and PC12 cells	50
	collagen		NGF	51
	collagen/magnetic nanoparticles		NGF	52
CS	gelatin methacryloyl/CS/PEDOT nanoparticles		SCs and PC12 cells	53
	CS/ZIF-8 nanoparticles		SCs	54
	CS/Pluronic F-127 hydrogels		SCs	55
	CS		BDNF and vascular endothelial growth factor	56
Alginate	Gelatin Alginate Hydrogel		SCs	57
Gelatin	polycaprolactone/gelatin		Basic fibroblast growth factor (bFGF) and NGF	58
	gelatin/silk		NGF	59
SF	PEDOT nanoparticles SF		SCs	60
	SF	Hydrogel	NGF	61
	SF		SCs	62
	SF/poly(l-lactic acid-co-ε-caprolactone)		HUVECs	63
HA	Poly(D, l-lactic acid)/β-tricalcium phosphate	CS, HA	NGF, neuronal cells	64
	SF/HA		mouse embryonic stem cell	65

Note: BDNF: Brain-derived neurotrophic factor; CS: chitosan; HA: hyaluronic acid; HUVECs: human umbilical vein endothelial cells; NGCs: nerve guidance conduits; NGF: nerve growth factor; PCL: poly(ε-caprolactone); PEDOT: poly(3,4-ethylenedioxythiophene); SCs: Schwann cells.

Collagen

Collagens are composed of diverse glycoproteins synthesized by fibroblasts, which are the most abundant proteins in mammals (approximately 30% of total protein mass).[48] Collagen is constructed with triple-helix polypeptide chains containing glycine, proline, hydroxyproline, lysine and aspartate,[66, 67] which provide potential positions for further modifications. As the primary component of the ECM and connective tissue,[1] the natural scaffold and porous structure of collagen promote nerve regeneration through mimicking native tissue, facilitating nutrient diffusion and waste exchange to develop a conducive environment for nerve repair. Forty-nine percent of peripheral nerve proteins consist of collagens I and III, where collagen plays a predominant role.

Owing to its superior biocompatibility, collagen I is employed for the majority of NGCs.[68] Procollagen IV produced by SCs forms the backbone structure of the endoneurium and perineurium. In the presence of the semipermeable feature of collagens, NGCs promote diffusion and resorption for up to 9 months, which is consistent with nerve regeneration profiles.[69] Compared with synthetic polymers, natural polymers display greater biodegradability and biocompatibility and minimal immunological rejection. Dai et al. provided examples of commercially available collagen conduits, including NeuraGen®, Neura Wrap™, NeuroMatrix™, Neuroflex™, and NeuroMend™.[70] An example of an intraoperative photo illustrates a collagen nerve conduit applied *in situ* for nerve repair (**Figure 5A**).[71]

However, collagen is prone to swelling and dissolution in aqueous environments. The combination of collagen and other gradients is an effective approach to improve its performance and broaden its applications in nerve regeneration. The layer-by-layer (LbL) technique contributes to electrostatic interactions of different surface charges to integrate various natural polymers and synthetic polymers.[72, 73] This method enables the simulation of natural ECM to improve cell outgrowth and adhesion and serve as a reservoir to store and release growth factors. LbL-coated NGCs are prevalent in tissue engineering, as they are stable under physiological conditions and can be effectively used. Pinzon-Herrera et al.[74] prepared a six-bilayer coating composed of heparin (HEP) and collagen (COL), named $(HEP/COL)_6$. $(HEP/COL)_6$ showed pronounced stability over 21 days of incubation with cell media, and a nearly 170% increase in human SC viability was observed when the commercial collagen conduit NeuraGen® was coated with $(HEP/COL)_6$.

Chitosan

CS is a type of polysaccharide derived from chitin and has become increasingly popular in the biomedical field because of its biocompatibility, biodegradability, and antimicrobial properties.[75] The ability of CS to form hydrogels and porous scaffolds is favorable for creating a conducive environment for cell adhesion and neurite outgrowth,[76] and and has been demonstrated to align the orientations of axons and SCs.[77]

The FDA approved a commercially available never conduit, Reaxon® Plus, made of CS for repairing peripheral nerve discontinuities up to 10 mm in size in 2018. Despite its many advantages, it has notable drawbacks, such as its brittle nature in the dry state, which leads to an increase in the risk of breaking during implantation surgery, poor mechanical strength in a humid environment and rapid degradation under physiological conditions. These disadvantages hamper the application of CS in bridging larger nerve defects because of the probability of collapse at the early stage and consequent blockage of nerve repair.

