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Research Article

New Advances in Classical Wnt/β-Catenin Signaling in Cancer

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ABSTRACT

Wnt/β-catenin-mediated signaling is a key pathway regulating tissue growth and development and tumorigenesis. This signaling pathway has received much attention in recent years. In addition to participating in healthy tissue and organ development, inappropriate activation of this pathway can cause a variety of tumors and other pathologies. It also plays a critical role in many processes such as proliferation, differentiation, apoptosis, migration, invasion, epithelial-mesenchymal transition and dry maintenance of human tumor cells. This review introduces the underlying mechanism of Wnt signaling pathway and highlights the most recent research progresses on the relationship between Wnt signaling pathway and tumor. Furthermore, the intrinsic link of Wnt signaling pathway to cancer stem cells is also discussed, aiming to curb the malignant progression of tumors from the root cause. Finally, possible clinical strategies harnessing the classical Wnt signaling pathway as a therapeutic target are summarized.

Introduction

The Wnt signaling pathway plays a crucial role in embryonic development, adult tissue homeostasis, and cancer [1]. Because of its role in determining cell fate and promoting tissue development, Wnt signaling has become the focus of current research in regenerative medicine [2]. In addition, the Wnt signaling pathway is also involved in many pathological processes such as proliferation, differentiation, apoptosis, migration, invasion, epithelial-mesenchymal transition, and dry maintenance of human tumor cells. Notably, the aberrant activation of Wnt/β-catenin signaling produces several modulators that antagonize the anti-tumor activity of T cells, which is likely to be attributable to the failure of cancer immunotherapy [3]. The adverse effects of Wnt signaling in tumors prompted researchers to study extensively to decode its mechanisms of action in cancer and to find valuable targets to expand cancer treatment strategies. Since the discovery of the Wnt signaling pathway about 40 years ago, the number of reports that Wnt signal regulates the proliferation and differentiation of cancer cells and the self-renewal of stem cells has never declined. The continuous research breakthrough has been gradually unraveling the intrinsic roles of the Wnt signaling pathway ever since. The Wnt family consists of 19 secretory glycoproteins rich in cysteine, which induce classical Wnt signaling

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through 10 Wnt crimp receptors like frizzled receptor protein (FZD) and co-receptors LRP5 and LRP6 to regulate cell fate and growth and repair of certain tissues [4]. Wnt protein precursors gradually form mature Wnt ligands after a series of biological modifications, such as porcupine palmitoylation, lipid modification, and glycosylation. Subsequently, the transmembrane protein Wntless/Evi (Wls) in ER assists in the transfer of Wnt ligands from the Golgi to the plasma membrane. Then, it is released from the cells as lipid-protein particles or exosomes [1, 5].

