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Frizzled7 as an emerging target for cancer therapy

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Abstract

Wnt proteins are secreted glycoproteins that bind to the N-terminal extra-cellular cysteine-rich domain of the Frizzled (Fzd) receptor family. The Fzd receptors can respond to Wnt proteins in the presence of Wnt co-receptors to activate the canonical and non-canonical Wnt pathways. Recent studies indicated that, among the Fzd family, Fzd7 is the Wnt receptor most commonly upregulated in a variety of cancers including colorectal cancer, hepatocellular carcinoma and triple negative breast cancer. Fzd7 plays an important role in stem cell biology and cancer development and progression. In addition, it has been demonstrated that siRNA knockdown of Fzd7, the anti-Fzd7 antibody or the extracellular peptide of Fzd7 (soluble Fzd7 peptide) displayed anti-cancer activity *in vitro* and *in vivo* mainly due to the inhibition of the canonical Wnt signaling pathway. Furthermore, pharmacological inhibition of Fzd7 by small interfering peptides or a small molecule inhibitor suppressed β -catenin-dependent tumor cell growth. Therefore, targeted inhibition of Fzd7 represents a rational and promising new approach for cancer therapy.

Keywords

frizzled 7; β -catenin; Wnt signaling; disheveled; cancer; drug target

1. Introduction

The Frizzled (Fzd) family of receptors consists of 10 members. Each contains an N-terminal signal peptide, an extracellular cysteine-rich domain (CRD), a seven-pass transmembrane domain, and an intracellular C-terminal PDZ domain. The CRD enables Fzd to interact with Wnt proteins, while the PDZ domain interacts with disheveled (Dvl) to transduce downstream Wnt signals [1]. The Fzd family is quite promiscuous in that each member of this family interacts with more than one of the 19 Wnt isoforms to activate canonical and/or non-canonical Wnt signaling, which function to turn on different downstream transcription factors that are essential for modulating cellular proliferation, polarity, and differentiation in invertebrates and vertebrates.

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Fzd7 is located on human chromosome 2q33, contains 3,869 nucleotides that are translated into a 574 amino acid seven-transmembrane protein that contains an N-terminal extracellular CRD and a C-terminal cytoplasmic PDZ domain. Another form of Fzd7, FzE3, which was isolated from esophageal carcinoma tissue via RT-PCR [2], shares 98% homology with Fzd7. Of the 10 Fzd family members, Fzd7 is the only evolutionary conserved family member that regulates developing gastric systems [3]. Over the past several years, evidence has been building that Fzd7 is an important cell surface receptor governing Wnt signaling in cancer cells. In this review, we summarize the current understanding of Fzd7 expression and function in various types of cancer and highlight evidence that Fzd7 may serve as a therapeutic target for certain cancers.

2. The canonical and the non-canonical Wnt signaling pathways

The Fzd receptors can respond to Wnt proteins only in the presence of the Wnt co-receptor low density lipoprotein receptor-related protein 5 (LRP5) or LRP6 to activate the canonical β -catenin pathway (Fig. 1). The central dogma of the Wnt/ β -catenin signaling pathway is that β -catenin is sequestered in a complex that consists of the adenomatous polyposis coli (APC) tumor suppressor, Axin2, glycogen synthase kinase-3 β (GSK3 β), and casein kinase 1 (CK1) when Wnt proteins are unable to bind to their receptors at the cell surface. The formation of this “destruction complex” induces the phosphorylation of β -catenin by CK1 and GSK3 β , which results in the ubiquitination and the subsequent degradation of β -catenin by the 26S proteasome. However, when Wnt proteins are secreted properly from cells they form a ternary complex with Fzd and LRP5/6, which results in the activation of Dvl followed by the inhibition of GSK3 β and the stabilization of cytosolic β -catenin. The β -catenin then translocates into the nucleus where it interacts with T-cell factor/lymphoid enhancing factor (TCF/LEF) to induce the expression of downstream target genes that regulate cell cycle, proliferation, and differentiation. In addition to the intracellular negative regulators of Wnt/ β -catenin signaling (e.g. GSK3 β , APC, and Axin2), the extracellular negative regulators consists of Cerberus, the Dickkopf (Dkk) protein family, Schlerostin/SOST, secreted frizzled-related proteins (sFRPs) and Wnt inhibitory factor-1 (WIF-1) [4, 5]. Mutations in Wnt/ β -catenin signaling components, aberrant epigenetic regulation of Wnt signaling antagonists and up-regulation of Wnt proteins and their receptors contribute to the development of a variety of diseases including cancer [4-6]. The mechanism responsible for β -catenin-associated tumorigenesis has been suggested to involve β -catenin and TCF-activated genes that control cell cycle processes, cell-extracellular matrix interactions and various transcription factors. Activation of Wnt/ β -catenin signaling has been found to be important for both initiation and progression of cancers of different tissues [4-6]. Disruption of Wnt/ β -catenin signaling represents an opportunity for rational cancer chemoprevention and therapy [7, 8].

