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# Wnt signaling in cancer: from biomarkers to targeted therapies and clinical translation

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## Abstract

The Wnt signaling pathway plays a crucial role in development and tissue homeostasis, regulating key cellular processes such as proliferation, differentiation, and apoptosis. However, its abnormal activation is strongly associated with tumorigenesis, metastasis, and resistance to therapy, making it a vital target for cancer treatment. This review provides a comprehensive insight into the role of Wnt signaling in cancer, examining its normal physiological functions, dysregulation in malignancies, and therapeutic potential. We emphasize the importance of predicting Wnt signaling sensitivity and identify key biomarkers across various cancer types. Additionally, we address the challenges and future prospects of Wnt-targeted therapies, including biomarker discovery, advancements in emerging technologies, and their application in clinical practice.

**Keywords** Wnt signaling pathway, Biomarkers, ncRNAs, Cancer therapy, Challenges and Future directions

## Introduction

Wnt signaling pathways are essential for various biological functions, including tissue homeostasis maintenance and embryonic development [1, 2]. Disruption of these pathways can lead to various diseases [3, 4], most notably cancer [5, 6], where it plays a role in cancer initiation [7, 8], progression [9], and metastasis [10, 11].

The sensitivity of cancer cells to Wnt signaling is a crucial factor in understanding the molecular complexities of tumorigenesis [12, 13]. This knowledge is important for the development of targeted therapeutic strategies [14]. In the rapidly evolving field of cancer research, significant efforts are focused on identifying and characterizing biomarkers associated with Wnt signaling susceptibility [15].

This review provides a comprehensive analysis of current biomarkers used to predict Wnt signaling activity in cancer, highlighting the complex interplay of Wnt pathway components as both prognostic indicators and therapeutic targets. We also explore the rationale behind investigating biomarkers as potential indicators of Wnt signaling susceptibility. Additionally, this review critically assesses the existing evidence supporting their use as reliable predictors of Wnt signaling sensitivity across different cancer types. In conducting this investigation, it's important to acknowledge the dynamic nature of biomarker research and the ongoing evolution of understanding in this field. Moreover, we also shed light on the role of non-coding RNAs (ncRNAs) in influencing Wnt Pathway. Additionally, we address the challenges and limitations currently faced in the discovery of biomarkers for Wnt signaling susceptibility and propose potential directions for future research. By critically examining the existing literature, this review offers valuable insights into the most recent biomarkers and sets the stage for future advancements in this crucial area of cancer biology.

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## Wnt signaling pathway in cancer

### *Normal functions and regulation*

The Wnt signaling pathway is vital in biological processes and has significant implications for the development of cancer [16, 17]. It is crucial to understand the role of the Wnt pathway in cancer, as it influences cell fate, tissue homeostasis, and embryonic development [18, 19]. Aberrant Wnt signaling in cancer is closely linked to processes like cell proliferation, differentiation, and the maintenance of cancer stem cells [20, 21].

In the canonical Wnt pathway, which is crucial for cancer, Wnt ligands inhibit the destruction complex comprising adenomatous polyposis coli (APC), Axin [22], GSK3β [23], thereby stabilizing β-catenin [24]. Stabilized β-catenin then enters the nucleus, where it forms a complex with lymphoid enhancer factor/T cell factor (TCF/LEF) transcription factors [25] to activate Wnt target genes [14, 26]. These genes are essential for cell cycle progression and survival [14, 27].

Non-canonical Wnt signaling pathways, such as the Wnt/Ca2 + and Wnt/planar cell polarity (PCP) signaling pathways, also contribute to normal cellular function and cancer. The Wnt/Ca2 + pathway affects cell migration and adhesion [28, 29], while the Wnt/PCP pathway plays a role in tissue polarity and cell motility [30, 31]. Dysregulation of these non-canonical pathways can influence cancer progression, affecting processes like invasion and metastasis [32, 33].

Controlling Wnt signaling is crucial for maintaining cellular homeostasis in cancer. Genetic mutations in key components, such as APC and β-catenin, can disrupt this regulation, leading to persistent activation of the pathway [34, 35]. For example, in colorectal cancer (CRC), APC mutations lead to sustained β-catenin activation, which is essential for tumor maintenance and cell proliferation. This is evidenced by the inhibition of tumor growth upon β-catenin suppression and the resumption of growth following reactivation of the pathway [36]. Similarly, in gastric cancer, nuclear accumulation of β-catenin and mutations in exon 3 of the β-catenin gene are frequently observed, particularly in tumors with active Wnt signaling, highlighting the pathway's contribution to carcinogenesis [37]. Frizzled (FZD) genes, which encode seven-transmembrane Wnt receptors that play a crucial role in carcinogenesis and embryogenesis. In gastric cancer, multiple FZD genes exhibit altered expression. Among gastric cancer cell lines, FZD7 is upregulated in MKN7, while FZD5 is elevated in MKN45. Additionally, FZD9 and FZD10 show co-upregulation in TMK1 and MKN74, whereas FZD2 is upregulated in multiple cell lines. In primary gastric cancer cases, FZD2, FZD8, and FZD9 are frequently upregulated, suggesting their potential role in tumor progression [38]. Among these, FZD7 is particularly significant in gastric cancer, as it facilitates Wnt signaling and promotes tumor growth. Its overexpression correlates with tumor invasion, metastasis, late TNM stages, and poor patient survival. Moreover, FZD7 is enriched in cancer stem cell populations and enhances epithelial-mesenchymal transition (EMT). Silencing FZD7 reduces proliferation, migration, and invasion in gastric cancer cells by attenuating canonical Wnt/β-catenin signaling [39]. Preclinical studies further confirm that genetic deletion of FZD7 or pharmacologic inhibition with vantictumab suppresses gastric adenoma growth. Notably, FZD7 deficiency impairs Wnt-driven proliferation, regardless of APC mutation status [40]. Recently, a novel antibody–drug conjugate (ADC) targeting FZD7, known as septuximab vedotin (F7-ADC), demonstrated strong anti-tumor activity and a favorable safety profile in preclinical models, further highlighting FZD7 as a promising therapeutic target [41].

Moreover, abnormal expression of Wnt ligands and changes in negative regulators [42] like Dickkopf (DKK) and secreted Frizzled-related protein (sFRP) contribute to sustained Wnt signaling in cancer [43]. For example, downregulation of DKK1 has been linked to the high proliferation ability of LM-MCF-7 breast cancer (BC) cells due to loss of control over Wnt/β-catenin signaling. Downstream effectors such as c-Myc, cyclin D1, and Survivin further contribute to tumor progression [44]. In HCC, DKK1 is commonly overexpressed, and its inhibition enhances the anti-tumor efficacy of sorafenib by suppressing the PI3K/Akt and Wnt/β-catenin pathways through GSK3β regulation [45]. Similarly, DKK1 inhibition in rhabdomyosarcoma, using both shRNA and the chemical inhibitor WAY-262611, activates β-catenin and reduces tumor proliferation and invasion, demonstrating its therapeutic potential [46]. In pancreatic ductal adenocarcinoma (PDAC), GATA6 promotes carcinogenesis by suppressing DKK1, leading to enhanced Wnt signaling and tumor progression [47].

SFRPs also play a critical role in modulating Wnt signaling and cancer progression by acting as extracellular antagonists or regulators. For example, SFRP4, highly expressed in endometrial stroma, suppresses Wnt7a signaling in both autocrine and paracrine manners, thereby inhibiting endometrial cancer cell proliferation [48]. Additionally, SFRP1, secreted via Rab37-mediated vesicle trafficking, suppresses Wnt signaling and cancer stemness. Low levels of Rab37 and SFRP1 are linked to poor prognosis in lung cancer [49]. In choriocarcinoma, downregulated SFRP2, due to promoter hypermethylation, promotes EMT and cancer stemness by activating canonical Wnt/β-catenin signaling, while increased SFRP2 levels inhibit invasion, migration, and EMT [50].

### *Dysregulation in cancer: implications for tumorigenesis*

Dysregulation of the Wnt signaling pathway is a hallmark of many cancers, significantly contributing to carcinogenesis [51, 52]. Persistent activation of key components is a defining feature of Wnt signaling pathway dysregulation in various cancers. Genetic abnormalities in important regulators cause β-catenin to accumulate in the cytoplasm, which facilitates its translocation to the nucleus [53]. This abnormal Wnt activation leads to uncontrolled expression of target genes which are crucial for promoting cell cycle progression and survival in cancer cells [54], underscoring the critical role of classical Wnt signaling in the cell division cycle [54].

Dysfunction in the Wnt signaling pathway promotes tumorigenesis by interfering with fundamental cellular mechanisms [55, 56]. Such as its dysregulation has been associated with the induction of EMT [57]. Importantly, dysregulation of this pathway is not an isolated event but interact with other signaling pathways to enhance its oncogenic effects [58]. For example, the PI3K/Akt/mTOR and MAPK contribute to the regulatory network of Wnt signaling in cancer cells [59]. Understanding these interrelationships offers valuable insights into the molecular complexity of cancer, providing potential pathways for targeted therapeutic interventions.

Identifying biomarkers that predict Wnt signaling sensitivity is crucial for advancing personalized cancer therapy. Analysis of genetic mutations in components of the Wnt signaling pathway serves as a key diagnostic tool [60]. For example, in melanoma, genetic aberrations in APC and β-catenin have been linked with immunotherapy response and overall survival [61]. Additionally, analyzing key regulatory molecules and Wnt target gene expression offers insights into Wnt signaling sensitivity in cancer. Extensive gene profiling studies have demonstrated Wnt/β-catenin pathway activation across various cancers [26]. However, despite years of research, no reliable, tissue-agnostic gene expression signature exists to predict Wnt pathway activation [62]. This gap highlights the need for continued research, particularly as advances in genomics and proteomics technologies are expected to reveal novel biomarkers that facilitate the prediction of Wnt signaling susceptibility. These technological advancements are not only crucial for biomarker discovery but also play a pivotal role in the development of modern cancer therapies. Indeed, the integration of oncoproteomics, computational biology, and genomic innovations has become essential for discovering and developing effective cancer treatments [63]. Among these approaches, proteomics has gained particular prominence in molecular sciences due to its ability to provide valuable information on protein identification, expression levels, and post-translational modifications [64].

## Current biomarkers for predicting wnt signaling sensitivity

Current biomarkers for predicting Wnt signaling sensitivity in cancer include a range of molecular indicators that reflect the activity of the Wnt pathway (Table 1). These biomarkers are involved in key regulatory steps of Wnt signaling and can help assess the tumor's responsiveness to Wnt-targeted therapies. Additionally, alterations in genes like APC, CTNNB1, and TCF/LEF transcription factors have been shown to correlate with varying degrees of Wnt pathway activation. These biomarkers can provide valuable insights into tumor-specific Wnt signaling profiles, guiding clinicians in selecting the most effective treatment strategies for individual cancer patients, thereby improving personalized therapy outcomes.

### *Adenomatous polyposis coli (APC)*

APC is a tumor suppressor gene that regulates β-catenin degradation [65, 66]. However, alterations in the APC gene impair Wnt signaling pathways, triggering the abnormal accumulation of β-catenin and facilitating the progression of tumors (Fig. 1). The identification of APC gene mutations serves as a fundamental biomarker, distinguishing cancer patients with increased susceptibility to impaired Wnt signaling [67]. The APC gene plays a critical role in determining Wnt signaling sensitivity in cancer, as its mutations significantly contribute to pathway dysregulation and the progression of various cancer types [68, 69]. For example, dysregulation of the Wnt pathway due to APC mutations plays a critical role in the early development of CRC [70, 71]. Consequently, detecting APC mutations through genetic testing serves as a valuable diagnostic tool for individuals at risk of developing CRC. Identifying biomarkers that predict response to Wnt signaling is crucial in CRC. Notably, these biomarkers provide valuable insights into understanding the potential of Wnt-targeted therapies [72, 73]. A primary biomarker in CRC is the presence of mutations in the APC gene [74]. Frequent mutations in APC lead to defects in Wnt signaling, notably through the abnormal accumulation of β-catenin [74]. While APC mutations are prevalent in familial adenomatous polyposis (FAP) and sporadic CRC, the presence and location of the mutation significantly influence the disease's progression and associated risks [75]. Interestingly, recent studies have revealed that a subset of early-onset CRC may lack APC mutations, instead exhibiting alterations in other Wnt pathway components like RNF43 or RSPO3, suggesting alternative mechanisms of Wnt activation. These APC mutation-negative (APC-mut-) CRC also show increased mitochondrial activation or heightened sensitivity to extracellular Wnt signals, which may open up new therapeutic possibilities [76]. Furthermore, APC mutations are associated with worse

**Table 1** Wnt signaling biomarkers in cancer: roles, mechanisms, and therapeutic implications

| Biomarker | Role | Mechanism of Action | Diagnostic/Prognostic Significance | Potential Therapeutic Implications |
|---|---|---|---|---|
| APC Gene Mutations | Regulator of Wnt signaling | Leads to defects in Wnt signaling; abnormal accumulation of β-catenin | Vital biomarker for increased susceptibility to Wnt signaling; Distinguishes cancer patients | Target for Wnt signaling therapies; Potential for personalized interventions |
| Aberrant β-Catenin Accumulation | Indicates dysregulated Wnt signaling | Caused by destruction complex malfunctioning; frequently linked to APC gene mutations | Direct biomarker for Wnt signaling activation; Reflects cancer susceptibility | Potential therapeutic target for modulating Wnt pathway |
| c-Myc and Cyclin D1 Expression | Key Wnt target genes | Increased expression in response to Wnt activation; Dysregulation initiates carcinogenesis | Valuable biomarkers for predicting sensitivity to Wnt-targeted therapies | Potential therapeutic targets; Indicate Wnt signaling activation |
| AXIN2 Gene Alterations | Negative regulator of Wnt signaling | Variations predict cancer risk and prognosis; Decreased expression leads to overactive Wnt pathway | Biomarker for understanding Wnt signaling regulatory mechanisms; Predictive of cancer risk | Target for Wnt signaling therapies; Indicates overactive Wnt pathway in cancer |
| DKK1 (Dickkopf-1) | Wnt signaling pathway inhibitor | Dysregulation correlates with abnormal Wnt signaling; Prevents Wnt, FZD, and LRP6 interaction | Biomarker for cancer prognosis and progression; Predicts outcomes of Wnt-targeted therapies | Potential therapeutic target for modulating Wnt pathway |
| SFRP1 Promoter Hypermethylation | Wnt signaling antagonist downregulation | Frequently downregulated in HCC through promoter hypermethylation | Indicates sustained activation of Wnt signaling; Potential diagnostic marker | Potential for targeted therapy to restore SFRP1 function |
| FRAT1 Overexpression | Positive regulator of Wnt signaling | Contributes to pathway activation by inhibiting beta-catenin phosphorylation | Potential biomarker for predicting Wnt signaling sensitivity | Insight into the regulatory environment for Wnt signals; Target for Wnt signaling therapies |
| Porcupine (PORCN) | Enzyme involved in Wnt signaling | Catalyzes the palmitoylation of Wnt proteins, essential for Wnt secretion | Critical biomarker for Wnt signaling activation; Indicates dysfunction in Wnt pathway | Target for Wnt signaling modulation; Potential for therapeutic inhibition to block Wnt signaling in cancer |
| Glycogen Synthase Kinase-3β (GSK-3β) | Negative regulator of Wnt signaling | Phosphorylates and promotes degradation of β-catenin, inhibiting Wnt pathway | Key biomarker for Wnt pathway regulation; Elevated GSK-3β activity may indicate impaired Wnt signaling | Target for Wnt signaling modulation; Inhibition may reactivate Wnt signaling in diseases like cancer |
| LEF/TCF Transcription Factors | Key mediators of Wnt signaling | ind to β-catenin to regulate Wnt target gene expression | Biomarkers for active Wnt signaling; Associated with tumor progression and metastasis | Potential targets for disrupting Wnt-driven transcription in cancer therapy |
| Microsatellite Instability (MSI) | Correlates with Wnt signaling dysregulation | Associated with hypermethylation of SFRP1; Different clinical trajectory in cancer | Biomarker for identifying cancer patients susceptible to Wnt-targeted interventions | Indicates sustained activation of Wnt signaling; May guide personalized interventions |

