

Research progress on the mechanism of action of acupuncture in the treatment of gastric cancer

Li Chen^{1,a}, Chen Jie^{2,b,*}, Fan Jin^{1,c}, Zheng Chao^{1,d}

¹First School Clinical Medicine, Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi, China

²Department of Oncology, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an, Shaanxi, China

^alichen13227901774@163.com, ^bchenjie0509@163.com, ^c744551830@qq.com, ^d763601201@qq.com

*Corresponding author

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Abstract: Gastric cancer is one of the deadliest malignant tumors, and recent studies have confirmed the clinical efficacy of acupuncture in the treatment of gastric cancer, which has been recognized and widely carried out in clinical practice both at home and abroad, while less research has been conducted on the mechanism of acupuncture in the treatment of gastric cancer. By reviewing the research on the anti-gastric cancer effects of acupuncture in recent years, we categorized and summarized from acupuncture regulating intestinal flora, acupuncture regulating body immunity, acupuncture regulating tumor markers, acupuncture regulating apoptotic genes, acupuncture regulating cell cycle of cancer cells, and acupuncture regulating signaling pathways to provide a new theoretical basis for acupuncture treatment of gastric cancer. It provides new ideas for future clinical application and research of acupuncture in gastric cancer.

Gastric cancer is a kind of refractory malignant tumor, with the fifth highest incidence rate and the third highest mortality rate in the world ^[1]. At present, there are many western medical treatments for gastric cancer, including surgery, radiotherapy, chemotherapy, molecular immunotherapy and targeted therapy, etc., which have large side effects and seriously affect people's quality of life. In recent years, Chinese medicine has achieved good efficacy in the prevention and treatment of gastric cancer, and its mechanism of action is more extensive and has received wide attention ^[2]. And acupuncture has a wide range of anti-tumor effects, low side effects, and easy operation ^[3]. Acupuncture has significant efficacy in the treatment of symptoms and adverse reactions related to gastric cancer, and its mechanism of action is less summarized at present. We summarize the mechanism of action of acupuncture in the treatment of gastric cancer to provide a better basis for the treatment of gastric cancer with acupuncture.

1. Acupuncture regulates intestinal flora

Acupuncture can promote the proliferation of beneficial intestinal flora, inhibit pathogenic

bacteria, reduce the virulence of pathogenic bacteria through the "probiotic effect", regulate the composition of intestinal flora, enrich the diversity of intestinal flora, and promote the homeostasis of intestinal microenvironment, and intestinal flora is closely related to gastric cancer. Xie Linyan ^[4] et al. found that the number of bifidobacteria and lactobacilli in the intestinal tract increased after acupuncture at the bilateral "Foot San Li" points. and the cell wall of bifidobacteria has intact peptidoglycan, which can enhance the immune response of the intestinal mucosa and inhibit the growth of spoilage bacteria, thus reducing the production of some carcinogenic substances and helping to inhibit the growth of tumor cells growth ^[5-6]; Lactobacillus inhibits the invasion of pathogens by competing for pathogenic sites and thus producing a large amount of organic acids and antibacterial substances such as hydrogen peroxide, reducing the stimulation and infiltration of chemotherapeutic drugs and tumors into the gastrointestinal wall, inhibiting cell oxidation, and delaying tissue aging ^[7].

2. Acupuncture regulates the body's immunity

The immune system removes diseased and aging cells in the body through immune response to ensure the health of the body, which is mainly divided into immune cells and immune factors, immune cells include T cells, B cells, NK cells, macrophages, etc. Immune molecules mainly include cytokines (e.g. interleukins, interferons, colony-stimulating factors).

2.1 Acupuncture regulates immune cells

T lymphocytes have an effector function by secreting various cytokines or activating other immune cells that play a role in tumor immunity, and Zhu Yanhua et al. showed that the serum immune indexes CD3+, CD4+, CD4+/CD8+ levels were increased and CD8+ levels were decreased by acupuncture at the acupuncture points of "Foot San Li and Qi Hai" ^[8]. The increase of CD4+ T lymphocyte ratio is an important marker of postoperative immune reconstitution, which can inhibit leukocyte aggregation, promote local circulation, affect the establishment of collateral circulation, reduce the vascular permeability of the body, and inhibit tumor recurrence in patients after surgery ^[9]. Liu Yu and Tan Jing et al. moxibustion has elevated CD4+ and CD3+ levels, moxibustion has certain inhibitory effects on tumor growth and metastasis, and blood vessels in the tumor are significantly reduced ^[10-11]. Related studies have shown that CD4+ T lymphocyte subpopulation assay helps to assess the immune status of the organism in patients with progressive gastric cancer, and the high level of CD4+ T cell infiltration shows better OS in gastric cancer patients, which is of clinical reference value for monitoring progressive gastric cancer ^[12-13].

