Review Article

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# Junction Plakoglobin – A Dual-Role Player in Cancer Biology

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**Abstract**

Junction plakoglobin (JUP) is a critical cell adhesion molecule implicated in mediating cell-cell adhesion. Cancer, characterized by the loss of normal cellular regulation, results in unchecked proliferation and the breakdown of cell-cell junctions, facilitating malignant cell invasion into surrounding tissues. Recent studies have highlighted the involvement of JUP in the transduction of various intercellular signaling pathways, underscoring its significant role in tumor initiation, progression, and prognosis. In contrast to its homolog β-catenin, the interplay between JUP and cancer remains underexplored. To clarify JUP's role and underlying mechanisms in cancer progression, this review examines recent advancements, focusing on JUP's regulation of key cancer-related signaling pathways, such as Wnt/β-catenin, p53, and cadherin-mediated pathways. The review also investigates JUP's relevance across various cancer types, including those of the reproductive, digestive, and urinary systems. Mechanistically, JUP exhibits context-dependent actions in different cancers, demonstrating dual roles in tumorigenesis. Lastly, the potential of JUP as a target for early diagnosis, effective treatment, and prognostic prediction in cancer is evaluated. In conclusion, targeting JUP offers a promising avenue for cancer therapy, providing valuable insights for future research.

**Keywords:** biomarkers, cadherins, cancer, junction plakoglobin, p53 protein, prognosis, therapeutic target, Wnt/ β -catenin

## Introduction

As the second leading cause of death worldwide, cancer progression is a complex, multi-stage process involving the aberrant activation and regulatory disruption of multiple intracellular signaling pathways. Advances in cancer research have increasingly focused on precision-targeted biological molecules and gene therapies, as well as the intricate dynamics of the tumor microenvironment[1,2]. Among the key molecules in tumor biology, Junction plakoglobin (JUP), also known as plakoglobin or γ-catenin, is a paralog of β-catenin. A member of the armadillo protein family, JUP is essential for cell adhesion[3–8], with reduced JUP levels impairing cell adhesion[9,10]. Additionally, JUP stabilizes the cytoskeleton through components such as desmosomes. Specifically, intermediate filaments, a cytoskeletal element, are anchored to desmosomes via desmogleins, which are part of the plakin protein family. Desmogleins (DSGs) interact with desmocollins (DSCs), plakophilins (Pkps), and JUP to form desmosomes, thus contributing to cytoskeletal stability[11–15]. Moreover, JUP maintains the dynamic structure of desmosomes[16], a process mediated by 14-3-3 proteins, a highly conserved family of acidic proteins. Among them, 14-3-3γ, which is involved in cell cycle regulation[17], binds to JUP, facilitating its translocation to the cell periphery and supporting desmosome formation and stability[18]. Subsequently, based on S100A11 (S100 calcium-binding protein A11), JUP in desmosomes can undergo nuclear translocation[19].

Recent studies have revealed that the functions of JUP extend far beyond its previously understood roles, particularly regarding its complex signaling mechanisms within the tumor microenvironment, which are closely linked to cancer initiation and progression. The central region of JUP contains 12 highly repetitive armadillo repeats, allowing it to bind to various molecules, such as T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), p53, mutations in adenomatous polyposis coli (APC), and epithelial cadherin (E-cadherin)[20,21], thus exerting tumor-suppressive effects by inhibiting tumor cell invasion and metastasis[10]. However, in certain contexts, elevated JUP expression may

## HIGHLIGHTS

- JUP is involved in the regulation of various cancer-related signaling pathways, such as the Wnt/β-catenin signaling pathway, the *p53* gene, and cadherin.
- JUP may have different biological functions in different types of cancer.
- Detection of JUP expression activity is beneficial for early diagnosis, effective treatment, and prognosis evaluation of cancer patients.

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promote tumorigenesis and metastasis, as seen in bladder and breast cancers[22,23]. Therefore, the role of JUP in cancer is likely multifaceted, influenced by factors such as cancer type, disease stage, and intracellular distribution of JUP[24], which will be further discussed.

As research into JUP's involvement in various cancers has advanced, it has emerged as a potential target for cancer treatment, metastasis control, and prognostic evaluation[25,26]. The aberrant expression of JUP and its contribution to cancer progression offer novel insights and strategies for targeted therapies. However, the precise mechanisms underlying JUP's actions in cancer remain to be fully elucidated, and its distinct roles and therapeutic potential across different cancer types warrant further investigation. This review aims to comprehensively analyze the mechanisms by which JUP influences cancer, exploring its functional pathways and therapeutic implications in diverse cancer types, ultimately offering new strategies for future clinical management of cancer.

## The main pathways through which JUP participates in the occurrence and development of cancer

JUP's involvement in cancer progression is primarily mediated through several potential mechanisms, some of which remain unclear. This review focuses on JUP's regulatory effects on the Wnt/β-catenin signaling pathway, as well as its interactions with the *p53* gene and cadherins.

### *Role of JUP in the regulation of the Wnt/β-Catenin signaling pathway*

#### Positive feedback loop between β-Catenin and Wnt signaling pathway

The Wnt signaling pathway is highly conserved and plays a pivotal role in tumor stem cell proliferation, making its regulators promising targets for cancer therapy[27–29]. β-catenin serves as a key downstream effector molecule in this pathway. In the absence of Wnt signaling, β-catenin forms a complex with APC, axis inhibition protein 1 (Axin), glycogen synthase kinase 3β (GSK-3β), and casein kinase 1 (CK1), where it is phosphorylated, ubiquitinated, and degraded. When Wnt signaling is active, Wnt ligands bind to Frizzled receptors (Fzd) and low-density lipoprotein receptor-related proteins 5/6 (LRP5/6), leading to the activation of Disheveled (Dvl) proteins. This activation inhibits GSK-3β, preventing β-catenin degradation and promoting its nuclear translocation[30–33]. Prior to the nuclear entry of β-catenin, TCF/LEF acts as a transcriptional repressor of Wnt target genes by interacting with Groucho/Transducin-like Enhancer of Split (Groucho/TLE) proteins. Upon nuclear translocation, β-catenin displaces Groucho/TLE proteins and binds directly to LEF-1 and TCF-4, converting TCF/LEF into activators of the Wnt pathway[31,34]. Within the nucleus, the β-catenin–TCF/LEF complex induces the transcription of Wnt/β-catenin target genes, such as c-Myc, MMP7, and Cyclin D, promoting tumor initiation and progression across various cancer types[35].

