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REVIEW

Expression and Role of Dickkopf-1 (Dkk1) in Tumors: From the Cells to the Patients

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Abstract: *Dickkopf-1* (*Dkk1*) is a secretory antagonist of the classical Wnt signaling pathway. Many studies have reported that *Dkk1* is abnormally expressed in tumor cells, and abnormal expression of *Dkk1* can inhibit cell proliferation or induce apoptosis through pro-apoptotic factors, However, due to the differences in tumor environment and the complex regulatory mechanisms in different tumors, *Dkk1* has different effects on the progression of different tumors. In many tumors, high expression of *Dkk1* may promote tumor metastasis. However, *Dkk1*, which is highly expressed in other tumors, can inhibit tumor invasion and metastasis. More and more evidence shows that *Dkk1* plays a complex and different role in tumor occurrence, development and metastasis in different tumor environments and through a variety of complex regulatory mechanisms. Therefore, *Dkk1* may not only be a useful biomarker of metastasis, but also a target for studying the metabolic mechanism of tumor cells and treating tumors in many tumor types. Therefore, this article reviews the research progress on the expression, mechanism and function of *Dkk1* in different tumors, and at the same time, based on the public database data, we made a further analysis of the expression of *Dkk1* in different tumors.

Keywords: dickkopf-1, Dkk1, Wnt signaling pathway, tumor mechanism, metastasis, biomarker, in vitro, in vivo

Introduction

Dickkopf-1(*Dkk1*), a typical secretory antagonist of Wnt signaling pathway, was discovered in 1998. *Dkk1* is a secretory glycoprotein with two conserved domains rich in cysteine and a connecting region of 50–55 amino acids. The full length of human *Dkk1* gene is 1815kb, which is located on chromosome 10q11.2.26. The *Dkk1* protein consists of 266 amino acids and its relative molecular weight is about 29 kDa. *Dkk2, Dkk3* and *Dkk4* have sequence homology in vertebrates, in which *Dkk2* and *Dkk4* can inhibit Wnt signal, but the inhibitory effect is weaker than *Dkk1*, and the mechanism of *Dkk3* is still unclear.[1–4]

Wnt signal pathway includes the classical pathway (Wnt/β-catenin) and the non-classical pathway.[5,6] In the classical pathway, the activity of Wnt is mediated by the close regulation of β-catenin stability.[7] Current studies have shown that *Dkk1* acts in these ways: *Dkk1* specifically inhibits the typical Wnt signal pathway by competing with the receptor *LRP5/6.57–59* for Wnt ligand; the other is that the formation of the complex of *Dkk1* with *LRP5/6* and KrementFrizzled leads to the phosphorylation of β-catenin, which inhibits the downstream regulation of cell cycle, tissue and organ fibrosis and other related target gene expression.[8,9]

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In the non-classical pathway, the Wnt pathway is activated in two ways, one is the non-canonical Wnt/PCP (planar cell polarity) pathway: Wnt ligand binding to frizzled receptors leads to activation of Dishevelled (Dvl) which recruits *DAAM1* (Dishevelled associated activator of morphogenesis 1) enhancing the stimulation of GTPases Rac (Ras-related C3 botulinum toxin substrate) and *RHOA* (Ras homolog gene family member A) leading to actin cytoskeleton rearrangement. In addition, Dvl activates Rac and finally *JNK* (c-Jun-N-terminal-kinase) thereby modulating cell migration;[10] The other is the Wnt/calcium pathway: Wnt ligands bind to frizzled receptors and Ror/Ryk co-receptors, activating Dvl and trimeric G-proteins (Gα,β,γ). This leads to the generation of *IP3* (inositol 1,4,5-triphosphate) and *DAG2* (diacylglycerol) through *PLC* (Phospholipase C) activation. *IP3* triggers the release of calcium ions (Ca2+) from the endoplasmic reticulum activating calmodulin and subsequently *CAMKII* (calcium/calmodulin-dependent kinase II), *TAK-1* (TGF-β activated kinase 1) and *NLK* (Nemo-like kinase) thereby inhibiting the canonical Wnt pathway. Moreover, calmodulin activation stimulates calcineurin and *NFAT* (Nuclear Factor of Activated T-cells) involved in adhesion and migration processes. This pathway activates also *PKC* (Protein Kinase C) and *Cdc42* (cell division control protein 42) rearranging the actin cytoskeleton.[11]

In the Wnt pathway, mutations at key sites, methylation of the promoter and stability of β-catenin have been shown to be associated with tumor progression and low survival in patients: The progression of chronic phase CML toward blastic crisis phase due to GSK3β mutations and β-catenin stabilization in GMP cells (granulocyte-macrophage progenitor cells).[12] And Wnt pathway inhibitor promoters (ie, SFRP,DKK and WIF-1) are hypermethylated in ALL and AML and are associated with low survival in patients.[13,14] Loss-of-function mutations in APC and RNF43 and gain-of-function mutations in *RSPO* (characterized by gene fusions) and *CTNNB1* was reported in the vast majority of colorectal cancers (CRC).[15]

Some studies have proven that high expression of *Dkk1* can occur in a variety of cancer cell lines (such as liver cancer, lung cancer, breast cancer, glioma, and cervical cancer) which induce apoptosis by inhibiting cell proliferation and transformation.[16,17] Therefore, some researchers believe that *Dkk1* has the potential to be used as a biological marker for the diagnosis and prognosis of a variety of cancers.[18–20] But in other tumors, the expression of *Dkk1* exists as a tumor suppressor. Because of the complex regulation mechanism in different tumors and the influence of different tumor environments, the effect of *Dkk1* on tumor shows two sides.

Expression of Dkk1 in Lung Cancer

Lung cancer is one of the leading causes of cancer death in the world. In recent years, advances in diagnosis and treatment have made remarkable progress in improving the survival of patients with lung cancer, but the survival rate of patients with lung cancer is still low of which Non-Small Cell Lung Cancer (NSCLC) accounts for the vast majority of lung cancer. A study shows that vasculogenic mimicry (VM) may be associated with the maintenance of tumor rich blood supply in highly invasive uveal melanoma,[21] while epithelial-mesenchymal transformed (EMT) and cancer stem cell-like cell (CSC) have been shown to be associated with VM in some tumors.[22–24] Wnt signaling pathway plays an important role in embryonic development and tumorigenesis, so it is closely related to EMT and CSC.[25,26] The analysis of tumor tissue samples from 205 patients with lung cancer showed that VM could lead to more aggressive cancer and poor prognosis, and it was found that *Dkk1* was related to histological classification and differentiation in VM. In addition, the overexpression of *Dkk1* was positively correlated with the existence of VM and the high expression of some VM-related proteins (*MMP2,MMP9* and *VE- cadherin*). In vitro and in vivo experiments also showed that *Dkk1* could fully induce EMT and promote the formation of VM. The data showed that CSC phenotype was related to VM and *Dkk1* overexpression, and in vivo studies showed that lung cancer cells overexpressing *Dkk1* had more CSC phenotype and more invasiveness than normal lung cancer cells. This study describes the previously unrecognized role of *Dkk1* and confirms the hypothesis that *Dkk1* promotes VM formation by inducing EMT-related proteins and developing CSC properties in NSCLC.[27]

