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Mechanism of PTPN18 for regulating the migration and invasion of endometrial cancer cells via the MYC/PI3K/AKT pathway

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Summary. Objective. Endometrial cancer (EC) is a prevalent gynecologic malignancy. The critical role of PTPN18 in EC has been reported, while its role in the aerobic glycolysis of EC cells remains unclear. Our current study focused on the mechanism of PTPN18 in the regulation of aerobic glycolysis in EC.

Methods. PTPN18 expression levels in endometrial stromal cells (KC02-44D) and EC cells (KLE, HEC-1-A, HEC-1B, and HEC-50) were determined. Following transfection of sh-PTPN18 in HEC-1-A cells, the changes in cell migratory and invasive abilities were assessed by the Transwell assay, and the changes in glucose consumption, lactic acid secretion, and ATP levels were detected using kits. The expression levels of glycolysis-related proteins HIF-1α, PKM2, and LDHA and the activation of the MYC/PI3K/AKT pathway were detected by Western blot. Additionally, sh-PTPN18 and pcDNA3.1-MYC were transfected into HEC-1-A cells to further explore their roles in the changes in aerobic glycolysis, migration, and invasion ability of EC cells.

Results. Expression of PTPN18 in EC cells was up-regulated (HEC-1-A>HEC-1B>HEC-50>KLE). PTPN18 knockdown suppressed EC cell migration and invasion. Additionally, PTPN18 knockdown reduced glucose consumption, lactate production, ATP levels, and glycolysis-related protein levels (HIF-1α, PKM2, LDHA). PTPN18 knockdown inhibited the activation of the MYC/PI3K/AKT pathway in EC cells. MYC overexpression partially annulled the inhibitory effects of PTPN18 knockdown on aerobic glycolysis, migration, and invasion of EC cells.

Conclusion. Our present study provided evidence that the knockdown of PTPN18 inhibited the aerobic glycolysis, migration, and invasion of EC cells by suppressing the MYC/PI3K/AKT pathway.

Key words: Endometrial cancer, PTPN18, MYC, PI3K/AKT, Aerobic glycolysis, Migration

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Introduction

As a gynecologic malignancy occurring on the inner epithelial lining of the uterus, endometrial cancer (EC) is historically categorized into type I (endometrioid) and type II (nonendometrioid) considering the different molecular phenotypes and histological subtypes (Chang et al., 2019; Makker et al., 2021). It represents one of the major causes of cancer-related incidence rates and mortality in women (Onstad et al., 2016). In China, the incidence rate of EC has been rising in recent years (Ye et al., 2016). The statistics have marked an overall 5-year survival rate ranging between 74% and 91% in those patients without metastasis following appropriate therapies (Morice et al., 2016). However, patients suffering from type II and advanced EC at stage III/IV have been reported to show poor response to currently available treatments, including chemotherapy, radiation, and total hysterectomy with bilateral salpingo-oophorectomy (Braun et al., 2016; Cai et al., 2021; Crosbie et al., 2022). As a result, further investigation into the underlying mechanism of metastasis is critical to identifying efficient treatment regimens against EC and improving the prognosis of patients.

Malignant cells can be distinguished from normal cells by aerobic glycolysis, which is also known as the Warburg effect, referring to the enhanced production of glycolysis and lactate even in the presence of sufficient oxygen (Hay, 2016). Meanwhile, aerobic glycolysis has has demonstrated potential benefits for tumor cell proliferation, invasion, and metastasis by generating lactate (Park et al., 2020). Emerging evidence suggests that the proliferation and invasion of malignant cells are orchestrated by dysregulated aerobic glycolysis in EC

(Han et al., 2015a, 2019; Li et al., 2023). Therefore, repression of aerobic glycolysis holds promise in suppressing cancer progression (Ganapathy-Kanniappan, 2018). Protein tyrosine phosphatase (PTP) non-receptor type 18 (PTPN18), located in Chromosome 2q21.1 as a member of the PTP family, is aberrantly expressed in EC cells, while the deregulation of PTPN18 triggers ferroptosis in EC (Wang et al., 2021). More importantly, PTPN18 silencing facilitates apoptosis of EC cells, acting as a disincentive to proliferation and metastasis (Cai et al., 2019). Additionally, there is proof that PTPN18 accelerates colorectal cancer progression via the c-MYC-CDK4 axis (Li et al., 2021). It is noteworthy that c-myc has been signaled to play a part in mediating EC cellular functions from the perspective of aerobic glycolysis (Zhou et al., 2021). Moreover, the expression and stabilization of MYC have been elucidated to be regulated by the PI3K/AKT signal transduction pathway as its target metabolic enzyme to stimulate glutamine metabolism (Jensen et al., 2011; Park et al., 2020). A hypothesis was therefore proposed that PTPN18 might produce a moderator effect in EC by mediating aerobic glycolysis through the MYC/PI3K/AKT pathway, yet currently available evidence is absent. Given the challenging management against EC, it is believed that an in-depth investigation of the metabolic reprogramming of aerobic glycolysis mediated by PTPN18 may lead to a deeper understanding of the biological complexity of EC. Herein, the present study is expected to serve the purpose of providing a reference for potential therapeutic alternatives against EC.

