Original Article

# UBE2C promotes the progression of pancreatic cancer and glycolytic activity via EGFR stabilization-mediated PI3K-Akt pathway activation

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**Background:** Pancreatic cancer (PC) is among the most prevalent and deadliest endocrine tumors, yet the mechanisms governing its pathogenesis remain to be fully clarified. While ubiquitin-conjugating enzyme E2C (UBE2C) has been identified as an important oncogene in several cancers, its importance in PC has yet to be established.

**Methods:** UBE2C expression in PC tumor samples and cell lines was examined via quantitative real-time polymerase chain reaction (qRT-PCR), while appropriate commercial kits were used to assess lactate production, ATP generation, and the uptake of glucose.

**Results:** UBE2C was found to be upregulated in PC patient tumors and correlated with poorer survival outcomes. In PC cell lines, the silencing of this gene suppressed the malignant activity of cells, thus supporting its identification as an oncogene in this cancer type. Mechanistically, UBE2C was found to promote enhanced matrix metalloproteinase (MMP) protein expression via activating the PI3K-Akt pathway. Moreover, it was found to bind to the epidermal growth factor receptor (EGFR), stabilizing it and driving additional PI3K-Akt pathway activation. UBE2C knockdown in PC cells impaired their uptake of glucose and their ability to produce lactate and ATP.

**Conclusions:** In conclusion, the results of this study support a role for UBE2C as a driver of metastatic PC progression owing to its ability to bind to EGFR and to induce signaling via the PI3K-Akt pathway.

**Keywords:** Epidermal growth factor receptor (EGFR); pancreatic cancer (PC); metastasis; PI3K-Akt; ubiquitin-conjugating enzyme E2C (UBE2C)

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## Introduction

Despite significant advances in the understanding and treatment of many cancers, pancreatic cancer (PC) remains one of the deadliest and most difficult forms of cancer to manage. Approximately 20% of newly diagnosed PC cases worldwide arise in China (1,2). The primary approaches to treating PC include surgical resection and chemotherapy (3), but the emergence of chemoresistance represents a major barrier to effective patient treatment. At present, the 5-year survival rate of PC patients remains under 5%, and this rate has not significantly increased in several decades (4,5). It is thus vital that the mechanisms governing the pathogenesis of PC be better clarified in order to guide the identification of novel therapeutic targets.

The ubiquitinase ubiquitin-conjugating enzyme E2C (UBE2C) is capable of catalyzing the 26S proteasome-mediated degradation of proteins into smaller peptides and amino acid subunits (6,7). UBE2C has been shown to regulate key oncogenic pathways including transcription, apoptosis, and cell cycle progression (8,9). The upregulation of UBE2C has been reported in patients with PC and is linked to poorer overall survival (OS) and progression-free survival (PFS) in these individuals (9). Moreover, UBE2C overexpression can promote colony formation, tumor cell growth, and malignant transformation *in vitro* and *in vivo* (10). Analyses of PC tissues included in the Gene Expression Profiling Interactive Analysis (GEPIA) database further revealed an increase in UBE2C mRNA levels in patients with PC. Despite its clear role as an oncogene in this cancer type, the molecular mechanisms through which UBE2C exerts its pro-tumorigenic effects in PC remain to be established.

In this study, the overexpression of UBE2C in PC patient tumors was confirmed, as was the association between the upregulation of this ubiquitinase and poorer patient survival outcomes. Subsequent loss-of-function assays revealed that UBE2C can act as an oncogene to promote the metastatic progression of PC in part via binding directly to the epidermal growth factor receptor (EGFR), thereby activating signaling pathways conducive to tumor growth. Thus, the activation of UBE2C might provide a novel way of curing PC. We present the following article in accordance with the MDAR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-516/rc).

**Table 1** qPCR primer sequences

| Primer | Sequence (5' to 3') |
|---|---|
| UBE2C forward primer | CAGATCCCTCTTCACCTACGA |
| UBE2C reverse primer | TCAACGTTTAAAGGGGGACA |
| Actin forward primer | TGTGGGCATCAATGGATTTGG |
| Actin reverse primer | ACACCATGTATTCCGGGTCAAT |

UBE2C, ubiquitin-conjugating enzyme E2C; qPCR, quantitative real-time polymerase chain reaction.

## Methods

### *Patient sample collection*

For the present study, tumor tissues and matched healthy tissue samples were obtained from 16 PC patients at Changhai Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study obtained the approval of the Ethics Committee of Changhai Hospital (Shanghai, China) (No. CHEC-Y2020-043) and written informed consent was obtained from all participants.

