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Transcriptional deregulation by FOXM1–JUP signaling confers dual oncogenic drivers for pancreatic tumorigenesis and therapeutic resistance

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Abstract

Purpose Junction plakoglobin (JUP/γ-catenin) is a dual-component cell adhesion molecule of adherens junctions and desmosomes, maintaining epithelial homeostasis while paradoxically involving oncogenic transformation. In pancreatic ductal adenocarcinoma (PDAC), the mechanistic role and clinical implications of JUP signaling in oncogenic reprogramming remains undefined.

Experimental design Gene expression and its association with clinicopathologic characteristics and therapeutic resistance of patients with PDAC were analyzed using IHC and bioinformatics and functionally validated by using mouse models. Protein expression and their regulation were measured by using gain- and loss-of-function assays and molecular biology methods.

Results Our immunostaining results and bioinformatics reveals JUP overexpression in pancreatic intraepithelial neoplasia (PanIN) and primary tumors, correlating with advanced TNM staging and diminished survival. Enforced JUP expression promoted PDAC proliferation, migration and invasion in vitro and PDAC growth and metastasis in vivo, whereas decreased expression of JUP exerted opposing effects. JUP expression was positively correlated with FOXM1 expression in PDAC tissues. Mechanistically, FOXM1 transcriptionally activated JUP expression by directly binding to the promoter region of JUP. Moreover, treatment of gemcitabine and oxaliplatin induced JUP expression and subsequently rendered PDAC cells therapeutic resistance, which was reversed by deletion of JUP, whereas knockdown of JUP also attenuated FOXM1-driven therapeutic resistance.

†Kailing Yang and Zhihong He KY and ZH contribute equally to this work and are considered co-first authors. The work represents partial fulfillment of their PhD requirements and integral parts of their doctoral dissertations.

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Conclusions Therefore, our findings suggest that JUP promotes PDAC tumorigenesis and progression through FOXM1-JUP transcriptional axis and the combination of FOXM1 and JUP be a more precise biomarker for targeted therapy and prognostic prediction, nominating this dyad as an actionable vulnerability for molecularly targeted interventions in PDAC.

Keywords Cell junction, FOXM1, Pancreatic cancer, Plakoglobin, Tumorigenesis

Translational relevance

Pancreatic ductal adenocarcinoma (PDAC) is aggressive, hard-to-treat malignancy. We used mouse PDAC models and human specimens to investigate the interaction between JUP and FOXM1 signaling and its mechanistic roles underlying PDAC tumorigenesis and therapeutic responses to gemcitabine and oxaliplatin. We found a FOXM1-JUP transcriptional axis and its role in promoting PDAC growth and chemotherapy resistance. Therefore, our findings suggest a novel mechanism for therapeutic resistance and its potential reversal in PDAC by targeting the interaction between JUP and FOXM1 signaling, thus having a significant effect on clinical management of PDAC.

Introduction

Pancreatic cancer (PDAC) is one of the most malignant diseases, which has a strong local invasive ability with frequent metastasis to distant organs [1]. Despite advances in early diagnosis, surgical techniques and adjuvant therapy, its 5-year survival rate remains at about 8% [2]. PDAC results from genetic alterations in a large number of genes that act through a number of pathways and processes, which makes it difficult to develop effective targeted therapy [3, 4]. Thus, there is an urgent need for a better understanding of the molecular mechanisms of and identification of novel therapeutic targets for PDAC [5].

Intercellular junctions are absolutely essential for the proper functioning of cells, including desmosomes, adherens, tight and gap junctions, which mediate adherence and communication between individual cells and maintain tissue integrity [6, 7]. Junction plakoglobin (JUP), also known as γ-catenin, is a component of both the adherens junctions and desmosomes, whose wide distribution and function in cell-cell adhesion is implicated in the regulation of cell proliferation and tumorigenesis [8, 9]. To date, deregulated JUP expression is observed in human cancers in lung, breast, colorectum and stomach [10–13]. Aberrant expression of JUP lead to phenotypic changes characteristic of transformation accompanied by genomic instability and acquisition of properties that could promote tumor progression and metastasis [14]. Moreover, JUP supports cancer progression by mediating survival through the inhibition of apoptosis and promotion of cellular proliferation [12]. However, the roles and mechanisms of JUP corresponding functional significance in PDAC development and progression remain unknown.

The forkhead box M1 (FOXM1) transcription factor is a member of the Forkhead box transcription factor superfamily, which consists of more than 50 members sharing a conserved winged-helix DNA-binding domain [15]. Interestingly, FOXM1 is shown to regulate formation of endothelial adherens junction assembly. Furthermore, adherens junction proteins, e.g., β-catenin, E-cadherin and α-catenin, are all transcriptional targets of FOXM1 [16–18]. Extensive studies have shown that FOXM1 facilitates the invasion, migration and distant metastasis, rendering poor prognosis of the cancer patients [19–21]. An important mechanism by which FOXM1 serves as a key biomarker in PDAC development and progression is through exuberant signaling by its overexpression and activation, and association with advanced clinicopathologic stages of PDAC and poor prognosis [22]. Downregulation of FOXM1 expression inhibits cell growth, invasion and metastasis [23]. Furthermore, FOXM1 stimulates the expression of numerous target genes involved in the pathogenesis of PDAC [24].

This study aims to explore the role of JUP and its potential signaling in PDAC pathogenesis. We investigated the expression of JUP in PDAC progression, and effects of JUP on malignant behaviors of PDAC cells. Moreover, to fully elucidate the mechanisms driven by FOXM1 in the regulation of PDAC malignant behaviors including therapeutic resistance, we investigated the interaction and crosstalk between JUP and FOXM1 signaling during PDAC progression. Our results revealed a novel role JUP functions as a tumor promoter in PDAC and FOXM1-JUP signaling could be a promising biomarker and therapeutic target for PDAC.

Materials and methods

Animals

All animal experiments were approved by the Animal Care and Use Committee of the South China University of Technology in accordance with the Guangdong Animal Ethics Association Requirements (#AE-2025082). C57BL/6 mice (8–12 weeks of age) were obtained from the Hunan SJA Laboratory Animal Co., Ltd (Hunan, China). Pancreatic duct ligation and caerulein (CAE) treatment were used to establish the mouse acinar-ductal metaplasia (ADM) models. Pancreatic intraepithelial neoplasia (PanIN) and PDAC models were established by

using KC and KPC mice [25, 26], which were purchased from Shanghai Model Organisms Center (Shanghai, China).

Mouse models of tumor growth and metastasis

PDAC cells were genetically engineered for JUP overexpression or knockdown. For tumor growth, 1×10^6 cells suspended in 100 μl PBS (knockdown group), while 1×10^5 cells suspended in 100 μl PBS (overexpression group) were injected into the right flank region (ectopic) or pancreas (orthotopic) of mice as previously described [27]. The sizes of subcutaneous tumors were measured once every 3–7 days. All mice were sacrificed at end of experiments and tumors were removed, weighed and fixed in 10% neutral buffered formalin. For experimental liver metastases, 1×10^6 cells in 100 μl PBS were injected into mice via the ileocolic vein. The mice were sacrificed day 20 after tumor-cell inoculation. The livers were removed and fixed in 10% buffered formalin. All tissues were further processed for H&E staining and histological evaluation as described previously [28].

Cell lines

HPNE and HPDE human normal ductal epithelial cell lines, AsPC-1, BxPC-3, CaPan-2, CFPAC-1, HPAC, HPAF- Ⅱ, MIA PaCa-2, PANC-1 and PL45 human PDAC cell lines, and Panc02 murine PDAC cell line were originally purchased from the American Type Culture Collection (ATCC, Virgin Islands, USA). PK-59 human PDAC cell line was purchased from the RIKEN BioResource Research Center (BRC, Saitama, Japan). All the cells were cultured in medium supplemented with 10% fetal calf serum, sodium pyruvate, nonessential amino acids and L-glutamine and incubated in a 37 °C, 5% CO_2, humidified atmosphere. All of the cell lines were obtained between 2020 and 2022, routinely tested for mycoplasma contamination within the last 6 months by using PCR, and used at passage numbers < 15 for this study after reception or thawing in our laboratory.

Immunohistochemistry (IHC) and scoring

Expression of JUP was analyzed using human normal pancreas and pancreatic tumor tissue arrays purchased from Superchip Biotech (Shanghai, China). Sections (4–5 μm) were processed for immunostaining and antibody information was listed in Table S1. Images were obtained under a microscope. The staining results were analyzed by ImageJ software and semiquantitative analyses were performed as described previously [29].

