RESEARCH ARTICLE

Tissue engineering for the repair of peripheral nerve injury

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Abstract

Peripheral nerve injury is a common clinical problem and affects the quality of life of patients. Traditional restoration methods are not satisfactory. Researchers increasingly focus on the field of tissue engineering. The three key points in establishing a tissue engineering material are the biological scaffold material, the seed cells and various growth factors. Understanding the type of nerve injury, the construction of scaffold and the process of repair are necessary to solve peripheral nerve injury and promote its regeneration. This review describes the categories of peripheral nerve injury, fundamental research of peripheral nervous tissue engineering and clinical research on peripheral nerve scaffold material, and paves a way for related research and the use of conduits in clinical practice.

Key Words: *nerve regeneration; scaffold; biomaterial; stem cells; nerve growth factor; peripheral nerve injury; peripheral nerve repair; tissue engineering; neural regeneration*

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Introduction

Repair of peripheral nerve injury is currently an important research field in neurosurgery and one that presents many difficulties (White et al., 2015). Surgical repair of peripheral nerve injury is different from the unique conditions required for the regeneration of the central nervous system (Hu et al., 2009). Various researchers have concentrated on different surgical repair procedures to better promote fiber regeneration across the abutment joint, as well as to protect the distal target organs effectively. The main tissue-engineering repair methods for peripheral nerve injury are shown in **Table 1**. The difficulties of repairing peripheral nerve injury have been reported (Jiang et al., 2006; Gu et al., 2014; Oprych et al., 2016). The three main concerns are (1) the effective and accurate connection of fibers with different characteristics, such as sensory and motor nerves in both distal and proximal ends of the injury site. (2) Whether the proximal end provides enough nerve fibers to innervate the proximal target organ. (3) To keep the motor end plates of distal target organ from destabilizing and minimize muscle atrophy before the regenerating proximal nerve fibers grow into and innervate the target organ. The aim of this review is to summarize the progress in tissue engineering for the peripheral nerve, to help newcomers familiarize themselves with this field and promote the development of the repair of peripheral nerve injury.

An electronic search of the Medline database for literature describing tissue-engineering for repair of peripheral nerve injury from its inception to 2018 was performed using the following conditions: ("peripheral nerve injuries" [MeSH terms] OR ("peripheral" [all fields] AND "nerve" [all fields] AND "injuries" [all fields]) OR "peripheral nerve injuries" [all fields] OR ("peripheral" [all fields] AND "nerve" [all fields] AND "injury" [all fields]) OR "peripheral nerve injury" [all fields]) AND ("tissue engineering" [MeSH terms] OR ("tissue" [all fields] AND "engineering" [all fields]) OR "tissue engineering" [all fields]). The results were further screened by title and abstract to present animals and humans. Non-peripheral nerve injury experiments were excluded.

Overview of Peripheral Nerve Injury

Peripheral nerve injury can be divided into several categories: neuropraxia, axonotmesis, neural mutilation and nerve defect (Al-Majed et al., 2000). The axillary, musculocutaneous, median, radial, ulnar, femoral, sciatic and peroneal nerves and the brachial plexus are all relatively easy to damage. Physical and sensory disorders of the extremities are the main symptoms. Surgical repair, decompression, lysis and functional exercise are important in recovering the function of a peripheral nerve (Sosa et al., 2005). The aim of the treatment is to promote nerve regeneration, maintain muscle mass, enhance muscle strength and promote functional recovery. Conservative treatment is relatively simple, while various types of scaffold materials can be used in surgical treatment (Yang et al., 2011).

Table 1 Summary of current tissue-engineering repair methods for peripheral nerve injury

