# Wnt signaling and tumors (Review)

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**Abstract.** Wnt signaling is a highly conserved evolutionary pathway that plays a key role in regulation of embryonic development, as well as tissue homeostasis and regeneration. Abnormalities in Wnt signaling are associated with tumorigenesis and development, leading to poor prognosis in patients with cancer. However, the pharmacological effects and mechanisms underlying Wnt signaling and its inhibition in cancer treatment remain unclear. In addition, potential side effects of inhibiting this process are not well understood. Therefore, the present review outlines the role of Wnt signaling in tumorigenesis, development, metastasis, cancer stem cells, radiotherapy resistance and tumor immunity. The present review further identifies inhibitors that target Wnt signaling to provide a potential novel direction for cancer treatment. This may facilitate early application of safe and effective drugs targeting Wnt signaling in clinical settings. An in-depth understanding of the mechanisms underlying inhibition of Wnt signaling may improve the prognosis of patients with cancer.

**Contents**



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## 1. Introduction

A wingless gene was discovered during *Drosophila* embryonic development >40 years ago (1). In 1982, Nusse and Varmus (1) cloned int gene (*Drosophila* homolog of the mouse mammary oncogene) that is homologous to wingless during carcinogenesis induced by mouse papilloma virus. This was termed Wnt gene. Wnt proteins bind to receptors on the cell membrane in an autocrine or paracrine manner. They subsequently undergo cascade reactions to activate intracellular proteins and transcription factors to promote target gene transcription. Wnt signaling is associated with cell differentiation, polarization and migration. Moreover, abnormalities in Wnt signaling serve an important role in the development of many diseases, including lung and breast cancer (2). The present review describes the role of Wnt signaling abnormalities in tumorigenesis, tumor development, metastasis, cancer stem cells (CSCs), radiotherapy resistance and tumor immunity (Fig. 1), as well as inhibitors that target Wnt signaling to explore novel avenues for cancer treatment.

## 2. Classical and non-classical Wnt signaling

A total of 19 Wnt and 10 frizzled (FZD) proteins have been identified in mammalian cells (3). These proteins activate Wnt signaling when the receptor binds to its ligand. At least three Wnt pathways have been identified: Classical Wnt/β-catenin pathway and two non-classical Wnt/planar cell polarity (PCP) and Wnt/$Ca^{2+}$ pathways.

*Classical Wnt/β-catenin signaling pathway.* Classical Wnt signaling, known as β-catenin-dependent signaling, has been extensively studied (4-7). This pathway comprises three primary components: Cell membrane proteins, degradation complexes and β-catenin. Cell membrane proteins include Wnt ligands (Wnt1, Wnt2, Wnt3a and Wnt8), seven transmembrane receptors (FZD), auxiliary receptors and low-density lipoprotein receptor-related proteins 5/6 (LRP5/6). The degradation complex is primarily composed of glycogen synthase kinase 3β (GSK-3β), adenomatous polyposis coli (APC), casein kinase 1α (CK1α) and scaffolding protein axin (4). GSK-3β is a serine/threonine protein kinase that phosphorylates residues Thr41, Ser33 and Ser37 on β-catenin. APC increases the affinity of other components of the complex to β-catenin, whereas CK1α is a tyrosine kinase that phosphorylates Thr45 on β-catenin. Furthermore, axin serves as a scaffolding protein that keeps the degradation complex tightly bound

and stable. β-catenin is a member of the connexin family. Activation of the Wnt/β-catenin signaling pathway also involves transduction of Wnt signaling in the cell membrane, maintenance of β-catenin stability in the cytoplasm, and activation of Wnt-associated target genes in the nucleus (5). When Wnt ligands are absent from the cell surface, most β-catenin located at the cell membrane junctions forms a complex with epithelial-type calcium adhesion protein (E-cadherin) and α-catenin to regulate the cytoskeleton and maintain intercellular adhesion. A small amount of unbound β-catenin in the free state is ubiquitinated by the degradation complex via amino-terminal phosphorylation and recognized by the E3 ubiquitin ligase β-transducin repeat-containing protein, which eventually leads to its degradation by the proteasome. The cytoplasm contains low levels of β-catenin in the free state. Therefore, it cannot enter the nucleus to initiate transcription of T cell factor/lymphoid enhancer factor (TCF/LEF), blocking the expression of downstream target genes (6). This blockage inactivates the Wnt pathway. In the presence of extracellular Wnt ligands, Wnt proteins bind to FZD and LRP5/6 to activate disheveled (DVL) proteins in the cytoplasm. Activated DVL inhibits GSK-3β in the degradation complex. Inactive GSK-3β cannot phosphorylate β-catenin, which gradually accumulates in the cytoplasm. When β-catenin reaches a certain level, it is transferred to the nucleus and initiates the transcription of c-Myc, cyclin D1, Dickkopf-associated protein 1, matrix metalloproteinase (MMP)-7, axin 2 and other downstream target genes by binding to TCF/LEF in the nucleus, leading to abnormal cell proliferation and resistance to apoptosis, thereby inducing tumor formation (7). Tumors are induced during this process.