Immunofluorescent staining (IFS)

Tissue Sects. (4–5 μm) were prepared for IFS. After nonspecific protein binding was blocked with 10% bovine serum albumin for 1 h at RT, the sections were incubated with primary antibodies overnight at 4 °C, then washed three times with TBST, and subsequently incubated with proper fluorescent secondary antibodies for 1 h at RT. After washing three times, the sections were mounted with an anti-fade mounting medium containing DAPI and observed under a microscope. The image data were quantitated using ImageJ software.

Western blot analysis

Proteins were extracted from cells or tissues using RIPA buffer containing 1% protease inhibitor cocktail. The proteins were separated on 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride membranes. After blocking with 5% skim milk, the membranes were incubated with indicated primary antibodies at 4 °C overnight and then with proper secondary antibodies for 1 h at room temperature. The membranes were developed with ECL solution (Millipore, Billerica, USA) and exposed to western blot imaging device to detect protein expression.

Small interfering RNAs and over-expression plasmids transfection

Small interfering RNAs (siRNAs) against the genes of JUP ("siJUP") and FOXM1 (siFOXM1") and control siRNA (siNC) were purchased from GenePharma (Shanghai, China), information was listed in Table S4.The expression plasmids pcDNA3.1-JUP (pJUP), pcDNA3.1-FOXM1 (pFOXM1) and control pcDNA3.1 vector (p3.1) were procured from HK1548 (Shanghai, China). Transfection of siRNAs and plasmids into PDAC cells was conducted using the Lipofectamine 3000 CD transfection reagents from Invitrogen (Carlsbad, USA). For transient transfection, cells were transfected with siRNAs or plasmids at different doses as indicated for 48 h before functional assays were carried out.

RT- qPCR

Total RNAs were extracted from cells or tissues using TRIzol reagent (Invitrogen), and cDNAs were synthesized using an iScript cDNA Synthesis Kit from Takara (Osaka, Japan). GAPDH was used as the house-keeping gene for data normalization. All RT-qPCR experiments were performed at least three times independently. The sequences of the PCR primers used are listed in supplementary **Table S2**.

Cell proliferation and growth assays

For cell counting Kit-8 (CCK-8) assay, cells were plated at 5000 cells/well in 96-well plates, and CCK-8 solution was added to each well and incubated for 1 h. The absorbance value at 450 nm was measured by Multiskan FC enzyme micro-plate reader (Tongren Institute of Chemistry, Kyushu, Japan) once per day for indicated days. For

colony formation assay, cell suspension was prepared using cells at logarithmic growth stage. One thousand cells/well in 500 μl of medium was plated in 12-well plate and incubated for 15 days. The cells were then fixed with 4% paraformaldehyde, stained with crystal violet dye, and the number of cell colonies was photographed and counted. For 5-Ethynyl-2'-deoxyuridine (EdU) labeling assay, PDAC cells were cultured in 12-well plates and subjected to EdU detection utilizing the Cell-Light EdU Apollo In Vitro Kit from Biyuntian (Shanghai, China). Cells were imaged using a fluorescence microscope, and the ratio of EdU-positive cells was calculated using ImageJ.

Cell migration and invasion assays

Standard transfection methods using Lipofectamine was performed to alter gene expression using expression vector (overexpression) or siRNA (knockdown) in indicated cells. Forty-eight h after transfection, the cells were used for assays. Wound healing assay was used to measure cell migration ability. Specifically, the cells were cultured in 6-well plate until full confluence. Wound was made on cell monolayer by scratch and its sizes (gap) was measured in multiple fields at indicated times under microscope (5x) as described previously [29]. Boyden chamber assay was used to measure cell invasion ability using Matrigel-coated transwell system. Specifically, 200 μL single-cell suspension containing transfected cells (5×10^5 cells) was added to the upper compartment of the chamber and the lower compartment contained RPMI supplemented with 500 μL DMEM medium10% FBS. After culture for 48 h, the upper chamber was taken out, cells at the upper surface of the filter were wiped off with a cotton swab. The remaining cells were fixed for 30 min using 4% paraformaldehyde. Filters were washed three times with PBS and stained with crystal violet and the cells were observed and photographed. The numbers of invasive cells that penetrated through Matrigel-coated filter were counted in 3 random fields identified within the lower surface of the filters under microscope (10x).

Chemotherapy resistance analysis

To investigate the relationship between JUP expression and chemotherapy resistance, we used gemcitabine (GEM) and oxaliplatin (OXA) (MedChemExpress, USA), commonly used drugs for PDAC chemotherapy. PL45, AsPC-1 and Panc02 cells were seeded in 96-well plates. The concentrations of GEM and OXA was 0, 0.01, 0.1, 1, 10, 100 μM with at least three replicate wells for each concentration. The CCK8 assay was carried out two days after the addition of the drug, and the absorbance at 450 nm were measured to calculate drug sensitivities among the different groups.

For in vivo experiments, 1×10^6 treated Panc02 cells were injected into the dorsal thighs of each mouse, GEM or OXA solutions were administered intraperitoneally every 3 days at a standard dose of 40 mg/kg, starting 7 days after tumor injection. Tumor volumes in the subcutaneous xenografts was measured every 3 days. Mice were sacrificed at the end of the experiment, and subcutaneous tumors were collected for further analysis.

Chromatin immunoprecipitation assay

PL45 and AsPC-1 cells (1×10^7) were prepared for a chromatin immunoprecipitation (ChIP) assay using a ChIP assay kit from Millipore (Billerica, USA) according to the manufacturer's protocol. Briefly, cell pellets were crosslinked with 1% formaldehyde for 15 min. Crosslinked chromatin was sonicated and incubated at 4 °C overnight with 1 μg anti-FOXM1 antibody (Santa Cruz Biotechnology, California, USA). The resulting precipitated DNA specimens were used to amplify fractions of JUP promoter region using RT-qPCR. Crosslinked chromatin was sonicated with probe and incubated at 4 °C overnight with 1 μg anti-FOXM1 antibody (Santa Cruz Biotechnology, California, USA). The resulting precipitated DNA specimens were used to amplify fractions of JUP promoter region using RT-qPCR. The RT-qPCR products were measured as they were accumulating, and data were collected as the reaction was proceeding. Finally, products were resolved electrophoretically on a 1.5% agarose gel and visualized by ethidium bromide staining.

Luciferase reporter assay

The JUP promoter sequence was synthesized and inserted into the PGL3-Basic vector (Promega, Madison, USA). The FOXM1 binding site 2 (#2) "ATAAACA" was mutated to "ATCCCCA". HEK293 cells were co-transfected with reporter gene vector and FOXM1-p3.1 using Lipofectamine 2000. The empty vector p3.1 was used as a control. Cells were collected at 30 h after transfection to perform renilla luciferase activity assay (Promega, Madison, USA).

Bioinformatics analysis

Transcriptomic data in TPM format and corresponding clinical data for PDAC and paraneoplastic noncancerous tissues from The Cancer Genome Atlas (TCGA) database were used. The normalization matrix for the dataset GSE was obtained from the Gene Expression Omnibus (GEO) database. Differentially expressed genes were certified using the Deseq. 2 or limma packages with the following criteria: log2 fold change (FC) ≥ 1, False Discovery Rate (FDR) < 0.05. Correlation analysis was performed using R package correlation plots. The samples were divided into high-risk and low-risk groups according to the expression levels of JUP, and survival curves were plotted using the

risk package and survival package. A prognostic model was constructed using COX regression results. Finally, the predictive performance of the model was verified using ROC curves and norm plots.

Statistical analysis

Statistical tests were performed using SPSS software program. The significance of the data was determined using the Student *t*-test (two-tailed) or one-way analysis of variance (ANOVA). *P* values less than 0.05 were considered statistically significant.

Results

Elevation of JUP expression is important in the process of PDAC initiation and progression

We first examined the expression of JUP in the tissues from human and mouse tissues of normal pancreas and PDAC at various stages (Fig. 1A-D). The JUP-positive staining in PDAC was higher than that in normal pancreatic tissues (Fig. 1A and C). Pancreatic acinar cells can dedifferentiate or transdifferentiate to an embryonic progenitor phenotype that expresses ductal markers in a process of ADM. Acinar cells undergoing such changes due to persistent expression of oncogenic KRAS or inflammation transdifferentiate to ADM cells that are incapable of redifferentiation, but instead further progress to duct-like cells and from pancreatic precancerous intraepithelial neoplasia, PanIN [30]. In mouse models, JUP expression was elevated in all pancreatic lesions from ADM, PanIN to PDAC, whereas JUP was weakly expressed in acinar and duct in the normal pancreas (Fig. 1B and D), establishing that JUP involved in PDAC initiation and progression. This notion was supported by our findings that JUP expression was consistently increased in PDAC and its precursor lesions through biosignature analyses using databases (GSE109227 and GSE132326) (Fig. S1A-C). Also, we analyzed the impacts of JUP expression levels on overall survival in PDAC patients using GEO and TCGA databases (Fig. S2A-C). The increase in JUP expression was associated with KRAS mutant of PDAC (Fig. S1D). The overall survival of PDAC patients decreased when the expression level of JUP was higher (Fig. S2E-F). Multivariate analysis of JUP with age, disease stage, treatment response and other factors showed that JUP was an independent prognostic factor (**Fig. S2G**). Our preclinical and clinical data strongly suggested that consistent elevation of JUP expression play an important role in the process of PDAC initiation and progression.