Research field	Categories and types	Superiority	Shortcomings	Repair scheme	Experimental model	Key result measures
Artificial synthetic material	PLA, PCL, PGA, and PLGA	Accelerate the repair process, guide the migration of Schwann cells, induce the formation of normal nerve structure, have good mechanical properties for repair long nerve defect, and good biocompatibility and biodegradability	Polymer monomers cost a lot of time and money, poor elasticity and hardness	Peripheral nerve scaffold, tube, and microspheres	Peripheral nerve defect and repair model in rat, rabbit, and primates	Number and morphology of regenerating myelinated fibers, nerve function index, nerve conduction velocity, motor end plate and triceps surae muscle morphology
Natural biomaterial	Type I collagen, gelatin, silk fibroin, and tropoelastin	Good arrangement and structure, aperture size, promote the release of related factors, providing more nutritional factors and more suitable microenvironment, make the repair process more convenient	Poor mechanical properties and waterproof effect, brittle and easy to fracture	Same as above	Same as above	Same as above
New type degradable material	Chitosan, graphene, and alginate	Give a relatively stable regeneration microenvironment locally, can be absorbed and degraded gradually, reduce scar formation in repairing spinal cord injury, reduce the inflammatory response and accelerate the migration of endogenous neuroblast	Short research time	Cellular transplant combined with above method	Same as above	Same as above
Seed cells	Schwann cells, embryonic stem cells, neural stem cells, and mesenchymal stem cells	Generate growth factors, affect the extracellular matrix, promote the formation of myelin, can be differentiated into multiple histiocytic cells	Lost the original activity and microenvironment *in vivo*	Same as above	Same as above	Same as above
Growth factors	NGF, BDNF, GDNF, NGF-β, FGF-2, NT-3, CNTF, and VEGF	Regulate microenvironment, promote sciatic nerve regeneration, neuronal survival, synaptic plasticity and neurogenesis	Destroyed under high temperature, high pressure or organic solvents easily	Same as above	Same as above	Same as above
Peripheral nerve assistive technology	Pulsed electromagnetic field, electrical stimulation, and ultrasound	Enhance the speed and accuracy of axon regeneration of sensory and motor nerve, promote the functional recovery of the sensory and motor nerves, promote the proliferation of growth factors and seed cells	Less research and clinically relevant large data samples	Specific device	Same as above	Same as above

PLA: Polylactic acid; PCL: polycaprolactone; PGA: polyglycolic acid; PLGA: poly lactic-co-glycolic acid ; PLGA:;NGF: nerve growth factor; BDNF: brain derived neurotrophic factor; GDNF: glial cell line-derived neurotrophic factor; FGF-2: fibroblast growth factor 2; NT-3: neurotrophic factor 3; CNTF: ciliary neurotrophic factor; VEGF: vascular endothelial growth factor.

Neural neuropraxia

In this kind of injury, there is no structural change in the nerve fibers, just mild compression injury, slight traction or some accumulated strain. The loss of effector sensory and motor functions is only temporary. The functions can be restored in a short time. No surgical treatment is required. The conservative method can restore the function of the nerve (Tzadik et al., 1982).

Neural axonotmesis

Blunt beating and continuous compression can cause this kind of injury. Degeneration or demyelination occurs at the distal end of the broken axon. The severity is between neural neuropraxia and neurotmesis. Nerve fibers are not completely disconnected. Some of its structure is preserved. Its endoneurium tube remains intact. The axons can grow along the surface of Schwann myelin sheath. Neurological dysfunction can recover by itself. There is no need for surgical treatment (Bridge et al., 1994; Zhang et al., 2018).

Neural mutilation injury

The key to successful neural mutilation injury repairing is accurate connection of the different characteristic nerve fibers. Epineurium suture and perineurium suture have

been used clinically for more than 100 years. It is difficult to assess the connection accuracy of nerve fibers with different heterogeneities in injured nerves (Ding et al., 2015). Researchers across the world have proposed various methods to achieve an effective connection of sensory fibers and motor fibers. For example, the connection of the capillary network in the injured epineurium was used to judge the connection success of different characteristic nerve fibers. Immunohistochemical staining of frozen sections during surgery was used to distinguish between sensory and motor fibers (Xianyu et al., 2016).

Neural defects

If there is a long distance between the broken ends after peripheral nerve injury and the end-end suture cannot be achieved, an autogenous nerve graft is the recognized golden standard procedure (Bhangra et al., 2016). However, this repair method of autogenous nerve graft has to sacrifice another healthy sensory nerve and the supply site of sensory nerves is limited. The alternative of applying a tissue-engineered artificial nerve requires study of the optimal time and conditions. The method is to study proper artificial nerve substitution to repair peripheral defects with long segment intervals, as described by Luo and others (2015).

Tissue-Engineering of Peripheral Nerves

The three elements of peripheral nervous tissue engineering are the biological scaffold material, the seed cells and various growth factors (Wongtrakul et al., 2002). A tissue-engineered artificial nerve is a bridge, functioning as a physical and nutritional support in repairing nerve injury (Ghasemi-Mobarakeh et al., 2011).