However, CS has several limitations, such as brittleness in its dry state and rapid degradation under physiological conditions, which can impact its mechanical strength and long-term stability in biomedical applications.[78] The mechanical strength and degradation properties have been improved via the incorporation of other components, such as polycaprolactone,[79] collagen,[80] and PLGA.[81]

Alginate

Alginate is an anionic linear polysaccharide extracted from brown algae or seaweed that is composed of α-L-guluronic acid and β-D-mannuronic acid repeated units.[82] It is well known for its enzymatic degradability, high biocompatibility, tunable chemical properties, negligible immunoreaction and similar structure to that of the ECM, indicating promising potential for nerve regeneration.[83] In the presence of cationic cross-linking agents, including Ca^{2+}, Zn^{2+}, Ba^{2+} and Al^{3+}, the carboxylate groups within the backbone of alginate form hydrogels via ionic bonding.[82] The ionic strength and pH during the gelation process impact the machinal properties of alginate hydrogels. Alginate is increasingly popular for treating central nervous system diseases, such as spinal cord injury,[83] injectable scaffolds with oriented structure[84] and acute cervical spinal cord lesions.[85] A 50 mm sciatic nerve defect in cats was successfully bridged on the basis of

alginate/poly(glycolic acid) (PGA) NGC.[86] The diameter of regenerated axons for a 10 mm nerve gap in rats was increased via alginate gels.[87] However, owing to the weak mechanical properties of natural alginate scaffolds, they exhibit low stability and fast degradation rates under physiological conditions. Low-molecular-weight (MW) alginate (MW < 50 kDa) can be removed by renal clearance.[88]

Owing to the absence of specific enzymes to cleave alginate bonds, although ionic cross-linked alginate hydrogels can be dissolved by dilution or substitution with divalent cations, the dissolved alginate hydrogel segments are unlikely to be completely removed by renal clearance.[89] In this context, innovative strategies have been proposed to improve the biodegradability of high-molecular-weight alginate to expand its biomedical applications. Common oxidizing agents include ozone, hydrogen peroxide, potassium permanganate, and periodate. The oxidation of alginate significantly strengthens its mechanical properties, improves its biodegradability, enhances cell adhesion and lowers its molecular weight. The combination of oxidized alginate and gelatin hydrogels promotes the proliferation and differentiation of adipose-derived mesenchymal stem cells, which are ideal autologous cell sources for nerve regeneration.[90]

Gelatin

Gelatin is a biodegradable natural polymer extracted from animal collagen that is increasingly used in nerve regeneration because of its superior biocompatibility and biodegradability and minimal immunogenicity. NGCs composed of gelatin provide a favorable environment for cell outgrowth, proliferation and differentiation. Gelatin consists of amine, carboxyl and hydroxyl groups for diverse chemical modifications. Gelatin attaches growth factors, peptides, proteins and other bioactive molecules through covalent bonding, hydrogen bonding or physical entrapment. Although gelatin can form flexible scaffolds to mimic the ECM, its poor mechanical properties, rapid degradation, temperature sensitivity and swelling behaviors limit its application in nerve regeneration. Notably, the degradation rate of gelatin depends on the cross-linking degree of gelatin.

Generally, gelatin is incorporated with various polymers to improve its mechanical properties through covalent bonding, physical interactions or layer-by-layer assembly. For example, PCL was introduced as the inner layer of triple-layered NGCs to enhance the mechanical properties and guide oriented cell growth along aligned filaments. Subsequently, gelatin served as the middle layer to mimic the native ECM and improve biocompatibility. PCL nanofibers fabricated by electrospinning were employed as the outer layer to enhance cell attachment (**Figure 5B**).[91] Gelatin/PCL cross-linked with heparin is an effective strategy to improve the stability and biocompatibility of artificial NGCs.

