

Research Progress of Massage on Repair of Peripheral Nerve Injury based on ‘Macrophages’

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Abstract: *The repair of peripheral nerve injury is a difficult problem in clinical treatment. As a mechanical stimulation, massage has achieved good results in the clinical treatment of peripheral nerve injury. It can promote the circulation of blood and lymph, accelerate the repair of injured nerves, and improve the metabolic function of the body, but its mechanism remains to be explored. The activation and activation of macrophages, the occurrence of Wallerian degeneration, and the activation of Schwann cells play a huge role in the process of Tuina repair of damaged nerves. Therefore, macrophages provide objective evidence for the repair of peripheral nerve injury by massage.*

Keywords: Macrophage, Massage, Injury of peripheral nerve, Review.

1. Introduction

Peripheral nerve injury refers to the occurrence of motor disorders, sensory disorders, autonomic dysfunction, and reflex abnormalities in the area innervated by the peripheral nerve plexus, nerve trunk, or its branches due to compression, tension, tearing, contusion, etc [1]. The number of patients with peripheral nerve injury in China is about 300,000 to 500,000 [2], which seriously reduces the quality of life of patients, affects their work ability, and even causes huge psychological burden to patients [3]. In addition, there is a trend towards younger individuals with peripheral nerve injuries [4], the treatment of peripheral nerve injuries deserves widespread attention. After peripheral nerve injury, macrophages are activated and become active, accelerating nerve repair by clearing tissue cell debris and releasing nutritional factors. It is worth noting that mechanical stimulation is involved in the progression of various diseases by affecting various changes in macrophages [5]. Traditional Chinese massage techniques, as a mechanical stimulation, can treat sensory and motor disorders caused by peripheral nerve injury, such as cervical spondylotic radiculopathy and lumbar disc herniation. They are widely used in clinical practice [6]. This article is based on the macrophage-immune theory to explore the mechanism of massage in repairing peripheral nerve damage.

2. Classification and Activation of Macrophages

Macrophages, as the "scavengers" of the human body, are innate immune cells that play an important role in promoting nerve regeneration and maintaining neural homeostasis. During the repair process of peripheral nerve injury, macrophages have the characteristic of a "double-edged sword" [7]. In the nervous system, macrophages are divided into resident macrophages and infiltrating macrophages. After peripheral nerve injury, resident macrophages are more involved in the recognition of injury, while infiltrating macrophages are more involved in the clearance of injury. The combined effect of the two promotes the repair of peripheral nerve injury [8]. Macrophages have heterogeneity

[9], and changes in the local microenvironment induce polarization of macrophages, which can be expressed in two phenotypes: M1 and M2. M1 type is a classically activated macrophage that induces injury and promotes inflammatory response, releases inflammatory mediators, promotes tissue degeneration and necrosis, and aggravates the degree of injury; M2 type is a substitute activated macrophage that produces anti-inflammatory factors, reshapes the regenerative microenvironment, clears cell debris, releases nutritional factors, reshapes the extracellular matrix, and repairs and regenerates damaged nerves [10]. In the early stage of peripheral nerve injury, macrophages are recruited to induce polarization into M1 type around damaged axons and neuronal bodies. With time and changes in molecular composition in the injury environment, macrophages polarize into M2 type and participate in peripheral nerve repair and regeneration [11]. In addition, M2 type can be further divided into four subtypes: M2a, M2b, M2c, and M2d. M2a secretes extracellular matrix components to promote tissue repair; M2b inhibits inflammation and regulates immune function; M2c inhibits inflammatory response and promotes tissue repair; M2d regulates vascular remodeling function [12]. Therefore, during the process of nerve injury repair, M2 macrophages that play a repairing role mainly play a key role in M2a and M2c types, which can significantly enhance tissue repair ability.

