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DCAF1 promotes the growth and metastasis of pancreatic cancer cells by activating the PTEN/PI3K/Akt signaling pathway

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Abstract. Pancreatic cancer is a common malignant tumor of the digestive tract characterized by high mortality, primarily due to its aggressive proliferation and metastasis. DDB1-CUL4-associated factor 1 (DCAF1) has recently been identified as a cancer‐promoting gene in hepatocellular carcinoma and melanoma. However, its role and mechanism of action in pancreatic cancer remain largely unexplored. Analysis of the GEPIA database and experimental validation revealed that DCAF1 is significantly overexpressed in pancreatic cancer tissues and cell lines. Functional assays demonstrated that DCAF1 knockdown inhibited the proliferation, invasion, and migration of pancreatic cancer cells. Moreover, DCAF1 suppression impeded EMT, as evidenced by decreased expression of mesenchymal markers N-cadherin and α-SMA and increased expression of the epithelial marker E-cadherin. Knockdown of DCAF1 can inhibit Phosphatase and Tensin Homolog (PTEN) ubiquitination, leading to inactivation of the PI3K/Akt signaling pathway. In addition, the use of IGF-1 in the replenishment experiment can reverse the effect of knockdown of DCAF1, suggesting that DCAF1 may promote pancreatic cancer metastasis by activating this pathway. These findings suggest that DCAF1 functions as an oncogene in pancreatic cancer, promoting cell proliferation, migration, invasion, and EMT through activation of the PTEN/PI3K/Akt signaling pathway.

Key words: DCAF1 — Pancreatic cancer — EMT — Migration and invasion — PTEN/PI3K/AKT

Introduction

Pancreatic cancer is one of the seven most common malignant tumors and is associated with a particularly poor prognosis. It currently ranks as the third leading cause of cancer-related deaths and is projected to become the second leading cause by 2030 (Klein 2021; Stoffel et al. 2023). Due to the aggressive biological behavior of the disease, including early local invasion and distant metastasis, only approximately 20% of pancreatic cancers can be surgically resected at the time of diagnosis. The remaining 80% of patients typically present with advanced disease, partly due to non-specific clinical manifestations and the lack of effective early diagnostic tools, rendering the overall 5-year survival rate < 6% (Karunakaran et al. 2021; Domagala-Haduch et al. 2024). These challenges underscore the urgent need to develop novel systemic therapeutic strategies to improve clinical outcomes.

DDB1-CUL4-associated factor 1 (DCAF1), originally identified as the HIV-1 Vpr binding protein (VprBP), is implicated in various physiological and pathological processes, including transcriptional repression, viral replication, cell growth, and proliferation (Zhou et al. 2020). Recent studies have reported a strong association between DCAF1 and the progression of multiple malignancies. For instance, in hepatocellular carcinoma, DCAF1 interacts with PARD3 and activates the Akt signaling pathway to promote tumor growth and metastasis (Zhang et al. 2024). In melanoma, VprBP/DCAF1 contributes to gene silencing through histone

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H2A phosphorylation (Shin et al. 2023). In colorectal cancer, DCAF1 facilitates tumor development by activating DICER1 and promoting proteasomal degradation *via* the CUL4A (DCAF1) ubiquitin ligase complex, thereby modulating the Jak-STAT3 signaling pathway (Ren et al. 2016). Additionally, DCAF13 has been shown to promote cell proliferation in head and neck squamous cell carcinoma (Tang et al. 2022) and DCAF1 expression has been implicated in other malignancies, such as prostate and ovarian cancers (Wang et al. 2017). Despite these findings, the biological function and regulatory mechanisms of DCAF1 in pancreatic cancer have not yet been elucidated.

The present study aims to investigate the role and molecular mechanism of DCAF1 in regulating the malignant phenotype of pancreatic cancer cells to provide a theoretical basis for the development of novel targeted therapeutic agents for pancreatic cancer.

Materials and Methods

Cell culture

The normal pancreatic epithelial cell line HPC-Y5 and the human pancreatic cancer cell lines PANC-1 and SW1990 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were cultured in complete Dulbecco's Modified Eagle Medium (DMEM; Thermo) supplemented with 10% fetal bovine serum (FBS; MediRay) and 2 mmol/l L-glutamine (Thermo), and maintained at 37°C in a humidified incubator containing 5% CO_2.

