Premalignant gastric lesions，Immunotherapy and Chinese medicine

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Abstract

Gastric cancer is a common gastrointestinal malignancy, and reducing the incidence and mortality of gastric cancer is a major public health problem that needs to be addressed urgently. The application of pharmacological interventions for precancerous states and lesions of the stomach is one of the important aspects of gastric cancer prevention, and recent studies have shown that Chinese medicine has unique advantages in this regard. In this review, we list the possible targets and mechanisms of action of TCM acupuncture or herbal formulations by compiling the understanding and therapeutic tools related to the treatment of gastric precancerous lesions, with a focus on their immunotherapeutic mechanisms. This study contributes to the understanding of the potential role of TCM multi-target and multi-pathway interventions of the immune system in gastric precancerous lesions, and also provides an outlook on the possible new targets and pathways.

Full Text

Preamble

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Abstract

Gastric cancer is a common gastrointestinal malignancy, and reducing its incidence and mortality represents a major public health challenge that requires urgent attention. Pharmacological intervention for precancerous states and lesions of the stomach constitutes an important aspect of gastric cancer prevention, and recent studies have demonstrated that Chinese medicine offers unique

advantages in this domain. This review compiles current understanding and therapeutic approaches related to the treatment of gastric precancerous lesions, enumerating the potential targets and mechanisms of action of traditional Chinese medicine (TCM) acupuncture and herbal formulations with a particular focus on their immunotherapeutic mechanisms. This work contributes to understanding the potential role of TCM' s multi-target, multi-pathway interventions on the immune system in gastric precancerous lesions and provides perspectives on possible novel targets and pathways.

Keywords: gastric precancer, signaling pathway, immune mechanism, Chinese medicine, target, network pharmacology

According to Global Cancer Statistics 2020 released by the International Agency for Research on Cancer (IARC), gastric cancer ranks fifth in incidence and fourth in mortality among malignant tumors worldwide [1]. Chinese cancer statistics for 2020 indicate that gastric cancer represents the third most common new cancer diagnosis in China, with the country accounting for 43.9% of new gastric cancer cases and 48.6% of gastric cancer deaths globally [2]. As aging and urbanization accelerate, coupled with unhealthy lifestyle patterns and high-pressure work environments, risk factors for gastric cancer are progressively increasing, intensifying the burden of this disease. Consequently, the prevention, control, and treatment of gastric cancer have become increasingly critical.

Gastric precancerous lesions (GPLs) represent a pathological state in which the gastric mucosa transforms from normal to malignant, primarily referring to moderate to severe dysplasia and incomplete colonic-type intestinal metaplasia. This stage constitutes a crucial phase in gastric carcinogenesis. Capturing the signals of precancerous gastric lesions and implementing timely, effective symptomatic treatment to interrupt disease progression can efficiently reduce gastric cancer incidence. Modern medicine largely attributes gastric cancer development to *H. pylori* infection and autoimmune mechanisms, with treatment primarily focused on HP eradication, acid suppression, and antioxidant therapy, which have limited efficacy in halting gastric mucosal transformation [3]. Since ancient times, Chinese medicine has embraced the concepts of "prevention before disease onset" and "prevention of disease progression," leveraging its unique advantages to control and even reverse disease development in a timely and effective manner. This paper examines clinical trials and experiential evidence of Chinese medicine and acupuncture in treating GPLs, exploring TCM approaches to regulating gastric precancerous lesions and summarizing the immune mechanisms through which TCM acts against GPLs. This work aims to provide clear etiological mechanisms for TCM intervention in precancerous lesions, enabling precise and symptomatic treatment to improve clinical efficacy and reduce patient suffering.

1. Modern Medical Research on the Mechanisms of GPLs

GPLs represent a disease progression process whose complete pathogenesis remains unclear. This section discusses the mechanisms from the perspectives of inflammatory factors, signaling pathways, oncogenes, and the tumor microenvironment [Figure 1: see original paper].