B lymphocytes synthesize immunoglobulins (mIg) with specificity in response to antigen stimulation. Immunoglobulins (IgM, IgA, IgG) play an important role in anti-tumor, anti-inflammatory, and immune surveillance. In the treatment of postoperative gastric cancer patients with warm acupuncture, Ig A, Ig M and Ig G in gastric cancer tissues were significantly increased after treatment ^[14]; Liu Yu [10] et al. showed that IgM, IgA and IgG were increased after the intervention of moxibustion at the bilateral "Foot three li" acupuncture points for gastric cancer chemotherapy patients. Li Wenhua et al. found that CD20+ B cells were significantly increased in gastric cancer compared with normal tissues, and the number of infiltrating B cells in early gastric cancer tissues increased significantly compared with advanced gastric cancer, suggesting a negative correlation between tumor infiltrating B cells and gastric cancer progression ^[15-16].

NK cells are the core component of the body's innate immunity and are the basis of tumor cell immunity. When warm acupuncture was used to treat patients with postoperative chemotherapy for gastric cancer, the number of NK cells increased significantly after treatment and improved the immune function of the body ^[17]. Lei Zehong found that the larger and less differentiated the tumor

of gastric cancer patients, the lower the expression of their NK cell activating receptors NKG2D and NKp30, indicating that the higher the malignancy, the lower the NK cell activity and the poorer the immune function [18]. CD3-CD161+ is an NK cell marker, and the CD3-CD161+ content increased significantly after moxibustion, thus stimulating the body's anti-tumor non-specific immunity [19]. Studies conclude that NK cells can induce apoptosis through ADCC-mediated GC cell death, release of perforin and granzyme, secretion of IFN- γ and TNF- α , or through the formation of FAS/FASL and TRAIL/TRAILR complexes; NK cells will inhibit vascular proliferation near the tumor, limiting the nutrition required by the tumor and thus limiting tumor growth [20-21].

2.2 Acupuncture regulates immune factors

Cytokines are mainly small molecule proteins secreted by immune cells and non-immune cells induced by stimulation, which have immunomodulatory and information transfer functions, and acupuncture enhances the anti-tumor function of the body by regulating immune factors. Wei Shaowu showed [22] that acupuncture combined with chemotherapy for advanced gastric cancer, the effect of serum factor levels after treatment IFN- γ , TNF- α levels increased, IL-4 and IL-10 levels decreased, IFN- γ is a cytokine secreted by Th1 cells, which can inhibit DNA synthesis, by upregulating the expression of Fas/FasL on the surface of IFN- γ cells, and upregulating the expression of IFN- γ cell expression and slowing down cell mitosis to retard tumor progression [23];

TNF- α is released by mononuclear macrophages and inhibits tumor value-added through the immune system. The level of TNF- α in gastric cancer patients is greatly increased, so the level of TNF- α can better reflect the changes of patients' conditions. Studies have demonstrated that TNF- α induces normal cell proliferation and differentiation, inhibits tumor cell proliferation and induces apoptosis through caspase-mediated signaling pathway, NF- κ B-activated signaling pathway, and JNK signaling pathway [24].

Interleukins are common inflammatory cytokines, and studies have demonstrated that IL-4 is a pro-oncogenic factor, and the level of IL-4 is higher in the serum of tumor patients than in normal subjects, and IL-4 promotes tumor cell invasion and metastasis by activating various signaling pathways such as AKT and ERK [25-26]. IL-10 affects the differentiation and maturation of T-cell subsets and promotes the growth of tumor cells through immunosuppressive effects [27].

3. Acupuncture tunes tumor markers

CEA, CA199 and CA125 are common serum markers for preoperative diagnosis, postoperative monitoring and efficacy evaluation of gastrointestinal malignancies, but with limited specificity. The guidelines of the Chinese Society of Clinical Oncology Collaborative Center (CSCO) all suggest that serum CEA can be used to monitor disease progression in patients with gastric cancer [28], and the effect of acupuncture MNNG-induced gastric mucosal intervention in rats with precancerous lesions and on serum CEA showed that acupuncture and moxibustion pretreatment rats were able to reduce the elevation of serum CEA caused by MNNG, suggesting that acupuncture played an inhibitory effect [29].