Shen et al[28] measured the serum levels of *Dkk1* autoantibodies in 206 patients with NSCLC and 99 healthy controls by indirect ELISA. The patients were followed up for 3 years to evaluate the correlation between the serological level of antibodies and the overall survival time (OS) and progression-free survival (PFS). The final results showed that the level of autoantibodies in sera of patients with NSCLC was much higher and was closely related to distant metastasis. Cox regression analysis showed that antibodies against Pep B subtype were independent

prognostic factors of NSCLC. The serum *Dkk1* levels of 470 patients with NSCLC (140 bone metastases, 178 extraosseous metastases and 152 complete remission) were quantified and analyzed. The results showed that the serum *Dkk1* levels of patients with bone metastases were significantly higher than those of the other two groups. After determining the threshold by ROC curve, it was found that the best cutoff value was 311.8 pg/mL, and the serum *Dkk1* was correlated with the number of bone lesions of bone metastasis, indicating that *Dkk1* can be used to detect bone metastasis of NSCLC.[29]

Expression of Dkk1 in Hepatocellular Carcinoma

A variety of causes, such as viruses and the environment, can cause Hepatocellular carcinoma (HCC). About 78,200 new confirmed cases are reported each year.[30,31] The 5-year survival rate of HCC patients varies from stage to stage, ranging from 50% to 75% in the early stage, while the 5-year survival rate in HCC patients with distant metastasis is reduced to 3%.[32,33] In clinical practice, serum Alpha-Fetoprotein (*AFP*) and ultrasound have been widely used in early screening of liver cancer.[34] However, when *AFP* is in the critical range of 20 ng/mL, its sensitivity is reduced to 53% and specificity is 90%. Therefore, western scholars exclude it from the diagnosis of liver cancer because of its poor sensitivity.[35–37] By comparing the serum *Dkk1* levels of 831 test cohort participants and 453 validation cohort participants, and the liver tissue *Dkk1* mRNA and protein levels of HCC patients and non-cancer patients, Professor Qin Wenxin[38] found that *Dkk1* can complement the measurement of *AFP* in HCC diagnosis, improve the differentiation of AFP-negative HCC patients, and distinguish HCC from non-malignant chronic liver disease.

Previous evidence has shown that *Dkk1* plays a role in promoting angiogenesis during tumorigenesis and inflammation,[39] Choi et al[40] stimulated human umbilical vein endothelial cells (HUVEC), with recombinant Dkk1 (rDDK-1) and conditioned medium of 293 cell cultures transfected with *Dkk1*. The expression of angiogenesis-related factors and EnMT-related markers were detected and formed through test tube. The effects of exogenous *Dkk1* on angiogenesis and EnMT were evaluated by cell invasion and wound healing tests. The results showed that the increase of EnMT potential of HUVEC stimulated by *Dkk1* was related to the activation of vascular endothelial growth factor receptor 2 (*VEGFR2*) and its downstream molecules such as Akt and Erk, while the expression of β-catenin and GSK3 β did not change significantly, indicating that *Dkk1* can induce angiogenesis by regulating *VEGFR2* independent of Wnt signal transduction pathway. Surgery (including local hepatectomy and liver transplantation) is still the most effective treatment in the treatment of liver cancer, but due to low diagnostic sensitivity and lack of health awareness, more than 60% of HCC patients are diagnosed with advanced disease or suffer from multiple diseases and lose the opportunity of operation.[41] Transcatheter arterial chemoembolization (TACE) once was the first choice for the treatment of inoperable advanced HCC patients. Randomized controlled trials show that TACE can improve the survival rate and quality of life of HCC patients.[42] However, due to the influence of disease heterogeneity caused by tumor burden, liver function, disease etiology and so on, not all patients who meet the treatment of TACE can benefit from it,[43] and frequent TACE may aggravate liver injury. Xiaoxia Wu[44] retrospectively analyzed the changes of serum *Dkk1* and circulating tumor cell (CTC) in 155 patients with HCC treated with TACE. It was found that after TACE treatment, the serum *Dkk1* and CTCs in the reaction group were significantly lower than those before treatment, and the overall survival time, disease-free survival time and 5-year survival rate of patients with positive serum *Dkk1* and CTC before treatment were significantly lower than those before treatment. It is suggested that the serum *Dkk1* and CTCs are effective biomarkers to predict the efficacy and long-term prognosis of TACE in patients with HCC.[45]

Expression of Dkk1 in Esophageal Carcinoma

Esophageal cancer (EC) is the sixth deadliest cancer disease in the world, and its incidence is increasing year by year. The main pathological type of cancer in Asian and African patients is esophageal squamous cell carcinoma (ESCC), while in European patients, esophageal adenocarcinoma (EAC) is more common.[46,47] Although great progress has been made in the treatment of EC, compared with its survival rate of only 14%,[48] it is still worthy of further study.

By using RT-PCR and Western blot to detect the expression of *Dkk1* in EC tissues, paired normal esophageal tissues and EC tumor cell lines, it was found that the expression of *Dkk1* gene was up-regulated at both mRNA

and protein levels in esophageal cancer tissues. At the same time, *Dkk1* gene was expressed to varying degrees in all four esophageal cancer cell lines analyzed. However, after the construction of EC9706 cell lines overexpressing *Dkk1*, it was found that the proliferation rate of overexpressed EC9706 cells increased. The proportion of S phase and G2/M phase increased, while the proportion of G0/G1 decreased, and the overexpression of *Dkk1* led to the enhancement of invasive ability of EC9706 cells. The results suggest that *Dkk1* may be a key regulator in the occurrence and development of carcinoma.[49] By comparing the serum *Dkk1* levels of 90 ESCC patients and 85 healthy patients by ELISA, it was found that the *Dkk1* level of ESCC patients was much higher than that of the healthy control group; the sensitivity and specificity for the determination of serum *Dkk1*, were 70% and 80% respectively, and the serum *Dkk1* level of ESCC patients increased before operation, which means that *Dkk1* may be a useful marker for diagnosing and judging the treatment and prognosis of ESCC patients.[50] The expression of *Dkk*1 protein in resected specimens of ESCC patients was compared with various clinicopathological parameters and prognosis (the relationship between disease-free survival (DFS)) showed that the DFS of patients with *Dkk1*-positive tumors was worse than that of ESCC-negative patients (5-year DFS;1.5% vs 53.6% DFS;1.5% 0.0062), indicating that *Dkk1* can be used as a new predictor of poor prognosis in patients with ESCC after radical resection.[51]

