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Study on the occurrence and development of colorectal cancer

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Abstract: *Colorectal 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 colorectal 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 colorectal cancer is beneficial for providing insights into the prevention and treatment of colorectal cancer. This article provides a review of the research progress on the relationship between the Wnt signaling pathway and the occurrence and development of colorectal cancer.*

Keywords: *colorectal cancer, Wnt/ β- catenin signaling pathway, Research progress*

1. Introduction

Colorectal cancer is one of the common malignant tumors in the digestive system. Its high incidence rate and mortality have posed a serious threat to human health, especially in recent years, the incidence rate of young people has shown an upward trend. Research shows that in the occurrence and development of colorectal cancer. The abnormal activation of Wnt/ β- catenin signaling pathway plays an important role [1]. Under normal circumstances, the growth and development of animals depend on their precise regulatory effects, such as regulating cell proliferation, differentiation, and movement. However, when oncogene mutations, tumor suppressor gene mutations, or Wnt pathway component mutations cause abnormal activation or dysfunction, it can lead to abnormal development of the body or the formation of tumors. In the pathogenesis of colorectal cancer, Abnormal activation of the Wnt/ β- catenin signaling pathway leads to β- catenin accumulates significantly in the nucleus, triggering excessive proliferation and malignant transformation of corresponding cells, ultimately leading to the occurrence of colorectal cancer and blocking. The key protein of the Wnt/ β- catenin pathway significantly inhibits tumor growth. Explore Studying the multiple components of the Wnt/ β- catenin signaling pathway and their interaction mechanisms can help develop strategies for Effective antagonists targeting specific targets of the Wnt/ β- catenin signaling pathway provide a novel approach for early prevention and treatment of colorectal cancer.

2. Wnt/ β- catenin signaling pathway

2.1 Wnt gene

The Wnt gene was originally discovered as an oncogene in mouse breast tumors that can transmit proliferation and differentiation signals between cells. It was later named the Wnt-1 gene (named after wingless and int) [2]. Wnt protein is a secreted glycoprotein rich in cysteine, which binds to the seven transmembrane receptor proteins of the frizzled family and has a promoting effect on cell tumorigenesis. The conduction of Wnt signals is determined by the level of β- catenin in cells, when the level of β- catenin is low, the Wnt pathway is closed, and when the level of β- catenin is high, the Wnt pathway opens. The Wnt signal is introduced into the cell through frizzled, causing phosphorylation of Dsh and inhibiting GSK-3 β Functionality, thereby enabling the concentration of β- catenin increases. Most colorectal cancer gradually transforms into malignancy on the basis of adenomas. A certain degree of Wnt signaling in the normal body is necessary to maintain the proliferation status of crypt stem cells. When the adenomatous polyposis gene (APC) mutates, it cannot mediate β- catenin degradation or the changes in β- catenin itself remove phosphorylation sites, it remains stable

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interaction between β- catenin and TCF4 activates target genes, leading to incorrect specialization of cells that should have differentiated and matured, while still maintaining the characteristics of stem cells, thereby expanding the separation space of stem cells and causing the formation of adenomas and even malignant tumors. Therefore, the initiating effect of Wnt signaling on colorectal cancer is mainly reflected in its regulation of stem cell proliferation. Now research has found that Wnt3a can also pass through Wnt/ β- catenin pathway upregulates the expression of vascular endothelial growth factor receptor 2 (VEGFR2) and vascular endothelial cadherin (VE cadherin), promoting the formation of vascular mimicry in colon cancer. Wnt3a can promote the metastasis of colon cancer cells by affecting epithelial mesenchymal transition (EMT).

2.2 β- catenin

β- catenin is a key link in the Wnt pathway and a multifunctional protein with two main functions: mediating intercellular adhesion and participating in gene expression. Widely present in various types of cells β- catenin, such as endothelial cells, osteoblasts, and fibroblasts, is involved in the proliferation, differentiation, and apoptosis of these cells β- catenin plays an important regulatory role. In the occurrence and development of colorectal cancer, the abnormal expression ofβ- catenin plays an important role [3]. Under normal circumstances, free colon mucosal cells β- catenin is mainly distributed on the cell membrane, and its free content is relatively low in the nucleus and cytoplasm; On the contrary, in the cell membranes of colorectal cancer and adenoma cells. The expression of β- catenin decreased. Numerous studies have shown that. The expression of β- catenin in the nucleus and cytoplasm of colorectal cancer is higher than that in normal colon mucosa and colon adenoma tissue. The cytoplasm of β- catenin aggregates and enters the nucleus, leading to β- catenin activates and activates downstream target genes p53, c-myc, cyclin D1, and NF- κ Class B plays a crucial role in the malignant transformation of colon adenomas. Research has found that the following three mechanisms can lead to β- catenin accumulates in the cytoplasm and nucleus: (1) inactivation of APC gene in colorectal cancer; (2) Mutations in the Axin gene in colorectal cancer; Both of the above mechanisms can lead to APC/Axin/GSK-3β/β-catenin protein complex is disrupted, which affects β- Phosphorylation of catenin; (3) β- Mutations in the catenin gene, especially β- TrCP （ Mutations in the amino acid sequence recognized by transducin repets containing protein can lead to β- catenin protein cannot be phosphorylated, resulting in increased stability. Simultaneous mutation causes abnormal structure of the binding site between β- catenin and E-cadherin, unable to form β- catenin/E-cadherin complex leads to a decrease or loss of cell adhesion function, promoting tumor cell infiltration and metastasis [4].