Biological scaffold materials

Originally, bioinert materials were used to repair tissue injury, but they could only provide support for the tissue to climb. However, these materials could not accelerate the repair. Thus, research began to study other materials (Rebowe et al., 2018). There are many kinds of biological scaffold materials, and the principal ones are as follows:

Artificial synthetic material

Polyester is the common synthetic material used in nervous tissue engineering such as polylactic acid, polycaprolactone and polyglycolic acid (Gonçalves et al., 2016). When combined with bone marrow mesenchymal stem cells, polylactic acid performed better and accelerated peripheral nerve repair (Costa et al., 2013). Polylactic acid guided the migration of Schwann cells and induced the formation of a normal nerve structure (Hu et al., 2008). Polycaprolactone is metabolized *in vivo* and can be excreted. Polycaprolactone material has a similar effect to that of autografts in repairing nerve and its performance was better than polylactic acid conduit (Shin et al., 2009). When combined with interleukin-β10, polycaprolactone nanofiber scaffolds promoted alternatively activated (M2) macrophages around the injured peripheral nerve, which are important to its repair (Potas et al., 2015). Polyglycolic acid also provides support for nerve repair (Bryan, 2004). Polyglycolic acid has good mechanical properties for the repair of a long nerve defect (Ichihara et al., 2015). Artificial synthetic materials have good biocompatibility and biodegradability. It is important that their decomposition does little or no harm to the organism. There are shortcomings to a single synthetic material. It costs a great deal of time and money to produce the highly pure polymer monomers needed to make the scaffold. Moreover, elasticity and hardness of such materials are poor. Chemical means such as copolymerization and chain extension, or physical means such as plasticizing and filling are often used to improve the properties of such materials (Nectow et al., 2012).

Natural biomaterial

There are three main natural biomaterials used in tissue repair, collagen, silk and gelatin. A type I collagen catheter is the most widely used biological material clinically. Purified type I collagen is widely applied in nervous tissue engineering (Faroni et al., 2015). When used for a long gap defect injury, it can obtain a similar effect to a nerve graft in aiding the recovery of function of the effector (Archibald et al., 1995). When combined with chitosan and gelatin in a suitable ratio, the microstructure of the material was good in all dimensions, including aperture size, which had a positive effect on rehabilitation of the injured nerve (Wang et al., 2012). Silk fibroin materials could promote the release of related factors such as nerve growth factor particles, and provide more nutritional factors and a more suitable microenvironment to promote nerve repair (Han, 2018). Silk fibroin has good compatibility with dorsal root ganglia neuron cells and supports cell growth (Yang et al., 2007). Gelatin materials could be used to repair peripheral nerve injury, and reduce the micromanipulation during nerve reconstruction, making the repair more convenient (Soucy et al., 2008). Combined with tropoelastin, gelatin degradated more slowly *in vivo*, indicating the potential to support the growth of slowly regenerating nerves. The above natural biomaterials are abundant and easy to obtain. Natural biomaterials also have good biocompatibility and biodegradability, and are easily absorbed in the organism. However, each natural biomaterial has its own disadvantages. Some are brittle and easy to fracture, or easily eroded in a moist environment. Some natural materials are insoluble in water and ordinary organic solvents, thus limiting its application. Chemical modification and mixing with other materials can improve their function and promote their use (Chiono et al., 2009).

New-type degradable material

Chitosan, made from the deacetylation of chitin, plays a supportive, protective and guiding role in the early stage of neural repairing and can give a relatively stable, localized

microenvironment during regeneration. Chitosan is absorbed and degraded gradually in the late phase of neural repairing and regeneration (Hu et al., 2016). When combined with bone marrow mesenchymal stem cells, a chitosan tube promoted the repair of peripheral nerve injury (Moattari et al., 2018). Compared with alginate scaffolds, chitosan scaffolds, used to repair spinal cord injury, resulted in less scar formation (Yao et al., 2018). Graphene is a two-dimensional carbon nanomaterial with good optical, electrical and mechanical properties. When nanoparticles of graphene are incorporated into chitosan/gelatin scaffolds and used to repair sciatic nerve injury in rats, it facilitated the regeneration of injured nerve (Wang et al., 2017). Graphene reduced the inflammatory response and accelerated the migration of endogenous neuroblasts (Zhou et al., 2016). The electrical conductivity and mechanical properties were raised by polyaniline/graphene in a dose dependent way, and the porosity, swelling ratio and *in vitro* biodegradability decreased in such materials (Baniasadi et al., 2015). These new materials are very novel therefore further research is needed to discover the advantages/disadvantages of these materials. Mass production of new materials can improve their application if standardization and costs improve. It is remains important to assess the costs and benefits of new versus traditional techniques for each nerve injury.