The Fzd receptors can also respond to Wnt proteins in the presence of the Wnt co-receptor Ror2, a tyrosine kinase receptor, to activate the non-canonical Wnt pathway. The non-canonical Wnt pathway has two intracellular signaling cascades that consist of the Wnt/ Ca^{2+} pathway and the Wnt/PCP pathway (Fig. 1). The Wnt/ Ca^{2+} pathway is mediated by heterotrimeric G-proteins that are activated by the Wnt/Fzd/Dvl complex. The G-protein complex increases intracellular Ca^{2+} levels that subsequently activate Ca^{2+} -dependent protein kinases, including calmodulin kinase II (CamKII) and protein kinase C (PKC) [9]. Studies have shown that activation of the Wnt/ Ca^{2+} pathway inhibits the Wnt/ β -catenin signaling pathway. There are several possible mechanistic actions of Wnt/ Ca^{2+} -mediated inhibition of Wnt/ β -catenin signaling. One mechanism may involve the activation of Nemo-like kinase (NLK), which phosphorylates and inhibits the DNA binding ability of TCF/LEF [10]. Indeed, Wnt5a inhibits NLK through the activation of CamKII and TGF β -activated kinase 1 [11]. An alternative mechanism may involve Wnt5a-induced up-regulation of

Siah2, which promotes the degradation of β -catenin [12]. It was shown that the Wnt/PCP pathway in *Drosophila* regulates the polarization within the plane of epithelium, which is perpendicular to the apical-basal axis [13]. When stimulated by Wnt5a or Wnt11, this pathway diverges following the activation of Dvl and transduces signals that activate Rho and Rac, which in turn activate Rho-associated kinase (ROCK) and c-Jun N-terminal kinase (JNK), respectively [13]. The ensuing cytoskeletal rearrangement executes cell polarity and epithelial-to-mesenchymal transition; the latter contributes to tumor metastasis.

3. Fzd7 in cancer

3.1. Colorectal cancer

Aberrant activation of the Wnt/ β -catenin signaling pathway is a necessary initiating event in the genesis of most colorectal cancers. Although genetic mutations of the Wnt/ β -catenin signaling intracellular components *APC*, *CTNNB1* (β -catenin encoding gene) and *Axin2* are major contributing factors for colorectal cancers, it is now recognized that additional modulation of Wnt/ β -catenin signaling is involved in colorectal tumor progression [6]. Indeed, recent studies indicate that Fzd7 plays an important role in colorectal cancer development and metastasis. The Fzd7 protein is abundantly expressed in colon cancer tissues and various colon cancer cell lines that also contain the *APC* or β -catenin gene mutations [14, 15]. Furthermore, it has been demonstrated that the Fzd7 protein is predominantly expressed by well differentiated tumor cells in central areas of carcinoma tissues, and is confined to proliferative areas of carcinomas [16, 17]. Ueno et al. [15] examined the mRNA levels of Fzd7 in 135 primary colorectal cancers by real-time PCR, and found that the Fzd7 mRNA levels were significantly higher in stage II, III or IV tumors than in non-tumor tissues, and that overall survival was shorter in those patients with higher Fzd7 expression.