*Non-classical Wnt signaling.* By contrast with activation of the classical Wnt/β-catenin pathway, activation of non-classical Wnt signaling is not dependent on β-catenin. Activation of the Wnt/PCP pathway is initiated by binding of cell-secreted Wnt ligand proteins to the cell membrane receptor FZD and co-receptors receptor-like tyrosine kinase and receptor tyrosine-kinase-like orphan receptor. These co-receptors control activity of small GTPases and regulate cytoskeletal remodeling (8). The binding of Wnt proteins to FZD recruits DVL to the cell membrane for activation (8). DVL activates DVL-associated activator of morphogenesis 1. This process is followed by activation of ϱGTPase, which further activates myosin and ϱ-associated kinase, thereby altering actin and cytoskeletal rearrangement in the presence of activated Rac GTPase. Activated Rac stimulates c-Jun amino-terminal kinase activation, leading to downstream target gene expression (9). Moreover, Wnt/$Ca^{2+}$ signaling is activated when Wnt binds to FZD, recruiting DVL to the cell membrane via guanine nucleotide-binding proteins. This activates phospholipase C and calmodulin-dependent kinase II, causing increased intracellular calcium ion release and further regulating downstream signaling pathways (10).

## 3. Role of Wnt signaling in tumors

Wnt signaling plays an important role in the development of many types of tumors, including non-small cell lung cancer (NSCLC). Smoking is a key risk factor for lung cancer and cigarette smoke can activate Wnt signaling (11). In a mouse lung cancer model with KRAS mutations, activation of the β-catenin pathway accelerates growth of lung cancer tumors (12). β-catenin, a key component of the classical Wnt/β-catenin pathway, is often aberrantly expressed in lung cancer (13). β-catenin levels in Wnt1-positive NSCLC are higher than those in Wnt1-negative NSCLC (14). Odd-skipped related 1 (OSR1) decreases Wnt signaling activity by inhibiting β-catenin expression in lung cancer OSR1-overexpressing H1299 cells (15). Furthermore, immunohistochemical staining shows that Wnt1 and Wnt5a are highly expressed in NSCLC. Overexpression of Wnt1 is causes more aggressive NSCLC by inducing expression of survivin (16), whereas Wnt7a is considerably decreased in NSCLC cell lines and lung tumors. Contrastingly, Wnt7a interacts directly with the Wnt receptor FZD9 (17). The total DVL expression is high in NSCLC cells but negative in normal bronchial and alveolar epithelial cells, suggesting DVL could promote the progression of NSCLC (18). Pygopus2, a downstream functional protein in Wnt/β-catenin signaling, is more elevated in the nucleus of NSCLC compared with normal lung tissues (19). In addition to lung cancer, β-catenin abnormalities are found in some digestive system cancers, such as liver, gastric and colorectal cancer (20-22). The gene catenin beta 1 (CTNNB1), which encodes β-catenin, is commonly mutated in hepatocellular carcinoma (23), whereas CTNNB1, TCF7L2 and APC are mutated in gastric cancer (24). Similarly, APC is mutated in colorectal cancer (22). Overexpression of Wnt11 may antagonize classical Wnt signaling by phosphorylating β-catenin in human hepatocellular carcinoma cells (25). However, activation or inhibition of Wnt signaling in hepatocellular carcinoma depends on the differentiation status of hepatocellular carcinoma cells. Classical and non-classical Wnt signaling serve complementary roles, with classical signaling inducing tumors and non-classical signaling promoting tumor progression (26). Overexpression of Wnt and β-catenin nuclear translocation are observed in gastric cancer (27). The localization of β-catenin from the cell membrane to the cytoplasm and nucleus has also been observed during colorectal cancer development (28). Similarly, Wnt10a and Wnt6 mRNA are detected in gastric cancer cell lines. Furthermore, upregulation of Wnt10a expression activates Wnt/β-catenin/TCF signaling, which is involved in gastric carcinogenesis (29). The expression of runt-related transcription factor 1 (RUNX1) is upregulated in colorectal cancer tissue. RUNX1 directly interacts with β-catenin to activate Wnt/β-catenin signaling (30). Wnt signaling is also aberrant in tumors common in female patients, such as breast and ovarian cancers (31,32). One study used microarray analysis to compare molecular changes in Wnt signaling in triple-negative breast cancer (TNBC) and non-TNBC (33). FZD7, LRP6 and TCF7 are overexpressed in TNBC. In addition, classical Wnt signaling associated with TCF7 is essential for breast carcinogenesis (33). Yoshioka *et al* (34) examined all Wnt ligands in malignant ovarian tumors and normal ovarian tissue and found high expression of Wnt7a and Wnt7b and low expression of Wnt3 and Wnt4. Additionally, Wnt1, Wnt5a, and Frizzled-1 levels are markedly higher in ovarian cancer than in normal ovaries (35).