3. Macrophages Participate in the Microenvironment of Neural Repair

Macrophages, as the "star cells" that determine the local microenvironment of damaged nerves, participate in Wallerian degeneration, enhance Schwann cell expression, control glial cell maturation, and promote damaged nerve repair. After peripheral nerve injury, on the one hand, M1 macrophages induce Wallerian degeneration, leading to axonal degeneration, necrosis, and myelin sheath disintegration in the distal segment, producing a series of tissue fragments that inhibit nerve repair; On the other hand, M2 macrophages respond to tissue damage and exert phagocytic activity to quickly and effectively remove cellular debris from damaged tissues, providing a favorable

microenvironment for the repair of damaged nerves [13]. Macrophages release cytokines, enhance the ability of Schwann cells to express nerve regeneration factors, reshape the extracellular matrix, regulate axonal growth, promote myelination, and induce nerve regeneration. In addition, macrophages can indirectly promote nerve regeneration by releasing oligodendrocyte inhibitors to control the maturation process and quantity of oligodendrocytes [14]. Although macrophages are the "star cells" that improve the local microenvironment of damaged nerves, considering their heterogeneity, clearing macrophages is also a key step in repairing damaged nerves. Research has shown that the interaction between Nogo receptors (NgRs) and related ligands is involved in macrophage clearance [15].

4. Massage Regulates Macrophage Activation

Macrophages are important members of innate immune cells and can mediate the occurrence and resolution of inflammation. Adjusting the balance between M1 and M2 macrophages and promoting their polarization towards M2 phenotype, targeting the different roles of macrophages, is expected to become another strategy for peripheral nerve injury repair. Research has shown [16] that mechanical stimulation can regulate macrophage polarization towards M2 type, thereby producing a series of anti-inflammatory factors to regulate the local inflammatory microenvironment and induce corresponding tissue regeneration. This indicates that macrophages are mechanically sensitive. Massage, as a gentle mechanical stimulation, can regulate macrophages to present M2 phenotype and exert corresponding functions.

5. The Effect of Massage on the Regeneration of Peripheral Nerve Injury

Mechanical stimulation contributes to the regeneration of various tissues [17]. Tuina, as an important external treatment technique in traditional medicine, belongs to the category of mechanical stimulation, which promotes blood and lymphatic circulation, accelerates the repair of damaged tissues, and improves the metabolic function of the body [18]. Through the specific effects of manipulation acupoints, it has significant therapeutic effects on various diseases [19].

Based on the theory of traditional Chinese medicine, discussions on peripheral nerve injury usually focus on "muscle injury", "bi syndrome", and "impotence syndrome" [20]. Muscle injuries are often caused by falls and falls, leading to local stagnation of qi and blood, blockage of meridians, and resulting in sensory disorders such as limb numbness and pain; Bi syndrome is often caused by deficiency of positive qi and invasion of evil qi, leading to loss of meridian nourishment, nerve compression, and motor and sensory dysfunction such as pain and muscle atrophy; The "impotence syndrome" is often caused by congenital deficiency of essence and qi, lack of nourishment in diet after birth, and external pathogenic factors, leading to organ deficiency, depletion of body fluids, and loss of nourishment of muscles and meridians, resulting in blocked meridians and loss of nourishment of muscles and meridians, leading to impotence [21]. In response to the above symptoms, massage therapy plays a role in relaxing meridians, promoting the circulation of qi and blood, improving local microcirculation,

stimulating the regrowth of damaged nerves, and thus achieving the goal of preventing and treating diseases [22]. Modern medicine believes that the repairing effect of massage on injuries is reflected in the biological resonance phenomenon where the frequency of manual force is close to or approximately equal to the natural frequency of the locally damaged tissue, and the manual force is transmitted to the deep part of the tissue through the penetration effect, causing the corresponding receptors in the body to be excited, thereby changing the local internal environment [23]. Peripheral neuropathy is mainly characterized by axonal damage, which causes almost complete loss of nerve conduction velocity. Wallerian degeneration occurs in the distal part, resulting in damaged cell fragments and necrotic tissue [24]. In this process, the mechanical stimulation of massage will produce a benign response to the local nerve damage, by improving the blood circulation of damaged nerve myelin sheaths, promoting Schwann cell proliferation, inducing immune stress response in the body, regulating macrophage activation, and thereby clearing damaged tissue fragments, restoring axonal growth, and providing conditions for the microenvironment required for nerve regeneration.