JUP expression is elevated in PDAC cell lines and required for PDAC cell proliferation

The protein expression levels of JUP were increased in most PDAC cell lines as compared with HPDE cells (Fig. S3A). To investigate the impact of altered JUP expression on PDAC biological characteristics, we reduced JUP expression by transfection of siRNA and increased JUP expression by transfection of JUP expression plasmid into AsPC-1, PL45 and Panc02 cells. The transfection efficiency was confirmed by RT-qPCR and Western blot analyses (Fig. S3B). We found that altered expression of JUP did not lead to alterations in expression of other desmosomal member proteins, including Desmoglein (DSG), Plakophilin (PKP) and Desmocollin (DSC) (Fig. S3C).

To examine the effect of altered expression of JUP on cell growth in vitro, we performed CCK-8 and colony formation assays (Fig. 2 A-B) and found that reduced expression of JUP suppressed PDAC cell viability and colony-forming abilities (Fig. 2A1, 2B1), whereas overexpression of JUP did the opposite (Fig. 2A2, 2B2). Also, we examined the effect of altered JUP expression on the proliferative capacity using the EdU assay and found that the rate of EdU incorporation was significantly reduced after JUP knockdown and significantly increased after JUP overexpression than that in the control (Fig. 2C1-2). Our results consistently show that JUP enhances the growth of PDAC cells.

JUP promotes PDAC tumorigenesis and metastasis in vivo

Given that JUP promotes cell growth in vitro, we further evaluated the impact of JUP expression on the tumorigenic ability of PDAC cells using mouse models. PDAC cells with JUP knockdown (Fig. 3A) or overexpression (Fig. 3B) were transplanted into groups of mice either via subcutaneous (ectopic model) or intra-pancreas injection (orthotopic model). In an ectopic model, Panc02 cells with JUP knockdown displayed reduced tumor volume and weight as compared with control cells (Fig. 3A1–3), whereas Panc02 cells with increased expression of JUP exhibited markedly increased tumor growth (Fig. 3B1–3). The orthotopic xenograft mode obtained results similar to those of subcutaneous model (Fig. 3A4–5, 3B4-5). IHC staining revealed a significant decrease of Ki67 expression (cell proliferation) in tumors formed by JUP knockdown cells (Fig. 3C1), whereas a significant increase in tumors formed by cells overexpressing JUP (Fig. 3C2). Single cell transcriptome data analyses of cell proliferation genes revealed significantly positive correlations among *MKI67*, *PCNA*, *CDK1* and *JUP* (Fig. S4A). We found that JUP knockdown inhibited pAKT and Wnt signaling pathway-related proteins, e.g., β-catenin, CD44, C-JUN and C-Myc, whereas JUP overexpression promoted AKT and Wnt signaling pathways (Fig. S4C). These results demonstrate that JUP accelerates the tumor growth in vivo and functions as an oncogene in PDAC tumorigenesis.

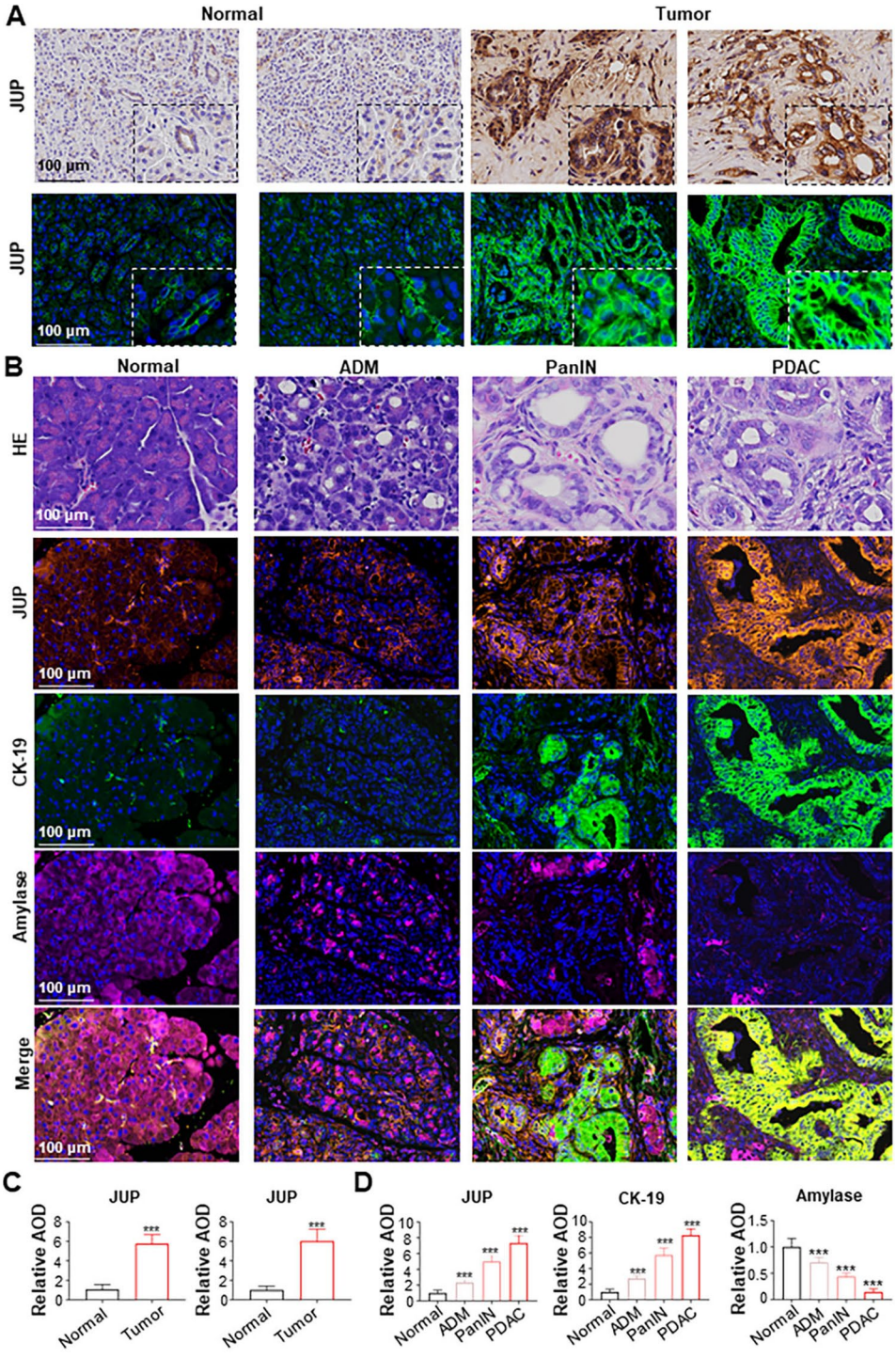


Fig. 1 JUP is highly expressed in PDAC and precancerous lesions. **A** The expression of JUP in normal and PDAC tissues were detected by IHC and IFS. Compared with normal tissues, JUP was highly expressed in PDAC tissues (n=25). **B** IFS of JUP in mouse pancreatic tissue samples (*n*=6). Orange, JUP; green, CK-19; purple, Amylase; blue, DAPI. JUP co-localized mainly with CK-19, and increased in ADM, PanIN and PDAC. **C** Quantitative and statistical analyses of IHC and IFS results in human pancreatic tissues. **D** Quantitative and statistical analyses of relative expression levels of JUP, CK-19 and Amylase in mouse pancreatic tissues. All data were expressed as mean ± SD. Statistical analysis: student t-test or ANOVA, *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ vs. control group. Scale bars, 100 μm

