Article

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Role of TRIM37 in Cervical Cancer: Its Effects on Tumor Cells Proliferation, Migration, and Invasion

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Background: Cervical cancer is the leading cause of cancer-related mortality among females worldwide. Although previous studies have implicated tripartite motif-containing protein 37 (TRIM37) in the progression of various malignancies, its precise role and the underlying molecular mechanisms in cervical cancer remain inadequately explored.
Methods: TRIM37 expression, both at protein and mRNA levels, was assessed in immortalized keratinocytes and cervical cancer cell lines using RT-qPCR and Western blotting, respectively. The cervical cancer cells were transfected with TRIM37-specific siRNA employing Lipofectamine. Cellular proliferation, migration, and invasion were evaluated using Transwell assays, flow cytometry, colony formation assays, and cell counting kit (CCK)-8. Western blotting analysis was used to assess the phosphorylation status of proteins involved in the Phosphatase and Tensin Homolog Deleted on Chromosome Ten (PTEN)/Phosphatidylinositol-3-Kinase (PI3K)/Protein Kinase B (Akt)/Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. Interaction between TRIM37 and PTEN was examined via co-immunoprecipitation assays. Furthermore, an *in vivo* nude mice xenograft model was successfully established to assess the impact of TRIM37 on tumor growth.
Results: TRIM37 was substantially upregulated in cervical cancer cell lines compared to immortalized keratinocytes ($p < 0.05$). TRIM37 knockdown significantly suppressed proliferation, migration, and invasion in cervical cancer cells, thereby promoting apoptosis ($p < 0.05$). *In vivo* analysis revealed that TRIM37 knockdown significantly inhibited the growth of tumor ($p < 0.05$). Moreover, TRIM37 silencing effectively suppressed the activity of the PTEN/PI3K/Akt/NF-κB pathway in cervical cancer cells ($p < 0.05$).
Conclusions: TRIM37 knockdown inhibits cell proliferation, migration, and invasion, as well as suppresses *in vivo* tumor growth, potentially through downregulation of the PTEN/PI3K/Akt/NF-κB signaling pathway.

Keywords: cervical cancer; TRIM37; PTEN/PI3K/Akt/NF-κB; proliferation; migration; invasion

Introduction

Cervical cancer is one of the leading causes of cancer-related mortality among females, accounting for approximately 7.5% of cancer-related deaths worldwide [1]. Despite significant advancements in vaccination programs, as well as improvements in screening and diagnostic approaches, recurrence and metastasis remain the primary contributors to cervical cancer-related deaths [2]. Persistent infections with high-risk human papillomavirus (HPV) are widely recognized as the primary risk factor; however, only a small proportion of infected individuals progress to develop cervical cancer, indicating that additional molecular mechanisms are likely involved in its pathogenesis [3]. Therefore, further investigation into the underlying biological processes and the identification of effective therapeutic targets are essential for improving clinical outcomes and disease management.

Tripartite motif-containing protein 37 (TRIM37), is an E3 ubiquitin ligase characterized by the presence of a really interesting new gene (RING) finger domain [4]. Aberrant overexpression of TRIM37 has been associated with the progression of various malignancies through its regulation of key oncogenic signaling pathways [5]. In pancreatic cancer, TRIM37 enhances tumor cell invasion, migration, proliferation, and modulate tumor immune microenvironment [6]. Similarly, in gallbladder cancer, TRIM37 promotes tumor growth by ubiquitinating Axin1, thereby activating the Wingless/Int (Wnt)/β-catenin signaling pathway [7]. In hepatocellular carcinoma, TRIM37 facilitates aerobic glycolysis and tumor progression via the K48-linked ubiquitination of p53 [8]. Moreover, TRIM37 enhances the invasiveness of ovarian cancer cells by binding to HUWE1 and increasing c-Myc expression [5]. In cervical cancer, limited studies have suggested a potential oncogenic role for TRIM37. For instance, circRNA_101996 has been reported to promote cervical cancer progression by regulating the miR-1236-3p/TRIM37 axis [9]. Nevertheless, the precise functions and regulatory mechanisms of TRIM37 in cervical cancer remain poorly defined and need further investigation.

The Phosphatase and Tensin Homolog Deleted on Chromosome Ten (PTEN)/Phosphatidylinositol-3-Kinase (PI3K)/Protein Kinase B (Akt)/Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway plays a crucial role in modulating cellular inflammation, proliferation, and survival; its abnormal activation has been closely linked to the development and progression of various human carcinomas [10]. Emerging evidence suggests that TRIM37 may influence this pathway by promoting the ubiquitination of PTEN, thereby alleviating its stability and modulating downstream signaling activity [11].

The current study aimed to evaluate the role of TRIM37 in the malignant progression of cervical cancer, specifically emphasizing its impact on cell proliferation, colony formation, migration, invasion, and apoptosis, as well as its potential regulatory interaction with the PTEN/PI3K/Akt/NF-κB pathway.

