

Research Progress on the Mechanism of Massage in Regulating Immune Function

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Abstract: *Massage, as a non-invasive and natural therapy, acts on specific parts of the human body through manual techniques to regulate organ function, unblock meridians, promote qi circulation and blood circulation, demonstrating a positive regulatory effect on immune function. This article comprehensively analyzes the positive effects of massage on the activity of immune cells, regulation of immune molecule secretion, improvement of immune organ function, and the immune system. Research has revealed that massage may exert its effects through various mechanisms such as neuroendocrine immune regulation, cellular signaling pathways, oxidative stress and antioxidant balance, non coding RNA regulation, and microbial community regulation. Intended to provide scientific basis for further research and clinical application of massage therapy.*

Keywords: Tuina, Immunity, Immune regulation, Traditional Chinese Medicine Theory, Neuroendocrine immune regulation, Signal transduction pathway, Oxidative stress, Non coding RNA, Microbial community.

1. Introduction

The immune system forms the core defense line against external invasion, recognizing and expelling pathogens to maintain the stability of the internal environment. In modern society, with the acceleration of the pace of life and the deterioration of environmental problems, the incidence rate of immune related diseases has gradually increased, posing a serious threat to human health. Although traditional medication can alleviate symptoms to some extent, long-term use may lead to side effects and resistance issues. As a non-invasive treatment method, massage therapy demonstrates unique therapeutic advantages due to its natural therapeutic properties. It regulates organ function, promotes qi and blood circulation, and corrects abnormal states of muscles and fascia by applying techniques to specific parts of the human body. Research has shown that massage can regulate immune function through various mechanisms such as neuroendocrine immune regulation, cell signaling pathways, oxidative stress and antioxidant balance, non coding RNA regulation, and microbial community regulation. This article aims to explore the mechanism of massage in immune regulation, in order to provide scientific basis for the promotion and application of massage therapy.

2. The Regulatory Effect of Massage on Immune Function

2.1 Regulation of Immune Cells

2.1.1 T lymphocyte subpopulation balance

The T lymphocyte subsets mainly include CD4+T cells and CD8+T cells. CD4+T cells are responsible for regulating immune responses, helping B cells produce antibodies, and activating other immune cells; CD8+T cells are primarily responsible for directly attacking and killing infected cells or cancer cells. Wang Jingliang et al. [1] performed massage therapy on children with recurrent respiratory tract infections

and found that the number of T lymphocyte subsets CD3+, CD4+, and CD4+/CD8 levels were significantly increased. The number of acute episodes of respiratory tract infections in patients decreased, and symptoms improved, suggesting that massage can effectively improve the T lymphocyte subsets of patients and enhance their immune system. Wang Zhihong et al. [2] established an immunosuppressive animal model by intraperitoneal injection of cyclophosphamide, and applied techniques such as direct pushing, massage, and spine massage to the back of rabbits. They found that back massage could increase the difference in body mass before and after intervention in immunosuppressive rabbits, effectively improve their physical condition, and increase the CD3+and CD4+content of immunosuppressive rabbits while reducing CD8+content, indicating the regulatory effect of back massage on immune function. A study has found [3] that through massage therapy on elderly people with aging CD4+T cell subsets, after 6 treatments, the percentage of CD4+T subsets decreased, especially CD4+28nlnKG2D+T cells, indicating that massage may improve immunity by reducing abnormal CD4+T cell subsets and can be an adjuvant therapy for improving the immune system of elderly people. Cao Juan et al. performed massage therapy on children with viral enteritis. Before treatment, the patient's CD4+T lymphocytes significantly decreased, resulting in a decrease in the CD4+/CD8+ratio. After treatment, the CD4+T lymphocyte level increased, bringing the CD4+/CD8+ratio close to normal. Tuina massage can improve the immune status of patients by increasing CD4+T lymphocyte levels.

2.1.2 Regulation of macrophages

Macrophages originate from hematopoietic stem cells in the bone marrow and differentiate into mature macrophages after entering tissues through blood circulation. Not only can it identify and eliminate foreign pathogens, but it also plays an important role in restoring damaged tissues and regulating the body's inflammatory processes. A study has found [5] that massage techniques such as one finger Zen pushing, cupping,

and plucking, combined with cervical rotation, can reduce the levels of CD68 and MMP-2 in macrophages within plaques and promote plaque stability; The increase in cervical rotation angle can lead to an increase in MMP-2 expression, thereby reducing plaque stability, revealing that massage may affect plaque stability by regulating the expression of macrophages and related proteases. Tuina massage regulates immune function by modulating the expression of TLRs [6-8].