### *Quantitative real-time polymerase chain reaction (qPCR)*

RNA was extracted from cells and tissue samples using the Trizol reagent, and a Nanodrop instrument was used to quantify RNA concentrations. Subsequently, cDNA was prepared and used to conduct qPCR analyses as detailed previously (11). Primers used for this study are compiled in *Table 1*.

### *Cell culture and treatment*

The human PANC1 and Mia-capa2 PC cell lines and the control HPDE6-C7 cell line were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) at 37 ℃ in a 5% $CO_2$ incubator. Cellular lentiviral infection and analysis of PI3K activity were conducted as in prior report (12).

### *Migration and invasion assays*

Cellular migration and invasion were analyzed as reported previously (12). Data are averages from 3 independent experiments.

 

**Table 2** Primary antibodies used for Western blotting and immunoprecipitation

| Antibody | Supplier |
|---|---|
| UBE2C | ab12290, Abcam, 1:1,000 |
| Actin | ab181602, Abcam, 1:1,000 |
| Vimentin | ab193555, Abcam, 1:1,000 |
| E-cadherin | ab194982, Abcam, 1:1,000 |
| N-cadherin | ab202030, Abcam, 1:1,000 |
| PTEN | ab32119, Abcam, 1:1,000 |
| Phosphorylated Akt (p-Akt) | ab38449, Abcam, 1:1,000 |
| Akt | Ab8805, Abcam, 1:1,000 |
| MMP-2 | ab97779, Abcam, 1:1,000 |
| MMP-7 | ab5706, Abcam, 1:1,000 |
| MMP-9 | ab38898, Abcam, 1:1,000 |
| HA-probe | sc-2362, Santa Cruz Biotechnology, 1:800 |
| FLAG-probe | F1804, Sigma-Aldrich, 1:2,000 |
| EGFR | ab52894, Abcam, 1:1,000 |
| FLAG M2-affinity gel | A2220, Sigma-Aldrich, 20 ml per reaction |

UBE2C, ubiquitin-conjugating enzyme E2C; MMP, matrix metalloproteinase; EGFR, epidermal growth factor receptor.

### *Cell proliferation*

The cells were pre seeded in 96 well plates, each well containing about $2\times10^3$ cells. Appropriate microRNA fragments were transferred to HepG2 Huh7 cells for 24 h, and then 10 μL cell counting kit-8 (CCK-8) solution (dojindo molecular technology, Kyushu, Japan) was added to each cell and incubated at 37 ℃ for 4 h. The absorbance is monitored by the calibrator (Bio-Rad Laboratory, Hercules, CA, USA) at 450 nm. Data was collected for 3 replicates.

### *Co-immunoprecipitation (co-IP)*

Co-IP was conducted as in prior study (13), using the antibodies compiled in *Table 2*. Simply put, paraffin sections were placed at 60 ℃ for 2 hours, and then washed with xylene solution (Sigma, St Louis, MO, USA), ethanol (Sigma, St Louis, MO, USA) and TBS (sigma, St Louis, Mo, USA). After extracting antigen with citric acid buffer solution (Sigma, St Louis, MO, USA), endogenous peroxidase (Sigma, St Louis, MO, USA) was blocked with 1% hydrogen peroxide. Tissues were incubated with primary antibody at 4 ℃ overnight. The sections were then incubated with HRP labeled Goat anti mouse/rabbit immunoglobulin G (1:200, cell signaling technology, Massachusetts, USA). The slices were visualized with diaminobenzidine (Sigma, St Louis, MO, USA). Then the slices were counterstained with hematoxylin (Sigma, St Louis, MO, USA), and washed with xylene solution and ethanol. Finally, the section was sealed with neutral Balm (Sigma, St Louis, MO, USA). Immunohistochemical staining results were analyzed by optical microscope (Olympus, Tokyo, Japan).

### *Glucose uptake and ATP generation analyses*

Glucose uptake and ATP generation were assessed using commercial kits based on provided directions. Glucose uptake, lactate production, and ATP production were measured, and cells were inoculated in 96-well plates and deprived of glucose supply by culture with 100 μL Krebs-Ringer phosphate HEPES buffer containing 2% BSA (bovine serum albumin) for 40 min. The cells were then incubated with 10 μL 2-DG (10 mM) for 20 min. Cells were collected and analyzed according to the instructions of the Glucose uptake colorimetric Analysis Kit (BioVision, Milpitas, CA, USA). Additional $5\times10^5$ cells were collected and homogenized in 50 μL lysis buffer as per manufacturer's instructions. The mixture was centrifugated and the supernatant was determined using lactic acid assay Kit II and ATP colorimetric assay kit (BioVision, Milpitas, CA, USA).