Methods

Cells Culture

Four human cervical cancer cell lines—C33A (HTB-36), CaSki (CRM-CRL-1550), SiHa (HTB-35), and HeLa (CCL-2)—as well as the human immortalized keratinocyte cell line HaCaT (ATCC, T0020001), were procured from the American Type Culture Collection (ATCC, Manassas, VA, USA). All cell lines were cultured in DMEM containing 10% fetal bovine serum (FBS) and 50 µg/mL penicillin-streptomycin (Gibco) in a humidified incubator maintained at 37 °C with 5% CO_2. Before experimentation, cells were authenticated using short tandem repeat (STR) profiling and evaluated for mycoplasma contamination.

Silencing of the TRIM37 Gene Expression

TRIM37 expression was silenced using siRNA-mediated transfection. Cells were transfected with either TRIM37-specific siRNA (sense: GCACCAGUUGCGGUCUUGUAGUAAG; antisense: CUUACUACAAGACCGCAACUGGUGC; Sigma, Tokyo, Japan) or negative control siRNA (RNAi Negative Control Lo GC, Ref: 12935200, Invitrogen, Carlsbad, CA, USA) using Lipofectamine RNAiMAX (13778-075, Invitrogen, Carlsbad, CA, USA), following the manufacturer's protocols. After successful transfection, the HeLa cells were exposed to 20 µM SC-79 for 24 hours.

Cell Proliferation, Colony Formation, and Apoptosis Assay

HeLa and SiHa cells were transfected and then seeded into 6-well or 96-well plates, followed by incubation for 72 hours. Cell proliferation was assessed using the cell counting kit (CCK)-8 assay (C0037, Beyotime, Shanghai, China). Following 2 hours of incubation with the CCK-8 reagent, absorbance was measured at 450 nm employing a microplate reader. Furthermore, for the colony formation assay, cells were seeded into 6-well plates at a density of 1000 cells per well and incubated under standard culture conditions for 14 days. After that, the colonies were fixed with 70% ethanol and stained with 0.5% crystal violet in ethanol. Additionally, apoptosis was evaluated using the Annexin V-FITC Apoptosis Detection Kit (IM3546, Beckman Coulter, Brea, CA, USA), following the manufacturer's instructions. The percentage of apoptotic cells was quantified using a Becton Dickinson Accuri™ C6 flow cytometer.

Transwell Assay

Cell migration was evaluated using Transwell chambers with uncoated inserts. Cells were seeded into the upper chamber filled with serum-free medium, while the lower chamber was filled with medium containing 1% FBS as a chemoattractant. After 24 hours, cells that had migrated to he lower surface of the membrance were fixed and stained with 0.1% crystal violet.

However, for the invasion assay, the upper chamber was pre-coated with Matrigel (Corning Incorporated, Corning, NY, USA). Cells were seeded into the upper chamber containing serum-free medium, while the lower chamber was filled with medium supplemented with 10% FBS. After 24 hours of incubation, cells that invaded the lower surface of the membrane were fixed and subsequently stained with 0.1% crystal violet.

Quantitative RT-PCR (qRT-PCR)

Total RNA was isolated from cultured cells using TRIzol reagent (15596026, Invitrogen, Carlsbad, CA, USA), and then complementary DNA (cDNA) was synthesized employing the iScript™ cDNA Synthesis Kit (1708890, Bio-Rad, Hercules, CA, USA). Quantitative real-time PCR was conducted on an ABI Prism 7500 RT-PCR (Applied Biosystems, Foster City, CA, USA) using SYBR Premix Ex Taq (Takara, Kusatsu, Japan). Relative gene expression levels were assessed using the $2^{-\Delta\Delta Ct}$ method, with β-actin serving as an internal control. The primer sequences used in this study were as follows: β-actin-forward 5′-CATGTACGTTGCTATCCAGGC-3′; reverse 5′-CTCCTTAATGTCACGCACGAT-3′ and TRIM37-forward 5′-TATGGAGAAATTGCGGGATGC-3′; reverse 5′-GTCAGCCACGCCTAATACAG-3′.

Western Blotting

Cells were lysed using RIPA buffer, and total proteins were quantified by empoying the BCA Protein Kits (P0010, Beyotime, Shanghai, China). Equal amounts of protein was resolved by SDS-PAGE and subsequently transferred onto polyvinylidene fluoride (PVDF) membranes. The membranes were then blocked with 5% non-fat milk at room temperature for 1 hour. After that, the membranes underwent overnight incubation at 4 °C with the appropriate primary antibodies

