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Kinase D-interacting Substrate of 220 kDa Is Overexpressed in Gastric Cancer and Associated With Local Invasion

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Abstract. *Background/Aim: Kinase D-interacting substrate of 220 kDa (Kidins220), also known as ankyrin repeat-rich membrane spanning protein (ARMS), is a transmembrane scaffold protein. Deregulated Kidins220 has been observed in various malignancies including melanoma, glioma, neuroblastoma, prostate cancer, pancreatic cancer, and ovarian cancer. Materials and Methods: In the current study, Kidins220 expression was determined at transcript and protein levels. A Kidins220 knockdown cell model was established to identify its role in cellular functions including cell cycle, proliferation, and invasion. Cell signalling was analysed by protein array and the TCGA gastric cancer cohort. Results: Kidins220 transcript levels were significantly increased in gastric tumours, compared with adjacent normal tissues. More advanced tumours (TNMIII and TNMIV) exhibited higher protein levels of Kidins220 compared with early-stage tumours (TNMI and TNMII). Increased expression of Kidins220 in gastric cancer was associated with poorer overall survival. Loss of Kidins220 promoted cell invasion and adhesion of gastric cancer and correlated to epithelial-mesenchymal transition (EMT) and matrix metalloproteinase (MMP) signalling. Knockdown of Kidins220 promoted proliferation of gastric cancer cells with an increased population at the G_2/M phase. Conclusion: Our study identified increased expression of Kidins220 in gastric cancer, which is associated with disease progression and poor prognosis. However, Kidins220 presented an inhibitory effect on the proliferation, invasion, and adhesion through a regulation of EMT, MMP and cell cycle.*

Approximately 989,000 people are diagnosed with gastric cancer (GC) globally, and about 738,000 patients die from this disease every year (1). It is hard to detect GC at an early stage, and most patients are diagnosed when the disease has progressed (2). Although great advances have been made in surgery, radiotherapy, and chemotherapy for the treatment of GC, the 5-year survival rate for patients with advanced GC is still less than 30% (3).

Kidins220/ARMS is a transmembrane scaffold protein with multiple binding domains (4). It was first identified as a substrate for protein kinase D (PKD) in neural cells and was mainly related to neurotrophin (5). It acts as a downstream regulator of several neuronal growth factors and regulates neuronal differentiation, survival, and cytoskeleton remodelling (6-8). The substantial involvement of Kidins220 has been previously shown in malignancies (9). In melanoma, Kidins220 inhibits the stress-induced apoptosis of melanoma cells through the MAPK signalling pathway

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(10). Moreover, Kidins220 plays a positive role in regulating the cell proliferation of neuroblastoma through a regulation of cyclin D1 and cyclin-dependent kinase 4 (CDK4) (11). As a direct target gene of miR-4638-5p, Kidins220 has been reported to be involved in regulating angiogenesis *via* the VEGF and PI3K/AKT pathways in prostate cancer (12). In pancreatic cancer, Kidins220 mediates the metastasis of pancreatic cancer through EGFR/Erk signalling (13). A recent study revealed that the XPR1-Kidins220 complex is vital for the cellular distribution and function of XPR1 and its regulated phosphate efflux. Impaired XPR1 function led to the accumulation of intracellular phosphate and reduced the viability of ovarian cancer cells (14).

To date, the role played by Kidins220 in gastric cancer remains unknown. We aimed to examine the involvement of Kidins220 in the disease progression of gastric cancer and explore how it affects cellular functions including cell proliferation and invasion of gastric cancer cells.

Materials and Methods

Cell lines and cell culture. HGC27 and AGS gastric cancer cell lines were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% foetal bovine serum. Materials and reagents were purchased from Sigma-Aldrich (Poole, Dorset, UK) unless otherwise stated.

Collection of clinical cohorts. Gastric tumours (n=324) together with paired adjacent (n=183) background tissues were collected immediately after the surgery and stored at –80˚C until use, with written consent from the patients at the Peking University Cancer Hospital. All protocols and procedures of the tissue collection were approved by Peking University Cancer Hospital Research Ethics Committee (MTA10062009).

IHC of gastric adenocarcinoma tissue microarray (TMA). Immunohistochemical staining was conducted on a gastric adenocarcinoma tissue microarray (TMA) (OD-CT-DgStm01-007, Biomax, Rockville, MN, USA). Proteins were probed with Kidins220 rabbit monoclonal antibody at 1:50 concentration (SC-48738, Santa Cruz Biotechnology, UK). The secondary antibody solution consisted of 100 µl biotinylated antibody stock at 5 ml dilution (Vectastain Universal Elite ABC Kit, PK-6200, Vector Laboratories, Peterborough, UK). The intensity of Kidins220 staining was calculated using the Image J software (Version 1.53, https://imagej.nih.gov, National Institutes of Health, MD, USA) by determining 10-20 cancerous cells by a subtraction of background of empty area for each sample from the duplicate cores.