#### The bidirectional role of JUP in the Wnt signaling pathway

JUP, a paralogue of β-catenin, performs analogous regulatory functions in the Wnt signaling pathway and can directly activate the expression of *Wnt* target genes in the absence of β-catenin. In the β-catenin-deficient NCI-H28 human malignant mesothelioma cell line, JUP binds to the TCF/LEF family (TCF-4 or LEF-1) and activates Wnt pathway target genes, though its binding affinity for TCF/LEF is relatively weak. Consequently, JUP's activation of *Wnt* target gene expression is less robust than that of β-catenin, yet it clearly performs a similar role in gene activation[36] (Fig. 1). A key distinction is that JUP and β-catenin bind different regions of TCF-4. β-catenin primarily interacts with the first 50 N-terminal amino acids of TCF-4, while JUP predominantly binds amino acid residues 51–80[37].

However, the role of JUP in the Wnt signaling pathway may not be limited to activation. Studies have demonstrated that in head and neck cancer cell lines, where DSG3 is silenced, increased nuclear translocation of JUP enhances its binding with TCF/LEF transcription factors; yet, this effect unexpectedly inhibits the expression of downstream Wnt target genes. This suggests that under specific conditions, JUP may exert an inhibitory influence on the Wnt pathway[38]. Similarly, in lung cancer cell lines with overexpressed desmoplakin (DSP), elevated JUP expression suppresses TCF/LEF transcription factor activity, thereby reducing the expression of downstream *Wnt* target genes[39] (Fig. 1). Other research has proposed that JUP does not directly activate *Wnt* target gene transcription but rather does so indirectly by increasing intracellular β-catenin levels[40]. This may be due to JUP's limited ability to activate TCF/LEF transcription factors. In the absence of β-catenin, JUP exerts a weak activation effect, but when β-catenin is present, elevated JUP competes with β-catenin for binding to TCF/LEF, thereby reducing the overall activation of TCF/LEF transcription factors and consequently diminishing downstream *Wnt* target gene expression.

### *Role of JUP in the regulation of p53 protein*

#### Structural basis of the interaction between JUP and p53

In the H1299 lung cancer cell line, p53 and JUP were transfected, with HA tags labeling the p53 protein and its domains (NT, DBD, CT), and FLAG tags labeling the JUP protein and its domains (ΔN, ΔArm, ΔC). Alaee, *et al* demonstrated that the interaction between p53 and JUP is mediated by the ΔC domain of JUP and the DBD domain of p53, with the ΔC domain of JUP being essential for its nuclear localization and interaction with p53[41] (Fig. 1). Additionally, the ΔN domain of JUP interacts with *Nm23*, a tumor suppressor gene (mainly *Nm23-H2*), leading to reduced translation and expression of SATB1 mRNA, an oncogenic chromatin remodeling factor, in SCC9 cells, highlighting JUP's role as a tumor suppressor[42,43].

#### Synergistic effect of JUP and p53

p53, a tumor suppressor, regulates the cell cycle and apoptosis in tumor cells, inhibiting cancer initiation and metastasis[44]. Previous studies have shown that JUP and p53 can interact[45,46]. For instance, JUP is not expressed in SCC9 cells (a human tongue squamous cell carcinoma line[47,48]), but transfection of JUP in SCC9 cells followed by co-immunoprecipitation (Co-IP) with p53 and JUP antibodies revealed that JUP and p53 cooperate on the p53 consensus binding sequence in the 14-3-3σ gene promoter, enhancing 14-3-3σ protein expression (Fig. 1). The 14-3-3σ protein, induced by p53 following DNA damage, regulates the cell

