

# RETRACTED ARTICLE: UPFI Participates in the Progression of Endometrial Cancer by Inhibiting the Expression of lncRNA PVT1

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**Background:** Endometrial carcinoma (EC) is the primary cause of death associated with cancer globally. Thus, the possible molecular mechanism of EC needs further exploration. Up-frameshift protein 1 (*UPFI*) is an ATPase depending on RNA/DNA and RNA helicase depending on ATP. Long noncoding RNA (lncRNA) placental cytotrophoblastic variant translocation 1 (*PVT1*) was dysregulated in diverse diseases.

**Methods:** qRT-PCR and Western blot were applied to detect *UPFI* and *PVT1* in EC. CCK-8, colony formation, and Transwell assay were used to test the effects of *UPFI*/*PVT1* on cell proliferation and migration. Cells were cultured with actinomycin D to observe mRNA stability, and RNA immunoprecipitation assay was applied to verify the relationship between *UPFI* and *PVT1*. Glucose consumption and lactate generation were measured when cells were transfected with siRNA.

**Results:** Results demonstrated that the expression of *UPFI* exhibited a remarkable decrement in EC tissues relative to that in non-tumor tissues. Subsequent functional experiments suggested that *UPFI* decrement stimulated EC cells to grow and migrate. Moreover, *UPFI* was discovered to be linked to *PVT1* and had an inverse correlation with *PVT1*. Besides, *PVT1* expression affected EC growth and migration, and *PVT1* decrement alleviated the influence of *UPFI* decrement on EC growth and migration and strengthened glycolysis in EC.

**Conclusion:** In this study, we found that *UPFI* was down-regulated in EC tissues, and *UPFI* might exert its role by regulating the expression of *PVT1*.

**Keywords:** endometrial carcinoma, *UPFI*, *PVT1*, cell growth, cell migration

## Background

Endometrial carcinoma (EC) is one of the three malignant tumors arising in the reproductive tract of women. It is an endometrial epithelial malignant tumor with secluded onset, and it is prone to metastasis and migration.<sup>1,2</sup> The onset of EC is generally believed to increase with age, and prognosis is poor.<sup>3</sup>

Up-frameshift protein 1 (*UPFI*) is an ATPase depending on RNA/DNA and an RNA helicase depending on ATP; it is an evolutionarily conserved phosphorylated protein with extensive expression.<sup>5</sup> *UPFI* exerts a crucial effect on nonsense-mediated decay (NMD) and non-NMD RNA decay.<sup>6</sup> In the NMD process, *UPFI* is related to a translation termination codon based on the translation termination complex. Additionally, *UPFI* stimulates cells to progress to G1/S, increasing the likelihood that NMD facilitates the decay of mRNAs encoding repressive proteins, which prevent evolution in this cell cycle stage.<sup>7</sup> A recent study discovered that *UPFI* modulates tumor formation.<sup>8</sup> However, reports about *UPFI* in EC remain limited.

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An increasing number of lncRNAs have been ascertained to modulate the expression of genes correlated with tumors at the transcriptional, post-transcriptional, chromatin, and genomic levels.<sup>4</sup> Thus, an investigation on the functions of pivotal lncRNAs in EC growth may contribute to the prediction of prognosis, elevation of early diagnosis rate, and increase in the survival rate in patients with EC.

In this study, we aimed to reveal the roles of *UPF1* in the occurrence and progression of EC. Given that *UPF1* can exert its roles by affecting downstream genes in many diseases, we also intended to explore the potential mechanism by which *UPF1* exerts its function and provide insight into the study of EC.

## Materials and Methods

### Patients

Twenty-four fresh EC tissues and paired adjacent non-cancerous tissue samples were obtained from patients who underwent surgical treatment at the affiliated hospital of Jiamusi University. None of the patients received anti-cancer treatment before surgery, including radiotherapy and chemotherapy. EC diagnosis was confirmed through pathology by three pathologists. This research gained the approval from the Institutional Review Board of the first affiliated hospital of Jiamusi University, and all subjects signed informed consent.

### Cell Culture

EC cell lines (AN3CA, KLE, RL95, HEC1A, and Ishikawa) and endometrial epithelial cells (HEL2S) were acquired from ATCC Cell Line (USA). All cells were cultured in DMEM with 10% fetal bovine serum (FBS) purchased from Thermo Fisher Scientific and McCoy's 5a medium. The culture environment was 37 °C and 5% CO<sub>2</sub>.

### Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

TRIzol reagent provided by Invitrogen (USA) was utilized to harvest total RNA from clinical specimens, followed by reverse transcription via a PrimeScriptRT reagent Kit from Promega (USA) following the manufacturer's protocol. The ABI7900HT RT-PCR system acquired from Applied Biosystems (USA) and SYBR Green Master Mix provided by Thermo Fisher Scientific (USA) were adopted for qRT-PCR, with GAPDH as internal control. The applied primers are shown below: *UPF1* (F:5'-ACCGACTTTACTCTTCCTAGCC-3'; R:5'-AGGTCCTTCGTGTAATAGGTGTC-3'), *PVT1* (F:5'-GTCTTGGTGCTCTGTGTTC-3';

R:5'-CCCGTTATTCTGTCCTTCT-3')

GAPDH (F:5'-CCATGTTTCGTCATGGGTGTGAACCA-3';

R:5'-GCCAGTAGAGGCAGGGATGATGTTG-3').

The 2<sup>-ΔΔCt</sup> method was employed to calculate the relative expression level of each gene.

### siRNA Synthesis and Cell Transfection

The *PVT1*- or *UPF1*-specific siRNAs, pcDNA3.1-*UPF1*, negative control siRNA (siR-NC), and pcDNA3.1 were provided by Riobio (China). Lipofectamine 2000 transfection reagent from Thermo Fisher Scientific (USA) was utilized to treat cells in accordance with the manufacturer's instructions. After transfection for about 24–48 h, cells from every group were collected and applied for subsequent research. In addition, plasmid treatment was carried out using the same method as above.

### Immunohistochemistry

Immunohistochemical detection was carried out with general approaches. Anti-*UPF1* (Abcam, Cambridge, UK) was used as the primary antibody. Image Pro Plus 6.0 (Media Cybernetics, Inc., Rockville, MD, USA) software was applied to calculate the mean optical density. For each tissue section, at least 10 non-overlapping cortical fields were analyzed.