RNA extraction, cDNA synthesis and RT-PCR. Total RNA was isolated using TRI Reagent (Sigma-Aldrich) from a 25 cm^2 flask. The cDNA was then synthesised from 500 ng of RNA using the GoScriptTM Reverse Transcription System kit (Promega, Corporation, Madison, WI, USA). PCR was performed with initial denaturation at 94˚C for 5 min, followed by 30-35 cycles of amplification at 95˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s, with a final extension step at 72˚C for 5 min. GAPDH was used as a housekeeping gene control.

Quantitative polymerase chain reaction (QPCR). Kidins220 and GAPDH in the gastric tissue samples were measured using the Ampliflour™ system (Intergen company, New York, NY, USA) with the following conditions: 94˚C for 10 min, 90 cycles of 94˚C for 10s, 55˚C for 35s, and 72˚C for 20s. Gene expression in the cell lines was determined using Sybr Green master mix (Sigma Aldrich). Primers of Kidins220 (forward: 5'-AGACGTTCCATGCTCAGA and reverse: 5'-ACTGAACCTGACCGTACATGCCTTCTTCGGTAAGTG) and GAPDH (forward: 5'-TGCACCACCAACTGCTTAGC-3' and reverse: 5'-GGCATGGACTGTGGTCATGAG-3') were used for qPCR.

Western blot. Proteins from gastric cancer cell lines were extracted using RIPA lysis buffer and then quantified using the Bio-Rad DC Protein Assay kit (Bio-Rad Laboratories, Hemel-Hempstead, UK). After separation of protein samples in the SDS-PAGE gel, proteins were transferred onto PVDF membranes and subsequently blocked with 10% milk for 1 hour at room temperature. The membrane was subsequently incubated with primary antibody and a corresponding peroxidise-conjugated secondary antibody. Antibodies against Kidins220 (sc-48738, 1:1,000) and GAPDH (sc-47724, 1:2,000) were purchased from Santa Cruz, and the protein bands were eventually visualised using a chemiluminescence detection kit (Supersignal™ West Dura kit, Pierce Biotechnology, Rockford, IL, USA).

Establishment of Kidins220 knockdown gastric cancer cell lines. Knockdown of Kidins220 was carried out in HGC27 and AGS gastric cancer cell lines. Anti-Kidins220 ribozyme was designed based on the secondary structure of Kidins220 mRNA. The ribozymes were synthesised using touch-down PCR and subsequently cloned into a pEF/V5 HIS TOPO TA plasmid vector (Invitrogen, Paisley, UK). The transfected cells were selected with 5 µg/ml blasticidin and maintained with 0.5 µg/ml blasticidin in DMEM culture medium. RT-PCR and western blot were used to verify the knockdown of Kidins220 (Kidins220KD) in comparison with the PEF controls which were transfected with empty plasmids.

Cell cycle assay. HGC27 gastric cancer cells were cultured in serum-free DMEM to synchronise the cell cycle for 36 hours. The cells were subsequently cultured in 10% FCS medium for 16 h. Propidium iodide (PI) was used to fix and stain the cells. DNA content was determined with FACS Canto TM II (BD UK Ltd, West Sussex, UK), and the cell cycle analysis was determined using FCS Express (v4.0, De Novo software, Los Angeles, CA, USA).

In vitro cell adhesion assay. The gastric cancer cells (20,000 cells/well) were seeded into a 96-well plate which was pre-coated with 5 µg of Matrigel (Corning Incorporated, Flintshire, UK). After an incubation of 40 min, adhered cells were then fixed with 4% formaldehyde and stained with 0.5% crystal violet. Absorbance of crystal violet was measured to quantify the adhered cells.

In vitro cell invasion assay. The 24-well transwell inserts with 8µm pores (Greiner Bio-One Ltd., Stonehouse, UK) were coated with 50 µg/well Matrigel. After air drying and rehydration, 20,000 cells were seeded. Cells that had invaded were fixed and stained after 72 h of culture. Absorbance of the crystal violet was then determined.

Statistical analysis. KM plotter analysis (http://kmplot.com/) was performed to evaluate the prognosis of gastric cancer patients, using a dataset of gene expression arrays of gastric cancer (15). In this study, *t*-test was employed for normally distributed data whilst non-normally distributed data were analysed using a Mann-Whitney *U*-test. $p<0.05$ was defined as statistically significant. Kaplan-Meier survival analysis was carried out using SPSS software (SPSS Standard version 13.0; SPSS Inc., Chicago, IL, USA).

