

Advances in Antitumor Research of Frizzled7 Inhibitors

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Abstract. Frizzled-7 (FZD7) is a key Wnt receptor that is frequently overexpressed in aggressive solid tumours and fuels therapy resistance. Over the past several years, a diverse arsenal of FZD7 inhibitors, including monoclonal antibodies, antibody–drug conjugates, bifunctional fusion proteins, small-molecule and peptides—has been discovered or synthesized by researchers, and it has been proven that tumor cell amplification or resuscitation can be controlled by inhibiting FZD7. Among them, Humanised antibody SHH002-hu1, the latest antibody targeting FZD7, achieves high affinity with low cross-reactivity. Yet no agent has progressed beyond phase Ib. After analyzing the latest researches, this article synthesise the current landscape, classifying inhibitors by modality, then provides a comprehensive reference for the new drug design of the target and suggests the future use direction of FZD7 inhibitors. In the future, the selectivity of targeted FZD7 antibodies may become the focus. At the same time, the combined drug use strategy of the target inhibitor with other anticancer drugs and the individualized medication method for different patients will also become the direction of research.

Keywords: Frizzled-7, Wnt signaling pathway, tumor suppression, preclinical studies.

1. Introduction

Non-small cell lung cancer (NSCLC) ranks among the world's deadliest cancers, with its high incidence and mortality posing a significant threat to public health. Despite recent advancements in diagnostic technologies and therapeutic approaches, patients still face low 5-year survival rates due to the tumor's aggressive nature, metastatic potential, and resistance to treatment. This underscores the critical need for identifying novel therapeutic targets and effective anti-tumor strategies. Frizzled-7 (FZD7), a core receptor in the Wnt signaling pathway, exhibits abnormally high expression in various malignancies and promotes tumor development, progression, and metastasis by activating this signaling network.

Recent breakthroughs in FZD7 inhibitor research have opened new avenues for treating NSCLC and other aggressive cancers. Vantictumab, currently the most clinically advanced FZD7-targeting drug, demonstrates efficacy against various cancers including triple-negative breast cancer (TNBC) and colorectal cancer (CRC), while synergizing with chemotherapy agents like paclitaxel or cisplatin to reduce cancer recurrence. Researchers have identified small molecule compounds that bind to specific regions of the FZD7 protein, inhibiting its activity and blocking downstream signaling pathways. These compounds also exhibit good blood-brain barrier permeability, making

them suitable for treating brain tumors. Additionally, microRNA molecules can bind to specific sites in the FZD7 protein gene, suppressing its expression. It may become a new idea for targeted inhibition of FZD7 and be applied to the treatment of a variety of cancers. Current FZD7 inhibitors primarily include antibodies, small molecule compounds, and peptide antagonists, though most remain in preclinical or Phase I trials. This is due to the high structural homology of FZD family proteins, which increases off-target risks for FZD7 inhibitors. Existing antibodies often cause bone-related adverse reactions, limiting their clinical application. Furthermore, the importance of Wnt pathway in maintaining tissue stability also poses safety concerns for long-term medication use.

This article provides a comprehensive review of the biological significance and unique tumor manifestations of FZD7, while elucidating its signaling mechanisms and the pathogenic mechanisms underlying cancer development through abnormal expression. The study systematically categorizes and synthesizes current research progress and clinical applications of FZD7 inhibitors based on their molecular types. Finally, it discusses the therapeutic potential, challenges, and future prospects of FZD7 inhibitors in various cancers characterized by abnormal receptor expression.

2. The tumor biology significance of FZD7

As a key member of the G protein-coupled receptor (GPCR) family, FZD7 serves as one of the core receptors in the Wnt signaling pathway. Under normal physiological conditions, FZD7 plays a role in regulating fundamental biological processes such as embryonic development, tissue homeostasis, and cellular polarity. However, in various malignancies, FZD7 expression is significantly upregulated, driving tumor development through activation of both the canonical Wnt/ β -catenin and non-canonical Wnt/PCP (planar cell polarity) pathways. Studies have revealed that FZD7 exhibits abnormally high expression in aggressive tumors including glioblastoma multiforme (GBM), triple-negative breast cancer (TNBC), colorectal cancer, and ovarian cancer. This abnormal expression is closely associated with maintaining stem cell characteristics, promoting epithelial-mesenchymal transition (EMT), and facilitating chemotherapy resistance formation.