Expression of Dkk1 in Gastric Cancer

Gastric cancer is the second largest cause of cancer-related death in the world.[52] Although the development of surgical techniques and targeted therapy has increased the 5-year survival rate of early gastric cancer (EGC) to more than 90%,[53] the survival rate of advanced gastric cancer (AGC) is still about 40%.[54]

A study compared the serum *Dkk1* of 153 patients with gastric cancer and 173 healthy controls, and the expression of *Dkk1* in 144 cancer samples of 153 patients and 265 consecutive gastric cancer specimens showed that the serum *Dkk1* concentration of patients with gastric cancer was significantly higher than that of healthy controls, the critical value was 31.9150 pg/mL, and the sensitivity and specificity for the diagnosis of gastric cancer were 87.6% and 87.9%, respectively. The survival rate of gastric cancer patients with serum Dkk1 level ≥ 60.0 pg/mL was significantly lower than that of gastric cancer patients with lower serum *Dkk1*.[55] But what is the expression of *Dkk1* in patients with gastric cancer and its clinical significance? Zhuang et al[56] detected the expression of serum *Dkk1* protein in 90 cases of gastric cancer, 50 cases of gastric benign disease and 40 healthy persons by ELISA, and the dynamic changes of serum *Dkk1* protein in gastric cancer patients undergoing radical operation for 1 month. It was found that the expression of serum *Dkk1* protein in the gastric cancer group was significantly higher than that in the gastric benign group and the healthy control group. The serum *Dkk1* level in patients with TNM stage III and IV was significantly higher than that in patients with TNM stage I and II. The level of serum *Dkk1* was related to microvascular infiltration, degree of differentiation, and depth of invasion. The level of serum *Dkk1* decreased significantly after radical operation. The results suggest that *Dkk1* detection can be used as a reference index for monitoring the progression and biological behavior of gastric cancer. The results of another meta-analysis also supported this result, and this meta-analysis also found that the overexpression of *Dkk1* was not only associated with vascular and lymphatic invasion, but also with distant metastasis and overall survival of patients with gastric cancer.[57] In the process of embryonic development and homeostasis of human tissue, Wnt signal cascade regulates cell proliferation, cell polarity, and cell development.[7] Solid tumors often show an imbalance in the Wnt signal pathway, which is related to the enhancement of malignant potential.[58] *Dkk1* is an antagonist of Wnt/β-catenin pathway. After examining the relationship between the co-expression of *Dkk1* and β-catenin in gastric cancer and clinical prognosis, it was found that the co-expression of *Dkk1* and β-catenin was significantly correlated with high N stage (N2 and N3). The overall survival (OS) and DFS of patients with high expression of *Dkk1* were poor. Multivariate analysis showed that high expression of *Dkk1* alone or high expression of *Dkk1* with β-catenin positive were independent prognostic factors for tumor recurrence and overall survival, indicating that high expression of *Dkk1* was an important prognostic factor for tumor recurrence and survival in resected AGC patients, regardless of the positivity of β-catenin.[59] The continuous activation of Wnt signaling pathway to maintain the self-renewal and tumorigenicity of gastric cancer stem cell (CSC) is considered to be a target for the treatment of gastric cancer. $CD44^+$ cells were isolated from primary gastric cancer cells and gastric cancer cell lines by fluorescence activated cell sorting. The expression of adenovirus receptor in $CD44^+$ cells and $CD44^-$ cells was

detected. Dkk1, a Wnt antagonist, was transfected into CD44*Dkk1* cells by Ad5/35 (Ad5/35-Dkk1). After *Dkk1* was introduced into $CD44^+$ cells, it effectively inhibited the endogenous Wnt/β-catenin signal transduction and reduced the tumorigenicity of $CD44^+$ cells in vivo, which verified the effectiveness of gene therapy targeting Wnt/β-catenin signal pathway in CSC cells.[60]

Expression of Dkk1 in Colorectal Cancer

Colorectal cancer (CRC) is a common malignant tumor of the digestive system[61] and the fifth leading cause of cancer-related deaths in the Chinese population.[62] It is closely related to the abnormal activation of Wnt/β-catenin signal pathway.[63,64] In recent years, the incidence of CRC has gradually increased, and tumor metastasis is the main cause of death in patients with CRC.[65] In metastatic patients, the 5-year survival rate was only about 10% ~15%.[66]

In an earlier study, some scholars found that *Dkk1* was methylated in CRC cells, and when the expression of *Dkk1* was restored, there was a decrease in cell colony density and tumor growth inhibition in nude mice.[67] A large cohort study showed that *Dkk1* was methylated in 95% of CRC patients, and its methylation level was closely related to tumor microvessel density.[68] Immunohistochemistry showed that the expression of *Dkk1* was down-regulated in colorectal adenoma-carcinoma sequence, and the expression of *Dkk1* was related to the decrease of microvessel density and the expression of vascular endothelial growth factor (*VEGF*). At the same time, in vitro culture showed that HCT116 with overexpression of *Dkk1* inhibited the formation of the tubular structure of human umbilical vein endothelial cells and down-regulated the expression of *VEGF*, and the tumor size, microvessel density and *VEGF* expression of CRC cells with high expression of *Dkk1* decreased.[69] Because the low expression of *Dkk1* indicates the abnormal activation of the Wnt pathway and is related to the poor prognosis of patients with CRC, it is suggested that we can increase the expression of *Dkk1* by reducing the factors that inhibit the expression of *Dkk1* (such as reducing the level of methylation or inhibiting the expression of *CSN5*) to produce anti-tumor effect. Therefore, the detection of the decrease of *Dkk1* expression can be used as a warning of tumor progression in patients with CRC and provide an idea for the treatment of tumors. COP9 signalosome (*CSN*) is a highly conserved polyprotein complex in eukaryotes, which plays an important role in the regulation of the cell cycle, DNA damage response, and apoptosis. Microarray analysis of CRC cell lines showed that the expression of *Dkk1* and the level of *Dkk1* protein depended on the increase of *Dkk1* secretion after *CSN5* gene knockout, which affected the Wnt signal transduction of SW480 cells. It is suggested that *CSN5* may actively drive abnormal Wnt signals by inhibiting Wnt antagonist *Dkk1*, thus promoting the development of colorectal cancer.[70] Therefore, understanding the molecular link between *CSN5* and Wnt signals may help to design and develop new targets for the treatment of colorectal cancer. MicroRNA (miRNA or miRs) has been proven to be an important post-transcriptional regulator in tumorigenesis. At present, as the focus of tumor mechanism research, through the in vitro study of SW-480 and HCT-116 CRC cell lines, Wang et al[71] found that miR-410 was up-regulated in CRC cell lines, and proved that *Dkk1* is the direct target of miR-410. Knocking down miR-410 can promote the expression of *Dkk1*, inhibit the proliferation, migration and invasion of CRC cells, and induce apoptosis, while the overexpression of miR-410 shows the contrary. Another study also found that the expression level of the long non-coding Long-stranded non-coding RNA (lncRNA) HOXA transcript at the distal tip (*HotTip*) at the end of CRC cells was significantly higher than that in corresponding adjacent normal tissues, and the expression level of *HotTip* was higher in patients with larger tumor size, pathological stage or distant metastasis. Silencing the expression of *HotTip* can inhibit the migration and invasion of colorectal cancer cells. Mechanism studies have shown that *HotTip* regulates the metastasis of colorectal cancer cells by down-regulating the expression of tumor suppressor gene *Dkk1*. Therefore,[72] the potential of miRNA and lncRNA as tumor candidate markers in the diagnosis and treatment of CRC is still worthy of further study.

