

# TRIM6 Promotes Cell Cycle and Growth by Modulating p53 Signaling Pathway in Lung Adenocarcinoma

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**Objective:** Accumulated evidence suggested that tripartite motif-containing (TRIM) proteins have a pivotal role in cancer progression. The function of TRIM6 remains largely unknown in lung adenocarcinoma (LUAD). This study aimed to clarify the role of TRIM6 in the LUAD pathogenesis.

**Methods:** The genes involved in TRIM were selected by differential gene expression analysis and Cox regression analysis. TRIM6 was identified and verified in LUAD specimens and in paired normal tissues using immunohistochemistry. A correlation analysis was conducted comparing the expression of TRIM6 and clinicopathologic features. The role of TRIM6 in vitro and in vivo was evaluated by cell proliferation assays, cell apoptosis, cell cycle and a tumor xenograft model. Finally, we investigated downstream proteins regulated by TRIM6 by Western blotting.

**Results:** Among TRIM proteins, TRIM6 expression was significantly elevated in LUAD tissues. The prognosis analysis demonstrated that high expression of TRIM6 was associated with unfavorable survival, which was consistent with the findings of Cox regression analysis. Further correlation analysis concluded that high TRIM6 expression was also associated with TNM staging. TRIM6 knock-down suppressed proliferation, induced cell apoptosis and cell cycle arrest in the G2/M phase. Furthermore, the exact effect of TRIM6 on LUAD cells was examined using in vivo experiments. Mechanistically, TRIM6 enhanced the biological capacity of LUAD cells through the p53 signaling pathway.

**Conclusion:** Our study identifies TRIM6 is a potential oncogene and a prognostic target through the regulation of p53 signaling pathway in LUAD.

**Keywords:** lung adenocarcinoma, TRIM6, cell cycle, proliferation, P53 signaling pathway

## Introduction

Lung cancer has a major impact on public health, ranking first in the world's cancer-related deaths.<sup>1</sup> Lung adenocarcinoma (LUAD) is the most prevalent lung cancer with the very poor 5-year survival rate.<sup>2</sup> Although improvements have been made in molecular diagnosis, most patients present with locally advanced or distant metastasis, which further contribute to poor prognosis.<sup>3,4</sup> Therefore, knowledge of promising biomarkers is urgently needed to guide diagnosis and treatment.

Human Tripartite motif-containing (TRIM) proteins are composed of three characteristic structures and play an important role in carcinogenesis and immune regulation.<sup>5</sup> Importantly, previous studies have demonstrated that TRIM proteins act as crucial regulators for cell growth, metabolism, cancer transformation, and gene transcription.<sup>6,7</sup> TRIM47 is overexpressed in colorectal cancer tissues and can promote cell growth and invasion by interacting with SMAD4.<sup>8</sup> In ovarian cancer, TRIM52 knockdown inhibited cell migration, invasion and proliferation by targeting the NF- $\kappa$ B signaling pathway.<sup>9</sup> In addition, TRIM7 mediates chemoresistance in osteosarcoma.<sup>10</sup> It was well known that  $\beta$ -catenin is aberrantly elevated in various tumors, and facilitates tumor progression. TRIM33 suppresses tumor growth and development through the degradation of  $\beta$ -catenin.<sup>11</sup> TRIM6, a member of the TRIM family, has E3-ubiquitin ligase activity

and is involved in facilitating the antiviral response and the activation of immune-related pathways.<sup>12,13</sup> Furthermore, several studies have demonstrated that TRIM6 is involved in the regulation of carcinogenesis and cancer metastasis. The upregulated expression of TRIM6 enhances the capacity of cell migration and invasion in colorectal cancer.<sup>14</sup> In breast cancer, TRIM6 promotes the growth of breast cancer via the YAP1 signaling pathway.<sup>15</sup> Only one study to date has identified TRIM6 as a prognostic biomarker for LUAD based on a bioinformatics analysis. However, the potential functions and signaling pathways of TRIM6 remain, to our knowledge, unclear in LUAD.

Given the role of TRIM proteins in the malignant progression of tumors, we explored their application in LUAD, and identified TRIM6 as a potential target. In this study, we found that TRIM6 was an independent prognostic factor for patients with LUAD. In addition, the expression of TRIM6 was markedly upregulated in LUAD tissues and was positively correlated with clinicopathological features. We clarified the exact mechanisms of TRIM6 activity on the biological functions in LUAD cells using *in vitro* and *in vivo* models. Finally, the mechanisms modulated by TRIM6 in LUAD were investigated. Our findings may provide basic insights into TRIM6 as a potential target to predict survival and treatment in patients with LUAD.

## Materials and Methods

### Bioinformatics Analysis

The data were obtained by searching and downloading the RNA-Seq data and clinical data of TCGA-LUAD from The Cancer Genome Atlas (TCGA, <http://cancergenome.nih.gov/>). First, we utilized the R package “DESeq2” to conduct a differential analysis on the diseased and normal samples (COUNT data) in the dataset, aiming to identify the differentially expressed genes (DEGs). Next, we employed the “ggpubr” and “pheatmap” packages to plot the volcano plot and heatmap, respectively. Subsequently, we further evaluated the prognostic characteristics of the TRIM family genes (TPM data) through univariate and multivariate Cox regression analyses. Eventually, TRIM6 was determined as the target gene with the help of the “forestplot” function, and the expression profile of this gene was retrieved. After that, through clinicopathological correlation analysis, we explored the associations between the expression level of TRIM6 and clinicopathological features. Finally, we used the “survival” and “survminer” packages to draw the Kaplan - Meier survival curve for TRIM6.

