Study on the occurrence and development of gastric cancer

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Abstract: Gastric cancer is a malignant tumor with high incidence rate and mortality. Research has shown that the activation and inhibition of the Wnt signaling pathway are closely related to the occurrence and development of gastric cancer, and the Wnt signaling pathway is influenced by many factors. Studying the relationship between the Wnt signaling pathway and the occurrence and development of gastric cancer is beneficial for providing insights into the prevention and treatment of gastric cancer. This article provides a review of the research progress on the relationship between the Wnt signaling pathway and the occurrence and development of gastric cancer.

Keywords: gastric cancer, *Wnt*/ β - catenin signaling pathway research progress

1. Introduction

Gastric cancer is a malignant tumor with high incidence rate and high mortality. Its incidence rate ranks fifth among all cancers, and its incidence rate is higher in East Asia, especially in South Korea, Mongolia, Japan and China. In China, the incidence rate of gastric cancer in men and women respectively ranks the second and fifth in the incidence rate of malignant tumors, and the mortality rate of gastric cancer respectively ranks the third and second in the mortality rate of malignant tumors. Currently, gastric cancer has become one of the important issues affecting human health.

In recent years, targeting signaling pathways for anti-tumor therapy has become a hot topic in the biomedical field. As an evolutionarily conserved pathway, the Wnt signaling pathway was initially believed to play a crucial role in embryonic development, cell fate determination, and tissue homeostasis processes, including cell proliferation, stem cell self-renewal, and cell differentiation. Large scale sequencing has revealed frequent mutations in genes encoding components of the Wnt signaling pathway in various cancers, and it has been proven that abnormal activation of this pathway is also widely involved in various processes of cancer, including tumor initiation, tumor growth, cell aging, cell death, differentiation, and metastasis. The pathogenesis of gastric cancer is not yet fully understood. As a crucial regulatory pathway in gastric cancer, the abnormal activation of the Wnt signaling pathway is closely related to the occurrence and development of gastric cancer^[1]. In depth research on the Wnt signaling pathway and exploration of its related inhibitors aims to provide new ideas for the early diagnosis, treatment, and prognosis evaluation of gastric cancer.

2. Wnt/ β- catenin signaling pathway

The Wnt gene is a collective term for homologous genes Int and Wingless, and the Wnt protein encoded by it is a collection of secreted glycoprotein families consisting of 19 Wnt protein members^[2]. The Wnt signaling pathway is composed of transcription regulatory factors, functional proteins, enzymes, etc., mainly including extracellular low-density lipoprotein related receptor proteins, loose proteins, glycogen synthase kinase 3, Wnt ligand related proteins, receptor curl proteins on the cell membrane surface, colorectal adenomatous proteins, axons, casein kinase 1, etc. Among them β -Catenin is a multifunctional effector protein and a key component of the Wnt signaling pathway. Its N and C terminals have binding sites with glycogen synthase kinase-3 and T cytokines/lymphokines, respectively. It plays an important role in maintaining intercellular adhesion and the morphological structure of adjacent tissues. The Wnt signal can regulate various cellular functions, including proliferation, differentiation, migration, apoptosis, and migration. Therefore, it is crucial in embryonic development and regulates the homeostasis and stem cell function of adult tissues, including the intestine, stomach, breast, and liver ^[3].

The first Wnt gene, Wnt1 (formerly known as Int-1), was discovered by Nusse and Varmus in 1982, who described the cloning of a new mouse oncogene. Subsequently, it was observed that its fruit fly homolog lacks wings, which is an essential gene for fragment polarity during embryonic development. Further research has shown that Wnt1 belongs to a highly conserved gene family, known as the wingless mouse mammary tumor virus integration site (Wnt) gene family. There are currently 19 Wnt genes in the known mouse and human genomes, which transmit signals through three different pathways: the typical Wnt pathway, the atypical planar cell polarity pathway, and the atypical Wnt/calcium pathway. Although different, there is considerable crosstalk between each Wnt path, so Wnt signaling can be more widely regarded as a signaling network containing different arms. Wnt ligands are secreted glycoproteins that activate signaling pathways by interacting with cell surface receptors of the curl protein family. There are 10 curl protein genes in mammals that can form complexes with other curl proteins and bind to co receptors such as low-density lipoprotein related proteins. The most common ones are LRP5/6, ROR2, or Ryk, which transmit signals to cells.

