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Research Progress of Wnt/β-catenin Pathway in Tumor Therapy

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Abstract: The Wnt/beta catenin signaling pathway is closely related to the occurrence and development of cells. embryonic development, cell fate determination, tissue and organ formation, as well as tumorigenesis. Aberrant activation This pathway is closely related to the occurrence, development, metastasis, and immune evasion of various cancers. This review summarizes the composition, activation, and regulatory mechanisms The Wnt/beta catenin signaling pathway is overactivated in tumor tissues and closely associated with tumor stemness and immune evasion. Previous studies have found that, Abnormal activation of the Wnt/β - catenin signaling pathway can regulate c-Myc CyclinD1 and other important targets enhance the stemness of liver cancer cells. Further research has found that this pathway can promote immune escape of tumor cells by upregulating PD-L1 and other mechanisms. There have been some developments in small molecule inhibitors targeting this pathway, including small molecule compounds targeting the Wnt pathway such as β - catenin and BCL9. Some of these inhibitors have entered preclinical or clinical trial stages, offering new strategies and hope for tumor treatment.

Keywords: Wnt/beta Catenin pathway, anti-cancer, Targeted Therapy

1. Introduction

Wnt/beta catenin is a highly conserved signaling pathway is triggered when Wnt proteins attach to membrane protein receptors. It controls a range of biological functions. From fruit flies to humans, this pathway is essential for important biological processes such as cancer, tissue and organ morphogenesis, cell fate determination, and The development of embryos. The Wnt/beta catenin pathway is finely regulated under normal conditions. However, this pathway and its downstream target genes can also undergo abnormal activation[1] This process involves mutations in multiple key pathway elements, epigenetic modifications, and interactions with other signaling pathways. This will have an impact on the occurrence, development, metastasis, and production of cancer[2], [3].

At present, The activation of the Wnt/beta catenin pathway can be divided into three types: classical Wnt/alpha catenin pathway, non classical planar pathway Wnt/Ca2+pathway [4], [5]. Among these genes, beta catenin is the central molecule of the Wnt pathway, but not the main molecule of the classical Wnt pathway [6]. Due to the close association between the Wnt/beta catenin signaling pathway and the onset of cancer, anti-cancer drugs targeting the Wnt/beta catenin signaling pathway have become a research hotspot become a research hotspot. However, drugs targeting this pathway have not been widely applied in clinical practice due to severe adverse reactions.

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This article Current research status of Wnt/beta catenin signaling pathway in tumor therapy, analyzes the difficulties and challenges faced in this field, and looks forward to future research directions, aiming to provide basic knowledge and research suggestions for related fields.

2. Activation and Regulation Mechanisms of the Wnt/β-catenin Pathway

In 1982, Roeland Nusse et al. [7]accidentally discovered a special gene during the study of the introduction of mouse mammary tumors by mouse mammary tumor virus. Since the This activation is achieved by implanting a tumor virus called Int-1 into the breast of mice. Further research has shown that Int-1 shares high homology with a small polarization related protein, Wingless, in fruit flies. On this basis, Wingless synthesizes a new Wingless with Int-1, namely Wingless and Int-1, and is officially referred to as the Wnt gene.

Wnt/beta catenin pathway is made up of many different components, including wnt proteins, frizzled proteins, LRP5/6 (LRP5/6) is a newly discovered pathogenic gene in recent years. The expression of Ribosin, axin protein, E.coli gene product of adenomatous polyposis, β - catenin protein, β - catenin protein, β - transporter protein, casein kinase 1, glycogen synthase kinase 3 β, GSK3 β and other proteins binding proteins, and transcription factor families For example, T-cell cytokines/lymphotropic growth factors[8]. Mammals typically use three steps to activate and deactivate Wnt/β - catenin pathway: The key genes downstream of Wnt enter the nucleus, and the stability regulation of β - catenin in the cytoplasm and the transmission of Wnt signaling in the cell [9]. The activation mechanism is shown in Figure 1.