The overexpression of Fzd7 in colon cancer cell lines harboring *APC* and/or *CTNNB1* mutations robustly increases β -catenin/TCF activity and the subsequent expression of Wnt/ β -catenin target genes; whereas, siRNA knockdown of Fzd7 in colorectal cancer cells decreases β -catenin/TCF activity, Wnt/ β -catenin target gene expression, cell viability, cell migration, and cell invasion [14, 15]. In addition, liver metastasis of stable Fzd7 siRNA HCT-116 cell transfectants in SCID mice was decreased to 40-50% compared to controls [15]. Moreover, transfection of a plasmid expressing the Fzd7 extracellular domain induces morphological changes and attenuates tumor growth in colon cancer cells [18]. Together, these findings indicate that FZD7 plays a critical role in Wnt/ β -catenin signaling activation in colorectal cancer cells despite the presence of the *APC* or *CTNNB1* mutation and that Fzd7 is a potential therapeutic target for colorectal cancer.

Recently, Fzd7 was demonstrated to be a downstream target of β -catenin in colorectal cancer cells [17]. This finding may explain why Fzd7 expression is up-regulated in colon cancer. Increased Fzd7 expression, due to aberrant the canonical Wnt signaling pathway, may serve as a feed-forward mechanism to perpetuate Wnt/ β -catenin signaling, thus facilitating colorectal cancer progression and metastasis.

3.2. Hepatocellular carcinoma

Wnt/ β -catenin signaling has emerged as a critical player in both the development of normal liver as well as an oncogenic driver in hepatocellular carcinoma (HCC) [19, 20]. It has been reported that 40%-70% of HCC patients have tumors with high levels of β -catenin accumulation [21-24]. Mutations in the β -catenin gene were found in 12-26% of HCCs, while mutations in *APC* and *Axin2* are very rare [25]. Recent studies indicate that dysregulation of Wnt/ β -catenin signaling in HCC is also due to the aberrant epigenetic regulation of several Wnt signaling antagonists [26-30] and/or the up-regulation of cell

surface Wnt proteins and their receptors [20]. The Fzd7 steady-state mRNA levels are up-regulated in hepatitis B, C, and nonviral-induced HCC cell lines and mouse models [27, 31, 32]. It was found that Fzd7 and/or Wnt3 were up-regulated in 60-90% of human HCCs and 35-60% of the surrounding pre-neoplastic liver tissues [27, 31, 32], and that there was a functional interaction between Wnt3 and Fzd7 leading to activation of the Wnt/ β -catenin signaling pathway in HCC cells [33]. Furthermore, the up-regulation of Fzd7 expression correlated with increased levels of cytosolic/nuclear β -catenin and cell migration, whereas enforced overexpression of a dominant-negative Fzd7 mutant in HCC cells suppressed Wnt/ β -catenin signaling and reduced cell motility [27, 31, 32]. Finally, pharmacological inhibition of Fzd7 with small interfering peptides displayed anti-tumor properties in hepatocellular carcinoma [34].

3.3. Breast cancer

Wnt/ β -catenin signaling has been implicated in different stages of mammary gland development and is important for mammary oncogenesis [35]. While genetic mutations of the Wnt/ β -catenin signaling intracellular components *APC*, *CTNNB1* and *Axin2* are rare, dysfunction of the Wnt/ β -catenin pathway at the cell surface could result in the aberrant activation of Wnt/ β -catenin signaling in breast cancer cells [35, 36]. Triple negative breast cancer (TNBC; ER, PR, and HER2-negative breast cancer) is one of the most difficult subtypes of breast cancer to treat due to a lack of targeted therapy. Studies have demonstrated that activation of Wnt/ β -catenin signaling is preferentially found in TNBC and is associated with a poor clinical outcome [37, 38]. It was recently discovered that Fzd7 was up-regulated in TNBC and TNBC-derived cell lines, and that Fzd7 modulated TNBC cell tumorigenesis through the canonical Wnt signaling pathway [39]. shRNA knockdown of Fzd7 significantly decreased TNBC Wnt/ β -catenin signaling and subsequent cell proliferation, migration *in vitro*, and tumor growth *in vivo* [39].

