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ORIGINAL RESEARCH

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Potential role of TRIM3 as a novel tumour suppressor in endometrial cancer development

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Abstract

This study investigates the biological functions of Tripartite motif-containing 3 (TRIM3) in endometrial cancer (EC). The expression patterns of TRIM3 in EC using the UALCAN and Kaplan-Meier Plotter databases, and investigated the relationship with the progression of EC in patients. EC cell lines, Ishikawa and HEC-1A were transfected with a vector expressing TRIM3 after pre-treated with/without pifithrin-α (an inhibitor of p53). Subsequently, *in vitro* cell proliferation and apoptosis were evaluated. Overexpression of TRIM3 resulted in inhibition of cell viability and clone formation and induced G1 phase arrest in Ishikawa and HEC-1A cells. Additionally, after TRIM3 was overexpressed, cell apoptosis was increased, and higher levels of Bax and lower levels of B-cell lymphoma-2 (Bcl-2) were observed in cells. Furthermore, heightened levels of p53 and p21 proteins were observed in Ishikawa and HEC-1A cells overexpressing TRIM3. However, pifithrin-α could counteract the effects of TRIM3 overexpression on EC cells. These data indicate that TRIM3 exerts a tumor suppressor effect in EC by activating the p53/p21 pathway.

Keywords

Endometrial cancer (EC); TRIM3; p53; Proliferation; Apoptosis

1. Introduction

Endometrial cancer (EC) is a gynecological malignancy [1]. The incidence of EC is increasing annually, especially among younger women, posing adverse effects on their overall health and well-being [2, 3]. Despite significant improvements in the treatment of EC, which have contributed to better prognoses for patients [4, 5], future study into the pathological mechanisms of EC is essential for enhancing patient survival rates.

Members of the tripartite motif (TRIM) family, known for their E3 ubiquitin ligase activity, play crucial roles in various cellular processes such as intracellular signal transduction, autophagy, carcinogenesis and other biological pathways [6–8]. Studies have indicated that TRIM3, a member of the TRIM family, affects the development and prognosis of breast cancer, liver cancer, colorectal cancer and cervical cancer through regulating the cell cycle, apoptosis, invasion and other processes [9–12]. However, there is currently a dearth of research on TRIM3 in EC, necessitating further investigations to authenticate its function and regulatory mechanisms in the progression of EC.

p53 is a vital tumor suppressor protein that predominantly regulates cell cycle regulation, apoptosis and DNA repair processes [13]. Mutations in the p53 gene are often observed in EC, leading to the impairment of the p53 protein function and exacerbating the progression of EC [14, 15]. Evidence also indicates that the restoration of p53 function or inhibiting the negative regulator of p53 could be a promising approach for treat EC treatment [16, 17]. A previous study conducted earlier demonstrated that TRIM3 plays a role in inhibiting tumor growth in colorectal cancer through the stabilization of the p53 protein [18]. But whether TRIM3 exerts functions in EC by regulating the p53 protein is unclear.

In this study, examination of the UALCAN and Kaplan-Meier Plotter Databases indicated that individuals diagnosed with EC and exhibiting low levels of TRIM3 expression tend to experience unfavorable prognosis. Further *in vitro* TRIM3 gain-of-function studies were performed to clarify the effects of TRIM3 on EC cells and determine whether the p53 pathway was involved.

2. Materials and methods

2.1 Cell culture and transfection

Human EC cell lines (Ishikawa and HEC-1A), which were authenticated by short tandem repeat (STR) and were mycoplasma-free, were obtained from the Chinese Academy of Science Cell Bank (Shanghai, China). Ishikawa and HEC-1A cells were cultured in Roswell park memorial institute 1640 (RPMI 1640) and Dulbecco's modified eagle medium

(DMEM) medium, respectively, containing 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin.

The TRIM3 overexpression plasmid (pcDNA3.1-TRIM3, TRIM3) and the empty pcDNA3.1 vector (Vector, used as a negative control) were provided by Hanbio (Shanghai, China). Lipofectamine 3000 reagent (L3000008, Invitrogen, Carlsbad, CA, USA) was used for cell transfection. Cells were collected for further analysis 48 h post-transfection. For pifithrin-α treatment, cells were pre-treated with 10 μM pifithrin-α (p4236, Sigma-Aldrich, Burlington, MA, USA) for 2 h before transfection.