### *Statistical analysis*

Data were analyzed using SPSS 19.0. Data are reported as means ± SE, with $P<0.05$ as the threshold of significance. All the data in this study are presented as mean ± standard deviation (SD).

## Results

### *PC patients exhibit UBE2C upregulation, correlating with poor survival outcomes*

Initial analyses of the GEPIA database revealed that PC patient tumor tissues exhibited increased UBE2C expression relative to normal tissue samples (FC >1.5, $P<0.05$, *Figure 1A*). This was further confirmed through a qPCR analysis of 16 separate human PC tumor and adjacent normal tissue (ANT)

 

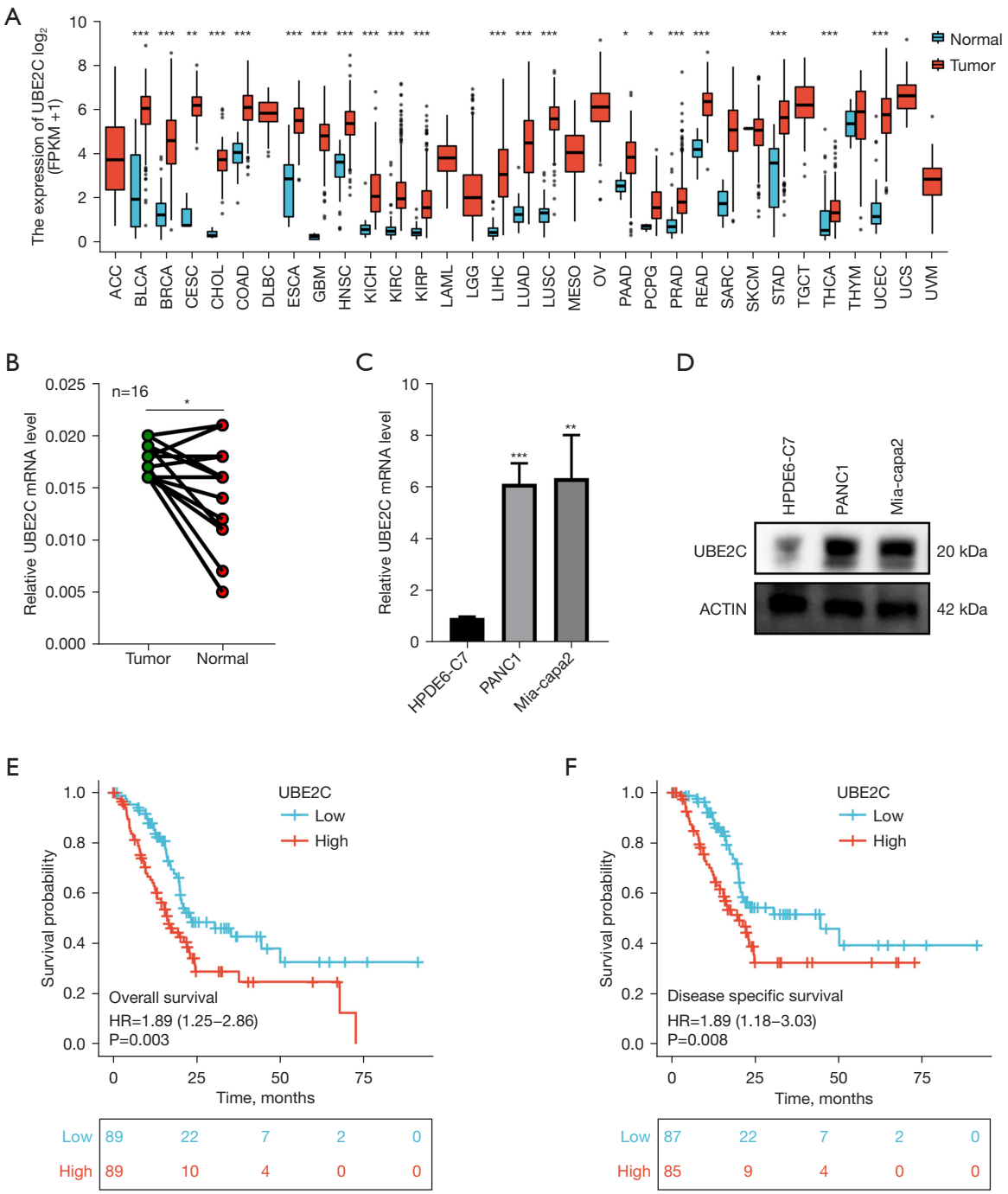


**Figure 1** UBE2C upregulation in PC correlates with poor survival outcomes. (A) Data from the GEPIA database revealed increased UBE2C expression in PC tissues relative to normal tissues (fold-change >1.5, P<0.05). (B) UBE2C mRNA levels were analyzed in 16 pairs of PC tumors and adjacent normal tissues via qPCR. Data were analyzed via Student's *t*-tests. UBE2C mRNA (C) and protein (D) levels were analyzed in PANC1, Mia-capa2, and HPDE6-C7 cells. (E,F) OS and DSS in PC patients with high UBE2C expression