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REVIEW

Jiang et al: sFRP4 in cancer – Dual roles

Secreted frizzled-related protein 4 (sFRP4) in cancer – Dual roles in tumorigenesis and therapeutic potential: A review

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ABSTRACT

Secreted Frizzled-Related Protein 4 (sFRP4), the largest member of the Secreted Frizzled-Related Protein (sFRP) family, contains two functional domains: a cysteine-rich domain (CRD) homologous to the Wnt-binding region of Frizzled (FZD) receptors and a netrin-like (NTR) domain structurally similar to axonal guidance proteins. By modulating the Wingless/Integrated (Wnt) signaling pathway, sFRP4 regulates essential cellular processes including proliferation, differentiation, apoptosis, and tissue homeostasis. This review aims to provide a comprehensive overview of the dualistic roles of sFRP4 in cancer, highlighting its tumor-suppressive and tumor-promoting functions, underlying molecular mechanisms, and therapeutic potential. A systematic literature search was conducted in PubMed and Web of Science databases (1996–2025) using predefined keywords, and from 277 identified publications, 47 studies were included that comprised clinical data, *in vitro* cell models, and *in vivo* experimental systems. Findings demonstrate that sFRP4 frequently acts as a tumor suppressor by sequestering Wnt ligands, suppressing cancer stem cell-like properties, reprogramming tumor metabolism, inhibiting angiogenesis, and enhancing chemosensitivity. Its downregulation is often driven by promoter hypermethylation or repression mediated by microRNAs (miRNAs). Conversely, in gastrointestinal and prostate cancers, sFRP4 is frequently upregulated, where it promotes Wnt pathway activation, invasion, stemness, chemoresistance, and reshaping of the tumor immune microenvironment. Mechanistic insights indicate that post-translational modifications and nuclear localization of sFRP4 further contribute to its paradoxical context-dependent functions. In conclusion, sFRP4 exerts dual roles in tumorigenesis, acting either as a tumor suppressor or promoter depending on tissue type, tumor microenvironment, and regulatory mechanisms. This complexity underscores both the challenges and opportunities of targeting sFRP4 in oncology, and future therapeutic strategies incorporating recombinant proteins, synthetic peptides, and nanoparticle-based delivery systems hold promise for harnessing its anti-tumor potential while overcoming resistance mechanisms.

Keywords: sFRP4, tumorigenesis, dual role, oncotherapy.

INTRODUCTION

The sFRP (Secreted Frizzled-Related Protein) family is the largest group of Wnt inhibitors. The prototypical member of this protein family, designated Frizzled-related zinc-binding protein (Frzb), was initially characterized through evolutionary analysis, which revealed significant amino acid sequence homology with the ligand-binding domains of Frizzled (FZD) transmembrane receptors[1]. FZD are a class of transmembrane proteins belonging to the GPCR (G protein-coupled receptor) superfamily and play a critical role in the Wnt signaling pathway[2],In 1997 Leyns et al. demonstrated that sFRP1 functions as a Wnt antagonist[3]. This was followed by Melkonyan, who identified other members of this family[4]. The sFRPs family encompasses five evolutionarily conserved paralogs that segregate into distinct phylogenetic clusters based on their genomic architecture. Phylogenetic analysis revealed subgroup I (*SFRP1/2/5*) encoded by tri-exonic genes (chromosomal loci 8p12-p11.1, 4q31.3, 10q24.1), whereas subgroup II (*SFRP3/4*) exhibits multi-exonic organization (six coding exons) with chromosomal localization at 2q31-q33 and 7p14-p13, correlating with alternative splicing patterns in Wnt signaling modulation[5].

sFRP4 (Secreted Frizzled-Related Protein 4) is the largest member of the sFRP family and plays a significant role in the extracellular environment by regulating biological processes, such as cell signaling and cell proliferation. Structurally, sFRP4 contains an N-terminal cysteine-rich domain (CRD) with a frizzled-like motif and a C-terminal heparin-binding netrin-like (NTR) domain. The cysteine-rich CRD domain is closely related to antagonizing the Wnt signaling pathway[3]. This domain is identical to the CRD of Frizzled, which interacts with Wnt. The CRD of sFRP4 has relatively high sequence similarity, contains 10 conserved cysteine residues, and features highly conserved disulfide bonds[6]. The NTR domain consists of approximately 120 amino acids and 6 cysteine residues. In addition to sFRPs, there are up to seven different protein families or subfamilies (such as axonal guidance factors (netrins), complement proteins C3, C4, C5, and procollagen C-endopeptidase enhancer protein (PCOLCEs), etc.) whose N-terminal domains are homologous to the

NTR domain of SFRPs[7]. Compared to other family members, the NTR domain of sFRP4 possesses a lower positive charge, suggesting it may be more easily transported from the secretion site to act on distant cells. Consequently, sFRP4 exhibits weaker heparin binding affinity but demonstrates stronger binding to Wnt proteins via its CRD[8]. Both the CRD and NTR domains are indispensable for optimal Wnt inhibition[9].

sFRP4 is widely recognized as an inhibitor of the Wnt/β-catenin signaling pathway[10]. The Wnt/β-catenin cascade is an ancient and well-preserved signaling pathway that exists in various species, including Drosophila and mammals. The Wnt family is comprised of numerous members that function in an autocrine or paracrine manner. The Wnt protein family comprises 19 secreted proteins that have been identified in humans. The initiation of Wnt/β-catenin signaling primarily depends on Wnt1, Wnt2, Wnt3, Wnt3a, Wnt8b, Wnt10a, and Wnt10b[11]. Upon secretion, these Wnt proteins bind to Frizzled (FZD) receptors and LRP5/6 co-receptors, triggering a signaling cascade. The key downstream effector β-catenin escapes ubiquitin-mediated degradation by avoiding phosphorylation by the cytoplasmic APC/Axin/GSK3β destruction complex. This leads to β-catenin accumulation and its nuclear translocation. Within the nucleus, β-catenin uses its armadillo repeat domain to form a tripartite transcriptional activation complex with TCF/LEF transcription factors and chromatin-modifying coactivators, which drives the expression of Wnt target genes[12]. sFRP4 exhibits general affinity for Wnt [13]. Throughout this process, β-catenin serves as a central signaling mediator.

sFRP4 regulates Wnt signaling through multiple distinct mechanisms:

(1) sFRP4 competitively inhibits Wnt signaling via CRD- or NTR-mediated ligand sequestration, effectively blocking Wnt-Frizzled receptor complex formation and the subsequent LRP5/6 co-receptor engagement[14].

(2) sFRP4 may antagonize other sFRP family members, modulating their activity[15].

(3) Wnt is prevented from binding to FZD and transmitting downstream signals[16].

(4) In some contexts, sFRP4 promotes Wnt-FZD interactions by simultaneously binding to both molecules, thereby enhancing signal activation[17,18].

(5) sFRP4 participates in the extracellular transport of Wnt ligands[19,20].

Conversely, the production and intracellular transport of sFRP4 are modulated by Wnt-mediated signaling mechanisms[21]. Given the critical role of Wnt signaling in oncogenesis, sFRP4 is generally considered a tumor suppressor. However, owing to the complex crosstalk between Wnt and other signaling pathways, potential context-dependent oncogenic properties of sFRP4 have also been proposed[22].

While previous studies primarily characterized sFRP4's extracellular functions as a secreted Wnt modulator, recent evidence reveals that it also exerts concentration-dependent bidirectional roles within the nucleus. In cells with high β-catenin and low sFRP4 levels in the nucleus, β-catenin and sFRP4 bind exclusively via their C-terminal regions, implying a higher binding affinity of the sFRP4 C-terminus for β-catenin. This selective interaction upregulates the transcriptional activity of β-catenin. Conversely, under conditions of low β-catenin and high nuclear sFRP4 levels, sFRP4 engages β-catenin at both its N- and C-termini. Notably, the inhibitory effect of sFRP4-β-catenin N-terminal binding outweighs the promoting effect of C-terminal binding[23]. This stoichiometry-dependent switch provides the molecular mechanism for sFRP4's context-dependent roles in tumorigenesis. Furthermore, sFRP4 exhibited DNA-binding capacity in the nucleus. Luciferase assays and ChIP-qPCR confirmed the recruitment of sFRP4 to the Dickkopf-1 (Dkk1) promoter, another Wnt antagonist, thereby functioning as a transcription factor that regulates Dkk1 expression[24].