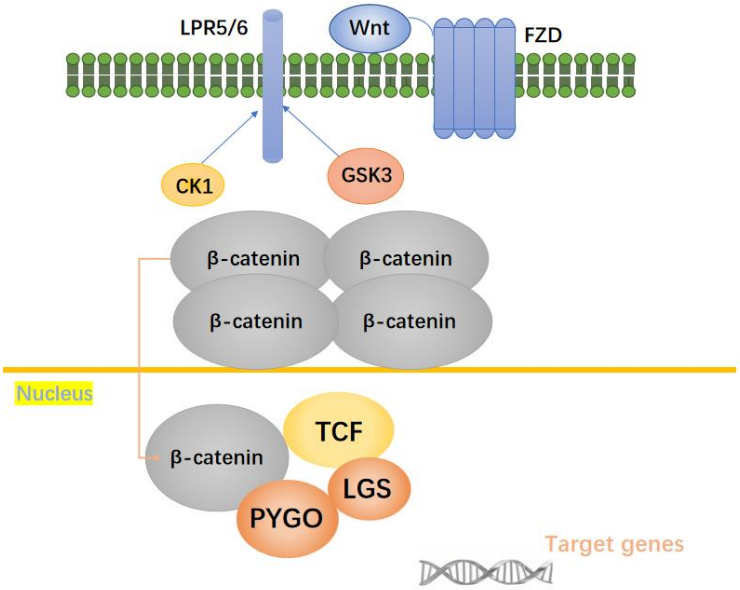

Figure 1: Wnt/β-catenin signal pathway activation mechanism.

2.1. Wnt Protein Family

Wnt is a secreted protein that highly expresses cysteine glycoproteins, with multiple family members identified to date. These proteins act as signaling molecules outside the cell, initiating signal transduction by binding Sensors on the cell membrane. The secretion and stability of Wnt proteins are regulated by various factors, including protein modifications and interactions with other molecules.

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2.2. Receptors and Co-receptors

2.2.1. Frizzled (Fz) Receptors

Frizzled receptors are a class of seven-transmembrane proteins and are the main receptors for Wnt proteins. If Wnt protein is linked to a coiled receptor,they can activate downstream signal transduction.

2.2.2. Low-density lipoprotein receptor-related proteins 5/6 (LRP5/6)

LRP5/6 is an important class of co receptors. work in conjunction with Fz receptors to enhance the efficiency of Wnt signal transduction.

2.3. β-catenin

A multipurpose protein, β-catenin is essential for intracellular signal transmission. A degradation complex consisting axin, Colonic polyposis E. coli, Regulation of beta catenin expression by glycosylthalase kinase 3 β, case-1, case-1in the cytoplasm when Wnt signal activation is absent. The ubiquitin-proteasome system degrades β-catenin as a result of this complex's promotion of phosphorylation. Dishevelled proteins are activated when the Wnt signal is triggered because Wnt proteins attach to Fz receptors and LRP5/6. GSK3β is inhibited by activated Dvl proteins, This protein can inhibit the phosphorylation and degradation of beta catenin. During this process, beta catenin aggregates in the cytoplasm and enters the nucleus. TCF/LEF transcription factors bind and activate beta Catenin in the nucleus[10], [11], [12], [13], [14], [15].

2.4. Transcription Factors

Our previous research found that beta catenin can regulate downstream target gene expression in the nucleus by interacting with transcription factors such as TCF/LEF. The target gene is a gene that plays an important role in the maintenance and differentiation of stem cells, and cell proliferation.

3. Abnormal Activation of the Wnt/β-catenin Pathway in Cancer

Gene mutations or abnormal DNA methylation can activate the Wnt/beta catenin pathway, leading to tumorigenesis. The variation of tumor suppressor genes can promote cancer by reducing the activity of the cleavage complex. Losing function mutations in RNF43 increase the number of Wnt receptors on the cell surface, which lowers receptor-level negative feedback and increases tumor susceptibility to Wnt inhibitors, both of which further encourage tumor development. Its target of action::WIF1, SFRP, DKK1, DACT, SOX7/17, β-TrCP, E-Cadherin, APC, AXIN-2, Wnt7a/9 Aclass exhibit transcriptional abnormalities due to the loss of DNA methylation. Histone changes like methylation, acetylation, and phosphorylation affect the onset, development, and metastasis of cancer by regulating the Chromatin accessibility and expression of various factors in the Wnt signaling pathway. During the occurrence and development of tumors, non coding RNA can regulate the Wnt/beta Catenin signaling pathway.