Materials and methods

Cell culture

Human endometrial stromal cell line, KC02-44D, immortalized with human telomerase reverse transcriptase (hTERT), and EC cells KLE, HEC-1-A, HEC-1B, and HEC-50 were all acquired from the American Type Culture Collection (Manassas, VA, USA). All selected cells were cultured in Dulbecco's modified Eagle's medium (less sugar, 1 g/L), comprising 1% penicillin/streptomycin and 10% fetal bovine serum (FBS) (all from Thermo Fisher Scientific, Waltham, MA, USA) with 5% CO_2 at 37°C.

Cell transfection

HEC-1-A cells in the logarithmic growth phase were collected and spread in 6-well plates (1.0×10^5 cells per well) until they reached 70-80% confluence. PTPN18 shRNA or its negative control (shRNA NC) and pcDNA3.1-MYC or its negative control (pcDNA3.1-NC) were introduced into HEC-1-A at a concentration of 50 nM using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) as per the manufacturer's instructions. After 48h, cells were collected for follow-up experiments. The transfectants were synthesized and purified by GenePharma (Shanghai, China).

HEC-1-A cells were divided into: 1) the Blank group (without any treatment); 2) the sh-NC group (transfected with shRNA NC); 3) the sh-PTPN18 group (manipulated with PTPN18 shRNA); 4) the sh-PTPN18 + oe-NC group (simultaneously transfected with pcDNA3.1-NC and PTPN18 shRNA); 5) the sh-PTPN18 + oe-MYC group (simultaneously manipulated with pcDNA3.1-MYC and PTPN18 shRNA).

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

RNA was extracted from cells using TRIzol reagent (azyme, Nanjing, Jiangsu, China). The concentration and purity of the obtained RNAs were determined with the help of a NanoDrop 2000 (Thermo Fisher Scientific). Thereafter, complementary DNA was synthesized with the FastQuant RT Kit (with gDNase, Tiangen, Beijing, China). RT-qPCR was then performed on the ABI7500 system (Applied Biosystems, Foster City, CA, USA) using SYBR Premix Ex Taq II (Takara, Tokyo, Japan). The reaction conditions were pre-denaturation at 95°C for 10 min, 40 cycles of denaturation at 95°C for 10 s, annealing at 60°C for 20 s, and extension at 72°C for 34 s. The data were analyzed by $2^{-\Delta\Delta Ct}$ with GAPDH as the internal parameter (Schmittgen et al., 2008). The primers were synthesized by Sangon Bioengineering (Shanghai, China). The sequences are shown in Table 1.

Western blot

Total protein extraction from the cells was carried out using radio-immunoprecipitation assay lysate containing protease inhibitors (Beyotime Biotechnology, Shanghai, China), with its concentration measured using the bicinchoninic acid protein quantification kit (Beyotime Biotechnology). In short, equivalent proteins were subjected to electrophoresis in sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred onto the polyvinylidene fluoride membranes. After that, the membranes were blocked with 5% skim milk in Tris buffered saline-Tween 20 (50 mM Tris-HCl,

Table 1. Primer sequences.

Gene	Forward 5'-3'	Reverse 5'-3'
PTPN18	TTAATGGCAACTTCATCCG	TCACCTTGACCCCAAACTC
GAPDH	CAATGACCCCTTCATTGACC	TGGACTCCACGACGTACTCA

pH 7.6, 150 mM NaCl, 0.1% Tween 20) at room temperature for 1h, and then subjected to incubation with the primary antibodies rabbit polyclonal to PTPN18 (1:1000, ab230300, Abcam, Cambridge, UK), rabbit monoclonal to HIF-1α (1:1000, ab179483, Abcam), rabbit monoclonal to PKM2 (1:1000, ab85555, Abcam), rabbit monoclonal to LDHA (1:1000, ab52488, Abcam), rabbit monoclonal to MYC (1:2000, ab185656, Abcam), rabbit monoclonal to PI3K (1:1000, ab191606, Abcam), rabbit polyclonal to PI3K p607 (1:500, ab182651, Abcam), rabbit polyclonal to AKT (1:500, ab8805, Abcam), rabbit polyclonal to AKT p308 (1:500, ab38449, Abcam) overnight at 4°C, with rabbit polyclonal to β-actin (1:1000, ab8227, Abcam) as the internal reference. The secondary antibody IgG H&L (HRP) (1:5000, ab6721) was then incubated for 1h at room temperature. Afterward, the protein bands were visualized with the help of an Amersham ECL detection kit. Protein quantification was implemented by applying Image J software (RRID: SCR_003070).

