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# Desmoglein 3 contributes to tumorigenicity of pancreatic ductal adenocarcinoma through activating Src–FAK signaling

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**ABSTRACT**

Desmogleins (DSGs), with the ability to link adjacent cells, have been shown to participate in the development of malignancy. DSG3 was up-regulated in various cancers, including lung, head and neck, and esophagus squamous cell carcinoma, which contributed to the tumor progression. The role of DSG3 in pancreatic ductal adenocarcinoma (PDAC) still remains elusive. Here, the expression of DSG3 was found to be enhanced in pancreatic cancer cell lines *in vitro*. Functional assays showed that shRNA-mediated knockdown of DSG3 decreased cell viability of pancreatic cancer cells and retarded the cell proliferation, migration and invasion. However, pcDNA-mediated over-expression of DSG3 exhibited reversed effect on pancreatic cancer cell progression. In addition, the *in vivo* assay demonstrated that transfection of shDSG3 lentiviruses into pancreatic cancer cells repressed the tumorigenicity of PDAC after the cancer cells were transplanted into mice subcutaneously. Elevated DSG3 expression promoted the phosphorylation of Src (p-Src), focal adhesion kinase (p-FAK) and AKT (p-AKT) *in vitro*, while silence of DSG3 reduced the expression of p-Src, p-FAK and p-AKT both *in vitro* and *in vivo*. In conclusion, DSG3, as an oncogene, contributed to the tumorigenicity of PDAC through activating Src–FAK signaling.

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## Introduction

Pancreatic cancer, a highly malignant tumor with poor prognosis, is one of the most common causes of morbidity and mortality worldwide (Chen et al. 2019). Although chemotherapy and medical technology have improved the overall survival of patients with pancreatic cancer, the five-year survival is only 6–22% (Mishra and Guda 2017). Surgical resection is currently regarded as the major therapy for treating pancreatic cancer, and the novel therapies are urgently needed (Buanes 2017). Pancreatic ductal adenocarcinoma (PDAC) contributes to more than 90% of pancreatic malignancies (Orth et al. 2019). The pathogenesis of PDAC is complex and not well understood yet. Tumor metastasis has been widely observed in majority of patients with PDAC before resection due to lack of early symptoms (Munis et al. 2018). Moreover, patients with PDAC may usually experience recurrence even after the surgery resection owing to the metastatic growth (Munis et al. 2018). Therefore, investigation on the pathogenesis, development process, invasion and metastasis mechanism of PDAC could provide experimental support and theoretical basis for the early diagnosis and molecularly targeted therapy of pancreatic cancer.

Desmogleins (DSGs), including DSG1, 2, 3, 4, function as cadherins and intercellular junctions in desmosome, which is important for the maintenance of tissue integrity and architecture (Delva et al. 2009). DSGs have been demonstrated to be implicated in various cellular processes such as cell proliferation, differentiation and morphogenesis (Thomason Helen et al. 2010). Besides, DSGs have been found to participate in tumorigenicity of various cancers through mediating the cell–cell adhesion and epithelial to mesenchymal transition (Dusek and Attardi 2011). DSG3 was reported to be either tumor suppressor or promoter (Brown and Wan 2015). For example, DSG3 was reduced in oral squamous cell carcinoma (Wang et al. 2007), which was verified to promote the metastasis (Xin et al. 2014). On the contrary, DSG3 was enhanced in inverted papilloma and squamous cell carcinoma (Huang et al. 2010), which facilitated head neck cancer cell growth and invasion (Chen et al. 2013). In PDAC, high DSG3



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expression showed significantly negative correlation with poor tumor differentiation and shorter patients' survival, which suggests that DSG3 is a potential prognostic biomarker of PDAC (Ormanns et al. 2015). However, the role of DSG3 in the progression of PDAC has not been reported yet.

This study investigated the *in vitro* and *in vivo* role of DSG3 in PDAC progression and the underlying mechanism. The meaning results would provide a new potential therapeutic target for treating PDAC.

## Materials and methods

### Cell culture and transfection

Four pancreatic cancer cell lines (SW1990, BxPC-3, PANC-1 and ASPC-1) and healthy control cell line (hTert-HPNE) were purchased from Biosci Biotechnology (Hubei, China) and cultured in Dulbecco's Modified Eagle Medium (DMEM) (Lonza, Basel, Switzerland) containing 10% fetal bovine serum (Thermo Fisher Scientific, Waltham, MA, USA). shDSG3 and pcDNA-DSG3 were separately constructed into pEGFP-N3 and pcDNA3-EGFP vectors by GenePharma (Suzhou, China) to induce the knockdown and over-expression of DSG3. BxPC-3 or PANC-1 was transfected with shDSG3 or pcDNA-DSG3, as well as the negative controls (shNC and empty vector) via Lipofectamine 2000 (Sigma Aldrich, St. Louis, MO, USA).