### CCK-8 Test

Following inoculation into a 96-well plate (2×10<sup>3</sup> cells/well), the cells were cultured for 24, 48, and 72 h. Thereafter, the wells were added with CCK-8 from Dojindo Laboratories (Japan) for 4 h of incubation. A Varioskan Flash Spectral Scanning Multimode Reader provided by Thermo Fisher Scientific (USA) was employed to examine the absorbance at 450 nm. Each experiment was repeated three times independently.

### Western Blot

On the basis of the manufacturer's guidelines, a standard BCA test was executed to determine the protein concentration in cell lysate. After isolation via SDS-PAGE (10%) electrophoresis, the proteins were transferred to PVDF membranes at 4 °C and sealed with skim milk (5%) in TBST for 1 h. These membranes were incubated with anti-GAPDH or anti-*UPF1* antibody (Cell Signaling, USA) overnight at 4 °C. The membranes were washed three times with TBST and incubated with secondary antibody at indoor temperature for 1 h. A Phototope-horseradish peroxidase Western blot detection kit (Cell Signaling Technology, Danvers, MA, USA) was applied

to detect the expression of proteins. The *UPF1* protein expression levels were normalized to that of GAPDH by calculating the relative expression levels.

### Colony Formation Experiment

A number of  $1 \times 10^3$  Ishikawa or HEC1A cells were put into agar (1.5 mL) on the top that was then added onto agar on the bottom in each well. Complete medium (2 mL) was replenished twice a week. After 3 weeks, colonies were dyed with 0.1% crystal violet (0.5 mL) for 1 h, and a TE2000-U dissection microscope acquired from Nikon (Japan) was used to quantify colonies  $\geq 0.5$  mm. Each experiment was repeated three times independently.

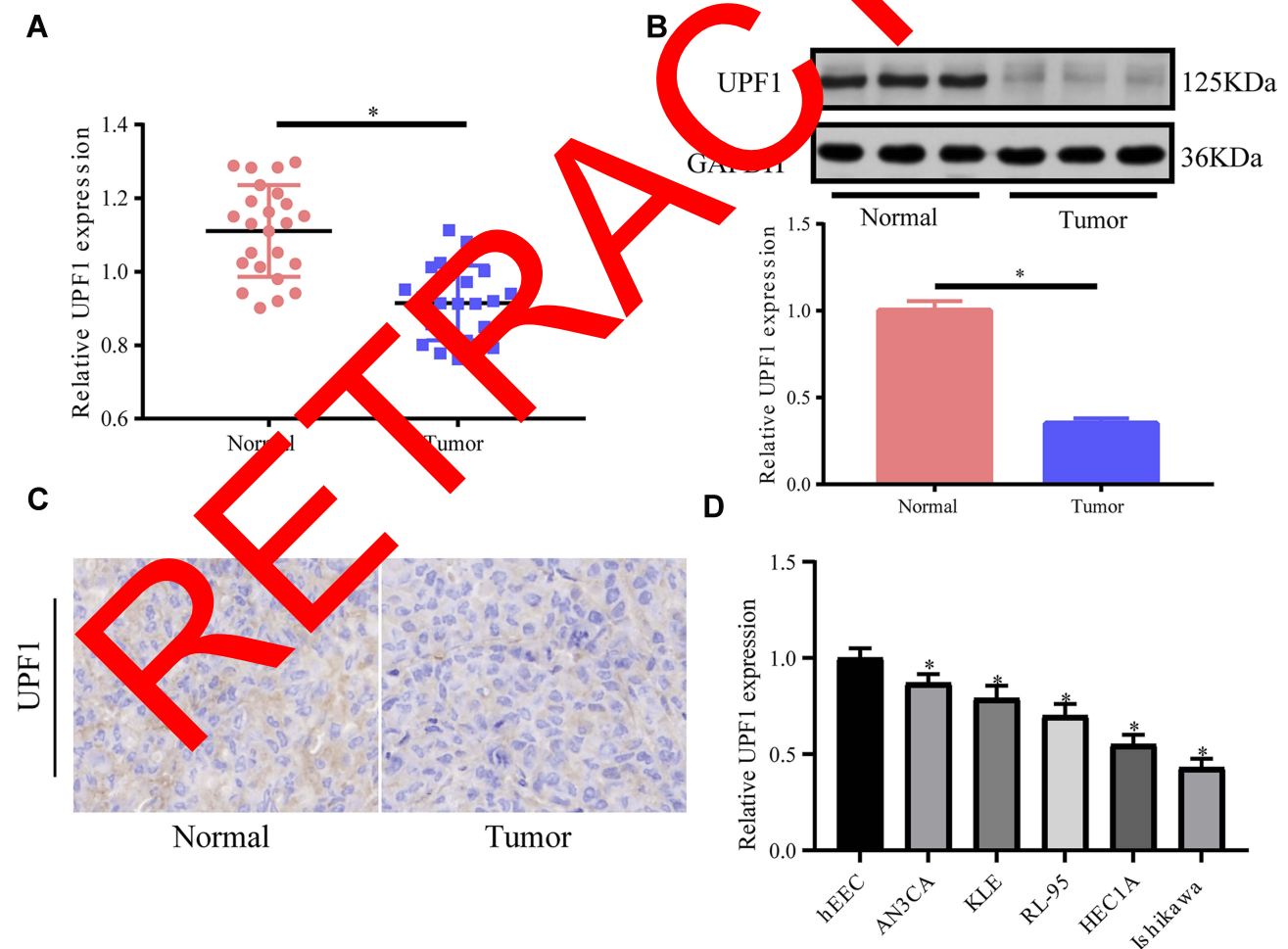
### Transwell Experiment

The ability of the cells to migrate was assessed by Corning Transwell insert chambers (Corning). Approximately

$1 \times 10^4$  (migration assay) of transfected cells in 200  $\mu$ L of serum-free medium was seeded in the upper well; the chambers were then incubated with medium plus 20% fetal bovine serum for 48 h at 37 °C to allow the cells to migrate to the lower well. The cells that had migrated through the membrane were fixed in methanol and stained with crystal violet (Invitrogen). Finally, the migrated cells were imaged and counted using a microscope.

### Detection of RNA Stability

HEC1A or Ishikawa cells undergoing treatment with siRNA specific to *PVT1/UPF1* or siR-NC were incubated using 5  $\mu$ g/mL actinomycin D (Sigma-Aldrich, USA) in the medium. Subsequently, total RNA was obtained at the designated time, and the mRNA expression level was evaluated by qRT-PCR. Finally, the half-life period of mRNAs was examined before and after



**Figure 1** *UPF1* expression in human EC tissues. (A) RT-PCR is implemented to test *UPF1* expression in 24 pairs of EC and no-tumor tissue specimens. *UPF1* expression is lowered in EC tissues. (B) *UPF1* expression in EC tissues relative to matched non-tumor tissues. Western blot is executed to test *UPF1* expression. (C) Immunohistochemistry also shows that the expression of *UPF1* in EC tissues is down-regulated. (D) The expression of *UPF1* in EC cell lines. (\* $P < 0.05$ ).