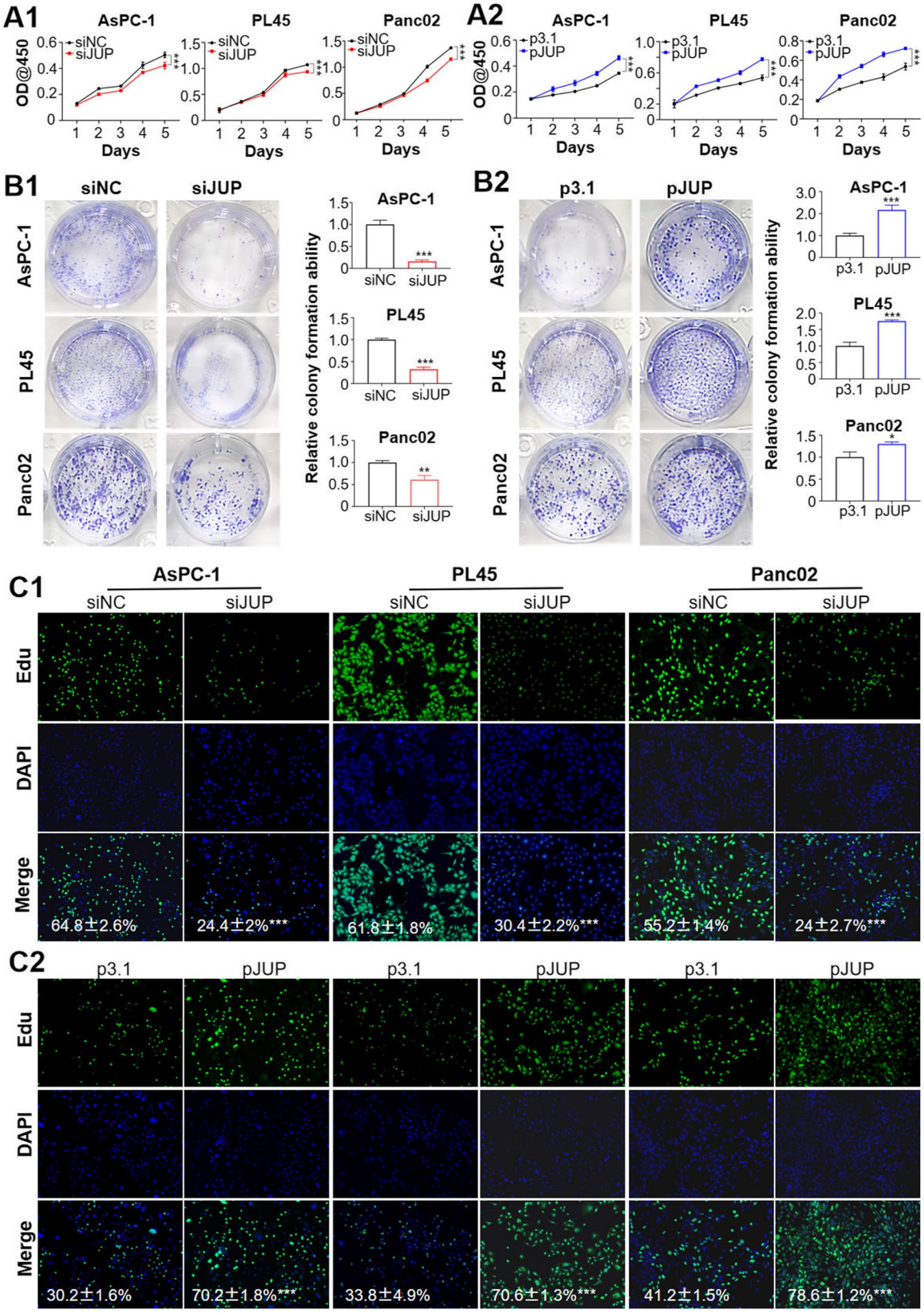


Fig. 2 (See legend on next page.)

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Fig. 2 JUP is essential for the growth of PDAC cells. Proliferative capacity of AsPC-1, PL45 and Panc02 cells with JUP knockdown or overexpression. **A**, CCK-8 assay: JUP knockdown suppressed PDAC cell proliferation (**A**1), overexpression of JUP promoted PDAC cell proliferation (**A**2). **B**, Clonogenic assay: siJUP suppressed the colony formation (**B**1). pJUP promoted the colony formation. (**B**2). **C**, EdU assay: JUP silence suppressed EdU incorporation (**C**1), JUP overexpression enhanced EdU incorporation (**C**2). All data were expressed as mean ± SD, $n = 3$. Statistical analysis: student t-test or ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. control group

JUP promotes the invasion and migration of PDAC cells in vitro

To evaluate the effect of altered expression of JUP on malignant behaviors of PDAC cells, we performed the wound healing and transwell assays and demonstrated that JUP knockdown significantly inhibited migration and invasion of PDAC cells (Fig. 4A), whereas the overexpression of JUP had the opposite effect (Fig. 4B). To determine the effect of altered expression of JUP on metastasis in vivo, we injected tumor cells into mice through the ileocolic vein. We found that decreased expression of JUP suppressed hepatic metastases (Fig. 5A), whereas increased expression of JUP promoted hepatic metastases (Fig. 5B). Staining of tumor cell marker CA199 clearly showed the sites of metastasis in liver tissues (Fig. 4C and D). We investigated the effect of JUP on epithelial-mesenchymal transformation (EMT)-related marker expression in our subsequent studies. WB and RT-qPCR revealed JUP knockdown decreased the expression of stromal cell markers N-cadherin and Vimentin, along with increased expression of epithelial marker E-cadherin. However, JUP overexpression had the opposite effect (Fig. S5C). Therefore, aberrant increase in JUP expression promoted PDAC invasion and metastasis by driving the EMT.

FOXM1 transcriptionally activates JUP expression

To elucidate the mechanism underlying JUP overexpression, we initially analyzed both FOXM1 and JUP expression in PDAC tissues (Fig. 5A). We found that JUP expression was directly correlated with FOXM1 expression in the PDAC tissues (Fig. 5A1–3). Analysis of TCGA data found that high expression of both FOXM1 and JUP was associated with poor survival in PDAC patients (Fig. S6A). To provide casual evidence for the direct relationship between FOXM1 and JUP, we determined the impacts of altered FOXM1 expression on JUP expression in PDAC cells. We found that enhanced expression of FOXM1 significantly increased the expression of JUP mRNA and protein, whereas knockdown of FOXM1 expression dramatically reduced JUP mRNA and protein (Fig. 5B-C). However, there was no significant changes in FOXM1 protein level in the cells with JUP-knockdown or -overexpression (Fig. S6B). To investigate the regulatory role of FOXM1 in JUP transcription, we analyzed JUP promoter region and identified two putative FOXM1-binding elements (referred to as DNA sequences #1 and #2) (Fig. 5D). We performed ChIP assay and found that FOXM1 directly bound to site #2, but not the site #1 of JUP promoter in both PL45 and AsPC-1 cells (Fig. 5E). Further validation was conducted by using luciferase reporter assays and vectors with either the intact or mutated JUP promoter. In the cells overexpressing FOXM1, the luciferase activity with intact promoter was significantly enhanced, whereas that with mutated promoter lacking functional FOXM1 binding sites showed no response (Fig. S6C). The data suggest that activation of JUP, at least in part, was resulted from the upregulation of FOXM1 in PDAC cells.

JUP mediates the cell functions of FOXM1 in PDAC cells

To further understand the role of JUP in FOXM1-driven proliferation of PDAC cells, we introduced JUP expression vector into PDAC cells with FOXM1 knockdown. Western blot and RT-qPCR were performed to detect the expression of FOXM1 and JUP (Fig. 6A1-2). We performed gain-of-function CCK-8 and colony formation experiments and found that FOXM1 depletion decreased cell proliferation, which was reversed by enforced increase in JUP expression (Fig. 6B-C). Similarly, FOXM1 knockdown decreased tumor growth in mice, which was reversed by enforced increase in JUP expression (Fig. 6D1-3), which results were consistent with the in vitro findings. IHC staining revealed a significant decrease of Ki67 expression in tumors formed by tumor cells with FOXM1 knockdown, whereas the increase in JUP expression effectively reversed this effect (Fig. S7). Also, scratch wound and transwell assays confirmed similar role of JUP in FOXM1-induced pro-tumor functions (Fig. S7). Therefore, JUP is critical to FOXM1-driven proliferation and tumorigenesis of PDAC cells.