in the GEPIA database were analyzed. *, P<0.05; **, P<0.01; ***, P<0.001. GEPIA, Gene Expression Profiling Interactive Analysis; PC, pancreatic cancer; OS, overall survival; DSS, disease-specific survival; qPCR, quantitative real-time polymerase chain reaction.

 

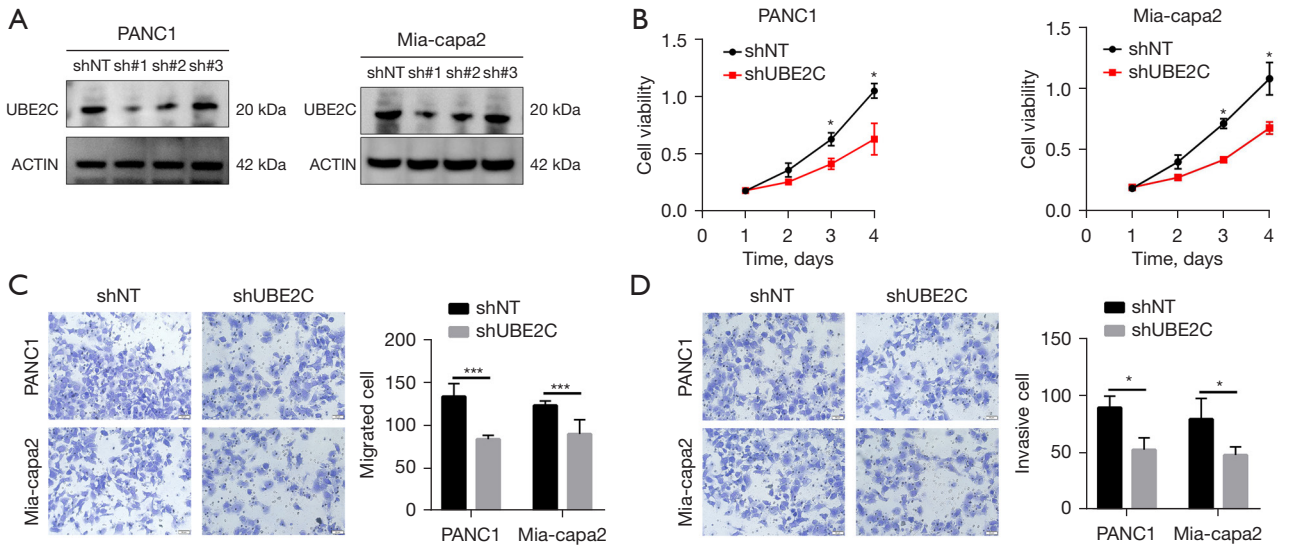


**Figure 2** UBE2C promotes metastatic activity in PC cells. (A) UBE2C knockdown (KD, shUBE2C) was successfully performed in the indicated cells. The impact of UBE2C knockdown on proliferation (B) was assessed. PC cell migration (C) and invasion (D) by 0.1% crystal violet staining after 24 hours (magnified ×200) were analyzed. Data in (B-D) were compared via Student's *t*-tests. *, P<0.05; ***, P<0.001. UBE2C, ubiquitin-conjugating enzyme E2C; PC, pancreatic cancer.

samples, with significantly increased UBE2C mRNA levels in tumors (*Figure 1B*). Consistently, UBE2C mRNA levels were significantly upregulated in PC cell lines relative to the control HPDE6-C7 cell line (*Figure 1C,1D*). Moreover, GEPIA database analyses revealed that elevated levels of UBE2C were associated with poorer patient OS and disease-specific survival (DSS) (*Figure 1E,1F*).