1.1 Inflammatory Factor Alterations Stimulate the Inflammatory Microenvironment and Promote Inflammation-Cancer Transformation

Inflammatory cells and epithelial cells produce reactive oxygen/nitrogen species (ROS/RNS), and chronic inflammation causes various damages to nucleic acids, proteins, and lipids through ROS/RNS production. The persistence of chronic inflammation promotes gastric cancer cell growth and increases the probability of gene mutation, eventually leading to the transformation of benign lesions to malignant tumors [4].

Interleukins (IL) are involved in the expression and regulation of immune responses, with IL-1, IL-4, IL-6, IL-8, and IL-10 being the most extensively studied. IL-1 is a multifunctional cytokine that controls inflammatory, immune, and hematopoietic functions. In the tumor microenvironment, IL-1 promotes cell expression and advances tumor invasion and progression [5]. IL-4, like most cytokines, affects multiple target cells through multiple mechanisms. IL-6 promotes host defense following infection and tissue injury. IL-8 and related cytokines are produced in response to infection, inflammation, ischemia, and trauma [6]. IL-10 regulates immune responses during organismal defense and plays important roles in autoimmune diseases, inflammatory conditions, and cancer [7].

Tumor necrosis factor alpha (TNF-α) participates in immune system maintenance, homeostasis, inflammation, and host defense [8]. Numerous studies have confirmed TNF-α involvement in multiple pathological processes including gastric carcinogenesis, cell proliferation, gastric cancer invasion and metastasis, epithelial-mesenchymal transition, and neovascularization [9].

COX-2 plays an important role in protecting gastric mucosa and promoting ulcer healing. COX-2 expression is low under normal physiological conditions but becomes highly expressed in inflammatory environments and upon stimulation by tumor cells [10]. Research has demonstrated that reducing COX-2 protein expression in gastric mucosa helps improve gastric mucosal inflammation, not only relieving patients' clinical symptoms but even reversing the pathological processes of mucosal atrophy and intestinal epithelial metaplasia [11].

The persistence and further development of inflammatory factors lead to formation of an inflammatory microenvironment in vivo. Inflammatory factors link inflammation to tumor development through activation and initiation of signaling pathways such as Rho/ROCK and NF- B, creating an inflammation-cancer transformation mechanism that drives tumorigenesis and progression.

1.2 Abnormal Pathway Expression, Altered Signaling, and Multi-Pathway Cooperation in Disease Progression

In recent years, molecular signaling pathways have been increasingly studied, providing new directions for understanding the pathogenesis of gastric precancerous lesions. The NF- B pathway regulates inflammatory responses and controls proliferation, anti-apoptosis, and angiogenesis, playing different regulatory roles in different cellular environments. In the complex tumor microenvironment, NF- B interacts with other molecular pathways, mutually promoting each other and jointly participating in the occurrence and development of precancerous lesions of gastric cancer (PLGC) [12]. MAPK is primarily present in the cytoplasm and mediates various cellular responses while intervening in cell growth and apoptosis [13]. p38, as a class of proteins in the MAPK pathway, participates in regulating inflammatory, tumor, and various stress signaling pathways in the body. EGFR regulates mucosal cell growth and development, repairs damaged mucosa, and participates in the differentiation, proliferation, and maturation of gastrointestinal epithelial cells, while EGFR overexpression accelerates the heterogeneous proliferation of epithelial cells [14].

The Wnt signaling pathway, JAK/STAT signaling pathway, and TGF-β/Smad signaling pathway [15-17] are involved in cell growth, proliferative transformation, and other physiological activities, representing among the most commonly dysregulated pathways during tumor formation and progression. Since signaling pathways influence and interact with each other, prevention and treatment of PLGC should involve simultaneous intervention and regulation of multiple signaling pathways [18].