Cell transfection

For *in vitro* experiments, small interfering RNA targeting DCAF1 (si-DCAF1) and a negative control siRNA (si-NC) were transfected into pancreatic cancer cells. All siRNA oligonucleotides were synthesized by GenePharma (Shanghai, China). Lipofectamine 3000 (Solarbio, Beijing, China) was used for transfection according to the manufacturer's instructions. Cells were harvested 48 h post-transfection for subsequent assays. The siRNA sequences used were as follows: si-DCAF1, UCACAGAGUAUCUUAGAGA; si-NC, UUCUCCGAACGUGUCACGU. Full-length human DCAF1 cDNA was amplified from PAAD cells using RT-PCR and inserted into the pHAGE puro 6tag vector (Invitrogen, USA). The developed lentiviral vector and an empty control were packaged in 293T cells with packaging plasmids. The culture medium with the lentiviral vector was filtered through a 0.22 μm filter by ultracentrifugation. Following infection, PAAD cells were treated with puromycin for 14 days at a multiplicity of infection (MOI) of one. Finally, Western blotting was used to confirm the expression of the construct.

Cell counting kit-8 assay (CCK-8)

After transfection, the cells were seeded into 96-well plates at a density of 4,000 cells *per* well and incubated for 48 h. Subsequently, 10 μl of CCK-8 solution was added to each well and incubated for 1 h. The optical density at 450 nm was measured using a Multiskan FC microplate reader (Thermo). All experiments were performed in triplicate.

Colony formation assay

A total of 1,500 transfected cells were seeded into each well of a 6-well plate. After one week of incubation, the colonies were fixed with formaldehyde, stained with crystal violet for 30 min, then washed with PBS, and the number of visible colonies was counted. Data were collected from three independent experiments for statistical analysis.

Sphere formation assay

To evaluate tumor spheroid formation, pancreatic cancer cells (2×10^3 cells/well) were cultured in DMEM/F12 medium supplemented with B27 (20 μl/ml) basic fibroblast growth factor (b-FGF, 20 ng/ml), epidermal growth factor (EGF, 20 ng/ml) and 1% penicillin-streptomycin. Cells were maintained for 10–14 days, and spheroid structures were observed under a microscope (Olympus, Japan).

Transwell assay

Cell migration was assessed using Transwell chambers (Corning). A total of 1×10^5 cells were suspended in 50 μl of serum-free medium containing 10 g/l bovine serum albumin and seeded into the upper chamber. The lower chamber was filled with medium containing 10% FBS to serve as a chemoattractant. After incubation, cells that had migrated to the lower chamber were fixed, stained, and counted. For invasion assays, the upper chambers were pre-coated with Matrigel (BD Biosciences), while all other steps were identical to those of the migration assay.

Western blot

Following cell lysis in cold lysis buffer, protein concentrations were determined using a BCA protein assay kit (Takara, Shiga, Japan). Equal amounts of protein samples were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; Bio-Rad) and transferred onto polyvinylidene fluoride (PVDF) membranes (Invitrogen). After blocking with 5% skim milk for 1 h at room temperature, membranes were incubated overnight at 4°C with the appropriate primary antibodies. Subsequently, membranes were incubated for 1 h at 37°C with a goat