3. Carcinogenic mechanism of FZD7

3.1. Abnormal activation of signal pathway

By binding to Wnt ligands, FZD7 stabilizes and promotes the changes in position of β -catenin protein in the nucleus, thereby activating the expression of downstream oncogenes and driving abnormal progression of cell cycle and uncontrolled proliferation.

When Wnt and LRP5/6 are not interacting, the level of β -catenin is controlled by the APC, axin, and GSK3 β complex. These three proteins promote phosphorylation of β -catenin by Ck1 and GSK3 β , leading to polyubiquitination followed by degradation via 26S proteasomes. However, when Wnt binds to LRP5/6 and FZD, the phosphorylation and degradation of β -catenin are inhibited. Instead, its accumulation allows binding with the TCF transcription factor, forming the TCF- β -catenin complex. This complex then activates Wnt target genes and multiple transcription factors through DNA binding.

3.2. Maintenance of tumor stem cells

Among various solid tumors, FZD7 has been identified as a surface marker of cancer stem cells (CSCs). These CSCs expressing FZD7 possess self-renewal capabilities, multi-directional differentiation potential, and drug resistance characteristics, serving as the root cause of tumor

recurrence. Studies indicate that in colorectal cancer stem cells, FZD7 maintains the survival and function of Lgr5⁺ stem cells through Wnt signaling, enabling these cells to remain dormant long-term after treatment and ultimately leading to tumor recurrence.

3.3. Reshaping of tumor microenvironment

By activating effector molecules such as Rho GTPase, FZD7 promotes cytoskeletal reorganization and tumor cell migration while modulating interactions between cancer cells and their microenvironment, thereby creating favorable conditions for metastasis. Given its limited expression in normal tissues where other FZD family members partially compensate for its functions, and its high-specificity expression and critical role in tumor tissues, FZD7 emerges as a highly promising therapeutic target. Targeting FZD7 not only directly inhibits tumor growth but also prevents recurrence and metastasis by eliminating CSCs, offering new avenues to overcome drug resistance and improve patient outcomes.

4. Classification and mechanism of action of FZD7 inhibitors

As a key member of the G protein-coupled receptor (GPCR) family, FZD7 serves as one of the core receptors in the Wnt signaling pathway. Under normal physiological conditions, FZD7 plays a role in regulating fundamental biological processes such as embryonic development, tissue homeostasis, and cellular polarity. However, in various malignancies, FZD7 expression is significantly upregulated, driving tumor development through activation of both the canonical Wnt/ β -catenin and non-canonical Wnt/PCP (planar cell polarity) pathways. Studies have revealed that FZD7 exhibits abnormally high expression in aggressive tumors including glioblastoma multiforme (GBM), triple-negative breast cancer (TNBC), colorectal cancer, and ovarian cancer. This abnormal expression is closely associated with maintaining stem cell characteristics, promoting epithelial-mesenchymal transition (EMT), and facilitating chemotherapy resistance formation.

4.1. Antibodies

Monoclonal antibodies (mAbs) have become a crucial component of targeted therapy due to their high specificity and long half-life. The SHH002-hu1 humanized antibody developed by the Shanghai Health Medical College team represents a significant breakthrough. Through hybridoma technology, the team screened for a mouse-derived anti-FZD7 antibody (SHH002) with high affinity, then performed humanization using Discoverystudio software, ultimately obtaining SHH002-hu1 with over 96% humanization. This antibody exhibits an affinity constant for FZD7 below 10^{-12} M and shows no cross-reactivity with other FZD family members, effectively reducing off-target risks. Its mechanism involves blocking Wnt ligand binding to FZD7, thereby inhibiting activation of the β -catenin signaling pathway. Studies demonstrate that this antibody can effectively suppress cell proliferation and metastasis in TNBC and NSCLC, while overcoming the systemic toxicity of traditional chemotherapy drugs [1].

