SPARKLING PUBLISHING GROUP

TYPE Review Article
PUBLISHED 15 June 2025
DOI 10.5883/ctr.2025.6.6.3

CLINICAL AND TRANSLATIONAL REPORTS

OPEN ACCESS
Vol 2, No.1

RUNNING TITLE
Targeting wnt/β-catenin in cancer

RECEIVED
06 April 2025

REVISED
17 May 2025

ACCEPTED
22 May 2025

PUBLISHED ONLINE
15 June 2025

Molecular mechanism analysis of Wnt/β-catenin signaling in cancer and its clinical translation

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Abstract

One phylogenetically conserved mechanism that controls tissue homeostasis and embryonic development is the Wnt/β-catenin pathway. It is aberrantly activated in a variety of cancers, driving malignant transformation, therapeutic resistance, and metastatic dissemination. The pathway regulates tumorigenesis by stabilizing β-catenin, which in turn activates TCF/LEF-mediated transcription of target genes. Uncontrolled cell proliferation, the maintenance of cancer stem cells (CSCs), the epithelial-mesenchymal transition (EMT), and metabolic reprogramming are all facilitated by dysregulated Wnt/β-catenin signaling, while forming an immunosuppressive tumor microenvironment (TME) through impaired dendritic cell (DC) maturation, reduced cytotoxic T cell infiltration, and upregulation of PD-L1. Notably, interactions with other pathways such as PI3K/AKT, Notch, and TGF-β amplify oncogenic signals, complicating therapeutic targeting. Due to the complexity of the pathway, tumor heterogeneity, and compensatory feedback, the clinical translation of Wnt/β-catenin inhibitors remains challenging. Current strategies include targeted inhibitors and combination therapies with immune checkpoint inhibitors (ICIs). Preclinical studies have shown that Wnt pathway blockade can enhance immunotherapy effects by reversing immunosuppression in the TME, while nanotherapeutics and natural compound-based therapies show promise in overcoming chemoresistance. This review integrates current insights into Wnt/β-catenin regulation and its integration with other oncogenic networks, and outlines clinical translational strategies targeting this master regulator, providing new strategies to block tumor progression and improve treatment durability.

DOI 10.58832/ctr.2025.6.6.3

KEYWORDS

Wnt/β-catenin signaling pathway, Tumor microenvironment, Cell proliferation, Epithelial-mesenchymal transition, Clinical translation.

Introduction

Uncontrolled cell proliferation, escape from programmed cell death, and the invasion and spread of many cancer cells make cancer one of the most dangerous health issues in the world(1). Despite years of research, the underlying molecular mechanisms driving tumorigenesis and therapeutic resistance continue to develop breakthroughs. Abnormally regulated signaling networks that govern cell fate, survival, and communication in the tumor microenvironment (TME) are at the heart of the intricate interactions between genetic, epigenetic, and environmental variables that have been shown in several studies. Among these networks, canonical signaling pathways, such as PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, NF-κB, and JAK/STAT, play an indispensable role in maintaining cellular homeostasis under physiological conditions(2). Dysregulation of these pathways in cancer can lead to malignant transformation, therapeutic resistance, and disease progression. For example, aberrant activation of the PI3K/Akt/mTOR pathway may lead to cancer through gene mutation, gene amplification, or dysregulation of upstream signaling. In order to activate the mTOR complex, create a signal cascade mechanism, and support protein synthesis and cell cycle progression, activated PI3K generates the second messenger PIP3, attracts Akt to the cell membrane, and phosphorylates it(3). The formation and progression of malignant tumors are significantly influenced by aberrant activation of the MAPK signaling pathway, which is the primary molecular mechanism controlling cell differentiation and proliferation. During the oncogenic activation process, growth factor receptors are activated after binding to Ras GTPases, forming a complex through protein interaction, thereby triggering the dual-specific kinase activity of downstream MEK1/2 to activate ERK1/2, thereby initiating key intracellular signaling cascades and promoting abnormal expression of proinflammatory cytokines (IL-6, TNF-α, etc.) and growth factors(4).