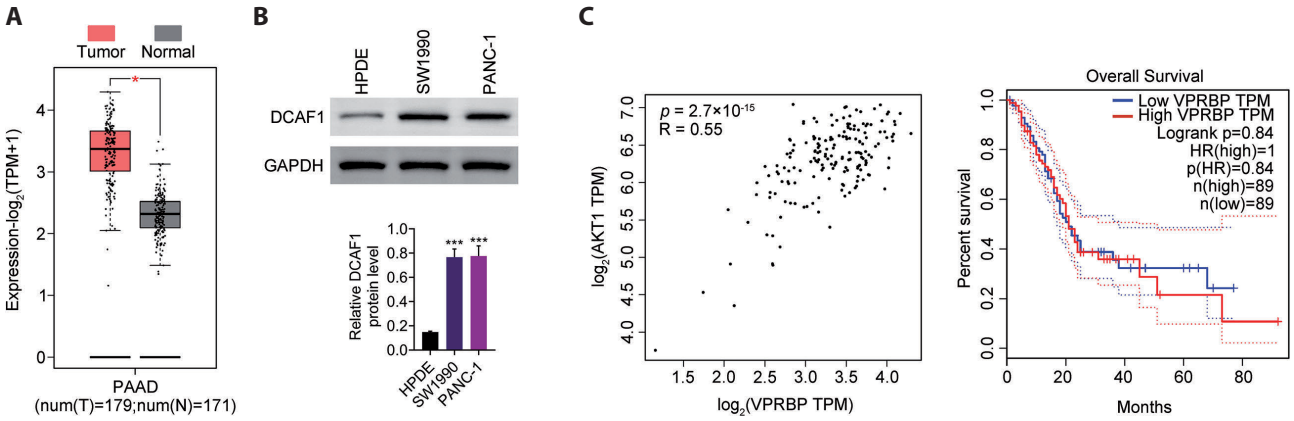

Figure 1. DCAF1 is highly expressed in pancreatic cancer. **A.** GEPIA database analysis of DCAF1 expression in normal pancreatic tissues and pancreatic cancer tissues**. B.** Western blot analysis of DCAF1 expression in human pancreatic cancer cell lines (PANC-1 and SW1990) and the immortalized pancreatic epithelial cell line HPDE. **C.** GEPIA database analysis of the correlation between DCAF1 and AKT in pancreatic cancer and survival analysis of DCAF1 expression in pancreatic cancer. Values are shown as mean ± SD. *** $p < 0.001$ vs HPDE group.

anti-rabbit IgG H&L secondary antibody (ab6721; 1:5000; Abcam). Protein bands were visualized using an enhanced chemiluminescence (ECL) detection system (Thermo), and images were captured with a Bio-Rad imaging system. The primary antibodies (all from Abcam) used in this study included: DCAF1 (ab202587; 1:1000), E-Cadherin (ab15148; 1:1000), N-Cadherin (ab76011; 1:1000), α-SMA (ab314895; 1:1000), CD44 (ab254530; 1:1000), PI3K (ab302958; 1:1000), phosphorylated PI3K (p-PI3K; ab139307; 1:1000), AKT (ab283852; 1:1000), phosphorylated AKT (p-AKT; ab8805; 1:1000), PTEN (ab267787; 1:1000) and GAPDH (ab9485; 1:1000), which served as the internal loading control.

Immunoprecipitation

Cell lysates were prepared in RIPA buffer with a protease inhibitor cocktail (Sigma-Aldrich) and a Halt phosphatase inhibitor cocktail. Primary antibodies (as indicated above) were added to cell lysates, which were then incubated on ice overnight. The next day, add 20–50 µl of protein A beads (Cat# 9863, CST, Danvers, MA, USA) and rotate the samples at 4°C for 3 h . The beads were rinsed on ice with lysis buffer at least six times the next day before being analyzed by Western blot.

Statistical analysis

All data are presented as mean ± standard deviation (SD) from at least three independent experiments. Statistical analysis was performed using GraphPad Prism 8.0 software (GraphPad Software Inc., La Jolla, CA, USA). Comparisons between two groups were analyzed using unpaired two-tailed Student's *t*-tests. In cases where no significant differences were detected, one-tailed *t*-tests were used for further assessment. A *p* -value of less than 0.05 was considered statistically significant.

Results

DCAF1 is highly expressed in pancreatic cancer

To evaluate the expression profile of DCAF1 in pancreatic cancer, we analyzed transcriptomic data using the GEPIA database. The analysis revealed that DCAF1 expression was significantly upregulated in pancreatic cancer tissues compared to normal pancreatic tissues (Fig. 1A). Consistently, DCAF1 protein levels were elevated in two pancreatic cancer cell lines (PANC-1 and SW1990) relative to those in normal pancreatic epithelial cells (HPDE6) (Fig. 1B). There was a significant positive correlation between DCAF1 and AKT, suggesting that DCAF1 and AKT may co-regulate certain biological processes in PAAD. Furthermore, although there was no statistically significant difference ($p > 0.05$), the trend suggested that high DCAF1 expression may be associated with poor survival prognosis (Fig. 1C). These findings indicate that DCAF1 expression is markedly increased in pancreatic cancer.