The Wnt signaling cascade demonstrates profound evolutionary conservation, functioning across phylogenetically diverse organisms from invertebrate models to mammalian systems, orchestrating multifaceted cellular activities, including mitotic regulation, lineage specification, programmed cell death, tissue equilibrium maintenance, and progenitor cell regeneration[25]. In cancers, aberrant activation of the Wnt pathway is closely associated with various malignancies such as liver and breast cancers[26]. The Wnt/β-catenin cascade is crucial for the regulation of cancer

stem cells[27], metabolic reprogramming of tumor cells[28], and chemoresistance[29].

In addition to exerting its functions through the Wnt signaling pathway, sFRP4 also plays critical roles via other signaling mechanisms. sFRP4 appears to sequester intermediates of the PI3K/Akt pathway, which may contribute to the induction of apoptosis, potentially through mechanisms independent of canonical Wnt signaling[30,31]. Furthermore, sFRP4 induces apoptosis by activating the ROS(Reactive oxygen species) pathway, which subsequently triggers the Fas-p53 pathway[32].

METHODS

To conduct a comprehensive literature review, we performed an extensive search of the Web of Science and PubMed databases using specifically tailored keywords to identify the most relevant publications. The search terms included “Secreted Frizzled-Related Protein 4” OR “sFRP4” AND “cancer” OR “neoplasm” OR “carcinoma”, covering publications from approximately 1996 to 2025. The initial search yielded 277 relevant articles. Subsequently, we applied further screening to refine the selection, with a specific focus on studies investigating sFRP4 across various tumor types. Priority was given to research comprising clinical data from human patients, *in vitro* cell line experiments, and *in vivo* animal studies to enable a comprehensive assessment of the role of sFRP4 in cancer. Following rigorous screening, a total of 47 articles were included for analysis

ANTI-TUMOR EFFECTS OF SFRP4

sFRP4 functions as a tumor suppressor, primarily by sequestering Wnt ligands and inhibiting β-catenin activation. It demonstrates significant anti-oncogenic effects across diverse malignancies, including hepatocellular carcinoma[33], ovarian cancer[34], glioma[35], uterine leiomyosarcoma[36], cervical cancer[37], and lung cancer[37,38]. Clinically, sFRP4 is a valuable diagnostic biomarker for diseases such as hepatitis-associated hepatocellular carcinoma, ovarian cancer, and endometrial

cancer[39,40]. Importantly, sFRP4 deletion or epigenetic silencing correlates with poor prognosis in breast cancer, underscoring its therapeutic potential[41]. Furthermore, sFRP4 exhibits progressive loss during malignant transformation from mucinous cystadenoma to borderline mucinous tumor, and ultimately to mucinous cystic carcinoma[42].

The decrease expression of sFRP4 in tumor

Downregulation of sFRP4 in tumors due to methylation

Promoter hypermethylation of *sFRP genes* (*sFRP1-5*) occurs in multiple cancers, including breast cancer, ovarian cancer, and cutaneous squamous cell carcinoma, leading to transcriptional silencing[43,44]. A systematic pooled analysis established epigenetic correlation between *sFRP4* promoter region hypermethylation and neoplastic risk elevation, particularly in ovarian, colorectal, cervical squamous, and renal cell carcinomas[45]. DNA methylation, an epigenetic modification associated with gene silencing, can be reversed using the DNMT (DNA methyltransferase) inhibitor 5-Azacytidine (5-Aza). Treatment with 5-Aza restored the expression of epigenetically silenced genes, including *sFRP4*. In cancer stem cells (CSCs), demethylation increases sFRP4, GSK3β, and phosphorylated β-catenin levels, functionally confirming methylation-dependent *sFRP4* silencing[43]. MBD2(Methyl-CpG-binding domain protein 2) and enhancer of EZH2(zeste homolog 2), core members of the methylated MBD (DNA-binding domain) and PcG (Polycomb group) protein families, respectively, mediate epigenetic regulation. Co-silencing of MBD2 and EZH2 synergistically restored *sFRP4* expression and more effectively suppressed colorectal carcinoma cell proliferation[46]. Notably, *sFRP4* promoter hypermethylation has potential as a diagnostic biomarker in cervical squamous carcinoma[47].

Repression of sFRP4 expression by microRNA in tumors

MicroRNAs (miRNAs) are small (~18-25 nt) non-coding RNAs that post-transcriptionally regulate gene expression by binding to target mRNA 3'UTRs, leading to translational repression or mRNA degradation. They critically influence

cellular differentiation, development, metabolism, and disease pathogenesis[48]. Elevated miR-96-5p expression in cervical squamous cell carcinoma specimens indicates stage-dependent elevation and lymphovascular involvement. Mechanistic validation identified sFRP4 as its functional target, with genetic ablation of sFRP4 rescinding miR-96-5p-mediated oncogenic transformation in cervical epithelial cells[49].miR-181a targets sFRP4, thereby regulating Wnt signaling to drive stemness and platinum resistance in ovarian cancer[50]. MiR-103b directly targets sFRP4 and serves as a potential biomarker for early diagnosis of lung adenocarcinoma[51,52].MiR-31 enhances cancer cell proliferation by suppressing sFRP4 expression in lung cancer cells. MiR-942 promotes the stemness phenotype in ESCC (esophageal squamous cell carcinoma) by inhibiting sFRP4 expression[53].

sFRP4 exerts its tumor-suppressive role via the Wnt signaling pathway

Suppressing cancer stem cell-like properties

The Wnt signaling pathway plays a pivotal role in tumorigenesis and progression. Wnt pathway activation is also associated with resistance to chemotherapy and radiotherapy, which compromises treatment efficacy[12]. The stemness of tumor cells describes their potential to acquire stem cell-like traits, including self-renewal, proliferation, differentiation, and tumorigenic potential. These cancer stem cells (CSCs) are critical in tumor development, recurrence, and drug resistance[54]. Beyond self-renewal and migratory capabilities, CSCs possess mechanisms to expel toxic compounds and chemotherapeutic agents, such as the overexpression of ATP-dependent efflux pumps (e.g., ABCG2) and enhanced DNA repair systems, which contribute to chemoresistance[55,56].

Enhancing tumor chemosensitivity

In various cancers, including breast cancer, glioma, and ovarian cancer cell lines, combination therapy using sFRP4 with chemotherapeutic agents reduces CSC viability, diminishes sphere-forming ability, downregulates stemness-related genes, upregulates pro-apoptotic markers, and enhances chemosensitivity[57]. sFRP4 upregulation was observed in the chemotherapy-responsive A2780 cell line, and

forced sFRP4 expression in cisplatin-resistant cell A2780-Cis resensitized them to platinum-based agents[42]. Similarly, activation of sFRP4 by inhibiting miR-181a reduces cisplatin resistance and stemness in high-grade serous ovarian cancer (HGSOC)[50].

