

# Advance of Peripheral Nerve Injury Repair and Reconstruction

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Peripheral nerve injury is a common clinical problem because the dysfunction of distal limb seriously affects patients' quality of life, and it results in a huge social and economic burden.<sup>[1]</sup> Repair of peripheral nerve injury is a very complex pathological process. Due to slow nerve regeneration, Wallerian degeneration of nerve stump, tissue adhesion, atrophy of muscles and motor end plates and other constraints, functional rehabilitation of the damaged nerve is always restricted. The ultimate goal of repairing peripheral nerve injuries is to restore the function of the distal target organs to their original level in both sensory and motor aspect. At present, the foreign as well as the domestic researches on peripheral nerve injury mainly focus on the methods of nerve repair, promotion of axonal growth, and the functional remodeling paralleled with anatomical restoration.

## PERIPHERAL NERVE REPAIR

The clinical administration of peripheral nerve injury is still the classic epineurium or perineurium neuroorrhaphy that dates back to more than 100 years ago.<sup>[2]</sup> However, efficient anastomosis of homogeneous nerve fibers in bilateral neural stumps cannot be achieved merely through these two surgical methods. Because of the discontinuity of basement membrane after peripheral nerve injury, the regenerated axons cannot correctively implant into the target organs without guidance of the endoneurial tube. If the nerve dominating the skin originally regenerates to the muscle, or the nerve controlling the muscle initially regenerates to the skin, it is impossible to restore the nerve function. Although we try to promote the growth rate and the amount of axons, inefficient accurate docking between nerve and target organ

leads to poor functional recovery or malfunction. So how to attain the precise regeneration between the peripheral nerve and target organs has become a difficult problem. The selective regeneration theory of peripheral nerve was generally considered as a turning point for the problem, first proposed by Forssman in 1898, when he found that the regenerated axon sprouts were capable of recognizing and moving toward their counterparts, as in sensory to sensory and motor to motor.<sup>[3,4]</sup> Jiang *et al.* make full use of the selective regeneration of peripheral nerve, proposing the "peripheral nerve repair with biodegradable conduit in small gap" based on animal experiments.<sup>[5]</sup> This innovative method ameliorates the traditional epi-/peri-neurium neuroorrhaphy, and the efficacy has been verified in Sprague-Dawley SD rats and rhesus monkeys in succession<sup>[6,7]</sup> before the recent conclusion of its multicenter clinical trial based on the human body. Peripheral nerve repair with biodegradable conduit in small gap can effectively promote the connection of different fibers between the distal stump and proximal stump, help restore the function of the distal target organ, and reduce the incidence of painful neuroma, the mechanism of which may involve the following factors: (1) It allows distal neural stump or target tissue to induce selective regeneration of the proximal stump; (2) it reduces the overflow of regenerated nerve fibers; (3) it helps maintain the local microenvironment

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and promotes the function of neurotrophic factors; and (4) the regenerative chamber provides the possibility and feasibility of repairing larger nerves with smaller nerves. The appliance of biodegradable conduit in small gap peripheral nerve injury repair may be a promising technological substitution in the field of peripheral nerve repair. In addition, during lack of neural innervation to muscle after neurological damage, neuromuscular electrical stimulation plays an important role in the clinical application of treating peripheral nerve injury, and implantable stimulation will be the future.<sup>[8]</sup>

## PROMOTE AXON GROWTH

The neuronal structure repair following peripheral nerve injury is still challenging. After peripheral nerve injury, neurons in the spinal cord and dorsal root ganglion can produce a series of changes in terms of biochemistry, gene expression, metabolism, morphology, resulting in possible necrosis or apoptosis, which varies by the type of injury, region of injury, age of patients, and type of involved neurons.<sup>[9]</sup> Molecules associated with tumor suppressor signaling networks play a key role in shifting the balance between growth and nongrowth during axon regeneration. In the molecular mechanism of tumor suppressor molecules in damaged neurons and their effects on specific stages of regeneration events, there may lie prosperous therapeutic interventions.<sup>[10]</sup> Studies have found that the inhibition of PTEN or Rb1 can promote the growth of DRG neurons after peripheral nerve injury.<sup>[11,12]</sup> Activation of p53 may be necessary to prevent Schwann cells from excessive proliferation and to induce their redifferentiation.<sup>[10]</sup> P21 knockout mice showed delayed functional recovery after compression injury of the sciatic nerve, associating with the excessive phosphorylation of nerve fibers that resulted in impaired motor conduction speed and delayed axonal outgrowth.<sup>[13]</sup> With the development of regenerative medicine, the nerve tissue engineering has developed so rapidly that the abundant biological and artificial nerve grafts can sometimes even replace the autologous nerve transplantation for large nerve defects. In general, nerve tissue engineering is based primarily on biomaterial scaffolds made of biodegradable biosynthetic materials and natural materials, incorporating a variety of biochemical components that can promote nerve growth. Natural biological materials mainly include two types: autologous nonneural tissue, allogeneic, or decellularized xenogeneic neural/nonneural tissues; natural polymers derived from extracellular matrix (ECM) (laminin, collagen, fibronectin, fibrin, and hyaluronic acid), polysaccharide (chitosan, sodium alginate, and agarose), and protein (silk fibroin, keratin).<sup>[14]</sup> In China, chitosan-based conduit we developed has been approved for clinical trials<sup>[15]</sup> with the national invention patent. The artificial synthetic materials are mainly aliphatic polybasic esters such as PLGA, PGA, PLLA, PCL, and so on. To improve the effect of peripheral nerve repair, the supporting cells, ECM, growth factors, and small molecule compounds can be administered into the