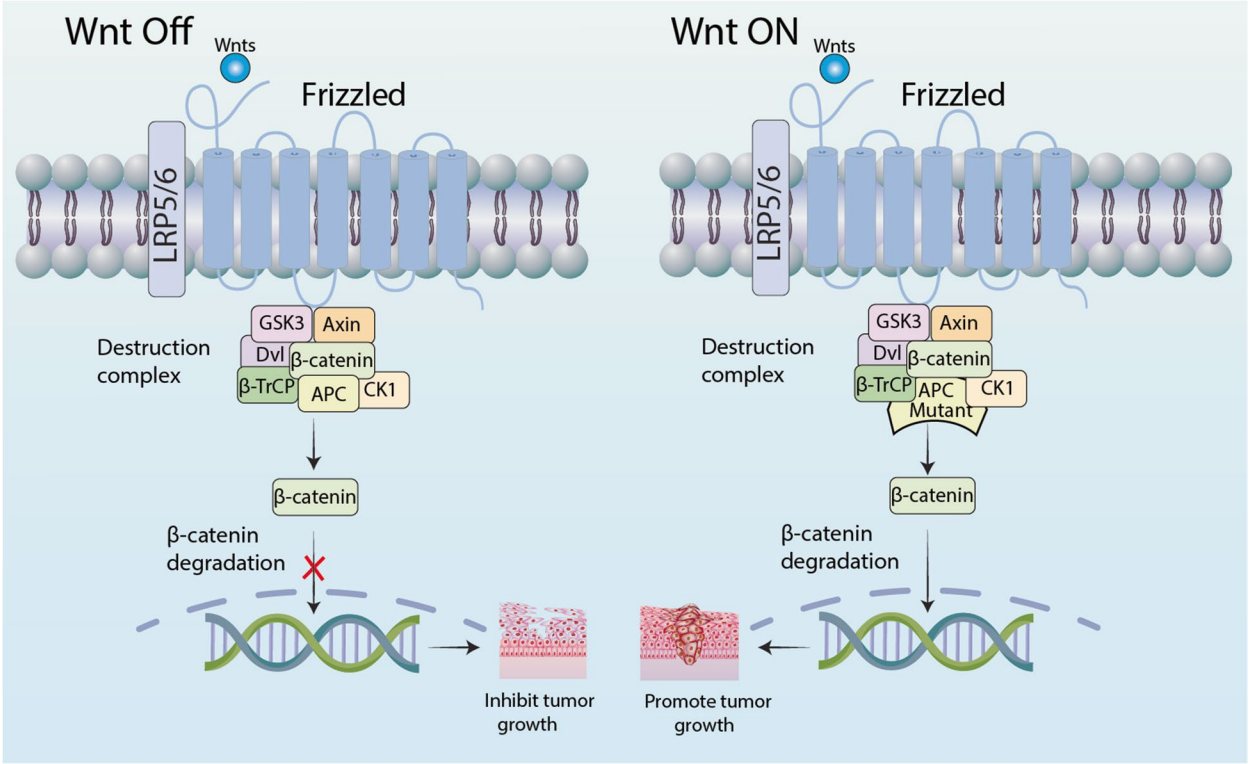


**Fig. 1** This figure illustrates the role of the APC gene within the Wnt signaling pathway and its significance as a cancer biomarker. It begins by depicting the normal Wnt signaling process, highlighting the sequential activation of Wnt ligands, receptors, and the downstream destruction complex. A key focus is on the APC destruction complex, showing its role in regulating β-catenin levels under normal conditions. The figure also demonstrates how APC gene mutations disrupt this complex, leading to the abnormal accumulation of β-catenin, a critical event in cancer initiation and progression

immunotherapy outcomes due to lower tumor mutational burden (TMB) and reduced immune checkpoint molecule expression. These mutations also correlate with diminished T cell infiltration in tumors. Consequently, APC serves as a negative biomarker for predicting immunotherapy response [77]. Importantly, APC-mutant CRC have shown sensitivity to statins, with a synthetic lethal interaction that reduces Wnt signaling and downregulates anti-apoptotic proteins, offering a novel therapeutic approach for APC-mutant cancers [78]. Moreover, APC mutations, particularly those involving the loss of the seven β-catenin-binding 20-amino acid repeats (20-AARs), have been identified as potential predictive biomarkers for CRC cell sensitivity to tankyrase inhibitors, which target the Wnt/β-catenin pathway. Specifically, tankyrases poly (ADP-ribosyl)ate and destabilize Axins, key β-catenin repressors, thereby upregulating β-catenin signaling. In CRC cells with "short" APC mutations lacking all 20-amino acid repeats (20-AARs), tankyrase inhibitors effectively suppress β-catenin levels and inhibit tumor growth. Conversely, CRC cells with "long" APC mutations, retaining two or more 20-AARs, demonstrate resistance to these inhibitors due to a dominant-negative effect that impairs Axin-mediated β-catenin degradation. Notably, APC mutations, alongside PIK3CA mutations, can predict the response to tankyrase inhibitors, providing insights into patient selection for future clinical trials of these targeted therapies [79, 80].

Moreover, APC plays a crucial role in the development of FAP. It was initially identified through its association with the MCC gene, and both genes are closely spaced, encoding proteins with coiled-coil regions [81]. Although, the APC gene has long been recognized as a tumor-suppressor gene in the intestine, but the precise mechanisms underlying its role in tumor suppression remain unclear. Studies utilizing an inducible Ahcre transgenic model and a loxP-flanked APC allele have revealed that loss of APC activates Wnt signaling through the nuclear accumulation of beta-catenin, leading to the disruption of cell differentiation, migration, proliferation, and apoptosis. This dysregulation results in APC-deficient cells maintaining a "crypt progenitor-like" phenotype [82].

Beyond CRC, APC gene mutations have been recognized as significant biomarkers in various cancers,

including lung, pancreatic, ovarian, prostate, and HCC. For example, in lung cancer, APC mutations are rare but contribute to disease progression by causing abnormal β-catenin accumulation, disrupting cell proliferation, and promoting tumor growth. Thus, detecting APC gene mutations serves as a vital biomarker, helping to distinguish lung cancer patients who exhibit increased susceptibility to Wnt signaling [83]. Similarly, in pancreatic cancer, while mutations in key Wnt pathway genes such as APC are less frequent, aberrant Wnt signaling still promotes tumor progression. Therefore, identifying APC gene mutations provides valuable insights into patient susceptibility to Wnt signaling and aids in developing personalized treatment strategies [84, 85].

In ovarian cancer, mutations in the APC gene, particularly the I1307K missense mutation, have been linked to increased cancer risk, especially when co-occurring with BRCA1/2 mutations [86]. Moreover, APC mutations in ovarian cancer also correlate with heightened Wnt pathway activation, suggesting a potential target for Wnt signaling inhibition [86, 87]. Similarly, in prostate cancer, APC gene mutations have been identified as promising biomarkers for Wnt pathway dysregulation, contributing to abnormal β-catenin accumulation and tumor progression [88, 89]. Notably, the interaction of APC mutations with BRCA1/2 mutations in prostate cancer further elevates cancer risk, warranting targeted therapeutic strategies.

In HCC, APC mutations frequently drive Wnt signaling activation, promoting abnormal β-catenin accumulation and tumor growth. Identifying APC mutations as biomarkers in HCC offers a promising avenue for developing tailored therapies aimed at reducing Wnt pathway activation [90]. Consequently, APC mutations not only serve as critical biomarkers for cancer diagnosis but also provide valuable prognostic and therapeutic implications across multiple cancer types. Overall, APC stands as a crucial biomarker, shedding light on the molecular intricacies of Wnt signaling dysregulation in CRC and guiding diagnostic, therapeutic, and prognostic strategies.

#### *β-catenin*

B-catenin is a key effector of the Wnt signaling pathway. It is another important biomarker, and its aberrant accumulation indicates dysregulation of Wnt signaling. It often resulted from dysfunction of the destruction complex [91, 92]. Elevated β-catenin levels in cancer tissues are considered a direct biomarker, reflecting Wnt signaling activation and sensitivity [93, 94]. For example, a study analyzing 201 CRC patients demonstrated that high expression of Wnt1 strongly correlated with elevated nuclear and cytoplasmic β-catenin levels ($p=0.0004$, $p=0.02$), while high Wnt5a expression was associated with membrane β-catenin levels ($p=0.03$). Furthermore, multivariate analysis identified nuclear β-catenin expression as an independent prognostic factor for survival ($p=0.04$), reinforcing its role as a reliable predictive biomarker of Wnt signaling activation and its impact on cancer progression [95].

In CRC, the aberrant accumulation of β-catenin within cancer cells, indicating dysregulation of Wnt signaling [73, 96]. This phenomenon often arises from mutations in the APC gene, which disrupt the destruction complex and lead to abnormal β-catenin accumulation [73, 96]. The presence of β-catenin in CRC tissues directly indicates enhanced sensitivity to Wnt signaling activation, serving as a marker of dysregulated Wnt pathway activity [73, 96]. Studies have shown that β-catenin overexpression, particularly its nuclear accumulation, is linked to aggressive tumor features, EMT, and poor prognosis in CRC patients. For instance, nuclear β-catenin expression at the invasive front of tumors correlates with advanced disease stages, lymph node metastasis, and poor survival outcomes [97]. In contrast, the membranous expression of β-catenin typically reflects less aggressive tumor behavior [98]. Interestingly, phospho-β-catenin has been identified as a potential marker for improved survival in CRC patients, independent of tumor grade and stage [99].

β-Catenin's journey extends beyond the cytoplasmic realm, as it translocates into the nucleus. Here, β-catenin collaborates with TCF/LEF to transcribe Wnt target genes, crucial for proliferation, survival, and differentiation, highlighting its role in cellular homeostasis. Dysregulation of Wnt pathway [100], results from mutations in destruction complex genes causing aberrant β-catenin accumulation and perpetuating Wnt pathway activation [101, 102]. This abnormal signaling cascade is mainly linked to tumorigenesis, tumor progression, and metastasis across diverse cancer types [103, 104].

Beyond CRC, β-catenin also serves as a direct biomarker for Wnt signaling dysregulation in various other cancers. For example, in lung cancer, abnormal β-catenin accumulation indicates dysregulated Wnt signaling, with alterations and degradation of β-catenin being critical events in its progression [105, 106]. Malfunctioning destruction complex, often linked to APC gene mutations, leads to abnormal β-catenin accumulation in lung cancer. Elevated β-catenin levels in lung cancer tissues serve as a direct biomarker for Wnt signaling activation and susceptibility [105, 106]. Nuclear presence of β-catenin functions as a transcriptional activator, triggering the expression of target genes associated with lung cancer [107]. Therefore, the detection of elevated β-catenin levels can deliver valuable insights

into the activation of Wnt signaling and the susceptibility of lung cancer to this pathway.

In both clinical and laboratory settings, β-catenin levels are routinely assessed through immunohistochemical techniques on tissue samples [108]. Aberrant cellular localization of β-catenin, whether in the nucleus or cytoplasm, serves as a robust indicator of Wnt signaling pathway activation [109, 110]. Beyond its diagnostic utility, β-catenin demonstrates prognostic value in cancer, with its expression pattern often correlating with clinical outcomes [111, 112]. Notably, elevated nuclear β-catenin concentrations in tumor tissue are associated with increased malignancy and a poorer prognosis in specific cancer types.

Similarly, in pancreatic cancer, the aberrant accumulation of β-catenin within cancer cells, indicating dysregulation of Wnt signaling [113]. β-catenin, a key Wnt effector, undergoes critical modification and degradation in the Wnt signaling pathway, influencing pancreatic cancer genesis and progression [84]. Detecting elevated levels of β-catenin in pancreatic cancer tissues serves as a direct biomarker of Wnt signaling activation and susceptibility.

In ovarian cancer the aberrant accumulation of β-catenin within cancer cells, indicating dysregulation of Wnt signaling [114]. There is often activation of receptors over-expression, disruption of destruction complex, and abnormal TCF transcriptional activity in high-grade serous ovarian endometrioid carcinoma (EOCs), resulting in impaired cell adhesion and uncontrolled cell proliferation [86]. In OEC, CTNNB1 mutations and nuclear β-catenin expression are linked to improved progression-free survival, possibly because tumors with these mutations tend to present at an earlier stage. Furthermore, β-catenin immunohistochemistry could serve as a reliable prognostic biomarker and surrogate for CTNNB1 mutations, particularly in reproductive-age patients or those diagnosed incidentally without upfront staging surgery [115]. Additionally, nuclear β-catenin accumulation has been observed in Twist2-induced EMT cells, facilitating ovarian cancer invasion and metastasis [116].

In HCC, abnormal β-catenin accumulation frequently occurs due to destruction complex malfunction [117, 118]. High levels of β-catenin in HCC tissues directly indicate Wnt signaling activation and susceptibility. Consequently, targeting β-catenin or its downstream effectors remains a promising therapeutic approach in HCC management.

The pivotal role of β-catenin in cancer development presents significant therapeutic potential, making it an attractive target for innovative cancer treatment strategies [119]. Ongoing efforts focus on strategies to inhibit Wnt signaling components, including β-catenin, as promising targets for therapeutic intervention [120]. Small molecules and antibodies designed to disrupt this signaling pathway are subjects of rigorous investigation in both preclinical and clinical studies [121, 122]. Given the pivotal role of β-catenin, the evaluation of its status in tumors has become increasingly integral in clinical practice. Tumors exhibiting defective Wnt signaling, evidenced by elevated β-catenin levels, may guide therapeutic decisions towards targeted interventions that modulate the signaling pathway. Hence, β-catenin stands as a crucial biomarker, providing profound insights into Wnt signaling sensitivity, tumorigenesis, and potential therapeutic avenues within the complex landscape of cancer biology.

#### c-Myc

c-Myc, a transcription factor that drives cell proliferation, metabolism, and cancer growth, serves as a key indicator of Wnt signaling sensitivity. Its elevated expression reflects pathway activation and is frequently associated with tumor progression and poor prognosis [123]. Therefore, monitoring the expression profiles of these target genes is a valuable biomarker, significantly contributing to the diagnostic toolkit for predicting susceptibility to Wnt-targeted therapies [124, 125]. For example, c-Myc is a frequently overexpressed oncogene in various cancers. It plays a pivotal role in tumor progression, therapy resistance, and metastasis. Elevated c-Myc expression is often linked to poor prognosis [126, 127]. Moreover, c-Myc serves as a central regulator of glycolysis and tumorigenesis. In cancers such as cervical and colon, proteins like FAM83F and complement factor I (CFI) promote tumor growth by activating the Wnt/β-catenin/c-Myc signaling axis. As a biomarker, c-Myc is associated with aggressive tumor behavior and treatment resistance [128, 129]. In CRC, the c-MYC oncogene acts as a major driver of tumor progression, primarily regulated by the APC/β-catenin/Tcf-4 signaling axis. Under normal conditions, the APC tumor suppressor gene inhibits c-MYC expression; however, its inactivation leads to abnormal β-catenin accumulation, which complexes with Tcf-4 to enhance c-MYC transcription, promoting tumor growth [130]. In murine models, simultaneous deletion of APC and Myc rescued defects in differentiation, migration, proliferation, and apoptosis caused by APC loss, even in the presence of high nuclear β-catenin, indicating that Myc is a critical mediator of early tumorigenesis. Gene expression analysis further confirmed that Myc is essential for activating most Wnt target genes following APC inactivation [131]. Beyond Wnt signaling, Myc regulation is influenced by epigenetic mechanisms, including the E2F-6 complex, which binds Myc-responsive promoters

in quiescent cells through Mga, Max, and chromatin modifiers, contributing to gene silencing [132]. Similarly, in pancreatic and ovarian cancer, c-Myc and Cyclin D1 overexpression are frequently observed, reinforcing their role as indicators of Wnt pathway activation [133, 134].

Thus, c-Myc not only predicts Wnt signaling sensitivity but also plays a central role in tumorigenesis [135, 136]. As a key downstream effector in the canonical Wnt pathway, its activation follows stabilized β-catenin nuclear translocation. Within the nucleus, the resultant β-catenin/c-Myc complex orchestrates the regulation of genes pivotal for cell cycle progression [137, 138], proliferation [125, 139], and apoptosis [140, 141], thereby exerting influence over cellular fate. In fact, C-Myc dysregulation is common in various cancers, with its overexpression often correlating with tumor aggressiveness [142, 143]. Particularly within the context of Wnt signaling, c-Myc functions as a crucial downstream mediator, contributing to the proliferative and anti-apoptotic effects associated with the activation of aberrant signaling pathways [144]. Notably, the dysregulation of Wnt/c-Myc signaling holds particular importance in cancer [73].

Routine assessment of c-Myc expression in tissue samples using immunohistochemistry is standard in both laboratory and clinical settings [145]. Elevated c-Myc levels in tumor cells are a strong indicator of aggressive tumor behavior [146, 147], particularly in cases where Wnt pathway activation is involved [148, 149]. Given the critical interaction between Wnt signaling and c-Myc, targeting c-Myc as a therapeutic strategy holds significant potential [150, 151]. For example, in a recent study, targeting Myc with OMO-103 has shown promising early-phase clinical results in overcoming its long-standing "undruggable" status. A phase 1 trial in advanced solid tumors demonstrated a favorable safety profile, with the most common adverse events being mild infusion-related reactions. Pharmacokinetic analysis indicated nonlinearity and tissue saturation at higher doses, with a terminal serum half-life of 40 h. Among evaluable patients, 42% exhibited stable disease, and one patient achieved a 49% tumor volume reduction. Transcriptomic analysis confirmed MYC target engagement, and soluble factors were identified as potential pharmacodynamic markers. These findings support the advancement of OMO-103 to phase 2 trials at a recommended dose of 6.48 mg/kg [152]. However, the complexity of c-Myc's regulatory mechanisms and diverse functions poses significant challenges for therapeutic development. In clinical practice, evaluating c-Myc expressions in tumors is crucial, particularly in assessing Wnt signaling sensitivity. This not only informs therapeutic decisions but also provides molecular insights into tumor properties, facilitating the development of personalized treatment strategies.