3.4. Other types of cancer

Growing evidence indicates that Fzd7 plays a role in the development and progression of other types of cancers. For example, the mRNA levels of Fzd7 are up-regulated in esophageal cancer [40], lung cancer [41], Wilm's tumor [42, 43], gastric cancer [44] and melanoma [41]. Although other Fzd receptors including Fzd2, Fzd8, and Fzd9 are also up-regulated in gastric cancer cells [44], Fzd7 is likely the most important Fzd protein in gastric cancer. This stems from the observation that Fzd7-positive gastric cancers are associated with poor patient prognosis compared to Fzd7-negative gastric cancers [45]. In acute lymphoblastic leukemia (ALL), Fzd7 and Fzd8 are highly expressed, but Fzd3, Fzd4, and Fzd9 are down-regulated [46]. Treatment of ALL cells from patients or ALL cell lines with Wnt3a conditioned media increased β -catenin stabilization and induced proliferation of ALL cells, suggesting that Fzd7 may facilitate ALL progression through the activation of Wnt/ β -catenin signaling [46].

4. Wnt signaling activated by Fzd7 in cancer

Fzd7 can activate the canonical and/or the non-canonical Wnt signaling pathways in different types of cancers based on the availability of the cognate Wnt proteins, the co-receptors, and the variation in sequence homology between the different Fzd isoforms. Fzd may interact with various intracellular adaptor proteins in addition to Dvl. It was demonstrated that after Wnt5a stimulation, Ror2 can associate with Fzd7 via its extracellular CRD to form a receptor complex that is required for the regulation of Dvl and activation of JNK/c-Jun [47]. However, the up-regulation of Fzd7 in cancer may promote tumor development and metastasis mainly via the activation of the canonical Wnt signaling pathway. As described above, Fzd7 transduces Wnt signals through the canonical Wnt

signaling pathway in colorectal cancer cells [14], HCC cells [27, 31, 33], TNBC cells [39], esophageal cancer cells [40], gastric cancer cells [44], ALL cells [46], and Wilm's tumor cells [48]. Furthermore, the inhibition of Fzd7 expression and function in cancer cells corresponds to the inhibition of Wnt/ β -catenin signaling and suppression of tumor cell migration and growth (see below section).

Although it is somewhat difficult to discern whether non-canonical Wnt signaling plays a significant role in tumorigenesis, there is increasing evidence that the non-canonical Wnt signaling pathways are involved in the development and progression of some types of cancers [47, 49, 50]. Transcriptional knockdown of Fzd7 expression not only decreased the expression of several β -catenin target genes but also inhibited the phosphorylation of JNK in HCT-116 and HT-29 colon cancer cell lines [15]. Furthermore, Li et al. [51] showed that Fzd2 and Fzd7 mediate canonical Wnt3a signaling in the human lung carcinoma H441 cell line. However, when both Fzd receptors are co-expressed with the Ror2 tyrosine kinase receptor, Wnt3a/ β -catenin signaling is potentiated by Fzd2 only. Fzd7 can also activate PKC δ (an nPKC family member, which is activated by diacylglycerol and not Ca²⁺) by recruiting it to the plasma membrane via Dvl, and active PKC δ in turn activates JNK in *Xenopus* embryos [52]. Interestingly, pharmacological inhibition of Fzd7 with small interfering peptides induced HCC cell apoptosis mediated by not only the degradation of β -catenin but also the activation of PKC δ [34].

It has been proposed that Wnt/PCP signaling has a biphasic role in carcinogenesis by acting early as tumor suppressor but later stimulating cancer progression via the regulation of tumor invasion, metastasis, and angiogenesis [13]. A plethora of Wnt/PCP signaling components are up-regulated in a majority of cancers [13]. For example, the collagen triple helix repeat containing protein 1 (Cthrc1), which is a secreted glycoprotein that contains a short collagen-like motif, is up-regulated in cancer of the colon, breast, lung, and melanoma [53, 54]. Previous biochemical studies also showed that Cthrc1 promotes the clustering of the Wnt/Fzd/Ror2 complex, which activates PCP signaling [55]. Therefore, it is possible that Fzd7 forms a complex with Cthrc1 to promote the progression of certain cancers through the activation of the Wnt/PCP signaling pathway.

