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Review

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.

Contents

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-3β; 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, *P*ost synaptic density protein (PSD95), *Drosophila* disc large tumor suppressor (Dlg1), *Z*onula occludens-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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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 dishevelled (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.

Fzd7 is located on human chromosome 2q33 and contains 3869 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 pathway

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-3β (GSK3β), 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 GSK3β, 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 GSK3β 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.* GSK3β, 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

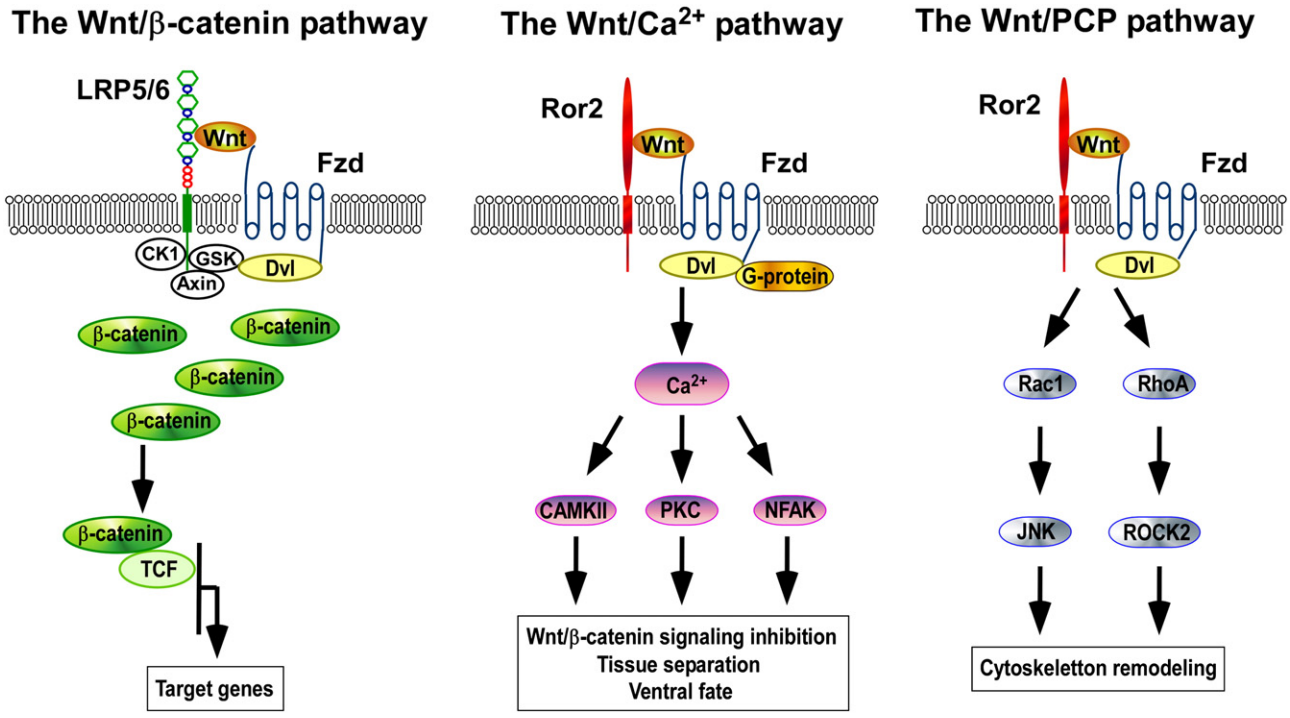

Fig. 1. The canonical Wnt/β-catenin and non-canonical Wnt signaling pathways. In the Wnt/β-catenin pathway, Wnt ligands form a ternary complex with Fzd and LRP5/6, which disrupts the Axin, CK1, GSK3β, and β-catenin complex *via* the activation of Dvl. Subsequently, cytoplasmic β-catenin stability increases which results in the formation of the β-catenin/TCF transcriptional complex and the ensuing expression of respective target genes. The Wnt/Ca^{2+} 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 Ca^{2+} 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.