Typical Wnt/ β - catenin signaling pathway plays an important role in different stages of tumor development, including cancer cell proliferation, migration, invasion, tumor occurrence, and metastasis. Under normal circumstances, cytoplasm β - Catenin is composed of axon protein, colon adenomatous polyposis protein, and casein kinase 1 α And glycogen synthase kinase 3 β Glycogen synthesis kinase-3 β , Encapsulated by the destructive complex composed of E3 ubiquitin ligase β - Tr CP and final protein degradation are the characteristics. When the secreted Wnt ligand binds to the surface receptors of the cell membrane, its homeostasis is disrupted, mainly by the Fz/LRP5/6 receptor complex. Subsequently, scattered proteins in the cytoplasm phosphorylate and form complexes with axons, which then bind to GSK-3 β . To block its activation. This combination further leads to the decomposition of degradation complexes, β - Catenin aggregates in the cytoplasm. Accumulated β -Catenin is transported to the nucleus and is recognized as the main event of activation of the typical Wnt pathway, which then interacts with TCF/LEF to form an activator complex, thereby initiating Wnt/ β - Catenin signal transduction target genes

Transcription, including c-Myc, cyclin D1, and MMP-7. Several mutated components of typical Wnt signaling molecules play important roles in the malignant transformation and invasion of gastric cancer, and these mutations further lead to abnormal activation of the Wnt/ β - catenin pathway. For example, human Wnts are involved in the progression of gastric cancer in an autocrine or paracrine manner. Atypical Wnt signal transduction and β - Catenin is stable and independent, and can be divided into Wnt/Ca²⁺and planar cell polarity pathways. The Wnt/Ca²⁺pathway activates transcription factors and nuclear factors related to T cells to regulate cytoskeleton rearrangement, cell adhesion, migration, and tissue separation. In the PCP pathway, activated Dvl triggers Rho and Rac signaling branches, which regulate myosin activation and actin polymerization in stimulated cells. These complex signal transduction processes are related to changes in the cytoskeleton, cell polarization, and movement during the formation of the intestinal germ.

3. Wnt/ β- catenin signaling pathway and gastric cancer

According to reports, the Wnt signaling pathway is dysregulated in over 50% of gastric cancer. Hp induces the production and expansion of gastric stem cells through the Wnt pathway, promoting the occurrence and development of gastric cancer^[4]. Cytotoxin associated protein A and vacuolar cytotoxin A are the most important virulence factors of Hp, among which cytotoxin associated protein A interacts with E-cadherin, leading to β - Catenin accumulates in the cytoplasm and nucleus, thereby promoting the occurrence of gastric cancer. Chen et al. found that inhibiting the Wnt pathway can inhibit the proliferation of gastric cancer cells and accelerate their apoptosis, which may be related to downstream targets regulated by the Wnt pathway The expression levels of β- catenin, c-myc, and human cysteine protease-3 are related. Li et al. also found that blocking the Wnt pathway can increase the sensitivity of gastric cancer cells to programmed cell death receptor 1 antibodies, indicating targeted inhibition/ β- Catenin and PD-1 may become potential effective treatment methods for gastric cancer patients. About 70% of colorectal cancer is accompanied by APC mutations; About 1/3 of hepatocellular carcinoma is accompanied by Wnt pathway mutations, among which β- Catenin mutations are the most common; 10% to 50% of Wnt signals in gastric cancer undergo mutations, with similar mutation rates for APC and RNF43. The exact reason for the tissue specificity of the Wnt signaling pathway in different cancer tissues is not yet clear, but studies have shown that different levels of Wnt signaling and mutations may affect cell adaptability. The mouse model confirms that compared to the two allele mutations in APC, The incidence of colon cancer caused by mutations in the

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a single β - catenin gene is relatively low. The absence of APC can drive the occurrence of gastric cancer in mice. But compared to colorectal cancer, Wnt in gastric cancer.