2.2 Real-time quantitative RT-PCR (qPCR)

Total RNA was isolated with Trizol reagent (Invitrogen), followed by cDNA synthesis. Next, qPCR was conducted using SYBR Green methods (Takara, Dalian, China) with TRIM3-specific primers (Forward: 5′-CTGTTCCAACGCGAGGCT-3′, Reverse: 5′-TTGTCCATTGGCTGGACCTC-3′) and β-actin (Forward: 5′-ACCCTGAAGTACCCCATCGAG-3′, Reverse: 5′-AGCACAGCCTGGATAGCAAC-3′) as the reference gene. An analysis of data was performed using the $2^{-\Delta\Delta Ct}$ method.

2.3 Cell counting kit 8 (CCK8) assays

Transfected cells (5×10^3), pre-treated with or without pifithrin-α, were plated per well in 96-well plates. Then, 10 μL of CCK8 (CK04, Dojindo, Tokyo, Japan) per well were added at different time points and incubated at 37 °C for 4 h. Next, microplate readers (ELx808, BioTek, Winooski, VT, USA) were employed to measure absorbance at 450 nm.

2.4 Colony formation assay

To initiate colony formation, approximately 3000 cells were evenly distributed per well in 6-well plates and cultured for about 14 d, with medium replacement every 48 h. Following this, the cells were washed, fixed and stained with 5% crystal violet. The plates were subsequently dried, images were taken and the number of cells in each well was recorded.

2.5 Cell cycle assay

For cell cycle distribution, transfected cells were fixed with 70% pre-cold ethanol. After incubating with Ribonuclease A from bovine pancreas (RNase A), propidium iodide (PI) solution was used to stain cells. The cell cycle distribution was then analyzed using an flow cytometer (Attune NxT, Thermo Fisher Scientific, Eugene, OR, USA).

2.6 Cell apoptosis analysis

Annexin V-Fluorescein isothiocyanate (FITC)/Propidium iodide (PI) staining (Solarbio, Beijing, China) was utilized, followed by flow cytometry to analyze cell apoptosis. Briefly, harvested transfected cells were resuspended in 500 μL binding buffer. Next, Annexin V-FITC and PI were sequentially applied to label cells. Cell apoptosis was monitored using an Attune flow cytometer.

2.7 Western blot

Western blotting was conducted as described previously [19]. The primary antibodies as follows: anti-Bax (ab243140, 1:5000, Abcam), anti-Bcl-2 (ab241548, 1:1000, Abcam), anti-p53 (ab179477, 1:2000, Abcam), anti-p21 (ab220206, 1:1000, Abcam), and anti-β-actin (ab8226, 1:1000, Abcam). The intensity of the protein bands in grayscale, observed through electrochemiluminescence, was quantified utilizing ImageJ software (6.0.1, BIO-RAD Laboratories, Hercules, CA, USA).

2.8 Statistical analysis

Three replications of each experiment were conducted. The data (which followed a normal distribution) were presented as mean $\pm$ Standard Deviation (SD) and analyzed using GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA, USA). One-way Analysis of Variance (ANOVA) was employed to assess significant differences among multiple groups. The significance level was defined as $p < 0.05$.

3. Results

3.1 TRIM3 is lowly expressed in EC

According to UALCAN database (https://ualcan.path.uab.edu), we first analyzed TRIM3 expression in EC samples from The Cancer Genome Atlas (TCGA) and found that TRIM3 was obviously downregulated in EC compared to the expression levels in normal tissues (Fig. 1a). Subsequently, the prognostic value of TRIM3 expression in EC was assessed using the Kaplan-Meier Plotter Database (http://kmplot.com/analysis/). As shown in Fig. 1b, EC patients with low TRIM3 expression exhibit a worse outcome. Moreover, qPCR analysis revealed a decrease in TRIM3 mRNA expression in HEC-1A cells (Fig. 1c). These findings indicate that low TRIM3 expression is correlated with poor prognosis in EC patients.