2.1.3 Effects on NK cells

Natural killer (NK) cells are a part of the human immune system, belonging to the innate immune system. They are the body's first line of defense against viral infections and tumors, and can quickly respond and eliminate abnormal cells in the body. In a randomized controlled trial of massage versus placebo treatment for premature infants [9], massage therapy was performed 5 times a week until discharge or up to 4 weeks. After treatment, there was no difference in NK cell count between the two groups; Infants who receive at least 5 days of massage have higher NK cell cytotoxicity, and those who receive massage have heavier body weight. Indicating that massage can enhance NK cell cytotoxicity, increase infant weight, improve the immune defense ability of premature infants, reduce the risk of infection, and promote their overall health and development.

2.2 Regulation of Immune Molecules

2.2.1 Regulation of immunoglobulin

Immunoglobulin (Ig) is a type of protein secreted by B cells that plays a crucial role in the body's defense mechanisms. Being able to accurately identify and bind specific antigens, such as bacteria, viruses, and toxins, to activate immune responses and eliminate or weaken harmful foreign substances. Tian Fuling et al. [10] used massage techniques such as tonifying the spleen, lung, and kidney meridians, clearing the lung and liver meridians, reversing the eight trigrams, and promoting the six viscera and three guan to treat children with chronic persistent asthma. After 3 months of treatment, the serum IgA, IgG, and IgM levels in children with asthma increased significantly compared to before treatment, while IgE levels decreased significantly, indicating that pediatric massage can enhance immune response and effectively improve the immune function of children with asthma. Chen Weige [11] treated children with recurrent respiratory tract infections by massage techniques such as lung shu, kidney shu, spleen shu, and spinal massage. After 2 weeks of treatment, the observation group showed a significant increase in serum immunoglobulin IgG and IgA levels, indicating that pediatric massage therapy is effective in treating recurrent respiratory tract infections in children, promoting a significant improvement in their immune system and reducing the frequency of infection attacks. Shang Kun et al. [12] used back massage techniques such as rubbing, pushing, tapping, rubbing, and patting to treat chronic fatigue syndrome (CFS). The levels of immunoglobulin IgA, IgM, and IgG in patients were significantly increased, indicating that back massage can effectively alleviate physical fatigue in CFS patients, regulate systemic syndrome, improve immune function, and enhance disease resistance.

2.2.2 Regulation of inflammatory factors

Inflammatory response is a complex process involving the interaction of multiple inflammatory and pro-inflammatory factors. Inflammatory response is part of the body's defense mechanism, helping to clear damaged cells and pathogens. Inflammatory factors refer to molecules produced during the inflammatory process that can cause or enhance inflammatory responses, while pro-inflammatory factors refer to factors that can initiate or promote inflammatory responses. Zhang Xin et al. [13] used techniques such as massage, pushing, and pinching to treat subacute aging and immunocompromised rabbits. They found that back massage can increase the levels of interleukin-33 (IL-33) in local skin and brain tissues of rabbits, indicating that back massage can enhance the body's local immune function by increasing IL-33 levels. Zhou Hongyan et al. [14] used methods such as clearing and tonifying, purging the spleen, pushing up the three guan points, and massaging the epigastric and navel to treat pediatric diarrhea. Enzyme linked immunosorbent assay was used to measure the serum levels of IL-10, IL-6, and TNF- α in the children. After 14 days of treatment, the inflammatory cytokine levels of IL-10, IL-6, and TNF- α in the children were significantly reduced compared to before treatment. Tuina massage can reduce cytokine levels, alleviate inflammatory reactions, and regulate the immune function of pediatric patients. Niu Yan et al. [15] used abdominal massage to intervene in exercise-induced (EF) fatigue rats and found that this therapy can reduce the levels of inflammatory factors TNF- α and IL-1 β in PBMCs. They believe that abdominal massage can alleviate PBMC apoptosis in EF rats and restore exercise-induced immune suppression.