Results

Overexpression of Kidins220 in gastric cancer and clinical relevance. The transcript level of Kidins220 in gastric cancer (n=324) and adjacent normal control (n=183) was determined using QPCR. The clinical and pathological information together with average Kidins220 transcript levels is shown in Table I. Kidins220 transcript levels were significantly increased in gastric tumour tissues compared to normal tissues ($p=0.015$, Figure 1A). Gastric tumours at advanced T stage (T3 and 4) presented a higher mRNA expression level of Kidins220 in comparison with early T stage (T1 & 3, $p=0.02$). More advanced tumours with lymph node metastases (TNMIII) exhibited higher transcript levels of Kidins220 compared with early-stage tumours (TNM I) ($p=0.038$). To examine the protein expression of Kidins220, immunohistochemical staining was performed on a gastric tumour tissue microarray, and representative figures are shown in Figure 1B. Gastric tumours of TNM III and IV exhibited stronger staining of Kidins220 protein in comparison with tumours at TNM I (Figure 1C). Furthermore, gastric tumour tissues at early stages (TNM I-II) presented weaker staining of Kidins220 compared with advanced stages (TNM III-IV, $p=0.001$).

The relevance of Kidins220 and the prognosis of gastric cancer patients. Kaplan-Meier survival analysis showed that gastric cancer patients with high expression of Kidins220 have a markedly shorter survival compared with patients with lower expression ($p<0.001$, Figure 2A). Patients with low expression of Kidins220 had a better progression-free survival ($p<0.001$, Figure 2B). By analyzing the recurrence of gastric cancer using public gene expression data (GSE26253), we found patients with high expression of Kidins220 had an increased recurrence possibility of gastric cancer ($p=0.0047$, Figure 2C). Furthermore, Kaplan-Meier analysis showed that high expression of Kidins220 in gastric tumours was associated with poorer overall survival in this cohort of gastric cancer patients (GSE26253) (Figure 2D).

Kidins220 is involved in regulating metastasis of gastric cancer cells. To investigate how Kidins220 affects cellular function of gastric cancer cells, a Kidins220 knockdown model was established using ribozyme in HGC27 and AGS gastric cancer cells. The knockdown of Kidins220 in both cell lines was then verified using RT-PCR and Western blot (Figure 3A), as well as qPCR (Figure 3B). Knockdown of Kidins220 increased cell adhesion in both HGC27 and AGC cancer cells (Figure 3C). Furthermore, an increased cell invasion was observed in HGC27 gastric cancer cells following the knockdown of Kidins220 ($p<0.001$). Knockdown of Kidins220 also promoted cell invasion in AGS gastric cancer cells ($p<0.001$, Figure 3D). Since the epithelial-mesenchymal transition (EMT) and matrix metalloproteinases (MMPs) are two major impactors in regulating the invasion of gastric cancer cells, our current study analyzed the correlation between Kidins220 and EMT-related molecules (snail, slug, twist, and vimentin) and MMPs using the TCGA database. The result showed that Kidins220 had a significantly positive correlation with slug (Figure 3E). Further, Kidins220 expression had a significantly negative correlation with MMP1, MMP3, MMP11, MMP12, and MMP15, and a positive regulation with MMP16, MMP19, and MMP21 (Figure 3F).

Kdins220 may regulate cell proliferation and cell cycle through cell cycle regulators. The cell cycle of the HGC27 gastric cancer cells was analyzed by flow cytometry. There was no significant change in the cell population at G_0/G_1 and S phase following the knockdown of Kidins220. However, there was a higher percentage of Kidins220-knockdown cells entering the G_2/M phase compared with the PEF control ($p<0.01$) (Figure 4A). Knockdown of Kidins220 also

Table I. *Kidins220 transcripts in gastric cancer.*

Category		No.	Mean (SEM)	*p*-Value
Tumor	Tumor	322	826412 (328468)	
	Normal	183	21842 (17364)	0.015
Sex	Male	229	1131295 (4604030)	
	Female	93	75679 (35369)	0.023
Invasion	Inv-WL	232	1081126 (4542962)	
	InvSubSe	37	277222 (1562622)	0.095
	InvMusc	30	32838 (162766)	0.022
	InvMucs	11	115871 (772817)	0.037
	Gastric	255	871501 (3985336)	
	Cardiac	52	765335 (565202)	0.88
	intersti	5	63627 (632645)	0.046
T stage	T1	16	79417 (54148)	
	T2	25	39406 (19322)	0.5
	T3	41	978768 (780698)	0.26
	T4	232	962057 (434486)	0.045
	T1+T2	41	55020 (239837)	
	T3+T4	273	964567 (386918)	0.02
TNM stage	I	25	62839 (35367)	
	II	59	626778 (539949)	0.3
	III	220	1023299 (458260)	0.038
	IV	9	204346 (132323)	0.33

SEM: Standard error of the mean.