3.2 TRIM3 suppresses the proliferation of EC cells

Subsequently, we investigated the impact of TRIM3 overexpression on cell proliferation in Ishikawa and HEC-1A cells. Western blot analysis showed that TRIM3 overexpression significantly increased TRIM3 protein expression in cells (Fig. 2a). The outcomes from the CCK8 assay showed a reduction in the viability of Ishikawa and HEC-1A cells following TRIM3 overexpression (Fig. 2b). Consistently, the colony formation assay revealed a decrease in the rate of clone formation in TRIM3-overexpressed Ishikawa and HEC-1A cells (Fig. 2c). These data indicate that TRIM3 overexpression exerts anti-tumor activity in EC by inhibiting cell proliferation.

3.3 TRIM3 induces EC cell cycle arrest

Flow cytometry analysis was conducted to examine how TRIM3 on cell cycle distribution in Ishikawa and HEC-1A cells. As shown in Fig. 3, compared with the Control and Vector groups, cells in the G1 phase increased evidently, while those in the S phase decreased in TRIM3 group. These

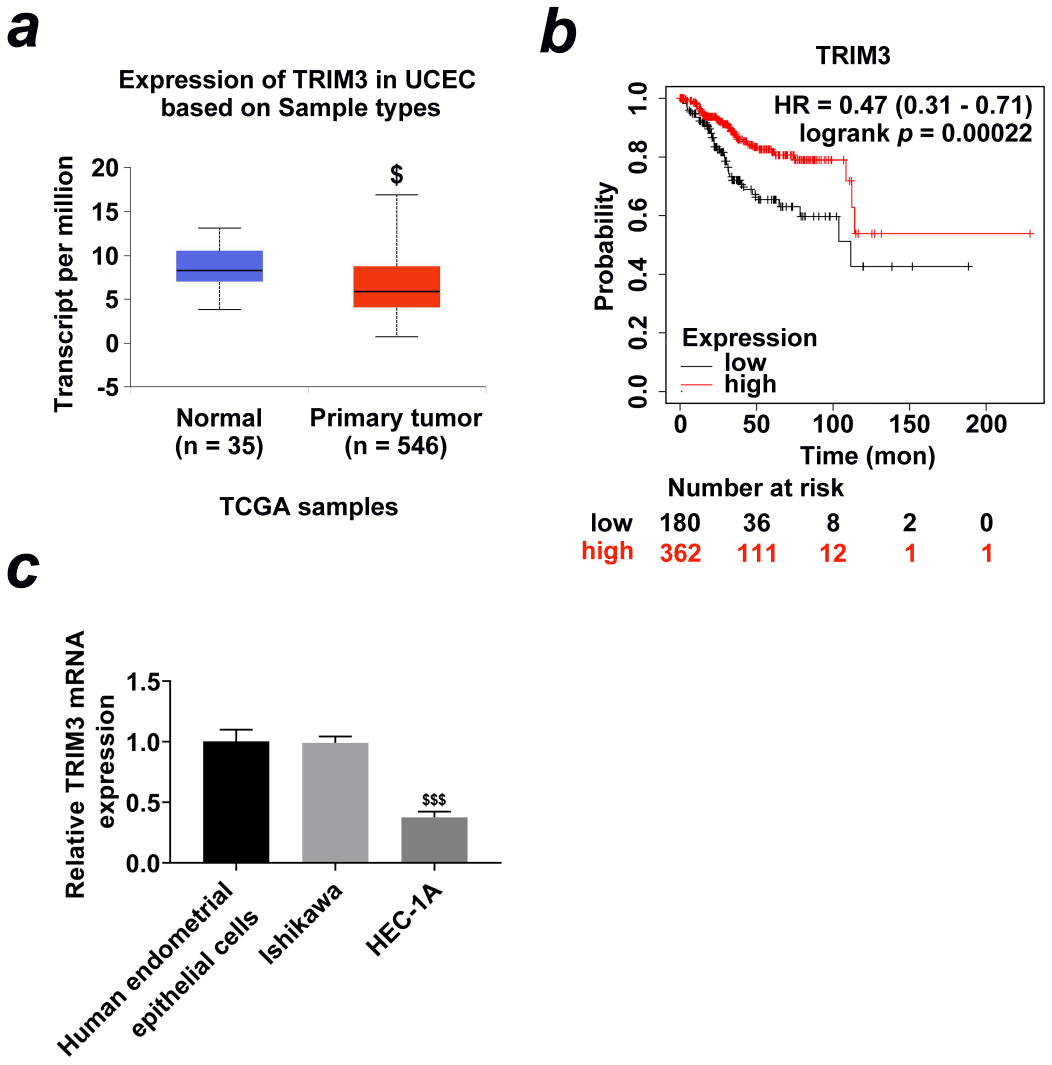

FIGURE 1. TRIM3 is downregulated in EC and associated with patient prognosis. (a) Analysis of TRIM3 expression in EC in the TCGA database through the UALCAN web-portal. $^{\$}p < 0.05$ *vs.* Normal. (b) Survival analysis of TRIM3 expression in EC was acquired from the Kaplan-Meier plotter database. (c) The mRNA expression of TRIM3 in EC cells was detected by qPCR. $^{\$\$\$}p < 0.001$ *vs.* Human endometrial epithelial cells. TRIM3: Tripartite motif-containing 3; UCEC: Uterine Corpus Endometrial Carcinoma; TCGA: The Cancer Genome Atlas; HR: Hazards Ratio; mRNA: messenger ribonucleic acid.

