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Review Article

Scaffolds for peripheral nerve repair and reconstruction

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ABSTRACT

Trauma-associated peripheral nerve defect is a widespread clinical problem. Autologous nerve grafting, the current gold standard technique for the treatment of peripheral nerve injury, has many internal disadvantages. Emerging studies showed that tissue engineered nerve graft is an effective substitute to autologous nerves. Tissue engineered nerve graft is generally composed of neural scaffolds and incorporating cells and molecules. A variety of biomaterials have been used to construct neural scaffolds, the main component of tissue engineered nerve graft. Synthetic polymers (*e.g.* silicone, polyglycolic acid, and poly(lactic-co-glycolic acid)) and natural materials (*e.g.* chitosan, silk fibroin, and extracellular matrix components) are commonly used along or together to build neural scaffolds. Many other materials, including the extracellular matrix, glass fabrics, ceramics, and metallic materials, have also been used to construct neural scaffolds. These biomaterials are fabricated to create specific structures and surface features. Seeding supporting cells and/or incorporating neurotrophic factors to neural scaffolds further improve restoration effects. Preliminary studies demonstrate that clinical applications of these neural scaffolds achieve satisfactory functional recovery. Therefore, tissue engineered nerve graft provides a good alternative to autologous nerve graft and represents a promising frontier in neural tissue engineering.

1. Introduction

The peripheral nerve is a fragile and unprotected tissue that can be easily damaged by a variety of physical injuries, including road traffic incidents, construction accidents, natural disasters, war damages, sports injuries, drug injection injuries, and electrical injuries (Feinberg et al., 1997; Gu et al., 2011; Noble et al., 1998). Peripheral nerve injury disrupts the messages between the central nervous system and target organs and thus may lead to disorder of motor, sensory, and/or autonomic functions. After injury, the peripheral nerve obtains certain intrinsic capability to repair itself and normally regenerates at the rate of 1–3 mm per day (Gutmann et al., 1942). However, the functional recovery of injured peripheral nerve is not always satisfactory. For severe peripheral nerve injury with a large nerve gap, the spontaneous regeneration is largely limited, successful rehabilitation is almost impossible, and surgery intervention is generally imperative (Lee and Wolfe, 2000; Li et al., 2014).

Currently, for peripheral nerve injury with no nerve tissue loss or a short nerve gap of less than 5 mm long, the commonly used surgical technique is end-to-end suturing (nerve coaptation) (Lee and Wolfe, 2000; Li et al., 2014; Matsuyama et al., 2000). For peripheral nerve injury with a longer nerve gap, direct suture closure will induce excessive tension and lead to inadequate surgical outcomes (Li et al., 2014). Therefore, nerve graft or nerve conduit is needed to be implanted to the gap area to help the establishment of a regenerative tunnel (Flores et al., 2000; Siemionow and Brzezicki, 2009). Implantation of autologous nerve graft collected from other part of the body achieves superior regenerative effect and is now recognized as the gold standard technique (Jiang et al., 2010; Millesi, 2000; Millesi et al., 1972, 1976). However, the transplantation of autologous nerve graft demands the sacrifice of a healthy donor nerve and the performance of at least two surgeries at both the donor site and the recipient site. Additionally, its application is largely restricted by the limited amount of autologous donor nerves for implantation, functional loss at the donor site, structural differences and resultant possible mismatch between the donor and the recipient site, and the possibility of forming neuroma at the donor site (Gu et al., 2011; Heath and Rutkowski, 1998; Panseri et al., 2008; Wang et al., 2001). Emerging attempts have been made to seek a feasible alternative to autologous nerve graft. Some of these alternatives have inherent shortcomings. For example, allogeneic and xenogeneic nerve grafts or other non-neural tissues (*e.g.*, vein and muscle) often come with antigenic and immunological issues (Keane and Badylak, 2015; Wong and Griffiths, 2014). With the fast development of tissue engineering and regenerative medicine, tissue engineered nerve grafts have been widely applied as a potential substitute for autologous nerve graft to repair peripheral nerve injury.

Tissue engineered nerve graft, similar as other engineered tissues, is combined with scaffold, cells, and biochemical and physiochemical

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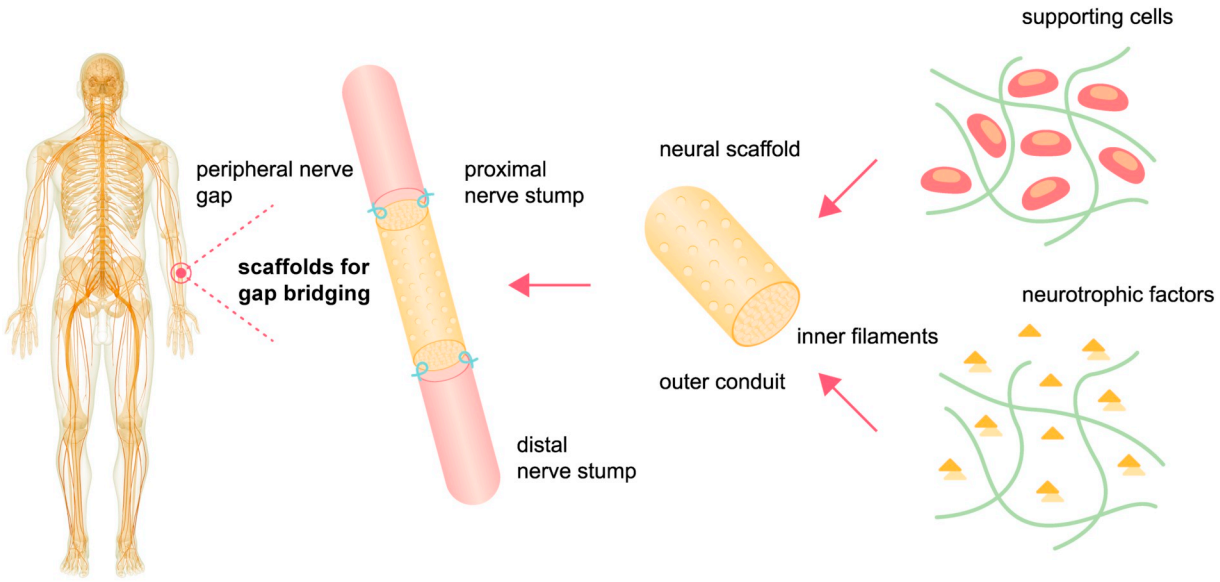