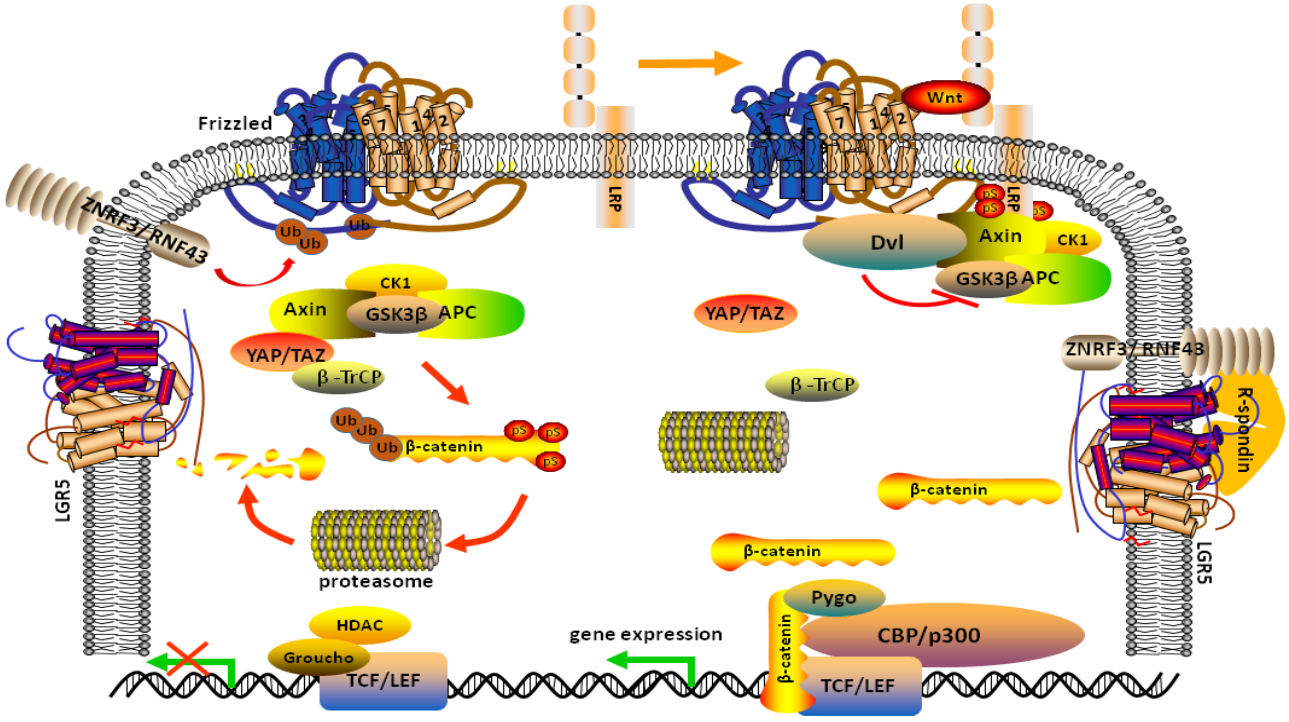

Figure 1: An overview of Wnt signaling pathway.

As shown in (Figure 1), Wnt ligand binds to its membrane receptor complex extracellularly to induce constitutive activation of Wnt/β-Catenin signaling, whereby a series of corresponding biochemical reactions occur in the organism. For instance, LRP receptor phosphorylation recruits Axin degradation and dishevelled (DVL) protein activation leads to the inactivation of degradation complexes, resulting in stabilization and accumulation of β-catenin [6]. Subsequently, β-catenin is transferred to the nucleus as a transcriptional coactivator along with the T cell factor (TCF)/ lymphocyte enhancer-binding factor (LEF) family of transcription factors to regulate key cell cycle mediators, such as AXIN2, cyclin D, and MYC [7]. In the absence of Wnt ligands, multimers composed of APC, GSK3β, Axin, and CK1α induce β-catenin phosphorylation, target ubiquitination, and proteasomal degradation [8].

Recently, a new complementary mechanism has been added to the classic Wnt signaling pathway. One is the Hippo signaling cascade, in which the nuclear effector YAP/TAZ plays an essential role. Under Wnt OFF conditions, YAP/TAZ resides in the disruption complex and promotes the degradation of β-catenin by recruiting β-TrCP, which ubiquitinates β-catenin. In this context, YAP/TAZ acts as a negative regulator of the Wnt signaling. Under Wnt ON conditions, Lrp5/6 displaces YAP/TAZ from Axin, resulting in the nuclear accumulation of YAP/TAZ and the promotion of gene expression involved in proliferative responses. At this time, YAP/TAZ becomes a positive regulator of the Wnt signaling [9]. The second is the RSPO-LGR4/5-ZNRF3/RNF43 module. ZNRF3/RNF43 can ubiquitinate FZD in the absence of R-spondin to cause endocytosis. However, when R-spondin binds to the LGR4/5/6 receptor and ZNRF3/RNF43, it blocks the ubiquitination of FZD and enhances the Wnt signaling cascade [10].

As illustrated on the upper left side of (Figure 1), a destruction complex, consisting of APC, GSK3β, axin, and CK1α, induces β-catenin phosphorylation in the absence of Wnt ligand, in which ubiquitination takes place via the action of β-TrCP recruited by the YAP/TAZ complex, leading to proteasomal degradation of the phosphorylated β-catenin. On the membrane, the E3 ubiquitin ligase ZNRF3/RNF43 promotes the ubiquitination of the FZD receptor, leading to lysosomal degradation of the FZD receptor. In the nucleus, the TCF transcription factor is in an inactive state due to its interaction with the inhibitory complex Groucho/HDAC, as shown on the lower left side of (Figure 1).