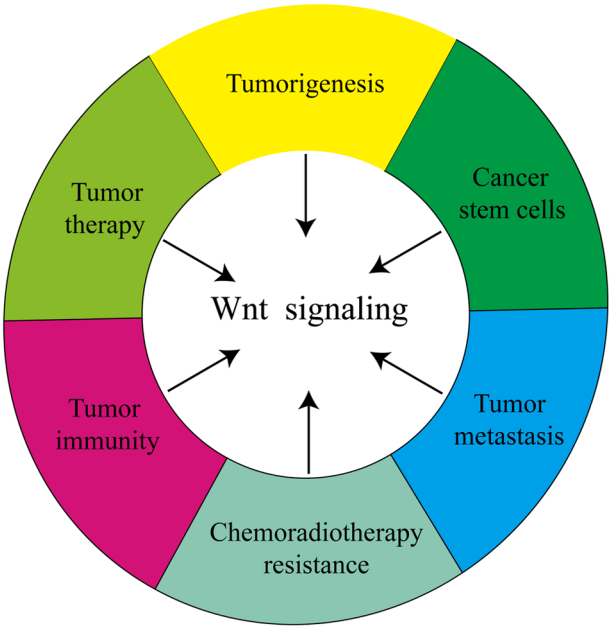


Figure 1. Wnt signaling is involved in tumorigenesis, cancer stem cells, chemoradiotherapy resistance and tumor metastasis, therapy and immunity.

## 4. Wnt signaling and CSCs

Tumors comprise a heterogeneous population of tumor cells, a small group of which are CSCs. Similar to normal SCs, CSCs have a self-renewal capacity and differentiation potential, two properties that make tumor cell populations heterogeneous. CSCs have high oncogenic potential and serve a major role in tumor initiation, metastasis, drug resistance and tumor recurrence (36). Wnt signaling maintains stemness in CSCs (37-39).

*Wnt signaling and lung CSCs*. SOX2 participates in various stages of embryonic development by activating Wnt signaling and maintaining CSC stemness. Colon cancer-associated transcript 1 (CCAT1) elevates the expression of SOX2 and activates Wnt signaling in A549 and H460 lung cancer cells. However, the self-renewal capacity of lung CSCs is lost when microRNA (miR)-Let-7c binds CCAT1 (40). In NSCLC cell lines, nuclear-enriched abundant transcript 1 may activate the Wnt pathway and promote the CSC phenotype by inhibiting epigallocatechin gallate-upregulated copper transporter 1 (41). Octamer binding transcription factor 4 (OCT-4) is a lung cancer surface marker of SCs whose expression is regulated by Wnt signaling. When cisplatin-resistant human lung adenocarcinoma A549/DDP cells are stimulated with lithium chloride, an inhibitor of GSK-3β, expression of Wnt signaling target genes Cyclin D1 and OCT-4 is upregulated. Moreover, the proliferation, clonogenic ability, migration and drug resistance of A549/DDP cells is enhanced (42).

*Wnt signaling and gastric CSCs*. Wnt signaling is also involved in the maintenance of gastric cancer stemness. Stable overexpression of Wnt1 increases proliferation and tumor sphere formation in the human gastric adenocarcinoma cell line AGS. Additionally, AGS cells express the CSC surface markers *OCT-4* and *CD44*. Activation of Wnt1 accelerates gastric CSC proliferation, suggesting that Wnt signaling contributes to self-renewal of gastric CSCs (37). Human epidermal growth factor 2 (HER2)-overexpressing gastric cancer cells induce increased stemness by regulating Wnt/β-catenin signaling (43). Placental growth factor (PlGF) is associated with gastric carcinogenesis. Thus, knockdown of PlGF expression induces apoptosis through Wnt signaling in gastric CSCs (44). Ring finger protein 43 is a member of the E3 ubiquitin ligase family and was originally identified in SCs. It attenuates the stemness of gastric CSC-like cells via Wnt/β-catenin signaling (45). The expression of bromodomain and extra-terminal domain protein is frequently upregulated in gastric cancer tissue and also promotes the stemness of gastric cancer cells by activating Wnt/β-catenin signaling (46).