Fig. 1. Schematic representation of the application of tissue engineered nerve graft in repairing injured peripheral nerve. The neural scaffold is typically constructed of an outer porous nerve conduit and numerous inner luminal fillers. Biochemical cues, including supporting cells and neurotrophic factors, are incorporated into the neural scaffold to generate tissue engineered nerve graft. Tissue engineered nerve graft is then implanted to peripheral nerve lesion to bridge nerve gap and guide axonal elongation.

factors (Fig. 1). The scaffold of tissue engineered nerve graft (so called neural scaffold) provides necessary physical support and guides nerve fibers towards target tissue or organ. Neural scaffold also serves as a carrier for cells and biologically active molecules since cells and biochemical cues are generally seeded and incorporated into the scaffold. Therefore, neural scaffold plays a central role in the construction of tissue engineered nerve graft. Considering the significance of neural scaffold in tissue engineering and regenerative medicine, here, we reviewed scaffolds for peripheral nerve regeneration, focusing on the material and design of neural scaffolds. In addition, we introduced the clinical applications of these neural scaffolds and proposed the construction of ideal peripheral nervous system tissue engineering.

2. Materials for neural scaffolds

As far back as Word War II, physicians tried to use bioinert materials such as medical grade silicone and polymethyl methacrylate to repair tissues and organs. These bioinert materials provide mechanical and physical strength for body restoration and support tissue regeneration with few or no adverse response. With the development of regenerative medicine, bioinert materials do not meet the requirements for biomaterials. Scientists are seeking for bioactive materials which not only obtain good mechanical properties but can also interact with the human body and facilitate the regenerative process. Till now, many synthetic and natural materials have been designed and constructed for neural tissue engineering. Commonly used materials for neural scaffolds are listed in Table 1 and specifically introduced in the following section.

2.1. Synthetic materials

2.1.1. Synthetic non-degradable polymers

Synthetic non-degradable polymer silicone is one of the first used materials for nerve repair. Tubulization of a 10 mm long sciatic nerve defect in rat with a single silicone chamber resulted in the regeneration of non-myelinated nerve fibers by 16 days and partial recovery of the titanic force of the gastrocnemius muscle by 120 days (Urabe et al., 1996). Clinical studies showed that the silicone chamber could repair nerve gaps of 3 mm to 5 mm long with excellent motor and sensory recovery after 3 years (Lundborg et al., 1991; Lundborg et al., 1994). A 5-year follow-up study showed that silicone nerve tubulization reached outstanding long-term outcomes (Lundborg et al., 2004).

Since silicone gets a fine result in repairing peripheral nerve injury, silicone has also been used as a template to assess the regenerative effects of biochemical cues. Hepatocyte growth factor added silicone graft showed faster regeneration of axons than the plain silicone graft, indicating that hepatocyte growth factor obtained a promoting effect on peripheral nerve repair (Mohammadi et al., 2013). Injection of let-7d antagomir into implanted silicone tube increased the migration of Schwann cells and the growth of axon fibers, suggesting that let-7d played an inhibitory role on peripheral nerve regeneration (Li et al., 2015).

Besides silicone, some other synthetic non-degradable polymers, such as polyethylene glycol, have also been used in peripheral nerve regeneration. Polyethylene glycol fusion of crush-severed or completely transected rat sciatic nerve retarded Wallerian degeneration, helped the re-establishment of the integrity of axons, and promoted the recovery of hindlimb motor functions (Bittner et al., 2012, 2016; Britt et al., 2010; Riley et al., 2015). However, the effect of polyethylene glycol on peripheral nerve regeneration may be controversial or at least not fully

Table 1
List of commonly used materials for neural scaffolds.

Category		Material	Advantage and disadvantage
Synthetic materials	Non-degradable	Silicone, polyethylene glycol	Stable, easy to made, chronic foreign body reaction
	Degradable	Polyglycolic acid, poly(lactin-co-glycolic acid)	Low immunogenicity, biological inert
Nature materials		Chitosan, extracellular matrix components, other proteins and polysaccharides	Bioactivity, immunogenic response

determined (Bittner et al., 2017; Robinson and Madison, 2016).

It is worth noting that the clinical usage of synthetic non-degradable polymers has its own inherent disadvantages. One of the main issues is that due to their non-degradable properties, these polymers will be left *in situ* after implantation and may induce chronic foreign body reactions. Therefore, a secondary surgery is commonly needed to remove residual materials and avoid long-term side effects (Gu et al., 2011). To solve this problem, synthetic degradable polymers that can dissolve away over time have been investigated and applied in regenerative medicine.

2.1.2. Synthetic degradable polymers

Polyglycolic acid is a polymer that has been used as a biomaterial to repair peripheral neural injury for a long period of time. Neurotube™ (Synovis Micro Companies Alliance, Birmingham, AL, USA), a neural scaffold device designed based on polyglycolic acid, has become commercially available for experimental and clinical use. These polyglycolic acid tubes collapsed and were biodegraded and absorbed *in vivo* after implantation (Ito et al., 2003). Morphological, electrophysical, and functional examinations showed that bridging peripheral nerve gap with a polyglycolic acid tube led to nerve repair and muscle reinnervation (Dellon, 2001; Merrell et al., 1986). The addition of polyglycolic acid fine mesh sheaths could also benefit nerve repair (Lolley et al., 1995). Combining polyglycolic acid tube with undifferentiated bone marrow stem cells or Schwann-like cells differentiated from bone marrow stem cells facilitated rat facial nerve regeneration and obtained better effects than plain polyglycolic acid tube (Costa et al., 2013). Molecular biological studies demonstrated that polyglycolic acid filaments could guide the migration of Schwann cells along filaments and promote the formation of bands of Bungner, showing the advantages of polyglycolic acid polymer from the cellular aspect (Hu et al., 2008).