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

According to reports, the Wnt signaling pathway is dysregulated in over 50% of gast Classic wnt/ β- catenin pathway is one of the key factors inducing colorectal cancer. β- catenin, as a positive regulatory molecule of the Wnt pathway, plays an important role in maintaining the survival of colorectal cancer cells and inhibiting cell apoptosis. In normal non proliferative colorectal epithelial cells, conjugated type β- catenin and E-cadherin is mainly expressed on the cell membrane to maintain the normal polarity and integrity of the epithelium. Free type β- catenin is only present in a very small amount within cells. The key to cancer caused by abnormal Wnt signaling pathway is the free type ectopic expression and dependence of β- catenin protein in cells activation of the target gene of β- catenin. Overactivation of the Wnt signaling pathway can inhibit c-myc induced cell apoptosis, thereby promoting the malignant transformation and tumorigenesis of normal colorectal cells; The overexpression of cyclin Dl induced by β- catenin can promote cell division, thereby promoting cell proliferation, while other downstream target genes in the Wnt signaling pathway, such as VEGF, are closely related to tumor cell angiogenesis. At present, the regulation of tumor occurrence and development by the Wnt pathway is mainly achieved through downstream target genes. On the one hand, activation of the Wnt signaling pathway can promote tumor cell proliferation, and on the other hand, it can antagonize the occurrence of cell apoptosis by promoting the transcriptional expression of anti apoptotic genes, such as survivin. ① Mutations in the β- catenin gene: Due to deletion or mutation of the β- catenin gene , β-catenin can not be degraded and accumulates in the cytoplasm, causing tumorigenesis. Although Mutations in the β - catenin gene can lead to Wnt Signal activation, but most colon cancer patients show the heterogeneity of β- catenin indicates the complexity of Wnt signal regulation APC gene mutation: Most colorectal cancers have APC gene deletion mutations or inactivation. The APC gene mutation site is located at the binding site with Axin, producing truncated

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APC protein, resulting in the inability to form a degradation complex for degradation β- catenin. The lack of APC function not only leads to the accumulation of β-catenin also promotes β- catenin and TCF4 form TCF/ β- catenin complex activates target genes downstream of the Wnt signaling pathway. Yoshie et al. compared the metabolite content of SW480 colorectal cancer cells expressing normal APC protein and truncated APC protein using gas chromatography. The results showed that the metabolite content of SW480 cells expressing truncated APC protein was significantly increased, indicating that APC mutations are involved in the development of colorectal cancer by altering the energy metabolism pathway. In addition, Bellis et al.'s study showed that asymmetric stem cell division was altered in APC mutated mouse adenoma cells, providing new clues for the development of colorectal cancer Axin gene mutation: Loss of Axin expression in colorectal cancer cell lines can lead to the accumulation ofβ-catenin leads to abnormal activity of the Wnt signaling pathway. Vermeulen et al. found through their study of Axin gene mutation patterns in colorectal cancer patients in the Kashmiri population that Axin1 and Axin2 gene mutations are involved in the occurrence and development of colorectal cancer, and found that Axin2 gene mutations may be a triggering factor for colorectal cancer in the Kashmiri population