### *UBE2C promotes PC progression*

Given that the above data suggested a potential role for UBE2C as a regulator of PC onset or metastatic progression, loss-of-function experiments were then conducted *in vitro* by using shRNAs specific for UBE2C to knockdown its expression in both PANC1 and Mia-capa2 cells (*Figure 2A*). UBE2C knockdown significantly suppressed the both of these cell lines (*Figure 2B*). These PC cells also exhibited reduced metastatic phenotypes relative to shNT control cells (*Figure 2C,2D*). Together, these results suggest a role for UBE2C as a mediator of PC cell malignancy and oncogenic progression.

### *UBE2C regulates MMP-2/7/9 expression via the activation of the PI3K-Akt pathway*

To analyze the regulatory role of UBE2C in the context of PC progression, the relationship between this ubiquitinase and the key metastatic epithelial-mesenchymal transition (EMT) process was next analyzed. However, UBE2C was found to have no impact on Vimentin, E-cadherin, or N-cadherin expression (*Figure 3A*), indicating that UBE2C-mediated EMT induction was unlikely to be involved in the metastatic progression of PC. Another key step in solid tumor progression entails the enhanced expression of matrix metalloproteinases (MMPs), which can degrade the extracellular matrix and thereby enable tumor cells to spread more easily through their proteolytic activity. In PC cells expressing elevated levels of UBE2C, increased MMP-2/7/9 expression was observed, whereas UBE2C knockdown decreased the levels of these 3 MMPs (*Figure 3B*). In addition, reductions in the levels of phosphorylated Akt (p-Akt) were observed in PC cells following UBE2C knockdown (*Figure 3C*), and Western blotting revealed that Akt signaling in these cells was dependent on PI3K rather than on PTEN (*Figure 3D,3E*). These data suggest that UBE2C can influence PC progression through the upregulation of MMP-2/7/9 in a manner mediated by PI3K-Akt signaling.

### *UBE2C stabilizes EGFR protein expression*

Next, the role of UBE2C in response to EGF (Epidermal

 