Triggering metabolic reprogramming

The metabolic profile of tumor cells differs significantly from that of normal cells. These metabolic alterations not only support rapid proliferation and survival but also confer adaptive advantages in harsh microenvironments, representing a hallmark of tumor cell metabolism known as metabolic reprogramming[58]. Compared with most tumor cells, CSCs may exhibit higher glycolytic activity. Studies have demonstrated that sFRP4 exerts anti-proliferative effects, induces spheroid disruption, and reduces glucose uptake, glutamine uptake, glutamate secretion, redox signatures, and signaling cascades critical for cell survival, while simultaneously promoting apoptosis within CSCs. These findings suggest that sFRP4 is a regulator of cancer stem cell metabolic reprogramming, potentially through modulation of Wnt/β-catenin-dependent bioenergetic pathways[59]. In malignant mesothelioma (MM) cells treated with sFRP4 and Wnt3a, cytochrome c oxidase levels were significantly decreased observed, indicating that sFRP4 may exert its function by suppressing cancer cell metabolism and ultimately inducing cell death[31].

Though CAF (Cancer-associated fibroblasts) secretion to inhibit tumor progression

CAFs are a critical cell type within the TME (tumor microenvironment), playing essential roles in tumor progression. CAFs are typically normal fibroblasts that undergo phenotypic and functional transformation under the influence of tumor cells or other signaling factors during tumor development. Among all stromal cells in the TME, CAFs are the most abundant and closely associated with tumor progression. CAFs secrete various growth factors, cytokines, and proteins, such as fibroblast growth factor(FGF) and transforming growth factor-β(TGF-β), which promote tumor cell proliferation and invasion. They release proteases, such as matrix metalloproteinases (MMPs), which facilitated stromal remodeling to support tumor

cell invasion and metastasis. CAFs regulate immune responses within the TME by suppressing immune cell activity, thereby aiding tumor immune evasion. CAFs participate in tumor-associated angiogenesis, promoting vascularization and nutrient supply to tumors[60]. sFRP4-expressing CAFs suppress Wnt pathway activation in mammary carcinoma through paracrine secretion of the sFRP4 protein, consequently restricting tumor cell motility and impeding molecular transitions associated with epithelial-mesenchymal plasticity[61]. Additionally, sFRP4 suppresses the differentiation of ADSCs (adipose-derived mesenchymal stem cells) into CAFs in breast cancer, thereby restraining tumor progression[62].

Suppressing the proliferation and migration of vascular endothelial cells

Angiogenesis plays a critical role in tumor growth and metastasis. The tumor neovascular network serves as a metabolic lifeline, delivering glucose and glutamine to fuel aerobic glycolysis while maintaining hypoxic niche optimization for malignant expansion and, facilitating the removal of metabolic waste to maintain tumor microenvironment homeostasis. Additionally, these vessels serve as conduits for tumor cells to enter the bloodstream and, promote metastasis. The aberrant structure of tumor vasculature may impair immune cell infiltration, enabling tumor immune evasion[63]. sFRP4 suppresses tumor angiogenesis by disrupting NO-cGMP signaling and elevating reactive oxygen species (ROS) levels, inducing endothelial dysfunction[64]. Both the CRD and NTR domains demonstrate anti-angiogenic effects: they increase intracellular calcium via the Wnt-Ca^{2+} pathway through distinct mechanisms: CRD disrupts vascular network formation, while NTR promotes endothelial cell apoptosis[65].

PRO-TUMORIGENIC EFFECTS OF SFRP4

Studies have demonstrated upregulated sFRP4 expression in gastrointestinal tract-derived tumors and prostate cancer. Gastric cancer specimens exhibit marked sFRP4 overexpression, correlating with unfavorable prognostic indicators; it also functions as a critical immune-related factor with significant implications for guiding

immunotherapy[66]. Compared to normal prostate tissue, sFRP4 expression is increased in prostate cancer and further elevated in high-grade tumors[67].

Promoting tumor progression via the Wnt signaling pathway

Emerging oncological investigations have demonstrated paradoxical sFRP4 expression dynamics and functional consequences in pan-cancer analyses, with inter-tumoral heterogeneity emerging as a critical confounding factor. sFRP4 expression is most upregulated in advanced gastric cancer[68], and correlates positively with tumor invasiveness[69]. sFRP4 and CDX1 (Caudal Type Homeobox 1) have been identified as predictive biomarkers for extra-gastric recurrence following radical gastrectomy[70]. Additionally, sFRP4 contributes to gastric cancer chemoresistance: cells resistant to cisplatin or oxaliplatin exhibit upregulated sFRP4 and β-catenin expression with nuclear translocation of β-catenin compared to their chemosensitive counterparts[71]. Colorectal cancer specimens demonstrated significant *sFRP1*/*sFRP5* mRNA downregulation in 85% and 80% of cases respectively, whereas *sFRP4* overexpression manifested in 80% of analyzed tumor samples. This distinct expression pattern suggests that sFRP4 exerts unique biological functions in gastrointestinal tumors compared with other sFRPs family members[72].

What leads to the upregulation of sFRP4 expression in gastrointestinal tumors? It has been found that sFRP4 in colorectal tumors exhibits the weakest Wnt signaling inhibitory activity among sFRPs, with a methylation frequency of only 17%[73]. Gastric carcinoma exhibits comparable *sFRP4* methylation prevalence in neoplastic and paraneoplastic tissues. In contrast, *sFRP2(Secreted Frizzled-Related Protein 2)* promoter hypermethylation demonstrated a progressive detection gradient (73.3% carcinomas vs 37.5% premalignant intestinal metaplasia lesions vs 20% mucosal controls)[74]. These findings indicate that differential promoter methylation patterns and varied Wnt inhibitory capacities likely drive sFRP4's distinct expression profiles across gastrointestinal malignancies.

Beyond this mechanism, the oncogenic role of sFRP4 is further implicated in its post-translational modification. Phosphorylation of sFRP4 by PKA at threonine

residues T186 and T189 enhances its affinity for the β-catenin/TCF4 complex, resulting in the potentiation of Wnt signaling transcriptional activity. PKA-dependent phosphorylation of sFRP4 switches it from a Wnt antagonist to a potent agonist, thereby driving stemness and chemoresistance[75].

Increasing the invasive tumor phenotype

Studies have consistently observed upregulated sFRP4 expression in prostate cancer cell lines (LNCaP, PC3, DU145, and 22Rv1) compared with that in control lines (PWR-1 and RWPE1)[76]. Cytoplasmic localization of sFRP4 has been identified as a biomarker for adverse prognostic outcomes[77]. Notably, sFRP4 may enhance osteoblast activity and promote metastatic progression in prostate cancer—a mechanism analogous to that of the Wnt inhibitor Dkk-1. It has demonstrated that Wnt inhibition by Dkk-1 reduces osteoblast differentiation and shifts lesions toward an osteolytic phenotype, driving aggressive prostate cancer. Furthermore, high sFRP4 expression in prostate cancer is closely associated with genomic instability[78].

Enhancing pro-tumor immunity

sFRP4 also modulates tumor immunity in pancreatic cancer. Studies have shown that sFRP4 expression is positively correlated with FOXP3+ Treg cell infiltration. sFRP4 promoted the secretion of T cell specific cytokines and increased the recruitment of CD4+ T cells, which may promote the Treg differentiation process. Collectively, these findings highlight sFRP4 as a novel prognostic biomarker and potential therapeutic target in pancreatic cancer[79].

CLINICAL TARGETING OF SFRP4 IN CANCER THERAPY

Recombinant sFRP4 (r-sFRP4) in preclinical models

Although the functional roles of sFRP4 in tumors remain context-dependent, therapeutic strategies targeting sFRP4 have demonstrated promising anti-tumor efficacy. Treatment of HeLa (cervical cancer) and A549 (lung cancer) cells with purified recombinant sFRP4 (r-sFRP4) resulted in a dose-dependent inhibition of cell growth by up to 40%. Increased levels of phosphorylated β-catenin and

downregulation of pro-proliferative genes (*cyclin D1*, *c-myc*, and *survivin*) indicated Wnt pathway suppression[37]. Similarly, r-sFRP4 treatment significantly reduced cell viability and migration while enhancing adhesion in uterine leiomyosarcoma cells[36]. In malignant mesothelioma (MM) cells, r-sFRP4 inhibits proliferation and migration, primarily mediated by its netrin-related motif (NTR), with limited contribution from the cysteine-rich domain (CRD). sFRP4 also suppresses Wnt3a signaling in MM cells [80]. Treatment of serous ovarian cancer cell lines with recombinant sFRP4 inhibited β-catenin-dependent Wnt signaling and reduced the transcription of Wnt target genes (*Axin2*, *CyclinD1*, and *Myc*). It also enhanced cell adhesion, decreased migration, and promoted a shift towards an epithelial phenotype, characterized by upregulated E-cadherin and downregulated mesenchymal markers (*Vimentin* and *Twist*)[81]. Furthermore, sFRP4 exhibits anti-proliferative activity against CSCs derived from breast, prostate, ovarian, glioblastoma, and head and neck tumors, while enhancing chemosensitivity[57,82,83]. These findings suggest that the combination of chemotherapy with sFRP4 may improve conventional treatment outcomes.