**AXIN2**

AXIN2 is a core component of the destruction complex in the canonical Wnt/β-catenin signaling pathway, playing a critical role in regulating β-catenin degradation in the absence of Wnt ligands [153, 154]. It is a key negative regulator of the Wnt/β-catenin signaling pathway. Its downregulation is frequently linked to tumorigenesis, driving cancer progression and metastasis across various cancer types. It functions as a negative regulator of the Wnt/β-catenin pathway, where it assembles with APC, GSK-3β, and CK1 to facilitate β-catenin degradation, thereby ensuring proper signal regulation [153]. However, AXIN2 expression is frequently altered in various cancers, resulting in β-catenin stabilization, hyperactivation of Wnt signaling, and tumor progression. As a result, AXIN2 has emerged as a critical biomarker for predicting sensitivity to Wnt signaling [155].

Notably, AXIN2 itself is a transcriptional target of Wnt/β-catenin signaling. Upon Wnt pathway activation, the destruction complex is inhibited, allowing β-catenin to accumulate and translocate to the nucleus, where it activates the transcription of AXIN2. This creates a negative feedback loop to regulate β-catenin stability and prevent excessive signaling activity [153, 154]. However, in many cancer types, alterations in AXIN2, such as downregulation or genetic mutations, disrupt this regulatory mechanism, leading to sustained β-catenin accumulation and uncontrolled cell proliferation, migration, and metastasis [155]. Furthermore, alterations in the AXIN2 gene have been extensively reported across multiple cancer types, contributing to aberrant Wnt signaling activation and tumor progression. In CRC, AXIN2 mutations have been strongly associated with defective mismatch repair (MMR), resulting in β-catenin stabilization and subsequent activation of β-catenin/TCF signaling, ultimately driving tumor development [156]. Additionally, somatic hypermethylation of AXIN2, especially in serrated adenomas and MSI cancers, correlates with its reduced expression and may drive tumorigenesis by promoting a mutator phenotype [157]. Germline mutations in AXIN2 have been linked to familial predispositions for both oligodontia and CRC, further highlighting its role in cancer susceptibility [158]. Moreover, AXIN2 gene polymorphisms, such as rs2240308, have been associated with CRC risk, with some studies suggesting that its expression levels could serve as prognostic markers for patient outcomes [159]. In stage II CRC, methylation of AXIN2, when combined with other Wnt pathway target gene methylations, has been shown to predict recurrence and poor prognosis, particularly in microsatellite stable (MSS) cancers [160].

Similarly, in BC, AXIN2 variations have been identified as critical indicators of both risk and prognosis. Elevated

AXIN2 expression has been observed in patients with BC, suggesting its involvement in regulating β-catenin degradation through the destruction complex. However, AXIN2 downregulation correlates with persistent Wnt signaling activation, allowing β-catenin accumulation and favoring tumor proliferation and metastasis [155, 161]. Variants such as AXIN2 rs11079571 and rs3923087 have been associated with increased BC risk while rs2240308, rs7224837 and rs1133683 did not increase the risk [162, 163]. While AXIN2's potential as a biomarker is promising, the functional consequences of its genetic alterations and their precise role in BC development require further elucidation through larger, more diverse studies. Reduced AXIN2 expression leads to persistent Wnt signaling activation, contributing to over-active Wnt pathway and BC development [164, 165]. AXIN2 exhibits the highest co-relativity with SOX7 in the Wnt/β-catenin signaling pathway, indicating a potential co-regulatory mechanism. Moreover, AXIN2, together with SOX7, regulates key downstream targets, including Smad7, to modulate Wnt/β-catenin signaling, thereby influencing tumor progression [166]. Evaluating AXIN2 alterations serves as a biomarker, offering insight into the regulatory mechanisms of Wnt signaling and potential sensitivity to targeted therapy in BC.

Additionally, mutations in the AXIN2 gene have been linked to lung cancer [167]. Variations in AXIN2 have been found to predict the risk and prognosis of lung cancer [155, 168]. Deletion of AXIN2 leads to an overactive Wnt pathway, contributing to lung cancer development and progression [105, 106]. Assessing AXIN2 alterations serves as a biomarker, providing insight into the regulatory mechanisms of Wnt signaling and potential sensitivity to targeted therapy in lung cancer.

Similarly, alterations in the AXIN2 gene have been identified in pancreatic cancer [155, 169]. Reduced AXIN2 expression is linked to sustained activation of Wnt signaling [84, 85]. Assessing AXIN2 alterations serves as a biomarker, providing insight into the regulatory mechanisms of Wnt signaling and potential sensitivity to targeted therapy in pancreatic cancer. Furthermore, AXIN2 gene alterations in ovarian cancer lead to aberrant Wnt signaling activation, hyperactivity of β-catenin [86], and sustained pathway activation [153]. Reduced AXIN2 expression results in β-catenin accumulation, activating the Wnt signaling pathway [153]. As a result of its involvement in a destruction complex, AXIN2 degrades β-catenin in the absence of Wnt ligands. When AXIN2 expression is suppressed, β-catenin accumulates and activates the Wnt signaling pathway [86].

AXIN2 has also been identified in prostate cancer. Reduced AXIN2 expression is connected to sustained activation of Wnt signaling [170]. Reduced AXIN2 expression allows β-catenin accumulation, activating the Wnt signaling pathway [171]. Therefore, Assessing AXIN2 alterations serves as a biomarker, providing insight into the regulatory mechanisms of Wnt signaling and potential sensitivity to targeted therapy in prostate cancer. Furthermore, alterations in the AXIN2 gene have been detected in HCC [172, 173]. Reduced AXIN2 expression is linked to sustained activation of Wnt signaling [174]. Therefore, assessing AXIN2 alterations serves as a biomarker, providing insight into the regulatory mechanisms of Wnt signaling and potential sensitivity to targeted therapy in HCC.

The therapeutic implications of AXIN2 are noteworthy, suggesting a potential avenue for modulating Wnt signaling activity in cancer therapy [155, 175]. Such as a recent study reported that OSR1 acts as a tumor suppressor in oral squamous cell carcinoma (OSCC) by regulating the AXIN2/β-catenin signaling pathway. Overexpression of OSR1 inhibits OSCC cell proliferation and migration, while silencing OSR1 has the opposite effect, highlighting AXIN2 as a potential therapeutic target for modulating the Wnt/β-catenin pathway in cancer treatment [176]. However, strategies targeting AXIN2 levels or function are complex and require further investigation. From a clinical perspective, the evaluation of AXIN2 expression in tumors holds considerable importance [177, 178], particularly in cancers where the Wnt signaling pathway is implicated [179]. Such assessments not only contribute to diagnostic evaluations but also provide crucial information about the status of the Wnt signaling pathway, thereby influencing treatment decisions and guiding therapeutic strategies.

#### *Dickkopf-1 (Dkk-1)*

Dkk-1 is a secreted protein that inhibits Wnt signaling. It is a pivotal biomarker predicting Wnt signaling sensitivity, by acting as a Wnt pathway antagonist [180]. This secreted protein binds to the LRP5/6 coreceptor [181], inhibiting Wnt ligand binding and preventing pathway activation. By disrupting Wnt signaling, Dkk-1 blocks β-catenin stabilization and nuclear translocation [182].

Beyond its role as a Wnt pathway antagonist [183, 184], Dkk-1 has garnered attention due to its association with cancer [180, 185]. High Dkk-1 expression is often associated with poor prognosis in multiple myeloma and certain solid tumors [185, 186]. The overexpression of Dkk-1 contributes to the dysregulation of Wnt signaling, creating a conducive environment for tumor growth, invasion, and metastasis [184, 185]. For example, in HCC, DKK1 facilitates cell migration and invasion via a β-catenin/MMP7 axis independent of canonical Wnt signaling [187]. In CRC, high DKK1 levels are associated with oxaliplatin resistance, with

DKK1-mediated AKT activation contributing to chemoresistance [188]. Additionally, in gynecologic cancers, DKK1 overexpression correlates with poor patient outcomes. Targeting DKK1 with neutralizing antibodies, such as DKN-01, has shown promising clinical activity [189].

In BC, DKK1 has emerged as a key prognostic and predictive biomarker, playing a multifaceted role in cancer progression and therapeutic response. Elevated serum DKK1 levels have been strongly correlated with advanced tumor stages, higher histological grades, lymph node metastasis, and HER2 expression, making it an independent prognostic factor for overall survival (OS) and relapse-free survival (RFS) [190, 191]. Notably, in triple-negative BC (TNBC), DKK1 expression is particularly significant, as it correlates with cytoplasmic and nuclear β-catenin, indicating poor patient outcomes [192]. Additionally, DKK1 levels were found to decrease after neoadjuvant chemotherapy (NACT), with reduced expression predicting better therapy response, especially in TNBC cases [193]. Furthermore, DKK1, in conjunction with β-catenin, plays a pivotal role in the Wnt/β-catenin signaling pathway, and its elevated expression in early-stage disease or patients without lymph node metastasis can serve as a valuable prognostic marker [194]. DKK1, as an antagonistic ligand, prevents Wnt, FZD, and LRP6 interaction, degrading β-catenin and inactivating the β-catenin/TCF transcription complex. This leads to downregulation of TCF-regulated downstream genes [185]. In HER2-positive BC, overexpression of DKK1, induced by cortactin, contributes to trastuzumab resistance by activating the Wnt/β-catenin pathway, enhancing cancer stem cell-like properties, and promoting poor prognosis. Inhibition of β-catenin signaling has shown promise in overcoming this resistance [195]. Furthermore, PRMT5, an epigenetic regulator, silences DKK1 and other Wnt antagonists, such as DKK3, thereby promoting Wnt signaling and enhancing tumor cell proliferation in BC. PRMT5 inhibition restores the expression of DKK1 and DKK3, reducing Wnt/β-catenin activity and inducing cell death, offering a potential therapeutic strategy [196]. Additionally, in the context of chemotherapy, paclitaxel treatment upregulates DKK1 through EGFR signaling, which not only diminishes the therapeutic efficacy by suppressing CD8 + T cell infiltration but also contributes to chemotherapy-induced peripheral neuropathy. Targeting DKK1 with specific antibodies has shown potential in improving the antitumor effects of paclitaxel while alleviating neurotoxicity, making it a promising approach in BC treatment [196].

The evaluation of Dkk-1 levels in serum or tissue samples is of utmost importance in clinical practice due to its critical diagnostic and prognostic implications [197, 198]. Elevated Dkk-1 levels serve as an indicator of aberrant activation of the Wnt signaling pathway, providing valuable insights into the molecular properties of tumors [180]. Furthermore, Dkk-1 expression associates with disease progression stages and signifies poor prognosis across various types of cancer [181, 183]. For example, a recent study reported that overexpression of DKK1 has been observed in various cancers, including head and neck squamous cell carcinoma (HNSC), lung squamous cell carcinoma (LUSC), and pancreatic adenocarcinoma (PAAD), where it is associated with adverse outcomes such as shorter OS and DFS. Bioinformatics analysis suggests that DKK1 influences multiple signaling pathways, making it a potential biomarker for targeted therapy and prognosis in specific cancers, though its role in hematological malignancies remains unclear [199]. The inhibitory role of Dkk-1 in Wnt signaling presents notable therapeutic implications, with ongoing research exploring strategies to modulate Dkk-1 levels or activity [200]. Such interventions aim to restore normal Wnt signaling, potentially halting cancer progression driven by pathway dysregulation [185]. In particular, the promising role of DKK1 as a diagnostic, prognostic, and therapeutic biomarker in BC warrants further investigation, especially regarding its potential to enhance the efficacy of existing treatment regimens and improve patient outcomes. Therefore, the evaluation of Dkk-1 levels provides essential information for refining treatment strategies and predicting tumor responsiveness to Wnt-targeted therapies. The diverse roles of Dkk-1 in the complex interplay of Wnt signaling across various malignancies highlight its significance as a biomarker with diagnostic, prognostic, and therapeutic implications [201]. A better understanding of Dkk-1's involvement provides valuable insights into the molecular landscape of tumors, forming the basis for personalized and targeted therapeutic approaches.

#### *sFRP (Secreted Frizzled-Related Protein)*

sFRP is a Wnt signaling antagonist that plays a dual role in cancer by either suppressing tumor growth through Wnt inhibition or promoting cancer progression depending on the tumor context. As a secreted glycoprotein, sFRP mimics the Wnt-binding domain of the Frizzled receptor, adding complexity to the regulation of the canonical Wnt pathway and serving as a crucial biomarker for predicting Wnt signaling susceptibility. Functioning as a decoy receptor, sFRP competitively binds to Wnt ligands, preventing their interaction with Frizzled receptors on the cell surface [202]. This disruption of the Wnt signaling cascade inhibits β-catenin stabilization [203, 204], and its subsequent nuclear translocation [203].

The inhibition of Wnt signaling by sFRP is particularly significant in cancer. Dysregulation of sFRP expressions,

often characterized by downregulation, is commonly observed in various malignancies [205, 206]. For example, they are frequently silenced through CpG methylation in gastric cancer, esophageal basaloid squamous cell carcinoma (BSCC), and gliomas. This silencing contributes to aberrant activation of Wnt/β-catenin signaling. SFRPs, particularly SFRP1, SFRP2, and SFRP5, play a critical role in suppressing tumorigenesis. They achieve this by downregulating T-cell factor/lymphocyte enhancer factor transcriptional activity, repressing Wnt target genes, and inducing apoptosis. In gastric cancer, methylation-mediated silencing of SFRPs leads to Wnt signaling activation [207]. In BSCC, hypermethylation of SFRP2 is strongly associated with nuclear β-catenin accumulation and tumor progression [208]. In gliomas, SFRP2 downregulation is linked to tumor aggressiveness, poor prognosis, and radioresistance. Restoration of SFRP2 expression in gliomas has been shown to inhibit Wnt/β-catenin signaling and reduce cancer stemness [209]. This dysregulation contributes to the aberrant activation of Wnt signaling, creating a conducive environment for tumor initiation, progression, and metastasis [210]. In clinical practice, the evaluation of sFRP expression levels holds diagnostic and prognostic value [202, 211]. Reduced sFRP levels indicate heightened activity of the Wnt signaling pathway and may serve as an indicator of tumor aggressiveness. Measuring sFRP levels in serum or tissue samples provides valuable insight into tumor molecular profiles, aiding in diagnostic evaluations [212, 213]. The inhibitory role of sFRP in Wnt signaling presents potential therapeutic implications [202]. Ongoing research is actively exploring strategies to modulate sFRP levels or activity as a potential cancer treatment [214, 215]. These approaches aim to restore Wnt signaling balance and prevent cancer progression driven by pathway dysregulation.

In cancers where Wnt signaling plays a pivotal role, assessing sFRP expression is crucial. Evaluating sFRP levels helps tailor treatment strategies and predict tumor responsiveness to Wnt-targeted therapies [216]. This thorough understanding of sFRP's involvement contributes valuable insights into the molecular characteristics of tumors, paving the way for personalized and targeted therapeutic approaches in cancer biology [217].

#### *FRAT1 (Frequently rearranged in advanced T-cell lymphomas 1)*

Frat1 is a critical regulator of the Wnt/β-catenin signaling pathway, with emerging roles in cancer progression and potential as a biomarker. This protein stabilizes β-catenin by inhibiting GSK-3β-mediated phosphorylation, which prevents β-catenin degradation [218]. As a result, β-catenin accumulates and translocates to the nucleus, where it activates TCF/LEF transcription factors. These transcription factors drive the expression of pro-proliferative genes, promoting cell growth and survival [219]. Additionally, Frat1 interacts with Dishevelled (Dvl) and Axin to form a ternary complex, facilitating Wnt signal transduction by promoting the dissociation of GSK-3β from Axin. This molecular bridging role positions Frat1 as a key amplifier of canonical Wnt signaling [220].