5. Fzd7 in cancer stem cells

Stem cells are responsible for maintaining differentiated cell numbers during normal physiology and at times of tissue stress. They have the unique capabilities of proliferation, self-renewal, clonogenicity and multi-potentiality. There is mounting evidence that many cancers contain a sub-population of self-renewing and expanding stem cells known as cancer stem cells (CSCs). CSCs are associated with resistant to chemotherapeutic agents and often lead to tumor recurrence, which exhibits poor patient prognosis [56-61]. The Wnt/ β -catenin signaling pathway has been implicated in the control over various types of stem cells and may act as a niche factor to maintain stem cells in a self-renewing state. A growing body of evidence also illustrates a pivotal role of Wnt/ β -catenin signaling in CSCs [62-65].

Studies have demonstrated that Fzd7 can be a novel embryonic stem cell-specific surface antigen with an important role in the maintenance of embryonic stem cell self-renewal capacity [66, 67]. It has been found that Fzd7 mRNA levels in human embryonic stem cells were up to 200-fold higher compared to differentiated cell types, and that shRNA-mediated knockdown of Fzd7 in human embryonic stem cells induced dramatic changes in the morphology of embryonic stem cell colonies, perturbation of expression levels of germ layer-specific marker genes, and a rapid loss of expression of the embryonic stem cell-specific transcription factor OCT4 [67].

Fzd7 expression is up-regulated in colonic crypt stem cells [68]. Colonic stem cells can either replicate or differentiate into columnar epithelial cells. Stem cells that harbor *APC* mutations tend to proliferate and form adenomas, which ultimately can become cancerous with ensuing metastasis [69]. It is interesting to note that Fzd7 expression was decreased when colonic stem cells differentiate into mature epithelial cells [68], which suggests that Fzd7/Wnt signaling may play a role in the transformation of colonic stem cells into adenomas.

It was recently demonstrated that Fzd7 is a potential tumor biomarker of the stem/progenitor population of Wilm's tumor [70]. Different Wilm's tumors can be grouped according to either sensitivity or resistance to an antibody specific to Fzd7. In the Fzd7-sensitive Wilm's tumor phenotype, the stem cell properties of Wilm's tumor cells such as sphere-formation and clonogenicity were abrogated following the Fzd7 antibody application [70]. Furthermore, Fzd7⁺ cells from Fzd7-resistant Wilm's tumor overexpressed Wilm's tumor 'stemness' genes and were also highly clonogenic/proliferative [70].

A novel approach to study CSC involves the use of the side population (SP) of cancer cell lines. The SP is characterized by the ability to efflux the DNA-binding dye Hoechst 33342. The SP cells share characteristics of CSCs, specifically, they are enriched for tumor initiating capacity, they express stem-like genes, and they are resistant to chemotherapeutic drugs [71]. Recently, Schmuck et al. [45] discovered that Fzd7 was up-regulated in the SP cells of several gastric cancer cell lines. This finding supports the observation that Fzd7 up-regulation in gastric cancers correlated significantly with a poor survival rate of the patients [45].

6. Targeting Fzd7 in cancer therapy (Fig. 2)

Fzd7 is likely to be a prime Fzd protein that can serve as a therapeutic target in cancer treatment, although other isoforms of Fzd are able to regulate the canonical and non-canonical Wnt signaling pathways too. The utilization of siRNA to knockdown the endogenous expression of Fzd7 decreases the invasive and metastatic potential of colon cancer cells [14, 15]. Furthermore, Fzd7 shRNA suppresses Wnt/ β -catenin signaling and subsequent cell proliferation and tumor growth *in vivo* using TNBC cells [39]. It may be advantageous to utilize RNA inhibition technology to decrease the expression of Fzd7 as a potential strategy to treat Fzd7-dependent cancers. Adeno-viral approaches could be used to selectively deliver shRNA to tumors to inhibit the expression of Fzd7. Indeed, adenoviral-mediated gene therapy to treat cancer is currently being explored [7]. However, several obstacles including the stigma surrounding this form of therapy and ways to prevent adverse immune responses to adenoviral therapy would have to be addressed before this form of technology could be used extensively to treat cancer.