The Wnt/β-catenin system, a canonical signaling pathway in cancer, has received significant attention for its involvement in stem cell maintenance and oncogenic transcriptional control. Throughout an organism's life cycle, the Wnt/β-catenin pathway is in charge of a signaling cascade that is crucial for embryonic development. It has been demonstrated that Wnt/β-catenin is crucial for apoptosis, genetic stability, and cell migration. In its canonical form, Wnt ligands suppress the β-catenin destruction complex, which is made up of Axin, APC, and GSK-3β, by binding to Frizzled receptors and LRP5/6 co-receptors. After translocating to the nucleus, stable β-catenin links to TCF/LEF transcription factors and activates genes linked to invasion, stem cell characteristics, and proliferation. Cancer cells exploit this cascade through genetic and epigenetic alterations, thereby exploiting developmental programs for unchecked growth(5). Mutations in genes like APC and CTNNB1 frequently cause aberrant activation of the Wnt/β-catenin signaling system, which has been linked to a number of cancers, including colorectal, hepatocellular, and breast cancer(6, 7). This dysregulation not only promotes tumorigenesis, but also leads to metastatic progression and treatment resistance. Given its ubiquity in malignancies, the Wnt/β-catenin signaling pathway has emerged as an attractive therapeutic target. Moreover, aberrant Wnt/β-catenin pathways do not function alone but engage in complex molecular crosstalk that amplifies oncogenic signals or counteracts tumor suppressive mechanisms. This dynamic interplay complicates therapeutic targeting, often leading to compensatory pathway activation and poor clinical efficacy. This review comprehensively analyzes the molecular mechanisms of Wnt/β-catenin signaling in cancer and describes emerging therapeutic modalities, aiming to inform the rational design of Wnt/β-catenin-targeted interventions, ultimately improving patient stratification and advancing precision oncology.

DOI 10.58832/ctr.2025.6.6.3

1.Mechanisms of canonical Wnt/β-catenin signaling pathways in cancer

The Wnt/β-catenin pathway works by regulating the stability of β-catenin. Under normal circumstances, β-catenin is phosphorylated by the "destruction complex" (including APC, GSK3β, etc.) and degraded through the ubiquitin-proteasome pathway. β-catenin escapes degradation and enters the cell nucleus when the Wnt ligand binds to the Frizzled/LRP receptor. It then binds to the TCF/LEF transcription factor, activates the transcription of downstream Wnt target genes, and promotes cell proliferation, differentiation, and stem cell properties(8) (Figure 1). A number of variables contribute to the aberrant activation of the Wnt/β-catenin pathway. Among them, β-catenin abnormally accumulates in the nucleus due to gene mutations or epigenetic abnormalities, which promotes cancer(9). While TRIP13 increases the activity of the system via controlling α-Actinin-4, which promotes the formation of cervical cancer(10), WSB2 overexpression speeds up the advancement of lung cancer by activating the Wnt/β-catenin pathway(11). However, the Wnt/β-catenin pathway can also lead to an imbalance in the cancer cells' regulatory network. For example, KDM6A, one of the H3K27me3 demethylases, is regulated by Wnt signals, and then silences the LEF1 promoter through epigenetic mechanisms, inhibiting Wnt/β-catenin signaling to form a positive feedback loop, which contributes to the heterogeneity of cancer(12).

