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ORIGINAL RESEARCH

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CPNE1 as prognostic marker and regulator of cell growth and glycolysis in endometrial cancer

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Abstract

Endometrial cancer (EC) is an epithelial malignant tumor in women. *Copine-1* (*CPNE1*) is an oncogene implicated in many tumors. Nevertheless, the influence of *CPNE1* on EC has not been fully determined. This study aims to determine the impact of *CPNE1* on EC. In this research, User-friendly Analysis of Cancer Gene Expression Data (UALCAN) was used to analyze *CPNE1* expression in uterine corpus endometrial carcinoma (UCEC) and its effect on patient survival probability. The levels of CPNE1, hexokinase 2 (HK2), phosphorylated Akt kinas/Akt kinas (p-AKT/AKT), and c-myc were examined by western blot or quantitative reverse transcription polymerase chain reaction (qRT-PCR). Cell proliferation was assessed by Cell Counting Kit-8 (CCK-8) assay and clone formation assay. The glucose consumption, lactate production, and adenosine triphosphate (ATP) levels in Ishikawa and KLE cells were measured by commercial kits. We found that the expression of CPNE1 was upregulated in EC and closely related to the development of EC. Silencing *CPNE1* suppressed proliferation and aerobic glycolysis of EC cells. Silencing *CPNE1* inhibited AKT/c-myc pathway in EC cells. Downregulation of *CPNE1* also inhibited proliferation and aerobic glycolysis of EC cells via regulating the AKT pathway. In conclusion, *CPNE1* plays an oncogenic role in EC and silencing *CPNE1* reduces proliferation and aerobic glycolysis of EC cells through modulation of the AKT pathway.

Keywords

Endometrial cancer; CPNE1; Proliferation; Aerobic glycolysis; AKT/c-myc pathway

1. Introduction

Endometrial cancer (EC) is an epithelial malignant tumor found in the lining of the uterus [1]. EC ranks 15th among global malignancies in developed countries but is one of the most common cancers in developing countries. Its incidence has been rising due to increasing rates of obesity, which is a major risk factor [2]. It primarily affects postmenopausal women, with the majority of cases diagnosed in women aged 50–70 years. However, around 20–25% of cases occur in premenopausal women, and 2–5% in women under 40 [2]. Surgical removal and postoperative adjuvant treatment of EC are well-established, including hysterectomy and conventional platinum/paclitaxel-based chemotherapy [3, 4]. Nevertheless, women with recurrent or advanced EC have a poor response rate to conservative treatment (non-surgical approaches aimed at preserving the uterus, like hormonal therapy) and poor clinical prognosis [5]. Therefore, it is still essential to further discover targeted therapeutic agents for EC patients based on an accurate understanding of the molecular pathogenesis of EC.

Copine-1 (*CPNE1*) is a gene located on human chromosome 20 and encodes for a Calpain-5 binding protein. *CPNE1* codes for a calcium-binding protein that plays an important role in cell signaling and cell processes [6]. *CPNE1* has been identified as an oncogene in few human cancers [7, 8]. The expression of *CPNE1* is increased in lung and prostate cancer, and upregulated *CPNE1* promotes the development and metastasis of lung cancer cells [9, 10]. CPNE1 can activate the AKT signaling pathway, which plays a vital role in glucose metabolism and cell energy homeostasis [11]. However, the role and mechanisms of CPNE1 in EC remain unclear.

c-myc is a crucial transcription factor associated with a variety of cell functions, including cell proliferation and energy metabolism [12]. By modulating these cell functions, c-myc is linked with tumorigenesis and stimulates the advancement of tumors [13]. It has been demonstrated that silencing upstream genes of the c-myc pathway can inhibit glycolytic-mediated tumor progression [14]. AKT modulates many cell processes, including cell proliferation, glycolysis and angiogenesis [15–17]. It is a downstream signal of phosphatidylinositol 3 kinase (PI3K) [18, 19]. Reduction of aerobic glycolysis mediated by AKT-c-myc signaling can inhibit tumor progression [20]. Therefore, we speculate that the AKT/c-myc signaling pathway plays a vital role in the advancement of EC.

Herein, UALCAN was utilized for the analyses of *CPNE1*

expression and clinical relevance in uterine corpus endometrial carcinoma (UCEC). The effects of CPNE1 on EC cell proliferation and aerobic glycolysis were confirmed with *in vitro* experiments. This study verified the influence of CPNE1 on EC and established its utility as a prognostic marker and therapeutic target.

2. Materials and methods

2.1 Bioinformatics analysis

UALCAN (http://ualcan.path.uab.edu/) was utilized to assess the expression and clinically related information of CPNE1 in UCEC. Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/detail.php) was applied to perform correlation analysis.