Transwell assay

The invasive and migratory capacities of EC cells were assessed using Transwell chambers (Corning, Corning, NY, USA) pre-coated with and without Matrigel (Becton Dickinson, San Jose, CA, USA). In brief, 100 μL of EC cells after treatment was seeded into the chambers on the 24-well plates (2.5×10^5 cells per well), also 600 μL of complete medium was added to the basolateral chambers. After 18h, the cells that did not invade and migrate into the lower surface of chambers were wiped off using a cotton swab, whereas those that invaded and migrated were fixed with methanol for 5 min and stained with Giemsa for 10 min. Ultimately, the stained cell numbers in the four randomly selected fields were counted under a light microscope (Leica, Wetzlar, Germany).

Glucose consumption

According to the manufacturer's instructions, glucose consumption was measured using the Glucose Uptake Colorimetric Assay Kit (K676; BioVision, Mountain View, CA, USA). After cell transfection, cells were cultured for 48h at 37°C, harvested, and seeded into the 96-well plates (1×10^4 cells/well). Subsequently, cells were glucose-starved through 40-min pre-incubation with 100 μL Krebs-Ringer-Phosphate-HEPES buffer (starves cells of glucose) and incubated for 20 min with 10 μL 2-deoxyglucose (10 mM) and with Reaction Mix A (NADPH generation) at 37°C for 1h. Afterward, cells were incubated with extraction buffer (90 μL/well) for 40 min at 90°C, followed by an ice bath for 5 min. After that, Reaction Mix B (recycling amplification reaction) was added to the cells in each well and centrifuged at 4°C and 16000 × g for 2 min. The optical value of the supernatant was assessed at 412 nm using a microplate analyzer (Varioskan LUX, Thermo Fisher Scientific).

Lactate production determination

Cells (2×10^5) were seeded into the 6-well plates and kept for 48h at 37°C for the measurement of cellular lactate production using the Lactate Colorimetric Assay Kit (K627, BioVision), followed by incubation in the FBS-free cell culture medium at 37°C for 1h with the supernatant harvested for lactate production determination. The reaction mixture was subjected to incubation at room temperature for 30 min in the dark, and the optical value of the supernatant was assessed at 450 nm employing a microplate reader (Varioskan LUX, Thermo Fisher Scientific).

Adenosine triphosphate (ATP) levels

ATP levels were evaluated using the ATP Colorimetric Assay Kit (MAK1900; Sigma-Aldrich; Merck KGaA) as per the provided instructions. In brief, cells (5×10^5) were added to 100 μL ATP Assay Buffer, centrifuged at room temperature for 5 min at 16000×g, and the optical value of the supernatant was assessed at 570 nm using a microplate reader (Varioskan LUX, Thermo Fisher Scientific).

Statistical analysis

Data were analyzed and mapped using SPSS 21.0 (IBM Corp. Armonk, NY, USA) and GraphPad Prism 8.01 (GraphPad Software Inc., San Diego, CA, USA) statistical software. The data were verified by Kolmogorov-Smirnov to confirm normal distribution and expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) analysis was employed for data comparisons among multiple groups, followed by Tukey's test. $P<0.05$ was considered statistically significant.

Results

PTPN18 was prominently overexpressed in EC cells

To investigate the role of PTPN18 in EC, we first examined the expression of PTPN18 in EC cell lines. As reflected by RT-qPCR, compared with endometrial stromal cell line KC02-44D, the expression of PTPN18 in EC cells was clearly up-regulated (HEC-1-A >HEC-1B >HEC-50 >KLE) (all $P<0.05$, Fig. 1A), which was consistent with the results of the Western blot assay (all $P<0.05$, Fig. 1B).

PTPN18 knockdown suppressed EC cell migration and invasion

The HEC-1-A cell line with the highest relative expression of PTPN18 was chosen to further explore the effects of PTPN18 on EC cell migration and invasion.

sh-PTPN18 was introduced into HEC-1-A cells. The results of the Western blot showed that, relative to the sh-NC group, PTPN18 expression in the sh-PTPN18 group was markedly diminished (P<0.01, Fig. 2A), indicating a successful transfection. Subsequently, the Transwell assay elicited that the migration and invasion abilities of cells in the sh-PTPN18 group were significantly blocked in contrast to those in the sh-NC group (P<0.05, Fig. 2B,C). These results indicate that PTPN18 knockdown can curb EC cell migration and invasion.