1.3 Activation of Proto-Oncogenes and Inactivation of Tumor Suppressor Genes Disrupt the Cell Proliferation-Apoptosis Balance

Genes regulate tumor generation, reproduction, and apoptosis. Activation of proto-oncogenes and inactivation of tumor suppressor genes lead to abnormal signaling pathways, representing important causes of carcinogenesis [19]. Abnormal activation of proto-oncogenes such as β-catenin, cyclinD1, C-myc, the ras gene family, tyrosine kinase transmembrane receptor (C-met), and tyrosine kinase cell surface receptor (C-erbB2) stimulates cell proliferation and promotes tumorigenesis. Down-regulation and inactivation of tumor suppressor genes such as phosphatase gene (PTEN), Runt-related transforming growth factor 3 (Runx3), Bcl-2, P16, P53, and P21 induce proliferation and migration of cancer cells. Mutations or malfunctioning expression of tumor-associated genes promote tumor cell proliferation, disrupt the homeostasis between proliferation and apoptosis in the cell cycle, and drive tumor development [20].

Free β-catenin enters the nucleus and binds to T-cell factors, initiating downstream target gene transcription and activating the Wnt/β-catenin signaling pathway, leading to tumorigenesis [21]. CyclinD1 plays a key role in cell proliferation and is a critical protein regulating the G1 to S phase transition [22]. As

a DNA-binding protein, the oncogene c-Myc plays important roles in regulating cell growth and metabolic cycles, stimulating angiogenesis, and promoting malignant transformation, proliferation, and differentiation of recombinant cells [23].

As the only tumor suppressor gene that dephosphorylates lipids, PTEN plays a key role in cell cycle arrest, cell invasion, migration, and apoptosis [24]. Methylation of the tumor suppressor gene RUNX3 is considered a hot topic in current research. Once methylation occurs, RUNX3 expression is suppressed, which affects apoptosis and promotes tumor development [25]. The Bcl-2 suppressor gene prolongs cell life and increases cell numbers by resisting cell death [26]. Mutation or inactivation of P16 shortens the G1 phase of the cell cycle, causing cells to enter the S phase prematurely and thus promoting uncontrolled cell proliferation [27].

1.4 Tumor Angiogenesis and Tumor Environment Formation

Sustained angiogenesis is one of the essential features of tumors. Factors associated with PLGC angiogenesis include vascular endothelial growth factor (VEGF), angiopoietin (Ang), and epidermal growth factor (EGF) [28]. Inhibition of VEGF overexpression improves the hypoxic state of gastric mucosa, inhibits microangiogenesis, and alleviates or even partially reverses gastric mucosal intestinal and heterogeneous proliferative lesions [29].

The acidic tumor microenvironment provides favorable conditions for malignant tumor growth and local invasion. Aerobic glycolysis is one of the important energy metabolic features of cancer cells [30]. Excess H+ produced during glycolysis contributes to microenvironment acidification, and the low pH extracellular microenvironment promotes cell invasion, metastasis, and proliferation [31].

2. Recognition of GPLs in Chinese Medicine

Gastric precancerous lesions represent a modern medical understanding of gastric cancer progression. In Chinese medicine, according to symptom development, they are categorized as “stomach pain,” “gastric regurgitation,” “vomiting,” and similar patterns. To better analyze the evidence, various physicians have examined their etiology and pathogenesis. Gastric cancer development represents a comprehensive result of multiple factors and stages, closely related to deficiency of the body’ s righteous qi and invasion of pathogenic factors. Deficiency of righteous qi refers to weakness of the spleen and stomach and dysregulation of internal organs. Pathogenic factors include qi stagnation, blood stasis, phlegm coagulation, stasis toxin, damp-heat, and similar pathologies.

Zhang Jinyue noted that “in regurgitation, food can still be ingested; when yang deficiency prevents transformation, warming and tonification are appropriate,” demonstrating that ancient physicians long recognized spleen-stomach weakness as the root of gastric diseases. Lu Zhi-Zheng believed that spleen-stomach deficiency and dysregulation of transportation and transformation form the basis

for stomach cancer development, noting that the spleen and stomach are the source of qi and blood production; when they do not operate smoothly, righteous qi deficiency easily arises, subsequently producing pathological symptoms such as stagnation and phlegm obstruction. Ye Tianshi stated, "At disease onset, qi becomes knotted in the meridians, but after prolonged illness, blood injury extends to the collaterals." Xu Jingfan also suggested that the evolution from gastritis to gastric cancer is based on "blood stasis." The concept that "evil distances itself from the stomach, which becomes poisonous after a long period" indicates that heat and toxic stasis are also key factors in disease development.