2.2 Cell culture

Human normal endometrial stromal cells (hESC cells) and EC cell lines (Ishikawa, KLE, RL95-2, and AN3_CA) were purchased from Genechem (Shanghai, China). Dulbecco's modified Eagle's medium/Nutrient Mixture F-12 (DMEM/F12; D0697, Sigma-Aldrich, St. Louis, MO, USA) was utilized to culture the hESC cells. The EC cell lines were cultured in DMEM (Sigma) containing 10% fetal bovine serum (FBS; TMS-016, Sigma-Aldrich, St. Louis, MO, USA) in 5% carbon dioxide (CO_2) at 37 °C.

2.3 Cell transfection

Small interfering RNA (siRNA) targeting CPNE1 (si-CPNE1#1 and si-CPNE1#2) and control (si-NC) were synthesized by Sangon Biotech (Shanghai, China). Lipofectamine 2000 (SITRAN-RO; 11668-027, Thermo Fisher Scientific, Waltham, MA, USA) was used for transfection following the manufacturer's instructions. In some rescue experiments, EC cells were treated with SC79 (an AKT activator; 0.2 μg/mL; A424572, Sangon, Shanghai, China) for 24 h prior to transfection to activate the AKT pathway. All cell functions were evaluated 48 h after transfection.

2.4 Western blot

The proteins of cells were extracted using lysis buffer (23227, Invitrogen, Carlsbad, CA, USA). Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was applied to separate the proteins, which were transferred to a polyvinylidene fluoride (PVDF) membrane. After blocking, the membranes were incubated overnight at 4 °C with primary antibodies against CPNE1 (ab272682; 1:1000; Abcam, Cambridge, MA, USA), Hexokinase II (HK2; ab209847; 1:1000; Abcam, Cambridge, MA, USA), p-AKT (4060; 1:1000; Cell Signaling Technology, Boston, MA, USA), AKT (9272; 1:1000; CST, Cambridge, MA, USA), c-myc (ab32072; 1:1000; Abcam, Cambridge, MA, USA), and β-actin (ab8226; 1:1000; Abcam, Cambridge, MA, USA). The following day, the membranes were exposed to goat anti-rabbit Immunoglobulin G (IgG) (ab205718; 1:2500; Abcam, Cambridge, MA, USA) for 2 h. Protein signals were detected using an ECL kit (41106004, Sigma, St. Louis, MO, USA). Protein expressions were semi-quantified using Image J software.

2.5 Quantitative reverse transcription polymerase chain reaction (qRT-PCR)

RNAs was extracted from Ishikawa and KLE cells using TRIzol (9109, TaKaRa, Dalian, Liaoning, China) and then reverse transcribed into cDNA using the PrimeScript RT Master Mix (RR036A; TaKaRa, Dalian, Liaoning, China). qRT-PCR was subsequently performed using the SYBR® Premix Ex Taq™ quantitative kit (RR420A, TaKaRa, Dalian, Liaoning, China) on an ABI7500 system (4397808, Thermo Fisher Scientific, Waltham, MA, USA). *β-actin* served as the reference gene for normalization, and relative gene levels were calculated using the $2^{-\Delta\Delta Ct}$ method. Please refer to Table 1 for the primer sequences.

TABLE 1. Primers for qRT-PCR.

Name		Primers for qRT-PCR (5′-3′)
CPNE1		
	Forward	TGCCTCGTACTTCATGCTGTT
	Reverse	TCCATGGCCTCAAAGTCAGC
β-actin		
	Forward	ATCGTCCACCGCAAATGCTTCTA
	Reverse	AGCCATGCCAATCTCATCTTGTT

qRT-PCR: quantitative reverse transcription polymerase chain reaction; CPNE1: Copine-1.

2.6 Cell counting kit-8 (CCK-8) assay

Treated EC cells (1×10^4 cells/well) were seeded in a 96-well plate and cultured for the indicated times. The cell viability was assessed using a CCK-8 kit (96992, Sigma, St. Louis, MO, USA). The optical density (OD) was measured at 450 nm using a Tecan Infinite M200 (M NANO, Tecan, Männedorf, ZH, Switzerland).

2.7 Clone formation assay

EC cells (600 cells/well) were cultured in 6-well plates and incubated in culture medium overnight to allow the cells to adhere. After different treatments, the EC cells were cultured for 10–14 days until colony formation. Colonies were then fixed with paraformaldehyde (4%; 8.18715, Sigma, St. Louis, MO, USA), washed, and stained with GIEMSA staining solution (32884, Sigma, St. Louis, MO, USA) to investigate colony formation.

2.8 Determination of glycolysis and adenosine triphosphate (ATP) levels

Glucose consumption, lactate production, and ATP levels in EC cells were detected in line with previously used protocol [21]. Treated EC cells (2×10^5 cells/well) were seeded into 6-well plates and cultured for 24 h. The culture media was collected and glucose concentration and lactate level were measured by utilizing a Glucose Assay Kit-WST (G264,

Dojindo, Kumamoto, Japan) and a Lactate Assay Kit-WST (L256, Dojindo, Kumamoto, Japan) following the manufacturer's instructions. Additionally, EC cells (5×10^5 cells) were collected and treated with ATP Assay Buffer (100 μL; MAK190, Sigma, St. Louis, MO, USA). The supernatant was subsequently collected for ATP determination using an ATP Colorimetric Assay Kit (MAK190, Sigma, St. Louis, MO, USA). Data were expressed as fold-change relative to the corresponding controls.