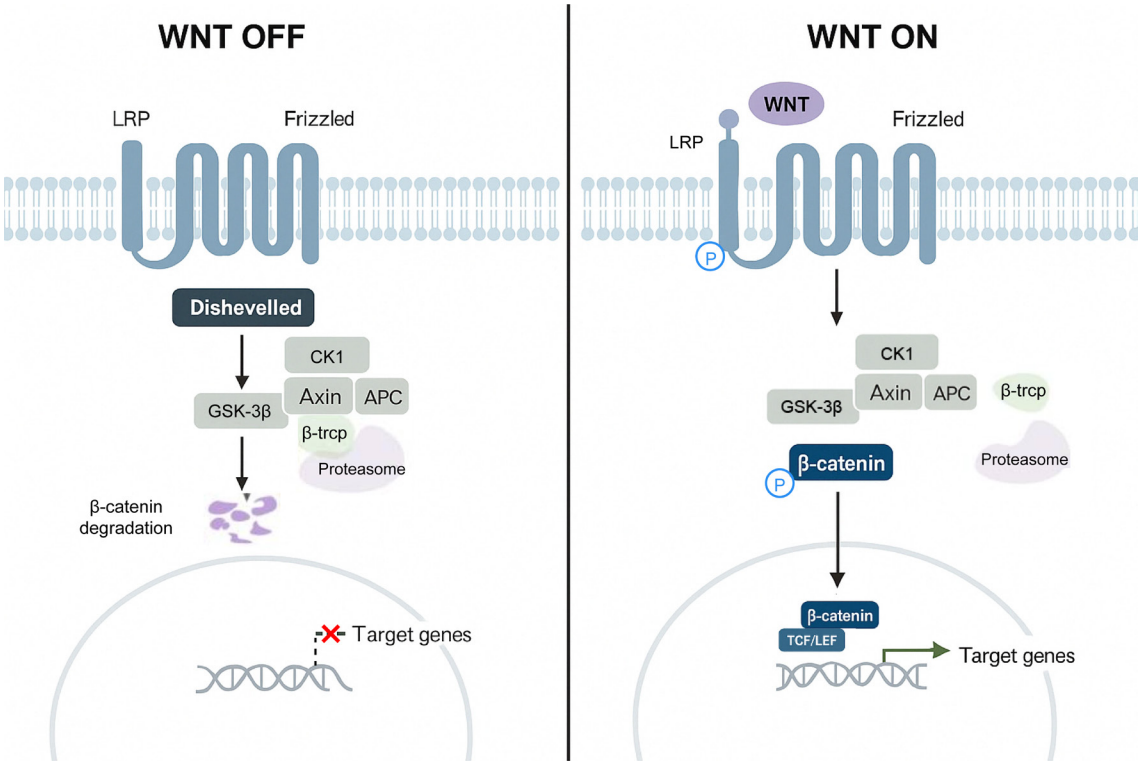

FIGURE 1
Molecular mechanism of Wnt/β-catenin pathway.

The WNT signaling pathway When WNT ligands are not present, CK1 phosphorylates the β-catenin that has accumulated in the destruction complex by AXIN and APC. GSK3β then ubiquitinates it, allowing β-TrCP and other proteasomes to breakdown it. Following the activation of WNT ligands, the destruction complex is destroyed when

DOI 10.58832/ctr.2025.6.6.3

AXIN and DVL are activated and recruited to the cell membrane by the binding of LRP5/6 and FZD co-receptors. This results in β-catenin stability and nuclear localization.

WNT target gene transcription is induced in the nucleus by β-catenin binding to TCF/LEF and enlisting co-activators p300 and CBP.

2.Role of Wnt/β-catenin pathway in cancer progression

A phylogenetically conserved regulatory axis, the Wnt/β-catenin system controls basic biological functions such stem cell maintenance, tissue homeostasis, and embryonic development(13). However, its aberrant activation is increasingly recognized as a hallmark of malignant transformation and tumor progression in different cancer types. Dysregulation of this pathway disrupts cellular homeostasis and drives oncogenic phenotypes through multifaceted mechanisms such as proliferation, stem cell properties, immune evasion, and metastatic dissemination. Increasing evidence highlights its key role in maintaining cancer cell survival, metastasis, and microenvironmental adaptation, making it a key mediator of tumor development(14). Proliferative signaling and activation of cancer stem cells (CSCs) by the Wnt/β-catenin pathway promotes uncontrolled tumor proliferation by orchestrating cell cycle progression and transcriptional reprogramming. The pathway directly upregulates cyclins and c-Myc, bypassing regulatory checkpoints to maintain mitotic activity. Notably, it enhances self-renewal capacity in CSCs, thereby enabling tumor recurrence after chemotherapy or radiation(15). Cholesterol-mediated coactivation of Wnt/β-catenin and lipoprotein receptors further amplifies proliferative signals while conferring resistance to cytotoxic agents(16). This dual function not only enables tumor persistence but also establishes chemoresistant CSC growth through β-catenin-dependent activation of DNA repair mechanisms and survival pathways.

Microenvironmental crosstalk and alterations in the tumor microenvironment (TME) drive Wnt/β-catenin immune escape mechanisms. Aberrant Wnt ligand secretion by malignant cells can induce β-catenin nuclear translocation in antigen-presenting cells, impairing dendritic cell (DC) maturation and cytotoxic T cell recruitment. This reprogramming of immunosuppression coincides with enhanced regulatory T cell infiltration and upregulation of checkpoint molecules, effectively subduing antitumor immunity(17). Concomitantly, Wnt/β-catenin activation in endothelial cells promotes a switch to angiogenesis induced by VEGF, thereby fostering a hypoxic environment conducive to metastatic spread(18). These coordinated adaptations highlight the pathway's systemic influence in sculpting an immunotolerant TME that supports tumor persistence. Wnt/β-catenin signaling operates as a master regulator of epithelial-mesenchymal transition (EMT), a phenotypic shift enabling tumor cell detachment and invasion. By suppressing E-cadherin and inducing Snail/Slug transcription factors, β-catenin dismantles intercellular junctions while enhancing matrix metalloproteinase (MMP) secretion for basement membrane degradation. This intricate network of oncogenic interactions positions Wnt/β-catenin signaling as both a biomarker and actionable target for managing advanced malignancies(19). Here, we summarize the current status of research on this signaling pathway in cancer phenotypes and progression.