Polyglycolic acid, when linked with lactic acid by ester linkages, yields a polymerization product called poly(lactic-co-glycolic acid). Poly(lactic-*co*-glycolic acid) is also approved by the Food and Drug Administration for its therapeutic usage due to its biodegradable and biocompatible characterizations. Poly(lactic-co-glycolic acid) conduit, when applied in neural tissue engineering, maintained a stable physical support, inhibited the invasion of exogenous cells, and facilitated peripheral nerve repair and regeneration (Bryan et al., 2004; Chang and Hsu, 2006).

Beside polyglycolic acid and its derivative poly(lactic-*co*-glycolic acid), nerve conduits made from some other synthetic degradable polymers also achieved superior regenerative effects. For example, using a nerve guidance conduit containing an outer poly lactic acid-caprolactone copolymer tube and an inner denatured skeletal muscle segment to bridge a 5 cm gap in rabbit sciatic nerve promoted sciatic nerve regeneration (Mligiliche et al., 2003). The incorporation of adipose-derived stem cells into polycaprolactone nanotube scaffolds further improved the regenerative outcomes when repairing rat sciatic nerve gaps of 15 mm in length (Kim et al., 2014). Nerve tubes made of poly(L-lactide):poly(glycolide) in a ratio of 90:10 and nerve tubes made of (DL-lactide-epsilon-caprolactone) copolyester were used to bridge 10 mm nerve defects in rat sciatic nerve. Both types of synthetic degradable polymers facilitated motor and sensory functional recovery throughout the healing period of 20 weeks (Luis et al., 2007). A comparative study was performed to determine the regenerative effects of a poly-DL-lactide-epsilon-caprolactone conduit, a type-I collagen conduit, a polyglycolic acid conduit, and a reversed nerve autograft in repairing 10 mm excisions of rat sciatic nerves. The functional outcomes of the autografts and the poly-DL-lactide-epsilon-caprolactone conduits were similar and were better than the collagen conduit and the polyglycolic acid conduit (Shin et al., 2009).

2.2. Natural materials

2.2.1. Chitosan

Chitosan is a linear polysaccharide made from chitin that shares many structural similarities with extracellular matrix component glycosaminoglycan. Due to its non-toxic and biodegradable characteristics, chitosan has been widely used as a promising biomaterial for the medical application (Alves and Mano, 2008; Freier et al., 2005; Jayakumar et al., 2007). *In vitro* biocompatibility evaluation showed that chitosan fiber or membrane supported the survival and growth of hippocampal neurons and Schwann cells, suggesting the potential use of chitosan in neural tissue engineering (He et al., 2009; Wrobel et al., 2014; Yuan et al., 2004). Suturing a chitosan neural scaffold into a 10 mm long or a 15 mm long rat sciatic nerve gap could induce a notable motor and sensory functional recovery (Gonzalez-Perez et al., 2015; Simoes et al., 2010). Constructed chitosan nerve guide could also been used to rebuild a long distance peripheral nerve defect in diabetic rat, reaching recovery outcomes similar as autologous nerve grafting (Meyer et al., 2016; Stenberg et al., 2016; Stenberg et al., 2017). Moreover, neurotrophic factors such as nerve growth factor can be immobilized onto chitosan nerve conduits to facilitate peripheral nerve repair (Wang et al., 2012).

Nerve conduits made from both chitosan and synthetic polymers have also been widely used as neural scaffolds. A dual-component artificial nerve conduit containing chitosan as the outer microporous tube and polyglycolic acid filaments as internal oriented fillers was developed to repair peripheral nerve injury. The artificial nerve conduit could bridge and repair a 30 mm long sciatic nerve gap in dog with nerve continuity restoration, neural functional recovery, and target muscle reinnervation (Wang et al., 2005). Such a chitosan/polyglycolic acid nerve graft could also repair a 10 mm long rat sciatic nerve defect which was maintained for 3 to 6 months, suggesting that this nerve graft could be used to repair long-term delayed peripheral nerve injury (Jiao et al., 2009). The artificial nerve graft consisting of a mixture of chitosan and synthetic polymers achieved even greater regenerative capacities after combining with supporting cells. For example, tissue engineered nerve graft constructed with a chitosan/poly(lactic-*co*-glycolic acid)-based neural scaffold and autologous bone marrow mesenchymal cells was used as an alternative to repair a 50 mm long sciatic nerve gap in dog. At 6 months after implantation, injured nerves were regenerated and target muscle was reinnervated (Ding et al., 2010). This tissue engineered nerve graft also effectively bridged a 60 mm dog sciatic nerve defect with similar outcomes as those of autografts (Xue et al., 2012). Likewise, implantation of tissue engineered nerve graft constructed by introducing dorsal root ganglion-derived Schwann cells to a poly(lactic-co-glycolic acid)/chitosan nerve conduit to a 10 mm sciatic nerve lesion in rat led to increased axonal diameter and area as well as improved motor function (Zhao et al., 2014).

Additional studies were performed to test the biological effects of chitooligosaccharides, the degradation product of chitosan. It was reported that chitooligosaccharides obtained defensive effects against neurotoxicity and could protect hippocampal neurons from apoptosis (Hao et al., 2017; Xu et al., 2011; Zhou et al., 2008). Moreover, chitooligosaccharides could increase the survival and proliferation of Schwann cells, enhance the myelination of axon, and increase the release of neurotrophic factors, including nerve growth factor and brain-derived neurotrophic factor (Jiang et al., 2014). Direct intravenous injection of chitooligosaccharides to rabbits with crushed common peroneal nerves elevated the compound muscle action potentials, increased the number of myelinated nerve fibers, increased the thickness of myelin sheaths, and improved the cross-sectional area of tibialis posterior muscle fibers (Gong et al., 2009). Repairing a 10 mm long sciatic nerve defect in rat with a silicone tube filled with chitooligosaccharides also accelerated peripheral nerve regeneration. Mechanical studies showed that the beneficial effect of chitooligosaccharides was through stimulating Schwann cell proliferation,

increasing macrophage infiltration, and establishing a permissive microenvironment (Wang et al., 2016; Zhao et al., 2017).

