

Research Progress of Traditional Chinese Medicine Regulating Notch Signaling Pathway in the Intervention of Gastric Cancer

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Abstract: Gastric cancer is a highly invasive malignant tumor of the digestive system with a complex pathogenesis involving the activation of multiple signaling pathways. The abnormal activation of the Notch signaling pathway plays a key role in its occurrence and development, which promotes the proliferation, apoptosis, invasion and metastasis of gastric cancer cells and enhances the characteristics of cancer stem cells. Integrated traditional Chinese and Western medicine is the main therapeutic approach for gastric cancer in China. In recent years, an increasing number of scholars have taken the Notch signaling pathway as a starting point in the field of traditional Chinese medicine (TCM) for the prevention and treatment of gastric cancer, and carried out experimental studies on the regulation of the Notch signaling pathway by various TCM extracts, monomers and compound prescriptions. This paper collects and sorts out the relevant literatures on TCM regulating the Notch signaling pathway to exert the effect of preventing and treating gastric cancer in recent years, summarizes the mechanism of the Notch signaling pathway in gastric cancer, and analyzes the current research status, aiming to provide references for subsequent research and new drug development. However, the existing research is mainly based on basic experiments, and multi-center clinical studies are urgently needed to verify its translational value. This paper provides a theoretical basis and research direction for TCM targeting the Notch pathway in the treatment of gastric cancer.

Keywords: Gastric cancer, Traditional Chinese Medicine, Notch signaling pathway, Research progress.

1. Introduction

Gastric cancer, also known as gastric adenocarcinoma, is a malignant tumor of the digestive system originating from gastric mucosal epithelial cells [1]. It ranks the 6th in terms of incidence and the 3rd in mortality worldwide, and is a highly invasive disease caused by multiple factors [2]. The latest gastric cancer data from the 2023 Global Cancer Statistics show that the incidence and mortality of gastric cancer in China both rank the 3rd among all cancer types, accounting for nearly 44.0% of new gastric cancer cases and 48.6% of gastric cancer-related deaths worldwide, both higher than the global average [3]. At present, the pathogenesis of gastric cancer has not been fully elucidated. Due to the occult and non-specific early symptoms and the limitations of diagnosis and treatment methods, the disease is often diagnosed at an advanced stage, missing the optimal treatment period. This largely means that most gastric cancer patients are difficult to achieve long-term survival, and its prevention and treatment has become one of the key tasks in the major public health field in China [4].

Surgery, radiotherapy and chemotherapy are the main current treatments for gastric cancer with obvious clinical efficacy, but the above therapeutic methods have certain limitations. Due to the cross-talk of multiple pathways in the pathogenesis of gastric cancer, the above treatments can no longer meet the clinical treatment needs of gastric cancer. Therefore, it is of great significance to explore new therapeutic methods for gastric cancer. TCM is widely used in the treatment of gastric cancer at early, middle and advanced stages, recurrence and metastasis, and postoperative period, with high safety and good curative effect, which can effectively improve the clinical symptoms and quality of life of patients [5]. TCM can intervene in gastric cancer through multi-target synergistic

effects such as inhibiting the expression of Notch receptors, degrading NICD and regulating downstream Hes1. This paper systematically summarizes the relevant research literatures from the perspective of exploring the mechanism of TCM regulating the Notch signaling pathway in the treatment of gastric cancer, aiming to provide references for subsequent research and new drug development.

2. Overview of the Notch Signaling Pathway

The Notch gene was first discovered in 1917 through genetic studies on mutant strains of *Drosophila melanogaster* with notched wings, and then isolated in 1983 [6]. The Notch signaling pathway is involved in multiple aspects of the animal life process, including cellular gene expression, embryonic and tissue development, tissue function and repair, as well as various non-cancerous and cancerous diseases [7]. The mammalian Notch signaling pathway consists of three main components: four transmembrane Notch receptors (Notch1-Notch4), six corresponding ligands (Jagged1-2, Dll1-4), and downstream target genes such as p21, Hes1 and Deltex [8]. Any change in these factors may affect the transmission of Notch signals.