Table 1. Targeting biomolecules for FZD

Molecular name	Binding site	Bioactivity	References
DRPB_Fz7	FZD1/2/7CRD (cysteine-rich domain)	1. Bind to FZD1/2/7 2. Moderately reduce the expression of Wnt target gene in the liver	[2]
Anti-human FZD7 antibody	FZD7CRD	1. Exhaust the stem cell characteristics of FZD7 2. Reduce the survival rate of FZD7	[3]
FZD7scFv	FZD7CRD	1. Inhibit the cell growth of TNBC cells and increase apoptosis 2. Reduce the expression of Wnt target genes	[4]
FZD7-NS	FZD7CRD	1. Inhibition of Wnt/ β -catenin dependent pathway 2. Reduce TNBC cell survival and in vitro mobility	[5]
FZD7-Fab	FZD7	1. Selective binding to FZD7 2. Inhibit β -catenin-dependent Wnt pathway with inducing Wnt-3a	[6]
F2 scFv	FZD1/2/7CRD	1. Bind to FZD1/2/7 (specific subtypes) 2. Combined with F3 (FZD) 5/8 antagonist can do harm to intestinal cells	[7]
Vantictumab (OMP-18R5)	FZD1/2/5/7/8CRD	1. Bind to FZD1/2/5/7/8 2. Inhibit Wnt pathway which depend on β -catenin 3. Inhibit several types of tumors 4. Efficacy enhancers with several standardized therapeutic drugs	[8]

Table 1 lists other antibody inhibitors that targeted FZD7. Ankyrin repeat proteins are genetically engineered antibody mimics that bind to target proteins with high specificity and affinity. Dang's team developed FZD subtype-specific inhibitors by computationally designing large surface regions of the CRD domains across FZD subtypes, generating subtype-specific variants through specific contact points in conserved interfaces. Their first innovation, DRPB_Fz8, demonstrated a "handshake" model binding pattern identical to FZD8's crystal structure, effectively blocking Wnt signaling from binding to FZD. Subsequent designs included DRPB_Fz4 and DRPB_Fz7 for FZD4/FZD7, along with DRPB_Fz7/8 targeting FZD7/FZD8. Crucial residues were identified through crystal structures, such as the Ala111Asp mutations in DRPB_Fz8 to DRPB_Fz7/8, which form hydrogen bonds and salt bridges interacting with FZD's lysine 7 (corresponding to glutamic acid 8). Additionally, CRD epitopes outside lipid-binding grooves could inhibit FZD. Small molecule antagonists binding to FZD8's CRD residues provided proof-of-principle evidence for receptor-targeting mechanisms[2].

Anti-FZD7 antibodies represent a major class of FZD-targeting biomolecules in cancer therapy. A commercialized FZD7 antibody (anti-FZD7Ab) can cause extensive cell death[3], by depletes stem cell characteristics in Wilms' tumor (WT) cells, which are sensitive to FZD7, while reducing FZD proliferation[9]. Other FZD-targeting antibodies such as single-chain variable (scFv) antibodies[10], which specifically bind to FZD7 and inhibit BC cell growth and promote apoptosis in anticancer trials. Riley et al. enhanced the efficacy of FZD-targeting antibodies by using nanoparticles, developing FZD7-NS that selectively binds to FZD-expressing TNBC cells and antagonizes the β -catenin-dependent Wnt pathway, outperforming free FZD antibodies[5]. FZD7-Fab protein specifically recognizes FZD7 and can be used for enrichment of human embryonic stem cells (hESC) expressing high levels of FZD7 via flow cytometry. FZD7-Fab treatment reduces

pluripotency markers in hESC and disrupts the Wnt-3a-induced Wnt pathway. Notably, the Fab does not prevent Wnt-3a from engaging FZD7; instead, it drives the proteolytic turnover and functional silencing of the receptor. Fernandez and co-workers hypothesized that FZD7-Fab induces FZD endocytosis, thereby activating the Wnt pathway. In this process, the E3 ligases Rnf43 and Znf3 exert negative feedback by ubiquitinating and clearing the FZD-LRP complex from the plasma membrane [11].