A more translatable method of combating cancer involves the utilization of antibodies to target specific receptors that are expressed only in tumors. In a recent study, the use of an anti-Fzd7 antibody (Fzd7-Ab) to isolate Fzd7⁺ Wilm's tumor cells, proved effective in reducing the proliferation and survival of those cells [70]. Furthermore, the expression of sFRPs and Dkk1 sensitizes Fzd7⁺ Wilm's tumor cells to Fzd7-Ab treatment. These results suggest that Fzd7-Ab therapy may show some promise in treating Wilm's tumor. One drawback to this form of treatment is that the Fzd7-Ab induces internalization of the Fzd7 receptor [70] rendering it unavailable for incessant targeting. Therefore, Fzd7-Ab therapy would have to coincide with other forms of chemotherapy for Wilm's tumor.

Another feasible method of treating cancer through modulation of Fzd7 may involve the use of soluble peptide fragments to antagonize Fzd7. It has been found that a recombinant soluble Fzd7 (sFzd7) peptide, which contains the extracellular domain of Fzd7, inhibited

Wnt/ β -catenin signaling and decreased proliferation and tumorigenesis of HCC cell lines [72]. The extracellular domain of Fzd receptors serves as binding sites for Wnt ligands. The effects of sFzd7 on abating Wnt/ β -catenin signaling were accomplished by the competitive binding of the Fzd7 extracellular CRD with Wnt3, which activates the canonical Wnt signaling pathway [72].

While activated, Fzd7 interacts by the binding of its cytoplasmic tail KTLQSW amino acid motif to the PDZ domain of Dvl [73, 74]. Nambotin et al. [34] employed small interfering peptides (RHPDs) to block Fzd7 function in HCC Wnt signaling and HCC progression [34]. The membrane-permeable RHPDs contain the KTLQSW motif of the cytoplasmic tail of Fzd7 and thereby are able to disrupt the interaction between Fzd7 and Dvl. It was found that RHPDs decreased viability of human HCC cell lines through degradation of β -catenin and activation of PKC δ , and displayed *in vivo* anti-tumor effects on a transgenic HCC mouse model [34].

The therapeutic utility of disrupting PDZ protein-protein interactions was also shown by a small molecule inhibitor FJ9 [75]. This compound was shown to disrupt the protein-protein interaction between the PDZ domain of Dvl and the C-terminal tail of Fzd7 [75]. FJ9 displayed β -catenin-dependent anti-cancer activities such as inducing apoptosis in the LOX melanoma cell line and the H460 and H1703 non-small cell lung cancer cell lines and attenuating *in vivo* tumor growth in the H460 lung cancer mouse xenograft model [75]. These findings warrant the further development of this strategy for the treatment of Fzd7-dependent cancers.

7. Conclusion and perspectives

Among the Fzd family, Fzd7 appears to be the most important Wnt receptor involved in cancer development and progression. Over-activation of Wnt signaling with the up regulation of Fzd7 expression in a variety of cancers and the roles of Fzd7 in CSC biology suggests that Fzd7 could be an attractive target for cancer therapy. Several studies have employed different methods of attenuating the actions of Fzd7 overexpressed in cancer cells [14, 15, 34, 37, 70, 75] (Fig. 2). FJ9 is the only reported small molecule inhibitor of Fzd7. However, only high doses of FJ9 were shown to display anti-cancer activities *in vitro* [75]. Therefore, it may be advantageous to design more potent small molecule inhibitors that could either block the interaction of Wnt proteins with the CRD of Fzd7 or the interaction of the PDZ domain of Fzd7 with Dvl. Furthermore, the Fzd family is listed by the International Union of Pharmacology (IUPHAR) as a novel and separate family of G-protein-coupled receptors (GPCRs) [76]. As major targets for drug development, GPCRs have been studied for decades. It is now well accepted that GPCR molecules exist in a conformational equilibrium between active and inactive biophysical states [77-80], and that ligands that shift the equilibrium toward the active/inactive receptor states can be used as GPCR modulators for different therapeutic purposes. Thus, small molecules that act as classic GPCR modulators targeting Fzd7 to regulate Wnt/ β -catenin signaling will be potential drug candidates of cancer.