LRP receptor is phosphorylated after the activation of the Wnt signaling as depicted on the upper right side of (Figure 1). The LRP phosphorylation recruits Axin-containing complex, and DVL proteins accumulate onto the plasma membrane, resulting in the disruption of the complex. Subsequently, β-catenin accumulates in the nucleus and interacts with histone-modified coactivators such as Pygo and CBP/p300. Then the β-catenin complex acts as a transcriptional coactivator to regulate the gene expression together with TCF/LEF family proteins. On the cell membrane, R-spondin interacts with the LGR4/5/6 receptor ZNRF3/RNF43, leading to the inhibition of

ZNRF3/RNF43 ubiquitination, resulting in the accumulation of FZD receptors on the cell surface.

Evidence is accumulating that Wnt/β-catenin signaling is one of the major drivers of malignancy, such as colorectal cancer, liver cancer, and breast cancer. This review, therefore, focuses on the latest research progress on the relationship between Wnt signaling pathway and tumor and discusses its intrinsic relationship with cancer stem cells. In addition, possible clinical strategies targeting the classical Wnt signaling are summarized, based on the recent advances in this field.

Colorectal Cancer and Wnt Signal

Colorectal cancer (CRC) is the third most common cancer in the world and the fourth most deadly cancer after lung, liver, and stomach cancer. A high CRC incidence is observed in developed countries [11]. The constitutive hyperactivation of Wnt/β-catenin signaling is a major marker of colorectal cancer and is associated with APC mutations in more than 70% of sporadic cases. APC is, therefore, considered to be the initiating episode and a driving event for most CRC tumors [12, 13]. Silencing APC in colon adenomas results in rapid regression and non-recurrence of tumor cells even after recovery of the APC gene and reconstitution of cryptic homeostasis in tumor tissues carrying Kras and p53 mutations [8]. In addition to APC as a major driver of Wnt/β-catenin signaling, new targets for Wnt/β-catenin signaling have been recently found in CRC, and colon cancer progression has been influenced by different regulatory mechanisms. For example, colon cancer metastasis factor 1 (MACC1) is inexorably linked to the development of colon cancer.

Studies have shown that MACC1 can be used as a transcriptional target of the inhibition of the Wnt/β-catenin signaling. The coactivator DBC1 promotes the self-renewal capacity and drug resistance of colon cancer by regulating the LEF1/β-catenin-dependent enhancer in the MACC1 intron [14]. Furthermore, the mTOR inhibitor Deptor promotes cancer cell proliferation and survival in CRC and is a potential target for novel cancer therapies. It was recently demonstrated that Deptor is a direct target gene for Wnt/β-catenin/c-Myc signaling [15]. Silencing Deptor induces differentiation and inhibition of CRC cells by increasing ketone production and by decreasing Bmi1 expression; however, at the same time increases mTOR activation.

It is, therefore, necessary to administer Akt/mTOR and Wnt/β-catenin inhibitors in combination to exert a powerful anti-tumor effect. Since the metastatic spread of colon cancer is the main cause of death in CRC patients, much attention has been paid to the relationship between tumor invasion and metastasis and the classical Wnt signaling components, such as small GTPase RHOA, and chromatin organizer SATB1. Whereas RHOA activation is generally thought to have a strong carcinogenic effect, this concept is completely subverted in CRC. Loss of RHOA induces a new pathway for activating the classical Wnt signaling. Its inactivation leads to increased proliferation, invasion, and differentiation of colon cancer cells. More interestingly, RHO GTPase has different tumor metastatic effects on different organs [16]. In addition, over-activation of Wnt signaling promotes the interaction of the TCF7L2/β-catenin complex with the *Satb1* promoter, resulting in a high level of SATB1 expression [17]. SATB1 has the effect on reprogramming, tumor growth, and metastasis-associated gene expression. By controlling the expression level of SATB1, the conversion between non-invasive phenotype and invasive phenotype of colon cancer is achieved, which affects the occurrence and progression of colorectal cancer.

Taken together, different roles of Wnt/β-catenin signaling in the development, progression, and metastasis of colon cancer have gradually been recognized. With the in-depth research on the relationship between Wnt signaling and colon cancer, its role and mechanism in tumor progression have been delineated. The clarification of the relationship between the Wnt signaling and CRC development and progression may open a new strategy for the prevention and treatment of colon cancer.