CRD and NTR-derived micropeptides

Synthetic micropeptides targeting the CRD and NTR domains of sFRP4 reduced CSC marker expression, inhibited angiogenesis, upregulated pro-apoptotic genes, and sensitized ovarian CSCs to cisplatin. The synthetic polypeptides exhibited a dual mechanism of action, attenuating the canonical Wnt/β-catenin signaling axis while concurrently interfering with the β-catenin-CD24 molecular crosstalk. Additionally, they effectively inhibit autophagy, a critical survival mechanism for CSCs[84]. Furthermore, overexpression of the isolated CRD and NTR domains in glioma cells downregulated the characteristic CSC traits. Notably, the NTR domain demonstrated more potent inhibitory effects than the CRD domain on MMP-2-mediated invasion and disrupted fibronectin assembly, consequently reducing adhesion in the LN229 glioma cell line[85].

Other therapy

To investigate targeted delivery, CS-DS nanoparticles encapsulating the sFRP4-GFP protein were delivered into MM cells. Both sFRP4 and NTR nanoparticles significantly reduced MM cell viability, with the NTR domain showing the strongest anti-tumor effects compared to CRD nanoparticles[86]. In a separate study, alginate-encapsulated Wharton's jelly derived mesenchymal stem cells (WJMSCs) were co-cultured with breast cancer stem cells (CSCs) in a three-dimensional(3D) microenvironment. Compared with 2D models, the 3D co-culture system upregulated sFRP4 expression, suppressed the Wnt pathway, and downregulated the expression of drug transporters, EMT-related markers, and angiogenesis-associated genes[87].

CONCLUSIONS AND FUTURE PERSPECTIVES

sFRP4 is widely recognized as an inhibitor of the canonical Wnt signaling pathway. However, accumulating evidence in recent years has revealed its paradoxical dual roles in cancer: it can function as a tumor suppressor to inhibit tumor progression, while substantial findings demonstrate its cancer-promoting effects in gastrointestinal tumors. sFRP4 exerts its functions through the Wnt and PI3K/Akt signaling pathways cascade. As an emerging therapeutic target in oncology, treatments targeting genes with oncogenic alterations and related signaling pathways are going to continue to be an important cancer treatment modality for the foreseeable future since cancer is a genetic disease driven by oncogenic alterations[88]. sFRP4 plays a critical role in regulating tumor growth, invasion, and the immune microenvironment. Although significant progress research has been made in current research, challenges such as drug resistance and targeting specificity remain to be overcome. In the future, sFRP4-targeted therapies, enabled by multi-target combination strategies, precision medicine, and novel technologies, hold promise for delivering more effective treatment regimens to patients with cancer, ultimately enhancing survival outcomes and quality of life.

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REFERENCES

1. Hoang B, Moos M, Vukicevic S, Luyten FP. Primary structure and tissue distribution of FRZB, a novel protein related to drosophila frizzled, suggest a role in skeletal morphogenesis. Journal of Biological Chemistry. 1996; 271(42):26131–7.
2. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017; 169(6):985–99.
3. Leyns L, Bouwmeester T, Kim SH, Piccolo S, De Robertis EM. Frzb-1 is a secreted antagonist of wnt signaling expressed in the spemann organizer. Cell. 1997; 88(6):747–56.
4. Melkonyan HS, Chang WC, Shapiro JP, Mahadevappa M, Fitzpatrick PA, Kiefer MC, et al. SARPs: A family of secreted apoptosis-related proteins. Proc Natl Acad Sci USA. 1997; 94(25):13636–41.
5. Garcia-Hoyos M, Cantalapiedra D, Arroyo C, Esteve P, Rodríguez J, Riveiro R, et al. Evaluation of SFRP1 as a candidate for human retinal dystrophies. Mol Vis. 2004; 10:426–31.
6. Üren A, Reichsman F, Anest V, Taylor WG, Muraiso K, Bottaro DP, et al. Secreted frizzled-related protein-1 binds directly to wingless and is a biphasic modulator of wnt signaling. Journal of Biological Chemistry. 2000; 275(6):4374–82.
7. Bányai L, Patthy L. The NTR module: Domains of netrins, secreted frizzled related proteins, and type I procollagen C-proteinase enhancer protein are homologous with tissue inhibitors of metalloproteases. Protein Science. 1999; 8(8):1636–42.
8. Mafakher L, Rismani E, Teimoori-Toolabi L. Evolutionary and structural assessment of the human secreted frizzled-related protein (SFRP) family. J Mol Evol. 2025; 93(3):350–69.
9. Bhat RA, Stauffer B, Komm BS, Bodine PVN. Structure–function analysis of secreted frizzled-related protein-1 for its wnt antagonist function. J of Cellular Biochemistry. 2007; 102(6):1519–28.

10. Cruciat CM, Niehrs C. Secreted and transmembrane wnt inhibitors and activators. Cold Spring Harbor Perspectives in Biology. 2013; 5(3):a015081–a015081.
11. Salik B, Yi H, Hassan N, Santiappillai N, Vick B, Connerty P, et al. Targeting RSPO3-LGR4 signaling for leukemia stem cell eradication in acute myeloid leukemia. Cancer Cell. 2020; 38(2):263-278.e6.
12. Song P, Gao Z, Bao Y, Chen L, Huang Y, Liu Y, et al. Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy. J Hematol Oncol. 2024; 17(1).
13. Agostino M, Pohl SÖG, Dharmarajan A. Structure-based prediction of wnt binding affinities for frizzled-type cysteine-rich domains. Journal of Biological Chemistry. 2017; 292(27):11218–29.
14. Lopez-Rios J, Esteve P, Ruiz JM, Bovolenta P. he netrin-related domain of Sfrp1 interacts with wnt ligands and antagonizes their activity in the anterior neural plate. Neural Dev. 2008; 3(1).
15. Yoshino K, Rubin JS, Higinbotham KG, Üren A, Anest V, Plisov SY, et al. Secreted frizzled-related proteins can regulate metanephric development. Mechanisms of Development. 2001; 102(1–2):45–55.
16. Bafico A, Gazit A, Pramila T, Finch PW, Yaniv A, Aaronson SA. Interaction of frizzled related protein (FRP) with wnt ligands and the frizzled receptor suggests alternative mechanisms for FRP inhibition of wnt signaling. Journal of Biological Chemistry. 1999; 274(23):16180–7.
17. Chuman Y, Üren A, Cahill J, Regan C, Wolf V, Kay BK, et al. Identification of a peptide binding motif for secreted frizzled-related protein-1. Peptides. 2004; 25(11):1831–8.
18. Häusler KD, Horwood NJ, Chuman Y, Fisher JL, Ellis J, Martin TJ, et al. Secreted frizzled-related protein-1 inhibits RANKL-dependent osteoclast formation. Journal of Bone and Mineral Research. 2004; 19(11):1873–81.
19. Takada R, Mii Y, Krayukhina E, Maruyama Y, Mio K, Sasaki Y, et al. Assembly of protein complexes restricts diffusion of Wnt3a proteins. Commun Biol. 2018; 1(1).
20. Tran THN, Takada R, Krayukhina E, Maruno T, Mii Y, Uchiyama S, et al. Soluble

frizzled-related proteins promote exosome-mediated wnt re-secretion. Commun Biol. 2024; 7(1).