Cancer typically exhibits rapid proliferation and strong invasive and metastatic capabilities. The activation and deactivation of The Wnt/beta catenin signaling pathway plays an important role in various life activities[16], [17]. The latest research has found that the Wnt/beta catenin signaling pathway can regulate the development of various tumors, including tumors[18], liver cancer [19], cervical cancer[20], lung cancer [21], and gastric cancer [22]. The regulation of Wnt/beta catenin signaling pathway is one of the important mechanisms in tumor progression[23] High expression of β - catenin in tumor tissue[19]. Our previous research found that in tumor tissue, the number of beta catenin changes, which can enter the nucleus and interact with TCF/LEF transcription factors

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(TCF/LEF), upregulating c-Myc Downstream target genes such as cyclinD1. Overexpression and uncontrolled expression of target genes can lead to cell cycle disorders, causing cells to enter the proliferative phase and potentially acquiring immortality, thereby promoting the occurrence of cancer [24], [25].

In addition, the abnormal activation of the Wnt signaling plays a crucial regulatory role in maintaining the stemness and directional differentiation of tumor stem cells. Our previous research found that beta catenin can interact with TCF protein in tumor cells, promoting the expression of related genes such as c-Myc and cyclinD1. HES1, and HEY1, thus maintaining the cancer stem cell population. By using retroviral transfection to express different β-catenin mutants in keratinocytes, it was found that an N-terminal truncated β-catenin mutant (which is not degraded due to the lack of a GsK-3B binding site) can increase the proportion of stem cell clones in cultured tumor cells [26].

The unusual activation of β-catenin can contribute to immune evasion in cancer. Presently, the The ligand PD-L1 of PD-1 is significantly expressed in several human cancers, such as breast, cervical, lung, colorectal cancers, and melanoma. Elevated levels of PD-L1 in tumor cells can cause dysfunction and fatigue in cytotoxic T cells, allowing the tumor to evade immune detection and hindering the elimination of cancer cells, which is a factor in the unfavorable clinical outcomes for cancer patients.[27]. Previous studies have found that in liver cancer, the activation or knockout of inherent oncogenic signaling pathways can cause T lymphocyte rejection, leading to a decline in the body's immune function. Wnt/beta catenin is the most representative oncogene. Moreover, beta catenin can also play an important role in cells cells can induce the transcription of STT3, which promotes the glycosylation and upregulation of PD-L1, thereby inducing tumor immune evasion [28].

4. Advances in the Study of Wnt/β-catenin Pathway Inhibitors in Cancer Therapy

Currently, many Inhibitors of the Wnt/beta catenin signaling pathway are a promising anti-tumor drug that has entered preclinical or clinical trials. This type of compound exerts anti-tumor effects by acting on important molecules in the Wnt pathway, reducing the Wnt pathway. According to the type of corrosion inhibitor, they can be divided into the following series particular target elements in the pathway: (1) inhibitors or antagonists at the extracellular or membrane level that target the Wnt ligand, as the Porcupine specific inhibitor LGK974; (2) Cytoplasmic inhibitors: these include Tankyrase inhibitors and Disheveled Using β - catenin Inhibitors targeting AXIN and APC (3) nuclear inhibitors: controlling target gene transcription, like the naturally occurring substance PKF115-584, which has been found to interfere with the β-catenin/TCF complex and prevent colorectal cancer cells from proliferating; (4) Inhibitors of cross-pathway interactions: these focus on how The Wnt/beta catenin pathway interacts with other signaling pathways (e.g., the Notch pathway) [29]; (5)Natural products like curcumin [30], [31], resveratrol [32], etc.