*Wnt signaling and colorectal CSCs*. Colorectal carcinogenesis and disease progression are caused by progressive accumulation of genetic mutations. APC or β-catenin mutations activate Wnt/β-catenin signaling and initiate tumor formation. This suggests that Wnt signaling serve a central role in the regulation of colorectal CSCs (47-49). Markers on the surface of colon CSCs include CD44, CD133, CD24, CD29, CD26, CD166, leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) and aldehyde dehydrogenase 1 (ALDH1) (50). ALDH1B1 is a member of the ALDH1 family that is highly expressed in colon cancer cells. It can activate Wnt/β-catenin signaling and may be involved in tumorigenesis of colon CSCs (51). Higher β-catenin expression levels induce the expansion of Lgr5(+) cells in colonic crypts and the formation of crypts (52). The transcription factor GATA6 is a key regulator of Wnt signaling in colorectal cancer. It directly drives Lgr5 expression in adenoma SCs. Moreover, GATA6 achieves CSC self-renewal by competing with β-catenin/TCF4 to bind the distal regulatory region of the bone morphogenetic protein locus (38). Homeobox A5 abrogates the self-renewal properties of CSC and blocks tumor growth and metastasis by inhibiting Wnt signaling in colon cancer (53).

*Wnt signaling and breast CSCs*. Wnt/β-catenin signaling contributes to the maintenance of breast CSC stemness. B cell lymphoma factor 11A (BCL11A) is overexpressed in TNBC cells and participates in tumorigenesis and invasion (54). The high expression of this transcription factor causes SC-like characteristics and maintains stemness in breast CSCs by activating Wnt/β-catenin signaling (39). Similarly, Lgr4 is frequently overexpressed in BC and is associated with poor prognosis. Lgr4 regulates Wnt/β-catenin signaling by mediating breast CSC maintenance (55). The expression of calmodulin 11 (CDH11), a type II calmodulin and mesenchymal protein marker, is positively correlated with β-catenin and Wnt2 in breast cancer (56). When CDH11 is inhibited, it may suppress the mammary CSC-like phenotype by regulating the Wnt/β-catenin pathway (56).

*Wnt signaling and ovarian CSCs*. The surface markers of ovarian CSCs include CD24, CD44, CD117, CD133, ALDH, SOX2, OCT-4, NANOG and epithelial cell adhesion molecule, also known as CD326, a single channel type I membrane glycoprotein. Increased expression of these

markers enables ovarian CSCs to become sphere-forming *in vitro* and tumorigenic *in vivo*, promoting development of epithelial ovarian cancer (EOC). This makes these cells more resistant to drugs and produces tumor progenitor cells that lead to tumor progression, metastasis and recurrence (57). Mounting evidence demonstrates Wnt/β-catenin signaling involvement in the acquisition of stemness in ovarian cancer cells (57-59). In one study, ALDH1A1 was overexpressed in cultured ovarian cancer spheres *in vitro* and was directly associated with key components of β-catenin signaling. This suggests that β-catenin-regulated ALDH1A1 maintains the sphere-forming ability of ovarian cancer cells (58). Another study confirmed that miR-1207 overexpression increases ovarian CSC-like properties *in vitro* and *in vivo*. The effects of miR-1207 are caused by Wnt/β-catenin signaling activation via inhibition of negative regulators of this pathway, such as secreted Frizzled-related protein 1 (SFRP1), axin 2, β-catenin inhibitor and TCF4 (59).