### qRT-PCR

Total RNAs extracted from pancreatic cancer cells were reverse-transcribed into complementary DNA (cDNAs). SYBR Green Master (Roche, Mannheim, Germany) was applied to determine the messenger RNA (mRNA) expression of DSG3 and GAPDH. GAPDH was used as internal reference. The primers were listed as below: DSG3: F 5′-TATGAACAACTACAAAGCGTGAAAC-3′ and R 5′-TTGGAAGCAGGACGGAAT-3′; GAPDH: F 5′-GGATTGTCTGGCAGTAGCC-3′ and R 5′-ATTGTGAAAGGCAGGGAG-3′.

### Cell viability and proliferation

The cell viability of pancreatic cancer cells was determined using cell counting kit-8 kit (Dojindo, Tokyo, Japan) and the absorbance at 450 nm was measured with a Microplate Autoreader (Thermo Fisher Scientific). For cell proliferation analysis, BxPC-3 or PANC-1 with indicated transfections was cultured in six-well plate for two weeks. Methanol-fixed and crystal violet-stained colonies were observed and photographed using microscope (Olympus, Tokyo, Japan).

### EdU (5-ethynyl-2′-deoxyuridine) and Green Fluorescent Protein (GFP) staining

BxPC-3 or PANC-1 cells were incubated with EdU or GFP solution (Sigma Aldrich) for 2 h. Paraformaldehyde-fixed cells were then incubated with 100 µL 1× Apollo® dyeing reaction solution (Sigma Aldrich) and 4′,6-diamidino-2-phenylindole (DAPI) solution (Sigma Aldrich) for another 1 h. The fluorescence was observed under fluorescence microscope (Olympus).

### Wound healing and transwell assays

BxPC-3 or PANC-1 cells with indicated transfection were plated and scratched by a plastic tips. Twenty-four hours later, the wound was calculated under the microscope. For transwell assay, BxPC-3 or PANC-1 supplemented with serum-free DMEM were seeded in the upper Matrigel-coated Transwell chamber (Corning Life Sciences, Oneonta, NY, USA), and the bottom chamber was filled with DMEM containing 20% fetal bovine serum. Forty-eight hours later, the paraformaldehyde-fixed and crystal violet-stained cells in the bottom chamber were counted under the microscope.

### Xenograft model

The study was approved by The Affiliated Cancer Hospital of Xinjiang Medical University. According to the National Institutes of Health Laboratory Animal Care and Use Guidelines, lentiviral-mediated silence of DSG3 by shDSG3 or the negative control (shNC) was generated by GenePharma, which was then transfected into HEK-293T cells to obtain the lentiviruses. The lentiviruses were transfected into BxPC-3 with 8 mg/mL polybrene through ViraPower™ Packaging Mix (Thermo Fisher Scientific). Cells with stable silence of DSG3 were obtained following treatment with 5 µg/mL puromycin (Sigma Aldrich) for seven days. Ten Balb/c nude mice (4–6-week-old and 18–20 g weight) were purchased from Shanghai Laboratory Animal Company (Shanghai, China) and randomly divided into two groups: mice with shNC group and shDSG3 group. Cells transfected with shDSG3 or shNC lentiviruses ($5 \times 10^6$) were subcutaneously injected into the right flank of mice. Seven days later, the tumor volume was measured every seven days for four weeks. The mice were sacrificed by cervical dislocation, and the tumors were harvested for further analysis after five weeks post-injection.

### Immunohistochemistry

Paraformaldehyde-fixed and paraffin-embedded tumor tissues were cut into 4-µm sections. Xylene-degreased

and gradient alcohol-rehydrated sections were incubated with sodium citrate buffer (pH 6.0) and then blocked in 3% $H_2O_2$. Following incubation with specific antibody against Ki67 (1:200, ab833, Abcam, Cambridge, MA, USA) overnight, the sections were incubated with corresponding secondary antibody and stained with diaminobenzidine and hematoxylin. Slides were observed under the microscope.

### *Western blot*

Proteins extracted from tumor tissue and cells were separated by Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and transferred to Polyvinylidene Fluoride (PVDF) membranes (Sigma Aldrich). Following blockade with bovine serum albumin (Sigma Aldrich) and incubation with primary antibodies against DSG3 (1:2000, ab218380, Abcam), Src (ab47405) and p-Src (1:2500, p-Tyr418, ab4816 Abcam), FAK (ab131435) and p-FAK (1:3000, p-Tyr397, ab81298, Abcam), AKT (ab235958) and p-AKT (1:3500, p-Ser 473, ab81283, Abcam), and β-actin (1:4000, ab8227, Abcam), the membrane was then incubated with HRP-conjugated secondary antibody (1:5000, ab205718, Abcam), and the signals were detected with chemiluminescence system (Tanon, Shanghai, China).

### *Statistical analysis*

All data were presented as mean ± S.E.M. and then Student's *t*-test and one-way analysis of variance in GraphPad Prism software were conducted. $p$ value < 0.05 was considered as statistical significance.