Briefly, Ikegami and coworkers proposed that heparin was immobilized on aligned electrospun polycaprolactone/gelatin nanofibers via covalent bonding; consequently, basic fibroblast growth factor and nerve growth factor (NGF) were immobilized on heparinized nanofibers to generate heparin/growth factor-immobilized artificial nerve conduits on the basis of gelatin/PCL. An *in vivo* assay revealed the desired immobilization efficiency of growth factors on nanofibers of up to 50% compared with (w.r.t.) their initial loading amounts. The excellent bioactivity and retention ability of NGF (~10% w.r.t. with respect to initial loaded amounts) were assessed through *in vivo* implantation of NGCs in a sciatic nerve defect model. Moreover, the *in vivo* biocompatibility of the fabricated NGCs was determined in a sciatic nerve defect model for up to 1 month, which supported the hypothesis that heparin/growth factor-immobilized artificial nerve guidance conduits possess pronounced structural stability and biocompatibility.[58] Gelatin also combines with PLGA, which is a biocompatible and processable copolymer that serves as an oriented nerve conduit for axonal outgrowth and promotes cell proliferation.[92] Conventional hydrogel NGCs are mechanically weak and prone to kinking or tearing, leading to mechanical fragmentation and irreversible structural deformation after implantation, which is detrimental for nerve guidance or even the inhibition of nerve regeneration. Therefore, gelatin and alginate are commonly used to fabricate hydrogel NGCs. A novel dual network hydrogel using alginate and gelatin was developed via a two-step crosslinking process involving chemical-free gamma irradiation and ionic crosslinking. *In vivo* studies using a rat model of sciatic nerve injury demonstrated significantly improved neurological recovery with dual network hydrogel NGCs compared with single network gelatin and commercially available silicone nerve conduits.[57]

Silk fibroin

Various invertebrates (e.g., spiders and silkworms) can produce the natural macromolecular protein silk, which is composed of sericin and two monofilament

fibers of SF enclosed within the innermost layer. In particular, silk from *Bombyx mori larvae* has been extensively applied in the textile industry and in clinical applications. SF is an insoluble natural protein derived from silk composed of 20 amino acids, including glycine, alanine and serine as the predominant components.[57, 92] SF is known for its superior biocompatibility, strong mechanical properties, tailorable degradation rate, ability to be processed into various formats and negligible immunogenicity,[93] and has been widely explored in nerve regeneration.

SF is a promising natural polymer for nerve regeneration that promotes cell adhesion, proliferation and migration; nutrient diffusion; and nerve growth and guidance.[94] SF promotes fibroblast proliferation and the production of vascular endothelial growth factor to facilitate angiogenesis within NGCs, which is an effective approach for nerve repair. Furthermore, it possesses excellent neuroprotective, anti-inflammatory and antioxidant properties that are favorable for nerve regeneration. However, although the mechanism is unclear, a proinflammatory reaction is induced via the combination of SF and silk sericin.[95]

SF, an FDA-approved biomaterial, shows outstanding neurobiocompatibility[96] and is employed in artificial NGC production, nerve scaffolds and lumen fillers.[93] A study designed a porous nerve conduit based on the SF for peripheral nerve repair. SF NGCs displayed more pronounced myelination ability than collagen NGCs in bridging an 8 mm nerve defect model in rats. SF NGCs also exhibit superior immunogenicity in a sciatic nerve defect model.[97] Another 10 mm sciatic nerve gap in rats was bridged with an SF graft composed of an SF nerve guidance conduit inserted with oriented SF fibers.[98] The SF nerve guidance conduit has an eggshell-shaped microstructure, which contributes to its favorable mechanical properties and enhanced permeability. Six months postmorphological and functional investigation suggested that regenerated nerve tissues gradually replaced the SF conduit without inflammation and that the function of the injured limbs had recovered. SF is easily converted into versatile formats via different strategies, such as freeze drying, which provides a porous scaffold structure to promote cell infiltration; electrospinning, which mimics the native ECM; casting and molding, which involves tailoring the specific shape of the 3D structure and forming films and gels; and microfluidics, which produces delicate microspheres and particles for bioactive molecule encapsulation and drug delivery systems; and layer-by-layer assembly, which is employed to construct multilayer devices for controlled release and further modifications.