2.2.2. Extracellular matrix components and their derivatives

Many commonly used natural materials for the constructions of neural scaffolds are components of the extracellular matrix, *e.g.* collagen, laminin, fibronectin, glycosaminoglycan, and elastin. Collagen, as the most abundant protein and the main structure protein in the human (Di Lullo et al., 2002), has been widely applied in the field of tissue engineering and regenerative medicine. Entubulation repair of a 4 mm long median nerve gap in rat or *Macaca fascicularis* monkey with a collagen-based nerve guide conduit, compared with nerve autografting, achieved similar evoked muscle action potentials (Archibald et al., 1991). Bridging a 5 mm long median nerve gap in *Macaca fascicularis* monkey with a collagen nerve guide tube, compared with the nerve graft, gained similar nerve fiber diameters, myelin G-ratios, and recovery rates of the compound muscle action potential amplitudes and the compound sensory action potential amplitudes (Archibald et al., 1995). Comparative experimental results suggested that rats repaired with collagen nerve conduits exhibited significantly better isometric muscle contraction force, axonal count, wet muscle weight, and axonal sprouting organization as compared with rats repaired with polyglycolic acid nerve conduits (Waitayawinyu et al., 2007). Gelatin, an irreversibly hydrolyzed and thermal denatured form of collagen, has also been used in neural tissue engineering (Chang et al., 2009; Koudehi et al., 2014; Tonda-Turo et al., 2017). Aligned gelatin fibers regulated Schwann cell phenotype, modulated axon organization, and thus could be used as promising internal fillers for the construction of tissue engineered nerve grafts (Gnavi et al., 2015). Aligned and random polycaprolactone/gelatin nanofibrous scaffolds also exhibited good biocompatibility and cellular affinity with Schwann cells (Gupta et al., 2009). Nowadays, collagen has been made into commercially available products, such as NeuraGen®, NeuroWrap™ (Integra Life Sciences Corp., Plainsboro, NJ, USA), Neuro*flex*®, NeuroMatrix®, and NeuroMend® (Collagen Matrix Inc., Oakland, NJ, USA) for repairing crushed, compressed, or severed nerves (Deumens et al., 2010; Gu et al., 2014a; Kehoe et al., 2012).

Besides collagen, many other components of the extracellular matrix have also been used to construct neural scaffolds. Laminin, a heterotrimeric extracellular matrix protein that regulated the proliferation, differentiation, and myelination of Schwann cells and the regeneration of axons (Chen and Strickland, 2003; Yu et al., 2007), could be used to build a neural graft for bridging an 8 mm sciatic nerve gap in rat (Kauppila et al., 1993). Laminin nanofiber meshes promoted cellular attachment and enhanced neurite extension without growth factor stimulation (Neal et al., 2009). Blended laminin and polycaprolactone aligned nanofibers retained the advantages of laminin, guided directional nerve outgrowth, and yielded good sensory function recovery in a 10 mm tibial nerve gap in rat (Neal et al., 2012). Fibronectin, a prominent glycoprotein that regulated cellular adhesion and migration (Austria and Couchman, 1991), could modulate the migration and adhesion of Schwann cells as well as the outgrowth of neurites (Ahmed and Brown, 1999; Mukhatyar et al., 2011). Orientated mats or cables of fibronectin could function as nerve conduits to promote the repair of injured nerves (Underwood et al., 1999; Underwood et al., 2001). Hyaluronic acid, an abundant non-sulfated form of glycosaminoglycan that promoted cell proliferation and migration and advanced wound healing (Neuman et al., 2015; Toole, 2004), could also be fabricated to neural scaffolds for nerve tissue engineering (Suri et al., 2011; Suri and Schmidt, 2010). Neural scaffolds designed based on elastic protein elastin or elastin-like polypeptides were also identified as ideal nerve conduits (Girotti et al., 2004; Hsueh et al., 2014).

Notably, different components of the extracellular matrix have been jointly used to repair peripheral nerve injuries. For example, a nano-silver-embedded collagen scaffold coated with laminin and fibronectin could partially restore the nerve function of a 10 mm long severed sciatic nerve in rat, gaining a comparable effect of an autologous nerve graft (Ding et al., 2011). Similarly, collagen-glycosaminoglycan (chondroitin-6-sulfate) matrix was filled into a collagen nerve conduit to repair a unilateral 10 mm long sciatic nerve gap in rat. The joint use of collagen and glycosaminoglycan achieved better function motor recovery than collagen alone (Lee et al., 2012). Schwann cells could also grow and migrate along aligned collagen-glycosaminoglycan matrix, suggesting that collagen-glycosaminoglycan matrix could mimick Schwann cell basal lamina and provide a growth-permission microenvironment for nerve regeneration (Shakhbazau et al., 2014).

Components of the extracellular matrix have also been jointly used with chitosan to bridge long sciatic nerve gaps. For instance, laminin-coated collagen fibers were filled into a collagen/polyglycolic acid tube to make an artificial nerve conduit. This artificial nerve conduit, after implanting to an 80 mm long lesion in the left peroneal nerve in dog, could guide nerve repair and elongation and lead to functional establishment (Matsumoto et al., 2000). Chitosan tubes immobilized with laminin peptides (peptide sequences CDPGYIGSR, CSRARKQAASIKVAVSAD, or YIGSR) were applied to repair sciatic nerve lesions of 15 mm long in rats. Electro-physiological and histological examinations demonstrated that the application of modified chitosan tubes led to increased percentage of neural tissue and evoked muscle action potentials (Itoh et al., 2005; Itoh et al., 2003). Likewise, bridging a 15 mm long rat sciatic nerve gap by using a chitosan nerve conduit prefilled with collagen, laminin, or fibronectin induced Schwann cell migration, attained muscle reinnervation, and promoted nociceptive sensibility recovery (Gonzalez-Perez et al., 2017).

2.2.3. Other natural proteins and polysaccharides

A variety of other natural proteins and polysaccharides, including alginate, keratin, spider silk protein, and silk fibroin protein, have also been used in neural tissue engineering alone or in combination with other components.

Alginate, also called alginic acid, is a commonly distributed polysaccharide in the cell walls of brown algae. Alginate could promote the viability and growth of Schwann cells and enhance the sprouting of neurite from embryonic dorsal root ganglia neurons (Mosahebi et al., 2001; Novikova et al., 2006). An interpolation of two pieces of alginate sponge or a polyglycolic acid mesh tube filled with alginate sponge was used to repair of a 50 mm sciatic nerve gap in cat, gaining successful axonal elongation and reinnervation (Sufan et al., 2001). The joint use of fibronectin and alginate achieved enhanced regenerative outcomes as well (Mosahebi et al., 2003).