In conclusion, stomach cancer results from internal deficiency of spleen-stomach function, organ dysregulation, plus the combined action of phlegm, stasis, heat, toxin, and other pathological factors. Therefore, its pathological mechanism represents a comprehensive response of multiple intertwined pathological processes.

3. Chinese Medicine Treatment

Under the holistic concept, Chinese medicine is characterized by pattern-based treatment. In treating gastric precancerous lesions, it has consistently emphasized the combination of supporting righteous qi and eliminating pathogenic factors. While treatment focuses vary among different schools, the overall therapeutic approach primarily involves fortifying the spleen and stomach, clearing heat and detoxifying, activating blood circulation and removing blood stasis, and similar methods. Combined with data mining and analysis of clinical medication patterns, this enables more efficient and scientific treatment targeting disease causes, precisely employing medicinals to halt disease progression and reduce patient suffering.

3.1 Single Herbs

Li [32] analyzed medication patterns for gastric precancerous lesions over the past decade, concluding that deficiency-tonifying drugs, heat-clearing drugs, and blood-stasis-activating drugs were commonly used, combined with qi-regulating and dampness-diffusing drugs modified according to pattern. The most frequently used single herbs were Bupleurum, Curcuma, Salvia, Atractylodes, and Semen/Poria. Yang Tao [33] summarized core drugs for gastric cancer treatment through data mining as Atractylodes macrocephala, Poria, Atractylodes lancea, Polygonum, Glycyrrhiza, Coix, Citri Reticulatae Pericarpium, Astragalus, and Panax ginseng.

Summarizing clinical experience reveals that treatment consistently focuses on nourishing the spleen-stomach and eliminating pathogenic factors. Professor Qian Bo-wen adopted the general principle of supporting righteous qi and promoting qi flow, frequently using qi-benefiting and spleen-strengthening drugs such as Ginseng, Astragalus, and Atractylodes macrocephala, combined with qi-activating drugs such as Aurantium, Citri Reticulatae Pericarpium, and Au-

rantium [34]. Professor Zhou Zhongying employed anti-cancer and detoxification herbs such as Hedyotis diffusa, Actinidia root, Ranunculus ternatus, and other medicinals as treatment principles [35].

Through systematic study of anti-cancer herbs for stomach disorders, research has demonstrated that herbal medicines play important roles in reducing inflammatory responses, repairing gastric mucosa, down-regulating gene expression, and inhibiting cell proliferation. Table 1 briefly introduces clinically used herbs for clearing heat, tonifying deficiency, and activating blood circulation to resolve blood stasis.

Heat-clearing and detoxifying herbs such as Andrographis paniculata, Scutellaria barbata, Taraxacum mongolicum, and Sophora flavescens clear dampness and heat from the middle jiao while removing blood stasis. Modern pharmacological studies suggest that anthraquinones, flavonoids, terpenoids, and steroids in Hedyotis diffusa effectively inhibit gastric cancer cell expression [36, 37] and exhibit good antitumor effects. Tian Hua [38] demonstrated that dandelion polysaccharide significantly downregulated ph-ERK1/2 and COX-2 expression, reduced inflammatory damage, and promoted repair of damaged mucosa in rat models. Yun-Yun Tsai [39] found that extracts of Semen nigra could interfere with tumor cell proliferation and metastasis.

Atractylodes macrocephala, Astragalus membranaceus, and Codonopsis pilosula are important deficiency-tonifying herbs with high clinical utilization rates. The atractylenolide, glycosides, polysaccharides, and amino acids contained in Atractylodes macrocephala primarily act on the gastrointestinal system and exhibit anti-tumor and gastric mucosa repair effects [40]. Flavonoids, polysaccharides, and saponins—the main components of Astragalus—produce various effects including improved immune function, enhanced metabolism, and antitumor activity [41]. Zhou J [42] found that Astragalus polysaccharides could reduce gastric mucosal lesions and inhibit gastric cancer cell proliferation in rats by decreasing EGFR, COX-2, and other expression levels. The polysaccharides, alkaloids, flavonoids, and acids [43] in Panax ginseng are known to regulate gastrointestinal function, protect gastric mucosa, improve immunity, and exert anti-tumor effects [44-46].