Knockdown of DCAF1 inhibits pancreatic cancer cell proliferation and stem cell formation

Uncontrolled cell proliferation is a hallmark of cancer, and stem-like features support tumor growth and heterogeneity. To investigate the biological role of DCAF1 in pancreatic cancer, we performed DCAF1 knockdown and overexpression in pancreatic cancer cells. Western blot analysis confirmed successful experiments and confirmed DCAF1

overexpression or silencing (Fig. 2A–C). Cell proliferation was subsequently assessed using the CCK-8 assay and colony formation assay. Both tests showed that DCAF1 overexpression can significantly promote the proliferation of pancreatic cancer cells, and knockdown of DCAF1 can significantly inhibit the proliferation of pancreatic cancer cells (Fig. 2B–F). To further evaluate the role of DCAF1 in tumor stemness, we conducted suspension sphere formation assays. Cells with reduced DCAF1 expression exhibited a marked decrease in spheroid formation efficiency and reduced expression of the stem cell marker CD44 (Fig. 2G,H). These results suggest that DCAF1 promotes pancreatic cancer cell proliferation and the maintenance of stem-like characteristics *in vitro*.

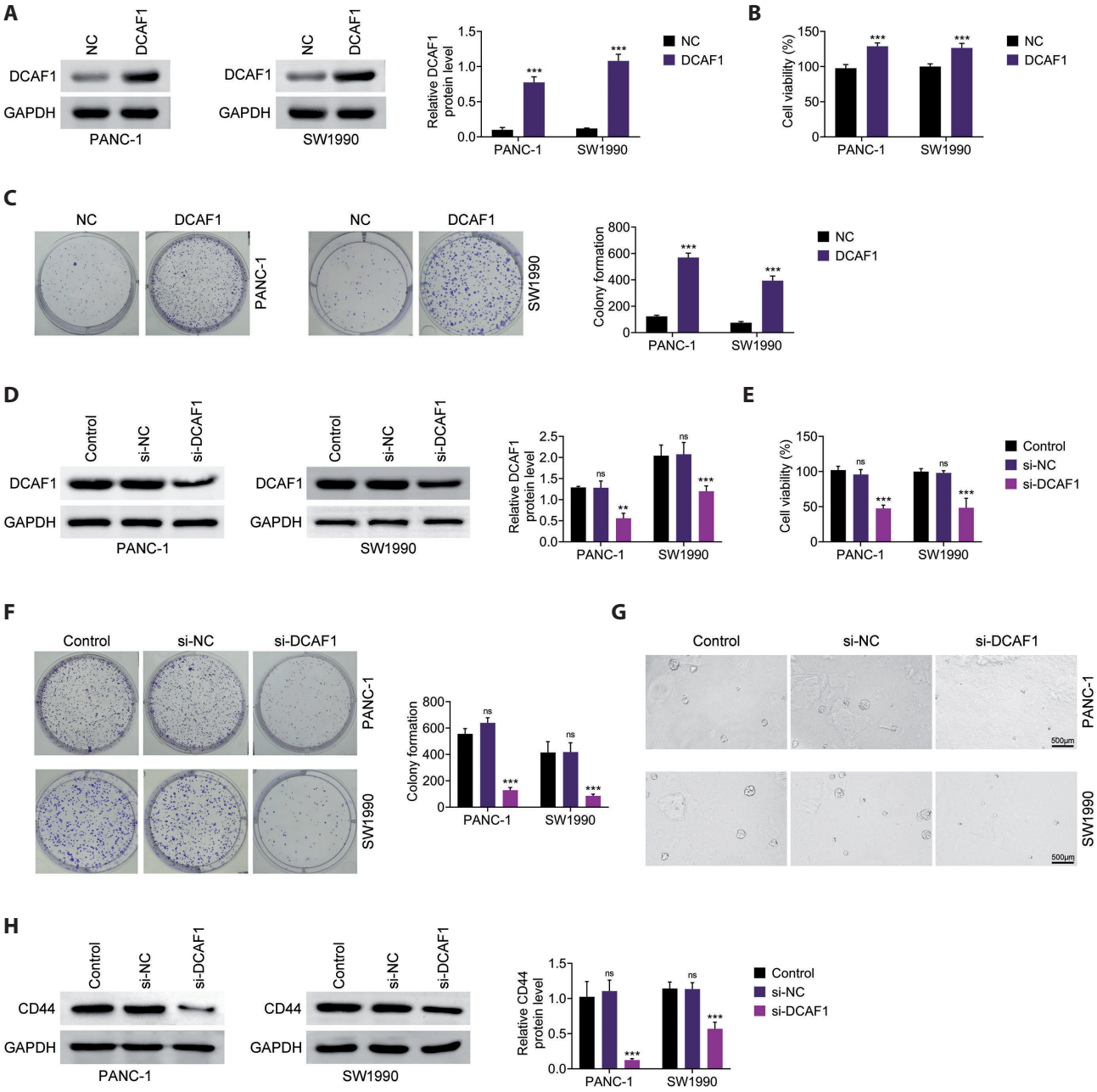

Figure 2. Knockdown of DCAF1 inhibits the growth of pancreatic cancer cells. **A,D.** Western blot showing DCAF1 expression in transfected and untransfected cells. **B,E.** Cell viability measured by CCK-8 assay. **C,F.** Colony formation ability assessed by crystal violet staining. **G.** Spheroid formation assay to evaluate stem cell-like properties. **H.** Expression of the stemness marker CD44 in transfected and untransfected cells. Values are shown as mean ± SD. $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ $^{**}p < 0.01$, $^{***}p < 0.001$ vs NC or si-NC group. ns, not significant