PTPN18 knockdown repressed aerobic glycolysis of EC cells

Next, the changes in glucose consumption, lactate production, and ATP levels in EC cells after PTPN18 knockout were analyzed, and the results revealed that all levels were substantially reduced in the sh-PTPN18 group *versus* the sh-NC group (all P<0.01, Fig. 3A-C). Subsequently, Western blot analysis uncovered that, in contrast to the sh-NC group, the expression levels of glycolysis-related proteins HIF-1α, PKM2, and LDHA in the sh-PTPN18 group were conspicuously declined (all P<0.01, Fig. 3D). These results suggest that the knockdown of PTPN18 suppresses aerobic glycolysis in EC cells.

PTPN18 knockdown blocked the activation of the MYC/PI3K/AKT pathway

Subsequently, we further explored whether PTPN18 was involved in the regulation of aerobic glycolysis in EC cells by regulating the MYC/PI3K/AKT pathway. Western blot results demonstrated that relative to KC02-44D cells, the expression of MYC (all P<0.01, Fig. 4A) and the levels of p-PI3K/PI3K and p-AKT/AKT (all P<0.01, Fig. 4B) in HEC-1-A cells were saliently elevated, while these trends were averted after PTPN18 knockdown (all P<0.01, Fig. 4A,B), indicating that PTPN18 knockdown inactivated the MYC/PI3K/AKT pathway in EC cells.

Overexpression of MYC partially annulled the inhibitory effects of PTPN18 knockdown on the aerobic glycolysis, migration, and invasion of EC cells

Furthermore, HEC-1-A cells were simultaneously transfected with sh-PTPN18 and pcDNA3.1-MYC to verify whether PTPN18 could participate in the modulation of EC cell aerobic glycolysis through the MYC/PI3K/AKT pathway. Western blot results indicated that the expression of MYC was remarkably increased in the sh-PTPN18 + oe-MYC group *versus* the sh-PTPN18 + oe-NC group (P<0.01, Fig. 5A), suggesting a successful cell co-transfection. The levels of p-PI3K/PI3K and p-AKT/AKT in the sh-PTPN18 + oe-MYC group were also elevated relative to the sh-PTPN18 + oe-NC group (all P<0.05, Fig. 5B). Further examination of aerobic glycolysis disclosed that, after overexpression of MYC, PTPN18 knockdown-mediated inhibitory effects on glucose consumption, lactate production, ATP, and glycolysis-related protein expression levels were partially abrogated (all P<0.05, Fig. 5C-F). The Transwell assay results elicited that the invasion and migration abilities of cells in the sh-PTPN18 + oe-MYC group were evidently promoted in contrast to the sh-PTPN18 + oe-NC group (all P<0.05, Fig. 5G,H). Based on these above findings, MYC overexpression can partially weaken the inhibitory effects mediated by PTPN18 silencing on EC cell aerobic glycolysis, migration, and invasion.

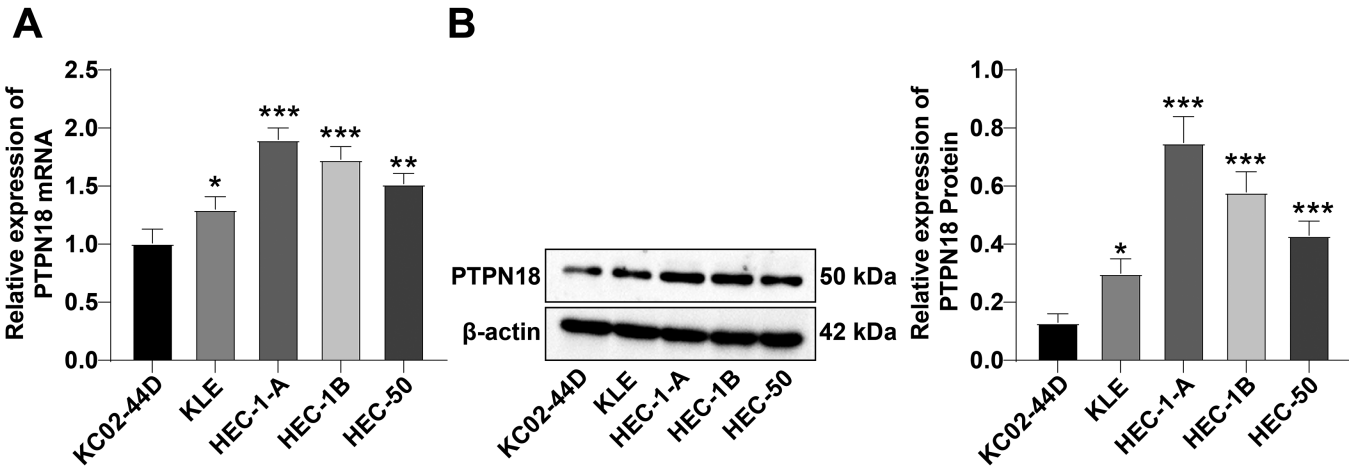

Fig. 1. PTPN18 was highly expressed in EC cells. **A, B.** RT-qPCR and Western blot were used to assess the expression of PTPN18 in EC cells. Cell experiments were repeated 3 times. Data were expressed as mean ± standard deviation. One-way ANOVA analysis was applied for data comparisons among groups, followed by Tukey's test. *P<0.05, **P<0.01, ***P<0.001.