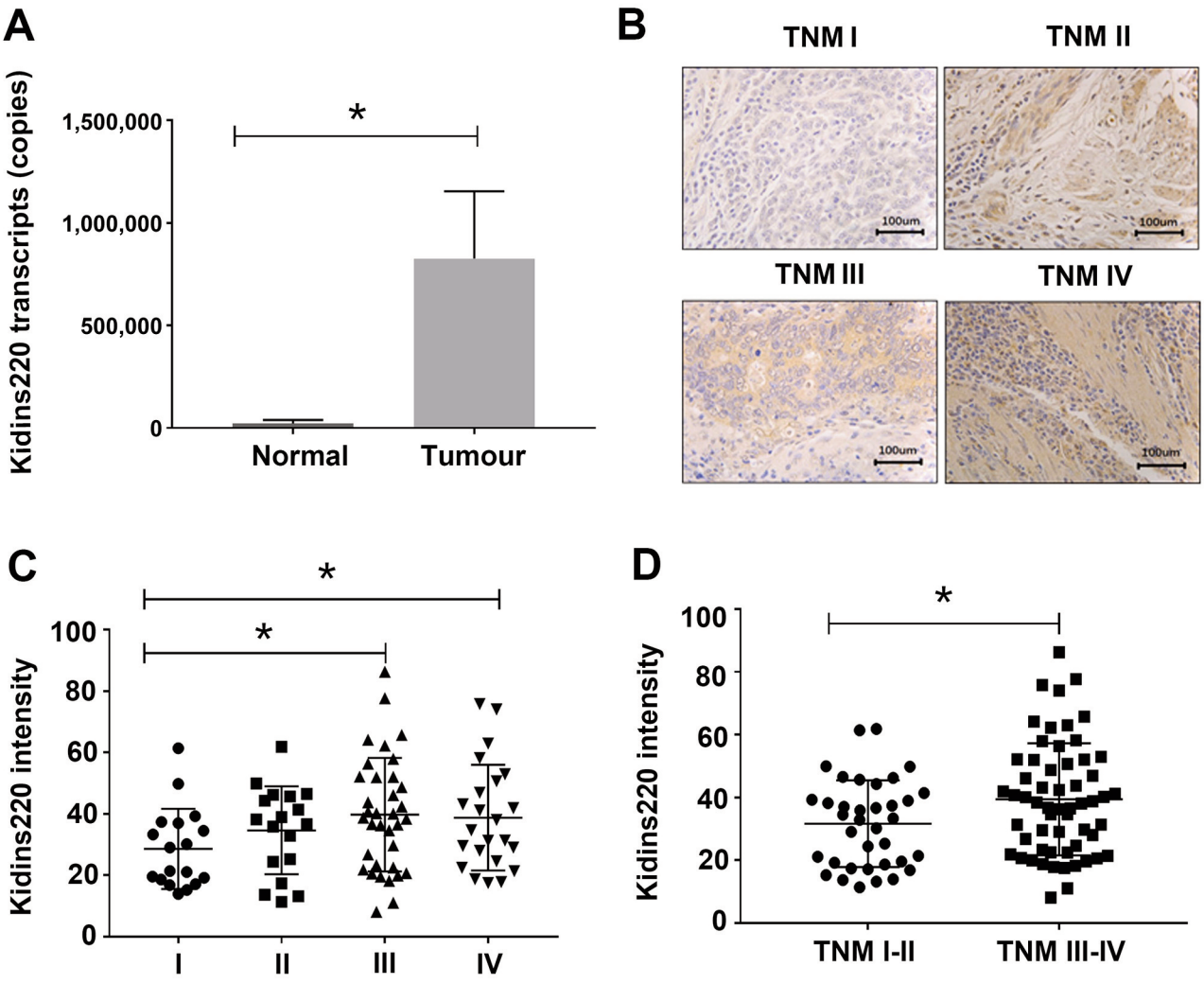

Figure 1. *Overexpression of Kidins220 is associated with disease progression in gastric cancer. (A) The gastric clinical cancer cohort showed that Kidins220 transcripts were increased in gastric tumor tissues compared with the adjacent normal tissues. Average transcript levels of Kidins220 per 50 ng RNA are shown. Error bars represent standard error of mean (SEM). (B) Representative images of immunohistochemical staining of the gastric tumor tissue microarray from different TNM stages are shown. The expression of Kidins220 protein was assessed in a gastric tissue microarray (OD-CT-DgStm01-007) with IHC staining (gastric tumor tissues from different TNM stages) for a comparison across TNM stages (C) and TNM I-II vs. TNM III-IV (D) using ANOVA and Mann-Whitney U-test, respectively. *p<0.05.*

promoted the cell proliferation in HGC27 gastric cancer cells in comparison with PEF control on day 3 ($p<0.001$) and day 5 ($p<0.001$). The effects of Kidins220 in regulating cell cycle and cell growth prompted us to further explore its correlation with cell cycle regulators. Pearson's correlation analysis showed that Kidins220 had a significantly negative correlation with CyclinB1 by using TCGA gene expression array data (Figure 4C). The correlation of Kidins220 with cell cycle regulators is presented in the heatmap in Figure 4D. Figure 4E presents the correlation between Kidins220 and certain cyclin dependent kinases (CDKs) which regulate cell cycle.