2.9 Statistical analysis

All experiments were performed in triplicate. Statistics were conducted as mean ± standard deviation. GraphPad Prism 8.0 software (GraphPad Inc., La Jolla, CA, USA) was applied for statistical analysis. Clinical factors associated with survival probability in EC patients were evaluated utilizing Cox regression and the Kaplan-Meier (Plotter: http://kmplot.com/analysis). Differences between groups were analyzed using Student's *t*-test or analysis of variance (ANOVA). $p < 0.05$ was considered statistically significant.

3. Results

3.1 *CPNE1* played an oncogenic role in EC

First, the high expression of CPNE1 in UCEC was confirmed using UALCAN (Fig. 1A). The correlation between CPNE1 and survival probability was assessed in patients with UCEC utilizing GEPIA data, which presented that CPNE1 high expression diminished survival probability in patients ($p = 0.049$; Fig. 1B). Furthermore, we found that the expression of CPNE1 was elevated in EC cell lines (Ishikawa, KLE, RL95-2 and AN3_CA) compared to hESC cells (Fig. 1C). Among these, CPNE1 upregulation was more pronounced in Ishikawa and KLE cells, so these two cells lines were selected for subsequent studies. Overall, these results demonstrated that the CPNE1 expression was enhanced in EC and CPNE1 was closely related to the development of EC.

3.2 Silencing *CPNE1* suppressed proliferation of EC cells

Next, we confirmed that the expression of CPNE1 was reduced by transfection with si-CPNE1#1 or si-CPNE1#2 in Ishikawa and KLE cells (Fig. 2A,B). Additionally, we found that the cell viability (FFig. 2C) and colony formation ability (Fig. 2D) were decreased following si-CPNE1#1 or si-CPNE1#2 transfection in Ishikawa and KLE cells. Hence, we uncovered that silencing CPNE1 suppressed proliferation of EC cells.

3.3 Downregulation of *CPNE1* inhibited aerobic glycolysis of EC cells

We then investigated the effect of CPNE1 on aerobic glycolysis of EC cells. We found that the glucose consumption (Fig. 3A), lactate production (Fig. 3B), and ATP levels (Fig. 3C) in Ishikawa and KLE cells were reduced following CPNE1 silencing. Moreover, the expression of HK2 was diminished after transfection with si-CPNE1#1 or si-CPNE1#2 in Ishikawa and KLE cells (Fig. 3D). Therefore, we suggested that downregulated CPNE1 inhibited aerobic glycolysis of EC cells.

3.4 Silencing *CPNE1* inhibited AKT/c-myc pathway in EC cells

In this part, we investigated the signaling pathway that CPNE1 may regulate in EC cells.

We found that the levels of p-AKT/AKT and c-myc were reduced by transfection with si-CPNE1#1 or si-CPNE1#2 in Ishikawa and KLE cells (Fig. 4). Among these, the inhibitory effect of si-CPNE1#1 was more pronounced, so it was selected for the subsequent rescue experiment.

3.5 Silencing *CPNE1* inhibited proliferation and aerobic glycolysis in EC cells by modulating the AKT pathway

Finally, we performed rescue experiments. We found that the levels of p-AKT/AKT and c-myc (Fig. 5A), the expression of HK2 (Fig. 5B), the cell viability (Fig. 5C), the glucose consumption (Fig. 5D), lactate production (Fig. 5E), and ATP levels (Fig. 5F) were reduced by si-CPNE1#1 transfection in Ishikawa and KLE cells, while these effects were mitigated by SC79 co-treatment. These results confirm that silencing CPNE1 inhibited proliferation and aerobic glycolysis of EC cells by repressing the AKT pathway.

4. Discussion

In this study, we found that the expression of CPNE1 was elevated in EC and CPNE1 was closely related to the development of EC. Silencing of CPNE1 suppressed proliferation and aerobic glycolysis of EC cells. Furthermore, downregulation of CPNE1 inhibited AKT/c-myc pathway in EC cells. Finally, we demonstrated that silencing CPNE1 inhibited proliferation and aerobic glycolysis of EC cells through modulating the AKT pathway. In conclusion, CPNE1 played an oncogenic role in EC and silencing CPNE1 inhibited proliferation and aerobic glycolysis of EC cells via the AKT pathway.