Keratin is a key fibrous structural protein found in human hair that protects cells against damage or stress. *In vitro* study suggested that keratin could enhance the attachment and proliferation of Schwann cells (Sierpinski et al., 2008). *In vivo* application of neural scaffolds derived from keratin could effectively repair a 4 mm tibial nerve defect in mouse (Sierpinski et al., 2008), a 10 mm sciatic nerve defect in rat (Pace et al., 2013), and a 15 mm sciatic nerve defect in rat (Apel et al., 2008; Lin et al., 2012). Keratin hydrogen filled NeuraGen® conduits successfully repaired 10 mm median nerve defects in *Macaca fascicularis* monkeys with enhanced motor recovery and accelerated nerve regeneration (Pace et al., 2013).

Spider silk protein is harvested from spider dragline silk. The spider silk protein possesses outstanding tensile strength, good elasticity, and long-term biodegradability. Cultured Schwann cells could adhere rapidly on spider silk fibers, making spider silk protein a competitive natural material for building neural scaffolds (Allmeling et al., 2006). Silk protein conduit containing spider silk protein based Spidrex® fibers could support neurite outgrowth *in vitro* and repair an 8 mm gap in rat sciatic nerve *in vivo* (Huang et al., 2012). A neural scaffold consisted of decellularized vein graft and spider silk fiber fillers could bridge a 20 mm sciatic nerve gap in rat (Allmeling et al., 2008) and a 60 mm tibial nerve gap in sheep (Radtke et al., 2011). To obtain moderate strength and flexibility, a regenerated spider silk protein fibrous

scaffold was fabricated by electrospinning and post treated with acetone (Yu et al., 2014). The regenerated spider silk protein was mixed with lysine-doped polypyrrole and poly(l-lactic) acid to generate a composite scaffold. The composite nerve conduits, after mixing with nerve growth factor, increased the migration of Schwann cells, promoted the regrowth of axon, and effectively bridged a 20 mm sciatic nerve gap in rat within 10 months (Zhang et al., 2015).

Besides silk protein from spider dragline silk, silk protein from the silkworm *Bombyx mori*, named silk fibroin protein, has also been broadly used in material science and regenerative medicine. Silk fibroin-based biomaterials supported the survival and growth of rat dorsal root ganglia neuron cells, hippocampal neuron cells, and Schwann cells and have good biocompatibility with peripheral nerve tissues and cells (Tang et al., 2009; Yang et al., 2007; Zhao et al., 2013). Neural scaffold constructed with silk fibroin protein was able to bridge peripheral nerve gap and guide nerve regeneration (Tang et al., 2012; Yang et al., 2011). Tissue engineered nerve graft constructed with silk fibroin scaffold and supporting cells (*e.g.*, rat bone marrow mesenchymal stem cells, dorsal root ganglia neuron cells, and Schwann cells) could repair peripheral nerve gap in rat with accelerated axonal growth and improved functional recovery (Tang et al., 2012; Yang et al., 2011). Silk fibroin could also be blended with collagen at a certain ratio to prepare an artificial scaffold with good biocompatibility and mechanical property. Transplantation of silk fibroin/collagen neural scaffolds seeded with co-cultured Schwann cells and adipose-derived stem cells accelerated nerve regeneration and successfully repaired 10 mm long sciatic nerve defects in rats (Xu et al., 2016). Supporting cells, such as allogeneic bone marrow mononuclear cells, could also be seeded onto an artificial neural scaffold consisting of an outer collagen nerve conduit tube and many inner silk fibroin filaments for neural tissue engineering. The developed tissue engineered nerve graft benefited axonal regrowth and achieved outstanding regenerative outcomes when repairing a 10 mm long sciatic nerve gap in rat (Yao et al., 2016).

2.3. The extracellular matrix

Besides the broad applications of various extracellular matrix proteins and polysaccharides in neural tissue engineering, nowadays, the extracellular matrix itself has been used as an appealing alternative to autograft. The extracellular matrix is composed of the interstitial matrix and the basement membrane. The extracellular matrix obtains unique three-dimensional structure and functions as a physical and mechanical support for surrounding cells. Moreover, the extracellular matrix provides biochemical signals to affect cellular behaviors and participates in tissue morphogenesis and remodeling (Yi et al., 2017).

A commonly used way of the extracellular matrix in tissue engineering is to remove cells from the entire tissue and/or organ to obtain decellularized biomaterial with minimized immune responses and side effects. Detergent or detergent-free decellularized donor sciatic nerve graft, after implanting into a 35 mm sciatic nerve gap in rat for 12 weeks, showed comparable regeneration and functional recovery (Vasudevan et al., 2014). Chemically decellularized peroneal nerve graft was also implanted into peroneal nerve defect in rat. It enhanced axonal regeneration, promoted functional reinnervation, and repaired a 20 mm long gap in rat. However, this decellularized nerve graft failed to reconstruct a 40 mm long gap in rat (Haase et al., 2003). Another study also showed that when repairing longer peripheral nerve gaps (20, 40, and 60 mm long), the regenerative effect of decellularized nerve allograft was not as good as autograft. The limitation in axonal regeneration might be related with increased senescence of Schwann cells (Saheb-Al-Zamani et al., 2013). Considering the significant role of Schwann cells in the process of peripheral nerve repair, our group innovatively applied Schwann cell-derived extracellular matrix in neural tissue engineering. Briefly, we cultured Schwann cells, collected the extracellular matrix derived from Schwann cells, and assembled Schwann cell-derived extracellular matrix into a chitosan/silk fibroin scaffold to construct an extracellular matrix-based tissue engineered nerve graft. The assembled nerve graft successfully bridged a 10 mm sciatic nerve defect in rat, gaining similar regenerative outcomes as decellularized nerve graft (Gu et al., 2014b). We further collected the extracellular matrix derived from bone marrow mesenchymal stem cells and found that bone marrow mesenchymal stem cell-derived extracellular matrix could also facilitate peripheral nerve repair. The implantation of chitosan/silk fibronin based, bone marrow mesenchymal stem cell-derived extracellular matrix-modified neural scaffold into a 10 mm long rat sciatic nerve gap achieved good regenerative outcomes (Gu et al., 2017). Similarly, skin derived precursor Schwann cell-generated acellular matrix modified chitosan/silk scaffolds was generated and used to bridge a 10 mm long rat sciatic nerve gap. The regenerative effects of the engineered neural scaffold were better than a plain chitosan-silk fibroin scaffold (Zhu et al., 2017).