Discussion

Kidins220 has been identified in several malignancies to act as a tumor suppressor or tumor promoter (10, 13, 16, 17). Kidin220 expression significantly promoted primary malignant melanomas and metastatic melanoma in comparison with benign nevocellular lesions (10). Likewise, the expression of Kidins220 was drastically increased in the primary melanomas of depths greater than 1.0 mm and the primary melanomas which had lymph node involvement and distant metastases (16). Increased expression of Kidins220

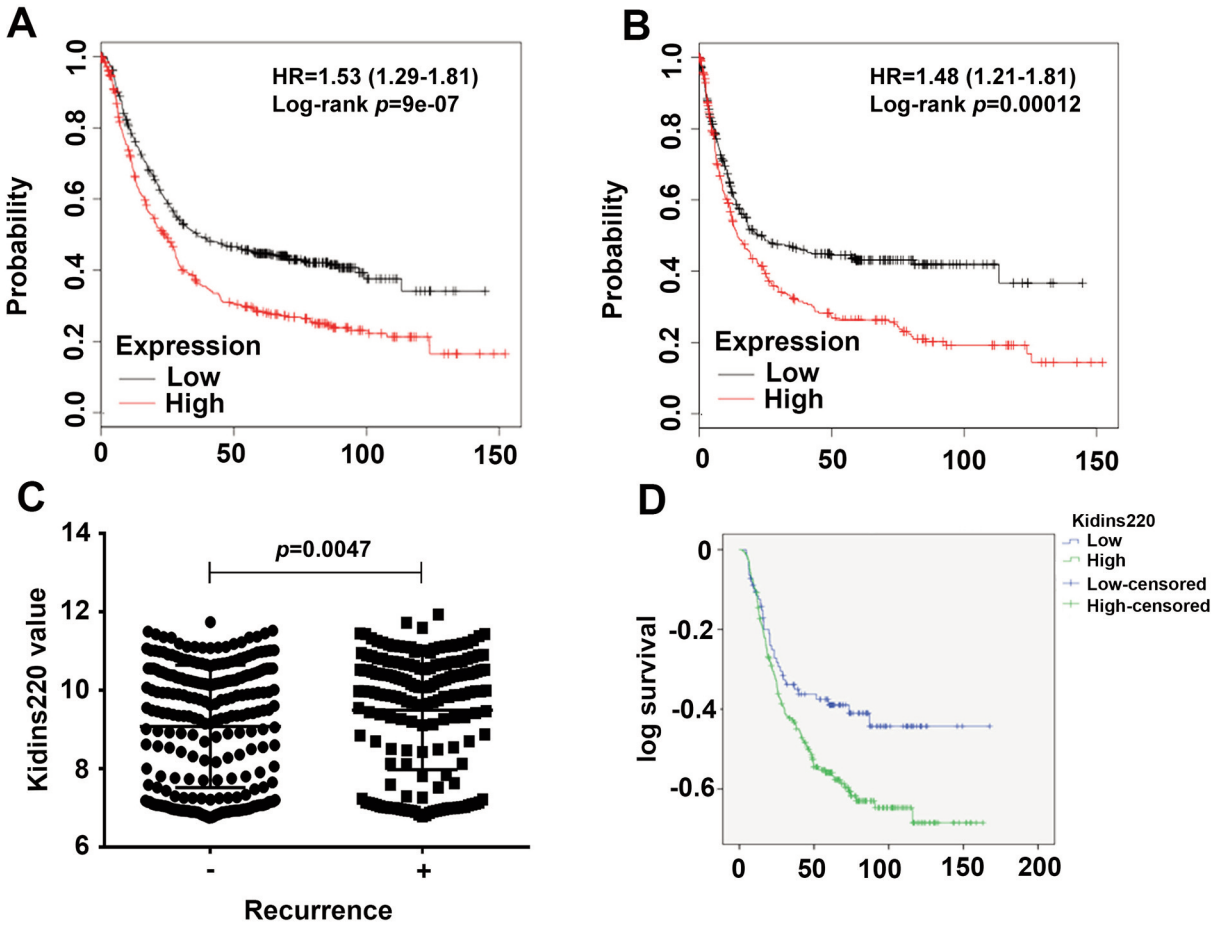

Figure 2. *Kidins220 and prognosis of gastric cancer. (A) Correlation between Kidins220 mRNA expression and overall survival of patients with gastric cancer using Kaplan-Meier survival analysis. (B) Correlation between Kidins220 mRNA expression and free progression of patients with gastric cancer using Kaplan-Meier survival analysis. (C) Kidins220 expression and recurrence of gastric cancer (GSE26253). (D) Recurrence free survival of gastric cancer, kidins220 high=green, low=blue, cutoff value=8.1 (GSE26253).*