Expression of Dkk1 in Pancreatic Cancer

Pancreatic cancer (PC) ranks fourth in cancer mortality in the United States.[73] From a pathological point of view, pancreatic duct adenocarcinoma (PDAC) accounts for about 90% of the pathological classification of PC.[74] Compared with other cancers of the digestive system, PC has a poor prognosis, with a 5-year survival rate of only 5% and a median survival time of less than 6 months.[75] Although surgical treatment is a feasible treatment, 80% of patients are in advanced stage or with metastasis at the time of diagnosis.[76]

A study from Japan observed that there was a significant up-regulation of *Dkk1* in PC cell line. After comparing the expression of *Dkk1* protein and mRNA in PC tumor tissue and normal pancreatic tissue, the high expression of *Dkk1* in tumor tissue was proved again. Further in vitro experiment found that the invasiveness of PC tumor cells with *Dkk1* knockout was significantly decreased.[77] In terms of the mechanism of *Dkk1* regulating PC, gene chip analysis showed that *Dkk1* was an abnormal gene associated with *GATA6* gene knockout. Immunoprecipitation and electrophoretic mobility shift analysis confirmed that *GATA6* directly bound to the *Dkk1* promoter. In the case of low *GATA6* knock down, it was found that the mRNA expression of *Dkk1* and the secretion of *Dkk1* protein increased. Therefore, it has been proven that *GATA6* negatively regulates *Dkk1* transcription by directly binding to the *GATA* motif in the *Dkk1* promoter region.[78] In order to explore the relationship between *Dkk1* and the prognosis of patients with PC, Han et al[79] followed up 140 patients with pancreatic adenocarcinoma and 92 patients without PC for 2 years, including serum *Dkk1* and *CA19-9* levels and tumor progression. This study found that serum *Dkk1* and *CA19-9* were increased in patients with advanced PC and chronic pancreatitis, but *Dkk1* was more effective in distinguishing PC from chronic pancreatitis than *CA19-9*, and the survival rate of patients with high expression of *Dkk1* was significantly lower than that of patients with low expression of *Dkk1*. PCR detection of PDAC and paired normal tissues showed that the expression of *Dkk1* was increased in PDAC tissues, which was confirmed by independent microarray analysis. Kaplan-Meier analysis of *Dkk1* expression and patient clinical data showed that OS and relapse-free survival (RFS) decreased in patients with high *Dkk1* expression, and the expression of *Dkk1* was significantly correlated with T stage and lymph node metastasis. Univariate and multivariate Cox regression analysis confirmed that *Dkk1* and lymph node metastasis were independent predictors of OS in patients with PDAC.[80] Based on the bioinformatics analysis of PDAC-related data sets in the GEO database, it was found that *Dkk1* and *HMGA2* are considered as hub genes with high connectivity, so *Dkk1* and *HMGA2* may become therapeutic targets and prognostic markers of PDAC.[81] In recent years, more and more attention has been paid to the role of lncRNA in PC.[82] In order to understand the expression and role of *LINC01133* in PC, the relationship between *LINC01133* and *Dkk1* promoter methylation was founded. After further detecting the expression of genes related to the Wnt signal pathway such as *LINC01133* and *Dkk1*, and using EDU staining, scratch method and Transwell method to detect their effects on tumor cells, it was found that *LINC01133* can down-regulate the expression of *Dkk1* to inhibit the Wnt signal pathway, thus promoting the growth and metastasis of pancreatic cancer.[83] In the exosome study of PDAC, it was found that the new receptor cytoskeleton-associated protein 4 (*CKAP4*) of *Dkk1* could be secreted through the small extracellular vesicle (*SEV*) of PDAC cells, and showed the characteristics of exosome. Histological and in vitro tumor detection showed that the level of *CKAP4* in serum of PDAC patients was higher than that of normal patients, and *CKAP4* monoclonal antibody could inhibit *Dkk1* and *CKAP4*, and finally inhibit the proliferation and migration of PDAC cells.[84]

Expression of Dkk1 in Cervical Cancer

Cervical cancer (CC) ranks fourth in tumor-related mortality among women.[85] The transformation from normal cervical epithelium to intraepithelial neoplasia (CIN) and finally to invasive cervical cancer is the most important pathological feature of CC.[86] Among the three histological types of adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma, squamous cell carcinoma is the most common, while human papillomavirus (HPV) is considered to be an independent risk factor in the occurrence of CC.[87,88] Corresponding vaccines have been developed for clinical prevention. And more and more studies have also pointed out that the carcinogenic effect of cervical cancer is designed to change a variety of genes.[89]

Some studies have found that the transcription of *Dkk1* in CC is inhibited in epigenetics, while further studies have found that there is a high level of methylation of *Dkk1* promoter CpG in CC cell lines, and histone deacetylation is the main epigenetic change, so cell line-dependent and differentiated epigenetic mechanisms may be used to silence *Dkk1* in CC cells.[90] By comparing the serum *Dkk1* and clinical information of patients with cervical cancer, it was found that the level of serum *Dkk1* in patients with cervical cancer was higher than that in healthy subjects, and it was related to the histological type and lymphatic metastasis of CC, so it may be helpful for the diagnosis of CC.[91] After simultaneously detecting the serum *Dkk1* of normal subjects, CIN patients and CC patients and following up their subsequent disease development data, it was found that the serum *Dkk1* level of CC patients was higher than that of normal subjects and CIN

patients, and the expression of *Dkk1* was related to lymphatic metastasis and tumor diameter of cervical cancer, and related to the prognosis of cervical cancer patients. It can be used for the detection and diagnosis of CC, and for the prognosis evaluation of CC patients[92] In view of the important role of lncRNA in the pathological process of cancer, some scholars have studied the role of lncRNA in CC and found that the promoting effect of *SNHG7* on the development of CC depends on the activation of Wnt pathway mediated by *Dkk1*, while the binding of *EZH2* and *Dkk1* promoter and the share of *H3K27me3* in *Dkk1* promoter are decreased after *SNHG7* silencing. It has been proven that *SNHG7* silences *Dkk1* through Wnt/β-catenin signal transduction pathway to aggravate the malignant degree of CC.[93]