## Results

### *DSG3 contributed to pancreatic cancer cell growth*

To investigate the role of DSG3 in PDAC, Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) was applied to determine the expression of DSG3 in pancreatic cancer cells. The result showed a significantly higher expression of DSG3 in the four pancreatic cancer cell lines (SW1990, BxPC-3, PANC-1 and ASPC-1) compared with that in the healthy control cell line (hTert-HPNE) (Figure 1A). BxPC-3 and PANC-1 were transfected with shRNA-mediated knockdown of DSG3 (shDSG3) and pcDNA-mediated over-expression of DSG3 (pcDNA-DSG3), respectively. The transfection efficiency is shown in Figure 1B. Cell viability of BxPC-3 was decreased by shDSG3, while cell viability of PANC-1 was increased by pcDNA-DSG3 (Figure 1C). shDSG3 transfected BxPC-3 exhibited lower expression of DSG3 than shNC transfected cells, but pcDNA-DSG3 transfected PANC-1 showed higher expression of DSG3 than empty vector transfected cells (Figure 1D). shRNA-mediated knockdown of DSG3 suppressed cell proliferation of BxPC-3 (Figure 1E), while pcDNA-mediated over-expression of DSG3 promoted the proliferation of PANC-1 (Figure 1E). Moreover, the result of EdU staining also confirmed the anti-proliferative effect of shDSG3 on pancreatic cancer cells (Figure 1F).

### *DSG3 promoted pancreatic cancer cell metastasis*

Cell migration of BxPC-3 was repressed by shRNA-mediated knockdown of DSG3, which was promoted in PANC-1 by pcDNA-mediated over-expression of DSG3 (Figure 2A). Transfection with shDSG3 also retarded cell invasion of BxPC-3 (Figure 2B), whereas transfection with pcDNA-DSG3 played an opposite role in PANC-1 (Figure 2B). These results verified the anti-invasive effect of shDSG3 on pancreatic cancer cells.

### *DSG3 facilitated the activation of Src–FAK–AKT signaling in pancreatic cancer cell*

Western blot analysis was applied to investigate the mechanism of DSG3-mediated pancreatic cancer progression. p-Src, p-FAK and p-AKT were reduced in shDSG3 transfected BxPC-3 though protein expression of Src, FAK and AKT were not changed by shDSG3 or pcDNA-DSG3 (Figure 3). Inversely, p-Src, p-FAK and p-AKT were increased in pcDNA-DSG3 transfected PANC-1 (Figure 3), suggesting that DSG3 promoted the phosphorylation of Src, FAK and AKT and facilitated the pancreatic cancer cell progression.

### *DSG3 boosted* in vivo *pancreatic cancer growth*

The *in vivo* regulatory role of DSG3 on tumorigenicity of pancreatic cancer was evaluated by a xenograft model. Mice were injected with BxPC-3 cells with stable DSG3 silence. Tumor growth and tumor volume were significantly decreased by injection with shDSG3 transfected BxPC-3 cells compared to shNC transfected cells (Figure 4A). The expression of Ki67 protein was decreased in tumor tissues isolated from mice injected with shDSG3 transfected BxPC-3 cells (Figure 4B). Moreover, injection of shDSG3 transfected BxPC-3 cells significantly reduced DSG3 expression, and Src, FAK and AKT phosphorylation (Figure 4C), indicating that knockdown of DSG3 repressed *in vivo* growth of pancreatic cancer through inactivating Src–FAK–AKT signaling.