2.1 Driver of cancer cells proliferation and tumor growth

The growth of cancer cells is mostly dependent on the Wnt/β-catenin signaling pathway. When Wnt signals are not present, the "degradation complex" consisting of APC, Axin, GSK-3β, and other components phosphorylates and ubiquitinates β-catenin. The degradation complex is inhibited, β-catenin builds up in the cytoplasm and enters the nucleus, attaches to the TCF/LEF transcription factor, activates downstream target genes, and promotes cell cycle progression and proliferation when the Wnt ligand binds to the Frizzled receptor and LRP5/6 co-receptor. Cyclin D1 controls the course of the cell cycle, VEGF induces angiogenesis, supports tumor growth, and c-Myc promotes the G1/S phase transition of the cell cycle, among other pro-proliferation actions of downstream target genes(20). Numerous studies have examined the role of the

DOI 10.58832/ctr.2025.6.6.3

Wnt/β-catenin signaling system in the growth of different types of cancer cells. For instance, APC mutation is the primary cause of aberrant Wnt pathway activation in over 90% of colorectal cancer cases(21), according to years of study. If the β-catenin/TCF complex is targeted, such as the small molecule inhibitor ICG-001, tumor growth can be inhibited(22). In hepatocellular carcinoma, β-catenin mutations lead to overexpression of Cyclin D1, driving abnormal proliferation of hepatocytes(23). β-catenin-dependent Wnt signaling promotes the invasive proliferation of oral squamous cell carcinoma cells by upregulating MMP9, and targeting this pathway can induce apoptosis(24). In addition, by triggering Wnt/β-catenin signaling, DSTYK deficiency encourages aerobic glycolysis in lung cancer cells, which accelerates tumor development(25).

2.2 Metastasis of cancer cells

During cancer metastasis, the Wnt/β-catenin signaling pathway promotes cancer cells to acquire invasion and migration capabilities by regulating EMT. Studies have shown that activated Wnt signals can induce decreased E-cadherin expression and upregulate transcription factors such as Snail and Twist, thereby weakening cell-to-cell adhesion and forming a highly invasive mesenchymal phenotype(26). At the same time, following its accumulation in the cytoplasm and subsequent translocation into the nucleus, β-catenin triggers downstream target genes including Cyclin D1 and c-Myc, which further encourage cell proliferation and cell cycle progression while supporting the cell pool for distant metastasis(27). For example, in liver cancer, PRMT5 drives metastasis by regulating β-catenin nuclear localization(28). Cancer cells can activate β-catenin signals in stromal cells by secreting Wnt ligands to form a pro-metastatic microenvironment. In order to encourage the vascularization of metastatic lesions, this route simultaneously controls angiogenesis-related molecules, including VEGF. In addition to promoting the aforementioned method of cancer cell proliferation, abnormal activation of the Wnt/β-catenin pathway in colorectal cancer also promotes liver metastasis through the regulation of LGR5+ stem cells and EMT(29). AXIN2 and Cyclin D1, two genes linked to metastasis, can have their expression levels decreased by blocking this pathway. In breast cancer, activation of this pathway induces DNA damage repair and enhances tissue invasion by upregulating MMP family proteins (such as MMP2/9)(30). Animal models show that inhibition of β-catenin can reduce the formation of lung metastases(31). Targeting the β-catenin/LEF1 interaction can inhibit the transcription of metastasis-related genes, while WSB2 protein promotes the metastasis of lung cancer by activating this pathway(32). Studies on hepatocellular carcinoma metastasis have found that the MTDH-PRMT5 complex enhances metastasis by regulating Wnt/β-catenin signaling, while TC2N protein promotes cancer cell invasion by stabilizing β-catenin(33). According to these investigations, the Wnt/β-catenin signaling pathway mechanism in cancer metastasis offers a methodical molecular network map that reveals tumor invasion and metastasis.