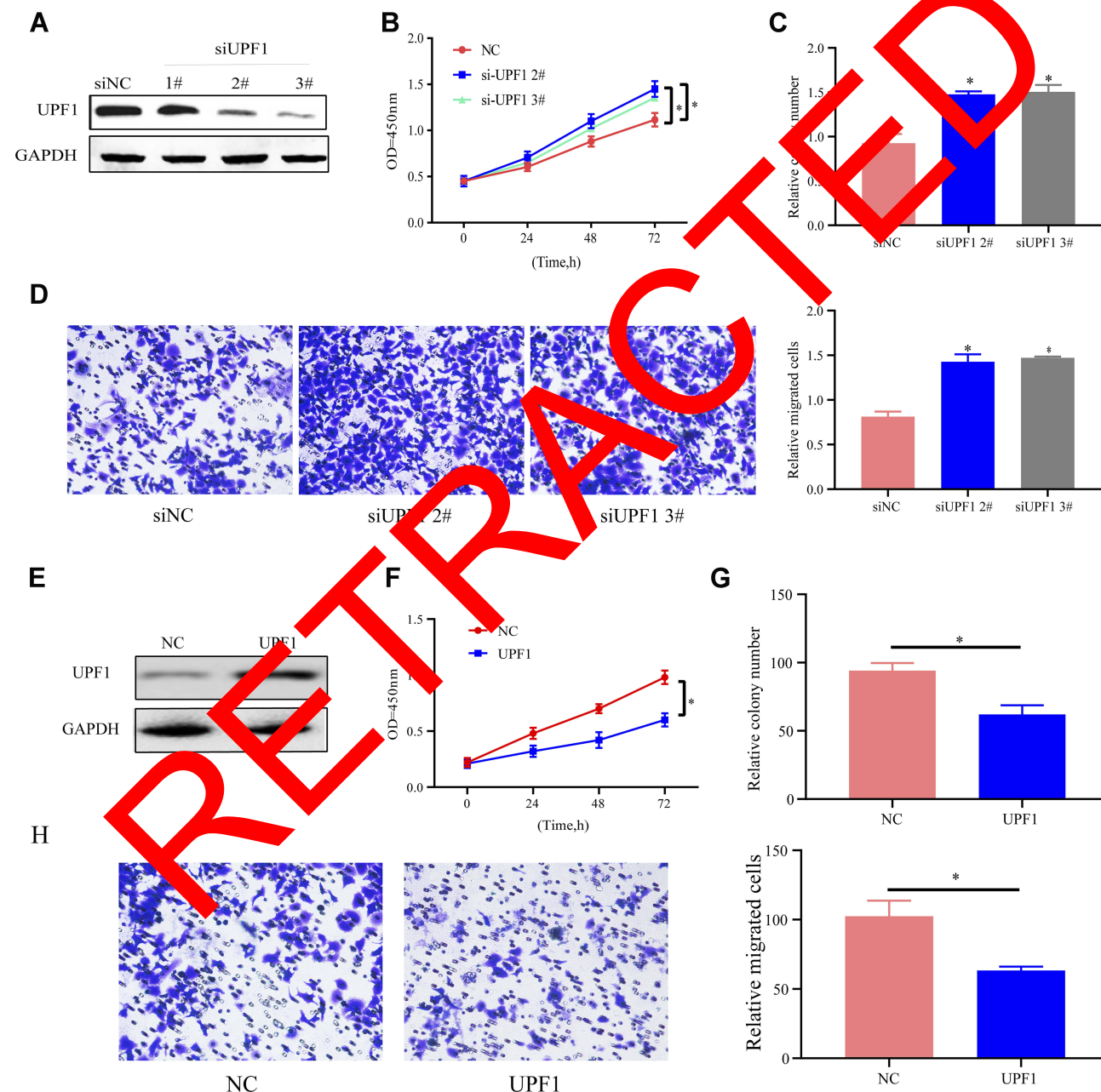
Actinomycin D addition. Each experiment was repeated three times independently.

## RNA Immunoprecipitation Assay

RNA immunoprecipitation (RIP) experiments were performed using a Magna RIP kit (Millipore, Bedford, MA) following the manufacturer's instructions. In summary,

a mixed buffer was utilized to obtain cells on ice for 20 min. Ten nuclei were subjected to 15 min of centrifugation at 2500 g through pelleting, and resuspension was carried out to obtain nuclear pellets in RIP buffer. Centrifugation was then implemented again to pellet nuclear debris and membrane. The supernatant was added with protein G beads and rabbit UPF1 or IgG

## HEC1A



**Figure 2** *UPF1* repression boosts HEC1A cells to migrate and grow. **(A)** *UPF1* decrement efficiency in HEC1A. **(B)** CCK-8 assay is used to test cell proliferation in HEC1A. **(C)** *UPF1*'s impact on cell growth is examined via colony formation experiment. **(D)** *UPF1* decrement predominantly aggrandizes the number of migrated cells. **(E)** *UPF1* overexpression efficiency in HEC1A is confirmed by Western blot. **(F–H)** Cell growth and migration are tested when *UPF1* is up-regulated. (\**P* < 0.05).