Expression of Dkk1 in Ovarian Cancer

Although the 5-year survival rate of patients with ovarian cancer has been stable for the past 20 years, it is still at a low level (30%~40%), making it the deadliest tumor in gynecological tumors.[85,94–96] Because its early clinical symptoms are not obvious, nearly 2/3 of the patients are in the late stage at the time of diagnosis.[97] Most (80%) of the patients who died had epithelial ovarian cancer (EOC).[98]

By using cDNA microarray to analyze the gene expression profile of metastatic EOC cells, it was found that *Dkk1* was significantly down-regulated in metastatic tumors.[99] Through the study of the progress of EOC cells, it was found that *STAT3* was overactivated in ovarian cancer, and the expression of *Dkk1* increased significantly after reducing the expression of *STAT3*. Further studies found that *STAT3* signal regulated tumor progression through miR-92a/β-1 and connected with Wnt/*Dkk1*-catenin signal, thus finding the metabolic pathway of tumor.[100] The member of 10–11 translocation (TET) family (*TET1-3*) is the key molecule of DNA demethylation,[101,102] and its expression is down-regulated in many cancers.[103,104] In the analysis of EOC, it was found that the expression of *TET1* was negatively correlated with the clinical stage of ovarian cancer. Overexpression could inhibit the colony formation, invasion, metastasis and epithelial-mesenchymal transformation of ovarian cancer cells. In terms of mechanism, it was found to be by *TET1* through demethylation of Wnt/β-catenin signal pathway antagonist *Dkk1*. Therefore, *TET1* plays an important anti-tumor role in ovarian cancer by activating Wnt/β-catenin signal inhibitor *Dkk1*.[105] Cordycepin (3-deoxyadenosineis) the main bioactive component of Cordyceps militaris, which has been reported to inhibit cell proliferation.[106–108] After further study on ovarian cancer, it was found that cordycepin kit-8 reagent based on cell count decreased the viability of ovarian cancer cells, Western blotting showed that cordycepin could increase the *Dkk1* and inhibit β-catenin signal transduction. Overexpression of *Dkk1* down-regulated the expression of *c-Myc* and *cyclin D1*, while silence down-regulated the expression of *Atg8*, *beclin*, and *LC3*, the results showed that cordycepin might inhibit the growth of ovarian cancer cells through synergistic autophagy and *Dkk1*/β-catenin signal transduction.[109] After the preparation of monoclonal antibody against *Dkk1* (DKN-01), the effect of *Dkk1* on tumor cell phenotype and tumor load was studied in vivo and in vitro. It was found that overexpression of DKN-01 had no significant effect on tumor cell phenotype and tumor load, but overexpression of *Dkk1* reduced the infiltration of $CD45^+$ leukocytes into the peritoneum and omentum, reduced natural killer (NK) and CD8T cells, and decreased the expression of interferon-γ (*IFN-γ*) on activated CD8T cells. Therefore, these results may indicate that the overexpression of *Dkk1* provides a microenvironment to promote tumor by inhibiting the anti-tumor immune population, so the inhibition of *Dkk1* may play the best role in combined immunoregulatory therapy.[110]

Expression of Dkk1 in Breast Cancer

Although today, with the rapid development of diagnosis and treatment technology, the prognosis of breast cancer patients is still poor.[111,112] Tumor metastasis is one of the main causes of death in patients with breast cancer,[113] so the research based on the mechanism of breast cancer progression and metastasis has become a hot topic.

Compared with normal subjects, the level of serum *Dkk1* in breast cancer patients was higher, and the level of *Dkk1* in patients with bone metastasis was higher than that in patients without bone metastasis.[114] The high expression of *Dkk1* in triple negative breast cancer patients was regulated with poor prognostic.[115] *Dkk1* is associated with the progression of osteolytic bone metastasis by damaging the activity of osteoblasts.[116] *P38* mitogen-activated protein kinase (MAPK) regulates intracellular responses related to cell cycle, apoptosis and tumorigenesis. Inhibition of *P38* in breast cancer cell lines can effectively inhibit the expression of *Dkk1* in breast cancer cells, whereas activation of *P38* can up-regulate *Dkk1*, suggesting that *p38* may play a role in regulating *Dkk1*

in osteolytic tumors.[117] Previous studies have shown that zoledronic acid and Atto vastatin can block mevalonate pathway to inhibit high expression of *Dkk1* in hormone receptor negative breast cancer.[118] But its dosage far exceeds the level of clinical safe use. A new study shows that zoledronic acid combined with low concentrations of statins can increase the inhibitory efficiency of human osteoblast tumor cells by 75%. When low concentrations of statins and zoledronic acid are used at low concentrations, the metastatic rate of *Dkk1*-mediated breast cancer bone metastatic cells can be reversed by at least 50%. Intratumoral injection of Atto vastatin and zoledronic acid can reduce serum *Dkk1* levels by 25%.[119] In the study of mesenchymal stem cell (MSC), it was found that MSCs from the rib perichondrium (PMSCs)-conditioned medium could significantly inhibit the growth, migration and invasion of breast cancer cells, and down-regulate the expression of Wnt/β-catenin pathway and its target genes, while neutralizing *Dkk1* in PMSC-conditioned medium could significantly reduce its inhibitory effect on tumor cells. In vivo, PMSCs can inhibit the growth of breast cancer and prolong the survival time of tumor-bearing rats, suggesting that *Dkk1* secreted by PMSC plays an important role in inhibiting the growth of breast cancer cells through Wnt/β-catenin pathway.[120] By comparing the serum *Dkk1* and *CA15-3* between breast cancer patients and healthy subjects, it was found that in the early stage of breast cancer, the sensitivity and specificity of *Dkk1* were higher than that of *CA15-3*, while the expression of *Dkk1* in HER-2-, ER-, and PR-positive patients was lower than that in HER-2-, ER- and PR-negative patients.[121] After comparing the serum *Dkk1* of 89 breast cancer patients and 86 healthy women, and comparing the *Dkk1* and β-catenin in adjacent non-neoplastic breast tissues, primary breast tumors, lymph node metastasis and bone metastasis tissues, it was found that the serum *Dkk1* in breast cancer patients were significantly higher than those in normal subjects, but the increase was more significant in patients with bone metastasis. The expression of *Dkk1* in lymphoid nodule metastatic tissue and bone metastatic tissue was lower than that in primary tumor tissue and non-neoplastic breast tissue.[122] Through identification, it was found that a small molecular chemical dorsomorphin could reduce the mRNA and protein levels of *Dkk1* in breast cancer cell lines by 70% and 90%, respectively, suggesting that dorsomorphin may be a therapeutic drug for breast cancer.[123]