Wnt/beta catenin signaling pathway inhibitors can effectively inhibit tumor cell proliferation. immunomodulatory effects. Immunocheckpoint inhibitors primarily target natural killer (NK) T lymphocytes play a crucial role in the body's anti-tumor immune response. The Wnt pathway is mediated by the Wnt pathway. controlling NK cells' anti-tumor activities, according to recent research[33]. For instance, NK cell maturation and function can be improved by blocking GSK3β, which activates the Wnt/β-catenin pathway [34]. But occasionally, Wnt signaling antagonists such Dickkopf 1/2 are secreted by cancer cells, helping them avoid NK cell-mediated anti-tumor responses [35], [36]. Based on this speculation, Some components of the Wnt pathway play an important regulatory role in the activation and invasion of NK cells.

BCL9 is a core Adjuvant transcription factors of WNT signaling pathway. The BCL9 gene is overexpressed in 71.5% of advanced hepatocellular carcinomas and 40% of colorectal cancers. It is a key molecule in the dynamic regulation between the primary and metastatic lesions of colorectal cancer liver metastasis and Inversely proportional to survival rate hepatocellular carcinoma patients.

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However, the mechanisms by which BCL9 regulates tumor metastasis and immune therapy resistance are still unclear. Studies have shown that targeting BCL9/BCL9L can regulate multiple tumor immunity-related processes, including plasma cell metastasis, T cell infiltration, B cell migration, and dendritic cell activation [37], [38], [39], [40]. This not only By exerting a killing effect on cancer cells, the growth and migration of cancer cells can be effectively reduced, and the recognition and killing of cancer cells by the body can be strengthened, achieving a synergistic effect.Therefore, BCL9/BCL9L, as a new target for immune therapy resistance and tumor metastasis, holds significant research value.

Further research has shown that blocking the BCL9/β-catenin protein interaction can enhance antigen presentation and activation in cDC1 cells. Small-molecule BCL9/β-catenin inhibitors containing a 3-phenylpiperidine urea structure not only enhance antigen presentation and activation in cDC1 cells [41] but also increase the proportion of cDC1 cells in PBMCs (peripheral blood mononuclear cells) and TdLNs (tumor-draining lymph nodes), thereby enhancing T cell-mediated immune responses. This study reveals a novel pharmacological mechanism for blocking BCL9/β-catenin protein interaction in anti-tumor therapy, which simultaneously inhibits tumor cell growth, promotes cDC1 cell activation, and activates T cells. In terms of mechanism of action, the inhibitor activates the Btk-Stat-Irf1 signaling axis, promoting the differentiation and maturation of cDC1 cells. In summary, these inhibitors can achieve significant anti-tumor effects by enhancing antigen presentation by cDC1 cells Inside the tumor.

5. Conclusion

The Wnt/beta catenin pathway essential for several physiological functions, These processes include cell division, maintenance of tissue homeostasis, and early development. The abnormal activation of this pathway and its downstream target genes can accelerate the development of cancer.which is caused by epigenetic changes, mutations in essential components, and interactions with other signaling pathways. Presently, treatments thatDrug development targeting the Wnt/beta catenin pathway the ability to treat cancer.[42].

At the same time, Wnt/beta catenin pathway also presents opportunities Research and treatment of tumors. This pathway has important regulatory functions in the immune system, such as promoting the T cells, The development and differentiation of B cells and dendritic cells,and maintaining immune homeostasis. Therefore, inhibiting this pathway may interfere with these processes, leading to impaired immune cell function and weakened anti-tumor immune responses. How to balance the pathway's regulation of the immune system while inhibiting tumor growth has become a key focus of related research.

Future research should focus on iIn depth study of Wnt/beta catenin signaling pathway regulates tumor immunity, revealing how it controls tumor cell proliferation, immune evasion, and immune microenvironment remodeling. This will be essential for developing more effective therapeutic strategies. On this basis, the development and application of more efficient pathway inhibitors should weigh their anti-tumor efficacy against potential impacts on the immune system, employing precision targeting strategies. Additionally, exploring combination immunotherapy approaches to optimize efficacy and reduce side effects is crucial. For example, developing tumor-specific inhibitors or using nanotechnology to minimize impacts on normal immune cells could be effective. Meanwhile, immune checkpoint inhibitors can serve as adjuvants to enhance anti-tumor immune responses and overcome immunosuppressive microenvironments[43]. Through these multidimensional research and application efforts, it is hoped that more precise and effective solutions for cancer treatment can be provided.

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