Peripheral nerve assistive technology for tissue engineering

As well as the constant reform and innovation of the artificial nerve material and design, various related assistive technologies have been developed. Pulsed electromagnetic field and electrical stimulation have been proven to effectively enhance the speed and accuracy of axon regeneration of sensory and motor nerves (Kubiak et al., 2018). Huang et al. (2010) used an electrically conductive scaffold with longitudinal pores as material to repair a 15-mm sciatic nerve defects in rats. Intermittent electrical stimulation beside the conduit was used to promote the functional recovery of the sensory and motor nerves. The design property was approved by the State Intellectual Property Office (Huang et al., 2010). Pulsed electromagnetic field affected the proliferation of Schwann cells and promoted the secretion of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. Pulsed electromagnetic field promoted the regeneration of crush-injured rat mental nerve (Seo et al., 2018). Combined with scaffold materials, pulsed electromagnetic field accelerated the functional recovery of transected sciatic nerve in rat, which was considered as an effective, safe and tolerable treatment for peripheral nerve repair in clinic (Mohammadi et al., 2014). Moreover, pulsed electromagnetic field also reduced diabetic neuropathic pain and repaired nerve injury (Weintraub et al., 2009). Combined with electrical stimulation, materials could accelerate cell proliferation, differentiation, neurite outgrowth, and myelination, and so promote the regeneration of peripheral nerve (Wang et al., 2018). Electrical stimulation could also affect severe neurological pain (Molsberger and McCaig, 2018). Thus, it improved the quality of life of the patients. Nerve ultrasound is a valuable tool to detect progress after traumatic nerve injury, and allow medical intervention to the injury in a timely manner (Fantoni et al., 2018). These assistive technologies are still in their infancy. Clinically relevant large data samples are needed to standardize and regulate these methods and produce an assistive technology operation manual.

Seed cells

Seed cells implanted in the injured nerve can generate growth factors and affect the extracellular matrix to promote nerve regeneration. The commonly used seed cells in neural tissue engineering are stem cells that differentiate into Schwann cells (Ren et al., 2012). Recent developments have promoted the use of embryonic stem cells, neural stem cells and mesenchymal stem cells as the preferred seed cells to be incorporated into an artificial nerve bio-scaffold (Zhang et al., 2005). Schwann cells are specific glial cells in the peripheral nervous system, which are important in the formation of myelin. Schwann cells provide support and nutritional factors for axons. Bhutto et al. (2016) found that nanofibers loaded with bioactive substances affected the proliferation and migration of Schwann cells. Schwann cells could affect peripheral nerve repair through many factors, such as microRNA or lncRNA. MiRNA-138 could inhibit Schwann cell proliferation and migration, whereas the decreased expression of lncRNA TNXA-PS1 could accelerate proliferation (Sullivan et al., 2018; Yao et al., 2018). Embryonic stem cells are separated from cell masses during the blastocyst period. Under appropriate culture conditions, embryonic stem cells can induce differentiation into a variety of cell types. Within an assistant 3-D scaffold, embryonic stem cells have a higher proliferation rate and higher production of nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) than a 2-D over a long time (Alessandri et al., 2014). When combined with a heterologous fibrin sealant, embryonic stem cells improved the regeneration of peripheral nerve repair (Mozafari et al., 2018). Neural stem cells are original cells with multiple differentiation potential in the development of the nervous system, and have low immunogenicity. Heparin crosslinked chitosan microspheres could improve the survival of neural stem cells. This material was superior in sustaining the growth of neural stem cells compared to standard culture conditions and has been used in the repair of central nerve injury (Skop et al., 2013). Mesenchymal stem cells, first found in bone marrow, are derived from early mesoderm and are pluripotent stem cells. Mesenchymal stem cells can differentiate into multiple histiocytic cells, and are ideal seed cells. When combined with a poly (lactic-co-glycolic acid) nanofiber scaffold, bone marrow mesenchymal stem cells improved transected sciatic nerve regeneration (Kaka et al., 2017). This is because the stem cells release neurotrophic factors and thereby regulate the microenvironment. As seed cells are always pre-loaded into

the scaffold materials, they lose much of their original activity and microenvironment. It is possible that these cells may play different roles in the repair of neurons *in vivo*. The best way to maintain cell viability and create an optimal peripheral environment for seed cells is crucial to their success in repairing injured nerves.