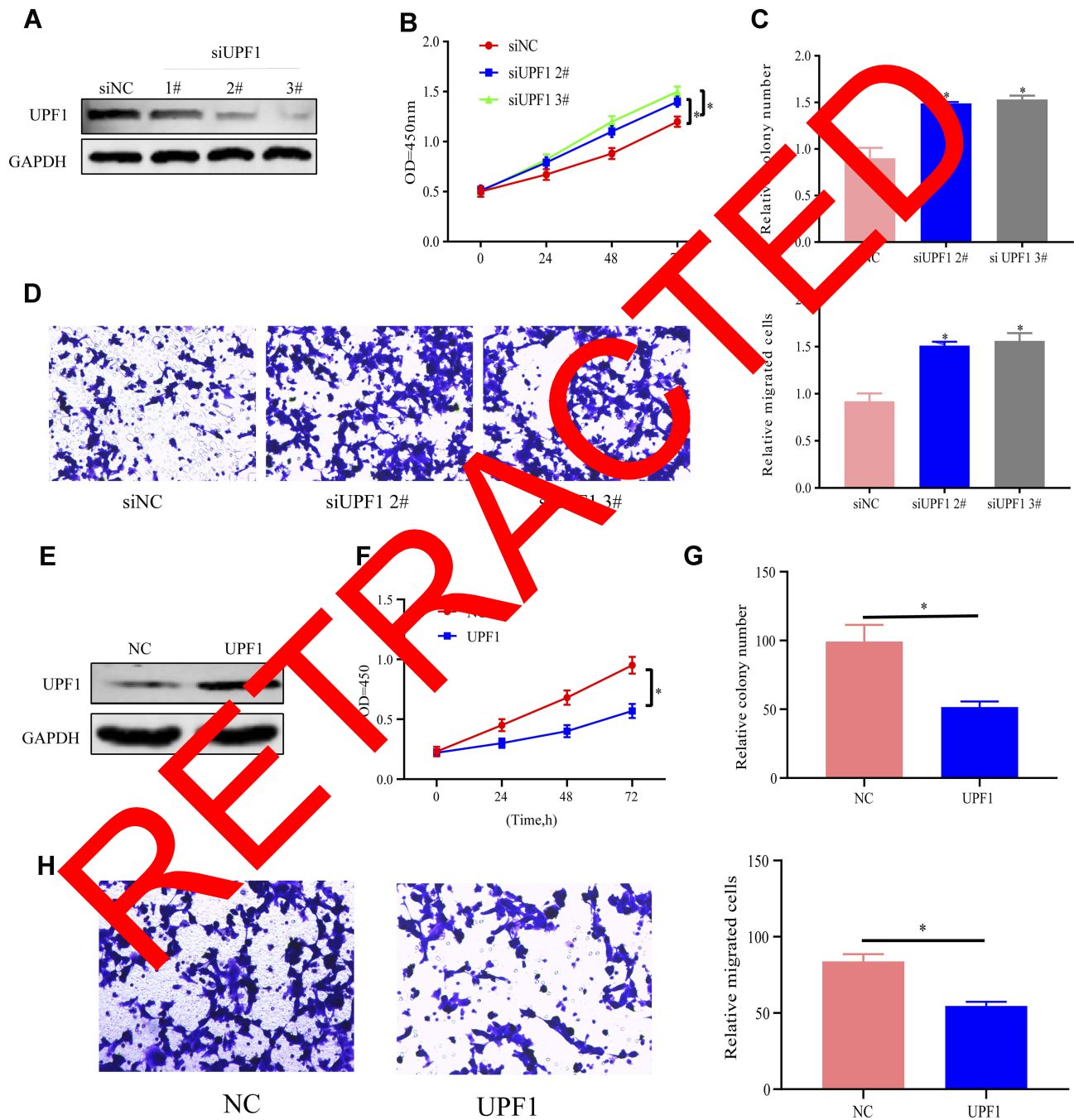


antibody from Cell Signaling (MA) for incubation overnight at 4°C. Finally, RNAs undergoing co-precipitation were separated, and PVT1 was subjected to qRT-PCR. Each experiment was repeated three times independently.

## Glucose Consumption and Lactate Generation Experiment

In accordance with the manufacturer's protocol, a glucose and lactate assay kit (BioVision, Milpitas, CA, USA) was