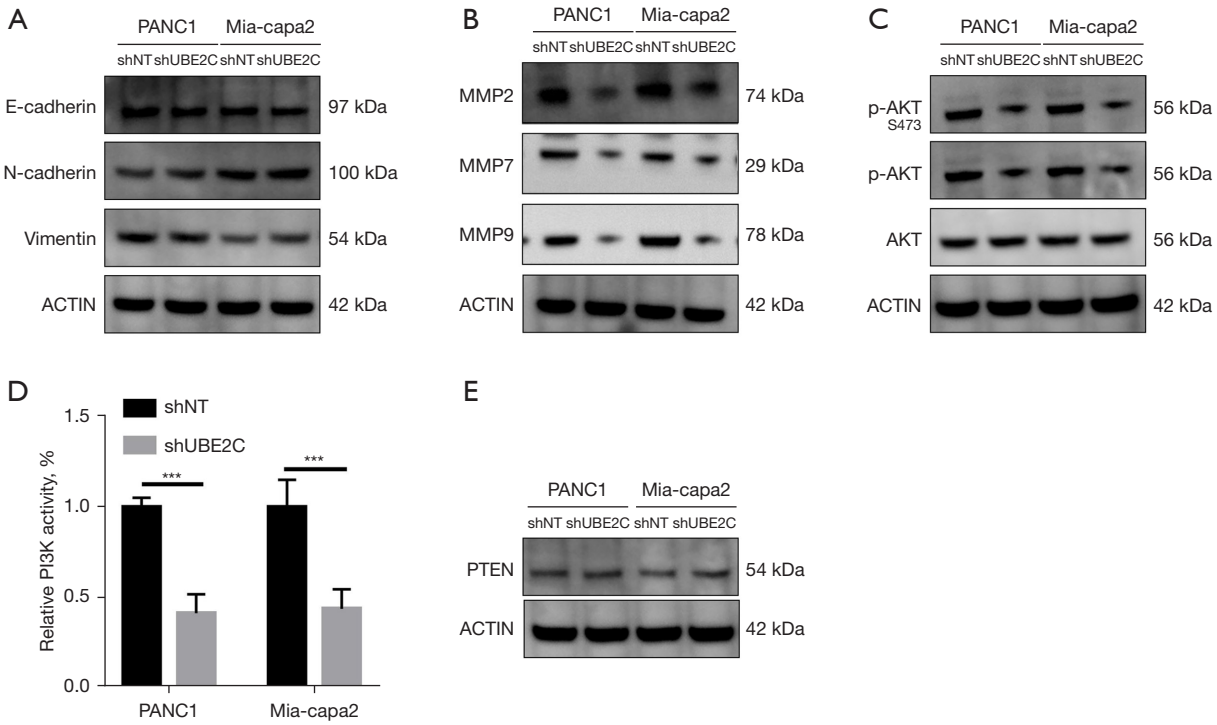


**Figure 3** UBE2C controls the expression of MMP-2/7/9 via the activation of the PI3K-Akt pathway. (A) EMT marker expression; (B) MMP-2, MMP-7, and MMP-9 expression was measured, with GAPDH as a loading control; (C) Western blotting was used to detect Akt and p-Akt expression, with GAPDH as a loading control; (D) the kinase activity of PI3K was analyzed in the indicated cell lines; (E) PTEN expression was assessed via Western blotting. ***, P<0.001. UBE2C, ubiquitin-conjugating enzyme E2C; MMP, matrix metalloproteinase; EMT, epithelial-mesenchymal transition.

Growth Factor) and HGF (Hepatocyte Growth Factor) expression was analyzed. UBE2C knockdown strongly inhibited the EGF-mediated activation of Akt relative to that observed in shNT-transfected cells, whereas no comparable change was observed in response to HGF stimulation (*Figure 4A*,*4B*). In light of these results, the ability of UBE2C to interact with EGFR was next examined. FLAG-UBE2C and HA-EGFR or HA-vector control constructs were co-expressed in PC cells, after which co-IP and Western blotting analyses were used to confirm the ability of UBE2C to directly interact with EGFR (*Figure 4C*). To assess the ability of UBE2C to influence the stability of the EGFR protein, de novo protein synthesis was inhibited by treating cells with cycloheximide (CHX). In this assay, the silencing of UBE2C resulted in a reduction in the stability of EGFR within CHX-treated PC cells (*Figure 4D*). Moreover, treatment with the proteasome inhibitor MG132 reversed this UBE2C silencing-dependent reduction in EGFR stability, indicating that UBE2C is capable of protecting EGFR against proteasomal degradation in these cancer cells (*Figure 4E*). Overall, these results suggest that UBE2C can promote PC cell proliferation at least in part by binding to EGFR and improving its stabilization.

### *UBE2C regulated PC cell glycolytic activity*

Given that EGFR serves as an important regulator of glycolysis and other metabolic pathways, a final set of experiments was conducted to assess glycolytic activity in PC cells. UBE2C knockdown suppressed both glucose uptake and ATP production in tested PC cell lines (*Figure 5A*,*5B*), as did EGFR knockdown (*Figure 5C*,*5D*). As such, UBE2C is likely to function as a regulator of PC cell glycolytic activity.

## Discussion

In order to identify effective approaches to treat PC, it is critical that the development and progression of this cancer type be fully understood (14-17). In this study, the role of

 