2.3 Immune escape of cancer cells

Numerous studies have demonstrated that the Wnt/β-catenin signaling pathway is essential for controlling TME and immune cell activities, which aids cancer cells in avoiding immune system monitoring. First, the location and activity of antigen-presenting cells are directly impacted by the activation of Wnt/β-catenin signaling. Inhibiting the release of chemokines (including CXCL9/10), decreasing antigen presentation capacity, and hence diminishing the activation level of tumor-specific T cells, abnormal activation of the Wnt/β-catenin pathway results in decreased recruitment of CD8+ T cells and DCs in the TME(34). In melanoma, the activation of this pathway is directly related to the lack of T cell infiltration(35). Mutations in CTNNB1 encoding β-catenin or other abnormal activation of the Wnt/β-catenin pathway are closely related to the loss of immune cell DCs and CD8+ T cells in the TME of hepatocellular carcinoma, resulting in poor clinical response to immunotherapy(36). Secondly, abnormal upregulation of β-catenin signals also promotes the secretion of immunosuppressive factors, like IL-10 and TGF-β. This process further promotes the accumulation of regulatory T cells (Tregs), making the immunosuppressive environment more stable, while Wnt ligands in the TME activate the β-catenin signal of APCs, inducing DCs to present an anti-inflammatory phenotype, reducing their antigen presentation ability, and promoting Tregs differentiation(37). In addition, β-catenin, as a transcription factor of PD-L1, directly upregulates PD-L1 expression on the surface of tumor cells by activating Wnt/β-catenin signals, helping tumors escape immune surveillance. At the same time, this pathway also indirectly enhances PD-L1 expression by activating STAT3(38). For instance, via controlling PD-L1

DOI 10.58832/ctr.2025.6.6.3

expression, the Wnt/β-catenin pathway in colorectal cancer encourages immune escape. By blocking the interferon-γ (IFN-γ) signaling pathway, the buildup of β-catenin in non-small cell lung cancer makes tumor cells resistant to immune response(39).

2.4 Tumor metabolism and microenvironment

In terms of tumor metabolism, Wnt/β-catenin signaling enhances tumor cell glucose uptake and lactate production by upregulating metabolic enzymes such as lactate dehydrogenase A (LDHA), thereby supporting rapid tumor proliferation and survival. In addition, this pathway directly regulates glycolysis-related genes (such as GLUT1 and HK2), promotes metabolic reprogramming, and meets the high demand for energy and biosynthetic precursors for rapid tumor proliferation(40). HO-mediated oxidative stress can regulate Wnt/β-catenin signaling and metabolic reprogramming of TME in colorectal cancer(41). The reconfiguration of lipid metabolism is also tightly linked to aberrant Wnt/β-catenin signaling activity, according to some experimental findings. This pathway not only meets the synthesis needs of tumor cell membrane components and signaling molecules by regulating fatty acid synthesis and oxidation processes, but also provides a metabolic basis for cells to cope with oxidative stress. In triple-negative breast cancer, long noncoding RNA TPTEP1 inhibits Wnt/β-catenin signaling through the miR-1343-3p/SIRT3/FOXO3a axis, thereby inhibiting fatty acid metabolic reprogramming and tumor progression(42).

The regulation of the tumor microenvironment is also significantly influenced by the Wnt/β-catenin signaling pathway. Its activation can affect the behavior of tumor-peripheral matrix and immune cells by secreting cytokines, chemokines and other microenvironment regulatory molecules(43). Specifically, Wnt ligands released by tumor cells can act on neighboring immune cells, prompting them to transform into an inhibitory phenotype, thereby inhibiting immune surveillance function. Mutations in this system are linked to a non-inflammatory TME phenotype in liver cancer, which is characterized by raised expression of immune checkpoint markers (such PD-L1) and enhanced polarization of M2 tumor-associated macrophages (TAMs)(44). In colorectal cancer, reactive oxygen species (ROS) activate Wnt/β-catenin signaling through heme oxygenase (HO)-mediated oxidative stress, promoting tumor cell metabolic adaptability and microenvironmental inflammatory response, thereby enhancing metastasis and treatment resistance(45). In addition, by controlling the release of inflammatory factors by macrophages, Wnt/β-catenin signaling in non-small cell carcinoma modifies the inflammatory state of TME. On the other hand, signaling pathway activation may also induce stromal cells and fibroblasts to express matrix metalloproteinases that support tumor growth and infiltration, further optimize the remodeling of the extracellular matrix, and change stromal cell interactions. In bladder cancer, endostatin changes intercellular communication in TME by inhibiting Wnt/β-catenin signaling in CSCs(46). Studies have shown that there is a bidirectional regulatory effect between Wnt/β-catenin signaling and tumor-associated macrophages (TAMs). Tumor cells change the local immune microenvironment by activating this signal, reducing T cell infiltration and activity, thereby promoting immune escape; conversely, factors released by TAMs can also react on the Wnt signaling pathway, forming a positive feedback regulatory loop, and ultimately forming a microenvironment that is conducive to tumor progression(47).