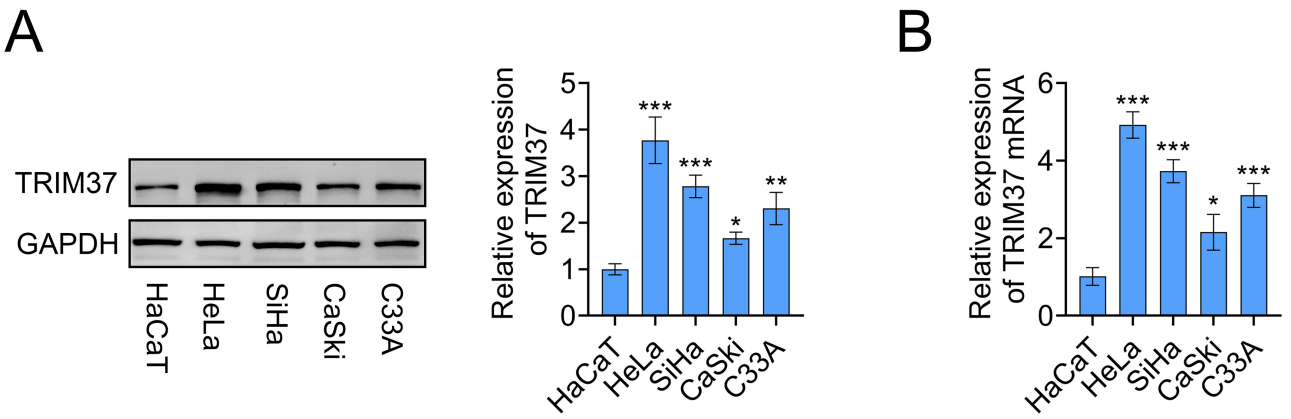

Fig. 1. Expression of TRIM37 in human cervical cancer cell lines. (A) TRIM37 protein expression in HaCaT, HeLa, SiHa, CaSki, and C33A cell lines. (B) TRIM37 mRNA expression in HaCaT, HeLa, SiHa, CaSki, and C33A cell lines. Data were presented as mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus the HaCaT group. n = 3. TRIM37, tripartite motif-containing protein 37; SD, standard deviation; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase.

(Abcam, Cambridge, UK), including Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH, 1:1000, ab8245), PTEN (1:1000, ab170941), p-Akt (1:1000, ab38449), Akt (1:1000, ab8805), p-PI3K (1:1000, ab302959), PI3K (1:1000, ab302958), p65 (1:1000, ab32536), and p-p65 (1:1000, ab31624). The next day, the membranes were washed and incubated with HRP-conjugated secondary antibodies (Anti-mouse IgG, HRP-linked Antibody, #7076, 1:3000; Goat Anti-Rabbit Immunoglobulin G (IgG) H&L(HRP), #35401, 1:3000; Cell Signaling Technology, Danvers, MA, USA) at room temperature for 1 hour. Protein bands were visualize using the BeyoECL Star Kit (P0018, Beyotime, Shanghai, China) and quantified by densitometry using ImageJ software (version 1.43, NIH, Bethesda, MD, USA).

Ubiquitination Assays

Cells were transiently transfected with HA-tagged ubiquitin (HA-Ub) and indicated plasmids. Following 48 hours of incubation, cell lysates were collected, and ubiquitinated proteins were detected using a Ubiquitination Detection Kit (Abcam, Cambridge, UK), following the manufacturer's protocol.

Co-Immunoprecipitation (Co-IP)

Cells were cultured in 15-cm plates and lysed with the same buffer used for chromatin immunoprecipitation (ChIP). Cell lysates were incubated overnight at 4 °C on a rotator with a mixture of 100 µL magnetic beads and 5 µg anti-TRIM37 antibody. The resulting antibody-protein-bead complexes were then washed with RIPA buffer, resuspended in SDS loading buffer, boiled for 10 minutes, and analyzed by using Western blotting analysis.

In Vivo Tumor Xenograft Model

Female Breeding Associate Laboratory Breeding colony (BALB/c) nude mice (n = 12), weighing 22–25 g and aged 4–5 weeks, were obtained from the Shanghai Experimental Animal Center, China. The experiments involving animals were approved by the Animal Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Approval No. YJSDW2022-057) and performed following the Guidelines of Care and Use of Laboratory Animals. The mice were housed under a specific pathogen-free environment, maintained a 12-hour dark/light cycle, and 22 ± 1 °C temperature and 60–70% humidity. Food and water were provided ad libitum. HeLa cells (1×10^6), transfected with either siTRIM37 or negative control siRNA (si-NC), were administered via subcutaneous injection into the right axilla of each mouse, with 6 animals per group. Tumor growth was monitored twice a week using calipers, and tumor volume was determined accordingly. On day 28 post-inoculation, mice were euthanized through cervical dislocation, and tumors were then excised, weighed, and recorded.

Immunohistochemical Staining

Paraffin-embedded tumor tissues were sectioned and subjected to immunohistochemical staining. Sections were incubated overnight at 4 °C with a primary antibody against Ki-67 (1:500, ab15580), followed by washing and a 30-minute incubation at 37 °C with a secondary antibody (Goat Anti-Rabbit IgG H&L, #35401, 1:1000). The intensity and distribution of Ki-67 staining were evaluated in three randomly selected microscopic fields per sample, focusing on positively stained areas or positive immunoreactivity.