JUP renders PDAC therapeutic resistance to gemcitabine and oxaliplatin

To determine whether JUP is critical in FOXM1-driven therapeutic resistance in PDAC [21–24], we first determined whether altered expression of JUP impacted chemosensitivity of PDAC cells. The expression levels of JUP were altered in AsPC-1, PL45 and Panc02 cells, the cells were then treated with different concentrations of GEM and OXA for 48 h and cell viability was determined by CCK8 assay. We found that increased expression of JUP significantly enhanced PDAC cells resistance to both GEM and OXA, whereas reduced expression of JUP did the opposite (Fig. 7A). We obtained similar results from in vivo therapy models, showing that increased JUP expression significantly reduced the therapeutic efficacy

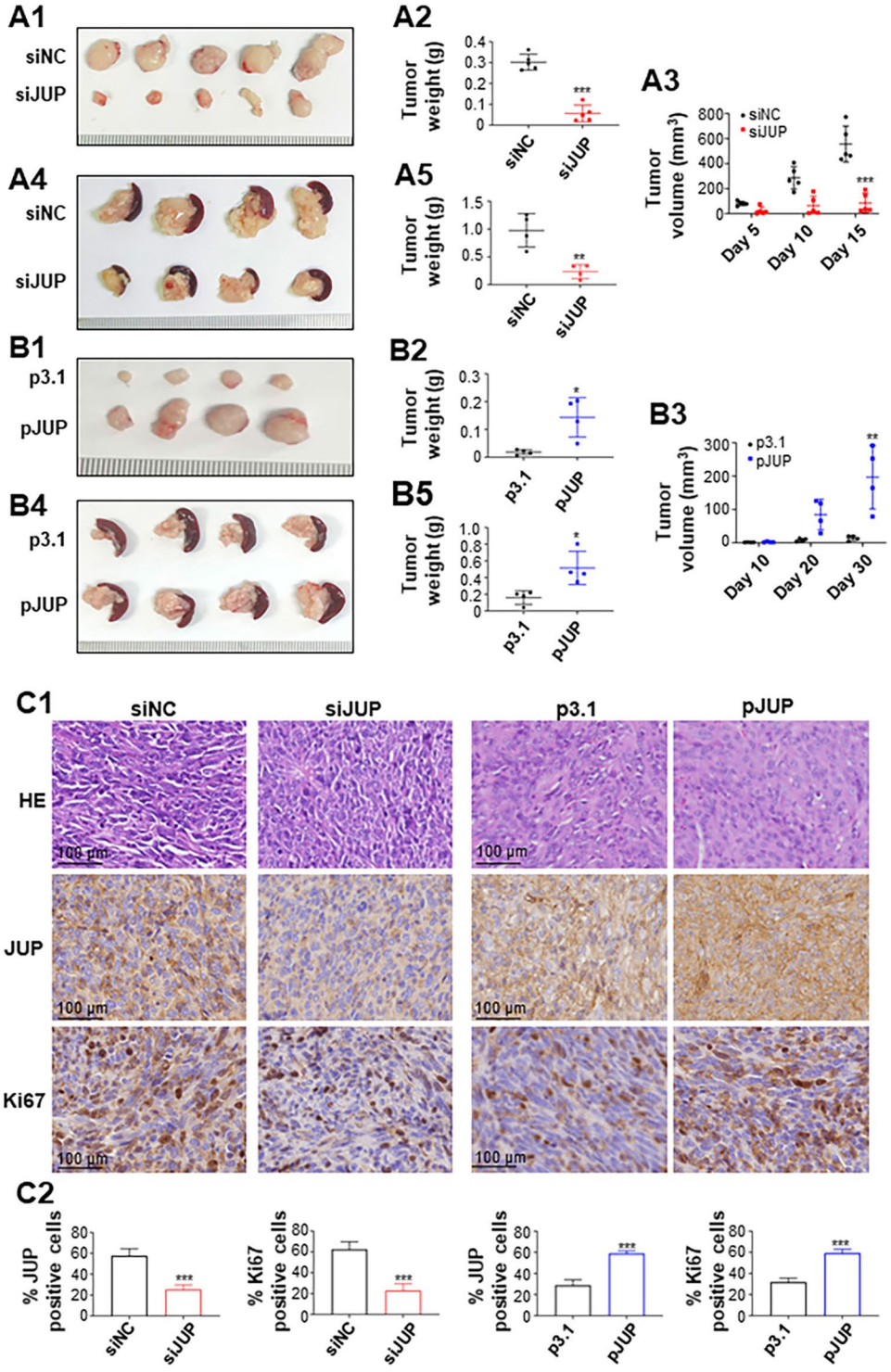


Fig. 3 JUP promotes tumorigenesis in vivo **A**, Mice were subcutaneously injected with JUP-knockdown Panc02 cells. Tumors in the mice (**A1**), tumor weights (**A2**) and tumor growth rate (**A3**) in each group were compared. knockdown-JUP Panc02 cells were injected into the pancreas of mice (orthotopic model) (**A4**), Weight of orthotopic tumors in mice (**A5**). JUP Knockdown consistently suppressed tumorigenesis. **B**, Subcutaneous tumor growth in mice with JUP overexpression (**B1**), tumor weights (**B2**), and tumor growth curves (**B3**) were shown. Orthotopic tumor growth in mice with JUP overexpression (**B4**). Weight of orthotopic tumors in mice (**B5**). JUP overexpression consistently promoted tumorigenesis. **C**, IHC: JUP knockdown inhibited the expression of JUP and Ki67 in tumors (**C1**). IHC: JUP overexpression promoted the expression of JUP, and Ki67 in tumors (**C2**). The data were presented as the mean ± SD of 6 different fields of view at low magnification (20x). All data were expressed as mean ± SD, $n = 4$. Statistical analysis: student t-test or ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. control group. Scale bars, 100 μm

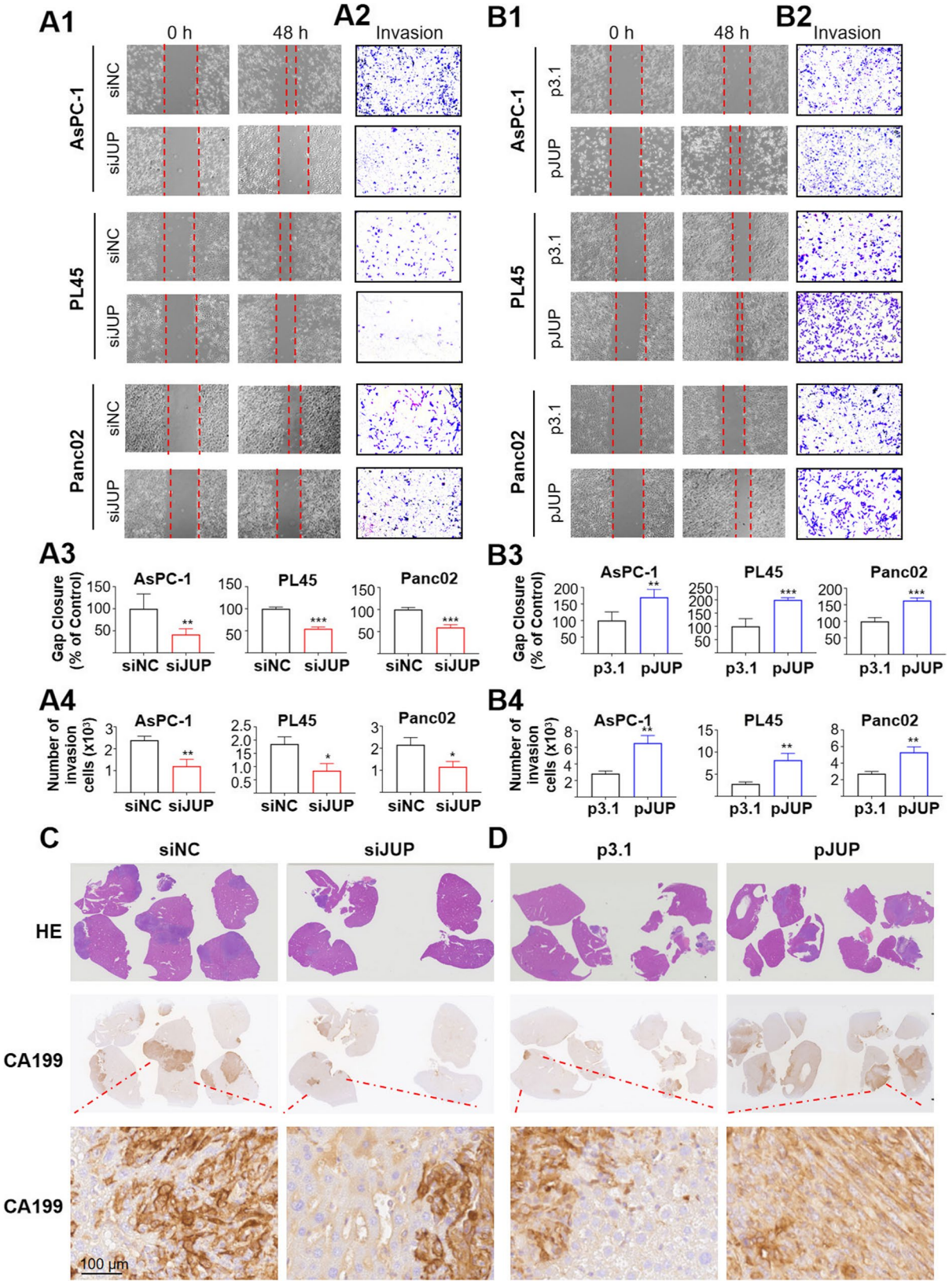


Fig. 4 JUP enhances the migration and invasion of PDAC cells. Scratch and transwell assays of PDAC cells with JUP knockdown (**A**) or overexpression (**B**). Silencing JUP attenuated the invasion and migration ability of PDAC cells, whereas overexpression of JUP enhanced the invasion and migration ability of PDAC cells. (**C**, **D**) Representative HE staining and CA199 staining of liver tissues. JUP promoted the formation of liver metastasis in mice. All data are expressed as mean ± SD, $n = 4$. Statistical analysis: student t-test or ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. control group