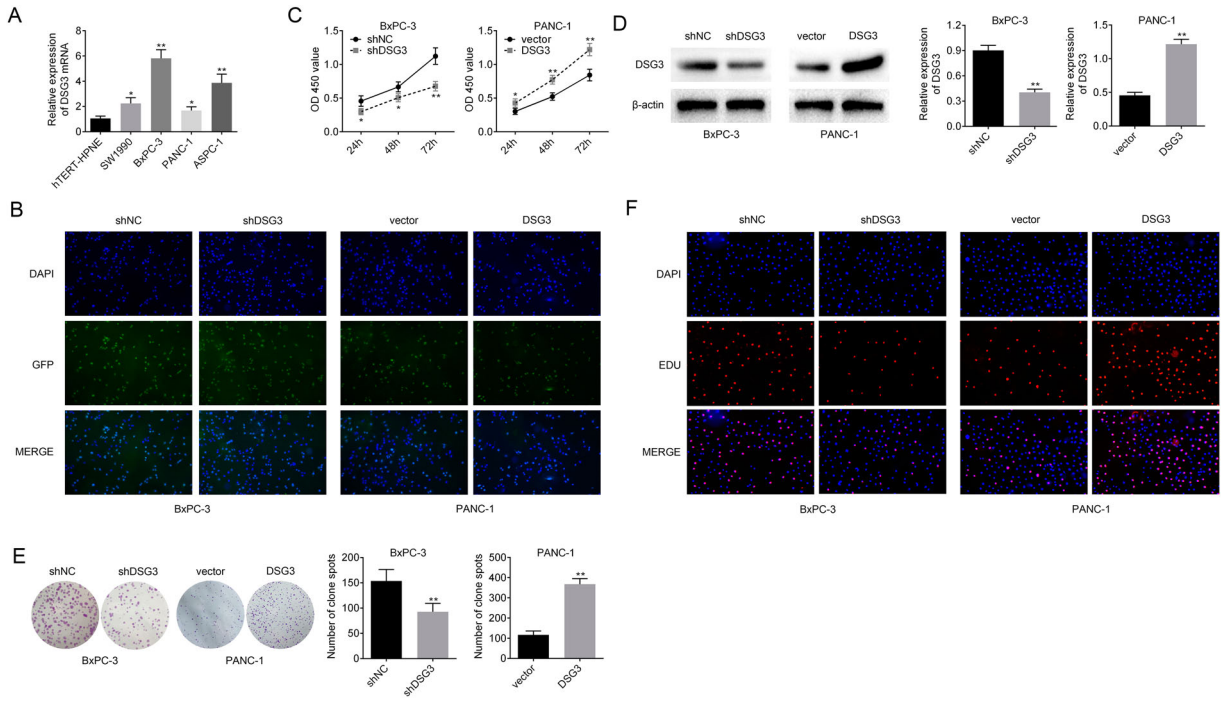


**Figure 1.** DSG3 promoted pancreatic cancer cell growth. (A) DSG3 was up-regulated in the four pancreatic cancer cell lines (SW1990, BxPC-3, PANC-1 and ASPC-1) compared to the healthy control cell line (hTert-HPNE). (B) Transfection efficiency of shRNA-mediated knockdown of DSG3 (shDSG3) and pcDNA-mediated over-expression of DSG3. (C) Cell viability of BxPC-3 was decreased by shDSG3 but increased by pcDNA-DSG3 in PANC-1. (D) shDSG3 transfected BxPC-3 exhibited lower expression of DSG3 than cell transfected with shNC, and pcDNA-DSG3 transfected PANC-1 showed higher expression of DSG3 than cell transfected with empty vector. (E) Cell proliferation of BxPC-3 was decreased by shDSG3, which was increased by pcDNA-DSG3 in PANC-1. (F) shDSG3 transfected BxPC-3 had less EdU positive cells than cell transfected with shNC, while pcDNA-DSG3 transfected PANC-1 had more EdU positive cells than cell transfected with empty vector. $^{**}p < 0.01$.

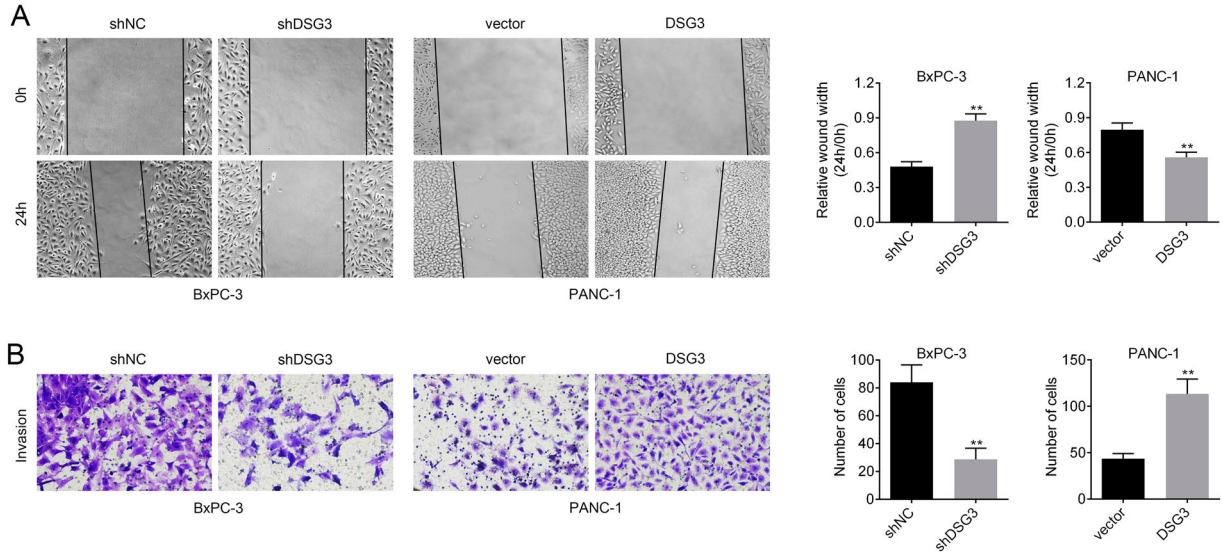


**Figure 2.** DSG3 facilitated pancreatic cancer cell metastasis. (A) Cell migration of BxPC-3 was decreased by shDSG3, which was increased by pcDNA-DSG3 in PANC-1. (B) Cell invasion of BxPC-3 was decreased by shDSG3, which was increased by pcDNA-DSG3 in PANC-1. $^{**}p < 0.01$.