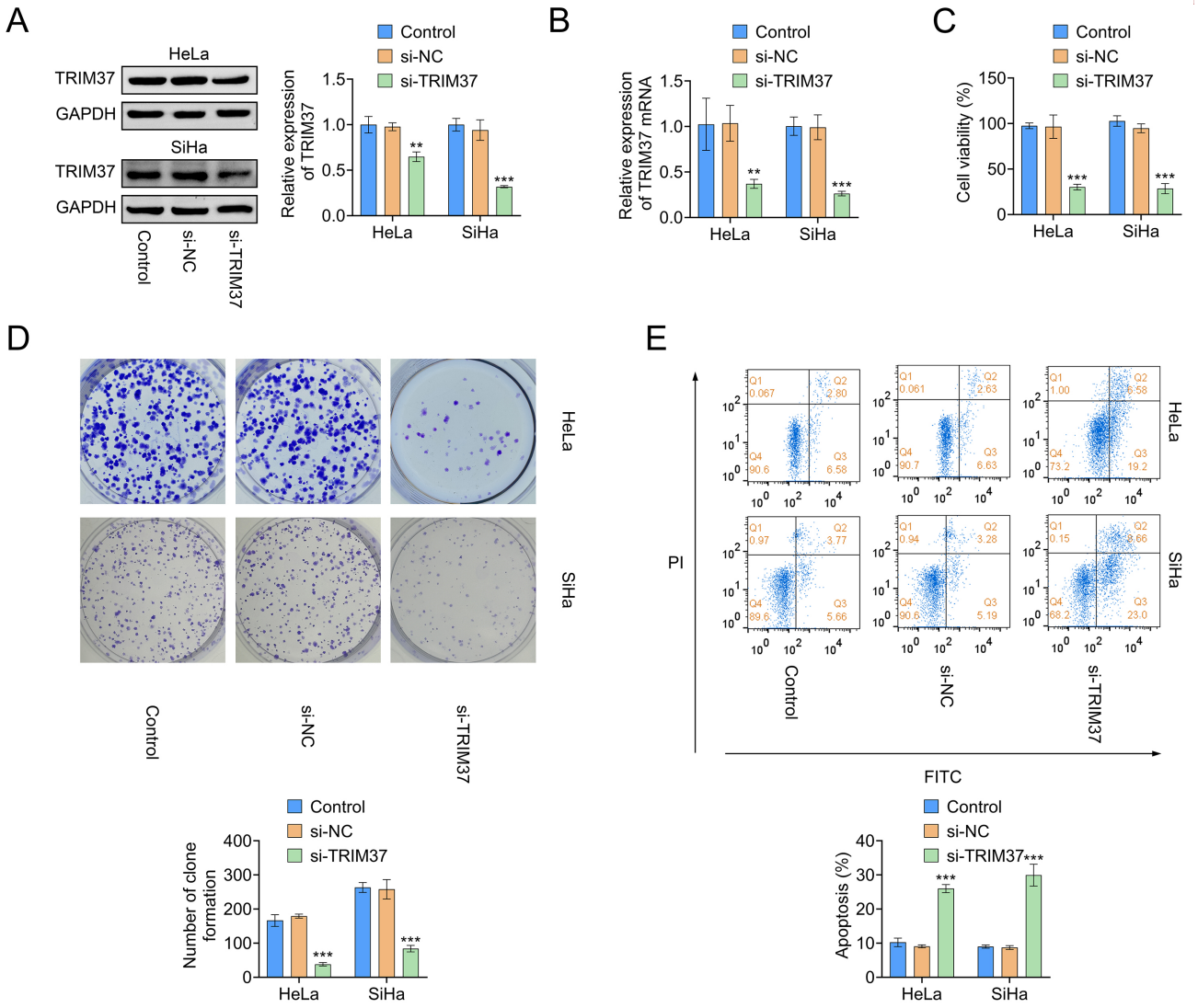

Fig. 2. TRIM37 knockdown inhibits the proliferation of cervical cancer cells. (A,B) TRIM37 protein and mRNA expression levels in negative control siRNA (si-NC) or si-TRIM37-transfected SiHa and HeLa cells. (C) Cell counting kit (CCK)-8 assay assessing cell viability. (D) Colony formation assay: representative crystal violet-stained colonies (left) and quantification of colony numbers (right). (E) Apoptosis rate measured by Annexin V/Propidium Iodide (PI) stained flow cytometry. Data were presented as mean ± SD. ** $p <$ 0.01, *** $p < 0.001$ versus the si-NC group. n = 3.

Statistical Analyses

Statistical analysis was conducted using GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA, USA). Pair-wise comparison (comparison between two groups) was performed using unpaired *t*-tests, whereas multiple groups comparisons were conducted using one-way ANOVA followed by Bonferroni's post hoc test. Data were expressed as mean ± standard deviation (SD). A *p*-value of less than 0.5 was considered statistically significant. Each experiment was independently repeated in triplicate.

Results

Expression of TRIM37 in Cervical Cancer Cell Lines

To assess the expression levels of TRIM37 in cervical cancer, its expression was evaluated in four human cervical cancer cell lines (C33A, CaSki, SiHa, and HeLa) and compared to a non-tumorigenic HaCaT cell line. Both RT-qPCR and Western blotting revealed significantly elevated TRIM37 expression at both the mRNA and protein levels in the cervical cancer cell lines compared to HaCaT cells ($p < 0.05$, Fig. 1). Among the cell lines evaluated, SiHa and HeLa exhibited the highest TRIM37 expression and were therefore selected for subsequent functional assays.