Frat1's overexpression has been linked to various types of cancer, with significant evidence pointing to its role in glioma. In these tumors, Frat1 expression is significantly upregulated, correlating with higher grades. Elevated FRAT1 expression is associated with a more malignant phenotype, characterized by increased cell proliferation, enhanced invasiveness, and greater angiogenesis. For instance, in gliomas, the proliferative index, as measured by PCNA, is significantly higher in FRAT1-positive tumors (45.59%) compared to FRAT1-negative ones (14.03%). Similarly, the MMP-9 invasive index is much higher in FRAT1-positive tumors (36.72%) compared to their FRAT1-negative counterparts (11.49%), and microvessel density, which reflects angiogenesis, is also significantly elevated. Moreover, patients with FRAT1-positive glioblastomas exhibit poorer survival outcomes, with a 2-year survival rate of only 5.56%, compared to 40% in patients with FRAT1-negative tumors, and a shorter median survival (12 months versus 18 months) [221].

While much of the research has focused on gliomas, Frat1 is implicated in the progression of other cancers as well. Its role in activating the Wnt/β-catenin pathway makes it relevant in a wide range of malignancies. For example, in NSCLC, FRAT1 expression is associated with tumor differentiation, TNM stage, and lymph node metastasis, with higher levels contributing to reduced survival rates [222]. Mechanistic studies have shown that FRAT1 regulates cell proliferation, apoptosis, and invasiveness in NSCLC and GC through its interaction with Wnt/β-catenin pathway. In GC, FRAT1's overexpression promotes cell invasion, while silencing FRAT1 impairs proliferation and induces apoptosis. Additionally, FRAT1 is modulated by ncRNAs, including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), which act as regulators of its expression, further influencing cancer progression. The interplay between FRAT1 and molecules like miR-361-3p, miR-3648, and β-catenin underscores its complex regulatory network, positioning FRAT1 as both a prognostic biomarker and a potential therapeutic target in cancer treatment [223, 224].

In terms of diagnostic and prognostic utility, Frat1 shows promise as a biomarker. Its expression correlates strongly with important pathological features such as tumor grade, proliferation, invasiveness, and angiogenesis in gliomas. In fact, multivariate analysis has identified

FRAT1 as an independent prognostic factor for GBM, with a significant *P*-value ($P=0.005$) [221]. These findings suggest that Frat1 could serve as a valuable biomarker for predicting disease progression and patient outcomes. Preclinical studies also suggest that silencing FRAT1 reduces β-catenin levels and suppresses tumor growth, highlighting its potential as a therapeutic target. While direct clinical examples of therapeutic targeting are limited, silencing Frat1 could theoretically disrupt Wnt-driven oncogenesis by restoring GSK-3β activity.

Overall, Frat1 plays a crucial role in regulating Wnt signaling, with its overexpression linked to the progression of aggressive cancers, particularly gliomas. As both a prognostic biomarker and potential therapeutic target, Frat1 provides valuable insights into tumor biology and clinical outcomes. However, challenges remain in its clinical application, including the need for standardized assays, such as immunohistochemistry or RNA profiling, to reliably detect FRAT1 expression across various cancer types. Additionally, while therapeutic approaches targeting Frat1, such as small-molecule inhibitors or RNA-based therapies, show promise in reversing Wnt pathway hyperactivation and inhibiting tumor progression, they remain experimental. Further research is needed to confirm Frat1's clinical relevance, standardize detection methods, and develop effective targeted therapies.

#### *Porcupine (PORCN)*

PORCN is a gene encoding an enzyme that palmitoylates Wnt proteins, essential for their secretion and function in the Wnt signaling pathway. As a membrane-bound O-acyltransferase, PORCN serves as a key biomarker for predicting Wnt signaling susceptibility and plays a central role in the canonical pathway by modifying Wnt proteins [225, 226]. This lipid modification is crucial for the maturation and secretion of Wnt ligands, highlighting PORCN's key role in the processing of Wnt proteins [226]. The acylation process mediated by PORCN is particularly important for the canonical activation of Wnt signaling [227, 228]. Specifically, palmitoylation facilitates the proper binding of Wnt ligands to the cell membrane, ensuring their efficient release into the extracellular space [227, 229]. Once processed, Wnt ligands bind to the Frizzled receptor and LRP5/6 coreceptor, initiating canonical Wnt signaling [230, 231], and leading to β-catenin stabilization and nuclear translocation [230, 231].

The association between PORCN and cancer is increasingly evident, particularly in malignancies driven by aberrant Wnt signaling. For example, in HCC, higher PORCN expression is associated with poorer patient survival and promotes cell proliferation and migration by activating the Wnt/β-catenin pathway [232]. Similarly, inhibition of PORCN in oral dysplasia and OSCC models reduces Wnt secretion, leading to decreased nuclear β-catenin levels and reduced cell migration, viability, and invasion [233]. Dysregulation of PORCN, through mutations or altered expression, can disrupt Wnt ligand acylation, impairing canonical Wnt signaling activation. This dysregulation contributes to uncontrolled cell proliferation, evasion of apoptosis, and tumor progression. In clinical practice, evaluating the expression level of PORCN is important for both diagnosis and prognosis. Notably, changes in PORCN activity serve as indicators of Wnt signaling dysregulation, offering valuable insights into the molecular profile of tumors [225]. Additionally, PORCN expression levels may contribute to a better understanding of malignancy and aid in the prediction of prognosis for specific cancers.

The therapeutic potential of PORCN is significant due to its central role in Wnt signaling. PORCN has emerged as a promising therapeutic target, with inhibitors currently under investigation to modulate Wnt signaling in cancer therapy [234]. For example, in recent studies, a novel PORCN inhibitor, WHN-88, was developed with a unique di-iodinated pyridone structural fragment, distinguishing it from previously reported inhibitors. WHN-88 effectively blocks Wnt ligand palmitoylation, preventing their secretion and inhibiting the downstream Wnt/β-catenin signaling pathway. Preclinical evaluations showed that WHN-88 significantly suppressed tumor growth in both spontaneous and xenograft models of Wnt-driven cancers, including murine breast tumors and human teratocarcinoma, and pancreatic carcinoma. Moreover, WHN-88 inhibited cancer cell stemness, further highlighting its potential as a therapeutic agent [235]. Thus, inhibiting PORCN activity offers a promising strategy to attenuate Wnt signaling and impede tumor growth and progression [236]. In clinical settings, assessing PORCN expression is particularly relevant in cancers where Wnt signaling plays a pivotal role. Evaluating PORCN levels provides critical information for tailoring therapeutic strategies and predicting tumor responsiveness to Wnt-targeted interventions. A comprehensive understanding of PORCN's role in Wnt signaling enhances diagnostic and therapeutic approaches, offering new avenues for managing malignancies driven by this pathway.

#### *Glycogen synthase kinase-3β (GSK-3β)*

GSK-3β is a serine/threonine kinase that regulates various cellular processes, such as glycogen synthesis, cell differentiation, and signal transduction. It is a pivotal biomarker for predicting Wnt signaling sensitivity and

playing a central role in the destruction complex of the canonical Wnt pathway [237, 238], which includes GSK-3β, APC, Axin, and CK1 [239]. The phosphorylation of β-catenin is coordinated by this complex, indicating it for ubiquitin-mediated destruction and inhibiting its cytoplasmic accumulation.

The regulation of canonical Wnt signaling relies on the dynamic interaction between GSK-3β and the destruction complex. Under normal conditions, GSK-3β phosphorylates β-catenin in the absence of Wnt, ensuring its destruction. However, upon Wnt activation, the destruction complex is inhibited, allowing β-catenin to accumulate in the cytoplasm and translocate to the nucleus [237, 240]. In the nucleus, β-catenin interacts with TCF/LEF transcription factors to initiate the transcription of Wnt target genes, which influence various cellular processes.

The importance of GSK-3β in cancer is underscored by its critical role in various tumor-related processes. Specifically, inactivating mutations or altered expressions of GSK-3β can disrupt the balance, resulting in the stabilization and accumulation of β-catenin. This phenomenon promotes uncontrolled cell proliferation, survival, and contributes to tumor progression [241, 242]. For example, in glioblastoma, the upregulation of spindle and kinetochore-related complex subunit 3 (SKA3) enhances Wnt/β-catenin signaling through the Akt/GSK-3β axis, promoting tumor growth and invasion [243]. Similarly, in BC, Ras-GTPase Activating SH3 Domain-Binding Protein 1 (G3BP1) stabilizes β-catenin by inhibiting its phosphorylation and degradation via GSK-3β, thereby stimulating cancer cell proliferation [244]. The diagnostic and prognostic utility of GSK-3β is evident in clinical practice. Changes in GSK-3β activity serve as an indicator of Wnt signaling dysregulation, offering valuable insight into the molecular profile of tumors. Furthermore, GSK-3β expression levels may contribute to understanding tumor malignancy and predicting the prognosis of certain cancers [245, 246]. For example, GSK-3β has emerged as a significant prognostic biomarker in cancers, including HCC, SCC of the tongue, CRC, and ovarian cancer. In HCC, reduced GSK-3β expression correlates with advanced stages and poor prognosis, suggesting its potential as a prognostic marker for clinical outcomes [247]. Similarly, in SCC, the inverse relationship between GSK-3β and cyclin D1 expression highlights its role in regulating tumor progression, with reduced GSK-3β expression linked to lower survival rates [248]. In CRC, high GSK-3β expression, particularly the β isoform, is associated with tumor budding and PD-L1 expression, contributing to worse prognosis, while GSK-3β inhibition shows promising therapeutic potential [249]. Additionally, in ovarian cancer, high GSK-3β expression is correlated with chemotherapy resistance and poorer survival, further supporting its role in cancer progression and treatment response [250].

GSK-3β has emerged as a promising therapeutic target due to its central role in Wnt signaling. Currently, inhibitors of GSK-3β are actively investigated as potential interventions to modulate Wnt signaling activity in cancer therapy. By inhibiting GSK-3β, β-catenin stabilizes, activating Wnt target genes, which may help impede the proliferation and progression of Wnt-driven cancers. From clinical considerations, the assessment of GSK-3β expression is particularly relevant in cancers where Wnt signaling plays a crucial role. Ultimately, evaluating GSK-3β levels provides important information to adjust therapeutic strategies and predict tumor response to interventions targeting the Wnt signaling pathway. A deeper understanding of GSK-3β's role enhances diagnostic and therapeutic approaches, offering new insights into the complex landscape of Wnt signaling in malignancies.

#### *LEF/TCF transcription factors*

LEF/TCF are transcription factors that mediate Wnt/β-catenin signaling, regulating gene expression critical for cell fate, proliferation, and differentiation. LEF/TCF acts as a pivotal biomarker to predict Wnt signaling sensitivity [251], serving as nuclear effectors downstream in the canonical Wnt pathway [252, 253]. Upon activation by Wnt ligand binding to Frizzled and LRP5/6, LEF/TCF inhibits the destruction complex [230], resulting in β-catenin stabilization and nuclear translocation [254].

The dysregulation of LEF/TCF transcription factors is frequently associated with various cancer processes, including metastasis, resistance to therapy, and tumor progression. For example, in CRC, hotspot mutations in SMAD4 enhance Wnt signaling through LEF1, leading to increased Wnt pathway activation and possibly heightened sensitivity to Wnt inhibitors [255]. In BC, LEF1 serves as a key biomarker of Wnt signaling activity, with its overexpression linked to tumorigenesis, immune cell infiltration, and poor prognosis [256]. Notably, LEF1 overexpression negatively correlates with HER2/neu status, defining a distinct subset of BCs and facilitating tumor invasion in both human and murine models [257]. Functional studies indicate that LEF1 enhances drug resistance, particularly to docetaxel, where its inhibition resensitizes tumor cells and downregulates resistance-related genes [258]. Furthermore, LEF1 modulates the glutathione system, strengthening antioxidative capacity and conferring resistance to therapeutic glutathione depletion, especially in brain metastases [259]. In lung adenocarcinoma, hyperactivation of the Wnt/TCF pathway facilitates metastasis to distant organs like the brain and bone, with LEF1 and HOXB9 mediating chemotactic invasion and colony outgrowth [260]. Additionally, in

endothelial cells, LEF1 promotes MMP2 expression and cell invasion in response to Wnt3a, linking Wnt signaling to angiogenesis [261]. Furthermore, in HCC, LEF1 upregulation contributes to acquired resistance to lenvatinib by enhancing EMT, migration, and invasion, thus highlighting LEF1 as a potential therapeutic target to overcome drug resistance [262].

The assessment of LEF/TCF transcription factors is crucial for diagnosis and prognosis. Alterations in their activity act as markers of disrupted Wnt signaling, providing valuable information about the molecular characteristics of tumors. Additionally, expression levels of LEF/TCF may contribute to understanding tumor malignancy and predicting the prognosis of specific cancers. Due to their central role in Wnt signaling, LEF/TCF transcription factors have emerged as potential therapeutic targets. Ongoing research endeavors to modulate their activity or disrupt their interaction with β-catenin, aiming to intervene in the aberrant cellular processes driven by abnormal Wnt signaling in cancer [263]. For example, research show that TCF7L2, a key member of the TCF/LEF family, forms intrinsically disordered region (IDR)-dependent condensates with β-catenin, which are essential for mediating transcription both in vitro and in vivo [264].

In clinical settings, evaluating LEF/TCF levels and activity is particularly important in cancers heavily reliant on Wnt signaling [265, 266]. This assessment provides crucial information for tailoring therapeutic strategies and predicting tumor responses to interventions targeting the Wnt signaling pathway [267, 268].

#### *Microsatellite instability (MSI)*

MSI stands out as a pivotal biomarker, playing a crucial role in predicting Wnt signaling sensitivity [269, 270]. Microsatellites, characterized by short tandem repeats in DNA, undergo alterations in length due to defects in the DNA mismatch repair (MMR) system, leading to MSI [271]. MSI has significant implications, as it is closely linked to dysregulation of the Wnt signaling pathway. Mutations in critical Wnt components often coincide with MSI in tumors [271, 272].

The relationship between MSI and dysregulated Wnt signaling has been extensively explored in several cancer types, including colorectal, lung, pancreatic, ovarian, prostate, and HCC. For example, in CRC, MSI is often accompanied by hypermethylation of secreted SFRP1, a potent Wnt antagonist, leading to sustained activation of Wnt signaling [273]. Reduced SFRP1 expression in MSI-high (MSI-H) tumors promotes β-catenin stabilization and nuclear translocation, subsequently driving tumor progression [274]. Additionally, MSI-high tumors exhibit a high rate of DNA replication errors, leading to genomic instability and activation of the DNA damage response (DDR). One key player in this response is ataxia-telangiectasia mutated interactor (ATMIN), whose reduced expression in MSI-high CRC correlates with advanced disease stages, deeper invasion, and increased lymph node metastasis. Functional studies have shown that reduced ATMIN expression enhances cell motility and invasion, thereby driving tumor aggressiveness. Further molecular analysis has revealed that ATMIN modulates the Wnt signaling pathway via interaction with PARP1, influencing β-catenin/TCF4 binding affinity and promoting metastasis. Inhibition of PARP1 has been shown to significantly reduce metastasis in ATMIN-depleted cancer cells, suggesting that targeting the ATMIN-PARP1 axis could serve as a promising therapeutic approach [275].

MSI has emerged as a valuable tool in clinical diagnostics, particularly for identifying lynch syndrome, a genetic disorder predisposing individuals to colon cancer [276, 277]. Lynch syndrome is characterized by germline mutations in MMR genes, resulting in MSI. Diagnostic approaches typically involve polymerase chain reaction analysis of microsatellite loci, enabling the identification of tumors exhibiting MSI [278].

Beyond CRC, MSI has also been correlated with dysregulated Wnt signaling in several other malignancies. In lung cancer, MSI-H tumors often demonstrate SFRP1 promoter hypermethylation, which results in decreased SFRP1 protein expression and prolonged Wnt signaling activation. This molecular alteration drives tumor progression and enhances cell proliferation. MSI status has thus been proposed as a potential biomarker in lung cancer, predicting patient susceptibility to Wnt-targeted therapies [279, 280]. Similarly, in pancreatic cancer, MSI-H tumors exhibit increased hypermethylation of the SFRP1 gene, suppressing its expression and allowing persistent activation of Wnt signaling [281, 282]. The identification of MSI in pancreatic cancer provides a critical opportunity for designing targeted therapeutic interventions by exploiting Wnt signaling sensitivity in MSI-H patients.

In ovarian cancer, MSI is frequently associated with reduced SFRP1 expression through epigenetic silencing, resulting in aberrant Wnt signaling activation [283]. Studies have reported that MSI-H ovarian tumors often demonstrate abnormal SFRP1 promoter hypermethylation, contributing to increased β-catenin activation and promoting tumor progression [284]. Consequently, MSI status has become a valuable biomarker in ovarian cancer, aiding in the identification of patients who may benefit from Wnt-targeted therapies. Moreover, emerging evidence has shown that MSI-H/dMMR (deficient mismatch repair) ovarian cancer patients respond favorably

to immune checkpoint inhibitors, with MSI serving as a molecular marker for immune sensitivity and improved patient outcomes [285].