was found in melanoma and was associated with shorter overall survival (16). Overexpression of Kidins220 was also detected in neuroblastoma tissue samples (17). A reverse expression of Kidins220 was detected in pancreatic cancer, whereas Kidins220 transcript was significantly reduced in pancreatic tumors in comparison with adjacent normal tissues, and malignant tumors exhibited weaker staining of Kidins220 in comparison with adjacent normal pancreatic tissues and normal pancreas (13). Here we report that Kidins220 transcripts are highly expressed in gastric tumor tissues in comparison with normal controls, and overexpression of Kidins220 is associated with poor prognosis of the disease.

In pancreatic cancer, more advanced pancreatic tumors (TNM III and TNM IV) had lower Kidins220 transcripts compared with those of early stages (TNM I and TNM II), while knockdown of Kidins220 promoted the invasion and migration of pancreatic cancer cells (13). In melanoma, Kidins220 promoted tumor migration/invasion through MEK/ERK signaling (16), however, loss of Kidins220 did not affect migration of neuroblastoma cells (17). Our current study found that the expression Kidins220 was increased in advanced tumor stages both at the mRNA and protein level, which provides evidence for personal management when evaluating its value for those patients with different cancer types. Knockdown of Kidins220 promoted cell invasion and focal adhesion in both HGC27 and AGS gastric cancer cells.

As a scaffold protein, Kidins220 acts as a binding domain for protein-protein interactions. It recruits receptor substrates to activate the downstream signaling pathways and attributes them to cellular activities of neural cells (18). Considering its multiple binding domains in regulating cell signaling, we speculated that Kidins220 did not regulate the cell invasion of