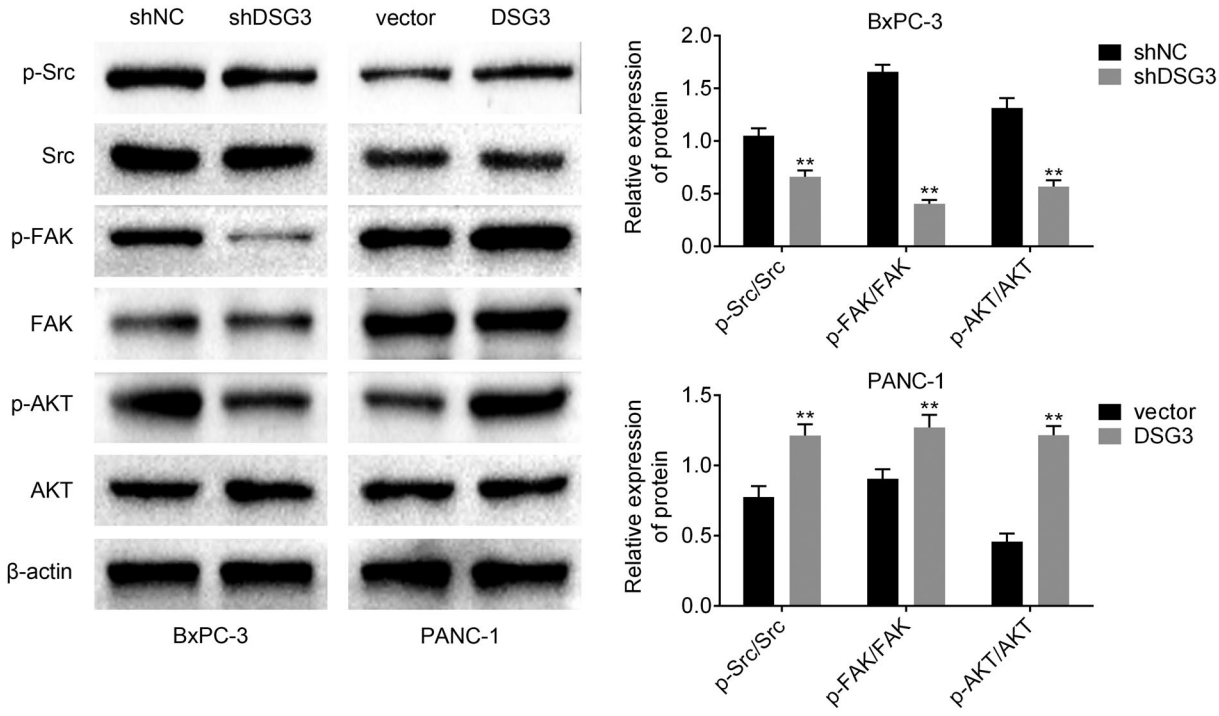


**Figure 3.** DSG3 activated Src–FAK–AKT signaling in pancreatic cancer cell. Protein expression of p-Src, p-FAK and p-AKT were reduced in shDSG3 transfected BxPC-3, while enhanced in PANC-1 transfected with pcDNA-DSG3. $^{**}p < 0.01$.

## Discussion

Loss of DSG1 and DSG2 in pancreatic tissues diminished the cell–cell adhesion, thus facilitating for pancreatic cancer cell invasion (Ramani et al. 2008). DSG3 cannot be detected in six independent sections of pancreatic adenocarcinoma or chronic pancreatitis tissues (Ramani et al. 2008). However, high expression of DSG3 in resected PDAC tissues significantly reduced the survival time of patients (Ormanns et al. 2015). Therefore, it is necessary to investigate the oncogenic effect of DSG3 on PDAC.

DSG3 was found to be up-regulated in pancreatic cancer cell lines (SW1990, BxPC-3, PANC-1 and ASPC-1), which contributed to the pancreatic cancer cell growth and metastasis. Nevertheless, silence of DSG3 impeded the cell growth and metastasis. Moreover, interference of DSG3 repressed the *in vivo* growth of pancreatic cancer, furtherly confirming the oncogenic role of DSG3 on PDAC. Additionally, activation of an epithelial-to-mesenchymal transition is obviously correlated with tumor growth and metastasis in PDAC (Rodriguez-Aznar et al. 2019). The proliferation of epithelial cells was impaired by knockdown of DSG3 (Mannan et al. 2011), so the effect of DSG3 on epithelial-to-mesenchymal transition of PDAC should be further explored.