Similarly, in prostate cancer, MSI status has been implicated in the dysregulation of Wnt signaling. MSI-H prostate tumors often display epigenetic silencing of SFRP1 through promoter hypermethylation, which facilitates sustained β-catenin activation. This persistent activation of Wnt signaling accelerates tumor growth and metastasis in MSI-H prostate cancer. Furthermore, MSI-H tumors have demonstrated favorable responses to immune checkpoint inhibitors, positioning MSI as a potential biomarker for both Wnt-targeted and immunotherapy approaches in prostate cancer [286].

In HCC, the correlation between MSI and Wnt signaling dysregulation has also been observed, although MSI occurrence in HCC is relatively low [287]. In MSI-H HCC, SFRP1 promoter hypermethylation leads to decreased SFRP1 expression, allowing for sustained activation of the Wnt signaling pathway [288]. This promotes uncontrolled cell proliferation and tumor progression. Despite its low prevalence, MSI status in HCC remains a potential biomarker for predicting response to Wnt-targeted and immune checkpoint therapies. However, further clinical validation is required to optimize its application in HCC treatment strategies [287, 289].

Beyond its diagnostic utility, the prognostic impact of MSI in cancer is noteworthy [290]. Tumors manifesting MSI exhibit distinct clinicopathological features and are linked with improved overall survival. The prognostic impact of MSI extends to other malignancies, though its effects vary depending on the tumor type [276, 291]. The therapeutic landscape is also significantly influenced by the presence of MSI, particularly in the context of immunotherapy. Tumors characterized by MSI-high status display heightened responsiveness to immune checkpoint inhibitors like pembrolizumab, targeting the programmed cell death protein 1 (PD-1) signaling pathway [292, 293]. The success of immunotherapy in MSI-high tumors highlights the therapeutic importance of understanding the molecular characteristics linked to Wnt signaling sensitivity.

### Role of ncRNAs in Wnt signaling

Non-coding RNAs, including miRNAs, lncRNAs, and circular RNAs (circRNAs), have emerged as important regulators of the Wnt signaling pathway. Their involvement in the regulation of Wnt components offers potential therapeutic avenues for cancer treatment.

#### MicroRNAs (miRNAs) in Wnt signaling

miRNAs are small, non-coding RNAs that primarily function by binding to the 3' untranslated regions (UTRs) of target mRNAs, leading to their degradation or translational repression. In the context of Wnt signaling, miRNAs can modulate the expression of key Wnt ligands, receptors, and downstream components (Table 2). Certain miRNAs target the Wnt ligands, thus affecting the activation of the pathway. For example, in hepatocellular carcinoma (HCC), miR-148a and miR-148b emerged as significant modulators. miR-148a expression is inversely correlated with the differentiation status of HCC, and its overexpression inhibits EMT and cancer stem cell (CSC)-like properties in HCC cells by targeting the Wnt signaling pathway. This regulation suggests that miR-148a suppresses HCC metastasis by modulating the Wnt1/β-catenin axis [294]. Similarly, miR-148b, often downregulated in HCC, functions as a tumor suppressor by regulating the WNT1/β-catenin signaling pathway, inhibiting cell proliferation, invasion, and promoting apoptosis [295]. Additionally, miRNAs can regulate the stability of β-catenin. For example, miR-146a and miR-1 exhibit opposing roles in regulating β-catenin levels, contributing to the fine-tuning of β-catenin signaling. miR-146a stabilizes β-catenin by promoting its accumulation in a dose-dependent manner, whereas inhibition of miR-146a activity results in β-catenin degradation [296]. In contrast, miR-1 facilitates the assembly of the β-catenin degradation complex, leading to a reduction in β-catenin protein levels and enhanced degradation [297]. These distinct regulatory mechanisms highlight the complex interplay of miRNAs in modulating β-catenin signaling, which is critical in various cellular processes, including cancer progression. By targeting β-catenin or its regulatory proteins, miRNAs maintain the balance of β-catenin levels in the cytoplasm, thereby controlling its nuclear translocation and subsequent transcription of target genes involved in cell proliferation and survival. The dysregulation of miRNAs in cancer can lead to aberrant activation of the Wnt pathway, contributing to uncontrolled cell growth, differentiation defects, and oncogenesis.

#### Long non-coding RNAs (lncRNAs) in Wnt signaling

lncRNAs are typically defined as transcripts longer than 200 nucleotides that do not code for proteins. They play crucial roles in regulating gene expression at various levels. This includes chromatin remodeling, transcription, and post-transcriptional regulation. In the Wnt signaling pathway, lncRNAs can interact with pathway components to modulate their activity (Table 3). Some lncRNAs can influence the stability and activity of key proteins in the Wnt pathways. For example, lncRNAs like FAST can enhance β-catenin stability,

**Table 2** miRNAs targeting Wnt signaling components and their roles in cancer

| miRNA | Target(s) in Wnt Signaling | Function in Cancer | Reference |
|---|---|---|---|
| miR-200 family | β-catenin | Suppresses Wnt activation, inhibits EMT and metastasis | Meningioma, hepatocellular carcinoma, gastric [361] |
| miR-122 | Wnt1 | Inhibits Wnt pathway, suppresses cell proliferation, promotes apoptosis | Hepatocellular carcinoma [362] |
| miR-148a | Wnt1 | Blocks metastasis by suppressing EMT and cancer stem cell-like properties | Hepatocellular carcinoma [294] |
| miR-181a | WIF-1 | Promotes tumor growth and liver metastasis | Colorectal cancer [363] |
| miR-522 | DKK1, SFRP2 | Promotes cell proliferation by activating Wnt signaling | Hepatocellular carcinoma [364] |
| miR-374a | WIF1, WNT5A | Activates Wnt/β-catenin signaling | Breast cancer, Lung cancer [365, 366] |
| miR-29a | DKK1, Kremen2, sFRP2 | Induces resistance to gemcitabine | Pancreatic cancer [367] |
| miR-92b | DKK3,NLK | Activates Wnt/β-catenin signaling | Glioma [368-396] |
| miR-185-3p | WNT2B | Enhances NPC radioresistance by modulating WNT2B | Nasopharyngeal carcinoma [370] |
| miR-324-3p | WNT2B | Contributes to the radioresistance of NPC by regulating the WNT2B signaling pathway | Nasopharyngeal carcinoma [371] |
| miR-26a | Wnt5a | Inhibits prostate cancer progression | Prostate cancer [372] |
| miR-487b | WNT5A | It suppresses Wnt signaling, inhibiting lung cancer growth, invasion, and metastasis | Lung cancer [373] |
| miR-329, miR-410 | WNT7B | miR-329/miR-410 loss drives OSCC proliferation and invasion via Wnt-7b | Oral squamous cell carcinoma [374] |
| miR-374b | WNT16 | miR-374b inhibits T-LBL growth and induces apoptosis via Wnt-16 repression | Lymphoblastic lymphoma [375] |
| miR-203 | FZD2 | miR-203 downregulateFZD2 mRNA and protein expression | Lung cancer [376] |
| miR-493 | FZD4 | miR-493 inhibits bladder cancer migration via RhoC and FZD4 downregulation | Bladder cancer [377] |
| miR-23a/b | FZD5, FZD7 | miR-23a/b promotes metastasis by targeting FZD5, FZD7, disrupting Wnt signaling and cell adhesion | Pancreatic cancer, Colon cancer [378, 379] |
| miR-613 | FZD7 | Represses prostate cancer cell proliferation and invasion through targeting FZD7 | Prostate cancer [380] |
| miR-1 | FZD7 | Suppresses breast cancer stem cell proliferation and migration by inhibiting the Wnt/β-catenin pathway | Breast cancer [381] |
| miR-27b | FZD7 | Inhibits Helicobacter pylori-induced gastric tumorigenesis by downregulating Frizzled7 | Gastric cancer [382] |
| miR-100 | FZD8 | Inhibits breast cancer cell migration and invasion by targeting FZD-8 and suppressing Wnt/β-catenin signaling | Breast cancer [383] |
| miR-513c | LRP6 | Inhibits glioblastoma proliferation by repressing LRP6 | Glioblastoma [384] |
| miR-610 | LRP6 | miR-610 downregulation drives hepatocellular carcinoma growth via Wnt/β-catenin activation | Hepatocellular carcinoma [385] |
| miR-603 | WIF1, CTNNBIP1 | miR-603 drives glioma growth by activating Wnt/β-catenin via WIF1 and CTNNBIP1 suppression | Glioma [386] |
| miR-1260b | sFRP1, DKK2 | Genistein inhibits Wnt signaling in renal cancer cells by downregulating onco-miR-1260b | Renal cancer [387] |
| miR-328 | sFRP1 | miR-328 enhances glioma invasion by activating Wnt signaling through SFRP1 suppression | Glioma [388] |
| miR-372/373 | DKK1 | β-Catenin/LEF1 activates the miR-371–373 cluster, regulating the Wnt/β-catenin signaling pathway | CRC, Breast Cancer [389] |
| miR-3127-5p | FZD4 | miR-3127-5p downregulation promotes EMT by regulating FZD4 and activating Wnt/β-catenin signaling in NSCLC | Non-small-cell lung cancer [390] |

**Table 2** (continued)

| miRNA | Target(s) in Wnt Signaling | Function in Cancer | Reference |
|---|---|---|---|
| miR-490-3p | FRAT1 | Epigenetic silencing of miR-490-3p drives aggressive colorectal cancer by activating Wnt/β-catenin signaling | Colorectal cancer [391] |
| miR-34b/c | β-catenin | FOXO3a regulates WNT/β-catenin signaling and inhibits epithelial-to-mesenchymal transition in prostate cancer cells | Prostate cancer [392] |
| miR-34a | LEF1 | miR-34a suppresses prostate cancer invasion by targeting LEF1 and inhibiting EMT | Prostate cancer [393] |
| miR-504 | FZD7 | miR-504 inhibits glioblastoma mesenchymal phenotype by targeting FZD7 and suppressing Wnt/β-catenin signaling | Glioblastoma [394] |
| miR-876-5p | Wnt5A | miR-876-5p inhibits gastric cancer proliferation, migration, and promotes apoptosis by targeting WNT5A and MITF | Gastric cancer [395] |
| miR-370-3p | Wnt7a | miR-370-3p suppresses Wnt7a, inhibiting canonical Wnt signaling and bladder cancer cell invasion | Bladder cancer [396] |
| miR-627-5p | Wnt2 | microRNA-627-5p suppresses colorectal cancer growth, migration, and invasion by targeting Wnt2 | Colorectal cancer [397] |
| miR-204-5p | Wnt11 | HD–SB inhibits colorectal cancer progression by suppressing the hsa_circ_0039933/miR-204-5p/Wnt11 axis, blocking Wnt signaling | Colorectal cancer [398] |
| hsa-miR-374a-3p | Wnt3 | Yiqi Jianpi Huayu Jiedu Decoction suppresses colon adenocarcinoma metastasis by reversing the hsa-miR-374a-3p/Wnt3/β-catenin pathway, inhibiting epithelial-mesenchymal transition and cellular plasticity | Colon adenocarcinoma [399] |
| miRNA-503 | WNT3A | Tumor suppressor miRNA-503 reduces cell invasion in head and neck cancer by targeting the WNT3A/MMP axis, suppressing the Wnt signaling pathway | Head and neck cancer [400] |
| miR-4757-3p | Wnt5a/Wnt8b | miR-4757-3p inhibits lung cancer progression by targeting Wnt5a/Wnt8b and suppressing the Wnt/β-catenin pathway | lung cancer [401] |
| miR-4723 | Wnt7A | CAV2 promotes pancreatic cancer proliferation, invasion, and metastasis by regulating the miR-4723/Wnt7A axis through endocytosis and epithelial-mesenchymal transition | pancreatic cancer [402] |
| miR-98-5p | FZD3 | In silico analysis suggests miR-98-5p inhibits colorectal cancer proliferation and metastasis by targeting FZD3 in the Wnt signaling pathway | Colorectal cancer [403] |
| miR-375 | FZD4 | Folate deficiency drives cervical squamous carcinoma progression in SiHa cells by activating the miR-375/FZD4/β-catenin signaling pathway | Cervical squamous carcinoma [404] |
| miR-548b-5p | FZD7 | miR-548b-5p inhibits gastric carcinoma cell migration and invasion by downregulating FZD7 | Gastric carcinoma [405] |

thereby activating the canonical Wnt pathway [298]. Furthermore, lncRNAs can interact with key transcription factors and epigenetic regulators, influencing the expression of genes downstream of Wnt signaling. For example, the lncRNA HOTAIR has been shown to interact with polycomb group proteins to regulate the expression of Wnt pathway components, thereby influencing cellular processes like differentiation and proliferation [299]. Aberrant expression of lncRNAs in cancer cells can disrupt the normal regulation of the Wnt pathway, contributing to tumorigenesis, metastasis, and resistance to therapies. For example, high HOTAIR expression is associated with poor prognosis and drug resistance in lung cancer by regulating Wnt pathway [300].

**Table 3** lncRNAs targeting Wnt signaling components and their roles in cancer

| lncRNA | Target(s) in Wnt Signaling | Function in Cancer | Reference |
|---|---|---|---|
| BCAR4 | β-catenin | LncRNA BCAR4 drives colon cancer progression by activating the Wnt/β-catenin signaling pathway | Colon cancer [406] |
| HAGLR | WNT2 | LncRNA-HAGLR promotes triple-negative breast cancer progression by sponging miR-335-3p to upregulate WNT2 | Triple-negative breast cancer [407] |
| RPPH1 | WNT2 | LncRNA RPPH1 drives non-small cell lung cancer progression by regulating the miR-326/WNT2B axis | Non-small cell lung cancer [408] |
| ASB16-AS1 | Wnt2 | ASB16-AS1 promotes cervical cancer cell proliferation, migration, and invasion by acting as a ceRNA to regulate the miR-1305/Wnt/β-catenin axis | Cervical cancer [409] |
| Linc01224 | Wnt2 | LINC01224 promotes endometrial cancer progression by regulating the miR-4673/TPX2 axis and activating the Wnt/β-catenin signaling pathway | Endometrial cancer [410] |
| HCP5 | Wnt5a | HCP5 promotes gastric cancer cell proliferation, invasion, and epithelial-mesenchymal transition (EMT) by regulating the miR-186-5p/WNT5A axis under hypoxic conditions | Gastric cancer [411] |
| H19 | Wnt5a | H19 drives glioma cell proliferation, migration, and angiogenesis by targeting miR-342 to activate the Wnt5a/β-catenin pathway | Glioma [412] |
| H19 | β-catenin | H19 drives epithelial-mesenchymal transition (EMT) and metastasis in gastric cancer by activating Wnt/β-catenin signaling | gastric cancer [413] |
| FGD5-AS1 | Wnt5a | FGD5-AS1 enhances doxorubicin resistance in osteosarcoma by promoting autophagy through the miR-154-5p/WNT5A axis | Osteosarcoma [414] |
| MSC-AS1 | Wnt5a | MSC-AS1 promotes kidney renal clear cell carcinoma progression by activating the Wnt/β-catenin pathway via the miR-3924/WNT5A axis | Kidney renal clear cell carcinoma [415] |
| ACTA2-AS1 | Wnt5a | Knockdown of lncRNA ACTA2-AS1 overcomes cisplatin resistance in ovarian cancer by inhibiting the miR-378a-3p/Wnt5a axis | Ovarian cancer [416] |
| FAM230B | WNT5A | FAM230B drives papillary thyroid cancer metastasis by sponging miR-378a-3p to upregulate WNT5A | Thyroid cancer [417] |
| PVT1 | Wnt6 | PVT1 promotes colon cancer proliferation and migration by regulating miR-1207-5p to activate the Wnt6/β-catenin2 pathway | Colon cancer [418] |
| CTBP1-AS2 | Wnt7a | CTBP1-AS2 drives glioma proliferation and migration by regulating the miR-370-3p/Wnt7a axis to induce epithelial-mesenchymal transition (EMT) | Glioma [419] |
| CASC15 | WNT7A | CASC15 enhances papillary thyroid carcinoma cell proliferation by modulating the miR-7151–5p/WNT7A axis | thyroid carcinoma [420] |
| HOTAIRM1 | Wnt10b | HOTAIRM1 promotes thyroid cancer cell proliferation and metastasis by targeting Wnt10b | Thyroid cancer [421] |
| LINC00355:8 | Wnt10b | LINC00355:8 promotes cell growth, migration, and invasion in hepatocellular carcinoma through the MiR-6777-3p/Wnt10b pathway | Hepatocellular carcinoma [422] |
| lincROR | WNT2B/WNT10A | LincROR enhances colorectal cancer tumor growth by modulating the miR-145/WNT2B/WNT10A/Wnt/β-catenin axis | Colorectal cancer [423] |
| HOXC13-AS | FZD6 | FTO-stabilized lncRNA HOXC13-AS epigenetically upregulates FZD6, activating Wnt/β-catenin signaling to promote cervical cancer proliferation, invasion, and EMT | Cervical cancer [424] |
| HOTAIR | FZD7 | HOTAIR drives breast cancer progression by modulating the miR-129-5p/FZD7 axis | Breast cancer [425] |
| CBR3-AS1 | β-catenin | CBR3-AS1 enhances lung adenocarcinoma cell proliferation, migration, and invasion by activating the Wnt/β-catenin signaling pathway | Lung adenocarcinoma [426] |
| SNHG11 | β-catenin | SNHG11 drives gastric cancer progression by activating the Wnt/β-catenin pathway and promoting oncogenic autophagy | gastric cancer [427] |
| FLVCR1-AS1 | CTNNB1 | FLVCR1-AS1 promotes breast cancer proliferation, migration, and Wnt/β-catenin signaling via the miR-381-3p/CTNNB1 axis | breast cancer [428] |
| SNHG10 | FZD3 | SNHG10 drives osteosarcoma proliferation and invasion by activating Wnt/β-catenin signaling | Osteosarcoma [429] |