nerve conduits. The most commonly used supporting cells are Schwann cells, which can provide basement membrane tubes to guide peripheral nerve regeneration. Bone marrow mesenchymal stem cells (BMSCs), just like Schwann cells, are also adopted as support cells within a neural scaffold. ECM derived from BMSC, a compound of multiple ECMs, presents better enhance effect than single ECM in peripheral nerve repair.<sup>[16]</sup> Small molecules can promote the conversion of many stem cells into precursor neural cell by inducing cell reprogramming.

## FUNCTIONAL REMODELING

A variety of clinical studies and animal experiments shows that the neurons have functional remodeling after peripheral nerve repair. Under certain conditions, neurons can achieve new function by giving up their original function to coordinate.

### Tendon transposition

It is hard to restore active extension of wrist, thumb, and digits after the radial nerve injury, which seriously affects patients' life quality. Clinically, the restoration of active extension of wrist can be obtained by tendon transfer in those who cannot still retain wrist active extension with by multiple nerve repair measures, when the flexor carpi ulnaris that originally controls the flexion of the wrist joint rehabilitates the extension function of wrist.<sup>[17]</sup> In addition, the foot cannot achieve active extension after peroneal nerve injury, which could obtain function of active extension by tendon transposition of the posterior tibial muscle.<sup>[18]</sup> At early stage after tendon transposition, the impulse supposed to flex the wrist can reversely extend it. After a period of training, this reverse can be corrected, which illustrates central nervous system, originally dominated the flexor carpi ulnaris, may develop functional remodeling under specific conditions. Similarly, after a period of training, the ankle joint with injured common peroneal nerve restores active extension independently. The above two clinical cases indicate that the spinal cord and brain may experience functional remodeling, so as to realize the function transformation of two nerves which are mutually antagonistic in function.

### Nerve transposition

Brachial plexus root avulsion could be clinically intervened using the contralateral healthy C7 nerve-root as autologous graft. After operation, the effector dominated by C5-C8 on the injured side changed to the contralateral side of the C7 nerve. The location, quantity, and function of effector of contralateral C7 nerve changed dramatically, but the motor and sensory functions of the injured brachial plexus recovered in some way.<sup>[19]</sup> In addition, the proximal peroneal nerve was used to repair both the distal peroneal and tibial nerve. The researchers found that the amounts of double-labeled motor neurons in peroneal domain of spinal cord decreased significantly to a level from 2 to 8 months after operation, accompanied with an obvious improvement in functional and morphological recovery of both tibialis anterior and

gastrocnemius. It shows that functional remodeling occurs in the anterior horn of the spinal cord.<sup>[20]</sup> Now, we are trying to study the functional remodeling of the cerebral cortex after peripheral nerve repair by two-photon imaging to achieve a complete process of functional remodeling.

### Amplifying and compensation of nerve

Our previous study showed asymmetric repair phenomenon, that is, the regenerated sprouts of the proximal stump projects into the distal one in a manner of one-to-many relationship, which allows the anastomosis of thin-to-thick ends. Moreover, mathematical relations have further been researched: an increasing ratio of distal stump axon numbers to proximal donor nerve axon numbers of 1.0, 1.83, 3.64, and 7.97 yielded ratios of regenerative myelinated axon numbers to proximal donor axon numbers of 0.98, 1.51, 2.39, and 2.89, respectively, estimating an approximate maximum value of 3.3 using the Hill function.<sup>[21,22]</sup> This phenomenon has also proved to exist in larger animal experiments,<sup>[7]</sup> where proximal regenerative axons can grow into distal endoneurial tubes by sprouting, indicating the reserved function of amplification and compensation.

In conclusions, although a lot of studies have been done on the peripheral nerve repair, the underlying mechanisms of functional remodeling after that will be the future focus.

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### Conflicts of interest

There are no conflicts of interest.

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