### Ishikawa

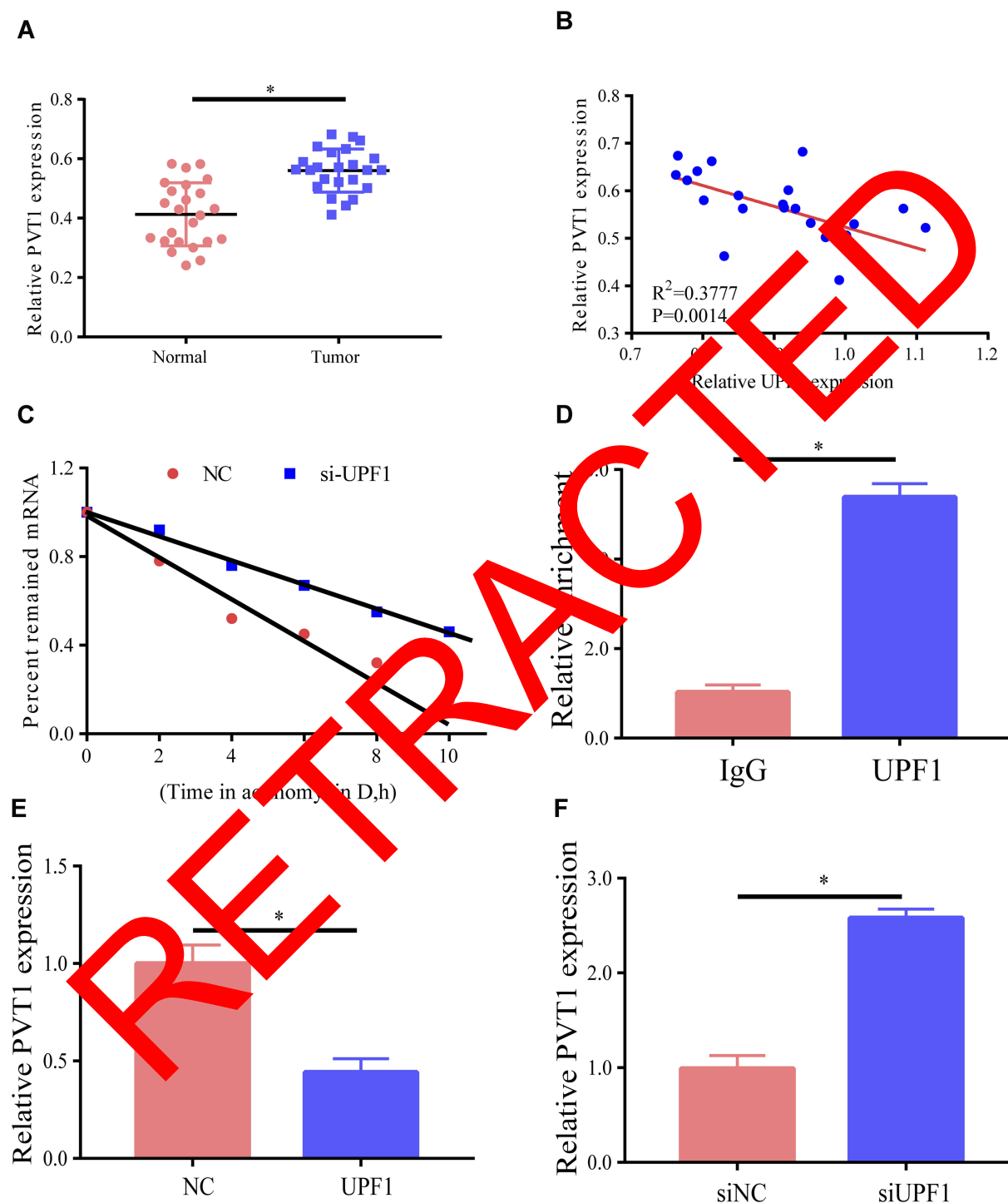


**Figure 3** *UPF1* repression boosts Ishikawa cells to migrate and grow. **(A)** *UPF1* decrement efficiency in Ishikawa cells. **(B)** Cell proliferation in Ishikawa. **(C)** *UPF1*'s impact on Ishikawa cell growth is examined via colony formation experiment. **(D)** *UPF1* decrement predominantly promotes Ishikawa cell migration. **(E)** *UPF1* overexpression efficiency in Ishikawa. **(F-H)** Ishikawa cell growth and migration are tested when *UPF1* is up-regulated. (\* $P < 0.05$ ).

employed to examine the harvested cell supernatants and assess lactate and glucose. Each experiment was repeated three times independently.

## Statistical Analysis

Statistical processing was executed with the use of SPSS.20 software (IBM, USA). Assays in this research



**Figure 4** LncRNA *PVT1* links *UPF1*. **(A)** *PVT1* expression is examined by RT-PCR, with *GAPDH* expression as normalization. **(B)** Association between expression levels of *UPF1* and *PVT1* RNAs in 24 EC tissues. **(C)** Actinomycin D is employed for cell treatment for the denoted time, and RT-PCR is implemented for the assessment of *PVT1* RNA level. **(D)** RIP test denotes the linkage between *UPF1* and *PVT1*. **(E)** *UPF1* overexpression reduces *PVT1* expression. HEC1A cells are treated with *UPF1* plasmid. **(F)** *UPF1* decrement in HEC1A cells raises *PVT1* expression. (\* $P<0.05$ ).

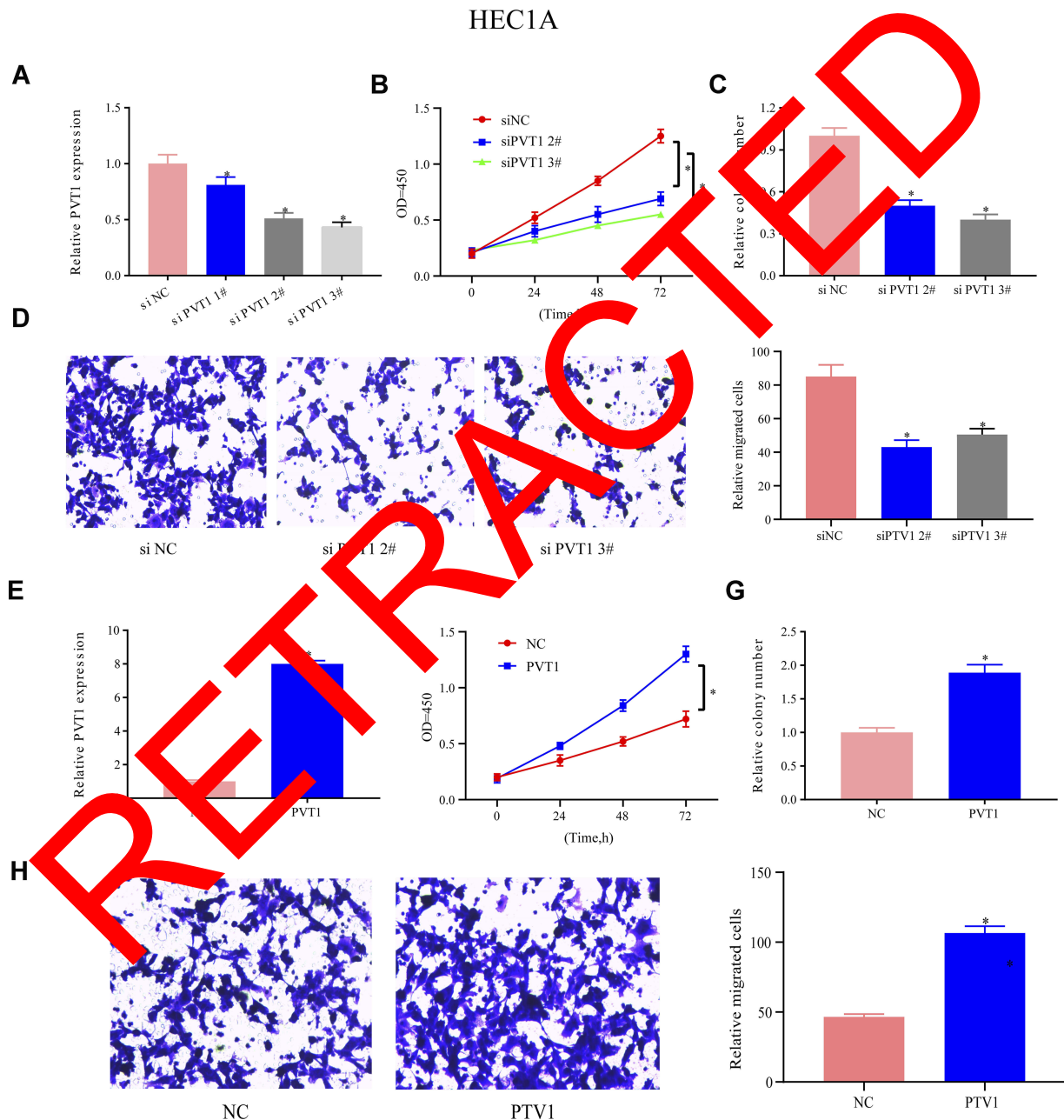
were carried out three times, and the mean  $\pm$  SD was applied to the present data. Student's *t*-test and one-way ANOVA were conducted to analyze the results. Statistical significance was set at  $p < 0.05$ .

## Results

### UPF1 Expression Declined in EC

First, *UPF1* expression in 24 EC tissues and 24 non-tumor tissues was tested via RT-PCR, and the mRNA expression of

*UPF1* was down-regulated in EC tissues (Figure 1A). The protein expression of *UPF1* was detected by Western blot, and it also declined in EC (Figure 1B). We also applied immuno-histochemistry to detect the expression of *UPF1* in EC tissues; *UPF1* was up-regulated in EC tissues (Figure 1C). Finally, we detected the expression of *UPF1* in EC cell lines, and *UPF1* was down-regulated obviously in both HEC1A and Ishikawa cell lines relative to the other cell lines (Figure 1D). Therefore, we chose these two cell lines for the subsequent experiments.