Recently, researchers have developed soluble Wnt mimetics to artificially activate the Wnt signaling pathway. Chen et al. created such mimetics by linking two scFv antibodies to FZD CRD and LRP6. By modifying the FZD-binding scFv, the team achieved selective Wnt activation. Interestingly, when used alone with the FZD-binding arm, the mimetic could be converted into a subtype-selective antagonist of FZD called [7].

The most advanced FZD antibody, which is close to market is the fully human monoclonal antibody vantictumab (OMP-18R5), which recognizes an epitope on FZD1, 2, 5, 7 and 8 and, in cell-based models, broadly suppresses β -catenin-mediated signaling. In vivo studies demonstrated its anticancer efficacy against various cancers and synergistic effects with standard chemotherapy drugs, inhibiting tumor recurrence after high-dose chemotherapy. However, development of vantictumab was halted in Phase 1b clinical trials due to bone toxicity [12,13].

4.2. Dual-function proteins

To enhance the antitumor effect and overcome tumor immune escape, researchers have developed a variety of dual-function fusion proteins based on FZD7 targeting.

4.2.1. SHH002-hu1-MICA

The innovative design integrates a humanized antibody targeting FZD7 with major histocompatibility complex class I chain-associated protein A (MICA) through genetic engineering. The fusion protein specifically binds to FZD7-expressing tumor cells via its antibody component, anchoring MICA molecules on the cell surface. Simultaneously, by binding MICA to natural killer cell surface receptor NKG2D, it recruits and activates NK cells, thereby restoring immune surveillance through the NKG2D pathway. This groundbreaking approach combines targeted Wnt signaling with immune system activation for dual therapeutic effects in cancer treatment.

4.2.2. FZD7 targeted nanoparticles

A research team at the University of Delaware has developed PLGA nanoparticles coated with anti-FZD7 antibodies for delivering the chemotherapy drug doxorubicin (DOX). Guided by FZD7 antibodies, these nanoparticles specifically deliver DOX to TNBC cells expressing FZD7. Studies show that FZD7-targeted DOX nanoparticles not only enhance drug accumulation in tumor tissues but also simultaneously inhibit Wnt signaling pathway, by increasing β -catenin phosphorylation and promoting its degradation. Compared with traditional DOX, this strategy significantly enhanced the antitumor effect and reduced the systemic toxicity[14].

4.2.3. Antibody-drug conjugate septusimab vedotin (F7-ADC)

The antibody–drug conjugate F7-ADC pairs a chimeric human/mouse anti-FZD7 antibody with the microtubule-disrupting agent monomethyl auristatin E. It homes in on human FZD7, eradicating ovarian carcinoma cells in culture and shrinking established tumors in mouse xenografts. To

evaluate the in vivo toxicity of F7-ADC, researchers developed mice carrying modified FZD7 genes that produce Fzd7 proteins responsive to the human-targeted F7-ADC. Treatment with these mice showed no acute toxicity, indicating potential safety in patients. Data suggest that antibody-drug conjugation may represent a potent clinical strategy against FZD7-expressing ovarian cancers[15].

4.3. Small molecule and peptide FZD7 inhibitors

Small molecule inhibitors have become an important strategy for FZD7 targeted therapy due to their good tissue permeability and oral bioavailability. In recent years, researchers have discovered a variety of small molecule compounds with FZD7 inhibitory activity through computer-aided drug design and natural product screening.