Growth factors

The neurotrophic effect of growth factors can affect the seed cells in the nerve conduit indirectly. Exogenous growth factors can be added to the neural conduit as a part of the neural transplantation of tissue engineering. The most commonly used are NGF, brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (Haastert et al., 2008). A chitosan/sericin composite scaffold loaded with NGF sustains the local release of bioactive components to treat chronic peripheral nerve compression injury. The degradation products of the composite scaffold upregulated the expression of GDNF, early growth response protein 2 and neural cell adhesion molecule and these genes were important for facilitating nerve function recovery (Zhang et al., 2007). Aligned core-shell nanofibers delivering NGF could also promote sciatic nerve regeneration across a gap of 13 mm in rat (Wang et al., 2012). BDNF is important in promoting neuronal survival, increasing synaptic plasticity and neurogenesis. When lentiviral vectors expressing BDNF were injected into the sciatic nerve injury site bridged by templated agarose multi-channel guidance scaffolds, it enhanced peripheral nerve regeneration (Gao et al., 2016). GDNF can support the survival of moto-neurons, provide nutrition for them and regulate the development and differentiation of neurons. GDNF, when conjugated to iron oxide nanoparticles to prolong its activity, accelerated the onset and growth of myelin significantly earlier compared with free GDNF or free or conjugated βNGF and fibroblast growth factor-2 (Ziv-Polat et al., 2014). Neurotrophic factor 3 (NT-3), ciliary neurotrophic factor (CNTF) and VEGF have also been used to repair peripheral nerve injury. When combined with in a poly(lactic-co-glycolic acid) conduit, neurotrophic factor 3 increased the differentiation of neural stem cells into neurons, that developed synaptic connections, exhibited synaptic activities and neurites were myelinated by the accompanying Schwann cells (Xiong et al., 2012). Neurotrophic factor 3 could affect peripheral nerve repair via changing biological characteristics of Schwann cells (Shakhbazau et al., 2012). CNTF was first isolated from the ciliary ganglion of birds, and belongs to non-targeting neurotrophic factor. Collagen scaffolds modified with CNTF and basic fibroblast growth factor effectively promoted facial nerve regeneration in minipigs (Cui et al., 2014). Laminin modified linear ordered collagen scaffolds loaded with laminin-binding CNTF guided axon growth and enhance the nerve regeneration as well as functional recovery (Cao et al., 2011). VEGF is highly specific and promotes the migration and proliferation of vascular endothelial cells. Multipotent progenitor cells have the potential to encourage VEGF-A dependent action for peripheral nerve repair in a nerve guide conduit (Zupanc et al., 2017). Growth factors are largely proteins. Their functions are easily destroyed in conditions of high temperature, high pressure or in contact with organic solvents, however, these processes are necessary for producing scaffold materials. The application of growth factors to scaffolds must be considered during the preparation of the material to enhance protection of the growth factor.

Clinical Application of Peripheral Nerve Scaffold Material

Many investigators have carried out clinical studies on scaffold materials for peripheral nerve repair (Anderson et al., 2015; Koppes et al., 2016; Vijayavenkataraman et al., 2018). At present, neural scaffold materials that have been used in clinics and approved by the Food and Drug Administration and European Union, include type I collagenous fiber catheters, such as NeuraGen, Neuroflex, NeuroMatrix, NeuraWrap and NeuroMend, polyglycolic acid catheters, such as Neurotube, and poly-DL-lactide-ε-caprolactone nerviduct, such as Neurolac.