Expression of Dkk1 in Bladder Urothelial Cancer

Research data from the United States show that bladder urothelial cancer (BUC) accounts for about 7% of new tumors and 4% of all cancer deaths.[32] At the same time, it is also one of the most common urogenital cancers in the People's Republic of China.[124] BUC is divided into muscle-infiltrating bladder cancer (MIBC) and non-muscle-infiltrating bladder cancer (NMIBC). The incidence of MIBC is high and easily recurs, while NMIBC tends to relapse within 2 years.[125,126]

Through the preoperative detection of serum *Dkk1* in patients with bladder cancer, it was found that the increase of preoperative *Dkk1* was closely related to tumor stage, grade and histological grade.[127] The serum samples of 94 patients with bladder cancer and 60 healthy subjects from the People's Republic of China showed that the serum *Dkk1* in patients with bladder cancer was significantly higher than that in healthy subjects, and the serum *Dkk1* was closely related to lymph node metastasis, distant metastasis and TNM staging. The higher the serum *Dkk1* the lower the survival rate of bladder cancer patients. Multivariate analysis showed that serum *Dkk1* was an independent prognostic factor for OS of bladder cancer.[128] Gao et al[129] demonstrated that up-regulation of *miR-543-3p* in bladder cancer can activate Wnt/β-catenin signal by directly targeting *Dkk1*, while the expression of *miR-543-3p* is up-regulated in bladder cancer tissues and cells, and is positively correlated with high-grade bladder cancer, suggesting a potential tumor intervention target.

Discussion

Based on the above studies, most of the human samples were studied in vivo and in vitro. Most studies have pointed out that *Dkk1* promotes the metastasis of various types of cancer, and is related to the late stage, metastasis and low short survival time of the tumor, and its diagnostic sensitivity is comparable to that of existing biomarkers, even beyond them.[38,79] But interestingly, in some tumors, *Dkk1* showed tumor inhibitory effect in tumors.[61–72]

Specifically, through the above research, we can find that *Dkk1* has been shown to promote tumor metastasis in the following tumors: NSCLC, HCC, EC, GC, PC, CC, Breast cancer, and BUC. But In CRC and ovarian cancer, *Dkk1* has been shown to play an inhibitory role in tumors.

According to the results of the above literature, we can observe that the high expression of *Dkk1* can significantly decrease the invasion and metastasis ability of CRC and EOC cells in vitro and in vivo. By comparing the serum samples of tumor patients and normal subjects, we also confirmed the protective effect of high expression of *Dkk1* on CRC patients. However, high expression of *Dkk1* was shown in other tumors to promote tumor progression. (Figure 1).

In terms of the mechanism of *Dkk1* in tumor, according to the correlation between *Dkk1* and tumor metastasis in vivo and in vitro, the mechanism of action, and the survival time of patients, we have made a summary of the above-mentioned literature, showing the mechanism of promoting tumor is mainly concentrated in the following aspects: 1) promoting tumor angiogenesis;[27,40,69] 2) methylated *Dkk1* promoter;[67,68,81] 3) *STAT3* regulates tumor progression through the interaction between miR-92a/β-1 pathway and Wnt/*Dkk1*-catenin signal;[100] 4) Synergistic autophagy and *Dkk1*/β-catenin signal transduction regulate tumor progression; and 5) change tumor immune microenvironment. However, in CRC, in vivo experiments showed that overexpression of *Dkk1* caused down-regulation of *VEGF* expression. Tumor formation experiments in vitro showed that the tumor size, microvessel density and *VEGF* expression of CRC cells with high expression of *Dkk1* decreased, and that *CSN5*, *miR-410* and *HotTip* could promote the progress of CRC by inhibiting the expression of *Dkk1*.[70–72] And in EOC, *TET1* plays a tumor suppressive role in ovarian cancer by activating *Dkk1* through demethylation. (Table 1)

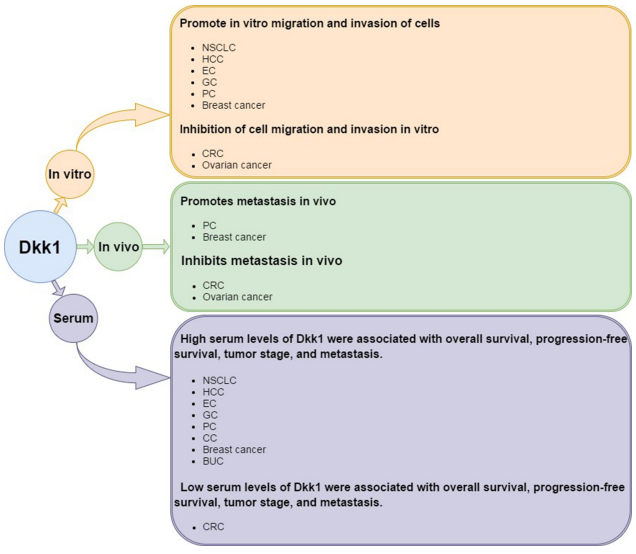

Figure 1 Summary of the research findings on the role of *Dkk1* in cancers from in vitro and in vivo experiments as well as from studies using serum from human patients.

Current studies have shown that *Dkk1* regulates tumor progression by inhibiting the downstream regulation of cell cycle, tissue and organ fibrosis and the expression of other related target genes. By downloading the oncology data of TCGA database and the expression data of normal tissue in GETx database, and used R to analyze the difference of *Dkk1* in normal tissue and tumor tissue of different organs, it is found that: the expression of *Dkk1* in ACC, CHOL, COAD, ESCA, GBM, HNSC, LGG, LIHC, LUAD, LUSC, PAAD, READ, STAD, TGCT, UCEC, and UCS was significantly higher than that in normal tissues, but in BLCA, KICH, PRAD, SKCM, and OV, the expression of *Dkk1* in tumors was significantly lower than that in normal tissues (Figure 2).