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Abbreviations

ALL Acute lymphoblastic leukemia

APC	Adenomatous polyposis coli
CamKII	Calmodulin kinase II
Cthrc1	Collagen triple helix repeat containing protein
CK1	Caseine kinase 1
CTNNB1	β -catenin gene
CRD	Cysteine rich domain
CSC	Cancer stem cells
Dkk	Dickkopf
Dvl	Dishevelled
ER	Estrogen receptor
Fzd	Frizzled
GPCR	G-protein coupled receptor
GSK3β	Glycogen synthase kinase-3 β
HER2	Human epidermal growth factor receptor 2
HCC	Hepatocellular carcinoma
JNK	Jun N-terminal kinase
LEF	Lymphoid enhancing factor
LRP5/6	Low density receptor-related protein 5/6
NLK	Nemo-like kinase
PCP	Planar cell polarity
PKC	Protein kinase C
PDZ	Post synaptic density protein (PSD95), <i>Drosophila</i> disc large tumor suppressor (Dlg1), <i>Zonula occludens</i> -1 protein (Zo-1)
PR	Progesterone receptor
RHPD	Small interfering peptides
ROCK	Rho associated kinase
SP	Side population
sFRP	Secreted frizzled related proteins
SOST	Schlerostin
TCF	T-cell factor
TNBC	Triple negative breast cancer
WIF-1	Wnt inhibitory factor-1

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Highlights

- Fzd7 is commonly upregulated in a variety of cancers.
- Fz7 suppression results in Wnt/ β -catenin signaling inhibition.
- FZD7 repression inhibits tumor growth.
- Fzd7 plays an important role in stem cell biology.
- Fzd7 is a promising therapeutic target for cancer.

Fig. 1.

The canonical Wnt/β-catenin and non-canonical Wnt signaling pathways. In the Wnt/β-catenin pathway, Wnt ligands form a ternary complex with Fzd and LRP5/6, which disrupts the Axin, CK1, GSK3β, and β-catenin complex via the activation of Dvl. Subsequently, cytoplasmic β-catenin stability increases which results in the formation of the β-catenin/TCF transcriptional complex and the ensuing expression of respective target genes. The Wnt/Ca²⁺ pathway is activated via the interaction of Wnt with Fzd and the Ror2 receptors. This interaction recruits Dvl to the plasma membrane where it interacts with Fzd and G-proteins to increase intracellular Ca²⁺ levels, which activate CamkII, PKC, and NFAK. Activation of these three kinases results in the inhibition of Wnt/β-catenin signaling, the induction of tissue separation, and the regulation of ventral fate, respectively. In the Wnt/PCP pathway, Wnt interacts with Fzd and Ror2 and activates Dvl. Dvl in turn activates Rac1/RhoA, which activate JNK and ROCK2, respectively. JNK and ROCK2 are involved in cytoskeletal remodeling.

Fig. 2.

Targeting Fzd7 in cancer. Based on the current literature, several methods have been designed to antagonize Wnt/β-catenin signaling by directly or indirectly targeting the Fzd7 receptor. For example, soluble Fzd7 peptide (sFzd7) binds to and inhibits the ability of Wnt proteins to interact with the CRD of Fzd7. The anti-Fzd7 antibody (Fzd7 Ab) blocks the ability of Wnt proteins to interact with Fzd7. Small molecule inhibitor FJ9 and small interfering peptides (RHPDs) disrupt the interaction of the C-terminal tail of Fzd7 with the PDZ domain of Dvl.