EC is a type of cancer that develops in the endometrial tissue of the uterus [22]. Cell proliferation and aerobic glycolysis are two important processes associated with tumor growth and metabolism [23, 24]. In EC, abnormal cells begin to proliferate uncontrollably, leading to tumor formation and growth. The process of cell proliferation is regulated by various factors, including hormones, growth factors, and signaling pathways [23]. Aerobic glycolysis is a cellular metabolic process where in cells convert glucose into energy in the presence of oxygen. This process involves multiple enzymes and metabolic pathways, ultimately producing ATP as an energy source. However, the metabolic pattern of cancer cells may differ from normal cells. In some cases, cancer cells preferentially generate energy through the glycolysis, a phenomenon known as the "Warburg effect" [25]. Although this metabolic pathway is less efficient than normal aerobic respiration, it provides a faster energy supply required for cancer cell growth and proliferation [24, 25]. In EC, there is a close relationship between cell proliferation and aerobic glycolysis. The proliferation of abnormal cells requires an increased energy supply

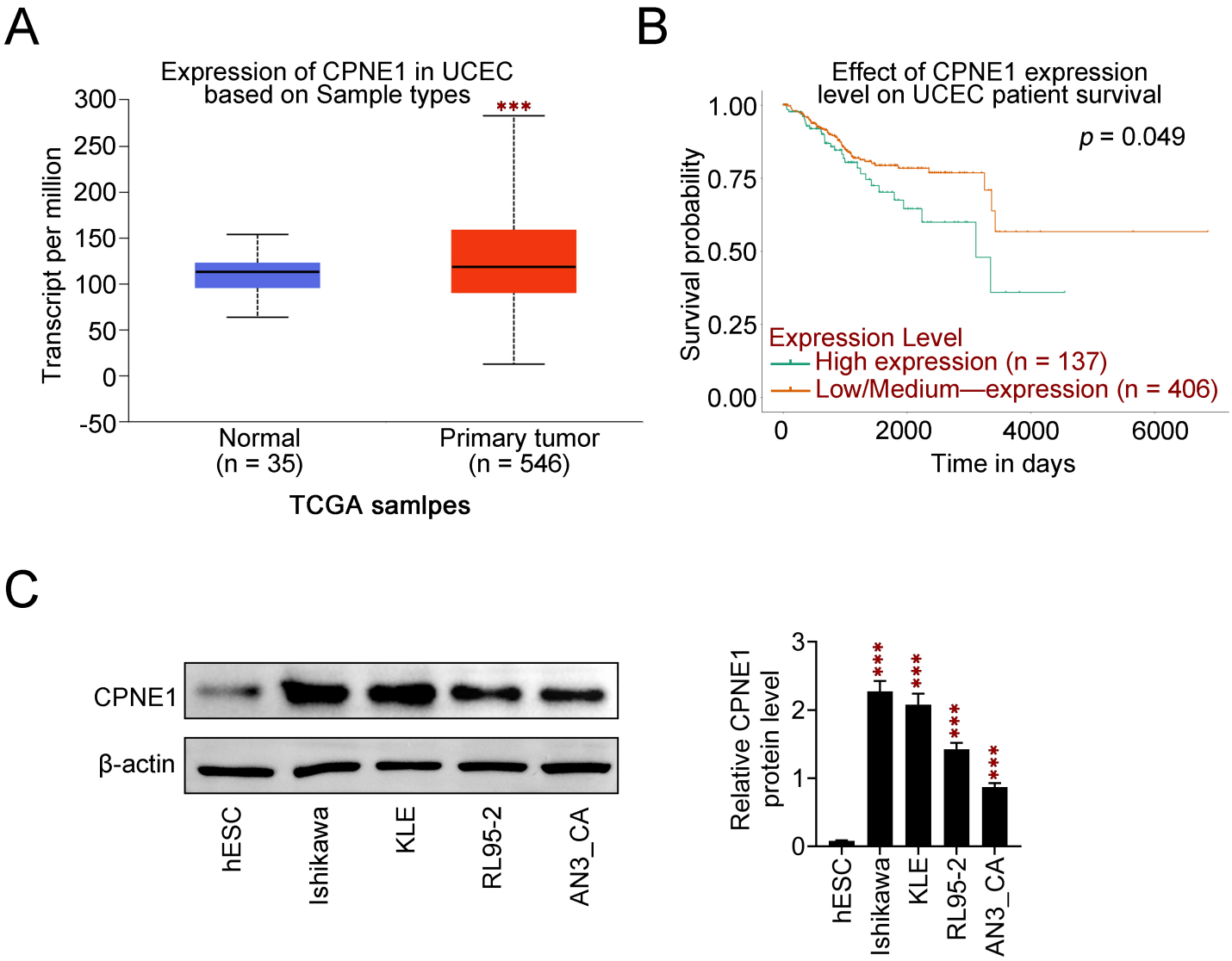

FIGURE 1. ***Copine-1* (*CPNE1*) played an oncogenic role in endometrial cancer (EC).** (A) Uterine corpus endometrial carcinoma (UCEC)-founded analyses of CPNE1 expression in UCEC. (B) Effect of CPNE1 expression in UCEC on patients' survival probability. (C) The content of CPNE1 was analyzed by western blot. ***$p < 0.001$. UCEC: uterine corpus endometrial carcinoma; hESC: Human normal endometrial stromal; TCGA: The Cancer Genome Atlas.

and biosynthetic precursors, and aerobic glycolysis provide a rapid energy source for cancer cells [26]. Additionally, aerobic glycolysis produces metabolic byproducts, such as lactate, which can influence the tumor microenvironment and immune response [25]. Therefore, aerobic glycolysis may play a vital role in the development of EC. In-depth research into mechanisms of EC can help us better understand and treat this disease.

