REVIEW ARTICLE

Prospective Applications of Marine Oriented Materials in the Repair of Peripheral Nerve Injury

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Peripheral nerve injury is a thorny problem for many years because it is difficult to find out appropriate drugs or materials that can maximize healing effects and minimize damages to human body. Among various methods, the use of biomaterial scaffolds on injured nerves has been favoured due to the biocompatibility, accessibility, and effectiveness. Marine oriented materials have attracted huge attention with their unique pro-regenerative potential. This article reviews the application of marine biological materials in the repair of peripheral nerve injury.

Introduction

Peripheral nerve injury is a prevalent devastating complication which is closely related to accidents, removal of cancerous tissues and diseases. For example, facial nerve injuries are commonly caused by trauma, surgical removal of benign or malignant head & neck tumours and petrous bone surgery [**1**]. Peripheral nerve injury most commonly arises from trauma and less frequently, secondary tumor resection or congenital defects [**2**]. When a patient's nerve is injured, clinical symptoms such as sensory, motor and nutritional disorders usually occur in the innervated area. Currently, the primary option is the use of hollow nerve guide scaffolds that will provide a microenvironment conducive to nutritional support and axonal growth and acting as a barrier against the surrounding tissue infiltration [**3**,**4**]. If serious peripheral nerve injuries cannot be repaired promptly and effectively, the nerve loop will be damaged and encounter motor and sensory abnormalities [**5**].

Application of biomaterial in repair of peripheral nerve injury

Overview on biomaterial

With significant advances in the research and application of biomaterials, they have been used to repair peripheral nerve injury for several decades, as a new type of treatment solution.

The biomaterial scaffolds are capable of guiding the regeneration of axons and function as a bridge to restore the gap [**6**]. The therapeutic effect of the nerve scaffold, also known as the nerve conduit, is improving with increasing choices of different material, new construction of scaffolds, and the inclusion of neurotrophic factors and support cells in the scaffolds. Improvements in functional outcomes are expected when these are optimized for use of clinical practice [**7**,**8**].

Present biomedical materials in the scaffolds

During the past few years, studies on peripheral nerve repair have concentrated on various scaffolds made of biomaterials, including natural material, non-degradable material and biodegradable synthetic materials. The main characteristic of these scaffolds is a longitudinal organization mimicking the natural structure of the nerve pathway. Scaffolds are designed to serve as tubes for axonal elongation and to direct regenerating axons to reconnect with their target neurons, therefore scaffolds should be flexible and have sufficient permeability for the exchange of fluids between the regeneration environment and the surrounding tissue [**9**].

At present, the materials commonly used for making scaffolds are non-biodegradable polymers, such as methacrylate-based hydrogels, polyols (polyvinyl alcohol - PVA), polystyrene, silicone, and poly (tetrafluoroethylene), and biodegradable polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly (ε-caprolactone) (PCL), polyurethanes, tri-methylene carbonate – co – ε - caprolactone, poly(D, L–lactide – co - ε-caprolactone) (PLCL) [**10-14**]. In addition, scaffolds using biodegradable materials, such as collagen, polyglycolic acid, polylactic acid, polyesters, and chitosan have been developed [**15**]. Wang *et al.,* incorporated Lycium barbarum polysaccharide (LBP) into core-shell structured nanofibrous scaffolds via coaxial electro-spinning [**6**]. They concluded that LBP, as a drug with neuroprotective potential, could be a potential candidate as tissue engineered scaffolds for peripheral nerve regeneration after being encapsulated into electrospun nanofibers. According to Archibald *et al.,* nerve regeneration using collagen scaffolds in the nonhuman primate is similar to that of autograft repaired, which can prove the effectiveness of scaffolds made of biodegradable materials in preclinical and clinical experiments [**16**].

The application of nerve scaffolds in repairing peripheral nerve injuries

Scaffolds loaded with different materials, as mentioned above, have extraordinary physical and chemical properties. Many scientists used different materials and methods to perform experiments. They finally proved that these scaffolds have potential clinical application prospects.

Zhang *et al.*, explored the potential use of human gingiva-derived mesenchymal stem cells (GMSCs) as the only cellular component in 3D bio-printed scaffold-free neural constructs that were transplantable to bridge facial nerve defects in rats [**1**]. They found that in vivo transplantation of the GMSCs-laden nerve constructs promoted regeneration and functional recovery for bridging segmental defects in rat facial nerves. Therefore, scaffolds loaded with GMSCs have potential applications for repair and regeneration of peripheral nerve defects.

Sivolella *et al.* reviewed electrospun and self-assembled nanofibrous scaffolds used in vitro and in vivo for peripheral nerve regeneration and its application in peripheral nerve injuries treatment [**17**]. They concluded that injured peripheral nerves, such as trigeminal and facial, might benefit from these treatments using nanofibrous scaffolds.