Research has shown that DSG3 participated in the activation of Rho GTPases, organization of specialized membrane domains, regulation of Wnt/β-catenin signaling and activator protein-1 to promote the cancer progression (Brown and Wan 2015). Src functions as a non-receptor cytoplasmic tyrosine kinase to transmit signals following the stimulation of membrane receptors and participates in multiple biological activities such as cell homeostasis, differentiation, proliferation, adhesion and migration (Guarino 2010). Increased activity of Src was reported to promote hyper-proliferation, migration, invasion and epithelial-to-mesenchymal transition during cancer progression (Guarino 2010). Src was over-expressed and activated in PDAC (Alcalá et al. 2020), which promoted the metastasis of PDAC (Ogawa et al. 2019). LY-1816, a Src inhibitor, has been demonstrated to have clinical therapeutic effect on PDAC (Yang et al. 2019). Some research has shown that DSG3 can activate Src as a cell surface regulator (Tsang et al. 2012). Increased DSG3 in cancer cells promoted the tyrosine phosphorylation of Src (Tsang et al. 2012) via the interaction with adherens junction proteins, E-cadherin (Tsang et al. 2010), or by competing with caveolin-1 (Wan et al. 2015). Consistent with published work, the results in this study also demonstrate that over-expression of DSG3 can promote the tyrosine phosphorylation of Src, while knockdown of DSG3 got opposite results both *in vitro* and *in vivo*. FAK and Src, most connected adhesion components, are potential therapeutic targets for cancer (Horton et al. 2016), and phosphorylation of FAK in a Src-dependent manner