findings imply that overexpression of TRIM3 may inhibit EC cell proliferation by inducing cell cycle arrest.

3.4 TRIM3 promotes EC cell apoptosis

Subsequently, the impact of TRIM3 on the apoptosis of Ishikawa and HEC-1A cells was evaluated using Flow cytometry. As shown in Fig. 4a, overexpression of TRIM3 resulted in a notable increase in cell apoptosis. Furthermore, the Western blot analysis showed that overexpression of TRIM3 increased Bax protein levels and decreased Bcl-2 protein levels in cells (Fig. 4b). The data presented suggest that TRIM3 promotes apoptosis in EC cells.

3.5 TRIM3 regulates the proliferation and apoptosis of EC cells by activating p53 pathway

Moreover, the Western blots analysis showed increased expression of p53 and p21 in TRIM3-overexpressing Ishikawa and HEC-1A cells (Fig. 5a). Subsequently, pifithrin-α, a p53 inhibitor, was additionally employed to validate that TRIM3 functions in its anti-tumor capacity through modulation of the p53/p21 pathway. The results indicated that the viability of TRIM3-overexpressing cells was reduced by treatment with pifithrin-α (Fig. 5b). Consistently, a lower expression of Bax and an elevated expression of Bcl-2 were observed in TRIM3-overexpressing cells after pifithrin-α treatment (Fig. 5c,d). These data substantiate that the activation of TRIM3 on p53/p21 pathway suppresses EC cell proliferation and triggers cell apoptosis.