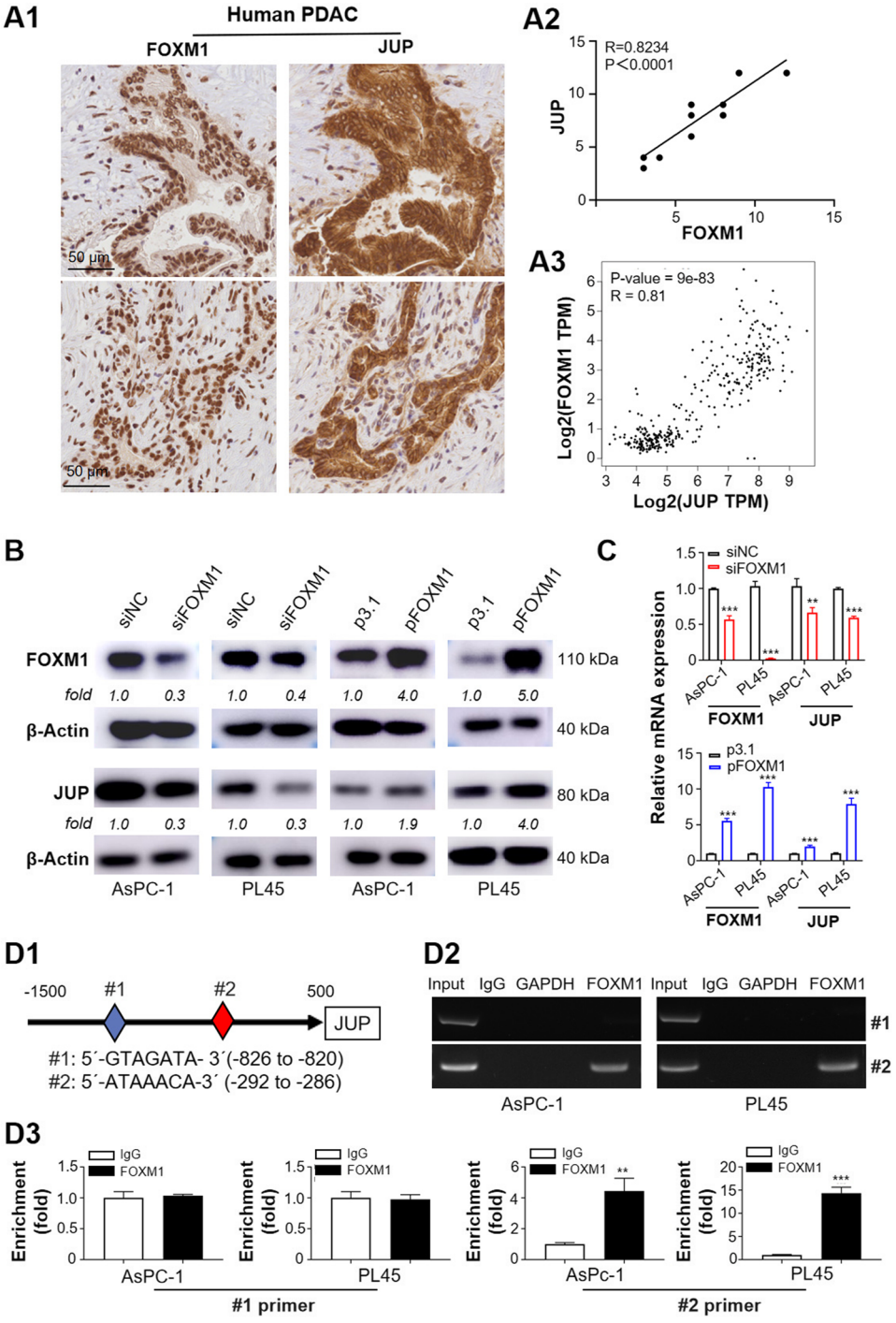


Fig. 5 FOXM1 transcriptionally regulates JUP in PDAC.**A**, IHC: Levels of JUP and FOXM1 protein expression in PDAC (**A1**). Linear regression analysis: the correlation of FOXM1 and JUP ($n=16$) (**A2**). Correlation analysis of FOXM1 and JUP expression in PDAC (http://gepia.cancer-pku.cn/) ($n=329$) (**A3**). **B-C**, Expression of FOXM1 was altered by transfection with siRNA or expression vectors. The impact of FOXM1 on JUP expression in PDAC cells by WB (**B**) and RT-qPCR (**C**) analyses. Note that FOXM1 inhibited the expression of JUP mRNA and protein in AsPC-1 and PL45, while the overexpression of FOXM1 increased the JUP mRNA and protein in AsPC-1 and PL45. FOXM1 regulated the expression of both JUP protein and mRNA. **D**, Direct binding of JUP to FOXM1 promoter. Sequences and positions of putative FOXM1-binding elements on JUP promoter (#1 and #2) (**D1**). Normal IgG was used as a control, and 1.5% of the total cell lysates was subjected to PCR before immunoprecipitation. The ChIP assay to test the direct binding of FOXM1 on the genomic locus of JUP promoter regions (**D2**). Quantitative analysis of ChIP results (**D3**). All data are expressed as mean ± SD, $n=3$. Statistical analysis: student t-test or ANOVA, $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ vs. control group