Freeze drying can also be combined with customized molds to produce NGCs with 250 μm oriented channels, which exhibit well-organized porous structures, the desired flexibility and stability, water absorption, and nutrient diffusion. This multifunctional nerve conduit allows targeted axonal outgrowth and leads to greater delivery of growth factors to targeted injury sites.[63] Magnetic properties are introduced in NGCs through the electrospinning technique because of the large ratio of surface area to volume and tailored porosity. Magnetic NGCs constitute a novel strategy for nerve regeneration through stimulation of focal tissue under an external magnetic field. Brito-Pereira and coworkers incorporated different amounts of $CoFe_2O_4$ particles and Fe_3O_4 particles into SF-based electrospun fibers to reduce their diameter (**Figure 5C**), maintaining the primary chemical structure and thermal stability.[98] Although the natural sources, nontoxicity and high biocompatibility of SF have attracted considerable attention, heterogeneity may exist between different batches of SF-based products.

Owing to their biocompatibility and low immunogenicity, silk proteins have attracted attention as promising materials for nerve regeneration. However, traditional cross-linking methods may result in instability and cytotoxicity. Conductive hydrogels were prepared via a three-step click–chemical reaction method comprising filipin protein, graphene oxide and polyethylene glycol diacrylate. The incorporation of fibroblast exosomes had a synergistic effect on facilitating recovery from peripheral nerve injury. Graphene oxide enhanced the electron transport capacity of the hydrogels, whereas fibroblast exosomes endowed them with the capacity to regulate cellular behavior, thereby promoting axonal and myelin regeneration.[99]

Hyaluronic acid

HA is a high-molecular-weight polysaccharide widely found in the ECM of neural, connective and vertebrate epithelial tissues.[100] It is a linear glycosaminoglycan consisting of disaccharides of β4-glucuronic acid (GlcUA)-β3-N-acetylglucosamine (GlcNAc) repeating units.[101] HA exerts considerable physiological functions, e.g., joint lubrication, the ability to regulate the permeability of blood vessel walls, and the ability to promote wound

healing. Moreover, because of its predominant moisture retention ability, biocompatibility, nonimmunogenicity and viscoelasticity properties, HA plays an important role in the pharmaceutical, biomedical and cosmetic industries because of its high commercial value.

Traditionally, HA is obtained from extracts from animal sources obtained from animal waste and byoroducts in the presence of cetylpyridinium chloride[102, 103] and microbial fermentation via bacterial expression systems in *Streptococci* or alternative safe approaches involves the selection of endotoxin-free microorganisms (e.g., *Bacillus* and *Escherichia coli*).[104] In addition, a series of creative synthetic strategies are currently available, including chemical synthesis (e.g., click chemistry reactions, UV irradiation and photoinitiators),[105] chemoenzymatic synthesis and enzymatic synthesis.[102] However, owing to safety concerns and purity issues, streptococcal fermentation is a predominant process in industrial production.[104] HA plays a considerable role in influencing cell migration, proliferation, differentiation, and other cell behaviors, as it is a dominant component of the ECM.[106] The molecular weight also affects cell behavior; for example, low-molecular-weight HA (~80 to 800 kDa) may induce the production of proinflammatory mediators, whereas high-molecular-weight HA (> 1600 kDa) suggests the suppression of proinflammatory mediators. HA shows superior water-retention properties, which provide a conducive environment for cell survival and axonal growth. In the presence of several functional groups within HA, including carboxyl, carbonyl, hydroxyl and amine groups, HA is easily chemically modified with different polymers or incorporated with various bioactive molecules. The ideal biodegradability of HA is realized through enzymatic degradation into nontoxic byproducts that gradually integrate into the host tissue.

Together, the described advantages of HA demonstrate its promising potential for application in nerve regeneration. Buckley et al.[107] modified HA with cysteamine HCl and methacrylic anhydride to obtain thiolated HA (HA-SH) and methacrylated HA (HA-MA) at an approximately 20% modification degree. This modification strengthened the inherent mechanical properties of HA and improved its interaction with receptors. This HA-based nerve conduit effectively loads and releases tyrosol, which has been identified as an effective compound that promotes SC proliferation *in vitro* at physiological pH.