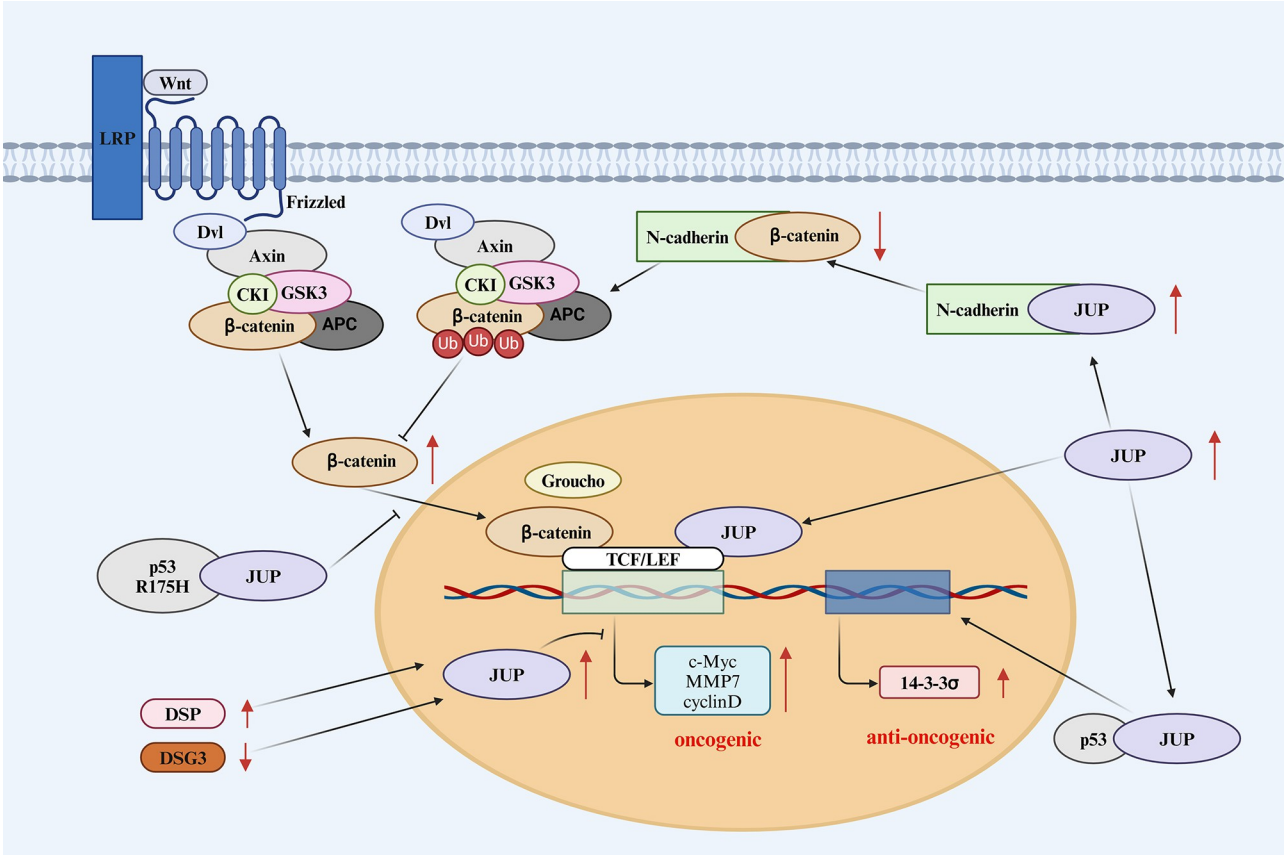


**Figure 1.** The intrinsic pathways through which JUP exerts its functions in tumor cells. JUP, functioning as a β-catenin analog, binds to TCF/LEF elements, thereby initiating the expression of downstream target genes (e.G., c-Myc, MMP7, and cyclinD). However, the transcriptional activation of oncogenes can be suppressed through DSP overexpression or *DSG3* silencing, which upregulates JUP expression levels. The mutation of *p53* will lead to the accumulation of β-catenin, and the interaction level between β-catenin and TCF-4 will be enhanced, while JUP can competitively bind TCF-4 with β-catenin to antagonize its effect. JUP and p53 jointly act on the p53 consensus sequence in the 14-3-3σ gene promoter, increasing the expression of 14-3-3σ protein.

cycle and inhibits cancer development, with lower transcriptional levels of 14-3-3σ observed in SCC9 cells[49].

Certain mutations in the *p53* gene can acquire oncogenic functions, with the p53R175H mutation being the most common[50]. JUP is also considered an endogenous interacting partner of both wild-type and mutant *p53*, and this interaction helps reduce the accumulation of β-catenin, thereby mitigating the cancer-promoting effects of *p53* mutations[45]. Specifically, p53R175H promotes β-catenin expression and nuclear translocation, increasing levels of its downstream targets (e.g., c-MYC and S100A4) in H1299 cells where JUP is silenced. This effect can be reversed by upregulating JUP levels[51,52]. In summary, JUP supports p53 in executing its normal biological functions.

### *Role of JUP in the regulation of cadherin protein*

#### JUP functions as a key molecular chaperone for cadherin in cell adhesion

Cadherin-mediated cell adhesion is critical for maintaining tissue integrity and cell-cell interactions. A reduction in cell adhesion can promote cancer metastasis and spread[53,54]. Both JUP and β-catenin can form complexes with cadherin and α-catenin, an actin-binding protein. The arm repeat sequences 6–13 of JUP are essential for its binding to cadherin (Fig. 1). Gene silencing strategies have been used to create β-catenin-deficient and β-catenin/JUP double-deficient mouse teratocarcinoma F9 cells, confirming that cadherin-mediated cell-cell adhesion is dependent on both JUP and β-catenin[55,56]. Furthermore, JUP can compensate for β-catenin's role in activating cadherin in the absence of β-catenin[57]. In summary, JUP plays a critical role in maintaining cell adhesion function and can even act independently of β-catenin.

#### The combination of JUP and E-cadherin inhibits tumor growth

JUP can reduce tumor growth rates, a function closely linked to cadherin. Transfection of mouse spindle-shaped cancer cells with JUP cDNA confirmed that, while JUP expression does not completely inhibit tumor progression, it reduces tumor cell growth rates. When combined with E-cadherin, the reduction in tumor growth is even more pronounced, with JUP and E-cadherin stabilizing each other[58]. The role of E-cadherin in cell contact inhibition is well-established, and re-expression of E-cadherin in tumor cells lacking it can prevent further tumor progression[59]. However, in mouse spindle-shaped cancer cells with very low JUP expression, E-cadherin fails to prevent tumor

deterioration[60]. In many cancers, N-cadherin expression is upregulated, while E-cadherin expression is downregulated. In the ES-2 ovarian cancer cell line, where both JUP and E-cadherin are absent and N-cadherin is overexpressed, tumor cell migration and invasion are enhanced. Re-expression of JUP in these cells upregulates E-cadherin levels and inhibits migration and invasion[45]. Additionally, JUP has been shown to competitively bind N-cadherin with β-catenin, leading to the degradation of β-catenin that does not bind N-cadherin, thereby reducing cellular β-catenin levels[61].