21. Perumal V, Krishnan K, Gratton E, Dharmarajan AM, Fox SA. Number and brightness analysis of sFRP4 domains in live cells demonstrates vesicle association signal of the NLD domain and dynamic intracellular responses to Wnt3a. The International Journal of Biochemistry & Cell Biology. 2015; 64:91–6.
22. Lin J, Song T, Li C, Mao W. GSK-3β in DNA repair, apoptosis, and resistance of chemotherapy, radiotherapy of cancer. Biochimica Et Biophysica Acta (bba) - Molecular Cell Research. 2020; 1867(5):118659.
23. Liang CJ, Wang ZW, Chang YW, Lee KC, Lin WH, Lee JL. SFRPs are biphasic modulators of wnt-signaling-elicited cancer stem cell properties beyond extracellular control. Cell Reports. 2019; 28(6):1511-1525.e5.
24. Yasmin IA, Dharmarajan A, Warrier S. A novel function of the wnt antagonist secreted frizzled-related protein 4 as a transcriptional regulator of dickkopf-1, another wnt antagonist, in glioblastoma cell line U87MG. Biochimica Et Biophysica Acta (bba) - Molecular Cell Research. 2025; 1872(3):119918.
25. Teeuwssen M, Fodde R. Wnt signaling in ovarian cancer stemness, EMT, and therapy resistance. JCM. 2019; 8(10):1658.
26. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene. 2017; 36(11):1461–73.
27. Wend P, Wend K, Krum SA, Miranda-Carboni GA. The role of WNT10B in physiology and disease. Acta Physiologica. 2012; 204(1):34–51.
28. El-Sahli S, Xie Y, Wang L, Liu S. Wnt signaling in cancer metabolism and immunity. Cancers. 2019; 11(7):904.
29. Nadin SB, Cuello-Carrión FD, Cayado-Gutiérrez N, Fanelli MA. Overview of wnt/β-catenin pathway and DNA damage/repair in cancer. Biology. 2025; 14(2):185.
30. Lacher MD, Siegenthaler A, Jäger R, Yan X, Hett S, Xuan L, et al. Role of DDC-4/sFRP-4, a secreted frizzled-related protein, at the onset of apoptosis in mammary involution. Cell Death Differ. 2003; 10(5):528–38.

31. Perumal V, Pohl S, Keane KN, Arfuso F, Newsholme P, Fox S, et al. Therapeutic approach to target mesothelioma cancer cells using the wnt antagonist, secreted frizzled-related protein 4: Metabolic state of cancer cells. Experimental Cell Research. 2016; 341(2):218–24.
32. Bhuvanalakshmi G, Gamit N, Patil M, Arfuso F, Sethi G, Dharmarajan A, et al. Stemness, pluripotentiality, and wnt antagonism: SFRP4, a wnt antagonist mediates pluripotency and stemness in glioblastoma. Cancers. 2018; 11(1):25.
33. Wu Q, Xu C, Zeng X, Zhang Z, Yang B, Rao Z. Tumor suppressor role of sFRP-4 in hepatocellular carcinoma via the wnt/β-catenin signaling pathway. Mol Med Rep. 2021; 23(5).
34. Jacob F, Ukegjini K, Nixdorf S, Ford CE, Olivier J, Caduff R, et al. Loss of secreted frizzled-related protein 4 correlates with an aggressive phenotype and predicts poor outcome in ovarian cancer patients. Aboussekhra A, editor. PLOS ONE. 2012; 7(2):e31885.
35. Yasmin IA, Dharmarajan A, Warrier S. iPSC-derived glioblastoma cells have enhanced stemness wnt/β-catenin activity which is negatively regulated by wnt antagonist sFRP4. Cancers. 2023; 15(14):3622.
36. Kagawa T, Mineda A, Nakagawa T, Shinohara A, Arakaki R, Inui H, et al. New treatment strategies for uterine sarcoma using secreted frizzled-related proteins. Exp Ther Med. 2024; 27(5).
37. Ghoshal A, Ghosh SS. Antagonizing canonical wnt signaling pathway by recombinant human sFRP4 purified from E. coli and its implications in cancer therapy. Mol Cell Biochem. 2016; 418(1–2):119–35.
38. Lee AY, He B, You L, Dadfarmay S, Xu Z, Mazieres J, et al. Expression of the secreted frizzled-related protein gene family is downregulated in human mesothelioma. Oncogene. 2004; 23(39):6672–6.
39. Xu C, Zeng XH, Wang L, Tao SQ, Wu QX, Zhu P, et al. sFRP-4, a potential novel serum marker for chronic hepatitis B-related hepatocellular carcinoma. Hepatobiliary & Pancreatic Diseases International. 2015; 14(2):164–70.
40. Turan H, Vitale SG, Kahramanoglu I, Della Corte L, Giampaolino P, Azemi A, et

al. Diagnostic and prognostic role of TFF3, romo-1, NF-κB and SFRP4 as biomarkers for endometrial and ovarian cancers: A prospective observational translational study. Arch Gynecol Obstet. 2022; 306(6):2105–14.

41. Wu ZH, Zhang Y jing, Yue JX, Zhou T. Comprehensive analysis of the expression and prognosis for *SFRPs* in breast carcinoma. Cell Transplant. 2020; 29:096368972096247.
42. Saran U, Arfuso F, Zeps N, Dharmarajan A. Secreted frizzled-related protein 4 expression is positively associated with responsiveness to cisplatin of ovarian cancer cell lines in vitro and with lower tumour grade in mucinous ovarian cancers. BMC Cell Biol. 2012; 13(1).
43. Deshmukh A, Arfuso F, Newsholme P, Dharmarajan A. Epigenetic demethylation of sFRPs, with emphasis on sFRP4 activation, leading to wnt signalling suppression and histone modifications in breast, prostate, and ovary cancer stem cells. The International Journal of Biochemistry & Cell Biology. 2019; 109:23–32.
44. Liang J, Kang X, Halifu Y, Zeng X, Jin T, Zhang M, et al. Secreted frizzled-related protein promotors are hypermethylated in cutaneous squamous carcinoma compared with normal epidermis. Bmc Cancer. 2015; 15(1).
45. Yu J, Xie Y, Li M, Zhou F, Zhong Z, Liu Y, et al. Association between SFRP promoter hypermethylation and different types of cancer: A systematic review and meta-analysis. Oncol Lett. 2019;
46. Xie Y, Wang F, Yu J, Zhang J, Liu Y, Li M, et al. Silencing of MBD2 and EZH2 inhibits the proliferation of colorectal carcinoma cells by rescuing the expression of SFRP. Oncol Rep. 2021; 46(6).
47. Brebi P, Hoffstetter R, Andana A, Ili CG, Saavedra K, Viscarra T, et al. Evaluation of *ZAR1* and *SFRP4* methylation status as potentials biomarkers for diagnosis in cervical cancer: Exploratory study phase I. Biomarkers. 2014; 19(3):181–8.
48. Ho PTB, Clark IM, Le LTT. MicroRNA-based diagnosis and therapy. IJMS. 2022; 23(13):7167.
49. Zhang H, Chen R, Shao J. MicroRNA-96-5p facilitates the viability, migration,

and invasion and suppresses the apoptosis of cervical cancer cells byNegatively modulating SFRP4. Technol Cancer Res Treat. 2020; 19.