HA represents a principal component of the extracellular matrix, exhibiting exceptional water retention characteristics. Nevertheless, HA hydrogels rapidly degrade *in vivo*, which limits their utility in nerve regeneration. The incorporation of chitosan has been demonstrated to increase resistance to degradation. Consequently, the potential of injectable chitosan-hyaluronic acid hydrogel-filled poly(D,L-lactic acid) (PDLLA)/β-tricalcium phosphate (β-TCP) NGCs with sustained release of NGF for the repair of sciatic nerve defects was explored. These findings indicated that the CS-HA/NGF injectable hydrogel could effectively promote nerve regeneration, indicating its suitability as a promising candidate in the field of neural tissue engineering.[64] Owing to the rapid degradation rate of HA *in vivo*, CS was cross-linked with HA in the presence of ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) to extend its degradation period (**Figure 5D**).[64]

Natural polymers are commonly utilized in the fabrication of nerve conduits, with ongoing debates surrounding the comparative efficacy of different biomaterials for use in nerve guidance conduits (**Table 2**).[69, 72, 75, 87, 91, 93, 94, 106, 108]

Furthermore, bacterial cellulose is known for its high purity, water absorption ability and excellent mechanical properties, which provide an ideal environment for nerve regeneration.[109] This material has potential for use alone or in combination with other biomaterials to promote nerve tissue repair.

There are various challenges for the utilization of biopolymers in preparing NGCs, such as the balance between biocompatibility and biodegradability, high production expenses, complex manufacturing processes, potential immune responses and inflammation. Despite these challenges, the promising potential of biopolymers is driven by a global increase in demand for biodegradable and eco-friendly products. Technological developments such as 3D printing and nanotechnology enable the fabrication of biopolymers into neural conduits with tailored microstructures and functionalities, significantly increasing the efficiency of nerve regeneration. Additionally, supportive policies and positive outcomes from clinical trials are also driving progress in this field. The emergence of new biopolymers, particularly those derived from natural proteins that exhibit excellent biocompatibility, biodegradability, and mechanical properties, suggests substantial potential for applications in neural repair. Therefore, the future prospects for the use of biopolymers in NGC applications are promising.