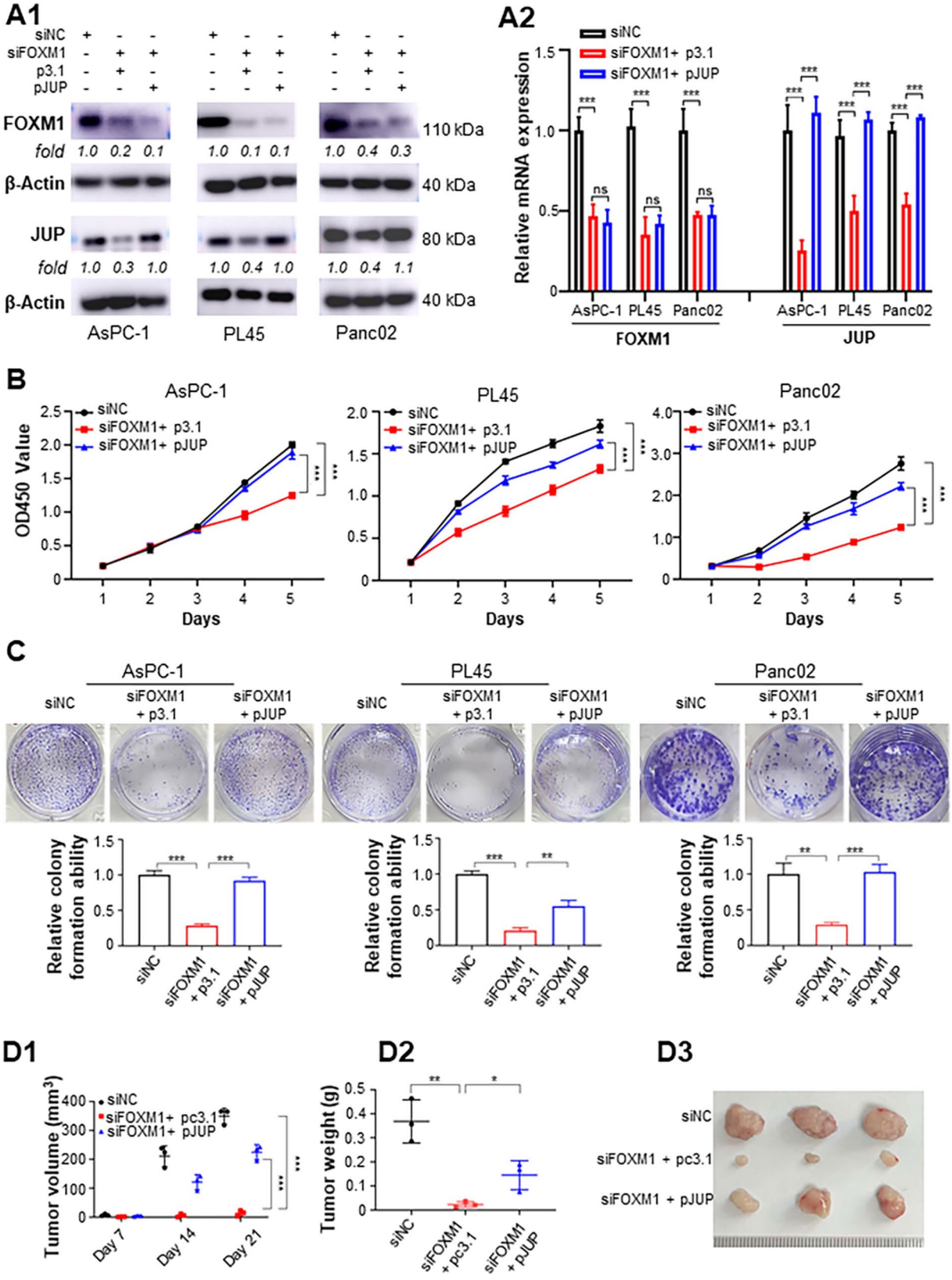


Fig. 6 (See legend on next page.)

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Fig. 6 FOXM1-mediated cancer cell proliferation requires JUP expression.**A**-**C**, FOXM1-silenced and JUP-overexpressing PDAC cells were established. The protein levels of FOXM1 and JUP were determined by Western blot (**A1**) and the mRNA levels by RT-qPCR (**A2**); cell viability by CCK-8 (**B**), and colony formation assay and the number of clones by ImageJ software. Note that JUP mediated FOXM1-induced PDAC cell proliferation and colony formation (**C**). **D**, PDAC cells were injected subcutaneously into mice. Tumor sizes were measured weekly (**D1**). The mice were sacrificed and the tumors were removed and weighed (**D2**, **D3**). All data were expressed as mean ± SD, $n = 3$. Statistical analysis: student t-test or ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. control group

of both GEM and OXA in mice (Fig. 7B-C). Upon treatment completion, tumor sections were stained with Ki67, Caspase3, and cell cycle arrest markers P53 and P21. As compared with the p3.1 control group, the pJUP group had lower expression levels of Caspase3, P53 and P21. GEM could induce the expression of those proteins, whereas the induction effect in the control group was significantly lower than that in the pJUP group (Fig. S9). Therefore, overexpression of JUP attenuated the promotional effect of GEM on cell cycle arrest and promoted uncontrolled cell proliferation and enhanced PDAC cells resistance to GEM.

Finally, we performed FOXM1 knockdown in the PDAC cells with or without gene transfection to maintain the expression of JUP (Fig. S8A). We treated the cells with GEN or OXA and found that FOXM1 knockdown sensitized PDAC cells to chemotherapy, while restoring the expression of JUP attenuated the effects of FOXM1 knockdown (Fig. S8B). Furthermore, treatment of both GEM and OXA drastically increased the expression of both FOXM1 and JUP (Fig. S8C). Therefore, aberrant expression of JUP renders PDAC therapeutic resistance and is necessary to FOXM1-mediated therapeutic resistance in PDAC.

Discussion

In this study, our comprehensive analysis has established a pivotal role for JUP in PDAC progression and its regulatory mechanism. We found that JUP up-regulation in human PDAC specimens and cell lines. High JUP expression was associated with low overall survival, poor prognosis and therapeutic resistance. Elevated expression of JUP promoted PDAC proliferation, migration and invasion in vitro and in vivo, whereas knockdown of JUP expression did the opposite. Mechanistically, FOXM1 transcriptionally upregulated JUP, thus promoting cell proliferation, migration and invasion. These novel discoveries reveal that FOXM1-JUP signaling axis may be a critical regulatory mechanism of JUP in PDAC and highlight the potential of JUP as a prognostic biomarker and therapeutic target.

Prior studies have shown that JUP regulates tumor growth and metastasis differently in different types of tumors, possibly by three mechanisms: modulation of the stability and subcellular localization of growth-regulating molecules [31], interaction with transcription factors involved in the regulation of cell growth and metastasis [32], and chelation of the oncogenic activity of β-catenin [33]. For example, alteration of the expression and nuclear translocation of JUP can modulate c-Myc signaling in breast cancer [34]. JUP overexpression leads to the differential upregulation of the PI3K/AKT and MAPK signaling pathways in the tumor microenvironment [35]. JUP is associated with dysregulation of effector gene, *PTTG*, which is likely to accelerate chromosomal instability and uncontrolled proliferation of tumor cells [14].

Tumor cells with loose intercellular contacts appear to have enhanced ability to invade and migrate, i.e., increased malignant characteristics [36, 37]. However, the contribution of JUP to cancer development has been linked to both adhesion-dependent and -independent mechanisms [38]. Our current study found that significantly increased JUP protein level contributed to cell proliferation and tumorigenesis during PDAC initiation and development. Silencing of JUP inhibited proliferation, migration, and invasion of PDAC cells. JUP is a key component of intercellular junctions, its variable expression levels within primary tumors raises the possibility that it might demarcate tightly adherent groups of cells [39, 40]. We found that abrogation of intercellular interactions due to JUP knockdown reduced their malignant potential, suggesting that PDAC cells be more dependent on JUP-mediated cell junctions than normal epithelial cells and benefit from additional or alternative pathways in forming intercellular connections. JUP loss did not lead to alterations in other desmosomal member protein levels, may also suggest that JUP is not essential for desmosomal assembly at least in PDAC cells, but may be required for PDAC formation and metastasis. These results strongly supported the new notion that JUP could function as signaling molecule, promoting PDAC pathogenesis as an oncogene.

The pathogenesis of PDAC involves in a variety of signaling pathways, including MAPK, AKT, PI3K, Notch and Wnt pathways [4]. The precise signaling role that JUP serves during pancreatic carcinogenesis is largely unclear. JUP is identified as a transcriptional factor involved in the modulation of Wnt signaling [41]. Increased JUP expression led to a transformed phenotype possibly through increased oncogenic β-catenin signaling. Like β-catenin, JUP can activate Wnt ligand stimulation [42]. Also, JUP promoted the phosphorylation of AKT in an EGFR-dependent manner, and that its overexpression promoted cell mobility and migration