## 5. Wnt signaling and tumor metastasis

Metastasis is a characteristic of advanced cancer and a major challenge in cancer treatment. Epithelial-mesenchymal transition (EMT) refers to loss of intercellular adhesion and acquisition of mesenchymal cell characteristics by epithelial cells. This enhances cancer cell invasion and metastasis (60). Activation of Wnt/β-catenin signaling can increase expression of adhesion molecule suppressors by reducing E-cadherin and increasing Snail, Slug, Twist, zinc finger E-box-binding homeobox (ZEB)1 and ZEB2 expression (61). Several molecules, such as forkhead box protein P3 (FOXP3), long non-coding RNA (lncRNA) JPX and WD repeat-containing protein 74 (WDR74) contribute to lung cancer metastasis via Wnt signaling (62-64). In previous *in vitro* and *in vivo* studies, FOXP3 promoted lung tumor growth and metastasis via FOX3-mediated Wnt/β-catenin signaling activation (62,65). Some biomolecules, such as serpin family H member 1 (SERPINH1), lncRNA miR-4435-2HG and LINC01606, cyclin G2 and Zic family member 1 contribute to EMT and invasive metastasis of gastric cancer via Wnt/β-catenin signaling (66-70). SERPINH1 is a member of the serine protease inhibitor H subfamily. Furthermore, expression of Wnt/β-catenin signaling proteins β-catenin, Wnt2, GSK-3β, Snail, Slug and Twist is downregulated in the SERPINH1-silenced gastric cell line SGC-7901. This suggests that SERPINH1 regulates gastric cancer progression via Wnt/β-catenin signaling (66). Tumor metastasis in female patients is associated with Wnt/β-catenin signaling abnormalities. Overexpression of SFRP attenuates Wnt signaling in cervical cancer CaSki cells and increases E-cadherin expression by repressing Slug, Twist, and Snail (71). By contrast, cysteine-rich intestinal protein 1 activates Wnt/β catenin signaling and promotes cervical cancer cell migration and invasion by increasing expression of c-Myc, cyclin D1 and cytoplasmic β-catenin (72). The early dissemination and metastasis of HER2(+) breast cancer depends on non-classical Wnt (Wnt5a, Wnt5b and Wnt11) signaling (73). In addition, Wnt/β-catenin signaling is involved in remodeling of the EOC extracellular matrix, a MMP-mediated process. MMP-2 expression is upregulated in ovarian cancer and promotes cancer cell invasion and metastasis (74).

## 6. Wnt signaling and chemoradiotherapy resistance

Chemoradiotherapy resistance often leads to tumor treatment failure. The causes of chemoradiotherapy resistance are complex and associated with tumor heterogeneity, drug efflux/inactivation and survival pathway activation (75). Wnt signaling can enhance tumor resistance to chemotherapeutic agents or radiotherapy. Furthermore, inhibitors of Wnt signaling can reverse this resistance and restore treatment sensitivity (76,77).

*Wnt signaling and chemoradiotherapy resistance in lung cancer.* Cancer cells expressing Wnt1 resist drug-induced apoptosis. Moreover, Wnt/β-catenin signaling induces transcription of drug resistance factors such as multidrug resistance 1 (MDR-1) that is a membrane glycoprotein encoded by the MDR gene, survivin and livin (76). Platinum-based chemotherapy is the first-line treatment option for advanced NSCLC. However, acquired cisplatin resistance is prevalent in patients with NSCLC (78). One study reported that cytoplasmic inhibition of GSK-3β activates Wnt/β-catenin signaling and upregulates survivin expression, leading to cisplatin resistance in NSCLC (79). In another study, *c-Myc*, a downstream target gene of β-catenin, regulated A549/DDP resistance to cisplatin (80). Examination of β-catenin expression in NSCLC cell line PC9 and gefitinib-resistant cell line PC9/AB (2) revealed increased nuclear translocation of β-catenin in PC9/AB (2) compared with PC9. In addition, expression of certain components of β-catenin signaling (phosphorylated-GSK-3β, DVL1, c-Myc, c-JUN) increases (81). GDK-100017, a 2,3,6-trisubstituted quinoxaline derivative, inhibits Wnt/β-catenin signaling, blocks β-catenin-TCF/LEF interactions and increases sensitivity of A549/Wnt2 cells to radiotherapy (82). FZD8 is a member of the frizzled Wnt ligand-receptor family. Disruption of FZD8 increases the sensitivity of lung cancer cells to the chemotherapeutic drug paclitaxel (83).

*Wnt signaling and chemoradiotherapy resistance in gastric cancer.* Several molecules are involved in resistance to chemoradiotherapy in gastric cancer. Caveolin-1 (Cav-1) increases cisplatin resistance in gastric cancer cells by activating Wnt signaling (84). Similarly, DOCK6, a guanine nucleotide exchange factor, promotes radiotherapy resistance in gastric cancer by regulating Wnt signaling (85). ICG-001, an inhibitor of β-catenin, reduces the chemoresistance of gastric cancer cells by binding to CREB-binding protein (CBP) and interfering with its interaction with β-catenin, thereby inhibiting Wnt signaling (86). Cheng *et al* (87) investigated the mechanisms underlying regulation of cisplatin resistance by homologous cassette gene transcript antisense RNA (HOTAIR) in gastric cancer cells. Low HOTAIR expression attenuates cisplatin resistance in gastric cancer cells by inhibiting Wnt signaling. The long noncoding RNA FAM83H-antisense RNA 1 silencing also increases the chemosensitivity of gastric cancer cells via Wnt signaling (88). Similarly, basic leucine zipper ATF-like transcription factor 2, a member of the type I activator protein-1 family, reverses multidrug resistance in gastric cancer cells by inactivating Wnt signaling (89).