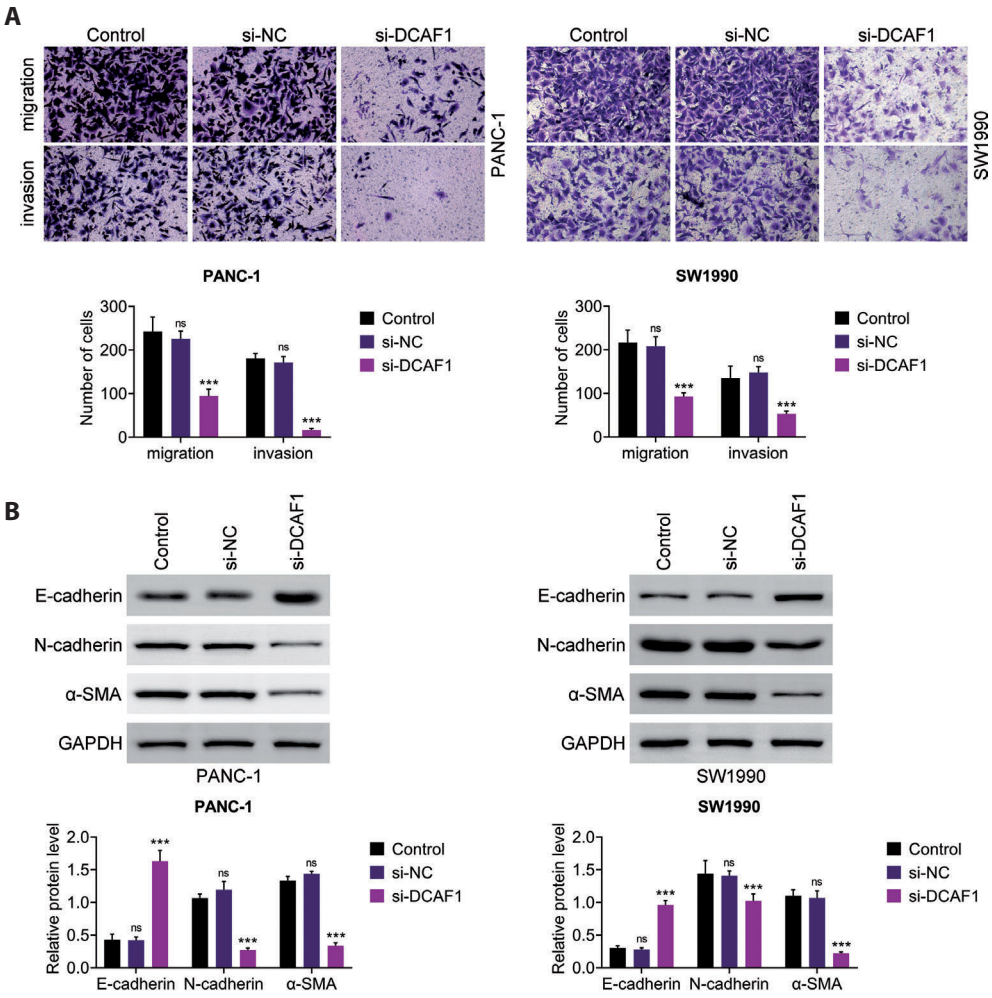

Figure 3. Knockdown of DCAF1 inhibits migration, invasion, and EMT in pancreatic cancer cells. **A.** Quantification of cell migration and invasion using Transwell assays. **B.** Western blot analysis of EMT-related proteins: E-cadherin, N-cadherin, and α-SMA. Values are presented as mean ± SD. $^{###}$ $p < 0.001$ *** $p < 0.001$ vs si-NC group. ns, not significant

Knockdown of DCAF1 inhibits the migration, invasion, and epithelial-mesenchymal transition (EMT) of pancreatic cancer cells

Cancer cell migration, invasion, and EMT are fundamental processes that drive malignant progression and contribute to tumor metastasis. To explore the role of DCAF1 in these processes, we conducted transwell chamber assays. The results demonstrated that DCAF1 knockdown markedly reduced the migratory and invasive capacities of pancreatic cancer cells, indicating a positive correlation between DCAF1 expression and these malignant phenotypes (Fig. 3A). During EMT, pancreatic cancer cells acquire a more mesenchymal-like and motile phenotype, which facilitates distant metastasis and local tissue invasion. EMT has been implicated in both the progression of pancreatitis to pancreatic cancer and in the metastatic dissemination of pancreatic tumors (Cao et al. 2020). To further investigate the molecular mechanism by which DCAF1 influences pancreatic cancer invasiveness, we examined the expression of EMT-associated proteins by Western blot analysis. Silencing of DCAF1 led to increased expression of the epithelial marker E-cadherin, accompanied by decreased expression of the mesenchymal markers N-cadherin and α-SMA (Fig. 3B). These findings collectively suggest that DCAF1 promotes pancreatic cancer cell migration, invasion, and EMT.

DCAF1 knockdown inhibits the PI3K/Akt signaling pathway

To elucidate the potential mechanism by which DCAF1 regulates pancreatic cancer progression, we examined the activation status of the PTEN/PI3K/Akt signaling pathway. Immunoprecipitation and immunoblotting analysis showed that in PANC-1 and SW1990 cell lines, the expression level of PTEN protein was significantly increased and the ubiquitination level was decreased after knocking down DCAF1, indicating that DCAF1 may affect the stability of PTEN through the ubiquitination pathway (Fig. 4A).