## The dual role of the JUP protein in different tumor types

JUP exhibits distinct mechanisms across various cancer types, and its role in cancer development can be both promotive and inhibitory, depending on the cancer type and context (Fig. 2). Notably, JUP demonstrates dual characteristics in cancer progression: it can promote metastasis in some cancers, like ovarian cancer, while inhibiting tumorigenesis in others, such as prostate cancer[62,63]. These dual characteristics are also evident in different stages or subtypes of the same cancer, potentially linked to the cellular localization of JUP. Specifically, nuclear JUP tends to promote carcinogenesis, while cytoplasmic JUP is more often associated with anticancer effects. For instance, in gastric cancer, as malignancy increases, nuclear JUP expression gradually rises while cytoplasmic JUP decreases, reflecting opposing roles in cancer progression[24]. Interestingly, JUP can exhibit opposing effects within the same cancer type. In breast cancer, autocrine human growth hormone promotes phenotypic transformation of breast cancer cells by upregulating DNMT3A and DNMT3B, leading to increased methylation of the *JUP* gene promoter[64]. Conversely, Aceto, *et al* found that the JUP gene contributes to the formation of circulating tumor cell (CTC) clusters in the peripheral blood of patients with breast cancer, thereby promoting distant metastasis[22]. This discrepancy may be attributed to the time- and space-dependent functions of JUP in breast cancer. In the tumor tissue, reduced JUP expression impairs intercellular adhesion, enhancing cancer cell invasion. However, when cancer cells enter the bloodstream, JUP's adhesive properties facilitate CTC cluster formation and metastasis (Table 1).

### *The role of JUP in reproductive system cancers*

CTCs are tumor cells present in peripheral blood, originating from the detachment of tumor cells at the primary site, and can give rise to new metastatic lesions. CTC clusters are formed when multiple CTCs aggregate. Although CTC-clusters are relatively rare, they possess a significantly higher metastatic potential compared to individual CTCs. An increase in CTC-clusters is associated with poor prognosis in patients with breast cancer, and the expression of JUP is closely linked to the formation of these clusters. Elevated JUP activity and expression can enhance CTC-cluster levels in the bloodstream, thereby increasing the likelihood of lung metastasis[22].

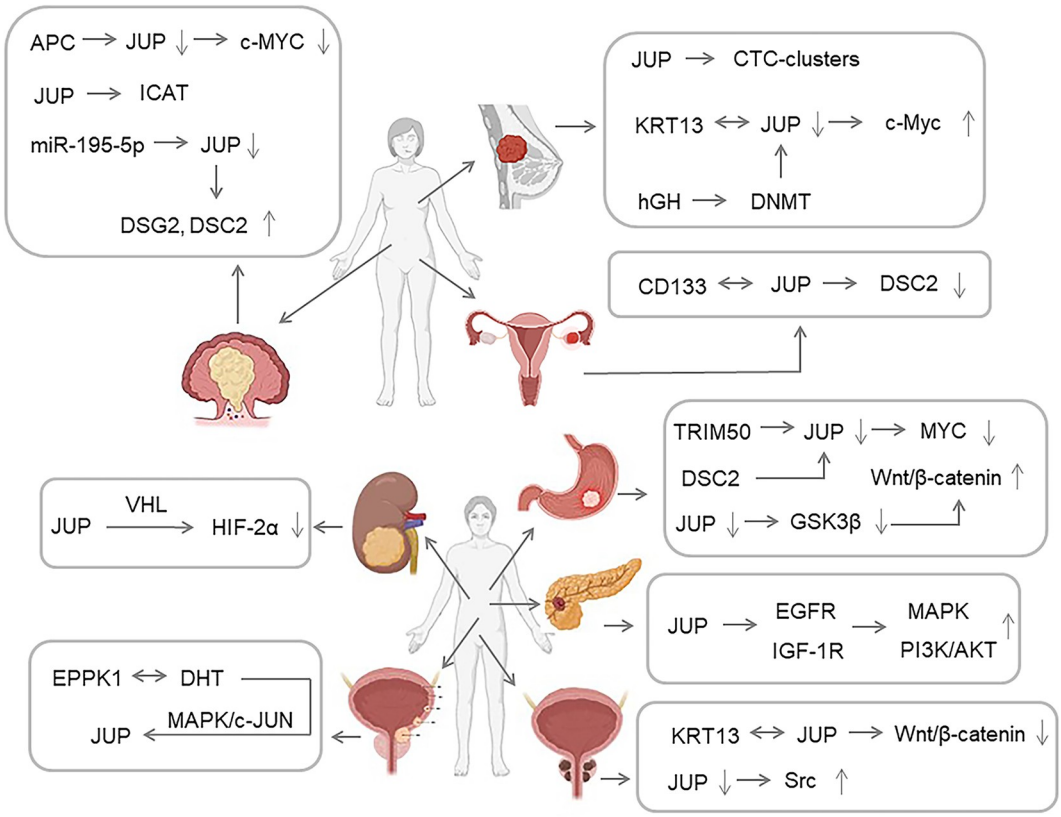


**Figure 2.** The specific role of JUP in different types of cancer. In this graph, we map the mechanisms of action of JUP in different cancers, including breast, ovarian, stomach, and bladder cancers, with the deepened arrows indicating biological processes and the finer arrows showing up-regulation and down-regulation.