2.5 Tumor drug resistance

The aberrant activation of the Wnt/β-catenin signaling pathway is directly linked to the mechanism of resistance to chemotherapy, radiation, and targeted treatment, in addition to its fundamental regulatory function in cell proliferation, differentiation, and stemness maintenance. Among its core resistance mechanisms, the enhancement of anti-apoptosis and survival signals is one of the mechanisms related to the Wnt/β-catenin signaling pathway and tumor resistance. The Wnt/β-catenin pathway inhibits tumor cell apoptosis by regulating downstream target genes (such as the BCL-2 family), thereby enhancing resistance to chemotherapeutic drugs and targeted therapy. For example, in breast cancer, activation of the Wnt/β-catenin signaling pathway can prevent drug-induced apoptosis(48). At the same time, the pathway can also induce DNA repair mechanisms such as homologous recombination repair (HRR) in breast cancer cells, reduce the sensitivity of radiotherapy and DNA-damaging chemotherapeutic drugs (e.g. platinum), and lead to radiation resistance and chemotherapy resistance(49).

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Secondly, by activating EMT-related transcription factors such as SNAIL and TWIST, the Wnt/β-catenin signaling pathway can promote tumor cells to acquire invasive and resistant phenotypes. In non-small cell lung cancer, Oct4/Nanog mediates EMT-related resistance through β-catenin(50). Some studies have found that by activating and upregulating pro-angiogenic factors such as VEGF, this pathway can promote the formation of a hypoxic microenvironment, reduce drug delivery efficiency, and promote endothelial cell survival. Additionally, by controlling the expression of transporters like ABCB1/MDR1, β-catenin may enhance the efflux of chemotherapy medications, according to some research. The latest studies have found that tumor cells can develop acquired resistance by activating alternative Wnt ligands (such as WNT5A) or reconstructing TCF/β-catenin transcriptional complexes(51). In addition, as the core regulatory pathway of CSC, Wnt/β-catenin enables tumor cells to evade conventional treatment by maintaining the self-renewal ability of stem cells. Especially in colorectal cancer and bladder cancer, the continued presence of CSC is closely related to chemotherapy resistance.

2.6 Cross-regulation with other signaling pathways

The cross-regulatory mechanisms of the Wnt/β-catenin pathway and other signaling pathways in tumors are complex and diverse, involving multiple aspects such as cell proliferation, differentiation, apoptosis, autophagy, tumor microenvironment remodeling, and treatment resistance. First, the Wnt/β-catenin and PI3K/Akt signaling pathways play a synergistic role in regulating cell survival and proliferation. In colorectal cancer, the Wnt/β-catenin and PI3K/AKT/mTORC1 pathways are closely associated. The two form a positive feedback loop by sharing molecular targets (such as GSK-3β) and regulating downstream effector molecules (such as c-Myc and Cyclin D1), jointly promoting tumorigenesis and drug resistance(52). For example, abnormal accumulation of β-catenin can activate the PI3K/AKT pathway, while phosphorylation of AKT can inhibit GSK-3β activity, further stabilizing β-catenin, forming a vicious cycle. A novel approach to the treatment of colorectal cancer is the investigation of combination inhibitors that target this relationship(53). Secondly, there is a complex bidirectional regulatory network between the Notch and the Wnt/β-catenin signaling pathway. By controlling β-catenin's phosphorylation state and rate of degradation, notch signaling can indirectly control the transcriptional activation function of β-catenin, according to experimental findings. Simultaneously, the Notch pathway may get a reaction from the β-catenin activation process that alters the expression level of its essential components(54). The Wnt/β-catenin and Notch signaling pathways are characterized as an integrated signaling device that contributes to carcinogenesis by controlling random cell functions including proliferation, differentiation, or death in the study of pancreatic neuroendocrine tumors. This integration may be achieved through shared downstream target genes or transcription factors, such as the synergistic effect of β-catenin and Notch signaling downstream effector molecules (such as the Hes family)(55). In the colorectal cancer liver metastasis model, Wnt and Notch signals were found to constitute a mutually compensatory regulatory loop(56). When the Wnt/β-catenin pathway is inhibited, the Notch signal is compensatory activated, resulting in tumor cell resistance to treatment. Inhibition of β-catenin alone cannot overcome drug resistance, and pan-Notch inhibitors (such as γ-secretase inhibitors) must be combined to effectively inhibit tumor sphere formation and metastasis(57). In breast cancer, Dll1+ tumor cells induce Wnt ligand secretion by activating Notch signaling in cancer-associated fibroblasts (CAFs), thereby driving β-catenin-dependent radioresistance and metastasis. In addition, both Wnt/β-catenin and Notch signaling can promote metastasis by regulating EMT and TME. For example, Wnt/β-catenin activates EMT-related genes, while Notch enhances EMT by regulating genes such as Hes1, and the two synergistically promote tumor cell migration and invasion. Because the Notch and Wnt pathways preserve the expression of stemness markers (such OCT4 and NANOG), they work together to enhance the survival and treatment resistance of CSCs.