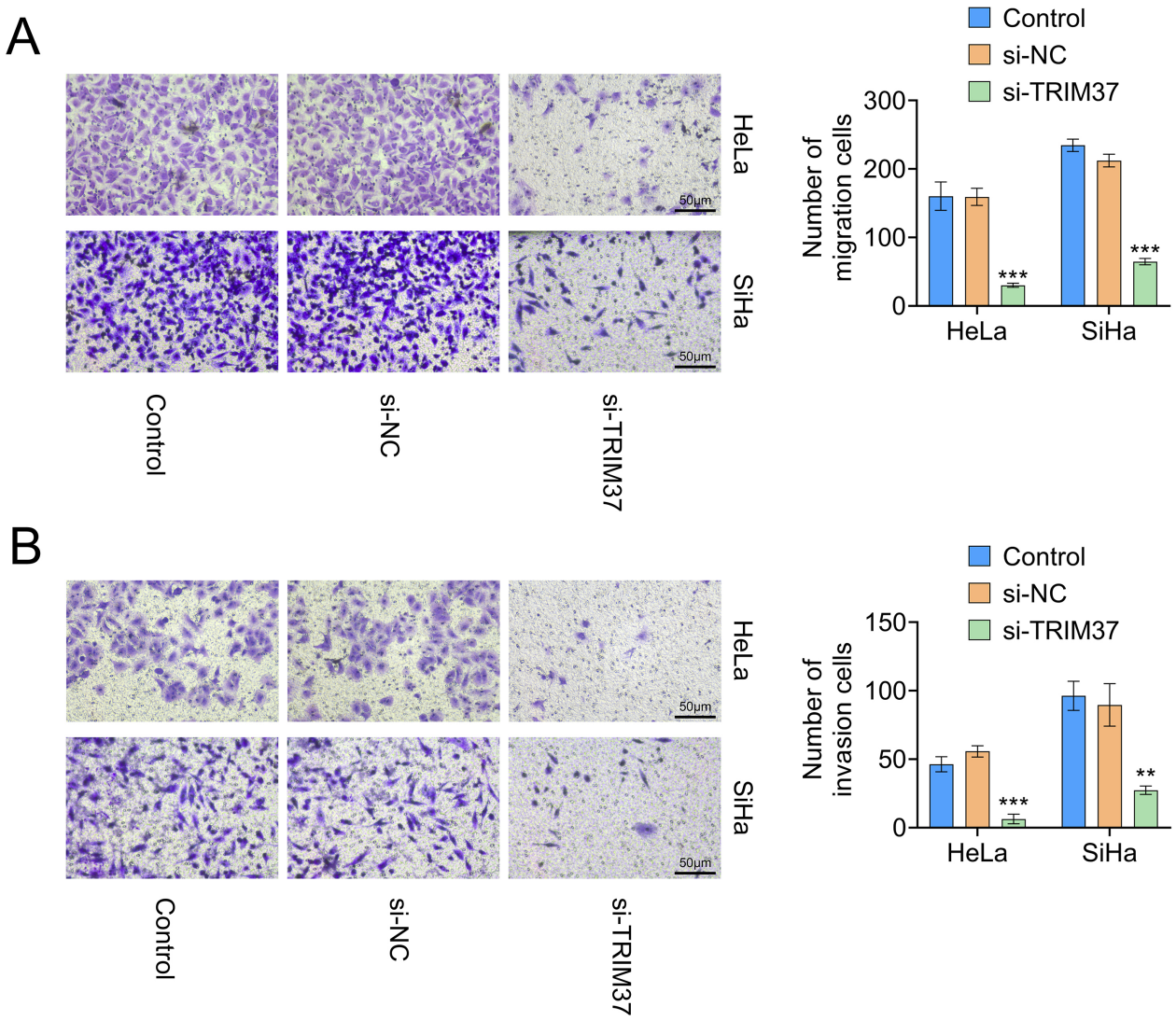

Fig. 3. TRIM37 knockdown inhibits cervical cancer cells invasion and migration. (A) Transwell migration assays: migrated cells quantification (right) and characteristic images (left). (B) Transwell invasion assays: invaded cells quantification (right) and characteristic images (left). Data were expressed as mean ± SD. ** $p < 0.01$, *** $p < 0.001$ versus the si-NC group. n = 3.

TRIM37 Knockdown Inhibits the Proliferation of Cervical Cancer Cell Lines

The imapct of TRIM37 knockdown on HeLa and SiHa cell proliferation was assessed using RT-qPCR and Western blotting analyses, indicating a substantial decrease in TRIM37 mRNA and protein levels following siRNA transfection ($p < 0.05$, Fig. 2A,B).

Furthermore, the CCK-8 assay demonstrated that TRIM37 silencing suppressed the proliferation of cervical cancer cells. Similarly, colony formation assays revealed a substantial reduction in the colony-forming ability of TRIM37-knockdown cells compared to the negative control ($p < 0.05$, Fig. 2C,D). Moreover, flow cytometry analysis using Annexin V/Propidium Iodide (PI) staining demonstrated a significant increase in the proportion of apoptotic cells after TRIM37 knockdown ($p < 0.05$, Fig. 2E). Overall, these results suggest that TRIM37 knockdown inhibits the proliferation of cervical cancer cells and promotes apoptosis *in vitro*.