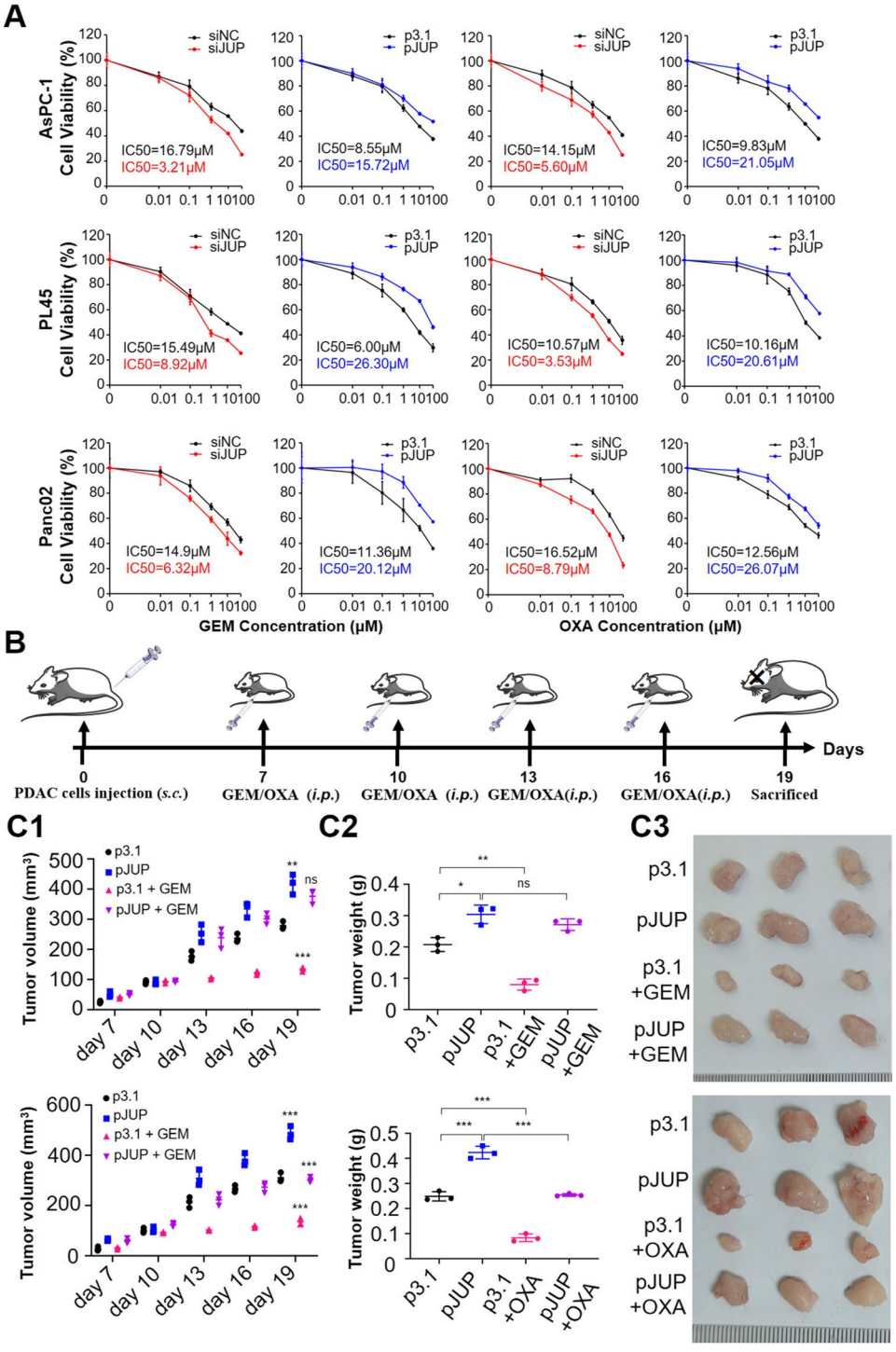


Fig. 7 FOXM1-mediated therapeutic resistance requires JUP expression. AsPC-1, PL45 and Panc02 cells were either transfection with siRNA (NC or siJUP) or expression vectors (p3.1 or pJUP) to alter the expression levels of JUP. **A**, The cells were then treated in vitro with different concentrations of GEM and OXA for 48 h and cell viability was determined by CCK8 assay. Note that increased expression of JUP significantly enhanced PDAC cells resistance to both GEM and OXA, whereas reduced expression of JUP did the opposite. **B**, GEM/OXA in vivo treatment model scheme. **C**, **D**, The cells with altered expression of JUP were subcutaneously injected into groups of mice, which then received treatment of drugs (**C**, GEM; **D**, OXA) for indicated times. The tumor growth curves (**C1**, **D1**), subcutaneous tumors from mice (**C2**, **D2**) and tumor weights (**C3**, **D3**) were shown. Note that increased JUP expression significantly reduced the therapeutic efficacy of both GEM and OXA. All data were expressed as mean ± SD, $n = 5$. Statistical analysis: student t-test or ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. control group

[14]. In invasive micropapillary carcinoma of the breast, JUP was observed to be overexpressed in metastatic tissue, and contributed to metastasis through activating the PI3K/AKT signaling pathway [43]. The alteration of JUP expression in epithelium-like gastric cancer cells causes EMT and promotes cell migration and invasion. Mechanistically, nuclear JUP interacted with nuclear β-catenin and TCF4 and played a synergistic role with β-catenin in promoting TCF4 transcription and its downstream target MMP7 expression [44]. Our present study demonstrated that aberrant increase in JUP expression promotes PDAC invasion and metastasis by driving the EMT. Overexpression of JUP also significantly activated the canonical Wnt and AKT signaling pathway in PDAC. Our results reinforce the notion that an inability of JUP to preserve junctional integrity and epithelial characteristics occur at this late stage of tumor development [45].

One of the hallmarks of cancer is unlimited proliferation of cancer cells [46]. FOXM1 is aberrantly overexpressed in a variety of tumors and is a vital hub gene that promotes cell cycle-related gene expression [47, 48]. FOXM1 regulates various downstream targets and forms a complex oncogenic network [49]. FOXM1 is a key regulator of Wnt/β-catenin signaling, including its interaction and control of Wnt target gene expression, facilitation of nuclear translocation of β-catenin and regulation of oncogenic Wnt signaling pathway [50–53]. JUP is paralog of β-catenin [9] and they have similar structures and functions [54], while the exact molecular mechanism of JUP function is poorly understood. We found a significant positive correlation between the expression patterns of FOXM1 and JUP in PDAC, suggesting a reciprocal positive regulatory relationship between FOXM1 and JUP. To determine the regulation between FOXM1 and JUP, we developed PDAC cells with FOXM1 or JUP knockdown and overexpression, and demonstrated that FOXM1 up-regulated JUP expression, establishing that JUP is downstream from FOXM1.

FOXM1 has multiple ways to regulate gene expression [55]. Among the mechanisms by which FOXM1 mediates gene expression, transcriptional regulation is the most important one. To explore the mechanism of FOXM1 regulation of JUP expression, we used RT-qPCR to detect the mRNA levels of JUP in FOXM1-knockdown and -overexpression cells. We found that mRNA level of JUP was downregulated in FOXM1-knockdown cells and restoration of FOXM1 expression increased JUP expression at the mRNA level. Analysis of public database and our ChIP assays further demonstrated that JUP was a direct target of FOXM1. Functionally, we found that JUP was required to maintain the phenotypes of enhanced cell proliferation, migration and invasion incurred by FOXM1 overexpression. These findings linked the established roles of FOXM1 to the newly recognized role of JUP, indicating a critical role of FOXM1-JUP axis in PDAC pathogenesis.

Finally, prior studies have shown that increased expression of FOXM1 leads to therapeutic resistance of PDAC cells, while the underlying mechanisms remain unclear [45–48]. We found that treatment of PDAC cells with either GEM or OXA resulted in increased expression of both FOXM1 and JUP. Increased JUP directly caused PDAC cells resistance to both GEM and OXA. A major difference was found in the expression of the pro-growth arrest genes P53 and P21, where GEM enhanced their expression (triggering arrest), whereas overexpression of JUP attenuated the GEM-mediated promotion of P53 and P21, suggesting that JUP inhibited cell cycle arrest markers and promoted uncontrolled cell proliferation and enhanced PDAC cells resistance to GEM. Interestingly, FOXM1-mediated therapeutic resistance is dependent on the expression of JUP, i.e., aberrant expression of JUP is essential for PDAC to gain chemoresistance, which directly correlated with increased FOXM1 expression, further supporting the notion that FOXM1 is upstream of JUP. Therefore, targeted this FOXM1-JUP signaling axis could effectively sensitize PDAC to chemotherapy. How JUP renders PDAC cell more malignant behaviors in detail warrants further investigation in the future [56–59].

In summary, we demonstrate novel roles and functions of JUP as tumor promoter in PDAC pathogenesis. Evidently, this novel FOXM1-JUP signaling axis promotes tumorigenesis in FOXM1-driven PDAC development and progression and could be potential biomarkers for prognostic prediction and molecular targets for effective PDAC treatment.

Conclusions

JUP up-regulation was evident in human PDAC specimens and cell lines. High JUP expression correlated with low overall survival, poor prognosis and therapeutic resistance. FOXM1 transcriptionally upregulated JUP and promoted PDAC proliferation, migration and invasion. These novel discoveries reveal that FOXM1-JUP signaling axis may be a critical regulatory mechanism of JUP in PDAC and highlight the potential of JUP as a prognostic biomarker and therapeutic target. The combination of FOXM1 and JUP be a more precise biomarker for prognostic prediction and targeted therapy, thus nominating this dyad as an actionable vulnerability for molecularly targeted interventions in PDAC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12964-025-02512-5.

Supplementary Material 1.

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Authors' contributions
KY and KX designed all the experiments. KY and ZH performed experiments and analyzed and interpreted the data. XL, TC, and TJ helped study supervision, experimental designs, and data analysis and interpretation. KX provided supervision and funding and contributed to manuscript writing and editing. All authors reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Use of the animals was approved by the Ethics Committee of the Animal Center of South China University of Technology (#AE-2025082). There was no participation of any human subjects for this study.

Consent for publication
All authors approved and consented the manuscript for publication.

Competing interests
The authors declare no competing interests.

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