**Table 1**

**Existing experimental studies exploring the mechanism of action of JUP in cancer**

| Cancer type | Promotion/ Inhibition | Experimental model | Detailed mechanism | References |
|---|---|---|---|---|
| Breast cancer | Promotion | LM2 cell line | JUP contributes to the formation of CTC-clusters and increases the rate of breast cancer metastasis. | [22] |
| | Promotion | MCF7 cell line<br>HCC1954 cell line | The interaction between KRT13 and JUP increases the expression level of c-Myc, leading to the metastasis of breast cancer. | [67] |
| | Inhibition | MDA-MB-231 cell line | Upregulation of JUP expression can increase the NPM protein level and inhibit the migration and proliferation of breast cancer cells. | [113] |
| Colon cancer | Promotion | HT29 cell line<br>RK3E cell line | APC and JUP reduce the expression level of c-Myc and are involved in tumor inhibition. | [21] |
| | Promotion | SW480 cell line<br>DLD-1 cell line<br>HCT116 cell line | Decreased JUP levels inhibit the role of ICAT in promoting colon cancer cell migration. | [73,74] |
| | Promotion | Caco2 cell line<br>LoVo cell line | miR-195-5p inhibits colon cancer migration by decreasing JUP levels and increasing DSG2 and DSC2 levels. | [75] |
| | Inhibition | HEK293T cell line<br>DLD-1 cell line | XAF1 promotes colon cancer migration by reducing JUP levels. | [25,76] |
| Gastric carcinoma | Inhibition | MGC-803 cell line<br>NUGC-3 cell line<br>NCI-87 cell line | Reduced JUP levels lead to the accumulation of β -catenin, which promotes the onset and progression of gastric cancer. | [24] |
| | Inhibition | MGC-803 cell line<br>SGC-7901 cell line | Increased JUP levels in the nucleus inhibit the onset and progression of gastric cancer. | [77] |
| | Promotion | MKN45/74/7 cell line<br>SNU-668 cell line<br>HGC27 cell line<br>AGS cell line | TRIM50 promotes the ubiquitination of JUP, decreases its nuclear translocation, and inhibits the onset and progression of gastric cancer. | [78] |
| Esophagus cancer | Promotion | KYSE450/510/140/70/30 cell line | The interaction between TOPK and JUP reduces intercellular adhesion and promotes the migration of esophageal squamous cell carcinoma cells. | [81] |
| Liver cancer | Inhibition | Contact-inhibited rat liver progenitor cells | JUP increases intercellular adhesion in mouse hepatocellular carcinoma cells. | [82] |
| Clear cell carcinoma of the kidney | Inhibition | ACHN cell line<br>OSRC-2 cell line<br>786-O cell line<br>SN12-PM6 cell line<br>ACHN cell line | JUP inhibits the tumor-promoting effects of HIF-2 α by reducing HIF-2 α levels. | [84] |
| Prostatic cancer | Inhibition | LNCaP cell line<br>PC3M cell line<br>MDA-MB-231 cell line | The interaction between SOX4 and JUP inhibits Wnt signaling and suppresses the onset and progression of prostate cancer. | [63] |
| | Promotion | LNCaP cell line<br>PC3M cell line<br>PC-3 cell line | Low levels of JUP can activate the Src signaling pathway and promote the development of prostate cancer. | [85] |
| Squamous cell carcinoma | Inhibition | SCC9 cell line | NM23 interaction with JUP reduces the tumor-promoting effect of SATB1 | [42] |
| | Inhibition | SCC9 cell line | JUP and p53 jointly act on the 14-3-3 σ gene promoter to enhance the activity of the *p53* gene. | [49] |
| Head and neck cancer | Promotion | OECM1 cell line<br>SAS cell line | The interaction between DSG3 and JUP can promote the development of cancer, but the increase of JUP level after silencing DSG3 inhibits the generation and migration of head and neck cancer cells. | [38] |
| Bladder cancer | Promotion | T24 cell line<br>5637 cell line<br>J28 cell line<br>UMUC3 cell line | DHT interacts with PPK1 to activate the P38 MAPK/c-JUN pathway, increasing JUP levels and promoting the migration of bladder cancer cells. | [23] |
| Pancreatic ductal carcinoma | Promotion | Pancreatic ductal cancer tissue | JUP is associated with differential upregulation of PI3K/AKT and MAPK signaling pathways. | [80] |

Conversely, downregulation of JUP expression also contributes to the progression of breast cancer. The proto-oncogene *c-Myc* plays a critical role in breast cancer development[65,66]. Research has shown that keratin 13 (KRT13) interacts with JUP, forming a complex with Desmoplakin that interferes with JUP expression and its nuclear translocation, leading to a reduction in nuclear JUP levels. This diminishes JUP's inhibition of *c-Myc* expression, thereby promoting breast cancer metastasis and progression[67]. Additionally, autocrine human growth hormone (hGH) upregulates the expression of DNA methyltransferases (DNMTs) in breast cancer cells. DNMT3A and DNMT3B methylate the promoter region of JUP, thereby inhibiting its expression, which in turn reduces cell adhesion and enhances the migratory potential of cancer cells[64,68].

JUP also plays a significant role in ovarian cancer. CD133, a well-established cancer stem cell marker, has been found to interact with JUP in ovarian clear cell carcinoma. This interaction leads to a reduction in DSC2 protein levels, weakening cell adhesion and promoting cancer cell invasion and metastasis[62]. Additionally, the loss of JUP expression correlates with a high incidence of squamous-differentiated endometrial cancer[69].

In conclusion, high JUP expression can promote cancer migration in reproductive system cancers by facilitating CTC-cluster formation in the bloodstream and reducing DSC2 protein levels. On the other hand, low JUP expression contributes to cancer progression by reducing its inhibitory effect on c-Myc and impairing its role in cell adhesion.

### *The role of JUP in digestive system cancers*

The *APC* gene is a critical tumor suppressor associated with colorectal cancer development. Mutations in *APC* can activate the Wnt signaling pathway, leading to the accumulation of β-catenin[70]. Although mutations in β-catenin itself can also result in its accumulation due to impaired degradation, *APC* mutations in colon cancer cells are far more prevalent than mutations in the *β-catenin* gene. *APC* mutations may alter the downstream regulation of β-catenin and JUP. Furthermore, E-cadherin and APC can competitively bind β-catenin or JUP, forming complexes, with the fourth armadillo repeat sequence of JUP playing a key role in its interaction with APC. In colon cancer cell lines, increased APC levels can reduce JUP levels, suppressing *c-MYC* expression[21,71].