As Ye Tianshi stated in the Qing Dynasty' s "Clinical Guide to Medical Cases," "Long-term pain in the ligaments causes qi and blood suffocation." The method of activating blood circulation and resolving blood stasis provides direction for treating precancerous gastric lesions. Salvia miltiorrhiza, Carthamus tinctorius, Ligusticum chuanxiong, Curcuma zedoaria, and Panax notoginseng function to activate blood circulation, resolve blood stasis, break blood, and stop bleeding. Modern pharmacological studies have shown that Panax notoginseng can improve gastric juice secretion, increase gastric mucosal blood flow, reduce proto-oncogene C-myc expression, and enhance tumor suppressor gene P16 expression in rats [47]. Both dihydrotanshinone I and tanshinone IIA in Salvia miltiorrhiza exhibit antitumor activity [48]. Wang Zhonghui [49] found that curcumol inhibited tumor cell proliferation, promoted

apoptosis, and blocked tumorigenesis development by regulating Bcl-2 protein and the ERK/NF- B signaling pathway. Cui Haoran [50] demonstrated through experiments that chuanxiongzine could also inhibit pathway activation, inducing apoptosis and autophagy in gastric cancer SGC-7901 cells and inhibiting their proliferation.

3.2 Chinese Medicine Compound Formulas

Compound formulas include classical formulas and modern physician-developed formulas, with relatively more research conducted on compound preparations. The sovereign-minister-assistant-courier structure of herbal formulas contains great wisdom that is gradually being confirmed through modern pharmacology, as shown in Table 2 . Liu Jiacheng [51] found that Banxia Xiexin Decoction could affect changes in the gastric mucosal tissue microenvironment and promote expression of tumor suppressor molecules, thereby influencing and blocking GPLs development. Dong [52] found that Shengyang Yigong Tang could interfere with GPLs progression by reducing NF- B expression levels and improving gastric mucosal status through rat experiments. Zhu Jingru [53] found that Chai Shao Liujun Tang could improve atrophic gastric mucosal lesions, with mechanisms potentially related to inhibition of abnormal NF- B/STAT1 activation and down-regulation of NF- B, mRNA, and STAT1 protein overexpression in gastric mucosal tissues. Zheng Xiaojia [54] demonstrated that modified Danggui Shaoyao San significantly improved the atrophic state of gastric mucosa in chronic atrophic gastritis (CAG) rats, down-regulated the JAK2/STAT3 signaling pathway, and reduced inflammatory factor production and apoptosis.

Self-prepared formulas include Xinyu Gastric Granules [55] developed by Professor Jingri Xie, which can decrease serum gastrin levels, increase serum growth inhibitor levels, reduce serum ET-1 levels, inhibit HP, and reverse GPLs processes in affected patients. Other therapies such as anti-pigmentation granules [56], Yangzheng Sanjie Tang [57], Phlegm-Dispersing Formula [58], and Spleen-Strengthening and Stasis-Resolving Formula [59] demonstrate certain pharmacological foundations and significant clinical efficacy.

3.3 Other Therapies

Acupuncture effectively improves immunity and reduces inflammation. Chen Y [60] found that acupuncture at Zusanli (ST36) and Liangmen (ST21) could improve the precancerous state of gastric mucosa in rats induced by MNNG and reduce serum CEA concentration. Zusanli and Liangmen are widely used for gastric diseases and have effects of improving immunity and nourishing righteous qi [61]. Emotional therapy improves patients' psychological status, providing positive psychological suggestions to relieve anxiety and alleviate excessive concern about their condition, thereby achieving balanced organ function and smooth qi-blood flow. Acupoint application therapy exerts medicinal effects by stimulating local acupoints and absorbing external drugs, which regulates physiological functions of internal organs and enhances body immunity. For example,

selecting Zhongwan (CV12) and Tianshu (ST25) sites for external stimulation can relieve pain, subdue rebellious qi, and stop vomiting, addressing symptoms of gastric precancerous lesions. As the principle states, "the ear is the gathering place of the ancestral chakra," and stimulating ear acupoints through auricular seed embedding can achieve disease prevention and treatment effects.