*Wnt signaling and chemoradiotherapy resistance in BC*. Wnt signaling plays a key role in chemoradiotherapy resistance in BC. The MDR1 gene encodes permeability glycoprotein, a transmembrane transporter glycoprotein that is a member of the ATP-binding cassette (ABC) transporter protein superfamily. This protein superfamily mediates drug efflux and is associated with tumor drug resistance. Pygo2 expression is upregulated in drug-resistant BC cells and activates *MDR1* via Wnt signaling, thereby mediating chemoresistance in BC (90). The expression of the membrane transporter protein Cav-1 is upregulated in BC chemoresistance. Cav-1 promotes drug resistance in breast CSCs via β-catenin/ABCG2 signaling (91). Activation of classical and non-classical Wnt signaling pathways is detected in the tamoxifen-resistant estrogen receptor (ER)(+) breast cancer cell line MCF7. Furthermore, Wnt3a increases tamoxifen resistance in MCF7 cells (92). Follistatin like protein 1, an extracellular matrix glycoprotein, is associated with regulation of cellular signaling pathways. Its expression is considerably upregulated in drug-resistant BC cells. Moreover, this gene can act through integrin β3-induced activation of Wnt signaling (93). Similarly, lncAFAP1-AS1 can induce radiotherapy resistance in TNBC via Wnt signaling (94).

*Wnt signaling and chemoradiotherapy resistance in ovarian cancer*. In addition to its involvement in BC resistance, abnormal ABCG2 expression is associated with drug resistance in ovarian cancer. The SC-associated receptor tyrosine kinase c-kit promotes ovarian cancer drug resistance via the Wnt/β-catenin/ABCG2 signaling axis. Low c-kit expression increases ovarian cancer cell sensitivity to chemotherapeutic agents such as cisplatin and paclitaxel (95). One study showed that chemoresistance in high-grade plasma ovarian cancer is associated with Wnt signaling activation. In addition, the sensitization of ovarian cancer-initiating cells to cisplatin is restored by a Wnt signaling inhibitor (96). Human copper transporter 1 is a transmembrane transporter that allows copper and cisplatin to enter cells through the membrane barrier. Wnt/β-catenin signaling inhibits expression of this protein in cisplatin-resistant EOC cells (97). MMP-10 is highly expressed in cancer stem-like/carcinoma-initiating cells in EOC and is associated with platinum resistance. It acts by inhibiting Wnt5a activation during Wnt signaling (98).

*Wnt signaling and cervical cancer chemoradiotherapy resistance*. Several studies have shown that Wnt signaling is associated with chemoradiotherapy resistance in cervical cancer (99-102). Therefore, β-catenin nuclear expression can be used as a predictive marker of chemoradiotherapy resistance in cervical squamous carcinoma (99). Fat mass and obesity-associated protein, an N6-methyladenine demethylase with upregulated mRNA expression in cervical squamous carcinoma tissue, enhances radiotherapy resistance by regulating β-catenin (100). One study showed that chemotherapeutic drugs activate Wnt/β-catenin signaling in a eukaryotic translation initiation factor 4 E (eIF4E)-dependent manner. This suggests that eIF4E/β-catenin signaling serves a positive regulatory role in chemoresistance in cervical cancer (101). Similarly, LGR5 acts as a cancer-promoting factor by activating Wnt signaling in cervical cancer. Thus, high LGR5 expression in cervical cancer cells promotes cisplatin resistance (102).

## 7. Wnt signaling and tumor immunity

The tumor microenvironment (TME) consists of immune cells, peripheral blood vessels, fibroblasts, signaling molecules and extracellular matrix (103). The overexpression of immune checkpoint molecules in the TME serves a key role in tumor immune escape and progression. Tumor immunotherapy is a novel approach for treating tumors and it activates or reactivates tumor immune circuits (104). Several immune checkpoint inhibitors (ICIs), such as ibritumomab, nabumab, pembrolizumab and atezumab, have been approved for cancer therapy. Ibritumomab is an anti-cytotoxic T lymphocyte-associated protein 4 antibody (anti-CTLA4), whereas nabumab and pembrolizumab are anti-programmed death receptor 1 antibodies (anti-PD-1). By contrast, atezumab is an anti-PD ligand 1 antibody (anti-PD-L1). Anti-PD-1/PD-L1 antibodies have clinical utility in 15 types of cancer (lung cancer, cervical cancer, gastric cancer, etc.). However, most patients with advanced cancers do not derive clinical benefits from these agents (105). This suggests that immunosuppressive mechanisms in the TME may limit the efficacy of ICIs (105).