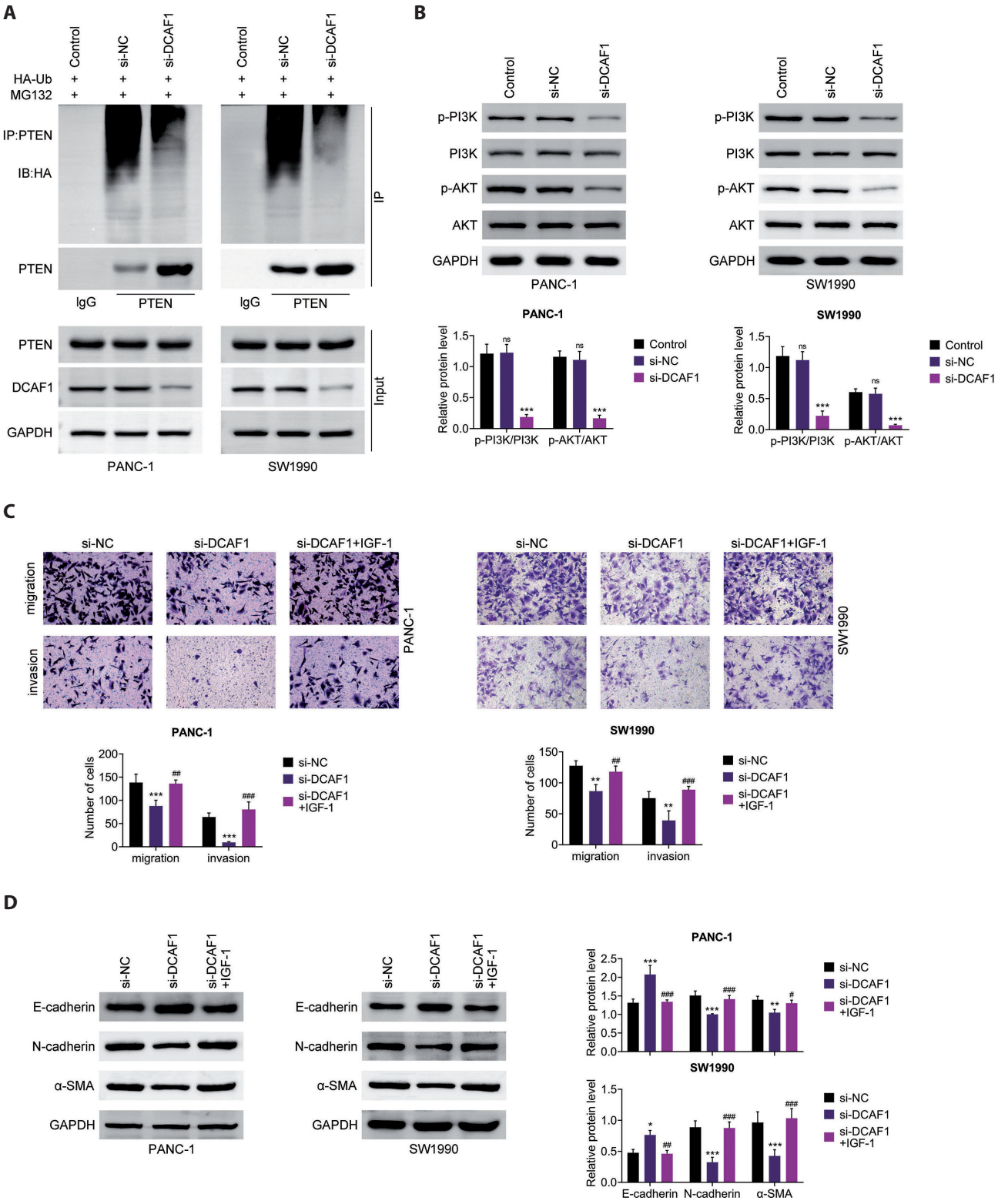

Figure 4. Knockdown of DCAF1 inhibits the PI3K/Akt signaling pathway. **A.** PTEN expression and ubiquitination levels. **B.** Western blot analysis of PI3K, p-PI3K, AKT, and p-AKT expression. **C.** Quantification of cell migration and invasion following IGF-1 rescue. **D.** Western blot analysis of EMT-related proteins after IGF-1 rescue: E-cadherin, N-cadherin, and α-SMA. Values are shown as mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs si-NC group; # $p < 0.05$, ## p < 0.01, ### $p < 0.001$ vs si-DCAF1 group. ns, not significant

While the levels of total PI3K and AKT proteins remained unchanged, DCAF1 knockdown resulted in a marked reduction in phosphorylated PI3K and AKT levels, indicating inhibition of pathway activation (Fig. 4B). Furthermore, rescue experiments demonstrated that stimulation of the PI3K/Akt pathway using insulin-like growth factor 1 (IGF-1) (Wang et al. 2016) reversed the suppressive effects of DCAF1 silencing on pancreatic cancer cell migration, invasion, and EMT (Fig. 4C,D). These findings suggest that DCAF1 may exert its tumor-promoting functions in pancreatic cancer, at least in part, by activating the PTEN/PI3K/Akt signaling pathway.

Discussion

Pancreatic cancer is a highly aggressive malignancy, with approximately 85% of patients presenting with incurable disease at the time of diagnosis (Pereira et al. 2020). Among the key factors implicated in pancreatic tumorigenesis are accumulated genetic alterations that orchestrate malignant transformation through multistep processes (Hayashi et al. 2021). In this context, our study focused on the role of DCAF1, a gene previously associated with oncogenic behavior in other cancer types but not yet explored in pancreatic cancer. Analysis of the GEPIA database revealed significantly elevated DCAF1 expression in pancreatic cancer tissues than normal counterparts, which was further validated in pancreatic cancer cell lines, where DCAF1 was consistently upregulated. Functional *in vitro* assays confirmed that DCAF1 knockdown led to reduced proliferation, migration, invasion, and EMT, suggesting that DCAF1 may function as a key promoter of pancreatic cancer cell aggressiveness.