2.4. Other materials

Many other materials, such as glass fabric, ceramics, and metallic materials, have been implanted to peripheral nerve lesions for the regenerative purpose. For example, fibers of bioresorbable glass 45S5 permitted the growth of Schwann cells and fibroblasts and guided axon regeneration across a 5 mm sciatic nerve gap in rat (Bunting et al., 2005). Another biodegradable and biocompatible glass, corglaes, was made to a flexible and porous wrap to repair a 5 mm long median nerve lesion in sheep (Jeans et al., 2007a, b). Bioglass nanoparticles could be mixed with gelatin to build a nano-bioglass/gelatin conduit for peripheral nerve repair (Koudehi et al., 2014). Glass fabric materials was also directly placed under cut end to repair facial nerve injury (Starritt et al., 2011). Yttrium and cerium doped SiO_2-SrO-Na_2O glass-ceramics directly contacted with Schwann cells, allowed the attachment and spreading of Schwann cells, and exhibited good bioactivity (Placek et al., 2016). Aluminum based Al/AI_2O_3 nanowires led to the alignment of axons and the contact guidance of rat dorsal root ganglion neurites (Lee et al., 2013). Magnesium and its alloys NZ20 (Mg-2Nd-Zn), ZN20 (Mg-2Zn-Nd), and Mg−10Li showed excellent cytocompatibility to dorsal root ganglion neurons with no toxicity, indicating that those alloys could be used as potential neural scaffolds for nerve regeneration (Fei et al., 2017).

3. Configuration and fabrication of neural scaffolds

In addition to the material property of neural scaffold, the structure and surface feature of biomaterial are also very important for the repair of injured peripheral nerves. Emerging studies show that the three-dimensional shape and texture of neural scaffold not only provide a passive structure for mechanical support, but also directly affect cellular attachment and cell fate (Kloczko et al., 2015; Zhou et al., 2013). Hence, the topography of neural scaffolds and relevant fabrications are discussed here.

3.1. Topographic structures

Considering the tube-like structure of nerves, neural scaffold was designed as a single hollow lumen nerve guidance conduit in early days. Constructed single hollow conduit generally is sufficient to repair short nerve gap. However, when repairing long distance gap, for example 2–3 cm long nerve gap in human and 1 cm long nerve gap in rat, the cylindrical nerve guidance conduit may lead to the dispersion of regenerating axons due to its hollow architecture (Brushart et al., 1995). Intraluminal channels or microtubes are incorporated into the single hollow conduit to generate a multichannel nerve conduit that mimics the architecture of nerve fascicles. The generated multichannel nerve conduit, compared with the single hollow conduit, achieved better outcomes in axonal regeneration when repairing a 1 cm gap of rat sciatic nerve, demonstrating the superiority of the multichannel nerve

conduit over the single hollow lumen conduit (Yao et al., 2010). However, the permeability, flexibility, and material degeneration of multichannel nerve conduits may be not as good as single hollow conduits (de Ruiter et al., 2008; Gu et al., 2011). To overcome these disadvantages, nerve conduits with physical lumen fillers are built by directly inserting filaments into the inner space of nerve tubes. This modification allows axons to grow and elongate along incorporated luminal fillers and thus largely avoids inappropriate axon dispersion and corresponding inaccurate target reinnervation. Moreover, this modification enlarges surface area and benefits the attachment of supporting cells and neurotrophic factors. Nowadays, a typical neural scaffold for neural tissue engineering is normally consisted of an external nerve conduit and many incorporated physical luminal fillers (Gu et al., 2011). The external conduit and the inner filament can be made of the same material, different materials, or blended materials (Gu et al., 2011). Synthetic polymers and natural materials are often jointly used to take the advantage of the superior mechanical properties and degradation abilities of synthetic polymers as well as the excellent biocompatibilities of natural materials (Tian et al., 2015).

3.2. Fabrication techniques

Multiple fabrication techniques, including freeze-drying and electrospinning, have been used to construct neural scaffolds. Freeze-drying technique can directly freeze water based polymer solutions and straightforwardly turn water phase materials to the gas phase. After sublimation, water is completely removed while the basic structures and compositions of materials are left intact. Freeze-drying technique is commonly used to construct outer nerve conduit, especially outer nerve conduit made of natural materials. By using freeze-drying technique, porous structures can be made. The porous structures benefit the infiltration of cells and blood vessels as well as the exchange of nutrients and gases.

Electrospinning technique is an electrostatic fiber production method that can manufacture randomly or longitudinally aligned nanofibers without using coagulation chemistry (Bhardwaj and Kundu, 2010). Electrospinning is a fiber production technique that commonly used to produce submicron-sized filaments by using electric force. Cylindrical nerve conduits can also be made by continuous rolling up jetted fibers (Wang et al., 2013). By using electrospinning technique, we can manufacture a scaffold with a structure that is similar as the natural extracellular matrix, including a variable degree of porosity, an adjustable mechanical strength, and a high surface to volume ratio that facilities cellular and molecular attachment (Chiono and Tonda-Turo, 2015; Sill and von Recum, 2008). Therefore, a typical tissue engineered nerve graft containing an outer nerve conduit and many inner filaments can be produced by the joint use of freeze-drying and electrospinning techniques (Fig. 2). Other techniques, such as injection molding, dip coating, porogen leaching, solvent or non-solvent induced phase separation, thermally induced phase separation, and laser-based fabrication have been applied in neural tissue engineering and regenerative medicine as well (Chiono and Tonda-Turo, 2015; Rajaram et al., 2012). Emerging studies have shown that rapid prototyping, a novel fabrication process that uses computer-aided design technique to fabricate complex architectures, has many benefits (Billiet et al., 2012; Derby, 2012). Rapid prototyping technique includes membrane lamination, ink-jet printing, fused deposition modeling, three-dimensional printing, and three-dimensional bioplotting. This advanced technique allows the design of a neural scaffold with customized structural integrity, controllable mechanical strength, and reproducible porosity and density (Hoque et al., 2012). These advantages make rapid prototyping technique a promising fabrication method for the generation of neural scaffolds for the treatment of peripheral nerve injuries.