CPNE1 plays multiple functional roles inside the cell, including involvement in cell membrane and organelle localization, cell adhesion and movement, apoptosis and cell proliferation [11, 27]. Studies suggested that CPNE1 might play a role in various diseases and physiological processes [28]. Wang *et al.* [29] other studies found that CPNE1 was upregulated in cervical squamous cell carcinoma, which was linked with differentiation and metastasis of cervical cancer. Additionally, Yang *et al.* [30] uncovered that CPNE1 overexpression in gastric cancer was apparently linked with poor prognosis. Although the functions and regulatory mechanisms of CPNE1 are still under extensive research, there is a preliminary understanding of its roles in cell biology and diseases. Further research is needed to uncover the specific functions and regulatory mechanisms of CPNE1 in different biological processes and diseases, providing a basis for its possible development as a therapeutic target. In this study, we found that the expression of CPNE1 was enhanced in EC and CPNE1 was closely related to the development of EC. These results were similar with the reports of Wang *et al.* [29] and Yang *et al.* [30].

Dysregulation of the AKT/c-myc pathway is commonly observed in cancer [31]. Constitutive activation of AKT or upregulation of c-myc is associated with uncontrolled cell growth, increased proliferation, and resistance to apoptosis, all of which contribute to tumorigenesis [32]. The AKT/c-myc pathway is often aberrantly activated in various cancer types and is implicated in tumor progression and aggressiveness [33]. Targeting the AKT/c-myc pathway has emerged