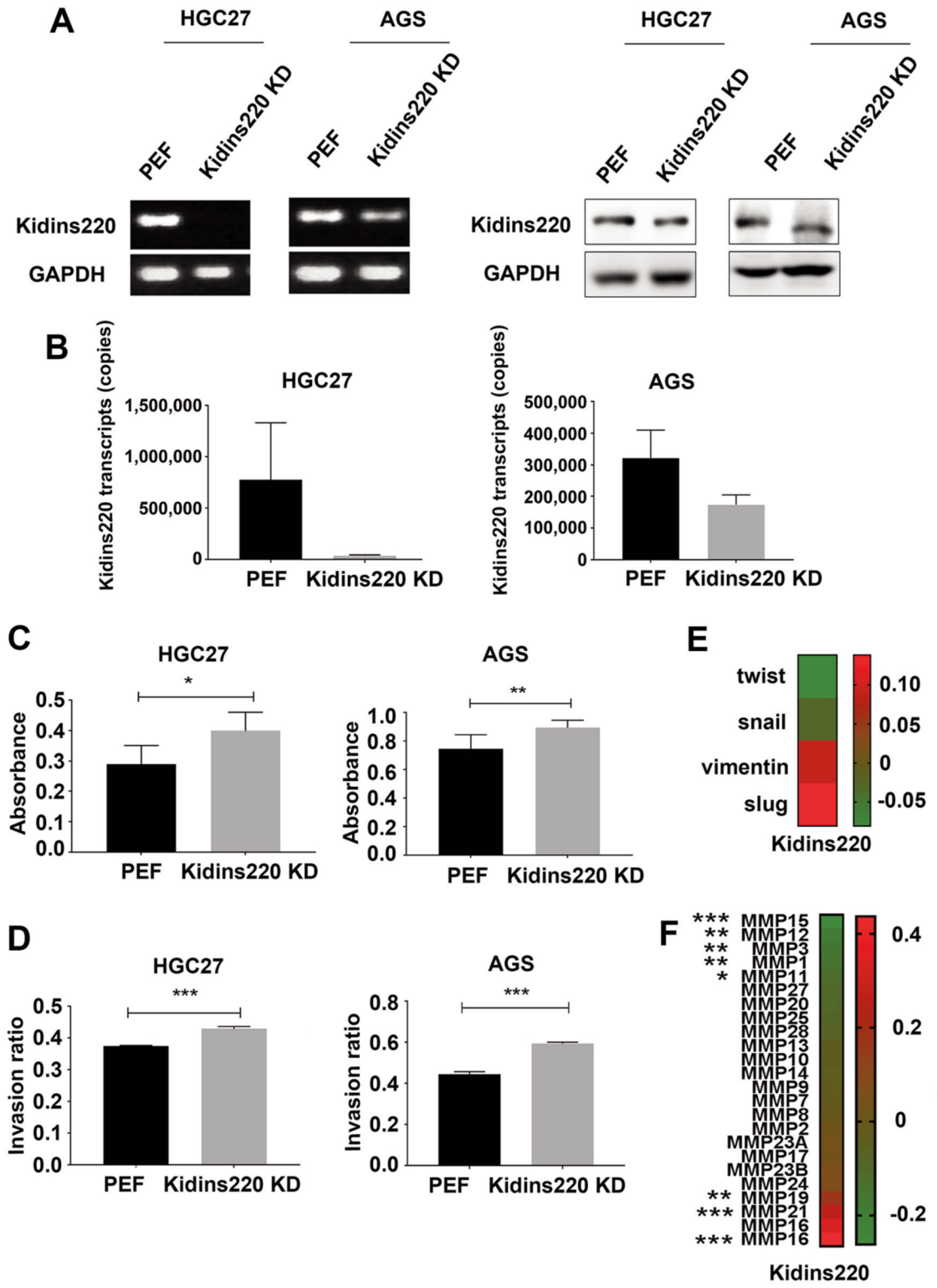

Figure 3. *Implication of Kidins220 in the metastasis of gastric cancer. (A) Knockdown of Kidins220 in HGC27 and AGS gastric cancer cells infected with Kidins220 ribozyme was verified at both mRNA and protein levels. (B) Verification of Kidins220 knockdown at transcription level using qPCR. (C) The impact of Kidins220 on cellular focal adhesion in vitro for HGC27 and AGS gastric cancer cell lines. (D) The influence of Kidins220 on cell invasion of HGC27 and AGS cell lines. (E) Kidins220 correlated with epithelial-mesenchymal transition (EMT) markers in gastric cancer. (F) The correlation of Kidins220 and matrix metalloproteinases (MMPs) in gastric cancer. *p<0.05, **p<0.01 and ***p<0.001.*