**Table 3** (continued)

| lncRNA | Target(s) in Wnt Signaling | Function in Cancer | Reference |
|---|---|---|---|
| FAM83H-AS1 | β-catenin | FAM83H-AS1 drives pancreatic ductal adenocarcinoma progression by stabilizing FAM83H mRNA, protecting β-catenin from degradation | Pancreatic ductal adenocarcinoma [430] |
| RBM5-AS1 | β-catenin | LncRNA RBM5-AS1 promotes breast cancer tumorigenesis by activating Wnt/β-catenin signaling | Breast cancer [431] |
| GAS5 | AXIN2/GSK3β | GAS5 suppresses bladder cancer cell proliferation and migration by regulating the miR-18a-5p/AXIN2/GSK3β axis to inhibit Wnt/β-catenin signaling | Bladder cancer [432] |

### Circular RNAs (circRNAs) in Wnt signaling

CircRNAs are a unique class of ncRNAs characterized by their covalently closed loop structure. These RNAs are known to function primarily as competing endogenous RNAs (ceRNAs), which sequester miRNAs, thereby preventing them from repressing their target mRNAs. circRNAs can modulate Wnt signaling by sequestering miRNAs that target Wnt components. In cancer, such mechanisms can lead to the aberration of the Wnt pathway, promoting tumorigenesis, stemness, and chemoresistance (Table 4). For example, multiple studies have demonstrated that circRNAs function as ceRNAs, sponging specific miRNAs to regulate tumor suppressor or oncogenic targets. For instance, hsa_circ_0009361 act as tumor suppressors by sponging miR-582, leading to the upregulation of APC2, thereby suppressing CRC progression [301]. Conversely, circRNA_100290 promotes CRC by sponging miR-516b to upregulate FZD4, resulting in the activation of Wnt/β-catenin signaling and enhanced tumor growth and metastasis [302]. These findings highlight the diverse roles of circRNAs in CRC pathogenesis and suggest that targeting circRNA-mediated regulatory networks could offer novel therapeutic strategies for CRC treatment. Additionally, circRNAs can influence the expression of stem cell markers and other regulators of stem cell biology, further underscoring their role in both cancer and normal development.

### Importance of predicting Wnt signaling sensitivity

Predicting Wnt signaling sensitivity in cancer is essential for advancing personalized treatment strategies. Tumors with heightened Wnt pathway activity often exhibit increased cell proliferation, resistance to apoptosis, and enhanced stem cell-like properties, contributing to poor prognosis and therapy resistance. By identifying patients whose tumors are particularly sensitive or resistant to Wnt signaling, clinicians can tailor more effective treatments, such as Wnt pathway inhibitors or combinatory therapies. This approach holds promise for improving therapeutic outcomes and reducing the risk of relapses in cancer patients.

#### *Personalized and targeted therapy in oncology*

Predicting and understanding the sensitivity of cancer to Wnt signaling is crucial for advancing personalized and targeted therapy in oncology. The central role of this pathway in tumorigenesis underscores the importance of understanding Wnt signaling sensitivity [303]. The aberrant activation of Wnt signaling in several cancers underscores the need for a personalized treatment approach, highlighting the importance of predicting individual variations in pathway responsiveness [304].

Advancements in biomarkers for predicting Wnt signaling sensitivity form the foundation of personalized therapy approaches. Mutations in APC and β-catenin are diagnostic biomarkers for various cancers [102, 305], affecting Wnt/β-catenin signaling [60, 306]; profiling target gene expression helps stratify patients for Wnt-targeted therapies [307]. This involves identifying Wnt targets through gene expression profiling or other genomic approaches.

The ability to predict Wnt signaling sensitivity paves the way for personalized therapy approaches tailored to individual patients. This customized strategy maximizes treatment efficacy, aligning seamlessly with the principles of precision medicine in oncology. Moreover, the ability to predict Wnt signaling sensitivity drives the development of targeted therapies. By understanding individual variations in pathway responsiveness, researchers can develop therapeutic agents that specifically target dysregulated components of the Wnt signaling pathway [267]. This targeted therapeutic approach holds immense potential for enhancing treatment efficacy while minimizing off-target effects, thereby optimizing the safety profile of anticancer treatments.

#### *Benefits of Wnt signaling-targeted therapy*

Predicting and assessing cancer sensitivity to Wnt signaling represents a significant advancement in personalized and targeted therapy. This capability allows clinicians to tailor treatment strategies to the unique molecular profiles of individual patients. Supporting this, a recent study highlights how m6A-dependent translational suppression of Wnt signaling enhances sensitivity to tyrosine kinase

**Table 4** circRNAs targeting Wnt signaling components and their roles in cancer

| circRNA | Target(s) in Wnt Signaling | Function in Cancer | Reference |
|---|---|---|---|
| circEIF4G3 | β-catenin | EIF4G3 inhibits gastric cancer progression by suppressing β-catenin through δ-catenin ubiquitin degradation and upregulating SIK1 | Gastric cancer [433] |
| circRNA_0067934 | β-catenin | circRNA_0067934 promotes glioma progression by modulating the miR-7/Wnt/β-catenin axis | Glioma [434] |
| MTCL1 | β-catenin | MTCL1 drives laryngeal squamous cell carcinoma progression by inhibiting C1QBP ubiquitin degradation and activating β-catenin | Laryngeal squamous cell carcinoma [435] |
| Circ_0008784 | CTNNB1 | Circ_0008784 promotes triple-negative breast cancer cell proliferation and inhibits apoptosis by activating the Wnt/β-catenin pathway | Triple-negative breast cancer [436] |
| CircLIFR | β-catenin | CircLIFR inhibits hepatocellular carcinoma progression by sponging miR-624-5p and blocking the GSK-3β/β-catenin signaling pathway | Hepatocellular carcinoma [437] |
| circPHF14 | WNT7A | circPHF14 drives pancreatic ductal adenocarcinoma growth and metastasis by stabilizing Wnt7a mRNA and activating the Wnt/β-catenin pathway | Pancreatic ductal adenocarcinoma [438] |
| circ_0017109 | FZD4 | CircRNA has_circ_0017109 promotes lung tumor progression by activating Wnt/β-catenin signaling through the miR-671-5p/FZD4 axis | Lung tumor [439] |
| CircIFT80 | CTNNB1 | CircIFT80 promotes colorectal cancer progression by sponging miR-142, miR-568, and miR-634 to upregulate β-catenin and activate the Wnt/β-catenin pathway | Colorectal cancer [440] |
| CircNIPBL | Wnt5a | CircNIPBL promotes bladder cancer metastasis by activating the Wnt/β-catenin pathway via the circNIPBL/miR-16–2-3p/Wnt5a/ZEB1 axis | bladder cancer [441] |
| Circ-ZFR | WNT5A | Circ-ZFR drives bladder cancer progression by sponging miR-545 and miR-1270 to upregulate WNT5A | Bladder cancer [442] |
| CircVAPA | WNT5A | CircVAPA promotes non-small cell lung cancer progression by regulating the miR-876-5p/WNT5A axis | Non-small cell lung cancer [443] |
| circKIF4A | Wnt5a | circKIF4A sponges miR-139-3p to upregulate Wnt5a, activating the Wnt/β-catenin pathway and promoting glioma progression | Glioma [444] |
| circ0101675 | WNT3A/5A | circ0101675 sponges miR-1278 to upregulate WNT3A/5A, promoting NSCLC progression | Non-small cell lung cancer [445] |
| circFOXP1 | WNT1 | circFOXP1 sponges miR-185-5p to upregulate WNT1, promoting LUAD progression | Lung adenocarcinoma [446] |
| circLMO7 | WNT2 | circLMO7 sponges miR-30a-3p to upregulate WNT2, activating the WNT2/β-catenin pathway and promoting GC progression | Gastric cancer [447] |
| circRNA_100367 | Wnt3 | circRNA_100367 sponges miR-217 to upregulate Wnt3, enhancing radioresistance in ESCC via the Wnt/β-catenin pathway | Esophageal squamous cell carcinomas [448] |
| circ_PVT1 | Wnt4 | circ_PVT1 indirectly activates the Wnt4/β-catenin pathway by targeting miR-21-5p/CBX4, promoting LC progression | Laryngeal cancer [449] |
| circRNA_001275 | Wnt7a | circRNA_001275 sponges miR-370-3p to upregulate Wnt7a, promoting cisplatin resistance in esophageal cancer | Esophageal cancer [450] |
| circPVT1 | FZD3 | circPVT1 sponges miR-30a-5p to upregulate FZD3, activating the Wnt/β-catenin pathway and regulating 5-FU chemosensitivity in ESCC | Esophageal cancer [451] |
| hsa_circ_0004712 | FZD4 | hsa_circ_0004712 sponges miR-331-3p to upregulate FZD4, promoting OC progression | Ovarian cancer [452] |
| circCSPP1 | FZD7 | circCSPP1 sponges miR-944 to upregulate FZD7, promoting DOX resistance and CRC progression | Colorectal cancer [453] |
| circPRKAR1B | FZD4 | circPRKAR1B sponges miR-361-3p to upregulate FZD4, promoting OS progression and chemoresistance | Osteosarcoma [454] |

inhibitors (TKIs) in lung cancer. The study suggests that repopulating and renewing stem-like cells could be an effective strategy for overcoming TKI resistance [308].

By adopting a precision medicine approach, clinicians can customize treatments based on how each tumor responds to Wnt-targeted therapy. Such as a recent research emphasizes the role of Wnt/β-Catenin signaling in cancer progression, influencing self-renewal, dedifferentiation, apoptosis suppression, and metastasis, with implications for enhancing precision in radiation therapy

[309]. Therefore, this tailored approach has the potential to minimize side effects and maximize therapeutic efficacy.

Targeting the Wnt pathway in cancer therapy offers several advantages (Fig. 2). One key advantage is that predictive biomarker-based patient selection can reduce the likelihood of unnecessary side effects. Identifying patients who are more likely to respond positively to Wnt-targeted therapy ensures that treatment is administered selectively, thereby improving therapeutic efficacy while minimizing adverse effects in those with low Wnt signaling susceptibility. This targeted approach ultimately enhances the safety profile of Wnt pathway-based interventions [14]. Another crucial benefit of predicting Wnt signaling sensitivity is the optimization of therapeutic efficacy. Customized therapies, based on the unique responsiveness of the Wnt signaling pathway, increase the likelihood of achieving desired effects on tumor cells [14, 91]. This optimization leads to improved therapeutic efficacy of Wnt-targeted therapies, resulting in better outcomes for cancer patients [14, 91]. Utilizing biomarkers to predict Wnt signaling susceptibility facilitates the stratification of patient cohorts based on their likelihood of responding to specific treatments. This stratification streamlines the treatment decision-making process, enabling physicians to allocate resources more efficiently and target interventions to those most likely to benefit. As a result, it helps avoid unnecessary treatments for patients with low expected sensitivity [26, 62].

Predictive biomarkers serve as crucial guides for clinical decision-making, providing physicians with valuable information about the expected response of a patient's tumor to Wnt-targeted therapy. These biomarkers guide the selection of the most appropriate treatment plan, supporting informed decision-making aligned with evidence-based medicine [310]. The ability to predict Wnt signaling susceptibility has far-reaching implications for drug development beyond individual patient care. Predictive biomarkers speed up the identification of patient subgroups most likely to gain from new Wnt-targeted agents. This targeted approach accelerates the drug development process, facilitating the translation of scientific discoveries into clinically effective treatments [91, 311]. Therefore, the advantages of predicting Wnt signaling sensitivity are of utmost importance in the field of cancer therapy. From fine-tuning treatment strategies and reducing side effects to optimizing therapeutic efficacy and accelerating drug development, sensitivity prediction is integral to advancing precision medicine in oncology.


**Fig. 2** The figure depicts the diverse advantages associated with targeting the Wnt signaling pathway in cancer therapy. One pivotal benefit is the ability to customize treatment plans, aligning with precision medicine principles and tailoring interventions to the unique molecular profiles of individual patients. Moreover, a deeper understanding of Wnt/β-Catenin signaling enhances precision in radiation therapy, influencing critical aspects such as self-renewal, dedifferentiation, apoptosis suppression, and metastasis. This targeted approach not only minimizes side effects by identifying patients likely to respond positively but also optimizes therapeutic efficacy. Customized therapies, shaped by the unique responsiveness of the Wnt signaling pathway, increase the likelihood of desired effects on tumor cells, leading to improved outcomes. Stratification of patient cohorts based on Wnt signaling susceptibility streamlines treatment decision-making, ensuring a more targeted and efficient allocation of resources. Additionally, predictive biomarkers guide clinical decisions, offering valuable insights into the expected tumor response to Wnt-targeted therapy. Lastly, the accelerated identification of patient subgroups likely to benefit from new Wnt-targeted agents expedites drug development, fostering the translation of scientific discoveries into clinically effective treatments

### *Toxicity and management strategies of Wnt-directed therapies*

Targeting the Wnt pathway for cancer therapy holds promise for cancers where aberrant Wnt signaling plays a key role in tumor progression. However, Wnt-directed therapies come with several toxicities (Fig. 3).

One of the primary concerns with Wnt-directed therapies is the broad biological functions of the Wnt signaling pathway. Wnt signaling is involved in the maintenance of normal stem cells, tissue homeostasis, and organ development [312]. Therefore, disrupting this pathway in normal tissues can lead to undesirable effects, such as gastrointestinal issues, skin toxicity, and developmental abnormalities. This is particularly relevant when using molecule inhibitors or monoclonal antibodies targeting components of the Wnt signaling pathway, such as the Frizzled receptors, β-catenin, or the Wnt ligands themselves. These agents may inadvertently affect normal stem cell populations, leading to toxic side effects. For example, in melanoma models, activation of β-catenin in the Wnt pathway suppresses the chemokine CCL4, which reduces dendritic cell infiltration into tumors, potentially hindering T-cell priming and immune response. This suggests that therapies targeting Wnt signaling may inadvertently impair immune surveillance or exacerbate immune evasion mechanisms [313, 314]. On the other hand, in liver or lung injury models, Wnt activation supports tissue regeneration but also contributes to fibrosis. Overly aggressive inhibition of Wnt signaling could disrupt these regenerative processes, leading to chronic tissue damage and fibrotic outcomes. This highlights the delicate balance required in targeting Wnt signaling for therapeutic interventions [315].