TRIM37 Knockdown Inhibits the Invasion and Migration of Cervical Cancer Cells

To further investigate the role of TRIM37 in cervical cancer progression, we evaluated its impact on cell motility. The Transwell assay was performed to assess the invasion and migration capabilities of HeLa and SiHa cells following TRIM37 knockdown. We observed that silencing TRIM37 substantially decreased the number of invading and migrating cells compared to the si-NC group ($p < 0.05$, Fig. 3A,B). These findings indicate that TRIM37 knockdown impairs the invasive and migratory potentials of cervical cancer cells, critical features associated with metastatic potential.

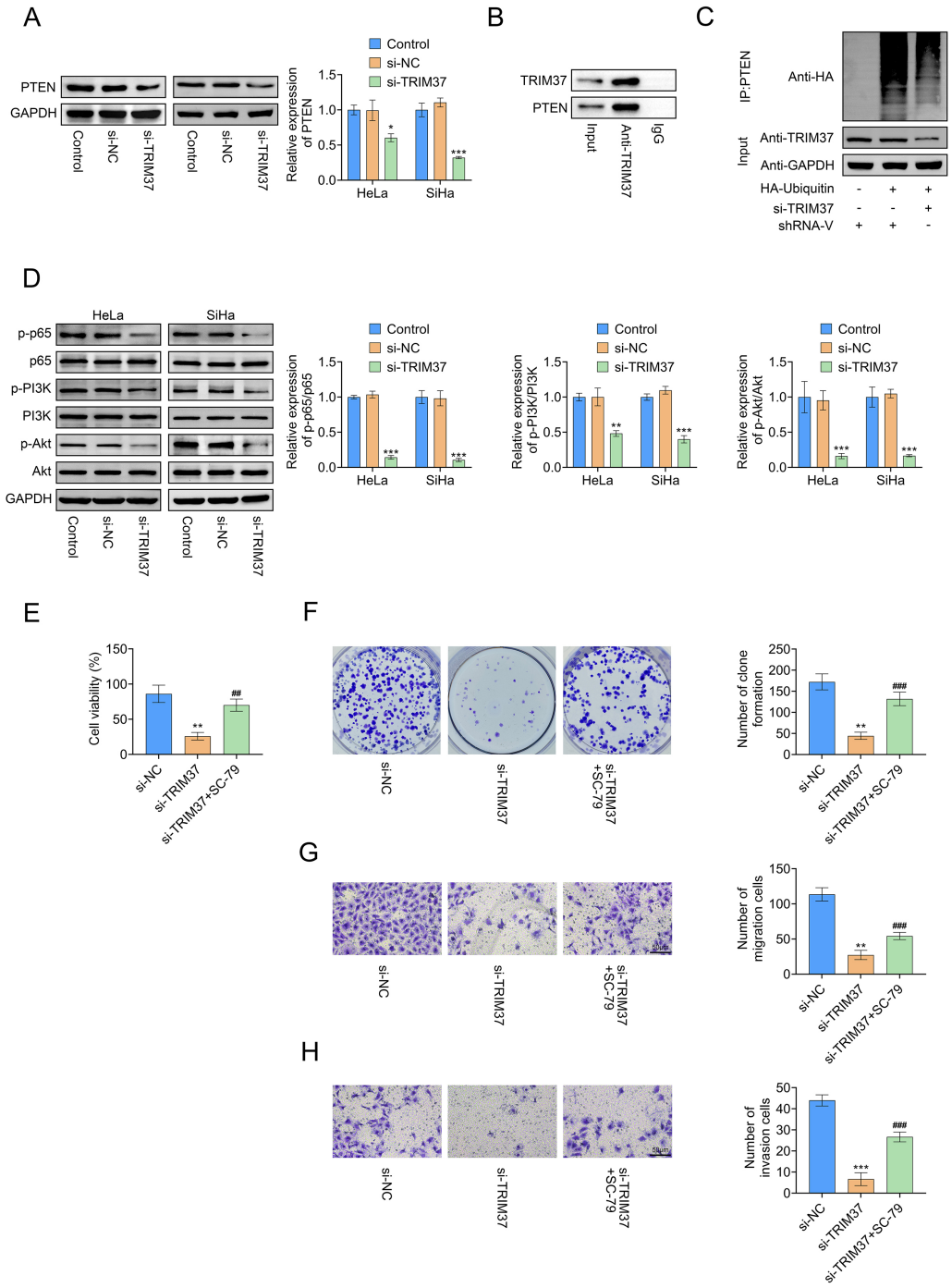

Fig. 4. TRIM37 knockdown inhibits the PTEN/PI3K/Akt/NF-κB signaling pathways. (A) PTEN protein expression in HeLa and SiHa cells. (B) Co-immunoprecipitation showing interaction between TRIM37 and PTEN in HeLa cells. (C) Ubiquitination levels of PTEN following TRIM37 knockdown. (D) Protein expression of Akt, p-Akt, PI3K, p-PI3K, p65, and p-p65 in HeLa and SiHa cells. (E) CCK-8 assays to assess cell viability. (F) Colony formation assays with crystal violet staining. (G) Transwell assay to assess cell migration. (H) Transwell assay to determine cell invasion. Data were presented as mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus the si-NC group. $^{\#\#}$ $p < 0.01$, $^{\#\#\#}$ $p < 0.001$ versus the si-TRIM37 group. n = 3. PTEN/PI3K/Akt/NF-κB, Phosphatase and Tensin Homolog Deleted on Chromosome Ten/Phosphatidylinositol-3-Kinase/Protein Kinase B/Nuclear Factor kappa-light-chain-enhancer of activated B cells.