The activation of the Notch signaling pathway is divided into the canonical pathway and the non-canonical pathway [9]. The canonical signaling pathway is mediated by G protein-coupled receptor 39 and enzyme-linked receptor 40, with multiple intermediates between membrane receptors and nuclear effectors. Notch receptors are transported to the nucleus after three cleavages to regulate the transcription of target genes [10]: the binding of ligands to the extracellular domain of Notch receptors initiates endocytosis. Notch receptors produced in the endoplasmic reticulum undergo the first cleavage at the S1 site under the action of Furin-like

convertase in the Golgi apparatus, generating the Notch extracellular domain (NECD) and transmembrane domain (TMD), which then form the mature heterodimeric Notch receptor through non-covalent bonding and are subsequently transported to the cell membrane. When cells make contact with each other, Notch receptors recognize and interact with transmembrane Notch ligands on adjacent cells, undergoing the second cleavage at the S2 site under the action of a disintegrin and metalloproteinase (ADAM) to produce two fragments. The N-terminal cleavage product of the middle segment is phagocytosed by ligand-expressing cells, and the C-terminal cleavage product undergoes the third cleavage at the S3 site by the γ -secretase complex, releasing the activated form of the receptor—the Notch intracellular domain (NICD). NICD is either degraded in the cytoplasm or transported to the nucleus to regulate the transcription of target genes, combining with the transcription factor CSL to further regulate the expression of downstream genes [11].

In addition to the canonical Notch pathway, Notch signaling can also be independent of transcription mediated by typical ligands, namely the non-canonical Notch pathway. A part of the mature Notch receptors on the cell membrane binds to ligands through the canonical pathway, while another part of Notch receptors is activated by Deltex, enters the cell through endocytosis, and is either degraded in lysosomes or activated in endosomes to participate in the non-canonical pathway [7].

3. The role of the Notch Signaling Pathway in the Occurrence and Development of Gastric Cancer

3.1 Oncogenic and Tumor-suppressive Effects of the Notch Signaling Pathway

The Notch signaling pathway regulates and exerts biological functions through cell-cell contact and crosstalk with other pathways, including cell differentiation, proliferation and apoptosis, tumor angiogenesis and inflammatory response [12]. Meanwhile, it is an important signal for T cell generation, and its regulation determines the normal or oncogenic fate of immune cells [13].

The type of cancer determines the effect of the Notch signaling pathway. The oncogenic effect of abnormal Notch receptors has been confirmed in breast cancer [14], lung adenocarcinoma, ovarian cancer and colorectal cancer [15]. For example, in lung adenocarcinoma, the high expression of Jagged1/Notch1 is positively correlated with the degree of tumor invasion, and the high expression of Notch3 promotes the proliferation and migration of lung adenocarcinoma cells [16,17]. At the same time, the Notch signaling pathway has been proven to have a tumor-suppressive effect in some cancers, including prostate cancer, small cell lung cancer, pancreatic neuroendocrine cancer, hepatocellular carcinoma, cervical cancer, myeloid leukemia, head and neck squamous cell carcinoma, and neuroblastoma. The anti-tumor mechanisms of the Notch signaling pathway include inducing p21, antagonizing P63, promoting cell cycle arrest, inhibiting the oncogenic AP1 signaling pathway, regulating the differentiation of precancerous stem cells and progenitor cells, and inhibiting proliferation [18].

3.2 Mechanism of the Notch Signaling Pathway in Gastric Cancer

The activation of Notch signaling is considered an important factor in the occurrence and development of gastric cancer. Its abnormal activation is widely involved in the proliferation, apoptosis, invasion and metastasis of gastric cancer cells, and the enhancement of cancer stem cell characteristics. The Notch signaling pathway plays an important role in the proliferation of gastric cancer cells. GRWD1 is an oncogene with increased expression in a variety of malignant tumors, including tumor tissues of gastric cancer patients [19]. A tumorigenesis experiment on nude mice confirmed that GRWD1 can promote the proliferation of gastric cancer through the NOTCH signaling pathway *in vivo*. The upregulated expression and oncogenic effect of Delta/Notch-like epidermal growth factor-related receptor (DNER) have been reported in gastric cancer [20]. Han et al. [21] found that DNER can regulate the proliferation, survival and invasion ability of gastric cancer cells by activating Notch signaling, thus possibly promoting tumor progression to an advanced stage.

Apoptosis is a programmed cell death process closely related to the inhibition of various tumors. A study by Tang et al. [22] showed that the expression of the apoptotic protein Caspase9 was significantly enhanced in oxaliplatin-incubated gastric cancer cell line SGC-7901, while the Notch signaling pathway inhibitor could significantly reverse the above abnormality, indicating that the activated Notch2 signaling pathway is involved in the apoptotic process of gastric cancer cells. Bcl-2 is an anti-apoptotic protein whose high expression can inhibit tumor cell apoptosis; Bax is a pro-apoptotic protein belonging to the Bcl-2 family whose high expression can induce tumor cell apoptosis. A study by Yang et al. [23] showed that sulforaphane can inhibit the expression of the anti-apoptotic protein Bcl-2 and induce the expression of the pro-apoptotic protein Bax in gastric cancer SGC-7901 cells, thereby reducing the Bcl-2/Bax ratio and promoting the apoptosis of gastric cancer cells.