Discussion

EC has ranked as the sixth most frequently occurring malignancy in women, with 417,000 new cases reported in 2020 on a global scale (Sung et al., 2021). A functional review has highlighted the potential implication of molecular alternations in EC for improving patients' clinical outcomes (Yen et al., 2020), emphasizing the role of the PTP family in EC (Giordano et al., 2018). Accordingly, the findings from this study supported the carcinogenic role of PTPN18 in EC. Returning to the hypothesis posed at the beginning of this study, it is now reasonable to state that PTPN18 silencing exerted anti-migrative and anti-invasive effects on EC cells by curbing aerobic glycolysis through inhibition of the MYC/PI3K/AKT pathway.

Initially, PTPN18 was found to be abundantly expressed in EC cells, conferring a potential role in EC carcinogenesis. Prior evidence has revealed the upregulation of PTPN18 in EC tissues, accompanied by enhanced proliferative and metastatic capabilities of EC cells (Wang et al., 2021). In addition, the potential carcinogenic property of PTPN18 has been suggested in glioblastoma, as evidenced by an unfavorable prognosis, suppressed immunity, and accelerated progression (Wang et al., 2023). Further knockdown of PTPN18 induced by sh-PTPN18 in our study was shown to exercise its restraints upon the migration and invasion of EC cells. Similarly, downregulated PTPN18 has been explored to impair proliferation, inhibit metastasis, and facilitate apoptosis of EC cells *in vitro*, and the results were also confirmed *in vivo* (Cai et al., 2019). To conclude, PTPN18 was highly expressed in EC cells, and its knockout limited the invasion and migration of EC cells.

Additionally, the deregulation of aerobic glycolysis plays a crucial role in the invasion, proliferation, and angiogenesis of cervical cancer cells (Han et al., 2015a, 2019). Aerobic glycolysis can induce excessive lactate accumulation, which not only promotes tumor growth and stimulates malignant progression but also confers resistance to conventional treatment modalities (Vaupel and Multhoff, 2021). It is accepted that aerobic glycolysis functions as the main energy provider for EC cells to consume glucose, so a downregulated glycolytic pathway may present anti-tumor activity (Han et al., 2015b; Li et al., 2023). For instance, the interplay