The percentage of pathway mutations is relatively low, indicating that other driving factors of tumor origin also play an important role in the occurrence and development of gastric cancer

As is well known, E-cadherin is β - Catenin is one of the components of the degradation complex, and it also plays a crucial role in negatively regulating Wnt signaling ^[5]. β- Catenin in calcium mucin and α - Catenin comes into direct contact with actin cytoskeleton, which interacts with actin to form tight cell-cell connections. The important role of cadherin in the cell adhesion junction mediated by catenin has been confirmed, and the cytoplasmic carboxyl end of E-cadherin can be associated with β -Chain protein binding inhibits its nuclear localization. On the contrary, Howard et al. reported βcatenin to bind to cadherin is necessary for its transcriptional activity, as cadherin may stabilize the membrane by competing for its degradation mechanism during epithelial mesenchymal cell transformation β - Catenin. In short, calcium mucin and β - catenins may be one of the mechanisms underlying the EMT process. Czyzewska et al. found that E-cadherin and β - Catenin has significant significance in tumor lymph node metastasis. Silva et al. studied 515 patients with gastric adenocarcinoma and divided them into a young group (age ≤ 40 years old) and an elderly group (age>40 years old) based on their age. Additionally, the young group was E-cadherin/ β - catenin membrane suggests that young gastric cancer patients may promote tumor development through multiple genetic pathways. Secretory curl related protein 1 is considered a regulatory factor of the Wnt pathway by binding to Wnt ligands, and its ectopic transcription has important clinical significance in the occurrence and development of gastric cancer. Qu et al. found that overexpression of secretory curl related protein 1 is associated with EMT induction, lymph node metastasis, and shortened survival time in gastric cancer cells. Han et al. established an EMT model by treating BGC-823 cells with doxorubicin and elaborated on it in detail β- catenin, LEF1, and the translocatable gene c-Myc indicates that β - catenin signal is activated. Afterwards, in the application of indomethacin or siRNA inhibition. When detecting sericin, it was found that the EMT biomarker was significantly reversed. Given that β-Catenin is crucial for calcium dependent cell adhesion. Due to the large number of similar molecules regulating Wnt during the occurrence and development of gastric cancer/ β - catenin pathway is involved in the occurrence of EMT, and further in-depth research on these potential targets to reverse the role of EMT in gastric cancer has important clinical significance.

Hp is a Gram negative bacterium classified as a Class I carcinogen of gastric cancer by the World Health Organization and the International Agency for Research on Cancer. According to statistics, 2% to 3% of Hp infected individuals will develop gastric cancer. Eradicating Hp can effectively prevent the progression of gastric mucosal pathological changes, but some patients still progress to precancerous lesions including gastric atrophy and intestinal metaplasia. The carcinogenic effect of Hp mediated by multiple signaling pathways, such as Wnt/ β- Catenin, mitogen activated protein kinase (MAPK), NFκB pathway, through which Hp mediates cell cycle regulation, apoptosis, and immune response. Hp can secrete cytotoxin related protein A (Cag A) and vacuolar toxin A in the gastric microenvironment γ -Toxic factors such as glutamyltransferase (GGT) can damage the gastric mucosal epithelium, leading to the secretion of inflammation related factors and immune tolerance. Among them, Cag A may play an important role in the occurrence of gastric cancer. Cag A enters the gastric mucosal epithelium, cooperates with CD44 and c-Met, and upregulates phosphorylated c-Met β - Catenin signaling promotes the proliferation of gastric mucosal epithelium. Other studies have found that Rspo3 expression is upregulated in Hp infected mouse models, promoting increased secretion of FZD receptors and the activation of the Wnt/ β - catenin signaling pathway leads to an increase in the number of Axin2⁺gastric stem cells, resulting in epithelial proliferation of the gastric mucosa. Another study found that Hp can activate Wnt by upregulating FZD7 expression/Knocking out the FZD7 gene through the β - catenin pathway can inhibit Hp infection induced proliferation and Hp colony formation in gastric cancer cells; Further research has found that mir-27b can inhibit Hp infection and activation of the Wnt signaling pathway by inhibiting FZD7. There are also studies showing that Hp regulates Wnt/ β - catenin pathway induces an upregulation of transient receptor potential cation channel protein 6 expression, thereby promoting the development process of gastric cancer. In addition to Hp infection factors, EB virus is also one of the risk factors for gastric cancer, with approximately 9% of gastric cancer being associated with this oncogenic herpes virus. Another pathogen associated with gastric cancer is human cytomegalovirus (HCMV), which has been reported to have lifelong latent infections in gastric cancer. Studies have shown that, β - Catenin Interacting protein 1 has an anti-tumor effect in gastric adenocarcinoma, while EBV and CMV can regulate the expression of CTNNBIP1, but the specific mechanism is still unclear.