Liver Cancer and Wnt Signals

According to the World Health Organization's International Cancer Research Center's survey in 2018, liver cancer is one of the world's high-mortal cancers, and hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide. β-catenin is expressed in the adult liver, which regulates the transcription and translation of genes of the hepatocytes under the control of Wnt and mediates the Wnt signaling in various aspects of liver biology. Therefore, the lack of Wnt/β-catenin signals could cause liver damages, mainly manifested as liver metabolism partition disorder and liver regeneration defect after hepatectomy. The recently discovered RSPO-LGR4/5-ZNRF3/RNF43 module is a major factor in the regulation of hepatic metabolism and liver development and regeneration by the Wnt/β-catenin signaling pathway [18]. Knocking down LGR4/5 in the mouse liver resulted in a loss of β -catenin signaling and hepatic metabolic partitioning. By supplementing RSPO1 or knocking down Znrf3/Rnf43, however, the liver Wnt/β-catenin signal gradient was extended in an LGR4/5-dependent manner, reversing the liver defect phenotype.

β-Catenin also induces liver regeneration (LR) after partial hepatectomy (PH) by modulating Cyclin-D1 gene expression, as indicated by the phenotype of β-catenin and Wnt co-receptor LRP5/6 conditional knockout [19]. Thus, Wnt/β-catenin signaling is critical for the development of the liver; however, abnormal activation of the β-catenin signal is also a marker for the progression of hepatocellular carcinoma and other liver lesions. Wnt/β-catenin signaling is constitutively upregulated in up to 30%-40% of hepatocellular carcinomas and 80%-90% of hepatoblastomas [20, 21]. Interestingly, in the mouse hepatocyte model, β-catenin activation only is not sufficient to induce liver cancer, and other mutation events must be involved in the development of cancer, such as Ha-ras mutation or Met mutation [22, 23]. This phenomenon may be related to the weak β-catenin activity in the mouse hepatocyte model. Studies have shown that there are weak mutations in the *CTNNB1* in HCC and HCA. For example, a mutation occurs at K335/N387, S45, or T41 of the *CTNNB1* [24].

With the in-depth study of Wnt/β-catenin signaling in various cancers, there is increasing evidence that Wnt signaling acts on tumor progression in a phase- and tissue-specific manner. Recent report has shown that Wnt signaling can mediate the development of colon and liver cancer using different downstream transcriptional cascades [25]. Unlike the widely studied Wnt/TCF-dependent transcriptional pathways in CRC, The

TCF4/FoxA transcription factor coordinates in HCC to modulate the expression of liver cancer-specific Wnt target genes, including TRIB2. In this pathway, TRIB2 regulates YAP and C/EBPa functions through interaction with βTrCP ubiquitin ligase and other E3 ligases, blocks YAP degradation and simultaneously promotes YAP/TEAD activation, resulting in HCC survival and transformation. Interestingly, TRIB2-induced nuclear accumulation of β-catenin does not activate Wnt/β-catenin signaling in hepatocellular carcinoma. Instead, TCF4/β-catenin ubiquitination is promoted by increasing the interaction of TCF4/β-catenin with TRIB2-related ubiquitin E3 ligase, thereby inhibiting Wnt/β-catenin/TCF4 signaling [26]. TRIB2 was, therefore, found to be an upstream inhibitory regulator and a downstream effector of liver cancer-specific Wnt signaling.

In addition, Wnt signaling pathways can also produce different responses at different stages of liver cancer and present different regulatory mechanisms, such as in the early stages of HCC. Since the high expression of GPC3 occurs only in hepatocytes under pathological conditions, GPC3 is a promising biomarker for the diagnosis and treatment of hepatocellular carcinoma. The regulatory mechanism of GPC3 plays a role in the progression of HCC by promoting the formation of Wnt-Frizzled signaling complexes [27, 28]. However, in the early relapse phase of HCC, studies have shown that the microtubule-associated protein PRC1 interacts with the β-catenin destruction complex to promote β-catenin stability and nuclear accumulation and regulates the transcriptional activation of liver cancer recurrence genes to promote early HCC recurrence [29].

In summary, Wnt signaling plays a crucial role in the growth and development of the liver. However, its excessive activation may lead to the development of hepatocellular carcinoma and other liver lesions. Wnt/β-catenin signaling plays a role in the progression of liver cancer in a phase- and tissue-specific manner. We must, therefore, carefully evaluate whether the therapy targeting Wnt/β-catenin signaling is the correct strategy for the disease background and target cell type.