4.3.1. Cycloartobiloxanthone

In a 2025 study, scientists discovered a plant-derived flavonoid compound that specifically binds to the CRD of FZD7 with exceptional affinity, achieving a binding energy as high as -65.2 ± 3.8 kcal/mol. This compound effectively blocks the binding site of Wnt3a ligands by inducing conformational changes in the TM6 helix of the FZD7 receptor's transmembrane region, thereby inhibiting downstream signaling pathways.

In glioblastoma model experiments, cycloartobiloxanthone demonstrated dual pathway inhibition: it not only disrupted β -catenin's nuclear translocation but also suppressed Rho GTPase activation while inducing mitochondrial apoptosis in tumor cells. This finding is particularly noteworthy, as the compound exhibits a logP value of 3.2 and Caco-2 permeability of 6.7×10^{-6} cm/s, indicating strong blood-brain barrier penetration capability—a crucial for brain tumor therapy [16].

4.3.2. Mir-1-3p

Elevated FZD7 markedly protected HO8910 and SKOV3 ovarian cancer cells from Erastin- or RSL3-triggered death, as evidenced by improved viability and diminished intracellular malondialdehyde. In terms of mechanism, the FZD7 transcript carries a functional miR-1-3p binding site in its 3'-UTR, when miR-1-3p occupied this site, FZD7 protein levels fell, sensitizing cells to ferroptotic stress. Introducing miR-1-3p mimics further suppressed survival ($P < 0.05$ – 0.001) and raised MDA content ($P < 0.01$), whereas blocking the microRNA had the opposite effect on both metrics ($P < 0.05$ – 0.001). MiR-1-3p analogs decreased the viability of Erastin or RSL3-treated cells and increased intracellular MDA levels, whereas miR-1-3p inhibitors significantly improved cell viability and reduced MDA levels. Importantly, forced expression of FZD7 reversed the heightened ferroptosis induced by miR-1-3p mimics ($P < 0.05$ – 0.01), confirming FZD7 as the key downstream effector [17].

4.3.3. Other small molecules

The GPCR F family comprises SMO and FZD, which share high sequence similarity. Based on the crystal structure of SMO and its antagonist LY2440680, as shown in Table 2, Zhang et al. developed a homologous model of FZD7 for virtual screening of 500,000 small molecules and 5,000 highly differentiated compound analogs. Six small molecules were identified to inhibit the Wnt/ β -catenin signaling pathway, with SRI37892 showing the most potent effect ($IC_{50}: 0.66 \mu M$) in suppressing TNBC cell proliferation and colony formation while reducing LRP6 phosphorylation. Although its selectivity against FZD was not evaluated, SRI37892 may exhibit activity against multiple FZD

[18]. Pinto et al. generated 100 homologous models of FZD7CRD using crystal templates of Wnt-3, Wnt-3a, and FZD, screening 29 compounds similar to palmitic acid. Four fatty acids (as shown in ZINC05972969 in Table 2) demonstrated comparable or superior binding affinity, though further in vitro studies are required to verify their effects on the Wnt pathway and selectivity [19].

Table 2. Targeted FZD7 small molecules

Molecular name	Structure	The presumed binding site	Bioactivity	References
SRI37892		FZD7 transmembrane domain (TMD)	In vitro inhibition of the proliferation of TNBC cells and the Wnt pathway which depends on β -catenin	[18]
ZINC0597296		FZD7 CRD	indeterminate	[19]

4.4. Peptide inhibitors

In addition, there are also peptide inhibitors targeting FZD7. Nile et al. screened a phage peptide library for peptides specifically binding to the hFZD7 CRD, with FZ7-21 demonstrating optimal efficacy, which is shown in Table 3. It effectively inhibited Wnt-3a-induced Wnt/ β -catenin signaling and stabilized β -catenin. The cysteine residue Cys10 was identified as the key determinant, with its replacement significantly reducing or eliminating inhibitory activity. Fluorescence size exclusion chromatography (FSEC) confirmed Fz7-21's selectivity for FZD1/2/7 subtypes. Crystal structure analysis revealed that Fz7-21 forms disulfide bond dimers through Cys10, interacting with novel residues in the hFZD7 CRD to deactivate the FZD7 dimer. Rather than blocking Wnt-3a from reaching FZD7, this binding mechanism prevents the three-way assembly of Wnt-3a, FZD7, and LRP6 [20]. Also, an optimized peptides enhanced potency by inhibiting the interaction between Clostridium difficile toxin B's and FZD, achieving IC₅₀ values in the low nanomolar range [21]. These peptides provide novel therapeutic approaches for FZD-related diseases including cancer and contribute to understanding FZD's roles in physiological and pathological processes.