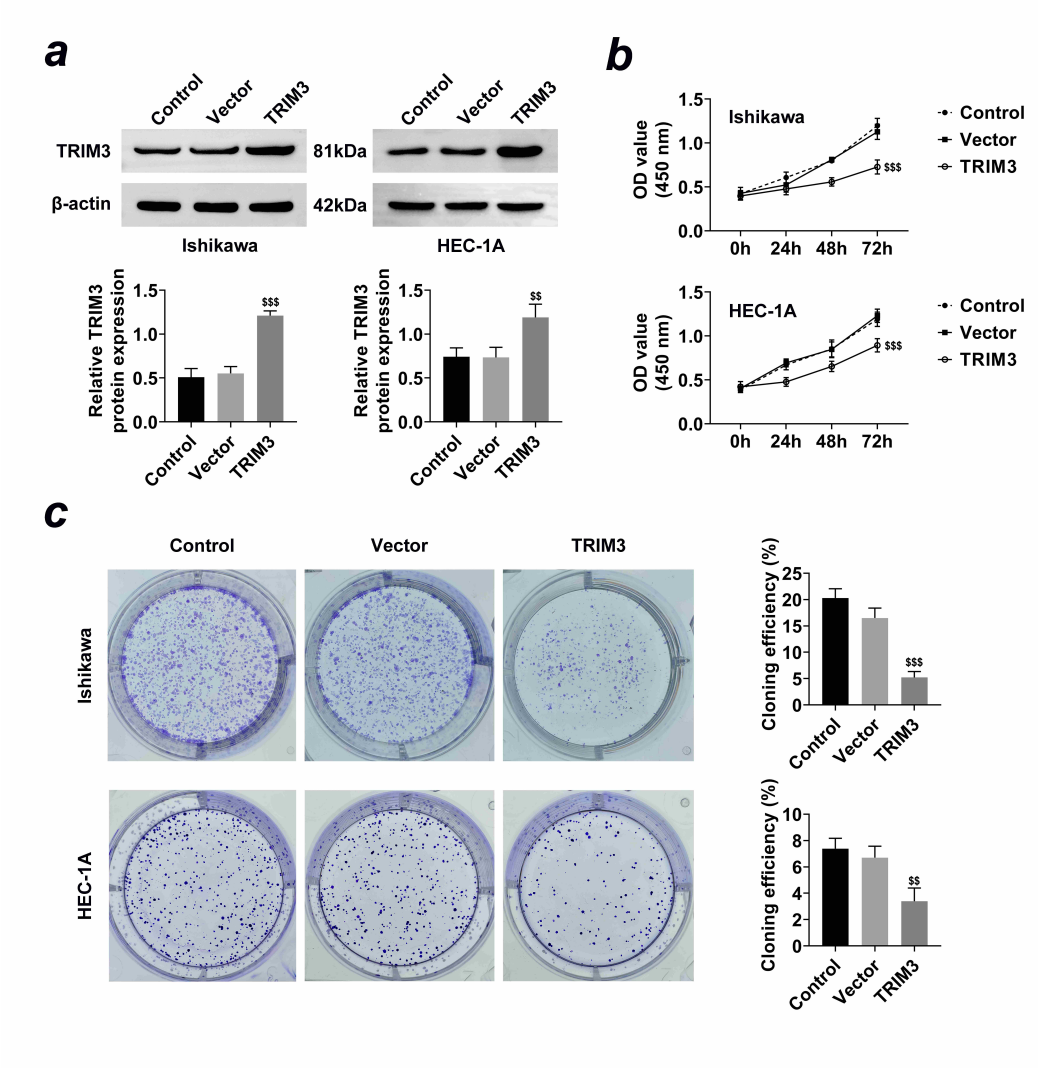

FIGURE 2. TRIM3 overexpression represses proliferation of EC cells. (a) Western blot confirmed the transfection efficiency of overexpression TRIM3 in Ishikawa and HEC-1A cells. (b) Cell viability assayed by CCK8. (c) Clone formation capacity of cells was evaluated by the clone formation assay. $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ *vs.* Control and Vector groups. TRIM3: Tripartite motif-containing 3; OD: Optical density.

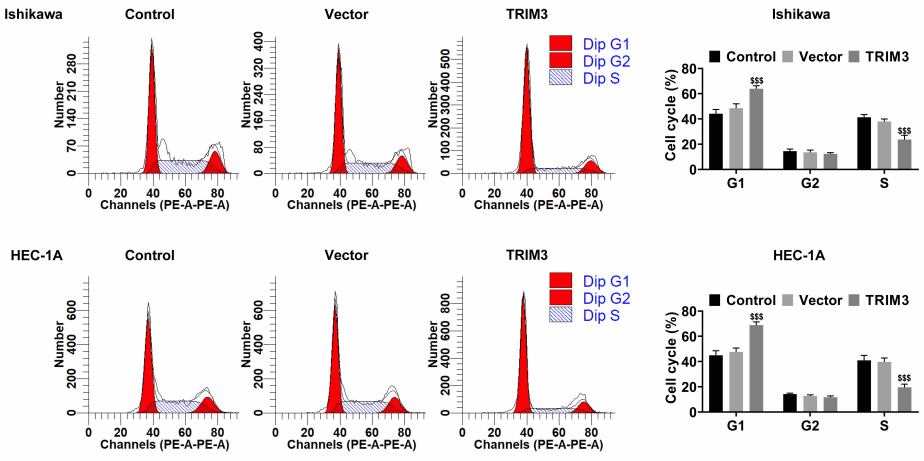

FIGURE 3. TRIM3 overexpression results in EC cell cycle arrest. Representative cell cycle distribution was measured (left) and the percentage of cells in different phases was determined (right) by flow cytometry. $^{\$\$\$}p < 0.001$ *vs.* Control and Vector groups. TRIM3: Tripartite motif-containing 3; PE: Phycoerythrin.