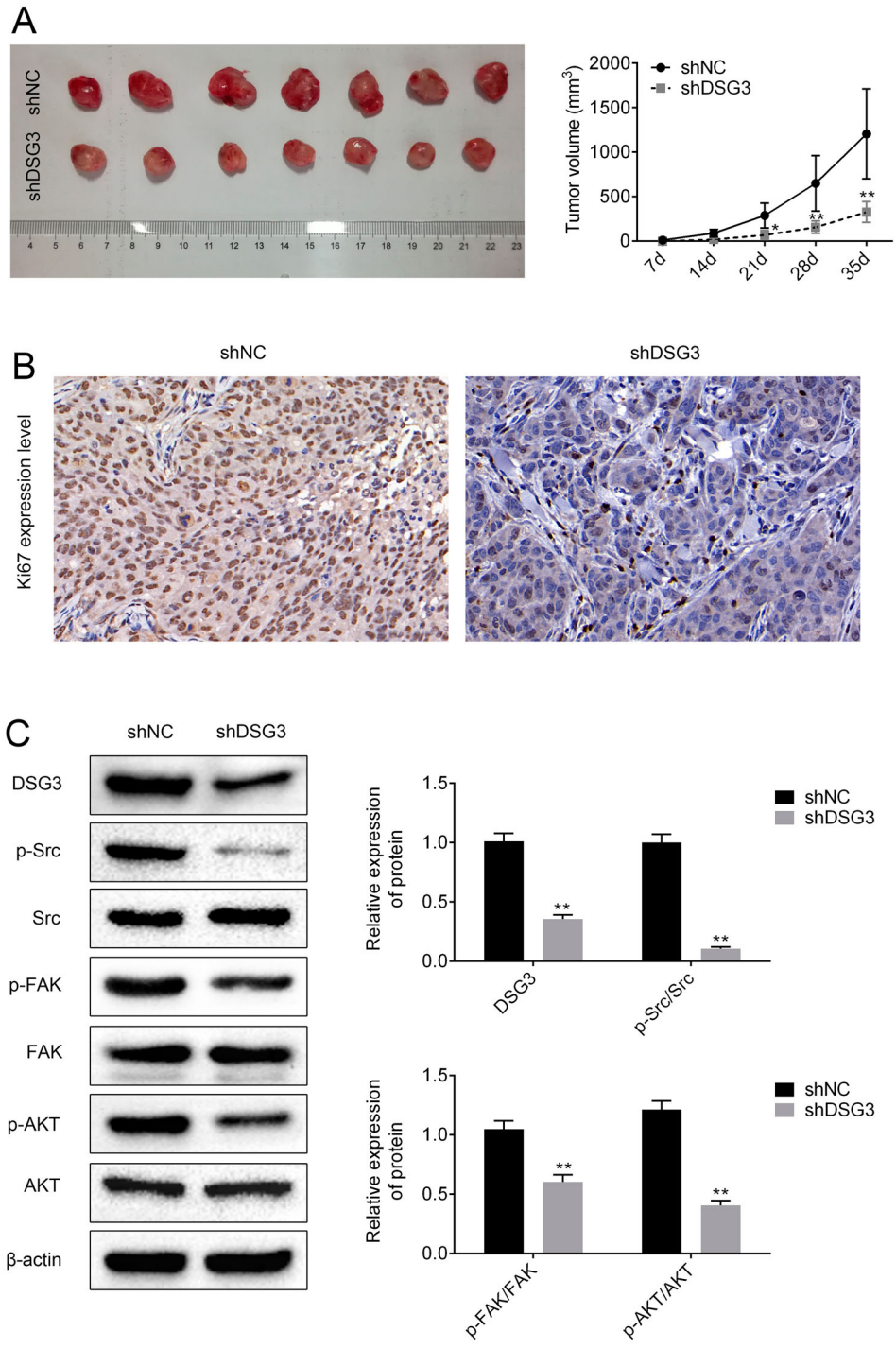


**Figure 4.** DSG3 stimulated pancreatic cancer growth *in vivo*. (A) Tumor growth and tumor volume were repressed and decreased by injection with shDSG3 transfected BxPC-3 cells (A) compared to the shNC transfected cells. (B) Protein expression of Ki67 was decreased in tumor tissues isolated from mice injected with shDSG3 transfected BxPC-3 cells. (C) Injection with shDSG3 transfected BxPC-3 cells significantly reduced protein expression of DSG3, p-Src, p-FAK and p-AKT. $^{**}p < 0.01$.

could bind to p85 regulatory subunit of phosphatidylinositol 3-kinase (Velling et al. 2004). FAK could also promote cancer cell growth and proliferation through taking part in p53 degradation (Zhou et al. 2019), while inhibition of Src/FAK signaling resulted in the regression of epithelial cell migration (Lee et al. 2018). In addition, suppression of FAK could radiosensitize PDAC cells (Mohamed et al. 2020). GSK2256098, an inhibitor of FAK phosphorylation, has been shown to inhibit PDAC cell growth and survival (Zhang et al. 2014). Coincidentally, our results also revealed that the increased DSG3 in PDAC cells and tissues activated

FAK/AKT signaling through increasing the phosphorylation of FAK and AKT. Moreover, interference of DSG3 reduced levels of p-FAK and p-AKT thus leading to the inactivation of FAK/AKT pathway.

In summary, this study indicated that DSG3 was upregulated in PDAC cells, which promoted the proliferation and invasion of PDAC through activating Src/FAK/AKT signaling. Silence of DSG3 contributed to the *in vitro* suppression of cell survival and *in vivo* tumor growth through inactivation of Src/FAK/AKT pathway. Inhibitors of DSG3 might suppress growth and metastasis of PDAC, which needs to be further investigated.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Ethics approval

Ethical approval was obtained from the Ethics Committee of The Affiliated Cancer Hospital of Xinjiang Medical University.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

Yimamumaimaitijiang·Abula and Chao Yi designed the study and supervised the data collection, Yating Su and Dilixiati·Tuniyazi analyzed the data and interpreted the data, and Chao Yi prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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## References

Alcalá S, Mayoral-Varo V, Ruiz-Cañas L, López-Gil JC, Heeschen C, Martín-Pérez J, Sainz B, Jr. 2020. Targeting SRC kinase signaling in pancreatic cancer stem cells. Int J Mol Sci. 21 (20):7437.

Brown L, Wan H. 2015. Desmoglein 3: a help or a hindrance in cancer progression? Cancers. 7(1):266–286.

Buanes TA. 2017. Role of surgery in pancreatic cancer. World J Gastroenterol. 23(21):3765–3770.

Chen H, Kong Y, Yao Q, Zhang X, Fu Y, Li J, Liu C, Wang Z. 2019. Three hypomethylated genes were associated with poor overall survival in pancreatic cancer patients. Aging. 11 (3):885–897.

Chen Y-J, Lee L-Y, Chao Y-K, Chang JT, Lu Y-C, Li H-F, Chiu C-C, Li Y-C, Li Y-L, Chiou J-F, et al. 2013. DSG3 facilitates cancer cell growth and invasion through the DSG3-plakoglobin-TCF/LEF-Myc/cyclin D1/MMP signaling pathway. PLoS One. 8(5): e64088–e64088.

Delva E, Tucker D, Kowalczyk A. 2009. The desmosome. Cold Spring Harbor Perspect Biol. 1(2):a002543.

Dusek RL, Attardi LD. 2011. Desmosomes: new perpetrators in tumour suppression. Nat Rev Cancer. 11(5):317–323.

Guarino M. 2010. Src signaling in cancer invasion. J Cell Physiol. 223(1):14–26.

Horton ER, Humphries JD, Stutchbury B, Jacquemet G, Ballestrem C, Barry ST, Humphries MJ. 2016. Modulation of FAK and Src adhesion signaling occurs independently of adhesion complex composition. J Cell Biol. 212(3):349–364.

Huang C-C, Lee T-J, Chang P-H, Lee Y-S, Chuang C-C, Jhang Y-J, Chen Y-W, Chen C-W, Tsai C-N. 2010. Desmoglein 3 is overexpressed in inverted papilloma and squamous cell carcinoma of sinonasal cavity. Laryngoscope. 120(1):26–29.

Lee JJ, van de Ven RAH, Zaganjor E, Ng MR, Barakat A, Demmers JJPG, Finley LWS, Gonzalez Herrera KN, Hung YP, Harris IS, et al. 2018. Inhibition of epithelial cell migration and Src/FAK signaling by SIRT3. Proc Natl Acad Sci USA. 115(27):7057.