50. Belur Nagaraj A, Knarr M, Sekhar S, Connor RS, Joseph P, Kovalenko O, et al. The miR–181a–SFRP4 axis regulates wnt activation to drive stemness and platinum resistance in ovarian cancer. Cancer Research. 2021; 81(8):2044–55.
51. Wu J, Feng Z, Wang R, Li A, Wang H, He X, et al. Integration of bioinformatics analysis and experimental validation identifies plasma exosomal miR-103b/877-5p/29c-5p as diagnostic biomarkers for early lung adenocarcinoma. Cancer Medicine. 2022; 11(23):4411–21.
52. Xi S, Yang M, Tao Y, Xu H, Shan J, Inchauste S, et al. Cigarette smoke induces C/EBP-β-mediated activation of miR-31 in normal human respiratory epithelia and lung cancer cells. Eickelberg O, editor. PLOS ONE. 2010; 5(10):e13764.
53. Ge C, Wu S, Wang W, Liu Z, Zhang J, Wang Z, et al. miR-942 promotes cancer stem cell-like traits in esophageal squamous cell carcinoma through activation of wnt/β-catenin signalling pathway. Oncotarget. 2015; 6(13):10964–77.
54. Hambardzumyan D, Becher OJ, Holland EC. Cancer stem cells and survival pathways. Cell Cycle. 2008; 7(10):1371–8.
55. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006; 444(7120):756–60.
56. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. Nat Rev Cancer. 2005; 5(4):275–84.
57. Deshmukh A, Kumar S, Arfuso F, Newsholme P, Dharmarajan A. Secreted frizzled-related protein 4 (sFRP4) chemo-sensitizes cancer stem cells derived from human breast, prostate, and ovary tumor cell lines. Sci Rep. 2017; 7(1).
58. Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. Cell. 2017; 168(4):657–69.
59. Deshmukh A, Arfuso F, Newsholme P, Dharmarajan A. Regulation of cancer stem cell metabolism by secreted frizzled-related protein 4 (sFRP4). Cancers. 2018; 10(2):40.

60. Chhabra Y, Weeraratna AT. Fibroblasts in cancer: Unity in heterogeneity. Cell. 2023; 186(8):1580–609.
61. Ning L, Quan C, Wang Y, Wu Z, Yuan P, Xie N. scRNA-seq characterizing the heterogeneity of fibroblasts in breast cancer reveals a novel subtype SFRP4+ CAF that inhibits migration and predicts prognosis. Front Oncol. 2024; 14.
62. Visweswaran M, Keane KN, Arfuso F, Dilley RJ, Newsholme P, Dharmarajan A. The influence of breast tumour-derived factors and wnt antagonism on the transformation of adipose-derived mesenchymal stem cells into tumour-associated fibroblasts. Cancer Microenvironment. 2018; 11(1):71–84.
63. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: Causes, consequences, challenges and opportunities. Cell Mol Life Sci. 2020; 77(9):1745–70.
64. Saran U, Mani KP, Balaguru UM, Swaminathan A, Nagarajan S, Dharmarajan AM, et al. sFRP4 signalling of apoptosis and angiostasis uses nitric oxide-cGMP-permeability axis of endothelium. Nitric Oxide. 2017; 66:30–42.
65. Longman D, Arfuso F, Viola HM, Hool LC, Dharmarajan AM. The role of the cysteine-rich domain and netrin-like domain of secreted frizzled-related protein 4 in angiogenesis inhibition in vitro. oncol res. 2012; 20(1):1–6.
66. Yu P, He W, Zhang Y, Hu C, Wu Y, Wang Y, et al. SFRP4 is a potential biomarker for the prognosis and immunotherapy for gastric cancer. Cui Q, editor. Journal of Oncology. 2022; 2022:1–15.
67. Sandsmark E, Andersen MK, Bofin AM, Bertilsson H, Drabløs F, Bathen TF, et al. SFRP4 gene expression is increased in aggressive prostate cancer. Sci Rep. 2017; 7(1).
68. Li H, Zhao J, Sun J, Tian C, Jiang Q, Ding C, et al. Demethylation of the *SFRP4* promoter drives gastric cancer progression via the wnt pathway. Molecular Cancer Research. 2021; 19(9):1454–64.
69. Busuttil RA, George J, House CM, Lade S, Mitchell C, Di Costanzo NS, et al. SFRP4 drives invasion in gastric cancer and is an early predictor of recurrence. Gastric Cancer. 2021; 24(3):589–601.

70. Kim YM, Kwon IG, Choi SH, Noh SH, Chun J, Youn YH, et al. SFRP4 and CDX1 are predictive genes for extragastric recurrence of early gastric cancer after curative resection. JCM. 2022; 11(11):3072.
71. Chen CH, Chen CJ, Huang YC, Huang PS, Chi HC, Chuang HC, et al. Secreted frizzled-related protein 4 induces gastric cancer progression and resistance to cisplatin and oxaliplatin via β-catenin dysregulation. Chemotherapy. 2024; 69(3):150–64.
72. Huang D, Yu B, Deng Y, Sheng W, Peng Z, Qin W, et al. SFRP4 was overexpressed in colorectal carcinoma. J Cancer Res Clin Oncol. 2010; 136(3):395–401.
73. Suzuki H, Watkins DN, Jair KW, Schuebel KE, Markowitz SD, Dong Chen W, et al. Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer. Nat Genet. 2004; 36(4):417–22.
74. Cheng YY, Yu J, Wong YP, Man EPS, To KF, Jin VX, et al. Frequent epigenetic inactivation of secreted frizzled-related protein 2 (SFRP2) by promoter methylation in human gastric cancer. Br J Cancer. 2007; 97(7):895–901.
75. Jhe YL, Lee S, Jung Y, Cheong JH. PKA-mediated phosphorylation of SFRP4 promotes wnt/β-catenin activation and cancer stemness in gastric cancer. IJMS. 2025; 26(12):5572.
76. Perry AS, O'Hurley G, Raheem OA, Brennan K, Wong S, O'Grady A, et al. Gene expression and epigenetic discovery screen reveal methylation of SFRP2 in prostate cancer. Intl Journal of Cancer. 2013; 132(8):1771–80.
77. Mortensen MM, Høyer S, Lynnerup AS, Ørntoft TF, Sørensen KD, Borre M, et al. Expression profiling of prostate cancer tissue delineates genes associated with recurrence after prostatectomy. Sci Rep. 2015; 5(1).
78. Hall CL, Bafico A, Dai J, Aaronson SA, Keller ET. Prostate cancer cells promote osteoblastic bone metastases through wnts. Cancer Research. 2005; 65(17):7554–60.
79. Yang MW, Tao LY, Yang JY, Jiang YS, Fu XL, Liu W, et al. SFRP4 is a prognostic marker and correlated with treg cell infiltration in pancreatic ductal

adenocarcinoma. Am J Cancer Res. 2019; 9(2):363–77.

80. Perumal V, Dharmarajan AM, Fox SA. The Wnt regulator SFRP4 inhibits mesothelioma cell proliferation, migration, and antagonizes Wnt3a via its netrin-like domain. International Journal of Oncology. 2017; 51(1):362–8.
81. Ford CE, Jary E, Ma SSQ, Nixdorf S, Heinzelmann-Schwarz VA, Ward RL. The wnt gatekeeper SFRP4 modulates EMT, cell migration and downstream wnt signalling in serous ovarian cancer cells. Samant R, editor. PLOS ONE. 2013; 8(1):e54362.
82. Warrier S, Balu SK, Kumar AP, Millward M, Dharmarajan A. Wnt antagonist, secreted frizzled-related protein 4 (sFRP4), increases chemotherapeutic response of glioma stem-like cells. oncol res. 2014; 21(2):93–102.
83. Warrier S, Bhuvanalakshmi G, Arfuso F, Rajan G, Millward M, Dharmarajan A. Cancer stem-like cells from head and neck cancers are chemosensitized by the wnt antagonist, sFRP4, by inducing apoptosis, decreasing stemness, drug resistance and epithelial to mesenchymal transition. Cancer Gene Ther. 2014; 21(9):381–8.
84. Sundaram SM, Varier L, Fathima KZ, Dharmarajan A, Warrier S. Short peptide domains of the wnt inhibitor sFRP4 target ovarian cancer stem cells by neutralizing the wnt β-catenin pathway, disrupting the interaction between β-catenin and CD24 and suppressing autophagy. Life Sciences. 2023; 316:121384.
85. Yasmin IA, Mohana Sundaram S, Banerjee A, Varier L, Dharmarajan A, Warrier S. Netrin-like domain of sFRP4, a wnt antagonist inhibits stemness, metastatic and invasive properties by specifically blocking MMP-2 in cancer stem cells from human glioma cell line U87MG. Experimental Cell Research. 2021; 409(2):112912.
86. Perumal V, Arfuso F, Chen Y, Fox S, Dharmarajan AM. Delivery of expression constructs of secreted frizzled-related protein 4 and its domains by chitosan–dextran sulfate nanoparticles enhances their expression and anti-cancer effects. Mol Cell Biochem. 2018; 443(1–2):205–13.