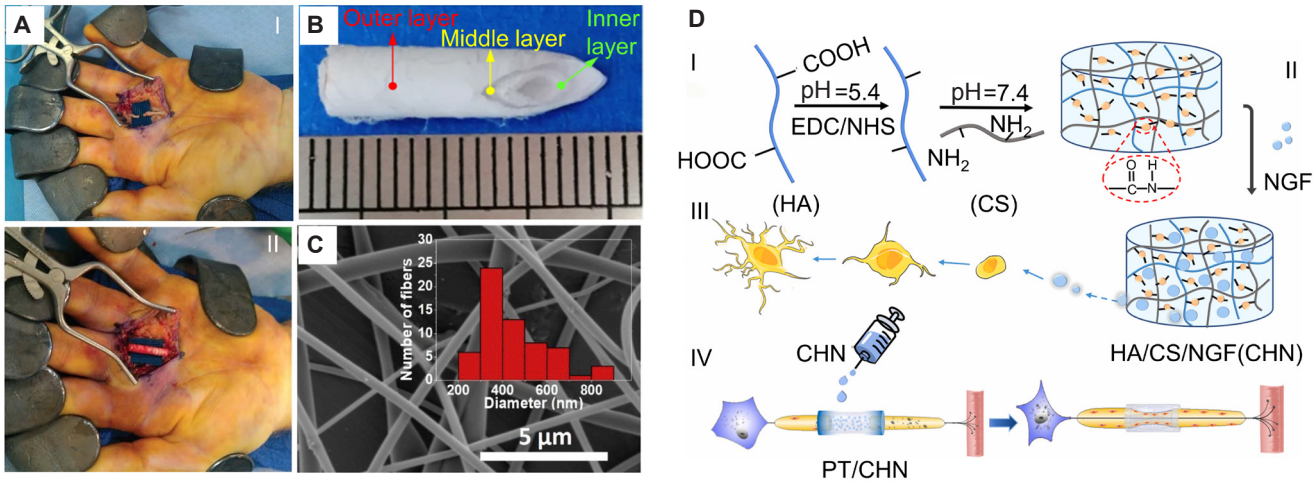

Figure 5: The application of nerve guidance conduits (NGCs).
Note: (A) Exemplar intraoperative photos demonstrating a common digital nerve to long/ring finger laceration before (I) and after (II) implantation of a 3-mm collagen conduit. Reproduced from Deal et al.[71] with permission from Wolters Kluwer Health, Inc. (B) Cross-section image of the conduits showing the triple-layer structure (red color: the outer layer of the triple-layer conduits; yellow color: the middle layer of the triple-layer conduits; green color: the inner layer of the triple-layer conduits). Reproduced from Liu et al.[91] with the permission of Elsevier Science Ltd., UK. (C) SEM images of representative SF-based electrospun fibers. Reproduced from Brito-Pereira et al.[98] with permission from Elsevier Science Ltd., UK. (D)(I) HA/CS synthesis. (II) NGF embedded in the HA/CS hydrogel. (III) The CHN hydrogel promotes neural cell differentiation. (IV) PT/CHN (PDLLA/β-TCP/HA-CS/NGF NGC (PT/CHN)) as a conduit loaded in a CHN hydrogel promotes 1 cm defect nerve regeneration and target muscle reconstruction. Reproduced from Xu et al.[64] with permission from Elsevier Science Ltd., UK. CHN: Chitosan-hyaluronic acid/NGF; CS: chitosan; HA: hyaluronic acid; NGF: nerve growth factor; PT: PDLLA/β-TCP nerve conduits; SEM: scanning electronic microscope; SF: silk fibroin.

Table 2: Controversies and comparisons of biomaterials for nerve guidance conduits

Materials	Effects	Advantages	Disadvantages	References
Collagen	Facilitate nutrients diffusion and waste exchange	Greater biodegradability	Swollen and dissolve in aqueous ambient	69, 72
Chitosan	Improve cell adhesion and neurite outgrowth	biocompatibility, biodegradability, and antimicrobial	Poorly mechanical strength	75
Alginate	Promote myelin regeneration	Significant chemical versatility	Low stability and fast degradation	87, 108
Gelatin	Mimic the native extracellular matrix and improve biocompatibility	Superior immunogenicity.	Poor mechanical properties	91
Silk fibroin	Promote cell adhesion, proliferation and migration, nutrient diffusion and nerve growth and guidance	Superior biocompatibility, tailorable degradation rate	Silk fibroin solution weak and fragile	93, 94
Hyaluronic acid	Influencing cell migration, proliferation, differentiation, and other cell behaviors	Predominant moisture retention ability, nonimmunogenicity and viscoelasticity properties	Low mechanical strength	106

Limitations

Although the review is straightforward and easy to understand, a more thorough examination of methodologies and results included in the studies could be optimized and include more profound insights into the efficacy of biomaterials in NGCs. The management of data across studies may have been constrained by their heterogeneity and complexity, affecting the robustness of the conclusions. The focus on specific biomaterials or applications may limit the generalizability of the findings. The discussion scopes may have influenced the interpretation of the results, emphasizing the need for a more rigorous approach to ensure objectivity.

Conclusion

The repair and regeneration of PNI is a challenging issue in the clinic, and several strategies have

been developed for injury treatment. Although autografts are considered the gold standard for nerve repair, NGCs have gained significant interest as alternatives for addressing donor-site morbidity and immunological rejection attributed to autografts. Owing to their pronounced biocompatibility, negligible immunogenicity, ability to promote cell behavior, and ability to mimic the ECM and versatile natural polymers such as collagen, SF and gelatin, NGCs have demonstrated considerable potential in nerve regeneration. The incorporation of bioactive gradients, SCs and therapeutic agents and the optimization of topographic structure via 3D printing are promising strategies to develop advanced NGCs, which present attractive prospects for nerve repair in the clinic.

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Author contributions

XZ: Literature collection, data curation, analysis, editing, and visualization. LY and YY: Data analysis and reference management. MF: Conceptualization, drafting, editing, and visualization. It is also responsible for intellectual content and visual elements. All the authors approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability statement

Not applicable.

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