**Figure 5** *PVT1* expression's functions in HEC1A migration and growth. (A) *PVT1* expression in HEC1A cells is repressed. (B) CCK-8 is utilized for assessment of HEC1A cell proliferation. (C) Colony formation experiment validates that *PVT1* decrement slows down HEC1A cell growth. (D) *PVT1*'s impacts on cell migration in HEC1A cells is also assessed by Transwell assay. (E–H) Up-regulation of *PVT1* accelerates the proliferation, growth, and migration of HEC1A cells. (\* $P < 0.05$ ).

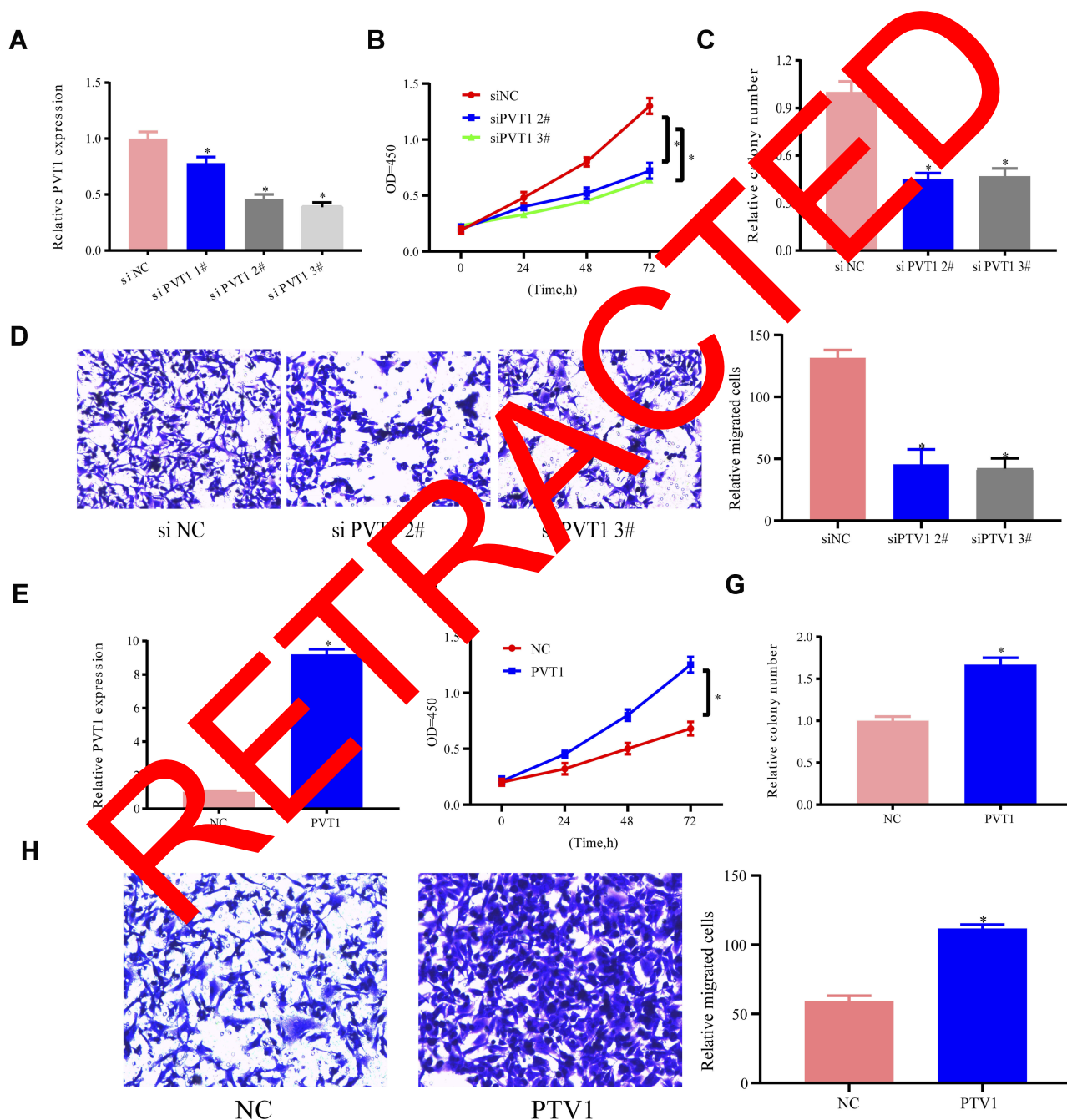
The above results revealed that *UPF1* might play a part in EC and predominantly influenced tumor evolution.

## UPF1 Silencing Facilitated EC Cells to Grow and Migrate

To determine *UPF1*'s function in EC, HEC1A cells were treated with siRNAs specific to *UPF1* to repress *UPF1*

expression (Figure 2A). Among three siRNAs, number #2 and #3 were highly effective, so the two were applied for later assays. CCK-8 and colony formation experiments showed that the HEC1A cells' proliferation and growth abilities were inhibited when *UPF1* expression was reduced (Figure 2B and C). On the basis of the obtained findings (Figure 2D), the number of migrated cells increased due to

## Ishikawa



**Figure 6** *PVT1* expression's functions in Ishikawa migration and growth. (A) si-*PVT1*'s efficiency in Ishikawa cells. (B–D) Ishikawa cell proliferation, growth, and migration are detected when *PVT1* is down-regulated. (E–H) Up-regulation of *PVT1* accelerates the proliferation, growth, and migration of Ishikawa cells. (\* $P < 0.05$ ).



*UPF1* decrement. By contrast, *UPF1* overexpression showed the opposite results (Figure 2E–H). Similar trends and results were also observed in the Ishikawa cell line when the expression of *UPF1* was up- or down-regulated (Figure 3A–H). In conclusion, *UPF1* repression boosted EC cells to grow and migrate.