87. Mandal S, Arfuso F, Sethi G, Dharmarajan A, Warrier S. Encapsulated human mesenchymal stem cells (eMSCs) as a novel anti-cancer agent targeting breast cancer stem cells: Development of 3D primed therapeutic MSCs. The International Journal of Biochemistry & Cell Biology. 2019; 110:59–69.
88. Sonkin D, Thomas A, Teicher BA. Cancer treatments: Past, present, and future. Cancer Genetics. 2024; 286–287:18–24.

TABLES AND FIGURES WITH LEGENDS

Table 1. The functions of sFRP4 on different types of cancers.

Function	Tumor type	Key findings	Ref.
Anti-tumor	Breast cancer	(1) sFRP4+ cancer-associated fibroblasts (CAFs) secrete sFRP4 to inhibit breast cancer cell migration and epithelial-mesenchymal transition (EMT). (2) Exhibits anti-proliferative effects and induces spheroid disruption, reduces glucose uptake, glutamine uptake, glutamate secretion, and redox signatures in breast cancer-derived stem cells, while also promoting apoptosis within CSCs. (3) Enhancing chemosensitivity of breast cancer-derived stem cells.	[57,61]
	Malignant mesothelioma	(1) Alter cancer cell metabolism (2) Inhibits mesothelioma cell proliferation, migration, and antagonizes Wnt3a via its netrin-like domain.	[59,80]
	Ovarian cancer	(1) sFRP4 target ovarian cancer stem cells by neutralizing the Wnt/β-catenin pathway, disrupting the interaction between β-catenin and CD24 and suppressing autophagy. (2) Enhancing chemosensitivity of ovarian cancer-derived stem Cells	[57,84]
	Head and	(1) Reverse EMT and restore the epithelial marker E-cadherin.	[83]

	neck cancer	(2) Disrupt spheroid formation of head and neck-derived stem cells.	
	Lung cancer	(1) In vitro cell lines, sFRP4 inhibit the Wnt signaling pathway and downregulate the expression of proliferation-related genes. (2) sFRP4 expression is down-regulated in lung cancer cell.	[37,38]
	Cervical cancer	In vitro cell lines, sFRP4 inhibit the Wnt signaling pathway and downregulate the expression of proliferation-related genes.	[37]
Pro-tumor	Pancreatic cancer	(1) High sFRP4 expression is positively correlated with FOXP3+ Treg cell infiltration, suggesting its role in shaping an immunosuppressive tumor microenvironment. (2) Mechanistically, sFRP4 promoted the secretion of T cell specific cytokines and increased the recruitment of CD4+ T cells, which may promote the Treg differentiation process.	[79]
	Gastric cancer	(1) In gastric cancer, sFRP4 is highly expressed and associated with poor prognosis. (2) sFRP4 promotes chemotherapy resistance in gastric cancer through activation of the Wnt signaling pathway.	[68,69,70,71,75]
	Prostate cancer	(1) sFRP4 expression is increased in prostate cancer and further elevated in high-grade tumors (2) sFRP4-positive stroma promotes bone metastasis of prostate cancer cells. (3) High sFRP4 expression is associated with genomic instability in prostate cancer.	[77,78]

Abbreviations: CAF, cancer-associated fibroblast; CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; FOXP3, forkhead box protein P3; NTR, netrin-like domain; sFRP4, secreted frizzled-related protein 4; Treg, regulatory T cell; Wnt, Wingless/Integrated signaling pathway.