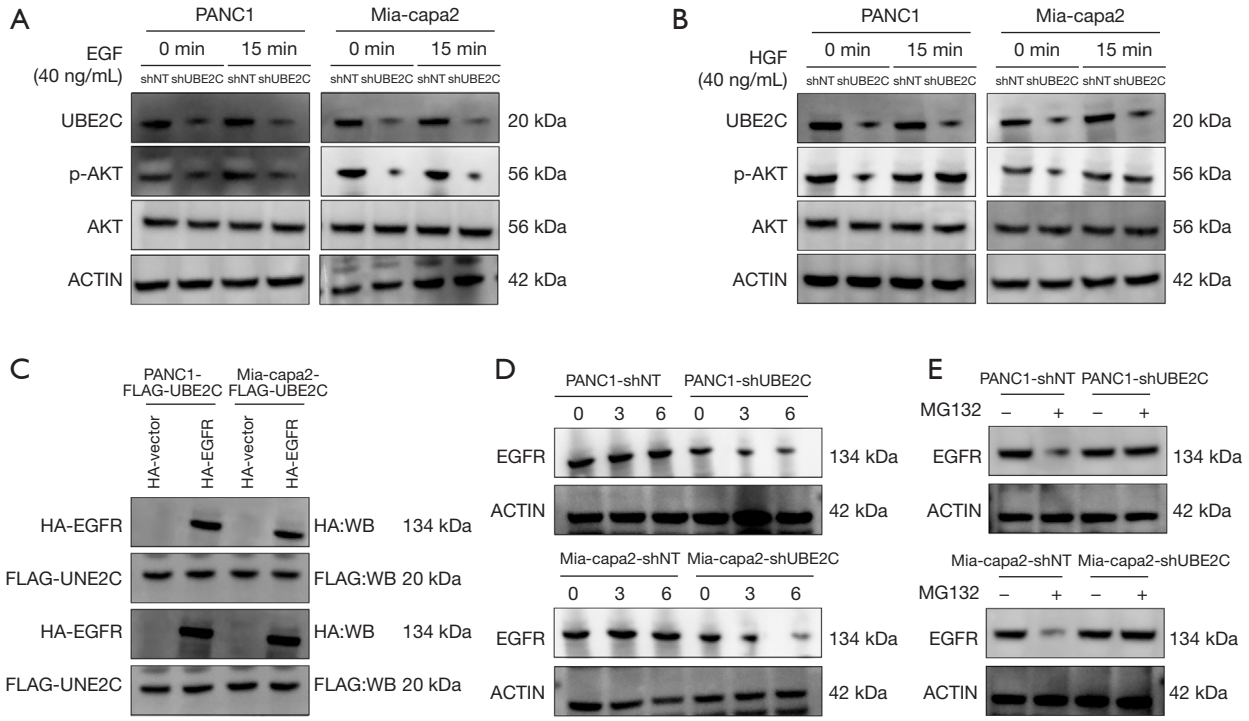


**Figure 4** UBE2C enhanced EGFR protein stability. Following stimulation for 0, or 15 min with EGF (A) or HGF (B), the expression of the indicated proteins was assessed in PANC1 and Mia-capa2 cells, with GAPDH as a loading control. (C) Anti-FLAG was used for co-immunoprecipitation analyses of PC cells following FLAG-UBE2C and HA-EGFR or empty vector control co-transfection as indicated. (D) The knockdown of UBE2C was associated with reductions in the stability of EGFR in cells that had been treated with CHX for 0, 3 or 6 hours. (E) The MG132 proteasome inhibitor was sufficient to ablate changes in EGFR degradation observed following the knockdown of UBE2C. –, absence; +, present. UBE2C, ubiquitin-conjugating enzyme E2C; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; PC, pancreatic cancer; CHX, cycloheximide.

UBE2C as a regulator of PC progression was analyzed. These analyses revealed that UBE2C promotes the PI3K-Akt-dependent upregulation of MMP-2/7/9 and stabilizes EGFR via a direct binding interaction in a manner conducive to PC cell survival and proliferation. As such, targeting UBE2C may represent a viable approach to inhibiting PC progression.

To fully clarify the regulatory roles played by UBE2C in human PC progression, analyses of the online GEPIA database were conducted, revealing increased UBE2C expression in clinical patient PC samples that was further confirmed in a separate set of samples and in PC cell lines. Moreover, UBE2C expression levels were correlated with post-treatment PC patient OS and DSS. The *in vitro* knockdown of UBE2C was sufficient to impair PC cell viability and invasiveness, suggesting that this ubiquitinase may be associated with the acquisition of pre-metastatic or metastatic phenotypes in PC. Monitoring UBE2C expression may thus represent an effective means of predicting PC patient prognosis and the risk of disease progression or recurrence.

The PI3K-AKT signaling is now identified as a potential target for treating metastatic tumors. AKT, as a key component in PI3K-AKT signaling, mediates PC progression (18-20). The relationship between UBE2C and EMT induction, which is also integral to metastatic tumor progression (18-24), was further analyzed, although no relationship between the two was identified. Further analyses revealed a strong association between Akt activation and the expression of UBE2C. Following the knockdown of UBE2C, reduced MMP expression was observed, whereas this was rescued by the exogenous overexpression of Akt, highlighting a direct link between UBE2C and the PI3K-Akt-mediated upregulation of MMP expression. Moreover, selective targeting of UBE2C within the EGFR/PI3K-Akt signaling pathway was sufficient to

 