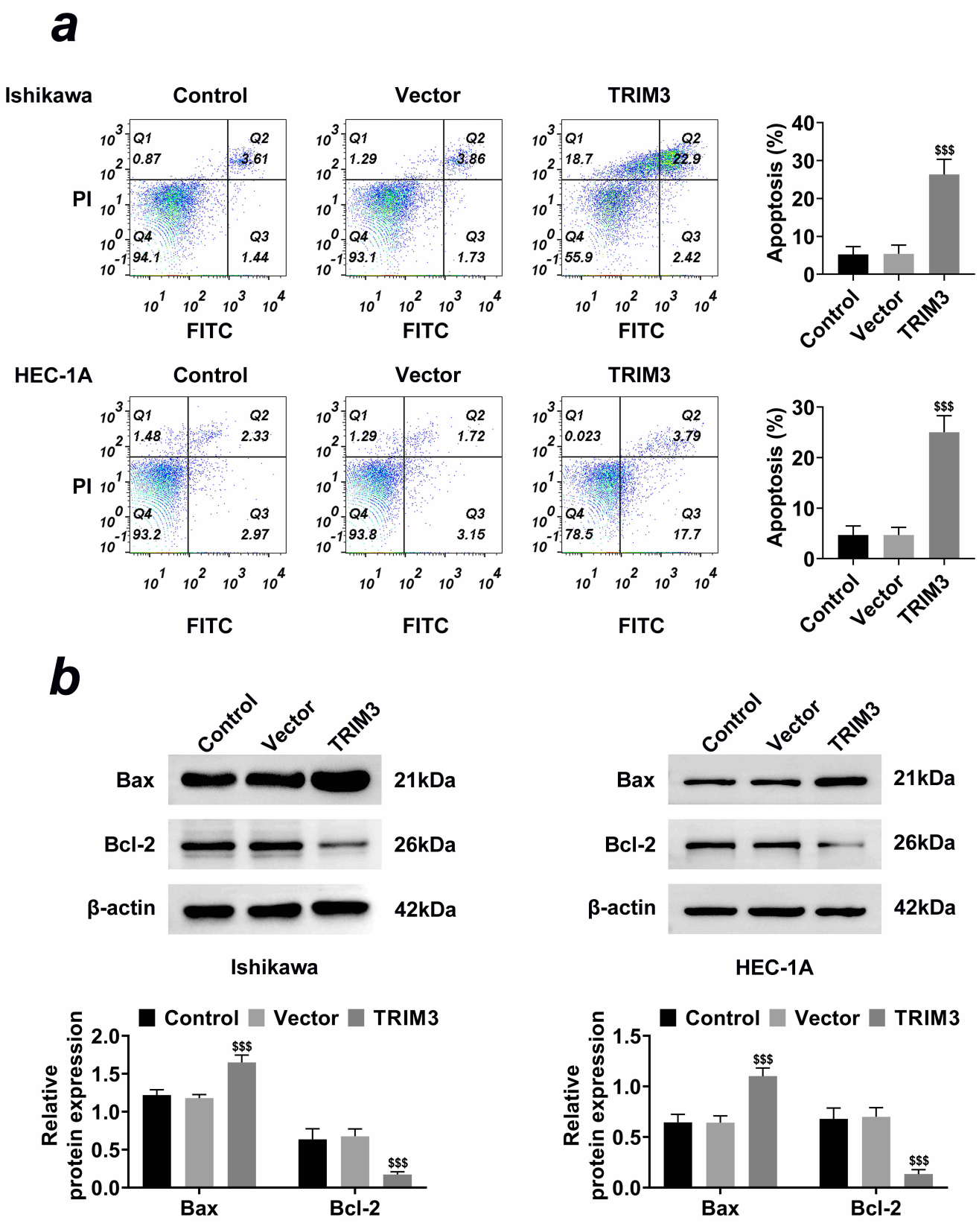

FIGURE 4. TRIM3 overexpression promotes EC cell apoptosis. (a) Cell apoptosis was determined by flow cytometry. (b) The protein levels of Bax and Bcl-2 were detected by western blot. $^{\$\$\$}p < 0.001$ *vs.* Control and Vector groups. PI: Propidium Iodide; FITC: Fluorescein Isothiocyanate; TRIM3: Tripartite motif-containing 3; Bcl-2: B-cell lymphoma-2.