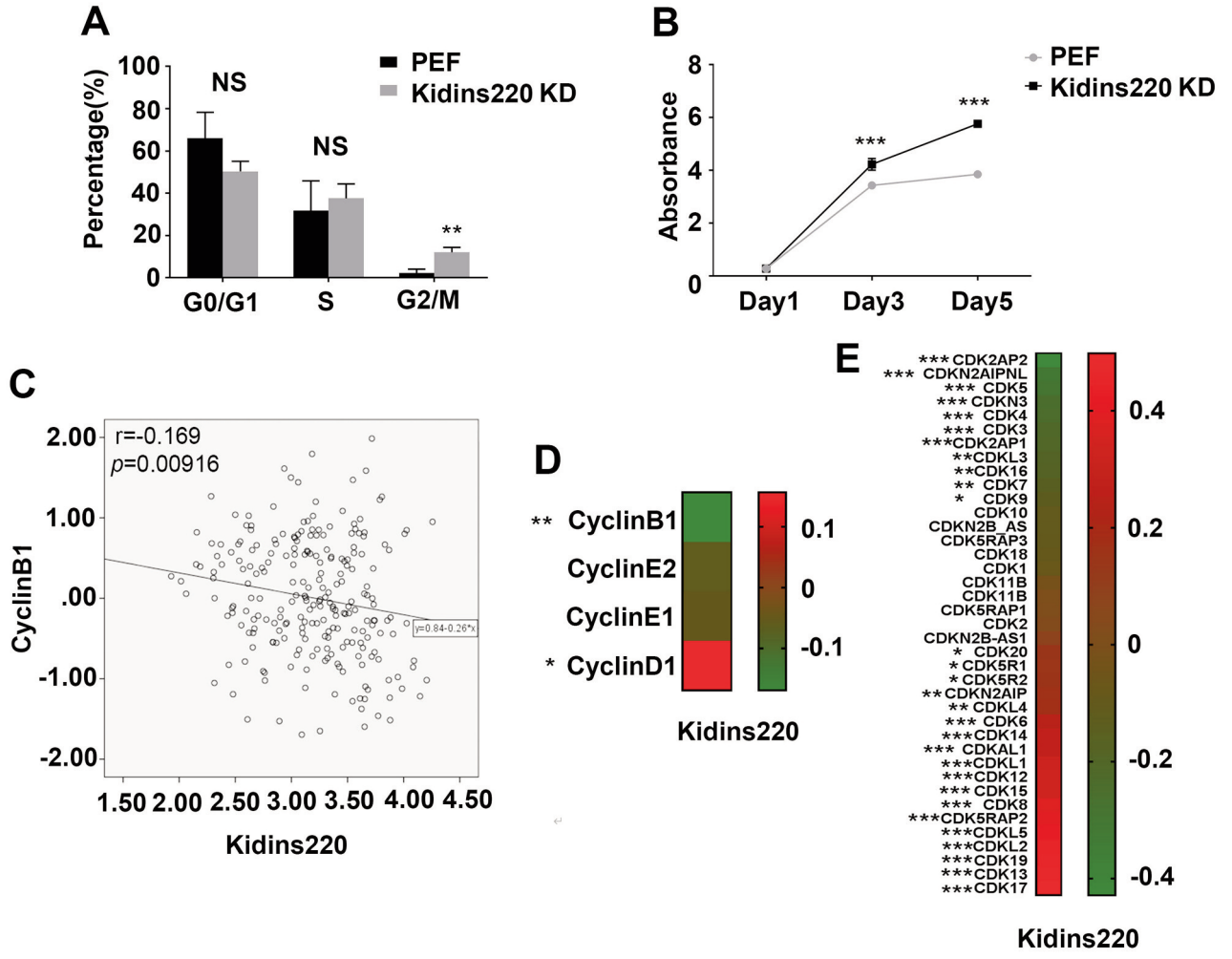

Figure 4. *Implication of Kidins220 in the proliferation of gastric cancer. (A) Impact of Kidins220 in the cell cycle of HGC27 gastric cancer cells. (B) Knockdown of Kidins220 promoted cell growth in HGC27 cells. (C) Kidins220 has a negative correlation with cyclin B1 in gastric cancer. (D) The correlation of Kidins220 and cell cycle regulators in gastric cancer. (E) The correlation of Kidins220 and cyclin dependent kinases (CDKs) is shown in the heatmap. Pearson correlation was used for the correlation analyses. *p<0.05, **p<0.01 and ***p<0.001.*

gastric cancer independently. Future studies may focus on exploring the multiple signaling pathways regulated by Kidins220 in cell invasion of gastric cancer. A previous study has indicated the role of Kidins220 in regulating the disease progression of pancreatic cancer with the involvement of EMT and MMPs, two important factors in the cell migration and invasion of cancer metastasis (13). During tumor progression, the majority of tumors undergo EMT to acquire infiltrating and metastasizing properties (19). In gastric cancer aggressiveness, the tumor epithelial cells lose cell polarity and cell-cell adhesion to have mesenchymal phenotype and acquire properties of cell invasion and migration (20). By analyzing the TCGA gastric cancer cohort, we found that Kidins220 has a positive correlation with slug and vimentin and a negative correlation with snail and twist. MMPs are known for their role in mediating the tumor microenvironment during tumor progression (21). MMPs enable the degradation of the barriers including extracellular matrix and basement membrane, facilitating the metastasis of tumor cells (22). An analysis was performed for the expression profile of MMPs in gastric cancer using TCGA data and the result showed that Kidins220 has a significantly positive correlation with MMP19, MMP16, and MMP21 and a significantly negative correlation with MMP1, MMP3, MMP11, MMP12, and MMP15. It is speculated that Kidins220 regulates gastric cancer cell invasion with the involvement of EMT and MMPs. However, the specific mechanism targeting cell invasion needs to be verified in future studies.

CyclinB1 is a critical regulator of G_2/M transition during the cell cycle. CyclinB1 accumulates progressively through the G_1/S phase and reaches the peak in G_2; subsequently it forms a complex with CDK1 (23). In neuroblastoma, knockdown of Kidins220 inhibits the growth of mouse neuroblastoma cells by slowing down the G_1 phase, which is regulated by the upregulation of the CDK inhibitor p21, and leads to a decrease in the protein levels of cyclin D1 and CDK4 (11). Here, we found knockdown of Kidins220 allowed more cells to enter the G_2/M phase in gastric cancer. Yasuda *et al*. have shown that CyclinB1 is overexpressed in gastric cancer patients and is associated with less aggressive tumor behavior (24). Our current study found that Kidins220 had a significantly negative correlation with CyclinB1. We also found that Kidins220 has a significant correlation with most cell cycle-promoting molecules by using TCGA data, providing evidence of the correlation between Kidins220 and the cell cycle.

Conclusion

In summary, Kidins220 was overexpressed in gastric cancer tissues, and the increased expression of Kidins220 was associated with disease progression and overall survival. Furthermore, knockdown of Kidins220 promoted invasion, focal adhesion, and proliferation of gastric cancer cells, leading to a higher percentage of Kidins220-knockdown cells entering the G_2/M phase. Our current study highlights possible mechanisms of gastric cancer progression affected by Kidins220, a potential therapeutic target for the treatment of gastric cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

LY and WGJ designed the study. SC, ZS, XG, KJ, FR, DS, XL, WGJ and LY performed the experiments. SC, ZS, DS, XL, WGJ and LY contributed to data analysis. SC, ZS, WGJ and LY prepared the manuscript. SC, ZS, CH, NF, KF, FR, WGJ and LY revised and proofread the article.

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