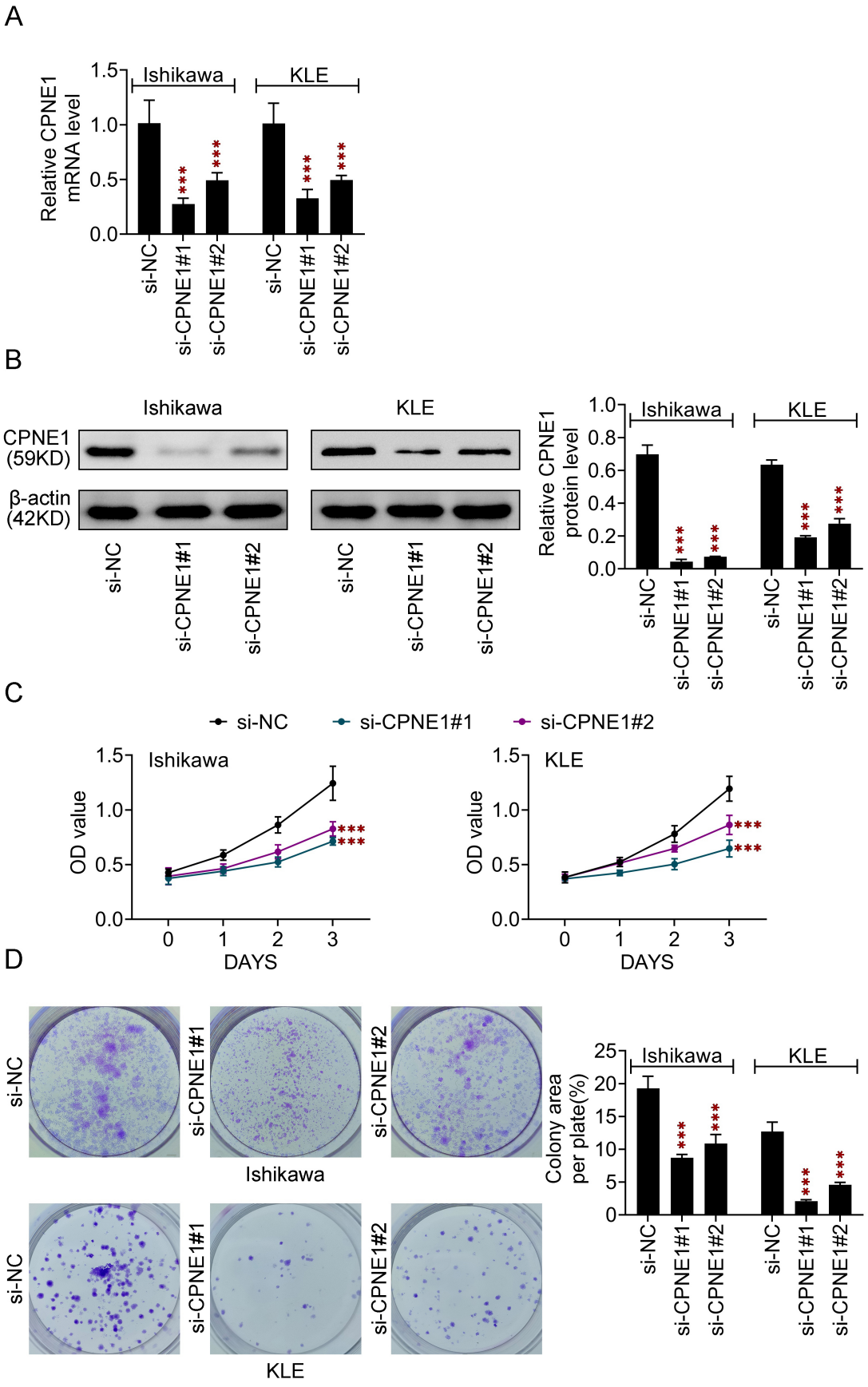

FIGURE 2. Silencing *Copine-1* (*CPNE1*) repressed proliferation of endometrial cancer (EC) cells. (A) The expression of CPNE1 mRNA was evaluated by quantitative reverse transcription polymerase chain reaction (qRT-PCR). (B) The expression of CPNE1 was analyzed by western blot. (C) The cell viability was observed with a Cell counting kit-8 (CCK-8) assay. (D) The cell proliferation was evaluated using a colony formation assay. ***$p < 0.001$. si-NC: control; OD: optical density.