Growing evidence demonstrates that Wnt signaling blocks all steps of the tumor immune cycle, including tumor antigen release and presentation, T cell initiation, activation and infiltration and clearance of tumor cells (106,107). The first step in the tumor immune cycle is processing of tumor antigens by dendritic cells (DCs) for presentation to effector T cells. Wnt signaling regulates maturation and activity of these DCs. One study on lung adenocarcinoma found that Wnt1 causes transcriptional silencing of CC/CXC chemokines, T cell rejection and cross-tolerance in classical DCs. Furthermore, Wnt1 target gene expression is upregulated in classical DCs within tumors and downregulated when Wnt1 is silenced through enhanced T cell toxicity (108). Another study revealed that Wnt5a suppresses CD14 ($^{+}$/low) monocyte-derived myeloid DC production and promotes CD14$^{+}$/$^{++}$CD16$^{+}$ monocyte production (109). CD8$^{+}$ T cells are the primary effector cells in the tumor immune cycle and can be activated by DCs and costimulatory molecules that infiltrate the tumor site to kill cancer cells (110). However, tumor cells evade immune clearance and reject or inactivate CD8$^{+}$ T cells to prevent CD8$^{+}$ T cell infiltration during tumor progression (111). Therefore, Wnt signaling is essential for T cell differentiation, polarization, effector function and migration (112). Tumor-infiltrating T cells substantially overexpress Wnt3a and β-catenin, leading to dysfunction and memory T cell depletion (113). In addition, Wnt-mediated β-catenin/TCF1 activation inhibits naïve T cell and terminal differentiation of effector CD8$^{+}$ T cells (113). Helper T (Th) cells mainly contribute to CD8$^{+}$ T cell antitumor responses by releasing cytokines. Wnt signaling also regulates Th cell development and function (114) by suppressing Th cells and impairing antitumor immunity. In colorectal cancer, β-catenin is activated and attenuates CD4$^{+}$ T antitumor immunity by suppressing interferon γ and elevating IL-17a expression (115). Autoimmune encephalomyelitis-induced endothelial Wnt signaling limits CD4$^{+}$ T cell infiltration, which is restored when signaling is suppressed (116). These findings

demonstrate that Wnt signaling serves a non-negligible role in immune cell function. Therefore, the influence of this pathway warrants consideration in tumor immunotherapy, especially when efficacy is poor.

## 8. Wnt signaling and tumor therapy

Numerous studies have confirmed involvement of Wnt signaling in onset, progression, metastasis and drug resistance of various cancers (75,117,118). Moreover, strategies targeting this pathway for cancer treatment are gaining attention (75,118). Preclinical research has revealed four approaches that target Wnt signaling: i) Blocking ligand-receptor interactions, ii) blocking FZD/LRP5/6 signaling [porcupine (PORCN) inhibitors], iii) promoting β-catenin degradation (tankyrase (TNKS) enzymes or inhibitors) and iv) blocking β-catenin-TCF interactions (β-catenin inhibitors) (119).

*Blocking Wnt ligand-receptor interactions*. Different tumors express specific Wnt ligands. Therefore, blocking specific Wnt ligand-receptor interactions can inhibit tumor cell proliferation (120,121). In one study, addition of anti-Wnt1 monoclonal antibodies to human NSCLC, BC, mesothelioma and sarcoma cell lines led to apoptosis. In addition, the antibodies inhibited tumor growth *in vivo* (122). Another study showed that Wnt2 inhibitors decrease clone formation and transplanted tumor volume in NSCLC cell lines (123). After transferring interfering RNA of Wnt5a into the human lung squamous carcinoma cell line H157 and human lung adenocarcinoma cell line A549, the proliferative capacity of both cell lines was decreased (124). The recombinant fusion protein ipafricept (known as OMP-54F28) is formed by fusing the cysteine-rich structural domain of FZD8 with the structural domain of immunoglobulin Fc, which blocks Wnt signaling by binding to Wnt ligands. Preclinical studies have shown that OMP-54F28 slows tumor growth and has a synergistic effect when combined with chemotherapeutic agents (125,126). This human monoclonal antibody interacts with five FZD receptors to block classical Wnt signaling and clinical trials have shown that it has good tolerability (125,127).