DCAF1 has recently been identified as a potential therapeutic target in various malignancies, including ovarian surface epithelial carcinoma, hepatocellular carcinoma, colon cancer, and melanoma (Pan et al. 2013; Ren et al. 2016; Ghate et al. 2023; Zhang et al. 2024). In hepatocellular carcinoma, DCAF1 has been shown to interact with PARD3 and activate the Akt signaling pathway, thereby promoting tumor cell growth, migration, and invasion (Zhang et al. 2024). Consistent with these findings, our study revealed that DCAF1 is significantly upregulated in pancreatic cancer tissues and cell lines. Moreover, functional assays demonstrated that silencing DCAF1 markedly inhibited the proliferation, migration, and invasion of pancreatic cancer cells. These observations support the hypothesis that DCAF1 plays a key oncogenic role in the progression of pancreatic cancer.

EMT is closely associated with tumor invasion and metastasis, and previous studies have established a strong link between EMT and the metastatic progression of pancreatic cancer (Ramesh et al. 2020; Guo et al. 2024). In our study, knockdown of DCAF1 led to an increase in the epithelial marker E-cadherin and a concomitant decrease in the mesenchymal marker N-cadherin, indicating a suppression of EMT. These findings highlight the pivotal role of DCAF1 in facilitating EMT in pancreatic cancer cells. EMT is a highly conserved and reversible biological process, primarily regulated by the PI3K/Akt signaling pathway, and is known to enhance the metastatic potential and malignant behavior of various cancer types (Peng et al. 2022). Importantly, the PI3K/Akt pathway is frequently dysregulated in pancreatic cancer and is recognized as a central driver of its initiation and progression. As such, it has been proposed as a promising therapeutic target for pancreatic malignancies (Mortazavi et al. 2022; Stanciu et al. 2022). Previous studies have also shown that DCAF1 can modulate the PI3K/Akt pathway in colon cancer (Ren et al. 2016). PTEN is a tumor suppressor gene that is suppressed in a number of human cancers. PTEN downregulation in pancreatic cancer could be a significant genetic event that contributes to tumor aggressiveness. Ubiquitination is an important post-translational alteration of PTEN in malignant tumors. Stabilized PTEN can block the PI3K/AKT pathway (Petrogiannopoulos et al. 2020). Our results showed that knockdown of DCAF1 significantly inhibited PTEN ubiquitination, increasing protein stability and thereby inhibiting PI3K and AKT phosphorylation, without changing total protein levels, suggesting reduced pathway activation. These findings suggest that DCAF1 may promote pancreatic cancer progression, at least in part, by regulating the PTEN/PI3K/ AKT signaling pathway.

Several limitations of this study should be acknowledged. First, all experiments were conducted *in vitro*, which limits the ability to fully evaluate the antitumor effects of DCAF1 knockdown *in vivo*. Second, while our results suggest that DCAF1 promotes pancreatic cancer progression through activation of the PTEN/PI3K/Akt signaling pathway, the underlying molecular mechanisms remain incompletely understood. Further in-depth studies, including *in vivo* models and broader pathway analyses, are required to clarify the precise role of DCAF1 in pancreatic cancer pathogenesis and to explore its potential as a target for therapeutic intervention.

Conclusion

In summary, our findings demonstrate that DCAF1 is highly expressed in pancreatic cancer tissues and cell lines, and that it promotes pancreatic cancer cell proliferation, migration, invasion, and EMT through activation of the PTEN/PI3K/Akt signaling pathway. These results suggest that DCAF1 may serve as a potential molecular target for the development of novel therapeutic strategies against pancreatic cancer.

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Ethics approval. This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of data and materials. The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

Author's contribution. JW, YW designed the study and carried them out; JW, YW, WX, QR supervised the data collection, analyzed the data and interpreted the data; JW, YW prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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