Liu *et al.* made a magnetic nanocomposite scaffold fabricated from magnetic nanoparticles and a biodegradable chitosan–glycerophosphate polymer [**18**]. They evaluated and characterized its structure, and investigated the combined effects of magnetic scaffolds (MG) with an applied magnetic field (MF) on the viability of Schwann cells (SC) and peripheral nerve injury repair as well. According to their current findings, the combined application of MGs and SCs with applied MF is a promising therapy for the engineering of peripheral nerve regeneration.

Applications of marine biomaterials in restoring peripheral nerve injury

There are more than 200,000 kinds of creatures of different sizes and shapes living in the vast ocean, including animals, plants and microorganisms. It is a huge treasure house for us to develop and utilize marine resources. These materials are easy to obtain and have unique molecular structure. Therefore, they are used widely (**Table 1**).

Alginate

As a kind of polysaccharide, alginate has good biocompatibility. It can be extracted from seaweed easily. Therefore, alginate could be used as a hydrogel inside the nerve scaffold for clinic application of nerve regeneration [**19,20**]. In Dariusz's research, they observed that calcium alginate had a supportive effect on nerve regeneration similar to autologous nerve transplantation [**21**]. Another research indicated that it could promote Schwann cells growth in vitro [22].

Table 1. Introduction of marine biomaterials in restoring peripheral nerve injury.

Marine biomaterials	Manufacturing progress	Application	Advantages
Alginate	Extracted from seaweed easily	Promote Schwann cells growth in vitro and in vivo	Good biocompatibility, low toxicity and relatively low price
Chitin	Extracted from marine arthropods	Promote muscle regeneration, inhibit fibroblast growth and prevent scar formation	Relatively rich resources, unique structure and special functions
Collagen	Extracted by hot water or enzymatic method	Function as scaffolds and carriers	Good biocompatibility, biodegradability and biological activity
Vitamin B12	Extracted from seaweed by microbial fermentation	Reduce the degeneration of nervous system and function as coenzyme in the nerve metabolism	Red blood cell maturation, carbohydrate, fat and protein metabolism, and nucleic acid synthesis

Chitin

Chitin is a kind of odorless and tasteless white amorphous substance. It can be extracted from marine arthropods. Previous research showed that chitin produced by acetylation of chitosan greatly improved its mechanical strength, purity and easier to process [**23,24**]. Chitin can be degraded by lysozyme, deaminase, and glucose. Besides, it may be absorbed by the human body. Chitin can promote the regeneration of muscle cells, inhibit the growth of fibroblasts and prevent scar formation [**25,26**]. Jiao et al. used a chitin nerve scaffold to repair a 10mm long sciatic nerve gap in rats, and found the scaffolds had good bridging effects on the injured sciatic nerve and promoted nerve regeneration significantly [**27**].

Collagen

Collagen is an important component of abundant protein and extracellular matrix in animals, which widely exists in sponge, jellyfish, fish and other marine organisms. It is mainly composed of three α - peptide chains or the peptide chains of α - chain. It is not easy to dissolve in alkali, weak acid and neutral salt, is not easy to be degraded by protease, and has the function of promoting coagulation and cell growth [**28,29**]. Compared with mammalian collagen, marine collagen is cheaper, easier to obtain, has lower melting point, and no risk of infectious diseases. Collagen has good biocompatibility, biodegradability and biological activity. Hadi et al. fabricated collagen hydrogel containing naringin and used as the scaffold for peripheral nerve damage treatment [**30**]. They found that the hydrogel reduced all the histological changes induced

from the nerve injury and it showed more resemblance to the normal sciatic nerve. However, the denaturation temperature of marine collagen is lower. It will have a wider application prospect after confirming its thermal stability [**31**].

Vitamin B12

Vitamin B12 is also an important and biocompatible agent. It is rich in seaweed. It has been reported that vitamin B12 not only reduces the degeneration of nervous system, but also plays an important role as coenzyme in the metabolism of the nervous system, such as participating in the biosynthesis of neurotransmitter and cell membrane [**32**]. According to Sun *et al.*, vitamin B12 could promote the regeneration of myelinated nerve fibers and the proliferation of Schwann cells, and promote the repair of peripheral nerve in rats with sciatic nerve injury by upregulating the expression of brain-derived neurotrophic factors [**33**].

Conclusion and future prospective

Currently, the effects of using biomaterial scaffolds to restore peripheral nerve injury are still far from satisfactory. Marine oriented materials and agents display huge potential in providing a suitable microenvironment and release regenerative factors for peripheral nerve regeneration. In future researches, more attention and focus should be placed on marine biomaterials concerning their promising healing effects and possible regenerative mechanisms. In addition, a combined use of marine biomaterials may provide better reparative outcomes since these materials share similar advantages and characteristics of good biocompatibility, wide ranges of sources, low prize and therefore they will play an important role in peripheral nerve regeneration. It is expected that ideal peripheral nerve restoration may be pursued with the vast and rapid development of the neuroengineering.

Author contributions

C. Fan and Y. Gu conceived the conceptualization and the study design. X. Ma and X. Wang searched databases and collected data information. Y. Gu drafted the manuscript. C. Fan revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing financial interests.

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Keywords

Peripheral nerve regeneration, nerve scaffold, marine materials, tissue engineering.

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