6. Massage Participates in Macrophage Mediated Neural Regeneration Microenvironment

Wallerian degeneration is an inevitable process for the generation of neural regeneration microenvironment, and satisfactory neural repair cannot be achieved without appropriate Wallerian degeneration. After nerve fiber injury, axonal injury induces reactions in the proximal and distal axonal remnants, with degeneration and disintegration occurring in the distal end. A large number of macrophages are recruited to the damaged nerve, engulfing fragments of degenerated axons and myelin sheaths, and playing an important role in the immune response, thus creating a favorable microenvironment for nerve regeneration [25]. At the same time, as the main mediator of Wallerian degeneration, Schwann cells begin to proliferate extensively to promote the expression and secretion of nerve growth factors, thereby providing impetus for myelin sheath regeneration and axonal recovery, and reshaping the microenvironment of nerve regeneration [26]. During this process, the proliferation of Schwann cells is closely related to the recruitment and infiltration of macrophages. So, the involvement of massage in the macrophage mediated neural regeneration microenvironment is achieved by increasing the number of Schwann cells, promoting the release of nerve regeneration factors, restoring axonal growth, and myelin formation.

6.1 Increase the Number of Schwann Cells

Schwann cells are glial cells that form and maintain myelin sheaths around axons and support axonal regeneration. They can secrete neurotrophic factors and have functions of supporting, nourishing, and protecting nerves [27]. As the "star cells" of neural repair, macrophages can activate Schwann cells and promote their proliferation, participating in neural repair [28]. Shao Shuai [29] used histological methods to observe the number of Schwann cells in the sham surgery group, model group, and massage group rats. The results

showed that regenerated nerve fibers were visible in the sciatic nerve of the massage group, and the number of Schwann cells outside the sheath was significantly increased compared to the model group. Indicating that massage can promote the repair of peripheral nerve damage by increasing the number of Schwann cells. Therefore, in this process, massage participates in the repair of the microenvironment of peripheral nerve injury by increasing the number of Schwann cells activated by macrophages.

6.2 Promote the Release of Nerve Regeneration Factors

The extensive proliferation of Schwann cells promotes the expression and release of nerve growth factors. Nerve growth factor (NGF) is one of the important nerve factors that constitute the microenvironment of nerve regeneration, which can promote the ability of peripheral nerve repair and regeneration [30]. Research [31] has shown that Schwann cells can increase the expression of axonal regeneration related transcripts (IncARAT), which can promote macrophage infiltration by increasing the expression of C-C motif ligand 2 (CCL2), indicating that Schwann cells can promote macrophage infiltration and recruitment. Secondly, macrophages can regulate the maturation of Schwann cells after peripheral nerve injury. The interaction between Schwann cells and macrophages indicates that macrophages can affect the secretion of nerve regeneration factors. Mei Rongjun used neurophysiological and immunohistochemical methods to observe the repair of brachial plexus injury in three groups: the brachial plexus injury model group, the mechanical vibration massage group, and the NGF intramuscular injection group. The results showed that the mechanical vibration massage treatment group was superior to the NGF treatment group and the model group, while the NGF treatment group was superior to the model group in terms of the recovery degree of the brachial plexus nerve trunk, nerve myelin sheath, and affected limb muscles, as well as changes in endogenous NGF concentration in the submandibular gland [32]. This indicates that massage can induce functional regulation of the immune and neuroendocrine systems, promote the secretion of glandular NGF, and thus have a significant therapeutic effect on brachial plexus nerve injury. Wang Chunhong used immunohistochemistry related detection methods to observe the nerve growth factor levels in the model group and the massage treadmill training intervention group of rats after sciatic nerve anastomosis. The results showed that compared with the model group, the NGF levels in the treatment group increased at intervention durations of 1 month, 2 months, 3 months, and 4 months [33]. This indicates that the combination of massage techniques and treadmill training promotes the expression and secretion of NGF, providing a suitable microenvironment for axonal regeneration. Guo Rubao used immunohistochemistry related methods to observe the nerve growth factor levels in the control group, model group, and massage group of rabbits. The results showed that compared with the control group and model group, the NGF levels in the massage group were significantly increased at each time point [34]. This indicates that massage techniques do indeed promote the expression of NGF in damaged peripheral nerves. Therefore, in this process, massage participates in the repair of the microenvironment of peripheral nerve injury by promoting the expression and

secretion of nerve growth factors influenced by macrophages.