Evidence suggests that suppression of JUP can inhibit the development of digestive system cancers. The prognosis of colorectal cancer is heavily influenced by the occurrence of distant metastasis. JUP facilitates metastasis by promoting tumor cell cluster formation, lymphatic invasion, and polyclonal lung metastasis. Using CRISPR-Cas9 to knock out the *JUP* gene reduces tumor cell cluster formation and lymphatic invasion, thereby inhibiting lung metastasis in colorectal cancer[72]. Similarly, *JUP* knockout has been shown to decrease colon cancer cell migration, as evidenced by the relationship between JUP and ICAT (T-cell factor inhibitor), which promotes cell migration in colon cancer. A reduction in JUP expression inhibits ICAT function, decreasing cancer cell migration[73,74]. Piccinno, *et al* demonstrated that miR-195-5p, a microRNA, can lower JUP expression, which indirectly increases DSG2 and DSC2 levels, thereby reducing colon cancer cell migration[75]. However, other studies suggest that XAF1 (XIAP-associated factor 1), a pro-apoptotic protein enriched in zinc, can promote colorectal cancer metastasis by downregulating JUP, highlighting its complex role in cancer progression[25,76].

In gastric cancer cells with reduced differentiation, cytoplasmic JUP levels gradually decrease, while nuclear JUP increases. The reduction in cytoplasmic JUP leads to the inactivation of GSK3β and the subsequent accumulation of β-catenin. In contrast, the increase in nuclear JUP promotes the nuclear translocation of β-catenin, enhancing the expression of downstream target genes in the Wnt/β-catenin pathway and ultimately facilitating gastric cancer invasion and metastasis[24]. The rise in nuclear JUP may be counteracted by DSC2, which binds to JUP and reduces its nuclear translocation, thereby controlling gastric cancer progression[77]. TRIM50, an E3 ligase downregulated in gastric cancer, has been identified as a binding target of JUP through Co-IP detection. Activated TRIM50 promotes the polyubiquitination of JUP at the K63 site, limiting its nuclear translocation, inhibiting the MYC signaling pathway, and restricting gastric cancer progression[78].

JUP is also implicated in the staging, metastasis, and poor prognosis of pancreatic cancer[79]. Upregulation of JUP stabilizes epidermal growth factor receptor (EGFR) and insulin-like growth factor-1 receptor (IGF-1R), triggering the PI3K/AKT and MAPK receptor-based signaling pathways, thereby promoting the development of pancreatic ductal adenocarcinoma[80]. In esophageal squamous cell carcinoma (ESCC), T-LAK cell-originated protein kinase (TOPK) interacts with JUP, affecting cell adhesion and enhancing ESCC invasion and migration[81]. Procházková, *et al* found that the exogenous aryl hydrocarbon receptor (AhR) agonist TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) reduces JUP expression in mouse hepatocellular carcinoma, though this effect was not observed in human liver cancer cells. This finding highlights the role of the AhR signaling pathway in reducing cell adhesion by downregulating JUP expression[82].

In summary, high JUP expression in the digestive system generally promotes cancer progression. However, certain findings suggest that decreased JUP levels can also facilitate cancer progression, as observed in the case of XAF1 downregulating JUP to promote colorectal cancer metastasis.

### *The role of JUP in urinary system cancers*

JUP predominantly acts as a tumor suppressor in urinary system cancers. One key mechanism involves the regulation of hypoxia-inducible factor 2-alpha (HIF-2α), which is often elevated in various cancers and linked to mutations in the von Hippel-Lindau (*VHL*) gene[83]. Overexpression of JUP can increase the ubiquitination of HIF-2α, destabilizing it and reducing its half-life, leading to lower levels of HIF-2α. This process requires VHL protein and has been observed to be significantly downregulated in renal clear cell carcinoma, highlighting the tumor-suppressing role of JUP through this pathway[84]. In prostate cancer, SOX4, a developmental transcription factor, interacts with JUP to inhibit the Wnt/β-catenin signaling pathway and suppress the expression of its downstream target genes, thus inhibiting prostate cancer progression[63]. On the other hand, reduced expression of JUP in prostate cancer leads to a reduction in the inhibition of Vitronectin (VN), which activates the Src signaling pathway[85]. Src is a non-receptor protein tyrosine kinase, and its abnormal activation is closely linked to cancer development, invasion, and metastasis. Therefore, low levels of JUP may promote prostate cancer metastasis and invasion by activating the Src signaling pathway[85,86].

However, JUP's role can also shift toward promoting tumor progression in certain cancers. For example, in bladder cancer, overexpression of JUP has been shown to promote cancer progression. This occurs through a mechanism where dihydrotestosterone (DHT) interacts with EPPK1 (a member of the plakin gene family), which upregulates JUP expression via the P38 MAPK/c-JUN signaling pathway, contributing to aggressive progression and poor prognosis in bladder cancer[23].

### *The role of JUP in other systemic cancers*

Current research on the role of JUP in cancer remains insufficient, with a predominant focus on the cancer types previously

discussed. Investigations into other malignancies are limited. For instance, JUP expression is either rare or absent in non-small cell lung cancer, and its re-expression has been shown to inhibit lung cancer cell growth[87]. In malignant mesothelioma, JUP expression is also reduced, correlating strongly with invasiveness and heterogeneity[88]. BCR-ABL1 (Philadelphia chromosome-positive)-induced B-cell acute lymphoblastic leukemia (B-ALL) may rely on JUP[89,90], which promotes self-renewal in primitive cells and contributes to leukemia onset[91]. However, Zhao, *et al* recently reported that JUP does not appear to play a major role in leukemia development[92]. In conclusion, JUP operates through complex mechanisms in cancer, performing diverse functions, necessitating further research to clarify its exact roles.