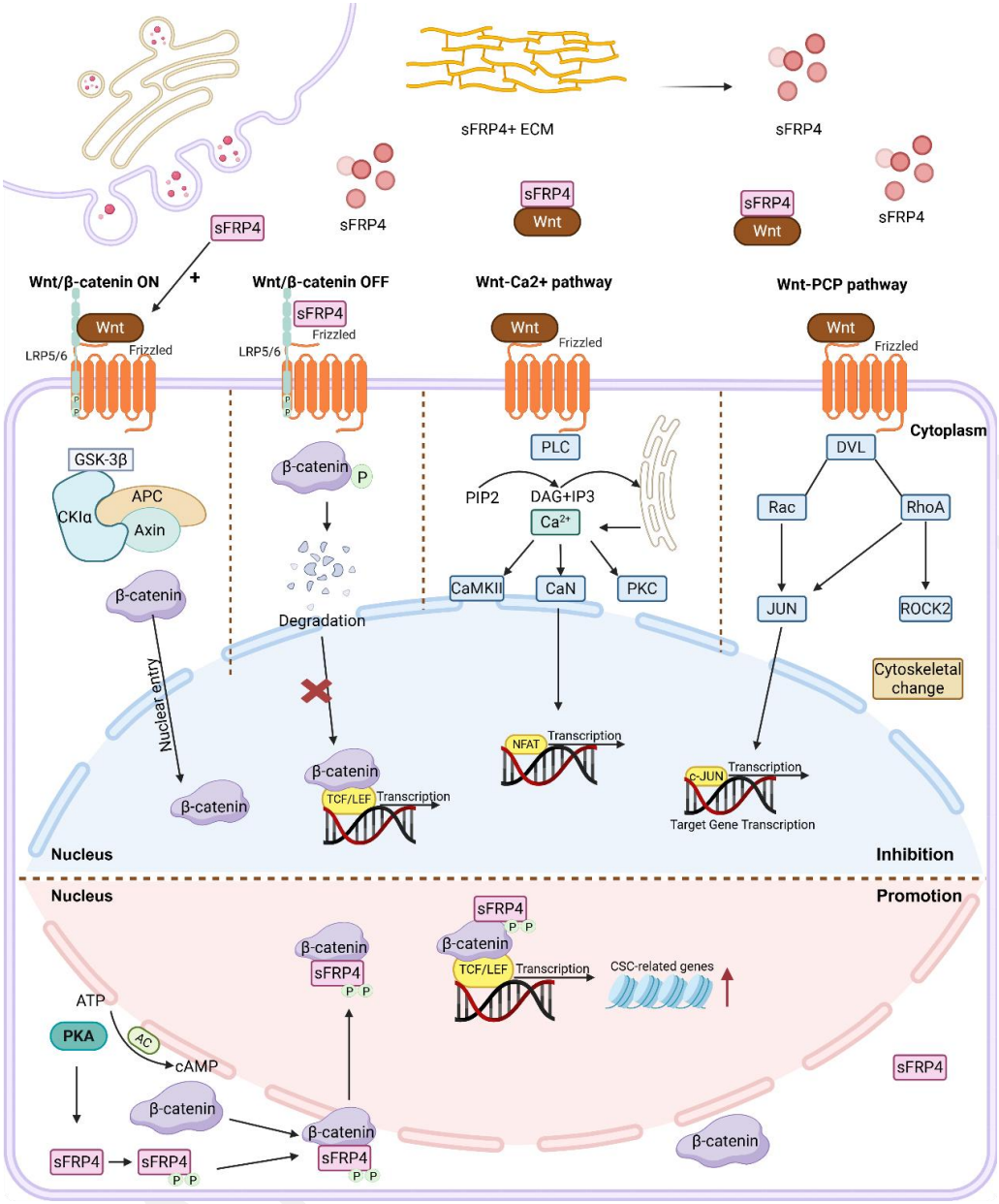

Figure 1. Mechanism of sFRP4 in regulating the Wnt signaling pathway in tumors. This diagram illustrates the main inhibitory mechanisms by which sFRP4 acts as an inhibitor of the Wnt signaling pathway. By binding to Wnt proteins through its CRD or NTR, sFRP4 sequesters Wnt ligands, preventing their interaction with downstream FZD and LRP5/6 receptors. During Wnt/PCP signaling, Wnt binds to the Fzd receptor, activating Dvl/Dsh. This in turn activates the small GTPases Rho/Rac and JNK, leading to the expression of genes related to cell polarity. In the Wnt/Ca^{2+} pathway, Wnt protein activates PLC, releasing intracellular Ca^{2+} and inhibiting the canonical Wnt signaling pathway. Under certain conditions,

sFRP4 promotes the interaction between Wnt and Fzd. PKA can phosphorylate sFRP4, and the phosphorylated sFRP4 binds to β-catenin and translocates into the nucleus, where it enhances LEF/TCF transcriptional activity, leading to increased transcription of stemness-related genes.

Abbreviations: APC, adenomatous polyposis coli; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CaMKII, calcium/calmodulin-dependent protein kinase II; CaN, calcineurin; cJUN, jun proto-oncogene; CRD, cysteine-rich domain; CSC, cancer stem cell; DAG, diacylglycerol; DVL/Dsh, dishevelled protein; ECM, extracellular matrix; FZD/Fzd, Frizzled receptor; GSK3β, glycogen synthase kinase 3 beta; JNK, c-Jun N-terminal kinase; LEF, lymphoid enhancer-binding factor; LRP5/6, low-density lipoprotein receptor-related protein 5/6; NFAT, nuclear factor of activated T-cells; NTR, netrin-like domain; PCP, planar cell polarity; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Rac, Ras-related C3 botulinum toxin substrate; RhoA, Ras homolog family member A; ROCK2, Rho-associated coiled-coil containing protein kinase 2; sFRP4, secreted frizzled-related protein 4; TCF, T-cell factor; Wnt, Wingless/Integrated signaling pathway.

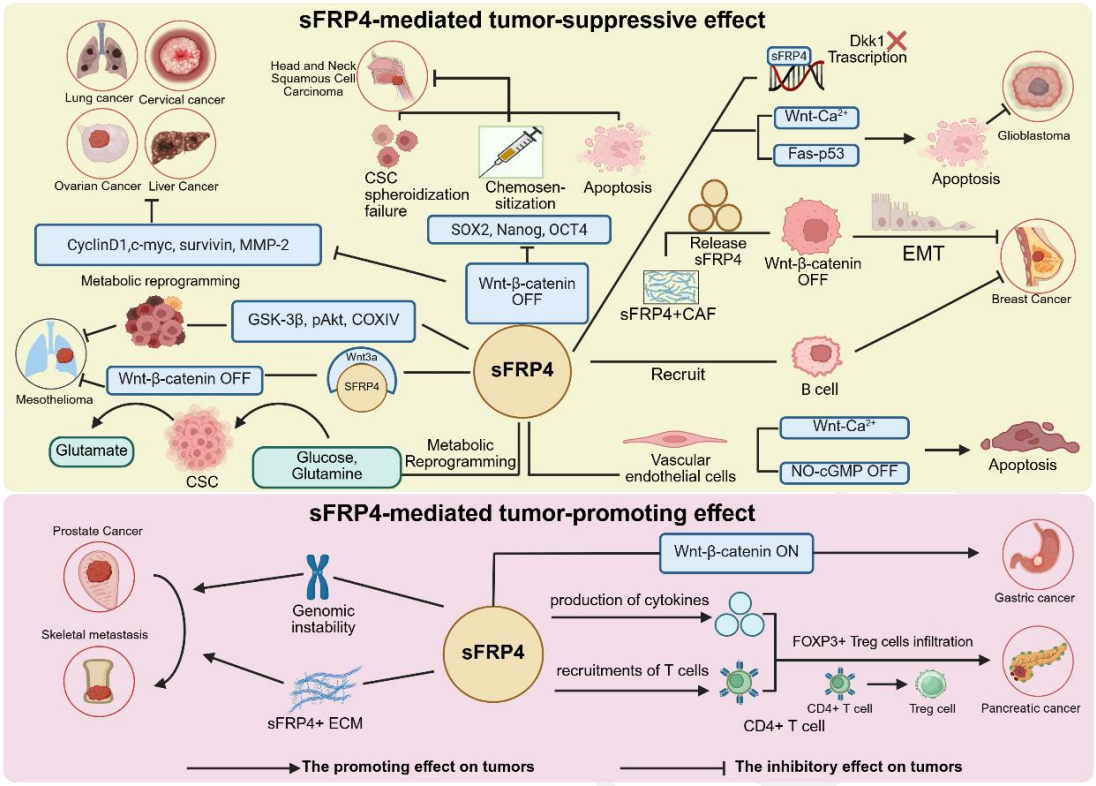

Figure 2. sFRP4 plays diverse roles in different tumors. In ovarian cancer, liver cancer, lung cancer, and cervical cancer, sFRP4 inhibits the Wnt signaling pathway, thereby suppressing the expression of Cyclin D1, c-Myc, Survivin, and MMP-2, which collectively restrain tumor progression. In head and neck squamous cell carcinoma, sFRP4 inhibits the Wnt pathway, leading to downregulation of stemness markers (SOX2, Nanog, OCT4) in cancer stem cells, resulting in impaired spheroid formation, increased apoptosis, and enhanced chemosensitivity. In breast cancer, sFRP4 recruits B cells to suppress tumor progression, and sFRP4-positive CAFs secrete sFRP4 to inhibit the Wnt pathway in tumor cells, further blocking EMT and tumor growth. In glioma, sFRP4 promotes tumor cell apoptosis by inhibiting the Wnt-Ca^{2+} and Fas-p53 pathways and acts as a transcription factor to regulate Dkk1 expression. In pleural mesothelioma, sFRP4 binds to Wnt3a to prevent Wnt pathway activation and induces metabolic reprogramming in cancer stem cells by modulating GSK-3β, pAkt, and COXIV, thereby suppressing tumor progression. Additionally, sFRP4 triggers apoptosis in vascular endothelial cells via the Wnt-Ca^{2+} and NO-cGMP pathways. sFRP4 exerts anti-proliferative effects,

disrupts tumor spheroids, and reduces glucose uptake, glutamine uptake, glutamate secretion, and redox activity. However, in prostate cancer, sFRP4 expression is positively correlated with FOXP3+ Treg cell infiltration. sFRP4 promoted the secretion of T cell specific cytokines and increased the recruitment of CD4+ T cells, which may promote the Treg differentiation process. Collectively, these findings highlight sFRP4 as a novel prognostic biomarker and potential therapeutic target in pancreatic cancer.

Abbreviations: CAF, cancer-associated fibroblast; COXIV, cytochrome c oxidase subunit IV; CSC, cancer stem cell; Dkk1, Dickkopf-related protein 1; EMT, epithelial-mesenchymal transition; FOXP3, forkhead box protein P3; GSK-3β, glycogen synthase kinase 3 beta; MMP-2, matrix metalloproteinase-2; NO, nitric oxide; OCT4, octamer-binding transcription factor 4; pAkt, phosphorylated protein kinase B; SOX2, sex-determining region Y-box 2; Treg, regulatory T cell; Wnt, Wingless/Integrated signaling pathway.