2.3 Regulation of Immune Organs

Immune organs are important components of the human immune system, responsible for generating, maturing, storing, and activating immune cells, as well as executing immune responses. Mainly including bone marrow, thymus, and spleen. Zhang Xin et al. [16] established a model by intraperitoneal injection of D-galactose, and applied massage, pushing, and spine massage techniques to the animal model. They found that the thymus index was significantly increased, indicating that massage can effectively improve the immune function of subacute aging animals. Gan Wei et al. [17] intervened in sub healthy guinea pigs with kidney yang deficiency by using pivot meridian massage, and intervened in Yongquan by pressing. They found that the thymus and spleen weights in the kidney yang deficiency massage group decreased, with indices lower than the blank control group but higher than the kidney yang deficiency model group; The thymus tissue of the massage group was close to that of the blank control group, indicating that massage can effectively reduce the atrophy of immune organs, improve immune function under sub-health conditions, and may have a positive impact on the number and arrangement of thymocytes. Pan Boyang [18] observed the effect of massage on the immune function of fatigue type sub-health model rats. The spleen index of the model group rats significantly decreased, while the thymus and spleen were damaged, and the early apoptosis rate of thymocytes was higher. The spleen index of the massage group was higher than that of the model group ($P < 0.05$), and its immune organ tissue and cell ultrastructure

were superior to those of the model group rats. The early apoptosis rate of thymocytes was significantly lower than that of the model group ($P < 0.05$). This indicates that massage has a protective effect on the immune organs of fatigue type sub-health model rats, which can improve the tissue structure of immune organs, reduce the apoptosis rate of immune cells, and protect and regulate immune function.

3. Study on the Mechanism of Massage on Immune Function

3.1 Neuroendocrine Immune Regulation

Neuroendocrine immune regulation forms a complex network in the human body, which interacts with various signaling molecules and pathways to maintain the stability and health of the internal environment. Research has shown [19] that massaging healthy adults twice a week increases the levels of oxytocin (OT) in their bodies, while the levels of arginine vasopressin (AVP) and cortisol (CORT) show a decreasing trend. Twice a week massage has little effect on circulating phenotype lymphocytes, but can increase levels of tumor necrosis factor- α , interleukin-1 β , and IL-2. Indicating that massage can affect the regulation of immune function by adjusting the levels of neurotransmitters and endocrine hormones. Another study [20] found that massaging C57/BL6 mice with hands significantly increased the number of T cells in the thymus and spleen. By combating the immunosuppressive effect of hydrocortisone in the body, massage reduced the intensity of noradrenergic innervation in the thymus and spleen, and reduced inhibitory noradrenergic innervation in the lymphatic organs to regulate immune function. Shang Kun et al. [21] used intraperitoneal injection of cyclophosphamide to create a model and observed the changes in β -EP content in different tissues (hypothalamus, plasma, and lymphoid tissue) of rabbits treated with back massage. They found that back massage not only activated the hypothalamus to increase the synthesis of β -endorphin (β -EP), but also promoted its entry into the bloodstream. Although the level of β -EP in plasma has decreased, the content of β -EP in lymphoid tissue has significantly increased, indicating that massage helps regulate the distribution of β -EP and enhance immune function. Xi Renjie et al. [22] found in their experiment that the regulation of NE concentration in immune organs by different massage techniques is related to the site of manipulation, and massage can reduce the NE concentration in sympathetic nerve endings in the thymus and spleen, reduce the inhibitory effect of NE on immune cells, and enhance immune function. Ma Chi et al. [23] investigated the effects of acupuncture on neuropathic pain in rats and found that the photothermal pain tolerance threshold of the acupuncture group rats significantly improved, approaching normal levels. The expression level of IL-6 in the spinal cord decreased, while the expression level of SOCS3 was higher. Wang Huijuan et al. [24] found that the "Da Tui Tian He He He" technique can affect the levels of 5-H and NE in the hypothalamus, indicating that changes in neurotransmitters are related to immune regulation. Massage intervention may help regulate the levels of these neurotransmitters, thereby affecting immune function.