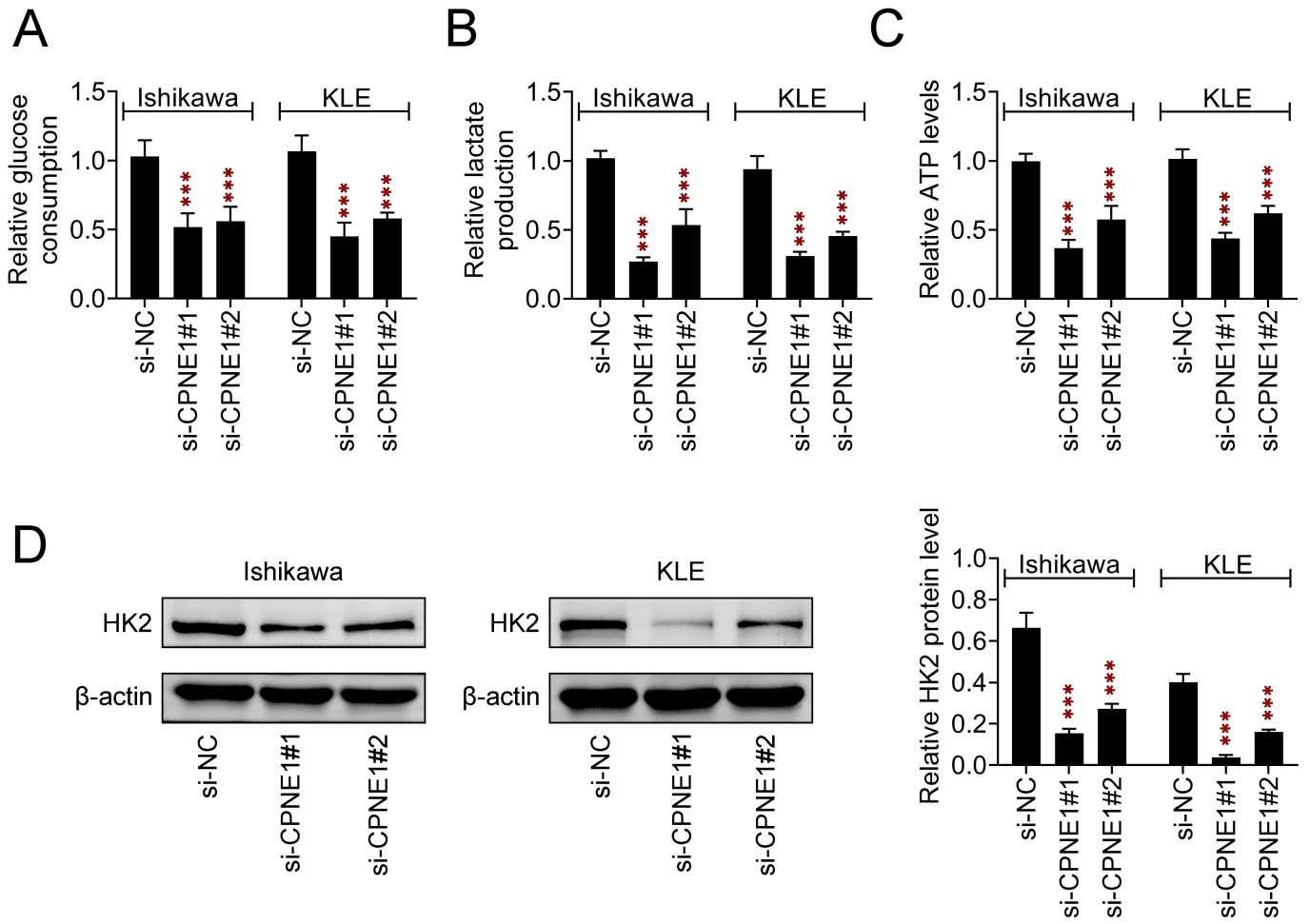

FIGURE 3. Downregulated *Copine-1* (*CPNE1*) inhibited aerobic glycolysis of endometrial cancer (EC) cells. (A–C) The glucose consumption, lactate production, and adenosine triphosphate (ATP) levels in Ishikawa and KLE cells were measured by commercial kits. (D) The content of hexokinase 2 (HK2) was analyzed by western blot. ***$p < 0.001$. si-NC: control.

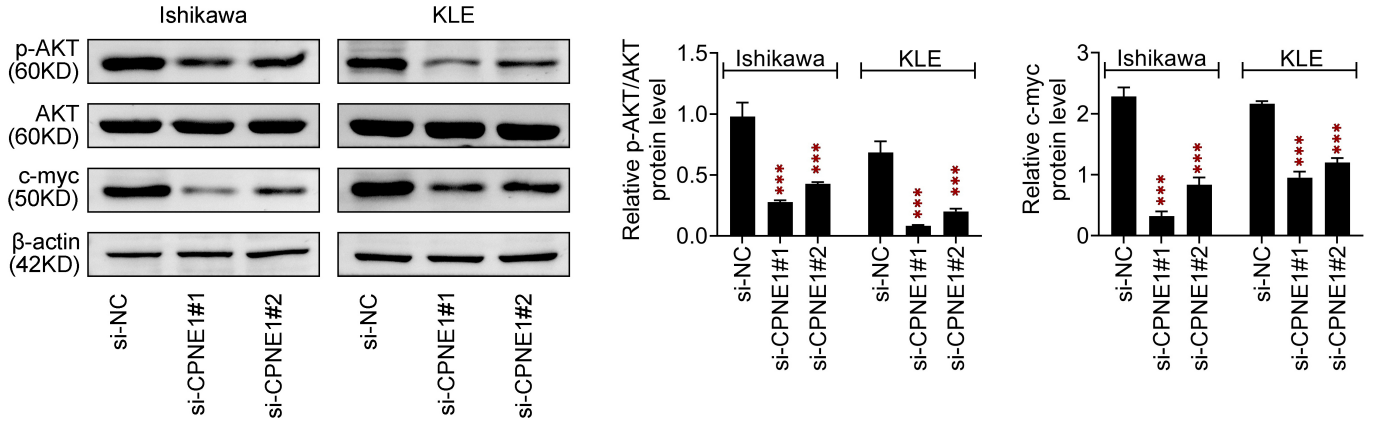

FIGURE 4. Silencing *Copine-1* (*CPNE1*) inhibited AKT/c-myc pathway in endometrial cancer (EC) cells. The levels of phosphorylated Akt kinas/Akt kinas (p-AKT/AKT) and c-myc were analyzed by western blot. ***$p < 0.001$. si-NC: control.

as a potential therapeutic strategy in cancer treatment [34]. Inhibitors of AKT or c-myc are being explored for their effectiveness in suppressing tumor growth and enhancing sensitivity to other anticancer therapies. In addition, Wang *et al.* [35] revealed that CPNE1 enhanced the growth, glycolysis and drug resistance of colorectal cancer cells by modulating the AKT-glucose transporter type 1 (GLUT1)/HK2 pathway. Shao *et al.* [36] confirmed that CPNE1 predicts poor prognosis of triple-negative breast cancer through AKT signaling pathway and promotes tumorigenesis and radiation resistance. In our study, we found for the first time that silencing CPNE1 suppressed proliferation and aerobic glycolysis of EC cells. Moreover, silencing CPNE1 inhibited AKT/c-myc pathway in EC cells. We revealed for the first time that silencing CPNE1 inhibited