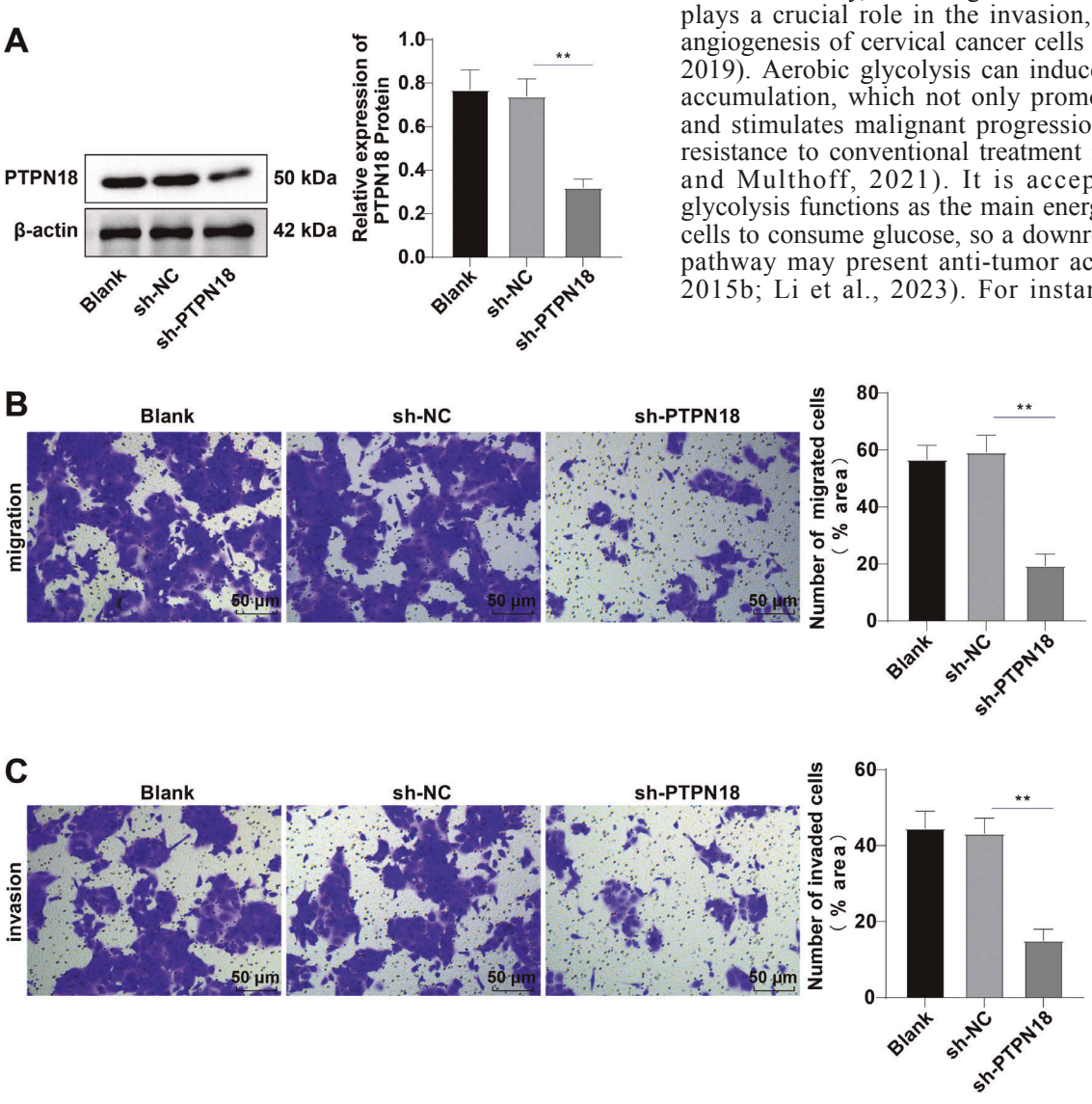

Fig. 2. Silencing PTPN18 inhibited EC cell migration and invasion. **A.** The expression of PTPN18 in EC cells was measured by Western blot; **B, C.** the Transwell assay was used to evaluate cell migration **(B)** and invasion **(C)**. Cell experiments were repeated 3 times. Data were expressed as mean ± standard deviation. One-way ANOVA analysis was adopted for data comparisons among groups, followed by Tukey's test. $^{**}P<0.01$.

between histone deacetylase-1 provoked strengthened aerobic glycolysis and advanced clinicopathological progression of patients with EC (Wu et al., 2021). Thus, we investigated the effect of PTPN18 on the aerobic glycolysis of EC cells, and experimental data were presented, demonstrating for the first time that aerobic glycolysis in EC cells was curbed by knocking down PTPN18. Notably, it has been documented that aerobic glycolysis in EC cells is expedited by kinesin family member C1 through the c-myc signaling pathway (Zhou et al., 2021). MYC can be responsible for the mediation of diverse biological processes and functions in multiple malignancies, mainly as a transcription factor that regulates gene expression directly or indirectly (Dang, 2012; Fatma et al., 2022). On the other hand, the rate-limiting enzymes in the glycolytic pathway, such as phosphofructokinase 1, hexokinase 2, and pyruvate kinase type M2, exert a vital effect on the modulation of aerobic glycolysis, which can be modulated by various mechanisms, including the PI3K/AKT pathway, c-Myc, noncoding RNAs, and HIF-1α (Feng et al., 2020). Evidence has accumulated regarding the implication of the PI3K/AKT signaling pathway in aerobic glycolysis in the context of malignancies, including hepatocellular carcinoma and breast cancer (Feng et al., 2020; Wu et al., 2020; Luo et al., 2021). It is common knowledge that Myc and PI3K/AKT signaling pathways are regulators of metabolic gene expression and boosters of metabolic enzyme activities in tumorigenesis and metastasis (Park et al., 2020). Subsequent mechanistic investigations revealed that activation of the MYC/PI3K/AKT signaling pathway was repressed by sh-PTPN18-mediated knockdown of PTPN18. Largely in agreement with our study, the MYC signaling pathway has been elucidated to be activated by PTPN18, contributing to the growth of colorectal cancer (Li et al., 2021). Also,