Invasion and metastasis are another biological behavior of malignant tumors besides excessive proliferation, and are also the main reasons for the poor curative effect and prognosis of malignant tumors. KDM1A is the first discovered histone demethylase, which has been confirmed to be upregulated in a variety of tumors and can promote tumor proliferation, invasion and metastasis. A study by Huang found that the increased expression of KDM1A can make gastric cancer cells have the morphological characteristics of mesenchymal cells, namely epithelial-mesenchymal transition (EMT), and further indicated that KDM1A may regulate the EMT of gastric cancer cells through the TGF- β /Notch signaling pathway to promote the invasion and metastasis of gastric cancer cells [24]. He et al. [25] found that miR-425-5p is upregulated and ZNF423 is downregulated in gastric cancer cells; miR-425-5p can activate the Notch signaling pathway by targeting ZNF423, promote the migration and invasion of gastric cancer cells, and thus promote the occurrence and development of gastric cancer.

Thrombospondin 2 (THBS2) is a key regulatory factor in the process of tumor occurrence and development, which shows

high expression characteristics in EMT, extracellular matrix (ECM) formation, and tumor invasion and metastasis stages [26]. Chang et al. [27] verified a significant correlation between the high expression of THBS2 and the poor prognosis of gastric cancer through clinical data analysis, and confirmed by *in vitro* and *in vivo* experiments that reducing the expression of THBS2 can effectively inhibit the proliferation, metastasis and stem cell characteristics of gastric cancer cells. Its upstream regulatory factor miR-29b-3p can promote EMT by activating the Notch signaling pathway, thereby enhancing the characteristics of cancer stem cells.

4. Regulation of the Notch Signaling Pathway by TCM for the Treatment of Gastric Cancer

The dual role of the Notch pathway in gastric cancer suggests its potential as a therapeutic target, and TCM can regulate this pathway through multiple approaches. In the process of combined treatment of gastric cancer, TCM plays an important role in improving patients' clinical symptoms, enhancing body immunity, reducing the toxicity and increasing the efficacy of chemotherapy, and preventing tumor recurrence and metastasis. Exploring gastric cancer therapeutic drugs with significant clinical efficacy and low toxic and side effects from traditional Chinese medicines has a good application prospect, and research on TCM anti-cancer targeting Notch signaling has never stopped [28]. This section classifies and discusses the relevant research literatures in recent years from two aspects: TCM monomer components and TCM compound prescriptions.

4.1 TCM Monomer Components

4.1.1 Glycosides

Glycosides, also known as glycosides, are a class of compounds formed by the connection of sugars or their derivatives with another non-sugar substance through the anomeric carbon atom of the sugar. The active component of ginseng is ginsenoside, and a number of *in vitro* and *in vivo* experiments have confirmed that ginsenoside has significant anti-tumor activity [29], which can induce cancer cell apoptosis, enhance body immunity and alleviate toxins. Cell experiments have found that ginsenoside Rg5 can inhibit the proliferation and migration of gastric cancer, and its anti-gastric cancer activity is higher than that of Rg3. It causes cell cycle arrest and inhibits cancer cell invasion and metastasis by inhibiting the expression of Notch1 protein [30].

4.1.2 Flavonoids

Luteolin is a natural flavonoid compound existing in a variety of plants, with anti-diabetic, cardiovascular protective, anti-inflammatory and anti-cancer effects [31]. Cell experiments by Zhang et al. [32] found that luteolin can effectively inhibit the activity of Akt, β -catenin and Notch signaling pathways, thereby inhibiting cell proliferation, migration and invasion, inducing cell apoptosis, and reversing EMT to significantly inhibit the progression of gastric cancer. Baicalin, isolated from the dried roots of *Scutellaria*

baicalensis, has a variety of biological functions such as anti-inflammatory, anti-allergic, antioxidant and anti-tumor effects [33], and can inhibit the progression of a variety of tumor cells such as breast cancer, pancreatic cancer and gastric cancer by inhibiting cell proliferation and migration and inducing cell apoptosis [34]. Baicalin can effectively inhibit the growth and induce the apoptosis of gastric cancer drug-resistant cell line SGC7901DDP by regulating the expression of Notch1 and indirectly upregulating the expression of lncRNA ak022798 [35].