## JUP is a novel biomarker, guiding cancer diagnosis, treatment, and prognosis

Considering JUP's unique involvement in cancer, its potential as a biomarker for early diagnosis, personalized treatment, and prognosis assessment has been explored extensively (Table 2).

### *JUP as a cancer diagnostic marker*

As a novel biomarker, JUP holds significant promise in cancer diagnosis. New detection methods, such as *in situ* hybridization (ISH), enable mRNA analysis in cells or tissues, offering novel insights into the expression changes of emerging biomarkers like JUP[93]. In prostate cancer, specific miRNAs, including hsa-miR-133a-3p and miR-1a-3p, are notably reduced, correlating with tumor invasiveness, while JUP and Golgi phosphoprotein 3 (GOLPH3) levels are significantly elevated. These miRNAs are negatively correlated with JUP and GOLPH3, and their reduced expression, due to promoter methylation, leads to the loss of regulatory control over JUP and GOLPH3, thereby facilitating prostate cancer development and invasiveness. Duca et al. demonstrated that combined detection of hsa-miR-133a-3p, miR-1a-3p, GOLPH3, and JUP offers valuable guidance for early prostate cancer diagnosis[26].

Additionally, Weiland, *et al* reported significantly elevated JUP levels in early-stage ovarian cancer, suggesting JUP as a specific biomarker for ovarian cancer screening. They further identified that the combined detection of JUP and CA125 exhibits high specificity for early ovarian cancer diagnosis[94]. Given

**Table 2**

**Significance of JUP as a biomarker in cancer diagnosis, treatment, and prognosis**

| Clinical behavioral | Cancer type | Experimental models | Detailed description | References |
|---|---|---|---|---|
| Diagnosis | Prostate cancer | Mouse prostate cancer tissue<br>TRAMP-C1 | The combined detection of specific mRNA, JUP, and GOLPH3 is beneficial to the early diagnosis of adenocarcinoma. | [26] |
| | Ovarian cancer | Patients with stage I ovarian cancer | The combination of JUP and CA125 is beneficial to the early diagnosis of ovarian cancer with high specificity. | [94] |
| | Uveal melanoma | UM cell line | A new UM-specific DNA-like ligand PZ-1 was developed, which binds UM cells to target JUP. Based on PZ-1, a "nanship" was constructed to stably release azithromycin to cancer cells. | [97] |
| Treatment | Non-small cell lung cancer | H157 cell line<br>H1299 cell line<br>A549 cell line<br>Beas2B cell | JUP enhances the sensitivity of the proto-oncogene *c-MET* to its inhibitor, HAI-1, thereby contributing to the inhibition of migration in non-small cell lung cancer. | [100] |
| | Epidermoid carcinoma of the mouth | Kb-cp20 cell line<br>7404-cp20 cell line | High expression of JUP increases the sensitivity of cancer cells to cisplatin, which is beneficial to cancer treatment. | [101] |
| | Liver cancer | BM samples<br>293 T cell line | JUP increases the survival rate of leukemia stem cells, and HDACis can counteract this effect, potentially offering a therapeutic strategy for leukemia treatment. | [103] |
| | Chronic myelogenous leukemia | H460 cell line<br>H1299 cell line<br>A549 cell line | HDAC7 reduces JUP levels and promotes lung cancer cell migration, positioning the HDAC7/JUP axis as a potential new therapeutic target for lung cancer treatment. | [104] |
| | Lung cancer | Ovarian clear cell<br>293 FT cell line<br>Caco-2 cell line | CD133 interacts with JUP to facilitate cell adhesion, a key process in ovarian cancer stem cell formation. This discovery could pave the way for new therapeutic approaches targeting ovarian cancer stem cells. | [62] |
| | Ovarian cancer | 2008 cell line<br>C13 cell line | JUP interacts with CBP to promote survivin transcription and aggravate disease progression, while ICG-001 can inhibit this process. | [114] |
| Prognosis | Chronic myelogenous leukemia | Oral squamous cell<br>HSC3 cell line | Low levels of JUP are associated with lower survival rates in patients with oral squamous cell carcinoma. | [105] |
| | Oral squamous cell carcinoma | Patients with lung adenocarcinoma | Low levels of JUP are associated with lower survival rates in patients with lung adenocarcinoma. | [106] |
| | Adenocarcinoma of lung | Patients with breast cancer after breast conserving surgery with NACT | In patients with breast cancer undergoing NACT, low JUP levels after breast-conserving surgery are associated with lower survival rates. | [109] |
| | Breast cancer | ESCC tissue | Low levels of JUP are associated with a lower survival rate for patients with esophageal squamous cell carcinoma. | [110] |
| | Esophageal squamous cell carcinoma | EJ cell line<br>J82 cell line | Low JUP levels are associated with lower survival rates in patients with bladder cancer. | [112] |

the strong association between endometriosis and ovarian cancer[95], Andrieu, *et al* observed increased serum JUP levels in patients with endometriosis. The combination of JUP and CA125 also demonstrated high specificity, indicating the potential of this combined detection approach not only for early ovarian cancer diagnosis but also for prevention[94,96]. Furthermore, in uveal melanoma (UM), Pan, *et al* identified the DNA aptamer PZ-1, which specifically binds to UM cells, with JUP being the target, highlighting JUP's potential as an early diagnostic biomarker for UM[97].