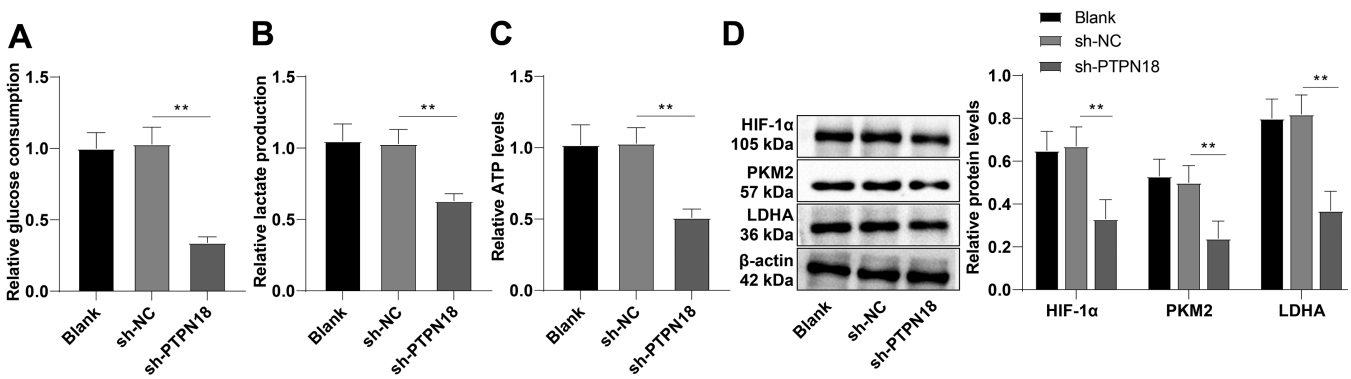

Fig. 3. PTPN18 silencing can repress aerobic glycolysis in EC cells. **A.** Glucose consumption. **B.** Lactate secretion. **C.** ATP levels in EC cells were determined; **D.** The expression patterns of glycolysis-related proteins HIF-1α, PKM2, and LDHA were determined by Western blot. Cell experiments were repeated 3 times. Data were expressed as mean ± standard deviation. One-way ANOVA analysis was employed for data comparisons among groups, followed by Tukey's test. ***P*<0.01.

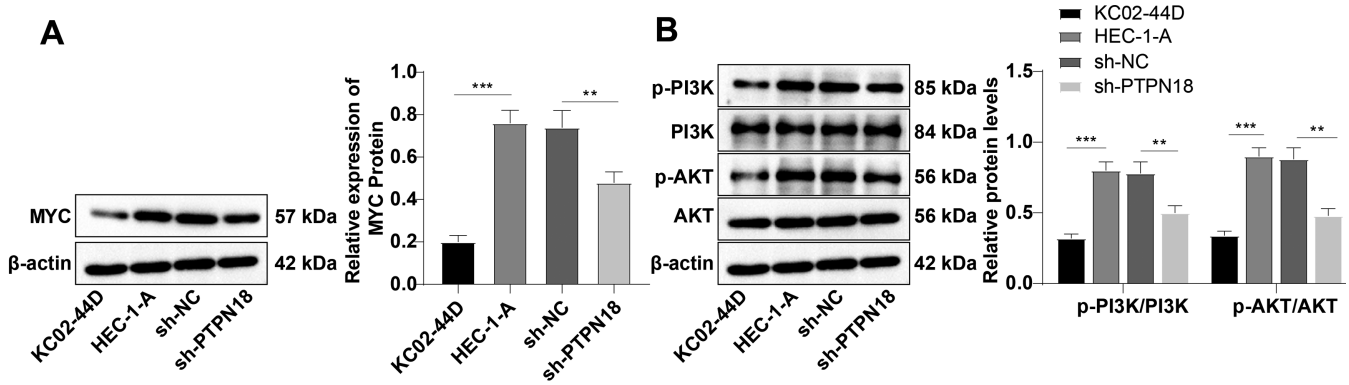

Fig. 4. PTPN18 silencing suppressed the activation of the MYC/PI3K/AKT pathway. The expression levels of MYC **(A)** and the PI3K/AKT **(B)** pathway-related proteins p-PI3K, PI3K, p-AKT and AKT in EC cells were assessed by Western blot. Cell experiments were repeated 3 times. Data were expressed as mean ± standard deviation. One-way ANOVA analysis was applied for data comparisons among groups, followed by Tukey's test. ***P*<0.01, ****P*<0.001.