4. Acupuncture regulates apoptotic genes

Apoptosis is a fundamental biological process that removes redundant or abnormal cells from multicellular organisms and plays a crucial role in the growth, development and other stages of an individual's life. The lack of apoptosis alters the endostasis between cells and may lead to tumorigenesis and promote tumor progression [30]. Lu Mei et al. found that both acupuncture and

moxibustion downregulated protein expression of p53 in bone marrow nucleated cells of CTX (cyclophosphamide) chemotherapy mice, upregulated the apoptosis suppressor gene bcl-2, and downregulated protein expression of the pro-apoptotic gene bax, which inhibited tumor cell apoptosis and promoted cell survival^[31]. bcl-2 family proteins include both pro-apoptotic and pro-survival proteins^[32], and notably pro-survival Bcl-2 proteins are often overexpressed in cancer cells and may also antagonize key factors mediated by oncogenes against apoptotic cycle arrest and apoptosis, and when Bcl-2 is highly expressed, cancer cells are resistant to apoptosis induced by various chemotherapeutic drugs^[33-34]. p53, as a transcription factor, regulates target genes mainly by binding to the DNA of p53 in target gene expression to achieve tumor suppressive function. p53 plays an important role in apoptosis and cell cycle arrest through transcriptional regulation of these genes^[35].

5. Acupuncture regulates the cell cycle of cancer cells

The cell cycle is the process that a cell undergoes through growth and division to form two cells, and the cell cycle includes interphase, which includes G1, S, and G2 phases and mitotic (M) phase, and cell proliferation in tumors is associated with cell regulation^[36], and Cyclin D1 binds to CDK4/6 and acts as a mitotic sensor to integrate extracellular mitotic signals and cell cycle progression. A study investigated the effect of acupuncture on the cell cycle of mouse bone marrow cells, the regulatory protein Cyclin D1 regulates the G1/S phase detection site, and the expression of the cell cycle regulatory protein Cyclin D1 was found to be down-regulated after acupuncture, Cyclin D1 inhibited cells from G1 phase into S phase, leading to increased cell genome stability and inhibiting the proliferation of gastric cancer cells^[37-38]. If Cyclin D1 is highly expressed, it activates cyclin-dependent kinase (CDK) activity, and the recently identified established CDK/cyclin complex regulates the cell cycle and is involved in the regulation of gene expression through phosphorylation of key components of transcription and pre-mRNA processing mechanisms. Current and growing data suggest that CDKs play a decisive role in tumor development, inhibiting proliferation and growth of tumor cells^[39-40].

6. Acupuncture regulates signaling pathways

Cell signaling pathway refers to the process by which cells feel the stimulation of external signals through located cell membrane or cell receptors, causing relevant effects and cellular responses, Nie Ruihua^[41] et al. moxibustion of stomach meridian points interfered with the effect of EGFR signaling pathway on the mediated growth of cancer cells, and found that moxibustion could delay the growth of tumors, EGFR belongs to the family of receptor tyrosine kinases, and EGFR promotes the proliferation, differentiation, survival, angiogenesis and metastasis of tumor cells by mediating PI3K/ AKT/mTOR promotes tumor cell proliferation, differentiation, survival, angiogenesis, and metastasis^[42].

7. Conclusion

At present, the incidence of gastric cancer is getting higher and higher, which has seriously affected people's life. The research on the mechanism of acupuncture for the treatment of gastric cancer mainly focuses on acupuncture to improve immune function, acupuncture to regulate intestinal flora, acupuncture to regulate body immunity, acupuncture to regulate tumor markers, acupuncture to regulate apoptotic genes, acupuncture to regulate the cell cycle of cancer cells, acupuncture to regulate signaling pathways, etc. There are shortcomings in the clinical and basic research of acupuncture for gastric cancer: (1) the lack of unified acupuncture operation

specification, such as acupuncture technique and time; (2) most of the experiments failed to analyze the experimental results from the theoretical basis of acupuncture, and could not convert from experimental results to mechanism excavation; (3) the lack of rigor in the experiments, animal modeling process and acupuncture point methods need further improvement. With the development of modern molecular biology, cytology, genomics and other disciplines and modern technical means, new ideas on the mechanism of acupuncture treatment for gastric cancer are constantly emerging, providing a new theoretical basis for acupuncture treatment of gastric cancer. Meanwhile, in order to improve the recognition of acupuncture treatment, we also need more in-depth, comprehensive, multi-faceted and multi-mechanism research and discussion to provide more targeted treatment for patients, to improve the shortcomings of the current stage of research.

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