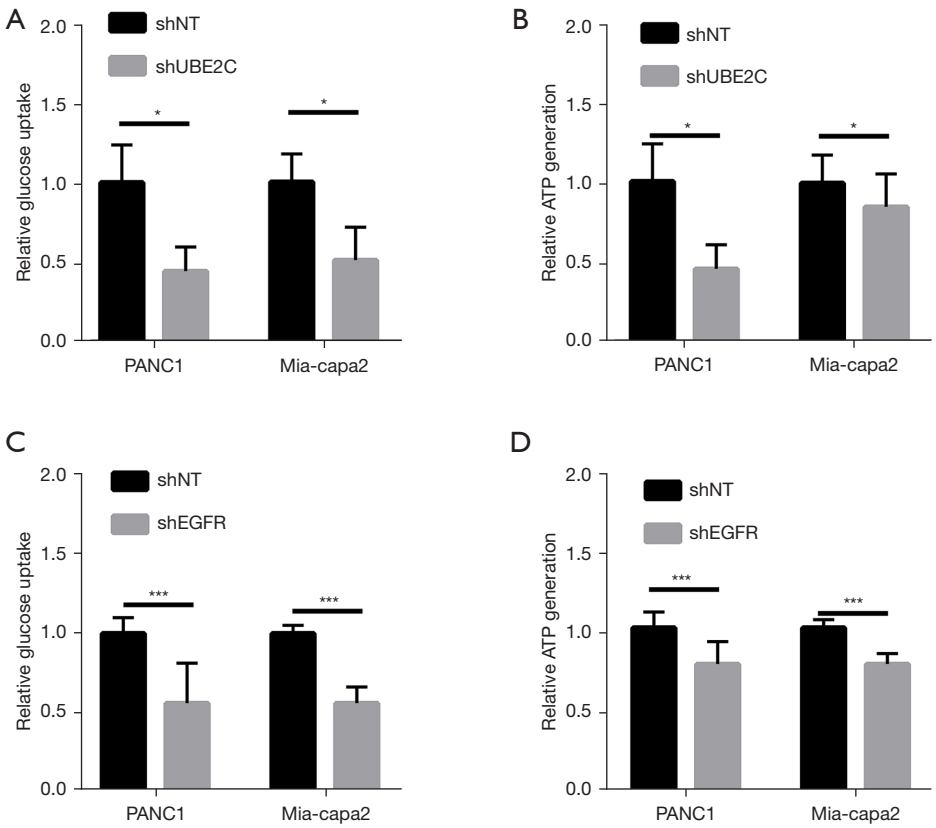


**Figure 5** UBE2C influences the glycolytic activity of PC cells. (A,B) Glucose uptake, lactate production, and ATP generation were analyzed in PC cells following shNT or shUBE2C treatment. (C,D) Glucose uptake rates, lactate production, and ATP generation were assessed in PC cells following shNT or shEGFR treatment. *, P<0.05; ***, P<0.001. UBE2C, ubiquitin-conjugating enzyme E2C; PC, pancreatic cancer.

modulate EGF-dependent signaling without impacting EGF signaling. Co-IP revealed an interaction between UBE2C and EGFR that led to the stabilization of EGFR, shielding it from proteasome-mediated degradation. As such, UBE2C is capable of promoting PC progression in part via influencing EGFR stability. Such stabilization may be mediated by either UBE2C-mediated changes in the degradation of EGFR via the lysosomal ubiquitination pathway or the UBE2C-induced dimerization of EGFR, thereby enhancing its stability. Our future research will thus focus on characterizing the mechanistic basis for such UBE2C-mediated EGFR stabilization in the context of PC progression in a comprehensive fashion.

Metabolic activity is central to the development and progression of cancer, contributing to the formation of an appropriate metabolic microenvironment (25). Metabolic recombination is critical to the maintenance of cellular viability and to the induction of differentiation, migration, and cell division. Even under oxygen-rich conditions, tumor cells increasingly rely on the process of oxidative glycolysis to promote glucose conversion into lactic acid via the Warburg effect, leading to the rapid production of large quantities of ATP conducive to amino acid, nucleic acid, and lipid synthesis in rapidly proliferating cells. Lactic acid production maintains the acidity of the tumor microenvironment, contributing to invasiveness, migration, and immune response induction. In this study, the relationship between UBE2C and EGFR was analyzed in PC, highlighting UBE2C inhibition as a promising approach to PC treatment.

In summary, the results of this study provide novel evidence that UBE2C-mediated EGFR stabilization can promote the metastatic progression of PC via the PI3K-Akt pathway, thus offering new insights into the mechanistic basis for tumor progression and underscoring new strategies for treating this deadly disease. This study still has its

 

limitations, and we need to expand the sample size in future studies to determine whether UBE2C is an independent factor affecting the prognosis of pancreatic cancer, and UBE2C combined with glycoly-related genes to construct a prognostic model to evaluate the prognosis of pancreatic cancer patients.

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## Footnote

*Reporting Checklist:* The authors have completed the MDAR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-516/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-516/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-516/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study obtained the approval of the Ethics Committee of Changhai Hospital (Shanghai, China) (No. CHEC-Y2020-043) and written informed consent was obtained from all participants.



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