Dkk1 plays a role in regulating tumor progression because of its inhibition of classical Wnt pathway in tumors.[8,9] Therefore, *Dkk1* is defined by most studies as a biological marker with the potential to evaluate tumor diagnosis and prognosis.[18–20] In most tumors, *Dkk1* promotes tumor growth and metastasis by promoting angiogenesis and regulating immune microenvironment. However, in other tumor studies, it has been found that *Dkk1* can inhibit the biological effect of tumor. Some scholars have put forward the following conjectures about the different biological effects of *Dkk1* in tumors: 1) according to the transduction mode of Wnt signal in cancer cells, inhibiting β-catenin dependent Wnt signal does not necessarily inhibit tumor; 2) the characterization of *Dkk1* as a β-catenin-dependent Wnt signal inhibitor in cancer cells is too simplistic, and it is important to consider other potential regulatory results of *Dkk1*; and 3) in some tumors, the classical Wnt signal pathway is structurally activated downstream of *Dkk1*. In this case, it can be assumed that *Dkk1* cannot inhibit the transduction of the classical Wnt signal pathway, thus eliminating its potential antitumor activity.[130]

In recent years, *Dkk1* antibodies have been tried in tumor therapy, but because Wnt signaling is extremely complex, and the role of *Dkk1* in promoting tumor growth and metastasis in cancer and immune cells in regulating this and other signaling pathways has not been fully elucidated. The close relationship between the expression level of *Dkk1* in serum of clinical tumor patients and prognosis makes *Dkk1* an attractive target for tumor

Table 1 Studies in Human Cancer Revealing the Role of *Dkk1* as a Cancer Biomarker

Study	Cancer Type	Experimental Approach	Metastasis in vitro (Cell Migration and Invasion)	Metastasis in vivo	Correlation with Malignant or Meta-Static Phenotype	Correlation with Decreased Survival	Suggested Mechanism of Action via the Pathway of
21–29	Non-Small Cell Lung Cancer (NSCLC)	Analysis of tumor tissue samples from 205 patients with lung cancer.[27] The serum levels of *Dkk1* autoantibodies were measured by ELISA in 206 patients with NSCLC and 99 healthy controls. And followed up for 3 years.[28] Serum *Dkk1* levels were quantified and analyzed in 470 patients with NSCLC (140 bone metastases, 178 extraosseous metastases and 152 complete remission).[29]	Yes	Yes	Yes	Yes	*Dkk1* promotes VM formation by inducing EMT-related proteins and developing CSC properties in NSCLC.
30–45	Hepatocellular carcinoma (HCC)	By comparing the serum *Dkk1* levels of 831 test cohort participants and 453 verification cohort participants, the contents of *Dkk1*mRNA and protein in liver tissues of patients with HCC and non-cancer patients were compared.[38] Evaluation of the effects of exogenous *Dkk1* on angiogenesis and EnMT by cell test.[39] Retrospectively analyzed the changes of serum *Dkk1* and circulating tumor cell (CTC) in 155 HCC patients treated with TACE.[44]	N/A	N/A	N/A	Yes	*Dkk1* induces angiogenesis by regulating *VEGFR2* independent of Wnt signal transduction pathway.
46–52	Esophageal carcinoma (EC)	The expression of *Dkk1* in esophageal cancer tissues, matched normal esophageal tissues and esophageal cancer cell lines was detected by RT-PCR and Western blot methods. Serum Dkk1 levels of 90 ESCC patients and 85 healthy patients were compared by ELISA.[49] The expression of *Dkk1* protein in surgical specimens of 170 patients with ESCC was compared with various clinical data.[51]	Yes	N/A	Yes	Yes	N/A
53–62	Gastric cancer (GC)	Comparison of serum Dkk1 levels in 153 GC patients and 173 healthy controls, and comparison of *Dkk1* expression levels in 144 cancer specimens of 153 patients and 265 GC specimens.[55] ELISA was used to detect the expression of serum *Dkk1* protein in 90 cases of gastric cancer, 50 cases of gastric benign diseases and 40 healthy persons, and to monitor the changes of serum *Dkk1* protein in patients with gastric cancer after radical operation for a month.[56] Detection of the relationship between the co-expression of *Dkk1* and β-catenin in gastric cancer and clinical prognosis.[59] To verify whether *Dkk1* can effectively inhibit endogenous Wnt/β-catenin signal transduction in $CD44^{+}$GC cells.[60]	Yes	N/A	Yes	Yes	Wnt/β-catenin signal pathway

63–75	Colorectal cancer (CRC)	Immunohistochemistry was used to detect the expression of *Dkk1* in 476 colon specimens. HCT116 cells overexpressing *Dkk1* were cultured in vitro and tumorigenesis was carried out in vitro.[69] Knock out *CSN5* gene in SW480 cells and detect the expression of *Dkk1*.[70] The relationship between *miR-410* and *Dkk1* expression was demonstrated in SW-480 and HCT-116 CRC cell lines in vitro.[71]	Yes	Yes	Yes	Yes	*CSN5*actively drives abnormal Wnt signals by inhibiting *Dkk1*. Overexpression of *miR-410* inhibits the expression of *Dkk1* in CRC cells, thus promoting the proliferation, migration and invasion of CRC cells. *HotTip*regulates the metastasis of colorectal cancer cells by down-regulating the expression of tumor suppressor gene *Dkk1*.
76–87	Pancreatic cancer (PC)	The expression levels of *Dkk1* protein and mRNA in normal pancreatic cells, PC cell lines, normal pancreatic tissues and PC tumor tissues were compared. Tumor invasiveness was detected after *Dkk1* knockout in vitro.[73] Co-immunoprecipitation and knockout methods were used to prove that *GATA6* negatively regulates *Dkk1* transcription by directly binding to the *GATA* motif in the *Dkk1* promoter region at the cellular level.[78] 140 patients with pancreatic adenocarcinoma and 92 patients without PC were followed up for 2 years to evaluate the levels of serum *Dkk1* and *CA19-9* and tumor progression.[79] Detection of *Dkk1* expression in PDAC tissues and matched normal tissues, and comparison with clinical data items of patients.[80] The expression of *LINC01133* and *Dkk1* and their effects on tumor cells were detected by ectopic expression test, gene knockout test and gene reporting test.[81] The interaction between *CKAP4* and *Dkk1* and its effect on PDAC cells were detected by texture detection and tumor formation in vitro.[84]	Yes	Yes	Yes	Yes	*GATA6* negatively regulates *Dkk1* transcription by directly binding to the *GATA* motif in the *Dkk1* promoter region. *INC01133* can down-regulate the expression of *Dkk1* to inhibit the Wnt signal pathway, thus promoting the growth and metastasis of pancreatic cancer.
88–96	Cervical cancer (CC)	Explore the epigenetic characteristics of *Dkk1* in CC cell line.[90] Testing serum *Dkk1* levels in patients with CC and comparing them with patient clinical information.[91] Simultaneous testing of serum *Dkk1* in normal subjects, patients with CIN, and patients with CC and follow-up of subsequent disease progression.[92] Demonstration at the cellular level that SNHG7 epigenetically silences *Dkk1* through the Wnt/β-catenin signaling pathway.[93]	N/A	N/A	Yes	Yes	*SNHG7* epigenetically silences *Dkk1* through the Wnt/β-catenin signaling pathway to exacerbate CC malignancy

(*Continued*)

Table 1 (Continued).