3.2 Regulation of Cellular Signaling Pathways

The cellular signaling pathway can transmit external signals to the interior of cells, thereby activating or inhibiting the function of immune cells. Not only does it mediate the activation and function of immune cells, but it also participates in regulating the metabolism of immune cells. These signaling pathways form a complex network that ensures precise and timely immune response. Fang Yanping [25] found through the effect of spinal therapy on the inflammatory response of chondrocytes in cervical spondylosis model rats that spinal therapy can reduce the expression levels of IL-6 and IL-8 in intervertebral disc chondrocytes of cervical spondylosis model rats. Downregulate the protein expression of MKK3/6 and p38MAPK in its tissue. This indicates that spinal therapy regulates immune function by affecting the MKK3/6 and p38MAPK signaling pathways, participating in the regulation of various biological processes such as cellular inflammation and apoptosis. Gao Tianjiao et al. [27] found through experimental research that abdominal massage can activate the SIRT1/NF- κ B signaling pathway, reduce the production of pro-inflammatory cytokines in adipose tissue, and promote macrophage polarization towards anti-inflammatory M2 type. This indicates that the SIRT1/NF- κ B signaling pathway plays a crucial role in regulating immune responses and inflammatory processes. Xue Huitian [28] found through the effect of massage massager (揉) on skeletal muscle injury in rabbits at different time points that massage massager (揉) can regulate the NF- κ B signaling pathway, inhibit the release of NF- κ B p65 protein in damaged tissues, increase the content of its inhibitory protein I κ B α protein, thereby downregulating inflammatory factors TNF- α and IL-1 β , reducing immune-mediated inflammatory response caused by skeletal muscle injury, promoting muscle cell regeneration, and improving the speed of skeletal muscle repair. This indicates that massage equipment (揉 method) may exert its therapeutic effect on skeletal muscle injury by regulating immune response. Chen Jinping et al. [29] investigated the effects of the "Three Methods and Three Points" massage technique on mild sciatic nerve chronic compression injury (MinorCCI) model rats and found that massage intervention can improve mechanical pain and cold stimulation sensitization by inhibiting the expression of IL-17A, IL-17RA, and C/EBP β signaling pathways in the spinal dorsal horn, thereby achieving immediate analgesia. Indicating that massage techniques may exert their analgesic effects by regulating immune related signaling pathways.

3.3 Balanced Regulation of Oxidative Stress and Antioxidant System

The balance between oxidative stress and antioxidant defense is one of the key factors in maintaining the function of the immune system. Oxidative stress occurs within cells due to an imbalance in redox balance caused by excessive accumulation of reactive oxygen species and nitrogen compounds. The antioxidant system neutralizes harmful substances through enzymes such as superoxide dismutase and non enzymes, protecting cells from damage [30]. Lu Yi et al. [32] used abdominal massage to treat chronic fatigue syndrome of liver depression and spleen deficiency type, and found that the levels of oxidative stress indicators malondialdehyde (MDA) and lipid peroxidation (LPO) decreased, while the activities of antioxidant enzymes superoxide dismutase (SOD) and

glutathione peroxidase (GSH Px) increased. This indicates that abdominal massage improves the immune status and alleviates fatigue symptoms by reducing oxidative damage and enhancing antioxidant defense ability, thereby improving the symptoms and quality of life of CFS patients. Song Yao et al. [33] treated children with cerebral palsy by warming yang and unblocking collaterals acupuncture and moxibustion combined with massage. They observed that the level of superoxide dismutase (SOD) in children's serum increased, and the levels of malondialdehyde (MDA) and cysteine aspartate protease 3 (Caspase-3) decreased, indicating that the treatment may improve the oxidative stress state, reduce the damage of free radicals to immune cells, and be conducive to the normal function of the immune system and the recovery of diseases. Cui Junyu [34] improved functional dyspepsia (FD) with the massage technique of "regulating the meridians and organs", and found that it can reduce the content of reactive oxygen species (ROS) in gastric tissue, increase the activity of superoxide dismutase (SOD), and reduce the release of malondialdehyde (MDA). Indicating that massage can alleviate oxidative stress, possibly reducing immune cell activation and inflammatory response.

3.4 Regulatory Role of Non Coding RNA

Non coding RNAs, including microRNAs (miRNAs), long non coding RNAs (lncRNAs), and circular RNAs (circRNAs), are important regulatory molecules within cells. Especially lncRNA and circRNA regulate gene expression through the absorption of miRNA in the ceRNA mechanism [35]. lncRNA not only guides the differentiation and development of immune cells, but also participates in maintaining the activation state of immune cells and regulating the expression of inflammatory genes. miRNA, as a key regulatory molecule, plays an important role in resisting pathogens and disease development by regulating innate immune responses and reducing the production of inflammatory factors [36-37]. Liang Yingye [38] found that by targeting the regulation of IL-1 related protein kinase 1 (IRAK1) and tumor necrosis factor receptor activator 6 (TRAF6) in the Toll like receptor 4 (TLR4) signaling pathway in neuropathic pain rats, the expression level of miRNA-146a can be upregulated, and the TLR4 signaling pathway can be downregulated, which can promote the expression of inflammatory factors TNF- α and IL-6. It has been demonstrated that miRNA-146a can regulate key molecules in the TLR4 signaling pathway, affect the release of inflammatory factors, and thus participate in the regulation of neuropathic pain. Zhou Kelin [39] intervened in depression rats through abdominal massage and found that it could reduce the levels of inflammatory factors IL-1 β , IL-6, and TNF- α in skeletal muscle tissue, increase the levels of anti-inflammatory factors IL-4 and IL-10, and upregulate miRNA-130b expression to inhibit the TLR4/MyD88/NF- κ B pathway, thereby inhibiting the activity of NLRP3 inflammasome and reducing inflammatory damage in skeletal muscle. Indicating that abdominal massage has a positive impact on the treatment of depression by regulating immune related pathways, inhibiting inflammatory responses. Wei Zongbo et al. [40] found in their experiment that before treatment, the expression level of lncRNA-GAS5 was low in the spinal dorsal horn of NPP rats, but increased after intervention with pivot massage, indicating that lncRNA-GAS5 can act as a "molecular sponge" to adsorb