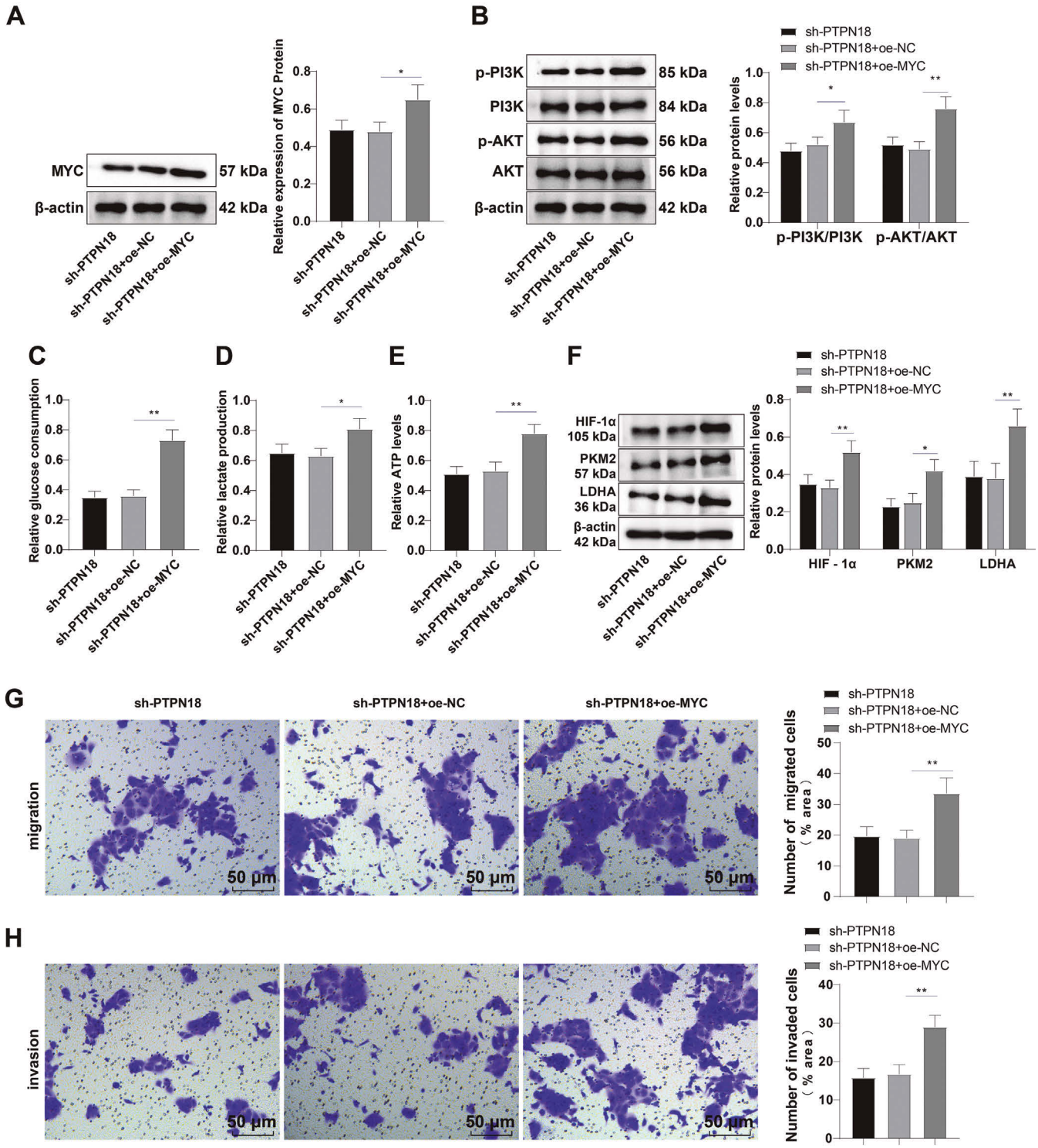

Fig. 5. Overexpression of MYC partially antagonized PTPN18 knockdown-mediated inhibitory effects on EC cell migration, aerobic glycolysis, and invasion. Western blot was used to assess the expression patterns of MYC **(A)** and the PI3K/AKT **(B)** pathway-related proteins p-PI3K, PI3K, p-AKT and AKT in EC cells. **C.** Glucose consumption. **D.** Lactate secretion. **E.** ATP levels in EC cells were assessed; **F.** The expression patterns of glycolysis-related proteins were determined by Western blot; the Transwell assay was used to evaluate cell migration **(G)** and invasion **(H)**. Cell experiments were repeated 3 times. Data were expressed as mean ± standard deviation. One-way ANOVA analysis was adopted for data comparisons among groups, followed by Tukey's test. **P*<0.05, ***P*<0.01.

the further findings of this study disclosed that the suppressive effect exerted by downregulated PTPN18 on aerobic glycolysis, migration, and invasion of EC cells was partially counterweighed by upregulating PTPN18, unequivocally validating our previous findings.

To conclude, our findings on the inhibitory action of PTPN18 downregulation on aerobic glycolysis provide new insights into the mechanism of EC. However, *in vivo* studies are highly recommended in the future for translational applications. Also, it is noted that upstream regulatory genes and other downstream signaling pathways of PTPN18 involved in the mediation of aerobic glycolysis in EC cells remain to be considered. Further investigation on the epigenetic regulatory mechanism by which PTPN18 inhibited MYC expression may provide reliable and valid experimental data to tailor therapeutic strategies.

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Conflict of Interest Statement. The authors have no conflicts of interest to declare.

Consent for publication. Not applicable.

Data Availability Statement. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Authors' contributions. Guarantor of integrity of the entire study: Shiqi Suo, Liyuan Zhou; study concepts: Song Chen, Ruili Xu; study design: Jingxia Li; definition of intellectual content: Jingxia Li; literature research: Shiqi Suo; experimental studies: Shiqi Suo, Song Chen, Wei Li; data acquisition: Wei Li; data analysis: Jingxia Li; statistical analysis: Liyuan Zhou; manuscript preparation: Shiqi Suo, Song Chen; manuscript editing: Shiqi Suo; manuscript review: Liyuan Zhou. All authors read and approved the final manuscript.

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