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3.Clinical transformation and treatment strategies

A common characteristic of many cancers is the aberrant activation of the Wnt/β-catenin signaling pathway. It is a desirable but difficult target for therapeutic intervention since it is essential for controlling cell proliferation, differentiation, EMT, CSC characteristics, and immune escape. The buildup of β-catenin in the nucleus over time and the accompanying transcriptional activation of downstream target genes implicated in cancer and progression are what give it its oncogenic potential. Due to the central role of Wnt/β-catenin signaling in tumorigenesis and progression, it has received increasing attention as a promising target for clinical intervention.

However, translating mechanistic insights into effective therapeutic strategies is extremely challenging. The pathway is complex in structure and has extensive interactions with other oncogenic signaling networks, making it difficult to identify specific and effective molecular targets. The heterogeneity within and between tumors further exacerbates treatment resistance, necessitating the development of combination therapies or interventions tailored to specific situations. Despite these challenges, multiple inhibitors targeting pathway nodes, immunotherapy, and other combination therapies have been developed to disrupt different nodes in the Wnt/β-catenin cascade. These drugs are currently being studied in preclinical models and early clinical trials and have shown varying degrees of efficacy and safety. Notably, the potential for treatment has increased due to recent developments in our knowledge of the TME and immune modulation. It has been demonstrated that Wnt/β-catenin signaling has a role in the development of an immunosuppressive TME, namely through the exclusion of cytotoxic T cells(58). This discovery offers a theoretical foundation for overcoming tumor immune resistance by combining immune checkpoint inhibitors with Wnt-targeted treatments. Recent advances in drug development, molecular profiling, and targeted delivery systems provide new opportunities for therapeutic development.

3.1 Inhibitors targeting nodes of the Wnt/β-catenin pathway

Based on different molecular targets in the signaling cascade, multiple types of Wnt/β-catenin inhibitors have been developed. These inhibitors include ligand/receptor secretion inhibitors, which inhibit pathway activation by blocking Wnt ligand secretion or interaction with receptors (such as blocking Frizzled or LRP5/6 receptor binding), destroying the stability of receptor complexes, etc. For example, porcupine inhibitors can block the post-translational modification and secretion of Wnt proteins(59). LGK974 is a representative porcupine inhibitor. Blocking the secretion of WNT ligands by LGK974 can significantly inhibit the occurrence and progression of HPV-driven squamous cell carcinoma(60). According to other research, the small molecule inhibitor LPD-01 stops the proliferation of HT-29 colon cancer cells by preventing the production of the genes and target proteins in the Wnt/β-catenin pathway(61). In chronic lymphocytic leukemia, Wnt ligands (such as WNT5A) and receptors (such as Frizzled) are significantly overexpressed, and inhibitors targeting these ligands/receptors can induce cancer cell apoptosis by inhibiting the β-catenin-dependent signaling pathway(62). Furthermore, it has been discovered that β-catenin inhibitors are effective in treating cancer. Multiple myeloma cells resistant to bortezomib (BTZ) have a highly active Wnt/β-catenin pathway, and the combination use of β-catenin inhibitors like PP or ICG-001 can greatly increase the effectiveness of BTZ(63).

On the other hand, monoclonal antibodies developed against Wnt ligands or receptors (such as LRP5/6 and Frizzled) can block signal transduction by neutralizing ligand activity or blocking receptor binding sites. Frizzled receptors are the main receptors of the Wnt pathway, and their abnormal activation is closely related to cancer occurrence. Studies have successfully blocked Wnt signal transduction by designing antibodies targeting Frizzled receptors, such as developing monoclonal antibodies that can specifically bind to Frizzled receptors and inhibit β-catenin accumulation. The latest study developed a bifunctional antibody that can simultaneously regulate upstream ligand binding and downstream signal transduction of the Wnt pathway by rationally designing antibody epitopes, and successfully achieved bone mass regulation in animal models(64). In addition, new antibody formats such as antibody-drug conjugates (ADCs) are also being explored to improve tumor targeting.