3.3. Incorporation of cells and neurotrophic factors

The properties of neural biomaterials, including material nature, orientation, and construction, fundamentally determine their restoration effects. Meanwhile, the recovery outcomes may be largely improved by the addition of cells and bioactive molecules (Saracino et al., 2013). From experimental studies mentioned above, it is suggested that the combination of Schwann cells, bone marrow stem cells, bone marrow-derived mononuclear cells, or adipose-derived mesenchymal stem cells to neural scaffolds facilitates axon growth and target organ reinnervation. Many other undifferentiated and multipotent cells also show great potential in promoting peripheral nerve regeneration and can be incorporated into neural biomaterials as supporting cells. For instance, it was demonstrated that the implantation of embryonic stem cell-derived neural progenitor cells into rat sciatic nerve gap could stimulate the regrowth and myelination of axons and advance the reconnection between proximal and distal nerve stumps (Cui et al., 2008). Transplantation of human hair follicle pluripotent stem cells into severed mouse sciatic nerve induced their differentiation into Schwann cells and led to nerve regeneration (Amoh et al., 2009). Tubulization of collagen nerve conduits filled with dental pulp stem cells in pig peripheral nerve defects resulted in morphological and function recovery as well (Spyridopoulos et al., 2015). Neural stem cells, the multipotent cells that can generate neurons and glial cells, also enhanced nerve regeneration when used to treat peripheral nerve injury (Lee et al., 2017; Xu et al., 2012). Additionally, emerging studies showed that induced pluripotent stem cells also accelerated the regeneration of injured peripheral nerves (Ikeda et al., 2014; Uemura et al., 2011; Wang et al., 2011).

Neurotrophic factors showed great potential in their applications in neural tissue engineering as well. Neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4/5, glial cell-lined derived neurotrophic factor, ciliary neurotrophic factor, and various neuropoeitic cytokines, promote neuronal survival, stimulate axonal sprouting, and provide significant biochemical cues for the functional recovery of injured nerves (Boyd and Gordon, 2003; Gu et al., 2011). Therefore, advanced immobilization and fabrication techniques that improve the delivery of neurotrophic factors and allow prolonged and controlled release of active neurotrophic factors from neural scaffolds will largely contribute to peripheral nerve regeneration and should become one of the research priority areas in regenerative medicine (Gu et al., 2014a).

4. Clinical trials

Till now, besides the use of silicone, various other novel biomaterials have been approved by supervisory organizations such as the US Food and Drug Administration, Conformit Europe, and China Food and Drug Administration for clinical trials (Meek and Coert, 2008). These approved neural scaffolds and tissue engineered nerve grafts have basically gained delightful outcomes for treating human patients with peripheral nerve injury.

Synthetic polymers have been commonly applied in neural tissue engineering. An assessor-blinded and randomized clinical study showed that according to the British Medical Research Council score and the manual muscle test, patients treated with poly[(R)-3-hydroxybutyrate] received better sensory recovery than patients treated with epineural end-to-end suturing (Aberg et al., 2009). Suturing injured inferior alveolar nerve into a custom-designed polyglycolic acid tube relieved facial nerve pain as well as perception of pressure and vibration (Crawley and Dellon, 1992). Polyglycolic acid tubes were used to bridge nerve defects of 5 mm to 30 mm long in 15 patients. Comparable to the outcomes of classic nerve graft techniques, 40% patients got excellent nerve reconstruction and 33% patients got good nerve reconstruction (Mackinnon and Dellon, 1990). In another study, treatments with polyglycolic acid conduits obtained 44% excellent results

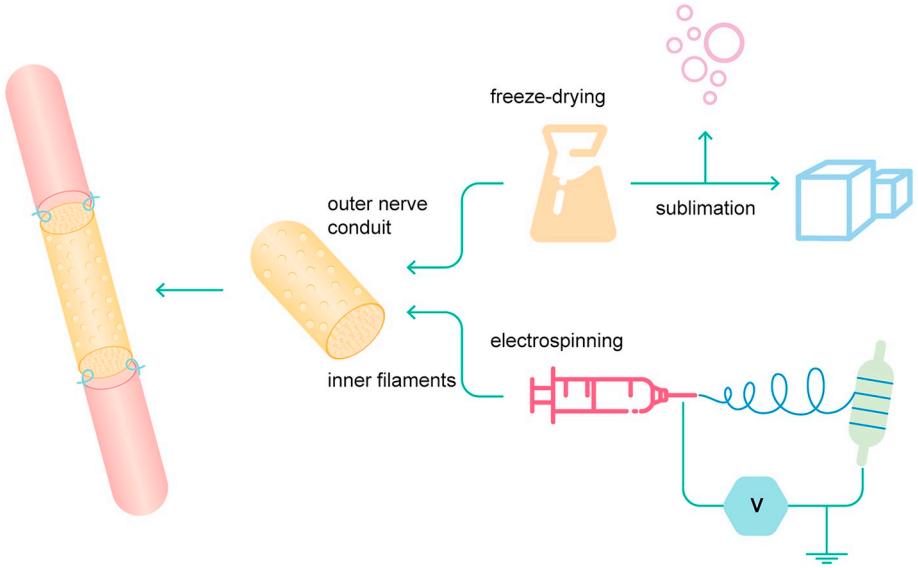

Fig. 2. Schematic representation of fabrication techniques for constructing a neural scaffold. External nerve conduit is normally constructed by freeze-drying while inner filaments are normally constructed by electrospinning.