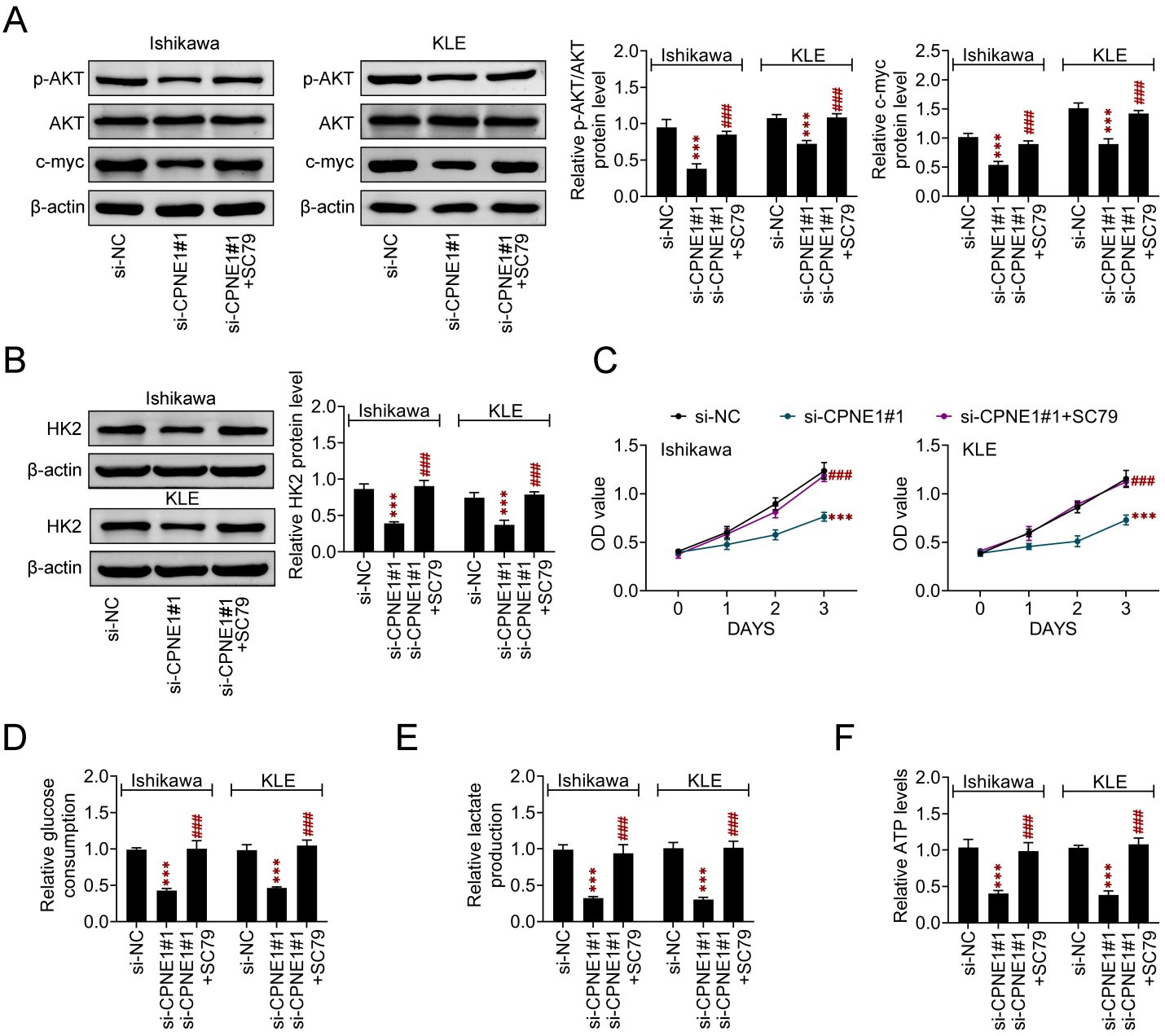

FIGURE 5. Silencing *Copine-1* (*CPNE1*) inhibited proliferation and aerobic glycolysis of endometrial cancer (EC) cells through modulating the AKT pathway. (A) The levels of phosphorylated Akt kinas/Akt kinas (p-AKT/AKT) and c-myc were analyzed by western blot. (B) The content of hexokinase 2 (HK2) was examined by western blot. (C) The cell viability was observed with Cell counting kit-8 (CCK-8) assay. (D–F) The glucose consumption, lactate production, and adenosine triphosphate (ATP) levels in Ishikawa and KLE cells were measured by commercial kits Compared with the si-NC group, $^{***}p < 0.001$; compared with the si-CPNE1#1 group, $^{\#\#\#}p < 0.001$. si-NC: control; OD: optical density.

proliferation and aerobic glycolysis of EC cells through modulating the AKT pathway. These results were similar with the conclusions of Wang *et al.* [35] and Shao *et al.* [36]. However, the study has some limitations. We only investigated the influence of CPNE1 in EC cells, and this conclusion need to be further validated in animal experiments. In the follow-up study, we will further verify our findings in mouse models and clinical practice.

5. Conclusions

In summary, we found that CPNE1 may serve as a prognostic marker in EC and its expression is closely related to the development of EC. Silencing CPNE1 inhibited the proliferation and aerobic glycolysis of EC cells by modulating the AKT pathway. Our study contributes to the early screening of EC and the prediction of patient prognosis, and it provides new therapeutic targets and strategies for inhibiting the progress of EC.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

XH—designed the study, completed the experiment and supervised the data collection. PLJ—analyzed the data, interpreted the data. WQL and GY—prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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