Another challenge is the potential for off-target effects. For example, Porcupine inhibitors, which block Wnt ligand secretion, have shown gastrointestinal toxicity [316, 317]. Similarly, disrupting Wnt signaling in

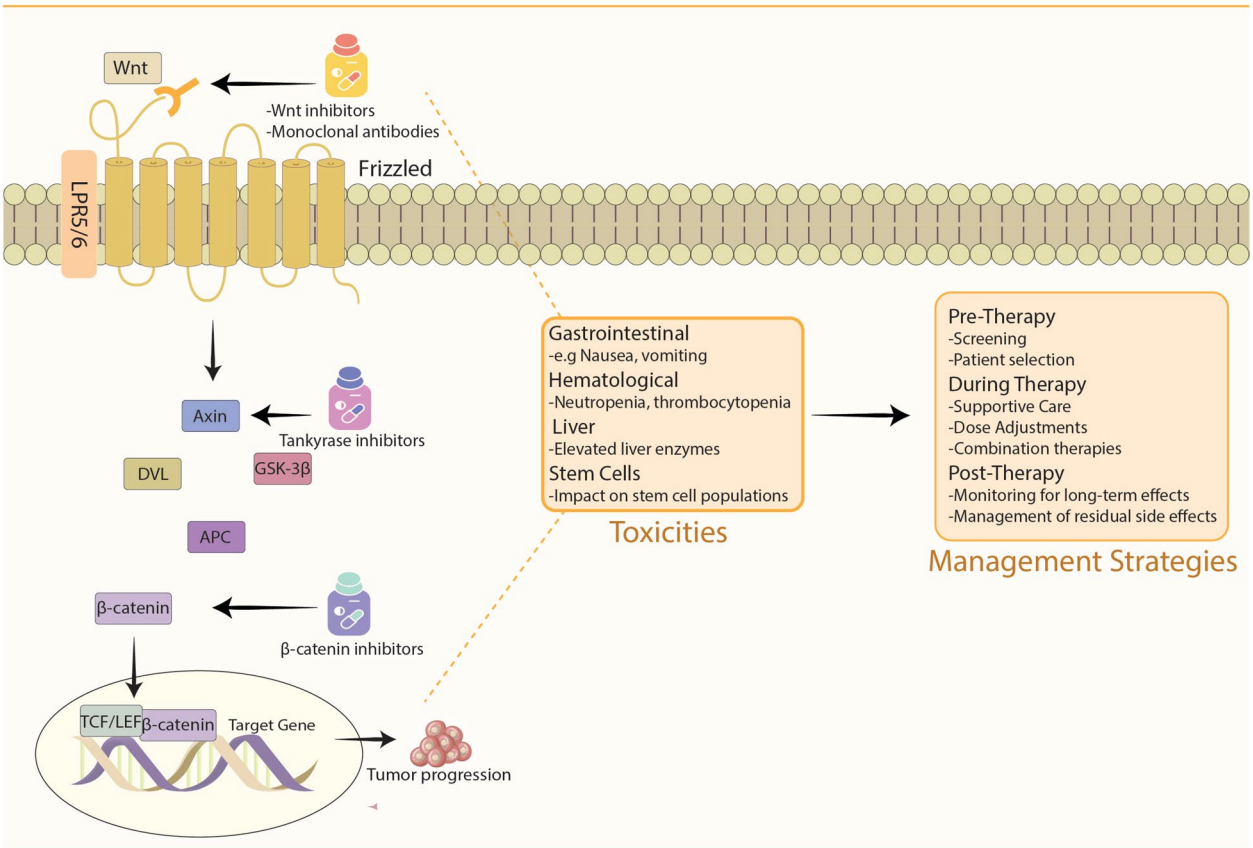


**Fig. 3** This figure illustrates the toxicity and management strategies associated with Wnt-directed therapies in cancer treatment. It highlights the Wnt signaling pathway, emphasizing key components such as Wnt ligands, Frizzled receptors, β-catenin, and TCF/LEF, which play crucial roles in cancer progression. Various Wnt-directed therapies are shown, including Wnt inhibitors, β-catenin inhibitors, tankyrase inhibitors, and monoclonal antibodies targeting Wnt receptors. The toxicity profile of these therapies is outlined, detailing both acute and chronic side effects, such as gastrointestinal issues, hematological toxicity, liver toxicity, and their impact on stem cell populations. Management strategies are categorized into pre-therapy, during therapy, and post-therapy phases

skin or hair follicles could lead to dermatological issues, such as rash or hair loss [318].

To overcome these toxicity challenges, several strategies are being explored. One promising approach is the development of more selective Wnt-targeted therapies. These therapies aim to selectively inhibit the tumor-specific aberrations of Wnt signaling while sparing normal tissue function. For example, v-ATPase inhibitors selectively inhibit Wnt/β-catenin signaling in CRC cells while sparing normal tissues. These agents target cancer-specific v-ATPase activity, reducing systemic toxicity. This can be achieved by using tissue-specific delivery systems, such as nanoparticle-based drug delivery, which can target the drug directly to the tumor site. By reducing systemic exposure, these strategies minimize off-target effects and toxicity in normal tissues [319, 320].

Another approach is to combine Wnt-directed therapies with other treatment modalities. This combination approach may allow for the dose of the Wnt inhibitor to be reduced while still maintaining therapeutic efficacy. For example, combining Wnt pathway inhibitors with immune checkpoint inhibitors synergizes anti-tumor effects and addresses resistance mechanisms [321]. Furthermore, biomarker-driven patient selection can play a crucial role in minimizing toxicity. By identifying patients whose tumors are heavily reliant on Wnt signaling, clinicians can tailor treatment regimens to those most likely to benefit from Wnt inhibition. For instance, patients with CRC carrying APC mutations, which are indicative of Wnt pathway activation, may be ideal candidates for Wnt-targeted therapies. Additionally, tumors exhibiting high levels of Wnt ligands could benefit from therapies targeting specific ligands, including monoclonal antibodies or ligand-specific antagonists [319, 322]. This selective approach reduces the likelihood of unnecessary side effects in patients whose tumors do not exhibit significant dependence on Wnt signaling. Advances in genetic profiling and predictive biomarkers are thus essential for the personalized application of Wnt-directed therapies, ensuring that patients receive the most appropriate treatment with the least amount of toxicity. Hence, while Wnt-directed therapies show great promise in cancer treatment, their associated toxicity remains a significant challenge.

#### Monitoring treatment responses

Understanding biomarkers associated with Wnt signaling susceptibility has significant clinical implications, particularly in the context of monitoring therapeutic responses. In this regard, monitoring treatment response is a key aspect influenced by biomarkers of Wnt signaling sensitivity [323]. Incorporating these biomarkers into the evaluation of cancer patients' responses to treatments targeting Wnt signaling is crucial. This monitoring process is necessary to evaluate the effectiveness of therapeutic strategies and make informed adjustments based on the dynamic changes observed in Wnt signaling biomarkers [323].

Tracking these biomarkers over the course of treatment provides important indicators of the status of Wnt signaling as it evolves in response to therapeutic intervention. Mutations in the APC gene serve as a fundamental biomarker for evaluating treatment response [78, 324]. Among these biomarkers, changes in the mutational status of APC during treatment may influence the susceptibility of Wnt signaling alterations and could guide therapeutic adjustments. For example, one study found that colon cancer mutations were associated with unfavorable immunotherapy outcomes. Specifically, TMB was lower, the expression of immune checkpoint molecules (PD-1/PD-L1/PD-L2) was reduced, tumor purity was higher, MSI-High was less frequent, and the infiltration of CD8 + T cells and follicular helper T cells was decreased [77].

In addition to APC mutations, the abnormal accumulation of β-catenin, another key biomarker, becomes a dynamic parameter to monitor and reflects the modulation of Wnt signaling under the influence of treatment [14]. Wnt pathway interventions, enhancing destruction complex production and disrupting β-catenin-dependent transcription factors, collectively inhibit tumor development, progression, invasion, metastasis, and recurrence [325]. Moreover, MSI has emerged as a specific biomarker with implications for monitoring therapeutic response. Changes in MSI status during the course of treatment provide valuable information about the effects of therapeutic interventions on Wnt signaling dysregulation [285]. When at least 30% of these DNA fragments include mutations, this is referred to as high microsatellite instability. MSI-high tumors are recognized by the body's immune system, which sends immune cells to the tumors to prevent them from spreading. As a result, immunotherapy works successfully for many people with MSI-high cancer [326]. Assessing changes in Wnt target gene expression, including genes such as c-Myc [91], and Cyclin D1 [327, 328], adds another layer to the monitoring process. Dynamic changes in the expression profiles of these target genes serve as indicators of the evolving Wnt signaling landscape during treatment.

Therefore, incorporating these biomarkers into treatment response monitoring can provide a more nuanced understanding of the efficacy of treatments targeting Wnt signaling. By implementing continuous evaluation and adjustment based on observed changes in these biomarkers, clinicians can refine treatment strategies and optimize outcomes for cancer patients.

### *Wnt signaling as a therapeutic target*

Targeting the Wnt signaling pathway in cancer therapeutics involves various strategies aimed at disrupting the abnormal activation seen in this pathway. Preclinical studies emphasize the effectiveness of small molecule inhibitors targeting crucial components like β-catenin and Porcupine. Significant progress has been made in developing a variety of Wnt inhibitors. These include porcupine inhibitors, tankyrase inhibitors, and β-catenin/coactivator disruptors. Additionally, researchers are exploring protein–protein interaction disruptors, casein kinase modulators, DVL inhibitors, and dCTPP1 inhibitors [329, 330]. For example, porcupine inhibitors, such as LGK-974 and RXC004, target Wnt secretion and have demonstrated potential in regulating the tumor microenvironment (TME). LGK-974 was shown to inhibit Wnt/β-catenin signaling in TAMs, thereby suppressing malignant behaviors in lung cancer cells, while RXC004 exhibited safety and tolerability in patients with advanced cancers and Wnt pathway-activated tumors, showing stable disease in some cases [331, 332]. Tankyrase inhibitors, including STP1002 and OM-153, provide an alternative approach by stabilizing AXIN proteins and antagonizing Wnt/β-catenin signaling. STP1002 showed preclinical efficacy in APC-mutated CRC without gastrointestinal toxicity [333]. Similarly, OM-153 reduced Wnt/β-catenin signaling and potentiated anti-PD-1 therapy in mouse melanoma models, demonstrating a promising therapeutic window [334]. These findings highlight the potential of porcupine and tankyrase inhibitors as targeted therapies for Wnt-driven cancers.

Concurrently, research is ongoing to evaluate the impact of monoclonal antibodies that target Wnt ligands or their receptors [14]. These antibodies aim to disrupt ligand-receptor interactions and downstream signaling events. Studies have shown that monoclonal antibodies, such as those targeting DKK-1, Wnt-1, and Wnt-2, can inhibit tumor growth and metastasis in various cancers, including osteosarcoma, melanoma, and BC. For instance, anti-DKK-1 antibodies have been shown to slow osteosarcoma xenograft growth and reduce metastasis, correlating with increased nuclear β-catenin staining and osteopontin expression [335]. Similarly, anti-Wnt-1 and anti-Wnt-2 antibodies induce apoptosis in cancer cells overexpressing these ligands, accompanied by changes in downstream signaling proteins like β-catenin and Dishevelled [336, 337]. Furthermore, the combination of the frizzled receptor inhibitor vantictumab with paclitaxel in metastatic BC patients demonstrated promising efficacy, with a clinical benefit rate of 68.8%, although fractures were noted as a significant adverse event [338]. Simultaneously, efforts are being made to investigate the regulation of negative regulators within the pathway to restore normal control of Wnt signaling [179, 303]. For instance, there is growing evidence that the transcription factors belonging to the Forkhead box (FOX) family regulate embryonic development and tissue homeostasis, partly by adjusting the output of Wnt signaling in a context- and tissue-specific way [339]. Several clinical trials have been conducted or are currently in progress to investigate interventions targeting the Wnt pathway in cancer. These trials aim to explore the therapeutic potential of agents specifically designed to modulate the Wnt signaling pathway, reflecting ongoing efforts in the field of cancer research to develop targeted treatments based on a deeper understanding of molecular pathways involved in tumorigenesis (Table 5).

Despite its therapeutic potential, targeting the Wnt signaling pathway presents challenges due to its fundamental role in normal physiological processes. Complete inhibition could lead to unintended side effects, necessitating a nuanced approach [340, 341]. Moreover, the complex interplay between Wnt signaling and other signaling cascades requires careful consideration to prevent unintended consequences [342, 343].

## Recent advances in Wnt signaling in cancer immunotherapy

In recent years, studies have reported that Wnt signaling pathways play a critical role in regulating immune responses within the TME has garnered significant attention. Dysregulation of Wnt signaling has been shown to impact immune cell function, tumor immunosurveillance, and the effectiveness of immunotherapies (Fig. 4). This pathway is essential for the development, differentiation, and function of various immune cells, including T cells, dendritic cells, macrophages, and natural killer cells. For example, Wnt signaling influences T-cell development in the thymus and modulates the tolerogenic role of dendritic cells [344]. Therefore, understanding the complex interactions between Wnt signaling and immune cells is pivotal for developing novel therapeutic strategies to enhance cancer immunotherapy.

Wnt signaling plays an essential role in shaping the immune landscape of tumors by influencing the differentiation, activation, and function of various immune cells. The TME is often characterized by immune suppression, which is mediated, in part, by aberrant Wnt signaling [27]. Studies have shown that hyperactivation of the Wnt pathway in tumors can promote the recruitment of immunosuppressive immune cells, such as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), which inhibit effective immune responses. Conversely, Wnt signaling can hinder the infiltration of effector immune cells, such as cytotoxic T lymphocytes (CTLs) into the tumor site [345]. The suppression of these

**Table 5** List of clinical trials of targeting Wnt pathway in cancer

| Clinical trial | Intervention / Treatment | Target | Study type and phase | Year | Cancer type | Status |
|---|---|---|---|---|---|---|
| NCT04474964 | Craniospinal, irradiation | N/A | Interventional (N/A) | 2020–2030 | Medulloblastoma | Recruiting |
| NCT05919264 | FOG-001 | N/A | Interventional (Phase I/II) | 2023–2027 | locally advanced or metastatic cancer | Recruiting |
| NCT01878617 | Cyclophosphamide, Cisplatin, Vincristine, Vismodegib, Pemetrexed, Gemcitabine, Aerobic, Training, Neurocognitive, Remediation | Smoothened (SMO) for Vismodegib | Interventional (Phase II) | 2013–2028 | Medulloblastoma | Active (Not recruiting) |
| NCT05556499 | Biomarker assays | N/A | Observational | 2022–2026 | Parathyroid Neoplasms | Not yet recruiting |
| NCT05848739 | ST316 | N/A | Interventional (Phase I) | 2023–2027 | Several type of cancers | Recruiting |
| NCT02278133 | WNT974, LGX818, Cetuximab | PORCN, BRAF V600E/K mutations, EGFR | Interventional (Phase I/II) | 2014–2017 | Metastatic Colorectal Cancer | Completed |
| NCT03787056 | Blood draws | N/A | Interventional (N/A) | 2018–2028 | Several type of cancers | Recruiting |
| NCT03176381 | N/A | N/A | Observational | 2017–2023 | Metastatic Castration-resistant Prostate Cancer | Completed |
| NCT00822458 | Vismodegib Laboratory biomarker analysis Pharmacological study | Smoothened (SMO) for Vismodegib | Interventional (Phase I) | 2009–2013 | Recurrent Childhood Medulloblastoma | Completed |
| NCT02006550 | N/A | N/A | Observational | 2010–2018 | Several type of cancers | Terminated |
| NCT03901950 | XNW7201 tablets | N/A | Interventional (Phase I) | 2019–2022 | Advanced Solid Tumors | Completed |
| NCT01351103 | LGK974, PDR001 | PORCN, PD-1 receptor | Interventional (Phase I) | 2011–2024 | Several type of cancers | Active (Not recruiting) |
| NCT02221245 | Tumor Biopsy via Ultrasound Endoscopy | N/A | Observational | 2013–2018 | Esophageal Cancer | Terminated |
| NCT03447470 | RXC004, Nivolumab | PORCN, PD-1 | Interventional (Phase I) | 2019–2023 | Several type of cancers | Active (Not recruiting) |
| NCT05544396 | Probiotic | N/A | Interventional (N/A | 2023–2024 | Gastric cancer | Recruiting |
| NCT03243331 | Gedatolisib, PTK7-ADC | PI3K/mTOR, PTK7 | Interventional (Phase I) | 2018–2020 | Breast cancer | Completed |
| NCT01606579 | PRI-724 | CBP/β-catenin | Interventional (Phase I/II) | 2012–2016 | Myeloid Malignancies | Completed |
| NCT02687009 | Niclosamide | Wnt/β-catenin | Interventional (Phase I) | 2017–2017 | Colon cancer | Terminated |
| NCT00256334 | Resveratrol | Multiple pathways | Interventional (Phase I) | 2005–2009 | Colon cancer | Completed |
| NCT00578396 | Grapes | N/A | Interventional (Phase I) | 2007–2007 | Colon cancer | Withdrawn |
| NCT05156905 | Cirmtuzumab | ROR1 | Interventional (Phase I) | 2022–2026 | Prostate cancer | Recruiting |
| NCT03167268 | Lycopene Placebo | N/A | Interventional (Phase II) | 2016–2021 | Colorectal cancer | Unknown |
| NCT02029352 | Sinecatechins 10%, Placebo | Multiple pathways (Antioxidant, Anti-inflammatory) for Sinecatechins | Interventional (Phase II/III) | 2014–2016 | Skin cancer | Completed |
| NCT01302405 | PRI-724 | CBP/β-catenin | Interventional (Phase I) | 2011–2015 | Solid tumors | Terminated |
| NCT04681248 | DKN-01 | DKK1 | N/A | N/A | Several type of cancer | Available |
| NCT01985763 | Genistein | Multiple pathways | Interventional (Phase I/II) | 2013–2018 | Colorectal cancer | Completed |
| NCT01358045 | Diclofenac, Diclofenac + Calcitriol | COX-2, Vitamin D receptor | Interventional (Phase II) | 2011–2013 | Basel cell carcinoma | Completed |
| NCT02649530 | WNT974 | PORCN | Interventional (Phase II) | 2018 | Squamous Cell Carcinoma, Head And Neck | Withdrawn |