## UPF1 Linked lncRNA PVT1

A recent study reported that numerous lncRNAs play a part in molecular regulatory pathways by interacting with proteins.<sup>9</sup> lncRNAs that possibly link *UPF1* were verified via bioinformatics analysis, and *PVT1* might be related to *UPF1*. First, *PVT1* expression level in EC was analyzed by RT-PCR, and the findings revealed that it was higher in EC tissues than in non-tumor tissues (Figure 4A). To continuously verify the association between *PVT1* and *UPF1* in EC, the relationship between their expression levels in EC tissues was tested. As shown in Figure 4B, they had an inverse relationship as indicated by RT-PCR. The stability of *PVT1* mRNA was then examined in EC cells with *UPF1* decrement. The results ascertained that *PVT1* decay rate increased in HEC1A after *UPF1* decrement (Figure 4C). The lineage between *UPF1* and *PVT1* was tested by RIP, and the results demonstrated that *UPF1* was specifically linked *PVT1* (Figure 4D). Moreover, HEC1A cells were treated with *UPF1* expression plasmids and *UPF1* overexpression was discovered to lower *PVT1* expression (Figure 4E), which was reversed by *UPF1*

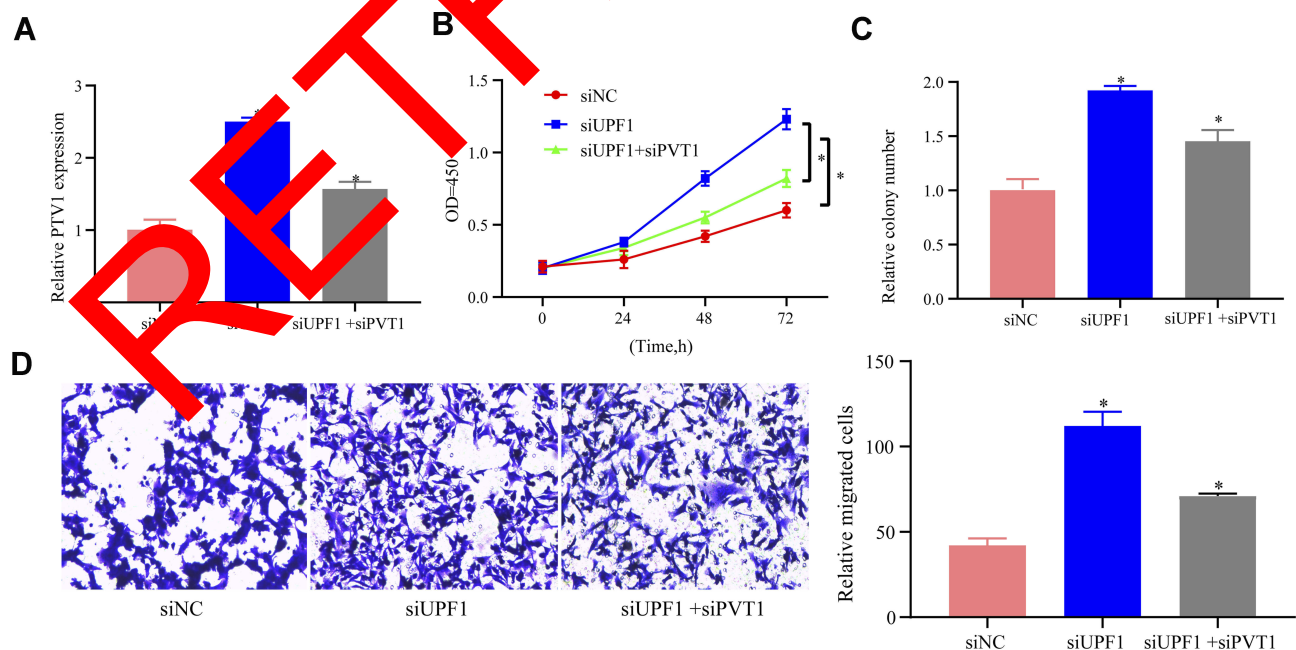
decrement (Figure 4F). In conclusion, *UPF1* linked *PVT1* and was likely to participate in EC evolution.

## Effects of PVT1 Expression on EC Growth and Migration

The expression of *PVT1* in HEC1A cells was lowered to determine *PVT1*'s function, and #2 and #3 siRNAs were more efficient *PVT1* targets for further assays than the other tested siRNAs (Figure 5A). The CCK-8 assay was executed to test the functions of *UPF1* in EC growth. In Figure 5B, *PVT1* decrement reduced the evolution of EC cells, and this phenomenon was reversed by *PVT1* overexpression. Furthermore, colony formation experiment demonstrated that *PVT1* decrement repressed the growth of HEC1A cells (Figure 5C). Subsequently, *PVT1*'s functions in cell migration were assessed through a transwell experiment. The decrement in *PVT1* expression weakened the migration ability (Figure 5D), but *PVT1* overexpression enhanced cell growth and migration (Figure 5E–H). In Ishikawa cells, these results could also be observed (Figure 6A–D). The abovementioned data denoted that *PVT1* may participate in EC migration and growth.

## PVT1 Decrement Alleviated the Function of UPF1 Decrement in EC Migration and Growth

To explore the functional association between *PVT1* and *UPF1*, EC cells were treated with *PVT1* siRNA



**Figure 7** *PVT1* decrement alleviates the influence of *UPF1* decrement on EC migration and growth. (A) Exploration of *PVT1* expression in HEC1A cells. (B) MTT is used to analyze cell proliferation. (C) Colony formation experiment. (D) Transwell assay is implemented for cell migration analysis. (\* $P < 0.05$ ).