Breast Cancer and Wnt Signal

Wnt signaling is involved in malignant progression of breast cancer growth, invasion, metastasis, and drug resistance. In healthy breast tissue, inhibition of Wnt/β-catenin activity leads to developmental disorders and reduced cell proliferation during pregnancy [30]. There is, however, increasing evidence that activation of β-catenin signaling mediates the progression of breast cancer. Studies have shown that β-catenin signaling plays a role in the development of ErbB2-induced breast tumors, and phosphorylation of β-catenin by Pak1 kinase is a prerequisite for the connection of ErbB2 and β-catenin [31, 32]. In recent years, research on microRNA regulation of Wnt signaling mediating the occurrence and metastasis of breast cancer has emerged in an endless stream. For example, microRNAs such as MicroRNA-374a and MiR-454-3p activate this pathway by directly inhibiting multiple negative regulators (such as WIF1, PTEN, AXIN2, etc.) in the Wnt/β-catenin signaling pathway, thereby promoting breast cancer growth and metastasis [33, 34].

In addition, functional targets of microRNAs in tumor progression have been determined to develop new treatments of cancer. For example, transmembrane protein 170B (TMEM170B) is a novel functional target for miR-27a, known as a poor prognostic factor for breast cancer, TMEM170B inhibits canonical Wnt signaling by promoting β-catenin phosphorylation and arrests tumor growth [35]. Inhibition of constitutive activation of Wnt/β-catenin signaling is, therefore, critical for breast cancer treatment. It was reported that breast cancer metastasis suppressor 1 (BRMS1L) inhibits breast cancer invasion and metastasis *in vitro* and *in vivo*, which is caused by BRMS1L-induced FZD10 silencing, leading to inhibition of WNT3a-β-catenin signaling [36]. On the contrary, the latest report indicated that targeting classical WNT may promote further development of metastatic cancer, suggesting that silencing of classical Wnt signaling drives cancer cells into dormancy, thereby allowing them to escape from the body's immune system against cancer cells [37].

Notably, the Wnt signaling pathway inhibitor DKK1 is shown to play a bipartite role in breast cancer metastasis, in contrast to the positive role of DKK1 in inhibiting breast cancer lung metastasis, which promotes breast cancer bone metastasis by activating classical WNT signaling. This mechanism suggests that we need to systematically review the treatment strategy in the treatment of metastatic tumors to ensure the safety of the treatment.

Cancer Stem Cells and Wnt Signals

The concept of defining cancer stem cells (CSCs) is that malignant tumors grow in a layered manner, in which CSCs have self-renewal characteristics and multi-directional differentiation ability, which can continuously maintain the replacement of new CSC tumorigenic subpopulations and differentiate into non-CSC progenies with tumor-carrying ability to maintain tumor proliferation [38]. At present, it is generally accepted that the cancerous part is originated from CSC. In colorectal cancer, $Lgr5^+$ CSCs showed higher tumorigenicity than $Lgr5^-$ tumor cells by limiting dilution transplantation studies, indicating that $Lgr5^+$ stem cells have tumor-initiating ability [39].

However, a recent study demonstrated that $Lgr5^-$ intestinal adenoma cells can also form Lgr5 heterogeneous tumors, suggesting that some intestinal adenomas do not stratify tissue into $Lgr5^+$ tumorigenic cells and $Lgr5^-$ non-tumorigenic cells [40]. This indicates that cancer may be derived from CSCs, or tumor cells may convert into CSCs leading to the tumorigenesis, but this requires additional factors (mutations, inflammation or changes in the microenvironment) to assist [41]. For example, hepatocytes, after induction by a hepatic toxin, produce tumor nodules that express progenitor cell markers [42]. Both targeting CSCs and preventing the production of CSCs from non-CSCs must be, therefore, considered in the treatment of cancer.