Mannan T, Jing S, Foroushania SH, Fortune F, Wan H. 2011. RNAi-mediated inhibition of the desmosomal cadherin (desmoglein 3) impairs epithelial cell proliferation. Cell Prolif. 44 (4):301–310.

Mishra NK, Guda C. 2017. Genome-wide DNA methylation analysis reveals molecular subtypes of pancreatic cancer. Oncotarget. 8(17):28990–29012.

Mohamed AA, Thomsen A, Follo M, Zamboglou C, Bronsert P, Mostafa H, Amen A, Mekawy M, Grosu AL, Brunner TB, et al. 2020. FAK inhibition radiosensitizes pancreatic ductal adenocarcinoma cells in vitro. Strahlenther Onkol. 197 (1):27–38. doi:10.1007/s00066-020-01666-0.

Munis A, Omar H, Iwaz S, Mahdavian M. 2018. Metastatic pancreatic adenocarcinoma presenting as a klatskin tumor. ACG Case Rep J. 5:e80–e80.

Ogawa K, Lin Q, Li L, Bai X, Chen X, Chen H, Kong R, Wang Y, Zhu H, He F, et al. 2019. Aspartate β-hydroxylase promotes pancreatic ductal adenocarcinoma metastasis through activation of SRC signaling pathway. J Hematol Oncol. 12(1):144–144.

Ormanns S, Altendorf-Hofmann A, Jackstadt R, Horst D, Assmann G, Zhao Y, Bruns C, Kirchner T, Knösel T. 2015. Desmogleins as prognostic biomarkers in resected pancreatic ductal adenocarcinoma. Br J Cancer. 113(10):1460–1466.

Orth M, Metzger P, Gerum S, Mayerle J, Schneider G, Belka C, Schnurr M, Lauber K. 2019. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol. 14(1):141.

Ramani VC, Hennings L, Haun RS. 2008. Desmoglein 2 is a substrate of kallikrein 7 in pancreatic cancer. BMC Cancer. 8(1):373–373.

Rodriguez-Aznar E, Wiesmüller L, Sainz B, Jr, Hermann PC. 2019. EMT and stemness-key players in pancreatic cancer stem cells. Cancers. 11(8):1136.

Thomason Helen A, Scothern A, McHarg S, Garrod David R. 2010. Desmosomes: adhesive strength and signalling in health and disease. Biochem J. 429(3):419–433.

Tsang SM, Brown L, Lin K, Liu L, Piper K, O'Toole EA, Grose R, Hart IR, Garrod DR, Fortune F, et al. 2012. Non-junctional human desmoglein 3 acts as an upstream regulator of Src in E-cadherin adhesion, a pathway possibly involved in the pathogenesis of pemphigus vulgaris. J Pathol. 227(1):81–93.

Tsang SM, Liu L, Teh M-T, Wheeler A, Grose R, Hart IR, Garrod DR, Fortune F, Wan H. 2010. Desmoglein 3, via an interaction with E-cadherin, is associated with activation of Src. PLoS One. 5(12):e14211–e14211.

Velling T, Nilsson S, Stefansson A, Johansson S. 2004. β1-integrins induce phosphorylation of Akt on serine 473 independently of focal adhesion kinase and Src family kinases. EMBO Rep. 5(9):901–905.

Wan H, Lin K, Tsang SM, Uttagomol J. 2015. Evidence for Dsg3 in regulating Src signaling by competing with it for binding to caveolin-1. Data Brief. 6:124–134.

Wang L, Liu T, Wang Y, Cao L, Nishioka M, Aguirre RL, Ishikawa A, Geng L, Okada N. 2007. Altered expression of desmocollin 3, desmoglein 3, and β-catenin in oral squamous cell carcinoma: correlation with lymph node metastasis and cell proliferation. Virchows Arch. 451(5):959–966.

Xin Z, Yamaguchi A, Sakamoto K. 2014. Aberrant expression and altered cellular localization of desmosomal and hemidesmosomal proteins are associated with aggressive clinicopathological features of oral squamous cell carcinoma. Virchows Arch. 465(1):35–47.

Yang W, Meng L, Chen K, Tian C, Peng B, Zhong L, Zhang C, Yang X, Zou J, Yang S, et al. 2019. Preclinical pharmacodynamic evaluation of a new Src/FOSL1 inhibitor, LY-1816, in pancreatic ductal adenocarcinoma. Cancer Sci. 110 (4):1408–1419.

Zhang J, He D-H, Zajac-Kaye M, Hochwald SN. 2014. A small molecule FAK kinase inhibitor, GSK2256098, inhibits growth and survival of pancreatic ductal adenocarcinoma cells. Cell Cycle. 13(19):3143–3149.

Zhou J, Yi Q, Tang L. 2019. The roles of nuclear focal adhesion kinase (FAK) on cancer: a focused review. J Exp Clin Cancer Res. 38(1):250.