Table 3. Targeted FZD biomolecules (The list of peptide FZD7 inhibitors)

Molecular name	Binding site	Bioactivity	References
Fz7-21	FZD7 CRD	1. Inhibition of the Wnt/ β -catenin pathway in Wnt3a-induced HEK 293 cells 2. Prevented the generation of Wnt 3a-FZD7-LRP6 protein complex 3. Inhibit the interaction between Clostridium difficile and FZD7	[2]

5. Clinical preclinical research progress of Fdz7 in several cancers

5.1. Colorectal cancer

Several FZD receptors, including FZD3, FZD6, and FZD7, are overexpressed in human intestinal tumors and cell lines. In APC-mutated SK-CO-1 colon cancer cells, FZD7 overexpression can be blocked by using a dominant negative extracellular domain to inhibit FZD7, which effectively suppresses cell growth. This indicates that FZD7 plays a crucial role in the proliferation of these cancer cells, with its normal function potentially contributing to tumor progression through processes like cell proliferation. Another potential strategy for FZD7 inhibition might target disseminated metastatic cells responsible for secondary tumor development, which typically emerge

years after primary tumor resection via surgery or chemotherapy. FZD7 coordinates metastasis evasion mechanisms (MET) in colon cancer cells, where MET is essential for mesenchymal metastatic cells to establish new tumors at distant sites. By modulating MET, FZD7 promotes tumor cell formation of metastatic foci in new locations, enabling cancer spread from the primary site to other regions.

As FZD7 is located on the cell surface, it serves as an ideal target for antibody-based therapies. The mAb OMP-18R5 (brand name Vantictumab), developed by Oncomed Pharmaceuticals, has entered Phase 1b clinical trials for treating various solid tumors including colorectal cancer, neuroendocrine carcinoma, breast cancer, sarcoma, pancreatic cancer, and non-small cell lung cancer [22]. Antibody-targeted therapy works by using mAbs to specifically bind to FZD7, thereby blocking its function to inhibit tumor growth and metastasis. While this approach offers advantages like high specificity, it also faces challenges such as antibody-related side effects. The most common adverse reactions associated with this FZD7-targeting antibody include nausea, hair loss, fatigue, and peripheral neuropathy, with a small number of patients experiencing fractures outside the dose-limiting toxicity (DLT) window[12]. Due to bone toxicity concerns, clinical trials for this inhibitor were halted at Phase 1b, limiting its application in clinical practice [23].

5.2. Gastric cancer with *Helicobacter Pylori* (H. Pylori) infection

In gastric cancer cells infected with *Helicobacter pylori*, the WNT signaling pathway shows abnormal activation. FZD7, a crucial co-receptor in this pathway, has been identified as a key regulator. Research demonstrates that *H. pylori* infection induces significant and dose- and time-dependent induction of FZD7. Knocking down FZD7 effectively inhibits *H. pylori*-induced proliferation of gastric cancer cells. As a predictive miRNA for FZD7, miR-27b exerts negative regulation through its interaction with the 3' untranslated region of FZD7. Overexpression of miR-27b significantly suppresses both *H. pylori*-induced cancer cell proliferation and WNT signaling pathway activation, establishing it as a promising molecular therapeutic target for this disease[24].

5.3. TNBC

R.S. Riley and E.S. Dai found that the multivalent nature of nanoparticles could significantly inhibit signaling in cancer cells. When they coated nanoparticles with the Frizzled 7 antibody, they were more effective at inhibiting the Wnt signaling pathway than free delivery of the antibody, reducing the survival rate of TNBC cells.