6.3 Restore Axonal Growth and Myelin Formation

The activation of nerve growth factors provides the driving force for axonal growth and myelin formation to reconstruct the local microenvironment of nerve regeneration [35]. In addition to increasing the expression of nerve growth factors, Schwann cells also play a key role in the axonal regeneration process of peripheral nerve injury by interacting with macrophages. During the process of peripheral nerve repair, macrophages reduce local inflammatory responses and Schwann cells guide axonal regeneration, creating a microenvironment that allows peripheral nerves to grow and extend to restore axonal regeneration [36]. Lu Mengqian observed the structure, morphology, and distribution of nerve fiber myelin sheaths, axons, and Schwann cells in the sham surgery group, sciatic nerve injury model group, and massage intervention group through electron microscopy. The results showed that compared with the sham surgery group and model group, the myelin sheath structure of the massage group was basically normal, the structure was arranged neatly, some myelin sheaths were swollen on the inner side, and the axons were basically normal. This indicates that massage can promote the regeneration of nerve fiber myelin sheaths by regulating the cytoskeleton of regenerating axon cells, thereby significantly promoting the repair and regeneration of ultrastructure after peripheral nerve injury [37]. This indicates that massage can promote the regeneration of nerve fiber myelin sheaths by regulating the cytoskeleton of regenerating axon cells, thereby significantly promoting the repair and regeneration of ultrastructure after peripheral nerve injury. Geng Nan used immunohistochemical methods to observe the expression of neurotrophic factor-3 (NT-3) and tyrosine kinase receptor C (TrkC) in the medullary ventral horn of rats in the normal group, sham operation group, model group, control group, and massage intervention group with sciatic nerve injury. The results showed that compared with each group, the massage group had the highest average optical density of NT-3 and TrkC, and an increase in the number of axonal nerves [38]. This indicates that massage can promote the expression of NT-3 and TrkC, inhibit cell apoptosis, increase the number of myelinated nerves in damaged nerve axons, promote the growth of neuronal cell bodies and processes, and thus promote the repair of nerve damage. Shen Yi used transmission electron microscopy to observe the myelin sheath thickness in the normal group, sham surgery group, sciatic nerve injury model group, and massage intervention group. The results showed that the model group had severe myelin sheath collapse, while the massage group showed significant improvement in the ultrastructure of nerve injury points, and the nerve fiber myelin sheath was preserved relatively intact [39]. This indicates that massage can improve the morphology of myelin sheaths at nerve injury sites and accelerate the recovery of sciatic nerves after injury. Therefore, in this process, massage participates in the macrophage mediated neural regeneration microenvironment by restoring axonal growth and myelin formation.

7. Summary and Outlook

After peripheral nerve injury, it seriously affects the quality of life of patients and is a common clinical problem. Unlike

central nervous system injury, peripheral nervous system injury has a certain ability to regenerate and repair. Appropriate treatment methods can accelerate the regeneration of damaged peripheral nerves and restore patients' quality of life. Macrophages play a significant role in the generation of the neural regeneration microenvironment during the repair process of peripheral nerve injury. Moreover, the mechanical sensitivity of macrophages has been recognized by everyone, and massage has also made some progress in repairing damaged nerves. Research has shown that the type of mechanical stimulation can affect the phenotype of macrophage activation [40]. This article explores the effect of massage on nerve injury repair from the perspective of macrophages. However, in the microenvironment repair of peripheral nerve injury, in addition to the involvement of macrophages, resident glial cells, vascular cells, and extracellular matrix all play important roles [41]. Therefore, for the research on the repair and regeneration of peripheral nerve injuries, these will be the next research directions for massage therapy for peripheral nerve injuries.

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