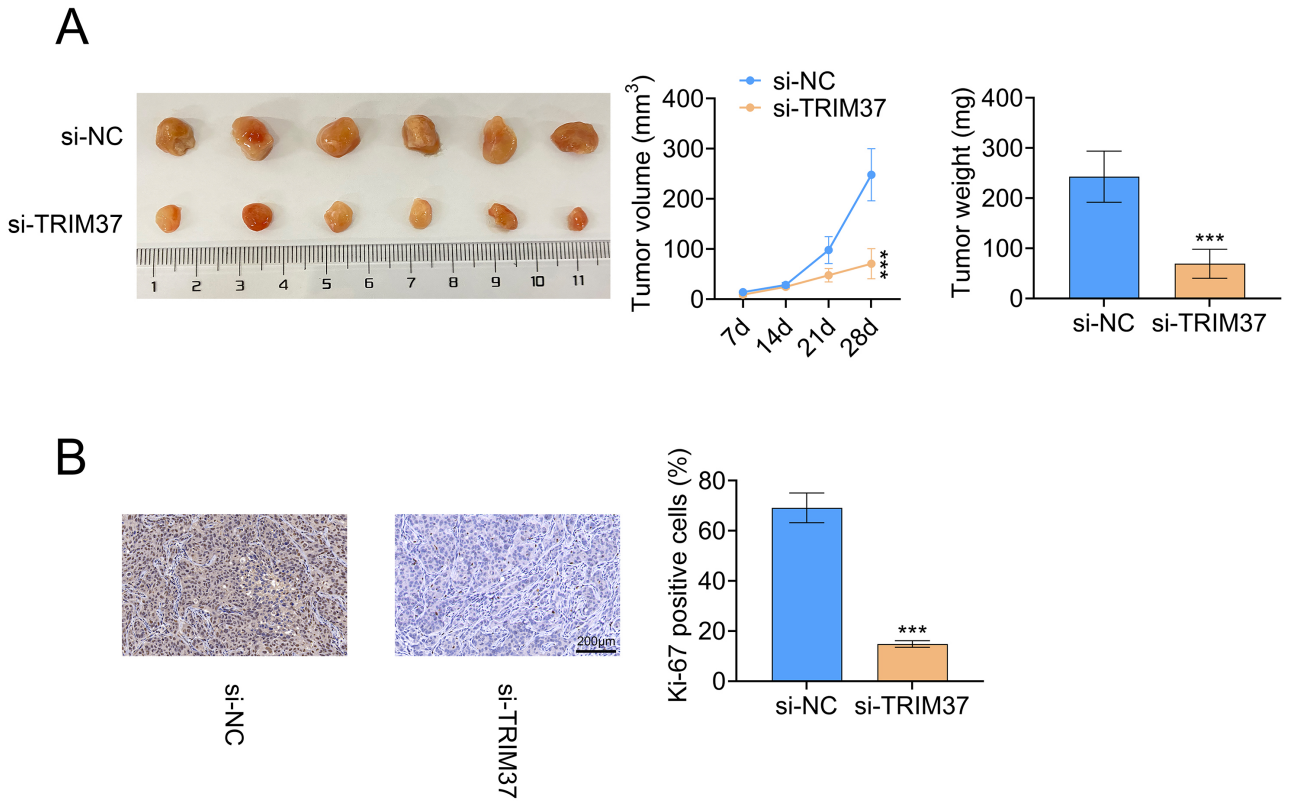

Fig. 5. TRIM37 knockdown suppresses tumor growth *in vivo*. (A) Representative images of the excised tumor and quantitative analysis of tumor volume and weight. (B) Immunohistochemical staining showing Ki-67 expression in xenograft tumor tissues. Data were expressed as mean ± SD. *** $p < 0.001$ versus the si-NC group. n = 6.

TRIM37 Silencing Inhibits the PTEN/PI3K/Akt/NF-κB Signaling Pathway

To elucidate the molecular mechanism underlying the oncogenic role of TRIM37, we investigated its regulatory effect on the PTEN/PI3K/Akt/NF-κB signaling pathway. Co-immunoprecipitation assays revealed a physical interaction between TRIM37 and PTEN. Moreover, TRIM37 knockdown significantly decreased PTEN protein expression and reduced PTEN ubiquitination ($p < 0.05$, Fig. 4A–C). Consistently, Western blotting analysis revealed that TRIM37 silencing significantly reduced phosphorylations of p65, PI3K, and Akt, while total protein levels remained unchanged ($p < 0.05$, Fig. 4D). To confirm the involvement of this pathway, HeLa cells were treated with 20 μM SC-79, the PI3K/Akt signaling pathway activator. We noted that SC-79 treatment effectively reversed the inhibitory impacts of TRIM37 knockdown on cell invasion, migration, proliferation, and colony formation ($p < 0.05$, Fig. 4E–H). These observations suggest that TRIM37 promotes cervical cancer progression by activating the PTEN/PI3K/Akt/NF-κB signaling pathway.