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3.2 Synergistic effect of Wnt/β-catenin pathway and immunotherapy

First, overactivation of Wnt/β-catenin signaling forms an immunosuppressive microenvironment by reducing DCs recruitment, excluding CD8+ T cells, and increasing the proportion of Tregs. In addition, this mechanism further suppresses T cell activity by causing cancer cells to produce PD-L1. The β-catenin/TCF inhibitor iCRT14 dramatically increases CD8+ T cell infiltration in colorectal cancer and boosts anti-PD-1/CTLA-4 treatment effectiveness(65). In ovarian and endometrial cancers, Wnt/β-catenin pathway inhibition improves immunotherapy response by increasing T cell infiltration and reducing the proportion of immunosuppressive cells in the TME(66). Secondly, Wnt/β-catenin signaling mediates the bypass resistance of tumor cells to immune checkpoint inhibitors (ICIs). Combining Wnt inhibitors can restore ICI sensitivity. For example, in melanoma, inhibiting this pathway enhances ferroptosis by regulating MITF, thereby synergizing the anti-PD-1 efficacy. Abnormal activation of Wnt/β-catenin is directly related to anti-PD-1/PD-L1 resistance. Nanopeptide drugs targeting this pathway combined with ICIs can overcome immune escape. Clinical data show that patients with Wnt-activated hepatocellular carcinoma may benefit from combined treatment with atezolizumab and bevacizumab(67).

3.3 Combining the Wnt/β-catenin pathway with other novel interventions

In recent years, research on the combination of physical therapy, natural compounds and other novel interventions with Wnt/β-catenin pathway inhibition strategies to treat cancer has made progress. Physical therapy can not only directly destroy tumor cells, but also provide a new technical platform for precise regulation of signaling pathways. For example, photothermal therapy (PTT) and magnetic hyperthermia are widely used in tumor treatment, and their mechanism is mainly based on local temperature increase to induce cell apoptosis or necrosis. It has been demonstrated that low-frequency repeated magnetic stimulation (rMS) inhibits the growth of neuroblastoma by downregulating the Wnt/β-catenin pathway(68).

At the same time, the application of natural compounds in cancer intervention has received widespread attention. Some natural compounds can directly inhibit β-catenin activity, inhibit pathway activity by disrupting the binding of β-catenin to the TCF/LEF transcription complex, or promote the ubiquitination and degradation of β-catenin. For example, chalcone derivatives (CXs) work by inhibiting Wnt signaling and colorectal cancer cell proliferation(69). Natural compounds can also target key nodes such as Wnt ligands/receptors and β-catenin destruction complexes. For example, baicalin has the capacity to control β-catenin stability and stop colorectal cancer from spreading(70). Furthermore, β-asarone inhibits the proliferation of retinoblastoma cells by inhibiting this pathway, while STS (a derivative of shikonin) inhibits melanoma metastasis by regulating EMT(71).

Conclusion

This review systematically expounds on the molecular mechanism and clinical transformation prospects of the Wnt/β-catenin pathway in tumorigenesis and development. Each study module demonstrates how this route is essential for controlling the cell cycle, preserving the properties of cancer stem cells, and altering the TME. These processes include tumor cell proliferation, metastasis, immunological escape, metabolic reprogramming, and drug resistance mechanisms. According to mechanistic research, Wnt signals cause nuclear β-catenin accumulation and activate TCF/LEF-dependent gene transcription, which in turn promotes cell proliferation, cell cycle progression, and the upregulation of genes that facilitate invasion and metastasis. This is because they destroy the original β-catenin degradation complex. In the process of cancer metastasis, β-catenin-induced EMT enables tumor cells to acquire an invasive phenotype, while tumor-associated stromal cells and immune cells are regulated by this signaling pathway to form an immunosuppressive microenvironment, providing a molecular basis for immune escape. At the same time, the intricate and tightly knit network structure for carcinogenesis

DOI 10.58832/ctr.2025.6.6.3

is created by the cross-regulation of Wnt/β-catenin signals with other classical pathways, which explains the root cause of many tumor resistance and clinical treatment difficulties. In terms of clinical transformation, precise inhibition strategies targeting this pathway have shown certain application prospects. Small molecule inhibitors, monoclonal antibodies, and natural compounds can all intervene in the signal transduction process at different levels. Currently, the use of Wnt/β-catenin targeted drugs combined with immune checkpoint inhibitors or other treatments has become an important direction for improving clinical efficacy and overcoming drug resistance. In summary, elucidating the multiple regulatory roles of the Wnt/β-catenin pathway in tumor biology points out the future development direction for exploring more effective and precise anti-cancer treatment strategies.

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