The increase in the concentration of puerarin has a significant inhibitory effect on the viability and proliferation of gastric cancer cells. A study by Li et al. [36] found that after adding the Notch1 receptor agonist Jagged1, the activation level of the Notch1/PI3K/AKT/mTORC1 pathway was significantly increased, and the migration and invasion activity of gastric cancer cells was enhanced. The results showed that puerarin can target the Notch1/PI3K/AKT/mTORC1 pathway to inhibit the proliferation, migration and invasion of gastric cancer cells, promote cell apoptosis, and ultimately inhibit tumor progression *in vitro* and *in vivo*.

4.1.3 Anthraquinones

Aloe-emodin is a natural anthraquinone active component that can be extracted from a variety of Chinese medicinal materials such as aloe, rhubarb and cassia seed. Cell experiments have found that Notch1 can promote cell growth and inhibit cell apoptosis by activating the PI3K/Akt signaling pathway [37]. The PI3K/Akt signaling pathway plays a key regulatory role in tumor cell survival, invasion and migration; activated Akt can directly phosphorylate IKK α to activate NF- κ B, thereby regulating tumor cell apoptosis. Cell experiments by Liu et al. [38] confirmed that aloe-emodin can significantly reduce the expression of Notch-1, Akt and P65 in gastric cancer SGC-7901 cells, that is, it blocks gastric cancer cells in the G0/G1 phase by inhibiting the expression of proteins related to the Notch-1/Akt/NF- κ B signaling pathway, inhibits their proliferation ability, reduces migration and invasion ability, and induces cell apoptosis.

4.1.4 Terpenoids

Triptonide is one of the main active components of *Tripterygium wilfordii*, with a broad spectrum of biological functions such as anti-inflammatory, immunosuppressive and neuroprotective effects. Studies have found that triptonide can promote the degradation of Notch1 protein through the ubiquitination pathway; Western blot showed that the expression of Notch1 in the treatment group was reduced by 60%, and the protein level of RBPJ, a transcription factor of the RelA family downstream of Notch1, was significantly reduced, thus effectively inhibiting the growth and metastasis of gastric cancer. At the same time, it inhibits the activity of nuclear factor- κ B, a downstream transcription factor of the Notch1 signaling pathway, by reducing the levels of IKK α and IKK β , the catalytic subunits in nuclear factor κ B kinase molecules, thereby inhibiting the Notch1 signaling pathway [39].

In summary, the listed glycosides, flavonoids, anthraquinones and terpenoids can mostly directly or indirectly control cell

differentiation, proliferation and apoptosis by regulating the expression of receptors related to the Notch signaling pathway, thereby effectively controlling the growth and metastasis of gastric cancer cells.

4.2 Single Chinese Medicinal Herbs and TCM Compound Prescriptions

In addition to monomers, TCM monomers and compound prescriptions regulate the Notch pathway through the synergistic effect of multiple components. However, the current research on TCM monomers and compound prescriptions regulating the Notch pathway to intervene in gastric cancer is relatively limited and still in the initial stage.

Hedyotis diffusa Willd, also known as Snake General, is the whole herb of Rubiaceae plant *Hedyotis diffusa* Willd, containing a variety of anti-cancer substances such as flavonoids, anthraquinones and terpenoids [40]. It can activate blood circulation, detoxify and relieve pain, and is used for the treatment of snake bites, enteritis and cancer. Signal transducer and activator of transcription 3 (STAT3) is a DNA-binding protein widely present in body cells, which can form polymers by combining with corresponding factor receptors and participate in the transcription of downstream effectors. After the Notch1 receptor combines with its ligand, the Notch intracellular domain is decomposed under the action of enzymes, which combines with nuclear target genes to promote the synthesis of downstream effector proteins. The combined action of STAT3 protein can promote cell carcinogenesis and improve the drug resistance of tumor cells. A study by Wang Hui et al. [41] found that *Hedyotis diffusa* Willd can reduce the protein expression levels of STAT3 and Notch1, increase the proliferation inhibition rate of cisplatin on gastric cancer cells, weaken glycolysis, promote their apoptosis, and reduce the chemoresistance of gastric cancer cells.

Yiqi Bushen Decoction is a TCM compound prescription composed of a variety of Chinese medicinal materials such as *Astragalus membranaceus*, *Ligustrum lucidum*, *Poria cocos*, *Polyporus umbellatus*, *Coix lacryma-jobi*, and *Lycium barbarum*, with the effects of nourishing yin and tonifying the kidney, invigorating the spleen and supplementing qi, inducing diuresis to excrete dampness, and activating blood circulation to detoxify. miRNA-139-5p is a miRNA with abnormal expression in tumors, which can act on multiple downstream signaling pathways by targeting and regulating the expression of multiple target genes. Cell experiments by Liu Yunxia et al. [42] found that Yiqi Bushen Decoction can exert the effect of anti-proliferation and metastasis of gastric cancer by regulating the miRNA-139-5p/Notch1/Jagged1 signaling pathway.