4. Mechanisms of TCM for GPLs

Numerous studies have demonstrated that TCM functions through bidirectional, multi-targeted regulation of the gastric cancer immune microenvironment. This section discusses the potential mechanisms by which TCM prevents and controls gastric cancer by regulating the tumor immune microenvironment through three aspects: protecting gastric mucosa and delaying mucosal lesions, improving the inflammatory microenvironment and inhibiting inflammation-cancer transformation, and inhibiting cancer cell proliferation while controlling cancer metastasis.

4.1 Protecting Gastric Mucosa and Delaying Mucosal Lesions

Gastric precancerous lesions essentially represent a transformation of gastric mucosal damage, and inhibiting gastric mucosal lesions can prevent gastric carcinogenesis. Xu Tingting [62] found that the Yi Qi Jian Pi Formula could improve the atrophic state of gastric mucosa in CAG rats. Jiang Yan [63] discovered through their study that this formula could elevate growth inhibitory hormone levels in gastric tissues of model rats, thereby exerting therapeutic effects on GPLs. Bai Yuning [64] found that the Jianshu Tongluo Detoxification Formula may regulate gastric mucosal epithelial cell apoptosis through NF- B/COX-2 and NF- B/Bcl-2 signaling pathways.

4.2 Control of Inflammatory Response and Inhibition of Inflammation-Cancer Transformation

Wu Tingting [65] demonstrated through experiments that the Yi Qi Huayu Detoxification Formula may control inflammatory response and inhibit cell proliferation by down-regulating factors such as IL-8 and IL-10. The downregulation of inflammatory factors such as IL-8 was more pronounced in patients receiving combined Baicalin Tang and Western medicine treatment compared to Western medicine alone [66]. Guo Min [67] found that strengthening the spleen and activating blood stasis could inhibit the inflammation-cancer transformation signaling pathway, upregulate expression of related tumor suppressor genes while downregulating proto-oncogene expression, thereby blocking disease transformation. By improving the microenvironment and regulating the immunosuppressive milieu composed of inflammatory factors, TCM enables suppression of inflammation-cancer transformation.

4.3 Inhibition of Cancer Cell Proliferation and Control of Cancer Metastasis

Yu Zhihong [68] confirmed through mouse experiments that the phlegm-eliminating and nodule-dispersing formula exhibited good tumor-suppressing effects, down-regulating serum IL-8 and TGF-β concentrations and inhibiting gastric cancer cell metastasis. Liu Jindi [69] found that Yixin Gastric Granules could reduce expression of corresponding genes, inhibit abnormal cell proliferation, and block or reverse GPLs progression. Banxia Xiexin Decoction can down-regulate EGFR expression in gastric mucosa of rats with gastric precancerous lesions, thereby regulating precancerous cell proliferation [70].

5. Summary

Gastric cancer has a high incidence rate that seriously affects patients' quality of daily life and psychological status, causing significant suffering. With the aid of Western medical diagnostic technology, clinical examination has improved. Leveraging TCM's pattern-based treatment characteristics can improve clinical symptoms and reverse pathological processes. Further improvement in basic research on GPLs pathogenesis aims to provide precise targeted treatment. This study compiled and analyzed the mechanisms of action and immunological effects of single and compound TCM targets on gastric precancerous lesions, hoping to expand clinical trials and mechanistic research on TCM, acupuncture, and characteristic TCM therapies to better demonstrate the unique advantages of TCM in treating gastric precancerous lesions.

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Note: Figure translations are in progress. See original paper for figures.