specific microRNAs (such as miR-21), thereby affecting the expression of target genes of microRNAs. The expression level of miR-21 may increase, and lncRNA-GAS5 can reduce its inhibitory effect on target genes by adsorbing miR-21, thereby affecting neuronal apoptosis and immune response.

3.5 The Regulatory Role of Microbial Communities

The gut microbiota has a significant regulatory effect on the immune system, by affecting the function of immune cells and inflammatory responses, regulating immune responses, defending against pathogen invasion, and playing a role in disease treatment. Microbial diversity is crucial for health, and imbalanced microbiota may lead to inflammation and autoimmune diseases [41]. Hu Dan [42] used massage therapy to treat pediatric diarrhea, which can regulate the ratio of fecal globules/bacilli, sIgA content, serum diamine oxidase, and procalcitonin (PCT), indicating that massage can restore the balance of intestinal microbiota, enhance mucosal immunity, regulate inflammatory response, and improve humoral and cellular immune function, working together on the immune system to promote the health and recovery of children. The mechanism may be related to improving the immune function of children and promoting the balance of intestinal microbiota in children. She Weiwei [43] observed the effects of syndrome differentiation and massage techniques on the immune function and gut microbiota of children with antibiotic associated diarrhea (AAD). It was found that the proportion of fecal cocci/bacilli significantly decreased, the content of fecal secreted immunoglobulin A (sIgA) significantly increased, and the levels of serum immunoglobulin A (IgA) and immunoglobulin M (IgM) increased. This suggests that massage can improve the immune defense ability of the intestinal area and restore the balance of intestinal microbiota to enhance immunoglobulin levels, thereby improving the resistance of children and promoting health recovery. Jiang Shuhong et al. [44] used acupoint massage to treat spleen deficiency syndrome after rectal cancer surgery. They selected acupoints such as Zusanli, Hegu, Zhongji, Neiguan, Sanyinjiao, Yinlingquan, Zhongwan, and Qihai for massage, and found that the number of beneficial bacteria such as Bifidobacterium and Lactobacillus in the intestinal microbiota increased significantly, while the number of harmful bacteria such as Enterococcus, yeast, and Escherichia coli decreased significantly. Tuina massage can maintain the balance of intestinal microbiota, restore intestinal function, improve immune function, enhance resistance, and reduce the occurrence of adverse reactions. Wang Zhe et al. [45] treated children with persistent diarrhea by massaging specific acupoints such as Tian Shu, Shen Que, Qi Jie Gu, and Gui Wei. After treatment, the number of lactobacilli, bifidobacteria, and fecal enterococci in the intestines of children who received massage at specific acupoints increased, and the levels of immunoglobulins (IgG, IgM, IgA) in the serum of children increased. This indicates that massage can regulate the structure, maintain the balance, enhance the immune defense ability of intestinal mucosa, reduce inflammatory reactions, improve the body's resistance to pathogens, and have a positive therapeutic effect on children with persistent diarrhea and spleen deficiency syndrome.

4. Summary

In recent years, research on the regulation of immune function through massage has made certain progress, by affecting the activity of immune cells, the level of immune molecules, and the status of immune organs, thereby enhancing the body's immune ability. Tuina is a multi-target, multi-channel, and all-round integrated regulation that not only involves fine regulation of the nervous endocrine immune system, but also includes direct intervention in signal transduction pathways and regulation of the balance between oxidation and antioxidant. In addition, the immune regulatory ability is further enhanced through the regulatory effects of non coding RNA and the adjustment of gut microbiota.

At present, tuina has demonstrated its unique therapeutic advantages in clinical treatment. In the future, more clinical trials should be focused on verifying its efficacy in various immune related diseases; Exploring the molecular mechanisms of tuina using modern molecular biology techniques; Consider individual differences and develop personalized treatment plans; And promote the standardization and interdisciplinary research of massage techniques. Through these measures, the treatment process can be optimized, treatment effectiveness and safety can be improved, thereby promoting the scientific and modern development of massage therapy.

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