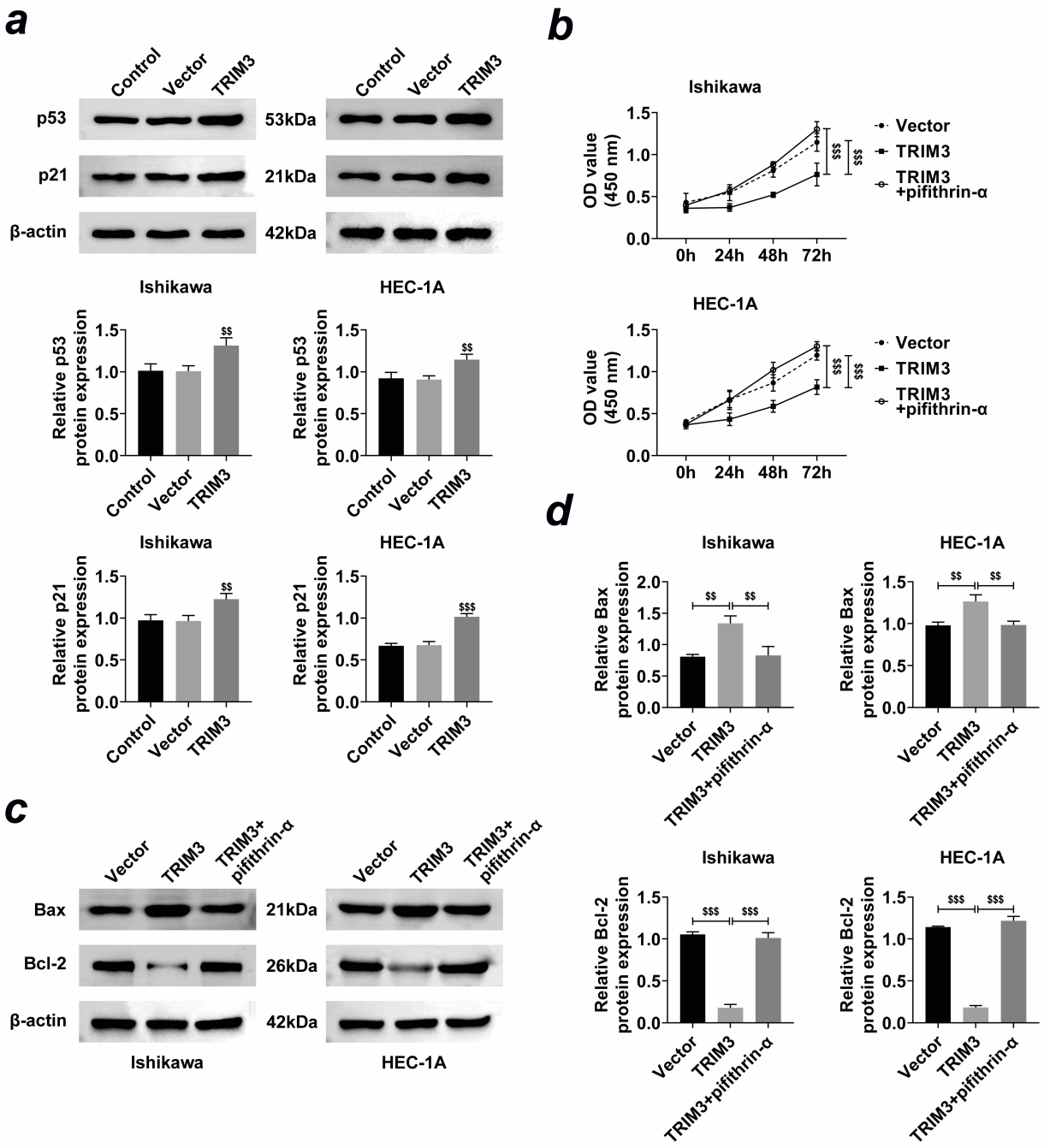

FIGURE 5. TRIM3 overexpression activates p53 to exert its regulation on EC cells. (a) Western blot analysis was performed to determine the expression of p53 and p21. $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ *vs.* Control and Vector groups (b) Cell viability assayed by CCK8. Western blot bands of Bax and Bcl-2 (c) and statistical results (d) are shown. $^{\$\$}p < 0.01$ and $^{\$\$\$}p < 0.001$. TRIM3: Tripartite motif-containing 3; OD: Optical density; Bcl-2: B-cell lymphoma-2.

4. Discussion

The downregulation of TRIM3 has been associated with various types of cancers. For example, Song *et al.* [20] discovered the deletion of TRIM3 in cervical cancer, and overexpression of TRIM3 led to reduced cell viability and enhanced cell apoptosis by suppressing the p38 pathway. According to the findings of Farhadi *et al.* [21], there was a positive correlation observed between decreased TRIM3 expression in gastric cancer and the heightened expression levels of Bcl-2 and Cyclin D. In addition, it has been verified that TRIM3 can halt the cell cycle in liver cancer, thereby inhibiting the progression of cancer [10]. Herein, utilizing bioinformatics techniques, we observed TRIM3 exhibited decreased expression in EC, and the diminished levels were linked to an adverse prognosis in EC patients. As anticipated, the outcomes of the experiment involving the overexpression of TRIM3 revealed that TRIM3 suppressed the viability of EC cells and their ability to form

clones, induced cell cycle arrest in G1 phase and cell apoptosis, as well as elevated Bax levels and reduced Bcl-2 levels in EC cells. These data suggested that TRIM3 functioned as a tumor suppressor in EC progression.

The abnormal operation of the p53 pathway in tumors is frequently associated with the onset and advancement of tumorigenesis [22, 23]. Research has demonstrated that approximately 50% of tumors display mutations or functional impairments in the p53 gene, leading to the inactivation or depletion of p53 protein [24–26]. Consequently, cells experience a loss in their capacity to control the cell division process and mend DNA damage, ultimately