*Blocking FZD-LRP5/6 signaling*. PORCN is a membrane-bound O-acetyltransferase that modifies Wnt proteins via palmitoylation; only such modified Wnt proteins can be secreted outside the cellular membrane to activate Wnt signaling by interacting with its co-receptors LRP5/6 and FZD (128). LGK974 is a small-molecule PORCN inhibitor that blocks Wnt signaling and induces tumor regression in MMTV-Wnt1 mice. In addition, LGK974 considerably attenuates clone formation in human head and neck cancer cell line HN30 (129). ETC-159 is another PORCN inhibitor that blocks secretion and activation of Wnt proteins. Preclinical studies have shown that ETC-159 is highly effective in treating mouse-transplanted tumors with R-spondin translocations in patients with colon cancer (127,130). In another preclinical study, combination of the PORCN inhibitor RX004 and anti-PD-1 enhanced antitumor immune effects (131). PORCN inhibitors have shown therapeutic potential in colorectal, pancreatic, hepatocellular and head and neck tumors. To date, no PORCN inhibitors have entered clinical use; only LGK974, ETC159, CGX1321 and RXC004 have been investigated in phase I clinical trials (132-135).

*Promotion of β-catenin degradation*. End-anchored polymerase (TNKS) is a member of the poly ADP-ribose polymerase (PARP) family, which includes two isoforms, TNKS1 (PARP5a) and TNKS2 (PARP5b). These isoforms regulate classical Wnt signaling via poly ADP-ribosylated axin proteins. TNKS inhibitors promote β-catenin degradation by increasing axin levels (120). Treatment of the NSCLC cell line A549 with XAV939 inhibits cell proliferation and migratory capacity. Furthermore, it decreases TNKS, β-catenin and c-Myc protein levels (136). This TNKS inhibitor also decreases proliferative capacity of the SCLC cell line H446 by inhibiting Wnt signaling (137). The combination of XAV939 and chemotherapeutic agent paclitaxel induces apoptosis and inhibits Wnt signaling in BC cells. In addition, this treatment suppresses EMT and angiogenesis. Similarly, combined XAV939 and low-dose (20 nM) paclitaxel results in comparable therapeutic effects in BC cell lines compared with high-dose (200 nM) paclitaxel alone (138). NVP-TNKS656, another TNKS inhibitor, decreases β-catenin protein expression in the nucleus of colorectal cancer cells when combined with PI3K or AKT inhibitors, thereby reversing resistance to PI3K or AKT inhibitors and inhibiting tumor growth (139). Moreover, the TNKS inhibitor G007-LK has a sensitizing effect on anti-PD-1 antitumor therapy (140).

*Blocking β-catenin and TCF interactions*. An effective way of targeting the classical Wnt signaling pathway is to block the interaction of β-catenin with downstream transcription factors (120,121). TCF4 is a member of the TCF/LEF family and binds to β-catenin to initiate target gene transcription when Wnt signaling is activated. Inhibitors of β-catenin-TCF4 interactions include PKF115-584, CGP049090, PKF222-815, PKF118-744, PKF118-310, ZTM000990, iCRT3/5/14, NC043, LF3 and UU-T02/03 (141). PKF115-584 inhibits β-catenin transcription and proliferation in the adrenocortical tumor cell line H295R in a dose-dependent manner (142). Similarly, CGP049090 and PKF115-584 effectively kill chronic lymphocytic leukemia cells (143). Three inhibitors, PKF118-310, PKF115-584 and CGP049090, downregulate the expression of TCF4/β-catenin target genes *c-Myc*, cyclin D1 and survivin in hepatocellular carcinoma. These inhibitors also induce apoptosis and cell cycle arrest and inhibit the growth of transplanted tumors in mice (144).

In addition, β-catenin can also interact with p300/CBP and BCL9 (141). Thus, pharmacological blockade of Wnt signaling seems promising in preclinical models (141-144).

## 9. Conclusion

The dysregulation of classical and non-classical Wnt signaling pathways in tumors has been extensively studied in recent years (117,118,132-134). The present review provides an overview of the role of Wnt signaling in tumorigenesis, progression, metastasis, CSCs, chemoradiotherapy resistance and antitumor immunity as well as inhibitors targeting Wnt signaling. Wnt signaling is increasingly recognized as an anticancer therapeutic target and several studies have demonstrated the

effectiveness of Wnt signaling inhibitors alone or in combination with other chemotherapeutic agents and ICIs in antitumor therapy (118,132-134,138). Furthermore, some Wnt signaling inhibitors (LGK974, ETC159, CGX1321, and RXC004) have been tested in phase I clinical trials (132,134,145,146). However, Wnt signaling serves an important role in physiological processes and the possible side effects after blockade are not well understood. Therefore, pharmacological effects and mechanisms underlying Wnt signaling and its inhibitors for early clinical application warrant further study. An in-depth understanding of these processes may improve prognosis in patients with cancer.

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HW and MJ designed the review and edited the manuscript. HW and LZ wrote the manuscript. HW, CH and HL collected and analyzed data. Data authentication is not applicable. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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