CSCs not only play an important role in the occurrence and development of tumors but also are closely related to tumor invasion, metastasis, and drug resistance. For the CSCs themselves, the differentiation gradient between CSCs and their non-CSC progenies results in the formation of tumor heterogeneity, which indicates that cells of different genotypes can exist in the same tumor, including subgroups with transferability. Because of this unique nature of tumors, CSCs have become the leading cause of drug resistance in cancer treatment. The Wnt/β-catenin signaling pathway plays an essential role in the reprogramming and dry maintenance of cancer stem cells and is an indispensable cytokine

network for promoting the progression of CSCs. It is demonstrated that the cell types of CMC-derivatives depend in part on the size of the graded Wnt signaling activity [43]. The classical Wnt signal is, therefore, bound to participate in the development of the malignant phenotype of the tumor by affecting the progression of CSCs.

It is currently believed that epithelial-mesenchymal transition (EMT) may play an important role in the early micro-metastasis mechanism of CSCs and may depend on the occurrence of classical Wnt signaling. In epithelial cells, Sox15 blocks EMT by interacting with the β-catenin/E-cadherin complex. The binding of the Sox15/β-catenin/E-cadherin complex to the proximal prokinetic region of CASP3 triggers caspase-mediated Twist1 cleavage. During EMT, however, this interaction is disrupted. Twist1 binds to phospho-β-catenin and enhances Wnt3a-mediated β-catenin/TCF transcriptional activity, thereby inducing expression of dry genes to promote lung cancer tumor initiation ability and metastasis [44].

In addition, silencing of the Wnt/β-catenin signaling network regulates CSC resting and tumor dormancy processes. After undergoing periodic proliferation and immune elimination bursts, a small subset of the offspring is transformed into latent cancer (LCC) cells, which exhibit a Sox-dependent dry phenotype. LCC cells actively silence the WNT signals and convert into a resting state through the expression of the WNT inhibitor DKK1, in which LCC down-regulates NK cell ligands to escape from NK cell-mediated immune clearance, thereby maintaining a latent state for a long time. However, once LCC cells undergo immunosuppression or abnormal signal networks, LCC cells will enter the cell cycle in advance, eventually leading to metastatic tumor cell outbreaks [45]. In addition, the quiescent state of CSCs can successfully escape from the killing of chemotherapy drugs; therefore, CSCs become the "bane" of tumor recurrence and metastasis.

Thus, Wnt signaling is an attractive therapeutic target for the development of novel anti-cancer therapies. It has been recently reported that retinoids triggered a high expression of HOXA5 in colon cancer. High levels of HOXA5 expression induce a stem cell phenotype loss by inhibiting Wnt signaling in tumors, preventing tumor growth and metastasis progression [46, 47]. The signaling network that regulates embryonic development is, however, not singular. The CSC phenotype is the result of crosstalk between multiple signaling pathways (such as Notch, Hedgehog, and Wnt). Elucidating the molecular and signaling mechanisms of cancer stem cell regulation will, therefore, help to understand key nodes in stem cell signaling networks, discover new targets for tumor therapy, and improve treatment strategies [48]. In addition, due to the crosstalk and redundancy of the CSC signal network, tumor therapy programs targeting CSCs require a combination of therapies to exert a powerful anti-cancer effect.

Conclusion

Wnt/β-catenin signaling is involved in the regulation of cell transduction in tumors, which is a multi-faceted and multi-level complex process. Due to its complexity, however, Wnt/β-catenin signaling is still being explored as a target for the treatment of cancer. Targeting multiple sites of this pathway can provide a new basis for the treatment of tumors.

As shown in (Table 1), there are three main types of tumor treatment strategies that direct the Wnt/β-catenin pathway. One is to block the binding of Wnt-receptor complexes. (1) The porcupine (membrane-bound O-acyltransferase, a key enzyme in Wnt ligand synthesis) inhibitors LGK974 and C59 can target Wnt-driven cancer at a therapeutically effective dose without significant intestinal toxicity and other pathological phenomena. In particular, LGK974 is harmless to normal Wnt-dependent tissues, whereas it effectively induces tumor regression [49, 50]. (2) OMP-54F28 is a chimera of a cysteine-rich domain in the fragile family receptor 8 (FZD8) and an immunoglobulin Fc domain that competes with the native FZD8 receptor for Wnt ligand and antagonizes Wnt signaling. At present, OMP-54F28 is in the clinical trial stage for the treatment of advanced solid tumors (ovarian cancer, pancreatic cancer, and hepatocellular carcinoma) [51]. (3) TET1 is a tumor suppressor that binds to the Wnt endogenous inhibitors DKK1 and SFRP2 gene promoters to maintain their hypomethylation, promotes DKK1 and SFRP2 transcription and exerts effective tumor-suppressive effects [52, 53]. TET1 can, therefore, be used as a new target for anti-cancer therapy.