Inhibition of the Wnt signaling pathway induces autophagy upregulation, leading to therapeutic resistance. The combination of autophagy inhibitor chloroquine (CQ) and FZD7-NS (a nanocarrier coated with Frizzled7 antibody) enhances treatment efficacy. FZD7-NS inhibits Wnt signaling targets and increases autophagy marker LC3 expression. When combined with CQ, it reduces stem cell gene expression in TNBC cells, inhibits migration and self-renewal, and demonstrates superior efficacy compared to single-agent use or free antibody conjugation[25]. This indicates that nanocarrier design is crucial for therapeutic success. In summary, the synergistic regulation of Wnt signaling and autophagy by FZD7-NS and CQ represents a promising strategy for anti-TNBC therapy.

5.4. Prostate cancer

FZD7 is highly expressed in prostate cancer cell lines and has been bioinformatically predicted as a target gene of miR-613, as verified by dual-luciferase reporter assays. Functional gain-of-function experiments demonstrated that miR-613 overexpression inhibits prostate cancer cell proliferation and invasion while downregulating the Wnt signaling pathway. Overexpression of FZD can counteract the inhibitory effects of miR-613. Notably, miR-613 expression is reduced in prostate cancer tissues and negatively correlated with FZD7 expression [26]. These findings indicate that miR-613 exhibits tumor suppressive activity, making FZD7 a potential therapeutic target for prostate cancer.

5.5. NSCLC

NSCLC, one of the world's deadliest cancers, is primarily driven by metastasis as a major cause of treatment failure. SHH002-hu1, a humanized antibody targeting Fzd7 developed by our research team, has demonstrated remarkable efficacy. Studies reveal that SHH002-hu1 specifically binds to FZD7-positive NSCLC cells and targets NSCLC tissues. It significantly inhibits cell migration and invasion, effectively suppresses Wnt/ β -catenin signaling activation, and reduces EMT in NSCLC cells. In both A549/H1975 subcutaneous xenograft tumor models and popliteal lymph node metastasis models, SHH002-hu1 effectively suppresses NSCLC xenograft growth and lymph node metastasis. Selective targeting of FZD7-positive NSCLC through disruption of Wnt/ β -catenin signaling, while inhibiting tumor invasion and metastasis [27], positions SHH002-hu1 as a promising candidate for NSCLC targeted therapy.

6. Conclusion

This article summarizes the current research on anti-tumor targeting FZD inhibitors. It is found that some studies on small molecules and peptides are in the early stage, and the specific mechanism of action is not clear, and the adverse reactions of macromolecular proteins such as antibody inhibitors need to be solved. In the future, we should first solve the off-target problem of FZD7 inhibitors, and reduce their cross-reaction with other FZD protein family members while further enhancing antibody affinity, so as to reduce adverse reactions. As an emerging target, clarifying the molecular details of the interaction between FZD7 and Wnt pathways can provide a basis for precise inhibition. In addition, it can be explored in combination with autophagy inhibitors (such as chloroquine), chemotherapy drugs (such as dolobicin nanoparticles) or immune checkpoint inhibitors to inhibit tumor growth and recurrence. Individualized medication is also a very important point. Due to the heterogeneity of the tumor, the response of each patient to FZD7 inhibitors is different. Future research should pay more attention to the personalized treatment of patients by analyzing the expression level, genetic mutation status and Wnt signaling pathway of FZD7 in the patient's tumor tissue. The activation situation, for patients who are sensitive to FZD7 inhibitors, more targeted treatment should be carried out to improve the effectiveness and safety of treatment. Existing preclinical studies show that FZD7 inhibitors have an inhibitory effect on a variety of tumor cells, and because the protein participates in maintaining the characteristics of tumor stem cells, such inhibitors can reduce the probability of chemotherapy resistance and recurrence of tumor cells. Therefore, FZD7 inhibitors have a broad application prospect.

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