### *JUP expression levels guiding anti-cancer treatment plans*

Research on JUP in cancer treatment primarily focuses on its molecular mechanisms, as discussed above. While this reflects JUP's indirect therapeutic potential, most findings remain at the basic research stage and require further clinical validation. For instance, molecules such as HIF-2α, ICAT, TRIM50, and miR-195-5p have been linked to cancer development through regulation by or of JUP, highlighting potential therapeutic targets[74,75,78,84,98]. Moreover, JUP's role in enhancing the efficacy of anti-cancer treatments is more evident in its capacity to reduce cancer resistance to chemotherapeutic drugs. In non-small cell lung cancer (NSCLC), the proto-oncogene c-MET is overexpressed and contributes to cancer migration[99]. HAI-1, an upstream inhibitor of c-MET, is regulated by JUP, which promotes HAI-1 expression, thereby sensitizing NSCLC cells to c-MET inhibitors. This JUP-based regulatory therapy may offer an effective strategy to inhibit cancer migration[100]. Cisplatin, a commonly used chemotherapy drug, often induces resistance after prolonged use. This resistance is associated with cisplatin-induced cleavage of JUP. Cells transfected with JUP are more sensitive to cisplatin than those without JUP, suggesting that JUP could serve as a resistance marker to guide cisplatin treatment[101]. In ALL, abnormal activation of β-catenin has been shown to contribute to chemoresistance, particularly through the β-catenin-NF-κB-FPGS pathway, rendering leukemia cells resistant to methotrexate (MTX)[102]. JUP also plays a pro-resistance role in leukemia, as quiescent leukemia stem cells (LSCs) contribute to chronic myeloid leukemia (CML) resistance to imatinib. Studies have shown that JUP enhances LSC survival, while histone deacetylase inhibitors (HDACis) can negate this effect. Mechanistically, HDACis promote the interaction of JSL-1 with γ-catenin, inhibiting JUP expression, which may offer a novel therapeutic approach for leukemia treatment[103]. Similarly, HDAC7 has been shown to promote proliferation, migration, and invasion in lung cancer by reducing JUP levels, suggesting that the HDAC7/JUP axis could be a promising therapeutic target for patients with lung cancer[104].

### *Predicting the prognosis of patients with cancer based on JUP expression levels*

JUP is closely linked to the prognosis of various cancers and holds considerable promise as a prognostic biomarker, with its significance varying across different tumor types due to its underlying mechanisms of action.

In some cancers, high JUP expression correlates with poor prognosis. For example, elevated JUP levels in oral squamous cell carcinoma (OSCC) are associated with enhanced proliferation, metastasis, and invasion, indicating a worse prognosis for patients with OSCC[105]. Similarly, high JUP expression in patients post-lung adenocarcinoma resection is linked to shorter disease-free survival (DFS) and overall survival (OS), highlighting its potential in prognostic assessment following lung adenocarcinoma surgery[106]. The relationship between JUP and CTC-clusters in breast cancer has been discussed previously. Through Cox analysis, Mu, *et al* confirmed that CTC-cluster detection provides greater prognostic value than individual CTCs, particularly in inflammatory breast cancer, further supporting JUP's potential as a prognostic marker in tumors[107]. In breast cancer, neoadjuvant chemotherapy (NACT) can facilitate breast-conserving surgery[108]. In patients with residual lesions after NACT, low JUP levels are indicative of better OS, suggesting that JUP levels could assist in the prognostic evaluation of treatment outcomes[109].

Conversely, low JUP expression in certain cancers can also signal poor prognosis. In esophageal squamous cell carcinoma (ESCC), reduced JUP expression correlates with lower survival rates, and Cox analysis identifies JUP as an independent prognostic factor for the survival of patients with ESCC[110]. In medulloblastoma, elevated JUP expression is linked to a favorable prognosis, positioning it as a potential prognostic marker for this malignancy[111]. Furthermore, low JUP expression in advanced bladder cancer enhances the migration ability of cancer cells and is associated with poorer survival, suggesting that JUP detection could help predict patient prognosis[112].

In conclusion, JUP plays a pivotal role as a biomarker across various cancers, offering significant potential for earlier and more precise diagnoses, personalized treatment strategies, and improved prognostic assessments for patients with cancer.

## Summary and outlook

As a key protein in cellular adhesion, JUP not only contributes to cell adhesion and tissue structural integrity but also regulates various cancer-related signaling pathways, including modulation of the Wnt/β-catenin pathway and interactions with the *p53* gene and cadherins. These functions underscore JUP's pivotal role in cancer initiation, progression, and metastasis. However, due to its complex and diverse mechanisms of action, JUP may have different biological effects depending on the type of cancer. For example, JUP primarily promotes cancer in the digestive system while exerting a suppressive role in the urinary system. Given this multifaceted nature, further studies are needed to unravel the specific and precise mechanisms of JUP in different cancers, which will provide a foundation for its clinical application.

The potential of JUP as a cancer biomarker has been established, and its expression analysis is crucial for early cancer diagnosis, effective treatment, and prognosis evaluation. For early diagnosis, future research should focus on exploring combined detection strategies, such as pairing JUP with other established biomarkers (e.g., JUP and CA125), followed by clinical statistical analysis to identify the most sensitive and specific diagnostic combinations, thereby enhancing current diagnostic capabilities. Regarding treatment guidance, much of the existing research remains in the basic science phase, facing challenges in clinical implementation. Future work should focus on developing drugs that regulate JUP expression and function, followed by pharmacodynamics and toxicology assessments through animal models. Optimal drug dosages and regimens must be

determined, and the feasibility and safety of targeting JUP in cancer treatment must be carefully evaluated, ultimately leading to novel cancer therapeutic options. For prognosis assessment, a multidimensional approach should be employed, including the detection of JUP molecular expression, gene levels, and mutations to enhance its prognostic value.

In conclusion, future research should emphasize the functional diversity of JUP in cancer and explore how to translate its complex roles into clinical practice, ultimately uncovering more precise and effective cancer management strategies.

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Ethical approval is not needed in this study.

## Consent

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## Author's contribution

W.D., J.S., and S.S.: conception, design, collection and assembly of data, and interpretation, and manuscript writing; Y.C.: conception, design, and manuscripting revising; F.C., Q.Y., and W.S.: collection and assembly of data, and interpretation, and manuscript writing. All authors were involved in the final approval of the manuscript.

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