boosting the survival and growth potential of cancerous cells [27, 28]. Furthermore, investigators have identified p21 as downstream target genes of the p53 pathway [29]. Upon activation, p53 upregulates the expression of p21, which subsequently interacts with and suppressed the activity of cyclin-dependent kinase complexes, thus controlling the cell cycle progression in the G1 and S phases [30, 31]. Previous research has demonstrated that TRIM3 controls the expression of p53 through ubiquitination, playing a role in the development of breast cancer and apoptosis induced by H_2O_2 in human lens cells [32, 33]. Additional data analysis indicated that the levels of p53 and p21 proteins were increased in EC cells that overexpressed TRIM3. Importantly, treatment with pifithrin-α reversed the effects of TRIM3 on viability, and Bax and Bcl-2 expression in EC cells. These data suggest a strong association between TRIM3-induced G1 phase cell cycle arrest and cell apoptosis and the activation of the p53-p21 pathway. Nonetheless, a thorough examination of the activation mechanism is essential. In addition, this research primarily emphasizes in vitro cellular experiments, lacking validation of clinical samples and in vivo experiments, thereby presenting certain constraints.

5. Conclusions

In conclusion, our results verify that upregulation of TRIM3 in EC cells can trigger the activation of p53, resulting in the halting of the cell cycle, consequently restraining cell proliferation and promoting cell apoptosis. This study presents preliminary evidence that TRIM3 could serve as a therapeutic target in EC treatment. However, substantiating these results will necessitate additional *in vivo* and clinical studies, and the objective of our future study will be to achieve this.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

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

AUTHOR CONTRIBUTIONS

MKW and YM—designed the study, completed the experiment and supervised the data collection. NY and YLC—analyzed the data, interpreted the data. LPL, SHZ, YZ and GQS—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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