Additionally, research has found that β- catenin can be activated by signals other than Wnt to exert its effects, β- catenin can be affected by factors including insulin/IGF/Akt, NF- κB. Notch, AMPK/TSC/GSK-3 β、 The regulation of multiple signaling pathways such as p53, p38MAPK, and ERK affects the proliferation, differentiation, and metastasis of colorectal cancer cells. In colorectal cancer cells β- catenin can regulate NF through TNFRSF19 (tuber ne cross factor receptor superfamily 19)- κ The activity of B. NF- κ B plays a crucial regulatory role in the occurrence, development, metastasis, and tumor angiogenesis of colorectal cancer by regulating genes such as cyclin D1, c-myc, COX-2, and intercellular adhesion molecule-1 (ICAM-1). β- catenin and NF- κ B can jointly regulate the urokinase type plasminogen activator/urokinase type plasminogen activator receptor (uPA/uPAR) system, affecting the invasion of colorectal cancer SW480 cells. Activated β- catenin can also interact with FOXO family proteins to interfere with the oxidative stress state of cells, thereby affecting their fate. Target genes of FoxO3a γ- Aminobutyric acid receptor A related protein 1（ γ- Aminobu ric acid A receptor associated protein like 1 (GAB ARAPL1) can inhibit Wnt by promoting autophagy to degrade Dvl2 protein/ β- catenin pathway. Wnt/ β- catenin pathway can regulate the growth of tumor cells. Research suggests that colon cancer cell spheres can reduce β- catenin adheres to the cell membrane and increases β- Cytoplasmic levels of catenin, cyclin D1, and c-myc, while downregulating Axin1 and phosphorylation β- catenin. The increased expression of β- catenin is closely related to TCF/LEF transcriptional activation, and RNA interference technology is used to Silencing the β-catenin gene can lead to a decrease in TCF/LEF, thereby reducing the formation of colon cancer cell spheres. On the contrary, upregulation of c-myc and TCF/LEF downstream effectors can significantly increase the generation of colon cancer balloon cells. Barker et al. knocked out the APC gene of Lgr5-Cre+intestinal crypt stem cells in mice and found that after 3-5 weeks, the stem cells still remained at the bottom of the crypt and formed visible Lgr5+adenomas, suggesting that the Wnt signaling pathway is involved in the transformation of normal intestinal stem cells into tumor stem cells.Therefore, in order to Studying the relationship between the Wnt signaling pathway and related signaling pathways, as well as the impact of these signaling pathways on colorectal cancer cells, with β- catenin as the center, can provide a new theoretical basis for the development of new anti-tumor drugs. Research findings Colorectal cancer with high expression of β-catenin protein in the cytoplasm and nucleus has strong invasiveness, higher postoperative recurrence rate, and shorter survival time for patients. The expression of β- catenin can also serve as an auxiliary evaluation criterion for the development and prognosis of colorectal cancer in clinical practice. Interference through adenovirus system or antisense nucleotides The expression of β- catenin, in turn, inhibits the regulation of downstream gene expression by TCF, which can effectively control the proliferation of tumor cells and is expected to become an effective treatment method for colorectal cancer in clinical practice[5].

Research has found that the anti-worm drug compound chloramphenicol can downregulate Wnt/ β-catenin signaling pathway counteracts the growth of colorectal cancer with APC mutations. MiR-93 can downregulate Wnt/ β- catenin signaling pathway inhibits the development of colorectal cancer. Fish oil can upregulate PPAR early on- γ And Wnt/ β- catenin signaling pathway counteracts dimethylhydrazine hydrochloride induced colorectal cancer. The combination of vitamin D3 and 5-fluorouracil can downregulate Wnt β- catenin, iNOS, and COX-2 expression upregulated by TGF-βenhances the antioxidant effect of 5-fluorouracil on azomethane induced colorectal cancer. Octreotide downregulates Wnt/ β- catenin pathway, reducing aggregation of β- catenin in the nucleus inhibits the activation of TCF-4, thereby inhibiting downstream target genes c-myc and cyclin D1, inhibiting the proliferation of colon cancer cells, inducing apoptosis, and causing cell arrest in the G1 phase. There

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are also studies indicating that the anti-tumor drug Exisulind (Apto synTM) and its analogues can activate PKG and directly phosphorylate it β- catenin is then degraded by the protein enzyme. This drug is effective against APC mutations and Different cell lines withβ- catenin mutations are effective and can cause tumor cell death. This process does not rely on APC and GSK-3 β， Provided a tumor treatment method that bypasses defects in the Wnt signaling pathway. In an experiment, human colorectal cancer HCT116 cells were intervened with blank group, physiological saline group, 5-FU group, and low, medium, and high-dose groups of Jianpi Xiaocancer Formula. Flow cytometry was used to detect cell cycle and apoptosis, and Western blot was used to detect the nucleus β- catenin protein expression, PCR detection of c-Myc and cyclin D1 mRNA expression. Confirming that the Jianpi Xiaocancer formula may regulate Wnt/ β- catenin signaling pathway promotes apoptosis in human colorectal cancer HCT116 cells. SW480 colon cancer cells were cultured in vitro and treated with low-dose and high-dose groups of dihydrotanshinone, as well as an equal amount of 0.9% physiological saline as a control group, to intervene at different times. It was found that dihydrotanshinone can effectively inhibit the proliferation of colorectal cancer SW480 cells, and its mechanism of action is related to the inhibition of c-Myc protein expression, which hinders Wnt/ β- catenin signal transduction is related. An experimental group found that an increase in the concentration of naked purple pearl in Wuzhishan, Hainan can lead to a downregulation of SW480 and SW620 cell colony numbers and an upregulation of inhibition rates, in a dose-dependent relationship. Hainan Wuzhishan Naked Flower Purple Pearl Activates the inhibitory effect of the Wnt/ β- catenin signaling pathway on the proliferation and growth of colon cancer cells

4. Conclusion

The occurrence of colorectal cancer is a complex process involving multiple factors, stages, and the accumulation of multiple genetic variations.

The result is an enhanced transcription of downstream target genes. Therefore, on the one hand, specific diagnosis and treatment can be carried out for the components of the Wnt pathway itself, and on the other hand, for its target genes. In addition, the human body is an organic whole composed of multiple signal transduction pathways interwoven into a network and working together. While studying the Wnt pathway, attention should also be paid to the roles of other pathways and the mutual influence between Wnt and other pathways.

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