Study	Cancer Type	Experimental Approach	Metastasis in vitro (Cell Migration and Invasion)	Metastasis in vivo	Correlation with Malignant or Meta-Static Phenotype	Correlation with Decreased Survival	Suggested Mechanism of Action via the Pathway of
97–114	Ovarian cancer	*STAT3* was demonstrated in EOC cells to regulate tumor progression via *miR-92a*/β-1 and to interconnect with Wnt/*Dkk1*-catenin signals.[100] *TET1* was demonstrated in EOC cells to inhibit the Wnt/β-catenin pathway through demethylation of *Dkk1* and thus tumor suppression.[105] Cell-level validation of cordycepin inhibits ovarian cancer cell growth through synergistic autophagy and *Dkk1*/β-catenin signaling.[109]	Yes	Yes	Yes	N/A	*STAT3* regulates tumor cell metabolism by regulating *miR-92a*/β-1 and combining the Wnt/*Dkk1*-catenin signaling pathway. *TET1* activates *Dkk1* and inhibits Wnt/β-catenin pathway for tumor suppression through demethylation. Cordycepsin inhibits ovarian cancer cell growth through synergistic autophagy and *Dkk1*/β-catenin signaling.
115–127	Breast cancer	Comparison of serum *Dkk1* in normal subjects, breast cancer patients, and patients with bone metastases.[114,115,121,122] In vivo experiments use drugs to interfere with *Dkk1* and thereby suppress tumors.[119,123] In vivo and in vitro experiments demonstrate that PMSC-secreted *Dkk1* inhibits breast cancer cell growth through the Wnt/β-catenin pathway.[120]	Yes	Yes	Yes	Yes	Possible role of p38 in regulating *Dkk1* in osteolytic breast cancer tumors. PMSC-secreted *Dkk1* inhibits breast cancer cell growth through the Wnt/β-catenin pathway. Statins in combination with zoledronic acid at low concentrations may inhibit tumor growth by reducing *Dkk1* levels. The small molecule dorsomorphin may produce tumor suppression by reducing the transcriptional level of *Dkk1*.
128–134	Bladder urothelial cancer (BUC)	Detecting *Dkk1* levels in BUC patients before surgery.[127] Determination of serum *Dkk1* levels in normal subjects and BUC patients and comparison of clinical data.[128] Investigating the role of *miR-543-3p* on tumors via *Dkk1* in BUC cells.[129]	N/A	N/A	Yes	Yes	Upregulation of *miR-543-3p* in bladder cancer activates Wnt/β-catenin signaling by directly targeting *Dkk1*.

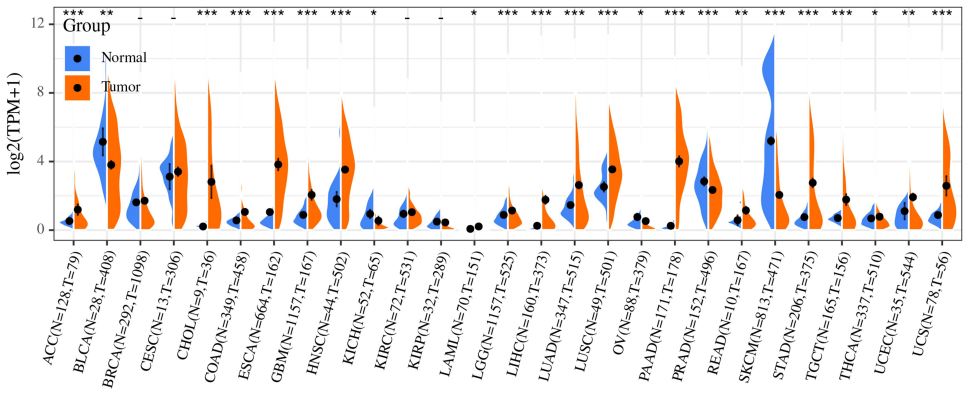

Figure 2 Analysis of differential expression of *Dkk1* in tumor tissues and normal tissues based on TCGA and GTEx database. **Abbreviations**: ACC, adrenocortical carcinoma; BLCA, bladder Urothelial Carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma.

therapy, and blocking the activity of *Dkk1* in mice can significantly reduce the ability of tumor invasion and metastasis in vivo. Therefore, although *Dkk1* has two sides in tumor measurement because its mechanism is not fully elucidated, it does not affect its potential as a target for targeted therapy of tumors.

Abbreviations

AGC, advanced gastric cancer; AFP, alpha-fetoprotein; BUC, bladder urothelial cancer; CAMKII, calcium/calmodulin-dependent kinase II; Cdc42, cell division control protein 42; CSC, cancer stem cell; CSC, cancer stem cell-like cell; CC, cervical cancer; CIN, cervical epithelium to intraepithelial neoplasia; CTC, circulating tumor cell; CRC, colorectal cancer; CSN, COP9 signalosome; CKAP4, cytoskeleton associated protein 4; DAAM1, dishevelled associated activator of morphogenesis 1; Dkk1, dickkopf-1; DFS, disease-free survival; EGC, early gastric cancer; EOC, epithelial ovarian cancer; EMT, epithelial–mesenchymal transformed; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; SEV, extracellular vesicle; HCC, hepatocellular carcinoma; HotTip, HOXA transcript at the distal tip; HPV, human papillomavirus; HUVEC, human umbilical vein endothelial cells; IFN-γ, interferon-γ; lncRNA, long-stranded non-coding RNA; MSC, mesenchymal stem cell; miRNA or miRs, MicroRNA; MAPK, mitogen-activated protein kinase; PMSCs, MSCs from the rib perichondrium; MIBC, muscle-infiltrating bladder cancer; NFAT, nuclear factor of activated T-cells; NLK, nemo-like kinase; NMIBC, non-muscle-infiltrating bladder cancer; NSCLC, non-small cell lung cancer; OS, overall survival; PC, pancreatic cancer; PDAC, pancreatic duct adenocarcinoma; RFS, relapse-free survival; PKC, protein kinase C; RHOA, Ras homolog gene family member A; TACE, transcatheter arterial chemoembolization; TAK-1, TGF-β activated kinase 1; VEGFR2, vascular endothelial growth factor receptor 2; VEGF, vascular endothelial growth factor; VM,vasculogenic mimicry.

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Disclosure

The authors report no conflicts of interest in this work.

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