When considering the treatment of peripheral nerve injury, Baoguo Jiang developed a deacetylation chitin conduit (State Intellectual Property Office patent number: 01136314.2) and proposed an innovative method to use it to bridge a small gap to repair a peripheral nerve injury. This method was successfully applied in Sprague-Dawley rats and rhesus monkey. A multicenter-clinical trial in humans has been completed. A small gap (2 mm) bridging by a biological conduit is used to repair a separation injury of the peripheral nerve. The conduit can promote an accurate abutment joint of nerve fibers with different heterogeneities in the distal and proximal ends of injured nerves. This improves the recovery of the functions of the distal target organs and decreases the incidence of nerve tumor pain. The possible mechanisms are as follows: The small gap established by the biologic conduit allows tissue-induced selective regeneration and reduces uncontrolled fiber regeneration. The established regeneration chamber protects the local microenvironment that benefits the effectiveness of neurotrophic factors. The regeneration chamber enables small nerves to repair larger nerves. The small gap (2 mm) is bridged by a biological conduit, replacing a traditional epineurium suture, to repair a separated injury of a peripheral nerve. This is an important technological advance in the field of peripheral nerve repair (Zhang et al., 2013; Chen et al., 2016; Yu et al., 2016; Wang et al., 2018).

Xiao-Song Gu from Nantong University of China used a nerve conduit and scaffold to establish an artificial nerve to repair peripheral nerve defect (Wang et al., 2005). Biodegradable chitosan was used as the catheter and polyglycolic acid as the scaffold to establish an artificial tissue nerve graft (China Patent ZL 01108208.9), which successfully repaired

a 30-mm peripheral nerve defect in a dog. Silk fibroin was used to establish an artificial nerve by tissue engineering and a China Patent (ZL200510094 683.2) was obtained and approved by the European Union (Gu et al., 2011; Yi et al., 2018). The results demonstrated that chitosan degradation products facilitated peripheral nerve regeneration by improving the macrophage-constructed microenvironments. Schwann cell precursors improve peripheral nerve regeneration. The results also showed some regulation mechanism of molecular level. For instance, microRNA-9 inhibited Schwann cell migration by targeting the collagen triple helix repeat containing protein 1 (Zhou et al., 2014). Let-7 affected NGF and participated in peripheral nerve regeneration (Li et al., 2015). Fibroblast-derived tenascin-C also promoted the migration of Schwann cells via the β1-integrin dependent pathway (Zhang et al., 2016). All these help explain the molecular mechanism of peripheral nerve injury repair.

In 2012, Xiao-Lin Liu from Zhongshan University of China developed an artificial nerve called the "God Bridge" to repair peripheral nerve defects and obtained a registration certificate of products from the China Food and Drug Administration (Zhong et al., 2015). A God Bridge is a sterile decellularized extracellular matrix obtained after chemical extraction of an allogeneic nerve. The God Bridge is a new type material, and may replace an autologous nerve to repair peripheral nerve defects. Since 2008, similar products have been used in clinics and are commercially available in the United States. Currently, the God Bridge is the material to repair nerve defects and the only one developed by us and is approved by the China FDA. A God Bridge preserves the scaffold structure of the natural nerve, including the microstructure of nerve basement membrane, perineurium and epineurium. The God Bridge guides the growth of the nerve cone of the severed nerve and provides support to newborn cells. The new born growth cone can then guide new cells growth, forming a virtuous cycle. Thus, the renewed nerve can reach the distally injured part and go on to innervate the effector. It is a bridge of nerve that paves the way for nerve regeneration. As it has the natural structure of the nerve, the God Bridge is equivalent to the extracellular matrix of neuron cells. The God Bridge has no need to degrade and has no adverse reactions. The God Bridge increases the effective nerve donor source and reduces the rejection reaction. It will play a leading role in clinics internationally in repairing peripheral nerve injury.

Biodegradability and compatibility are the basis of nerve conduit materials. We would expect to encounter nerve damage of different lengths and we should produce suitable scaffolds to aid repair in the clinic. The materials reviewed should save surgical time and promote nerve repair by their various mechanisms. The materials chosen will be more bionic and replace the necessity for using homologous nerves. In addition to traditional porosity and surface area, other properties such as antibacterial and conductive should be improved. These materials should be able to maintain the same body microenvironment as closely as possible. We can also artificially control the time of material degradation and the release of carrier components. Only in this way can we improve the quality of life of patients after the initial operation.

Conclusion

Clinical application is the final link of developing products associated with artificial nerve of tissue engineering. The study of tissue engineering in peripheral nerve regeneration involves basic research up to industrial production. The new products are being developed and commercialized (Gu et al., 2011). However, some issues still need to be solved. Selection of nerve growth factor, fixed operating and slow release technology, release kinetics and its relationship with regeneration all require further investigations.

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