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Drugs targeting the Wnt signaling pathway are currently a hot research field in the treatment of gastric cancer, but there is still a lack of approved targeted drugs for clinical cancer treatment. At present, research drugs targeting the Wnt signaling pathway can be roughly divided into three categories: targeted receptor signal transduction, targeted disruption complexes, and targeted gene transcription. Most clinical trials focus on targeted receptor signal transduction, such as the Wnt signaling pathway targets PORCN (porcupine), Rspo3, Wnt5a, Wnt2b, FZD5, FZD7, FZD10, which are currently in clinical trials, as well as corresponding drugs LGK974 (WNT974), OMP-131R10, Foxy-5 OMP-54F28 (Ipafricept), OMP-18R5 (Vantitumab), UC-961 (Cirmtuzumab), etc. Research has shown that small molecule ICG-001 binds to CBP, disrupting its interaction with β - The interaction of catenin inhibits the transcriptional activation of the Wnt/ β- catenin signal indicates that ICG-001 has played its anticancer role in certain tumors. Studies have shown that when used in combination with chemotherapy drugs, ICG-001 can significantly block the binding of β - catenin to CBP significantly inhibits the growth and metastasis of gastric cancer cells, inducing cell apoptosis. Some clinical trials have shown that regorafenib has anti-tumor activity in gastric cancer, and further studies have shown that regorafenib can reduce the transcriptional activity of Wnt/ β - catenin signaling pathway leads to a decrease in the expression of target genes in the Wnt pathway, effectively inhibiting the proliferation and invasion of gastric cancer cells. Another study suggests that ibuprofen can reduce the proliferation of gastric cancer stem cells by inhibiting the Wnt pathway, but the specific mechanism remains to be studied. The abnormal expression of the Wnt signaling pathway in cancer tissue makes therapeutic drugs targeting the Wnt signaling pathway have good application prospects. The different variations of the Wnt signaling pathway in different cancer tissues and the varying carcinogenicity of these variations on different tissues provide insights for the study of tissue-specific targeted drugs.

4. Conclusion

Wnt/ β - catenin signaling pathway is an important signaling pathway for maintaining the homeostasis of gastric cells, and its normal transmission is crucial for maintaining stem cell characteristics and epithelial cell transformation. Meanwhile, Wnt/ β - catenin signaling pathway is a key driving factor for the occurrence of gastric cancer, participating in the Wnt/ β - catenin signaling pathway regulation of tumor cell cycle, promoting tumor cell proliferation, and participating in cell EMT. It plays an important role in the development, invasion, metastasis, and even drug resistance of gastric cancer, and largely determines the prognosis of gastric cancer patients. Therefore, conducting in-depth research on Wnt/ β - catenin signaling pathway and gastric cancer can help improve the recurrence and metastasis of gastric cancer patients, and increase their 5-year survival rate.

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References

[1] Yang Jiaoyang, Shu Gege, Li Dongbao, et al. Research progress on the role of signaling pathways in gastric cancer metastasis [J]. Basic Medicine and Clinical, 2023, 43 (11): 1707-1712. DOI: 10.16352/j.issn.1001-6325.2023.11.1707

[2] Luo Gang, Xie Minhui, Yang Juan, etc. REG γ Through Wnt/ β - catenin signaling pathway affects the proliferation, migration, and invasion of gastric cancer cells [J]. Chinese Journal of Gerontology, 2023, 43 (21): 5285-5289

[3] Wang Yimei, Li Changping. HP, traditional Chinese patent medicines and simple preparations, Wnt/ β - catenin Research progress on the relationship between the signaling pathway and gastric cancer [J]. Modern Clinical Medicine, 2023, 49 (04): 303-306

[4] Zhang Xue, Zhao Lili, Yan Wenxian, etc. The effects of HER-2 on the biological behavior and EMT, Wnt pathways of gastric cancer cells [J]. Journal of Clinical Oncology, 2023, 28 (07): 585-591

[5] Jun-Nan W, Yi-Ran W, Heng-Yu LI, et al. Research progress on the role of mTOR and its inhibitors in clinical diagnosis and treatment of breast cancer[J]. Chinese Journal of Clinical Medicine, 2018.