Yisui Decoction is composed of twelve Chinese medicinal materials including *Carapax et Plastrum Testudinis*, *Astragalus membranaceus*, *Codonopsis pilosula*, *Atractylodes macrocephala*, *Polygonatum sibiricum*, *Cuscuta chinensis*, *Spatholobus suberectus*, *Lycium barbarum*, *Callicarpa bodinieri*, *Agrimonia pilosa*, peanut coat and jujube. The combined use exerts the effects of invigorating the spleen and tonifying blood, tonifying the kidney and benefiting the marrow, which can significantly improve the hematopoietic

environment, enhance the hematopoietic function of patients and improve anemia symptoms. Animal studies by Huang et al. [43] found that in the bone marrow suppression model group of gastric cancer-bearing mice after chemotherapy intervened with Yisui Decoction, the levels of peripheral blood immune cell subsets, serum levels of interleukin-3 (IL-3), IL-6, thrombopoietin (TPO), erythropoietin (EPO) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as the number of bone marrow nucleated cells (BMNCs) detected by Wright-Giemsa staining were significantly increased. It indicates that Yisui Decoction can improve the bone marrow hematopoietic microenvironment of gastric cancer mice after chemotherapy and enhance bone marrow hematopoiesis, and its effect may be related to inhibiting the excessive activation of the Notch signaling pathway.

Banxia Xiexin Decoction, created by Zhang Zhongjing, is composed of *Pinellia ternata* (processed), *Scutellaria baicalensis*, *Zingiber officinale* (dried rhizome), *Codonopsis pilosula*, *Glycyrrhiza uralensis* (roasted), *Coptis chinensis* and jujube, with the effects of regulating cold and heat, and elevating lucid yang and lowering turbid yin, and has a good curative effect in the prevention and treatment of gastric cancer. Li Huizhen et al. [44] established a gastric cancer-related rat model and compared the protein expression levels of Notch1, Jagged1, Dll4 and Hes1, as well as the expression levels of Ki67 and VEGFA in gastric tissues of rats in the blank group, model group and Banxia Xiexin Decoction group. It was found that Banxia Xiexin Decoction can significantly reduce the expression levels of Notch1, Jagged1, Dll4 and Hes1 in model mice, thereby inhibiting the activity of vascular endothelial cells around tumors, inhibiting gastric cancer proliferation and angiogenesis, and downregulating the expression of Ki67 and VEGFA. It indicates that Banxia Xiexin Decoction may be related to intervening in the Notch1 signaling pathway and regulating the expression of VEGF and Ki67, and can be used as a means to prevent and treat the occurrence and development of gastric cancer.

5. Conclusion

The Notch signaling pathway is closely related to the development of gastric cancer, mainly participating in cell proliferation, apoptosis, invasion and metastasis, epithelial-mesenchymal transition, and enhancement of cancer stem cell characteristics. By discussing the important role of the Notch signaling pathway in gastric cancer, this paper explores the potential role of TCM monomers and compound prescriptions in regulating this signaling pathway, aiming to provide clinical references and directions for researchers.

However, the research on TCM regulating the Notch signaling pathway to intervene in gastric cancer still has many limitations: (1) Most studies on TCM intervening in the Notch pathway for the prevention and treatment of gastric cancer are in the stage of in vitro cell experiments or in vivo nude mouse models, lacking corresponding clinical trial research. In the future, multi-center and large-sample clinical studies should be designed and carried out, the cross research with modern medicine should be strengthened, and the advantages of traditional and modern medicine should be combined to

further explore the direction of combined application of TCM and Western medicine. (2) The mechanism research on TCM herb pairs and compound prescriptions is still insufficient. In the future, it is necessary to further explore the commonly used classical prescriptions, empirical prescriptions in clinical practice, and comprehensively investigate the mechanism of TCM action. (3) The pathogenesis of tumors is complex, and Notch is involved in the mutual transduction of many other pathways, and the mechanism of their interaction is difficult to clarify. In the future, experiments need to be designed in a multi-dimensional, in-depth and multi-approach manner to further explore their interaction.

In summary, the research on TCM regulating the Notch signaling pathway for the treatment of gastric cancer still faces many challenges. However, it is believed that on the basis of more scientific and standardized basic research, the gradual transition to clinical research can provide ideas and references for the clinical treatment of gastric cancer.

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