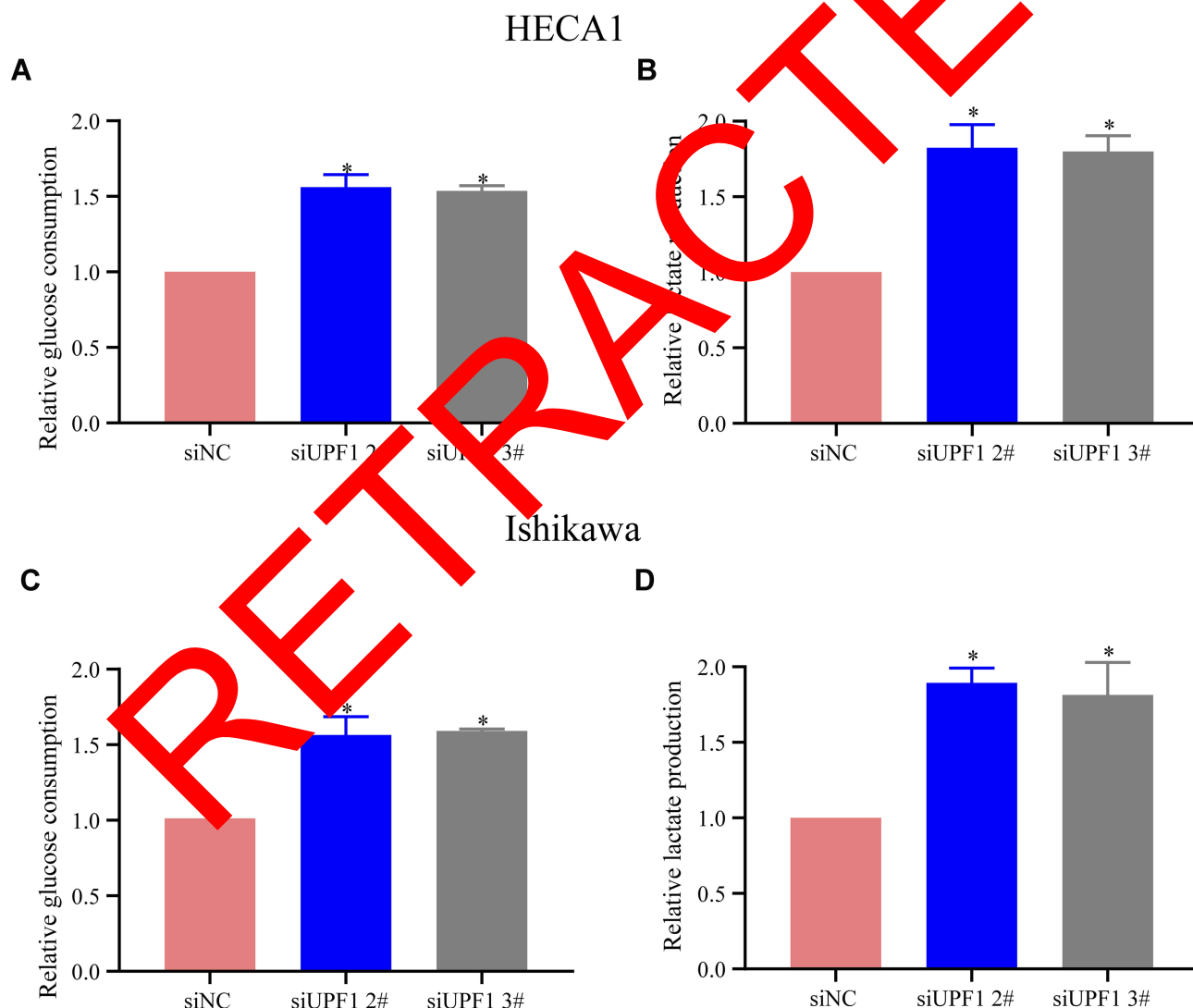
following *UPF1* decrement. First, RT-PCR showed that *PVT1* reduction repressed *PVT1* expression after *UPF1* decrement raised *PVT1* (Figure 7A). Second, CCK-8 assay proved that *UPF1* decrement facilitated the proliferation of EC cells, whereas *PVT1* decrement weakened the cell proliferation capacity (Figure 7B). Third, cell growth was continuously researched via colony formation experiment, and the results indicated that cell growth was also blocked following *PVT1* decrement (Figure 7C). Finally, *UPF1* decrement weakened cell migration ability (Figure 7D). Thus, *PVT1* decrement alleviated the influences on EC cell migration and growth exerted by *UPF1* decrement.

## UPF1 Decrement Strengthened Glycolysis in EC

In general, normal cells display a lower glucose metabolism rate than tumor cells,<sup>10</sup> and *PVT1* is reported to participate in the glycolysis of tumor cells.<sup>11</sup> In this research, glycolysis changes in EC cells with *UPF1* decrement were examined, and the results verified that *UPF1* decrement elevated the glucose consumption rate in EC cells (Figure 8A–D).

## Discussion

The UPF complex helps degrade abnormal mRNAs.<sup>12,13</sup> *UPF1* has been considered to be a mainstay factor for NMD,<sup>14,15</sup> and it plays a remarkable part in embryonic survival and growth.<sup>16,17</sup> In addition, *UPF1* represses



**Figure 8** *UPF1* decrement strengthens glycolysis in EC cells. (A) Analysis of glucose consumption in EC in HECA1 cells. (B) Examination of lactate generation in EC in HECA1 cells. (C) Analysis of glucose consumption in EC in Ishikawa cells. (D) Examination of lactate generation in EC in Ishikawa cells. (\* $P<0.05$ ).

cell growth but triggers apoptosis in *Drosophila melanogaster*,<sup>18</sup> and it functions in cancer evolution. Moreover, *UPF1* possibly modulates MALAT1, and the *UPF1*/MALAT1 pathway may be a target in gastric cancer therapy.<sup>19</sup> *UPF1* exhibits higher expression level in normal lung tissues relative to human lung adenocarcinoma tissues, implying that NMD decrement contributes to the formation of lung adenocarcinoma.<sup>20</sup> *UPF1* has also been reported as a tumor repressor, which is consistent with the findings of this research.

In the current research, *UPF1*'s association with EC was explored. RT-PCR revealed a reduction of *UPF1* expression in EC, and *UPF1* may affect tumor evolution. Additionally, *UPF1*'s functions in EC cells were confirmed using loss-of-function tests. The obtained data distinctly ascertained that *UPF1* decrement boosted EC cells to migrate and grow.

LncRNAs, with >200 nucleotides (nt), originated from the genome "noisy region." They are novel biomarkers for the relapse and evolution of disease.<sup>21</sup> Increasing attention has been paid to the impacts of lncRNAs on cell biology and tumor growth.<sup>22–24</sup> Plasmacytoma variant translocation 1 (*PVT1*), a lncRNA, is abnormally expressed in numerous cancer cells and tissues.<sup>25,26</sup> In particular, *PVT1* acts as an oncogene in tumor metastasis and growth.<sup>27–29</sup> Nevertheless, the molecular mechanism of *PVT1* in cancer evolution remains unclear. In this research, we found that *UPF1* was capable of binding *PVT1*, and they had an inverse correlation in EC. *PVT1* decrement in EC cells impeded cells to migrate and grow. Notably, we discovered that *UPF1* might perform its effects on cell growth and migration by binding to *PVT1*.

The current research unfolded a new mechanism mediated by *UPF1* on cell growth and migration by targeting lncRNA *PVT1* in EC cells. The findings revealed that *PVT1*/*UPF1* influenced EC formation and functions as a speculated target for diagnosing and treating EC.

## Ethics Approval and Consent to Participate

The study was carried out in accordance with the principles of the Declaration of Helsinki. All the patients provided written informed consent.

## Disclosure

The authors report no conflicts of interest in this work.

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