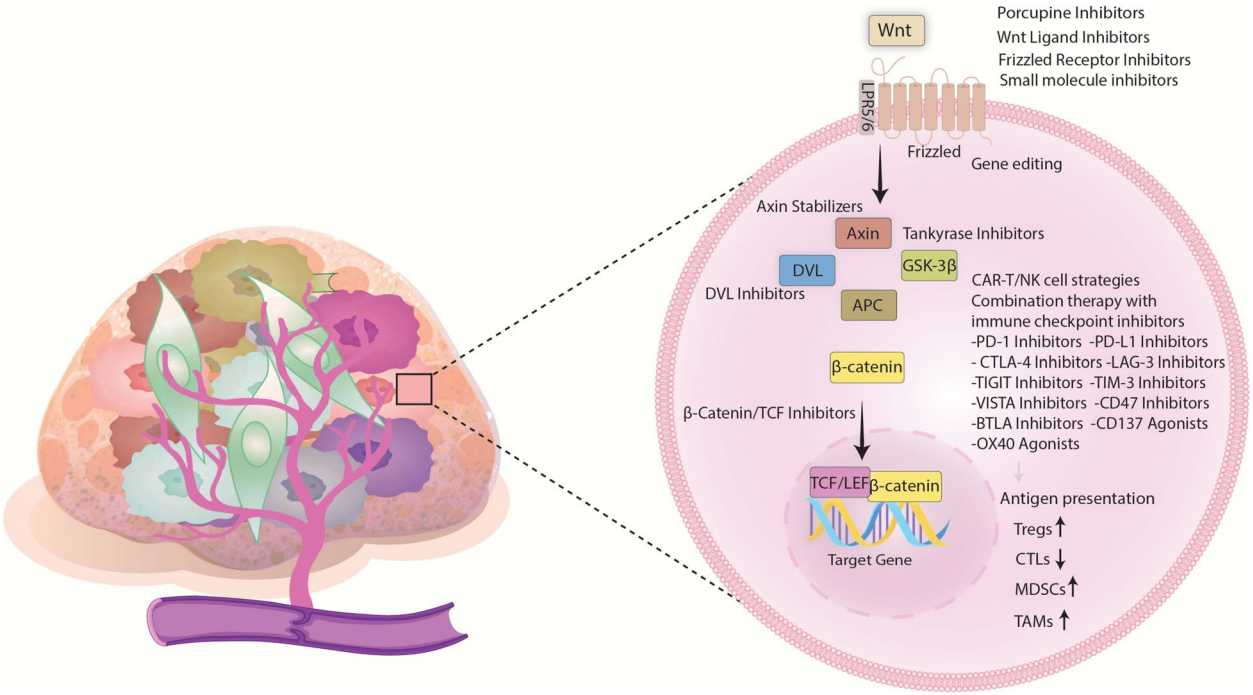


**Fig. 4** This schematic illustrates the role of Wnt/β-catenin signaling in tumor immune evasion and potential therapeutic strategies targeting this pathway. Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors, preventing the degradation of β-catenin by the destruction complex (Axin, APC, and GSK-3β). Stabilized β-catenin translocates to the nucleus, where it interacts with TCF/LEF transcription factors to drive the expression of immune evasion genes, leading to reduced antigen presentation, increased Tregs, MDSCs, and TAMs, while suppressing CTLs. Therapeutic approaches targeting this pathway include porcupine inhibitors, Wnt ligand and Frizzled receptor inhibitors, and small molecule inhibitors. Additionally, combination strategies with immune checkpoint inhibitors and CAR-T/NK cell therapies offer promising avenues for restoring anti-tumor immunity

immune cells not only reduces immune surveillance but also impedes the effectiveness of immunotherapies that aim to activate the immune system against tumors. For example, in melanoma, a strong Wnt signature correlates with T-cell exclusion. High β-catenin activity disrupts the recruitment of CD103 + dendritic cells, which are essential for T-cell priming against tumor antigens [346]. In breast and lung cancer, autocrine inhibition of Wnt signaling by DKK1 induces a slow-cycling state. This allows tumors to evade the innate immune response [347].

Moreover, Wnt signaling influences the balance between immune cell subsets, particularly within the TME, where it can drive a shift towards a more immunosuppressive phenotype. For example, Wnt/β-catenin signaling has been shown to play a context-dependent role in the regulation of myeloid-derived suppressor cells (MDSCs). It can inhibit MDSC maturation, potentially restricting their differentiation into functional myeloid cells [348]. Conversely, Wnt signaling also promotes MDSC accumulation by upregulating vascular endothelial growth factor (VEGF). This enhances MDSC recruitment and sustains their immunosuppressive functions within the tumor microenvironment [27].

A key feature of tumor progression is the ability of cancer cells to evade immune surveillance. Recent studies have demonstrated that Wnt signaling plays a significant role in this process. One critical mechanism of immune evasion is the upregulation of immune checkpoint pathways, such as PD-1/PD-L1 and CTLA-4, which prevent effective immune responses by inhibiting the activation of T cells. Emerging evidence suggests that Wnt signaling can modulate the expression of these immune checkpoints. For example, activation of the Wnt/β-catenin pathway has been linked to the upregulation of PD-L1 expression in tumor cells and immune cells within the TME [349]. This interaction creates a barrier to T cell-mediated cytotoxicity and contributes to immune resistance [350, 351]. Furthermore, the interplay between Wnt signaling and immune checkpoints offers an intriguing opportunity for combination therapies that target both pathways simultaneously, aiming to overcome immune resistance and improve the efficacy of cancer immunotherapy.

In addition to PD-1/PD-L1 and CTLA-4, other immune checkpoint molecules, such as TIM-3 and LAG-3, are also regulated by Wnt signaling. For example, in AML LSCs, TIM-3 signaling hijacks the canonical Wnt/β-catenin

pathway via LRP6 activation. This involves HCK kinase and p120-catenin, promoting self-renewal and immune evasion [352]. Targeting Wnt signaling in combination with immune checkpoint inhibitors may provide a more comprehensive strategy to boost antitumor immunity and reverse immune evasion mechanisms that hinder the effectiveness of conventional immunotherapy. For instance, in NSCLC with high TMB, active Wnt/β-catenin signaling excludes CD8 + T cells, leading to anti-PD-1 resistance. Blocking this pathway restores T-cell infiltration and enhances immunotherapy efficacy [353].

Targeting Wnt signaling has emerged as a promising strategy to enhance cancer immunotherapy, given its central role in regulating immune responses within the TME [354]. Small molecule inhibitors of the Wnt/β-catenin pathway can block β-catenin's transcriptional activity. They also disrupt its interaction with immune-suppressive factors. This promotes the infiltration of effector immune cells. Additionally, it enhances the efficacy of immune checkpoint inhibitors in preclinical models. Monoclonal antibodies represent another approach, targeting Wnt ligands or Frizzled receptors to modulate the pathway [355].

## Challenges and future directions

Wnt signaling biomarkers have emerged as pivotal elements in cancer research, providing crucial insights into tumorigenesis and potential therapeutic targets [356, 357]. Despite their promising potential, the integration of Wnt signaling biomarkers into clinical practice faces several challenges; however, future directions aim to address these through improved validation, standardization, and technological advancements (Fig. 5).

A primary challenge emanates from the inherent complexity of the Wnt signaling pathway, characterized by a multitude of components and intricate crosstalk with other signaling pathways. Deciphering this complex network of interactions poses a substantial hurdle, hindering the precise interpretation of biomarker data. Furthermore, the lack of standardization methodologies for

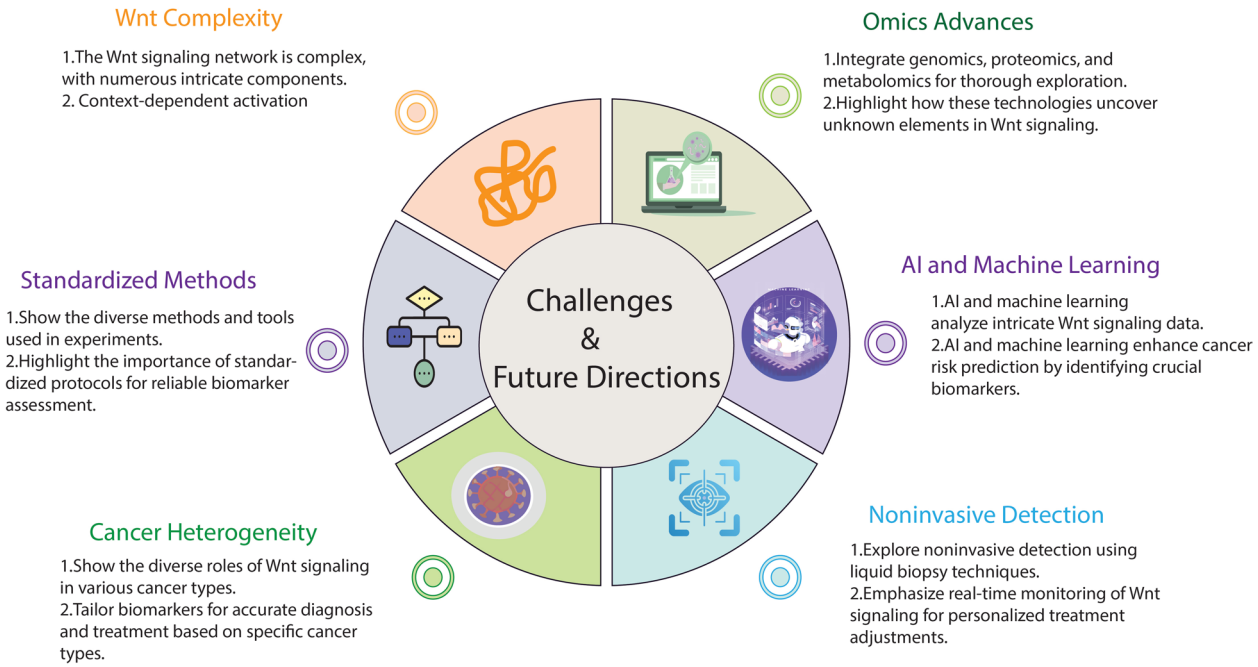


**Fig. 5** The use of Wnt signaling biomarkers in cancer research presents several challenges and future directions. One major challenge is the complexity of the Wnt signaling pathway, which involves numerous components and extensive crosstalk with other pathways, making biomarker interpretation difficult. Additionally, lack of methodological standardization is a critical issue, as variations in experimental techniques and analytical approaches across research groups often lead to inconsistent results. The heterogeneous nature of cancer types introduces additional challenges, requiring a nuanced comprehension of Wnt signaling's role in specific pathological contexts. Future research opportunities lie in the exploration and identification of novel biomarkers within the Wnt signaling pathway, aiming to enhance both specificity and sensitivity in cancer-related applications. Advancements in omics technologies, artificial intelligence, and machine learning offer promising avenues for discovering unknown components of Wnt signaling and improving data analysis. Efforts are also directed towards developing noninvasive methods, such as liquid biopsy techniques, for real-time monitoring of Wnt signaling dynamics. Interdisciplinary collaboration, facilitated by consortia and networks, is deemed essential to overcoming existing challenges and unlocking the full potential of Wnt signaling biomarkers in cancer research

assessing Wnt signaling biomarkers is a critical concern [358].

The diversity in experimental techniques and analytical approaches employed by different research groups introduces variability, leading to inconsistent results and compromising the reproducibility and reliability of findings. To overcome this challenge, it is essential to establish standardized protocols for biomarker assessment, including universally accepted quantification techniques and strict quality control measures. Additionally, implementing multi-center validation studies can enhance reliability and facilitate regulatory approval for clinical applications. Fostering collaboration and promoting data sharing among researchers through open-access databases and integrative bioinformatics platforms will further drive standardization efforts [64].

In addition, the clinical translation of Wnt signaling biomarkers encounters challenges associated with the heterogeneous nature of cancer types [179]. Wnt signaling's involvement varies across diverse cancers, necessitating a nuanced comprehension of its role in specific pathological contexts. Tailoring biomarker applications to individual cancer types and subtypes is essential for achieving accurate diagnosis, prognosis, and treatment stratification [359]. Furthermore, intra-tumoral heterogeneity and the plasticity of cancer cells add another layer of complexity, making it crucial to identify context-dependent Wnt biomarkers that retain predictive value across different disease stages.

Despite the challenges inherent in the utilization of Wnt signaling biomarkers, their potential in cancer diagnosis and treatment presents compelling opportunities for future research (Fig. 5) [360]. One noteworthy avenue involves the exploration and identification of novel biomarkers within the Wnt signaling pathway, aiming to enhance both specificity and sensitivity in cancer-related applications. This includes the identification of post-translational modifications of Wnt pathway components, which may serve as functional biomarkers reflecting pathway activity.

Advancements in omics technologies, including genomics, proteomics, and metabolomics, hold promise for the discovery of previously unknown components of Wnt signaling that may serve as robust biomarkers. The integration of these technologies enables a comprehensive exploration of the intricate molecular landscape associated with Wnt signaling in cancer. Single-cell sequencing and spatial transcriptomics are particularly promising in uncovering cell-type-specific variations in Wnt signaling, which could provide insights into tumor heterogeneity and resistance mechanisms.

The adoption of artificial intelligence (AI) and machine learning algorithms represents a progressive approach to address the complexity of Wnt signal data analysis. These computational methods have the capacity to unravel intricate patterns and interactions within signaling pathways, thereby facilitating the identification of clinically relevant biomarkers and enhancing the accuracy of cancer risk prediction. AI-driven integrative analyses of multi-omics datasets can also aid in predicting patient-specific therapeutic responses, paving the way for precision oncology approaches targeting Wnt signaling.

Furthermore, ongoing efforts are dedicated to developing noninvasive methods for detecting Wnt biomarkers, exemplified by the exploration of liquid biopsy techniques. This endeavor is crucial for enabling routine clinical applications, offering the potential for real-time monitoring of Wnt signaling dynamics and facilitating personalized treatment adjustments and timely interventions. The use of circulating tumor DNA (ctDNA), exosomal RNA, and methylation signatures associated with Wnt pathway alterations represents a promising frontier in noninvasive diagnostics.

Since Wnt signaling biomarkers are interdisciplinary, collaboration is essential to overcoming existing challenges and unlocking their full potential. The establishment of consortia and networks that unite clinicians, biologists, bioinformaticians, and computer scientists will foster a comprehensive understanding of Wnt signaling within the diverse contexts of cancer. International collaborations, coupled with large-scale patient cohort studies, will be instrumental in validating biomarker utility and expediting clinical translation. This collaborative approach aims to translate research findings into actionable clinical strategies, expediting the transformation of scientific insights into practical applications.

## Conclusion

In summary, this article provides an in-depth analysis of the Wnt signaling pathway in cancer, emphasizing the critical importance of predicting Wnt signaling sensitivity for personalized and targeted treatment. It offers a thorough and current overview of current biomarkers, their clinical implications, and the challenges associated with therapeutically targeting Wnt signaling. This review acknowledges the complexities involved in identifying reliable biomarkers, discusses cutting-edge technologies, and highlights the need to incorporate biomarker data into clinical practice. Moreover, it underscores the immense potential of precision medicine in cancer treatment, advocating for a multidisciplinary approach that combines genomics, bioinformatics, and artificial intelligence to enhance biomarker-based therapeutic strategies. With a strong focus on translational research, this review aims to advance our understanding of Wnt signaling sensitivity for more effective and individualized interventions, ultimately paving the way for improved patient outcomes in oncology.

**Abbreviations**

| | |
|---|---|
| PCP | Planar cell polarity |
| DKK | Dickkopf |
| sFRP | Secreted Frizzled-related protein |
| APC | Adenomatous polyposis coli |
| EMT | Epithelial-to-mesenchymal transition |
| FOX | Forkhead box |
| MSI | Microsatellite instability |
| CRC | Colorectal cancer |
| APC | Adenomatous polyposis coli |
| Dkk-1 | Dickkopf-1 |
| GSK-3β | Glycogen synthase kinase-3β |
| LEF | Lymphoid enhancer factor |
| TCF | T-cell factor |
| MSI | Microsatellite instability |
| LEF1 | Lymphoid enhancer-binding factor 1 |
| NSCLC | Non-small cell lung cancer |
| MSS | Microsatellite stable |
| PDAC | Pancreatic ductal adenocarcinoma |
| HCC | Hepatocellular carcinoma |
| MSI-H | High microsatellite instability |
| dMMR | Mismatch repair deficient |

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**Authors' contributions**
Muhammad Tufail: Conceptualization, Original Drafting, Visualization, Writing—Review & Editing. Can-Hua Jiang: Review & Editing. Ning Li: Supervision, reviewed, and Editing. All authors have reviewed and approved the final manuscript for publication.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
All authors have given consent for publication.

**Competing interests**
The authors declare no competing interests.

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