and 30% good results. The recovery rate of polyglycolic acid conduit was comparable to the recovery rate of standard repair technologies such as end-to-end suturing and nerve graft transplantation in repairing nerve gap of 4 mm or less and was even higher when repairing longer nerve gap (Weber et al., 2000). From the economic aspect, using polyglycolic acid neural scaffolds to reconstruct injured peripheral nerves is also very cost effective (Mundinger et al., 2012). Similar as polyglycolic acid conduits, biodegradable Neurolac nerve guides made from poly(DL-lactide-epsilon-caprolactone) (Polyganics B.V., Groningen, the Netherlands) were used to repair peripheral nerve defects up to 20 mm in the hand. 17 patients received Neurolac nerve guides and gained sensory recovery. The recovery effect was at least as good as 13 patients in the end-to-end suturing group (Bertleff et al., 2005). Neurolac® nerve conduits (Polyganics Innovations, Groningen, Netherlands) made from polycaprolactone were used to repair 12 patients with nerve gaps less than 25 mm. Physical examinations by monofilament testing and 2-point discrimination demonstrated that the applications of Neurolac® nerve conduits assisted peripheral nerve repair (Costa Serrao de Araujo et al., 2017).

Nerve conduits made from extracellular matrix component collagen has been used to treat patients with large-diameter gaps between 10 and 20 mm. Most patients reported free of pain, low disability scores, and superior functional recovery (Dienstknecht et al., 2013; Klein et al., 2016; Taras et al., 2011). A two year follow-up study of 43 patients with 44 nerve lacerations showed that using collagen nerve conduits to repair nerve gaps of less than 6 mm long generated sensory and motor function recovery equivalent to direct suturing (Boeckstyns et al., 2013).

Neural tubes designed by combining synthetic polymers and natural biomaterials have also been used in clinical trials. A cylindrically woven polyglycolic acid tube filled with a collagen sponge was used to repair a patient with a 20 mm long proper digital nerve defect or a patient with a 65 mm long superficial peroneal nerve defect. Both patients got objectively functional recovery (Inada et al., 2004). This designed bioabsorbable nerve tube also successfully reconstructed nerve of patient with posttraumatic unilateral eyebrow ptosis for 3 months (Inada et al., 2007). A chitosan/polyglycolic acid nerve guidance conduit developed in our laboratory achieved outstanding clinical results as well. The tubulization of a chitosan/polyglycolic acid artificial nerve graft for a 35 mm long median nerve defect at elbow of a 37 year-old patient obtained British Medical Research Council score of M4 and $S3^+$ level motor and sensory function during a 3 year follow-up period (Fan et al., 2008). The chitosan/polyglycolic acid nerve conduit also helped the functional recovery of an older patient (55 year-old) with a 30 mm long median nerve lesion. The implantation of the neural scaffold largely improved patient's palm abduction of the thumb and the thumb-index digital opposition, compound muscle action potentials, and perspiration function, reaching a $S3^+$ level recovery at thirty-six months after nerve repair. After surgery, the patient could even execute fine activities such as writing and chopstick handling for picking up coins (Gu et al., 2012).

5. Potential challenges and future perspectives

Peripheral nerve injury affects about 13 to 23 per 100,000 persons and leads to heavy social and economic burdens (Li et al., 2014; Tian et al., 2015). Autologous nerve graft transplantation, the gold standard for peripheral nerve injury treatment, despite its intrinsic drawbacks such as limited availability, only achieves a success rate of about 40% to 50% (Lee and Wolfe, 2000). The rapid and brilliant progress of tissue engineered nerve graft offers the prospect of supplying or even replacing autologous nerve graft in peripheral nerve injury treatment. Great efforts should be devoted to develop the key element of tissue engineered nerve graft, neural scaffold.

After implantation, the neural scaffold constitutes an appropriate physical and mechanical support substituting for the Schwann cell basal laminae, functions as a bridge to guide axon sprouting from the proximal nerve stump to the distal nerve stump, releases neurotrophic factors and other incorporated biochemical cues, and creates a permissive microenvironment for nerve repair. The neural scaffold must have certain safety and effectiveness. Moreover, an ideal neural scaffold should obtain sufficient mechanical property that help it to resist *in vivo* physiological loads, sufficient biocompatibility with no undesirable side effects, controllable biodegradability that matches the growth rate of regenerative nerves, certain porosity that allows nutrient and gas transport and blood vessel grow-in, as well as scaffold surface modification and functionalization (Chiono and Tonda-Turo, 2015; Gu et al., 2014a, 2011).

Although artificial tissue engineered nerve grafts developed rapidly, the clinical recovery effects of state-of-art neural scaffolds are still not fully satisfactory, specifically for repairing extremely long nerve gaps. Notably, the successful repair and regeneration of injured peripheral nerves requires not only a local permissive microenvironment for axonal regrowth but also the survival of the damaged neurons and the activation of neuronal intrinsic growth capacity. Neural scaffolds and

immobilized supporting cells and/or neurotrophic factors contribute to axonal outgrowth and nerve reinnervation. However, currently constructed neural scaffolds generally do not affect the intrinsic regenerative capability of neurons. The intrinsic regenerative capability of neurons is normally activated by factors such as the intracellular cyclic adenosine monophosphate (cAMP) (Chen et al., 2007). The joint use of neural scaffolds and activators of the intrinsic regenerative capability of neurons may further facilitate peripheral nerve repair and regeneration. Another barrier of the functional recovery of injured peripheral nerves is the in-accurate path-finding and the mismatch of regenerated axons (Gu et al., 2011). Following peripheral nerve injury, axons sprouts may not grow straightly along their original basal lamina tubes and thus may not connect with their target organs after outgrowth. A neural scaffolds with architecture of a nerve conduit filled with inner filaments, compared with a single hollow nerve conduit, reduces the mismatch of axons and the inappropriate reinnervation of nerves. A more profound understanding of the cellular and molecular mechanisms of axon path-finding is needed to improve the development of neural scaffolds (Gu et al., 2011).

Overall, treatment of peripheral nerve injury has come a long way from direct suturing closure. Current and emerging strategies for the constructions of tissue engineered nerve grafts have given a good prospect for peripheral nerve repair and regeneration. Preliminary clinical trials and case studies have also shown many effective outcomes. Engineers, scientists, and clinicians should work together to overcome existing challenges, explore effective tissue engineered nerve grafts, and achieve a step forward from bench to bedside.

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Conflicts of interest

None.

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