Table 1: Tumor treatment strategies Wnt/β-catenin signaling pathway.

Treatment Strategy	Target Receptor	Mechanism	Related Inhibitor	Ref
Prevents binding of Wnt-receptor complexes	Porcupine	Porcupine, a key enzyme that inhibits Wnt ligand synthesis, thereby limiting the synthesis of Wnt proteins	LGK974, C59, et.	[49-50]
	FZD8	Blocking the interaction of native FZD8 receptor with Wnt ligand	OMP-54F28	[51]
	TET1	TET1 binds to the Wnt of native FZD8 Receptor with Wnt ligand	———	[52-53]
Promotes β-catenin degradation	TNKS1/2	Inhibits the PARsylation activity of TNKS1/2 to stabilize Axin levels	G007-LK, G244-LM, NVP-TNKS6 56, JW55, et.	[54-57]

	USP7	Inhibition of USP7 enhances ubiquitination and degradation of β-catenin	P5091	[58]
	β-catenin	Promotes β-catenin citrullination to induce its degradation	NTZ	[59]
Disturbing TCF/ β-catenin transcription complex formation	TNIK	Inhibition of TNIK can disrupt the formation of TCF/ β-catenin transcriptional complexes	NCB-0846	[60]
	OVOL2	OVOL2 maintains the hypermethylation of Wnt target genes by promoting histone deacetylase 1 recruitment to the TCF4- β-catenin complex, inhibition of Wnt activity.	——	[61]

The second category is to promote the degradation of β-catenin. (1) Tankyrases (TNKS) 1 and 2 are coupled to Axin poly ADP-ribosylation (PARsylation), and the complexes are ubiquitinated by RNF146 and used for proteasomal degradation, thereby, significantly reducing Axin levels in the tumor cells [54, 55]. However, specific small-molecule tankyrase inhibitors (G007-LK, G244-LM, NVP-TNKS656, and JW55) stabilize Axin levels by inhibiting the PARsylation activity of TNKS1/2, reducing intracellular Wnt/β-catenin signaling [56, 57]. (2) USP7, a deubiquitinating enzyme, that is overexpressed in colorectal cancer cell lines and tissues and is associated with poor prognosis of the disease. Inhibitor P5091 enhances β-catenin ubiquitination and degradation by inhibiting USP7, thereby inducing tumor apoptosis and inhibiting growth [58]. (3) β-Catenin citrullination by small-molecule nitazoxanide (NTZ) induces the degradation of β-catenin by stabilizing PAD2, effectively inhibiting APC or CTNNB1 mutation-driven colorectal tumor growth [59].

The third category is to disrupt TCF/β-catenin transcription complex formation. (1) TNIK is an essential regulator of β-catenin and TCF4 transcriptional complexes and is the most downstream component of Wnt signaling. The inhibition of TNIK can thus disrupt the formation of TCF/β-catenin transcriptional complexes and prevent the activation of Wnt target genes [60]. (2) The Wnt signaling transcription factor OVOL2 maintains the hypermethylation of the Wnt target genes by promoting histone deacetylase 1 recruitment to the TCF4-β-catenin complex. Overexpression of OVOL2 inhibits Wnt activity and metastasis of colorectal tumors [61]. Taken together, Wnt/β-catenin provides new ideas and methods for the treatment of malignant tumors.

Acknowledgments

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Conflicts of Interest

None.

Abbreviations

APC: Adenomatous Polyposis Coli
CTNNB1: Catenin Beta 1
FZD: Frizzled Receptor Family
LGR: Leucine-Rich Repeat-Containing G-Protein Coupled Receptor
SATB1: Special AT-Rich Binding Protein 1
HCC: Hepatocellullar Carcinoma
HCA: Hepatocellular Adenoma
GPC 3: Glypican 3
PRC 1: Protein Regulator of Cytokinesis
DKK1: Dickkopf-Related Protein 1
CASP3: Cysteine- Aspartic Acid Protease (Caspase) 3
TET: Tet Methylcytosine Dioxygenase 1
SFRP2: Secreted Frizzled-Related Protein 2

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