TRIM37 Knockdown Suppresses Tumor Growth In Vivo

A HeLa cell-based xenograft mouse model with stable TRIM37 knockdown was successfully established to evaluate the *in vivo* role of TRIM37 in tumorigenesis. Four weeks after subcutaneous injection of cells into nude mice, tumor growth was assessed. As depicted in Fig. 5A, mice injected with TRIM37-knockdown cells developed significantly smaller and lighter tumors compared to the control group ($p < 0.05$). Furthermore, immunohistochemical analysis revealed that TRIM37 knockdown reduced expression of the proliferation marker Ki-67 in tumor tissues from the TRIM37-knockdown group (Fig. 5B), further validating the inhibitory effect of TRIM37 silencing on tumor cell proliferation.

Discussion

Cervical cancer is one of the most prevalent malignancies affecting women and is often linked to poorer prognosis due to its asymptomatic onset in early stages and a high likelihood of recurrence and metastasis [12]. The development of cervical cancer involves a complex, multistep biological process influenced by numerous factors, including the aberrant activation of signal pathways and the dysregulation of various protein kinases [13].

In the present study, we investigated the expression and role of TRIM37 in cervical cancer. Our findings demonstrated a substantial upregulation of TRIM37 in cervical cancer cell lines compared to non-tumorigenic keratinocytes, suggesting its potential involvement in tumor progression. Functional assays revealed that TRIM37 knockdown reduced cell proliferation, migration, and invasion and promoted apoptosis *in vitro*. Moreover, *in vivo* analysis confirmed that TRIM37 silencing significantly suppressed tumor growth in a xenograft mouse model. Collectively, these findings suggest TRIM37 as an oncogenic factor in cervical cancer and underscore its potential as a promising target for therapeutic intervention.

A key contribution of this study is the identification of the PTEN/PI3K/Akt/NF-κB pathway as a downstream effector of TRIM37, a pathway known to regulate critical cellular processes like metabolism, migration, survival, and proliferation [14]. Among its crucial components, NF-κB p65 plays a vital role as a transcription factor that promotes tumor progression primarily by increasing cell proliferation and upregulating anti-apoptotic gene expression [15]. Increasing evidence suggests that dysregulation of this pathway contributes to the pathogenesis of various malignancies. For instance, aldo-keto reductase family 1, member B10 (AKR1B10) enhances migration and proliferation of breast cancer cells by activating the PTEN/PI3K/Akt/NF-κB axis [16], while RAD51 associated protein 1 (RAD51AP1) accelerates pancreatic cancer progression via the same signaling pathway [17]. Our findings demonstrate that TRIM37 regulates the PI3K/Akt/NF-κB signaling pathway through its E3 ubiquitin ligase activity, providing mechanistic insight into cervical cancer progression. It was observed that TRIM37 exerts its oncogenic effects in cervical cancer by interacting with PTEN and promoting its ubiquitination, thereby destabilizing PTEN and sustaining activation of the PI3K/Akt signaling cascade. This mechanism is consistent with previous reports demonstrating that TRIM37 modulates similar signaling pathways in other malignancies, including pancreatic cancer [11]. By elucidating this regulatory axis, our study highlights TRIM37 as a potential molecular target in cervical cancer, suggesting that therapeutic strategies aimed at inhibiting TRIM37 or its downstream signaling components may be effective in suppressing tumor growth and metastasis.

This study has several limitations. Although several established cervical cancer cell lines were used in this study, these models do not fully represent the biological heterogeneity and complexity of cervical cancer observed in clinical settings. Furthermore, the experimental evidence was primarily based on *in vitro* cell-based assays and *in vivo* xenograft models. While these models are valuable for mechanistic insights, they do not entirely reflect the human tumor microenvironment. Notably, another crucial limitation is the lack of validation using patient-derived clinical samples, which limits the direct translational relevance of the findings. Future studies incorporating cervical cancer tissues from patients will be essential to confirm the clinical significance of TRIM37 expression and function, and to further support its potential as a therapeutic target.

Conclusions

This study shows that TRIM37 is upregulated in human cervical cancer cell lines and plays a crucial role in promoting tumor progression. *In vitro* analyses reveal that TRIM37 knockdown significantly inhibits the proliferation, invasion, and migration of cervical cancer cells, while *in vivo* xenograft models demonstrate that TRIM37 silencing reduces tumor growth. Mechanistically, these effects are mediated through the inhibition of the PTEN/PI3K/Akt/NF-κB pathway. Overall, our findings demonstrate that TRIM37 contributes to the cervical cancer cells' malignant behavior and can act as a potential therapeutic target for future clinical interventions.

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

All authors contributed to the study conception and design. Material preparation and the experiments were performed by AS. Data collection and analysis were performed by QZ, TZ and FG. The first draft of the manuscript was written by TS and all authors commented on previous versions of the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Approval No. YJSDW2022-057).

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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