### LUAD Tissue Specimens and Cell Lines

Twenty pairs of tumor and matched paracancerous tissues were all obtained from patients with LUAD undergoing surgery at the Tumor Hospital Affiliated to Xinjiang Medical University. Specimens were dehydrated and preserved in paraffin blocks until use. None of the enrolled patients received any radiotherapy, chemotherapy, or immunotherapy before surgery. The Ethics Committee of Tumor Hospital Affiliated to Xinjiang Medical University approved the sample collection (Approval number: K-2022016). All patients signed informed consent forms for study participation. Human LUAD cell lines SPC-A-1, H292, A549, H1299, NCI-H1975, and bronchial epithelial (HBE) were acquired from Shanghai Fuheng Biological Technology Co., Ltd. Cell lines were all maintained in Dulbecco's Modified Eagle's Medium (Gibco, Grand Island, USA) containing 10% fetal bovine serum (Cyagen, Suzhou, China).

### Immunohistochemistry and Hematoxylin and Eosin Staining

All tissue sections were sequentially deparaffinized and dehydrated. Next, citrate buffer and hydrogen peroxide were applied for antigen retrieval to ensure blocking of endogenous peroxidase activity. The tissue sections were exposed to the corresponding primary antibodies and incubated at 4°C after blocking with BSA for 30 minutes at room temperature. Next, tissue sections were treated with a secondary antibody, and then DAB chromogenic solution was added dropwise. To perform hematoxylin and eosin (HE) staining, the deparaffinized sections were submerged in a hematoxylin solution for staining. Next, 70% and 90% alcohol solutions were used for dehydration, and finally the sections were stained with eosin.

### Lentivirus Transfection

To knockdown TRIM6 expression, we infected A549 and H1299 cells with the TRIM6-shRNAs recombinant lentivirus (GenePharma, Shanghai, China). We used the empty lentiviral vector (sh-Ctrl) as a negative control. To select the stably infected cells, puromycin was added to the culture medium, selected cells were used for subsequent investigations.

## Cell Proliferation Assays

To evaluate the cell proliferation ability of LUAD cells, we used the Cell Counting Kit-8 (CCK-8), EdU, and colony formation assays. For the CCK-8 assay,  $5 \times 10^3$  cells were cultured in 96-well plates and were incubated with CCK-8 solution for 1 h. The absorbance was then measured at 450 nm using a microplate reader. For the EdU assays,  $1 \times 10^4$  cells were seeded in 96-well plates and were incubated with EdU solution for 2 h, followed by staining according to the manufacturer's instructions. Finally, cell viability was detected by fluorescent microscopy.  $1 \times 10^3$  cells were seeded into six-well plates as in the colony formation assay. Cells were fixed and stained with crystal violet solution after 2 weeks of incubation to establish stable clones. Next, we counted the number of colonies and obtained the images. All experiments were conducted with three independent replicates.

## Apoptosis and Cell Cycle Assays

For the detection of cell apoptosis, cells were digested with trypsin and resuspended in 100  $\mu$ L binding buffer. Apoptotic cells were identified by staining using the FITC Annexin V Detection kit (YEASEN, China). To analyze LUAD cell cycle distribution, all cells were fixed in 75% ethanol overnight and labelled with propidium iodide (PI, YEASEN, China). All experiments were conducted with three independent replicates.

## Western Blotting

We performed Western blotting to detect proteins. The radio-immunoprecipitation assay (RIPA) buffer was used to lyse cells on ice to obtain total proteins. After assessing the protein concentration, equal amounts of proteins were separated by SDS-PAGE. The migrated proteins were transferred to polyvinylidene fluoride membranes, which were sealed with blocking solution and incubated with the primary antibody, anti-GAPDH (1:10000, Proteintech, China), anti-TRIM6 (1:1000, Abcam, USA), anti-p53 (1:800, Proteintech, China), anti-p21 (1:1500, Proteintech, China), anti-cyclinB1 (1:1000, Abcam, USA), anti-CDK1 (1:1200, Proteintech, China), anti-CDK4 (1:2000, Proteintech, China), or anti-myc (1:1500, Proteintech, China) overnight. Finally, the blots were exposed to the chemiluminescent detection system. All three experiments were conducted with three independent replicates.

## Xenograft Models

The in vivo experiments were performed with BALB/c nude mice obtained from GemPharmatech. The sh-TRIM6 and sh-Ctrl A549 cells were resuspended in the PBS ( $2 \times 10^6$  cells/mice) and injected subcutaneously into the single flanks of mice, each group consisted of 6 mice. Subsequently, the xenografted tumor volumes were recorded every 3 days and the tumor weight was measured after excision at 28 days. The xenograft assay was approved by the Ethics Committee of Tumor Hospital Affiliated to Xinjiang Medical University (Approval number: K-2022016) and performed in accordance with institutional guidelines.

## Statistical Analyses

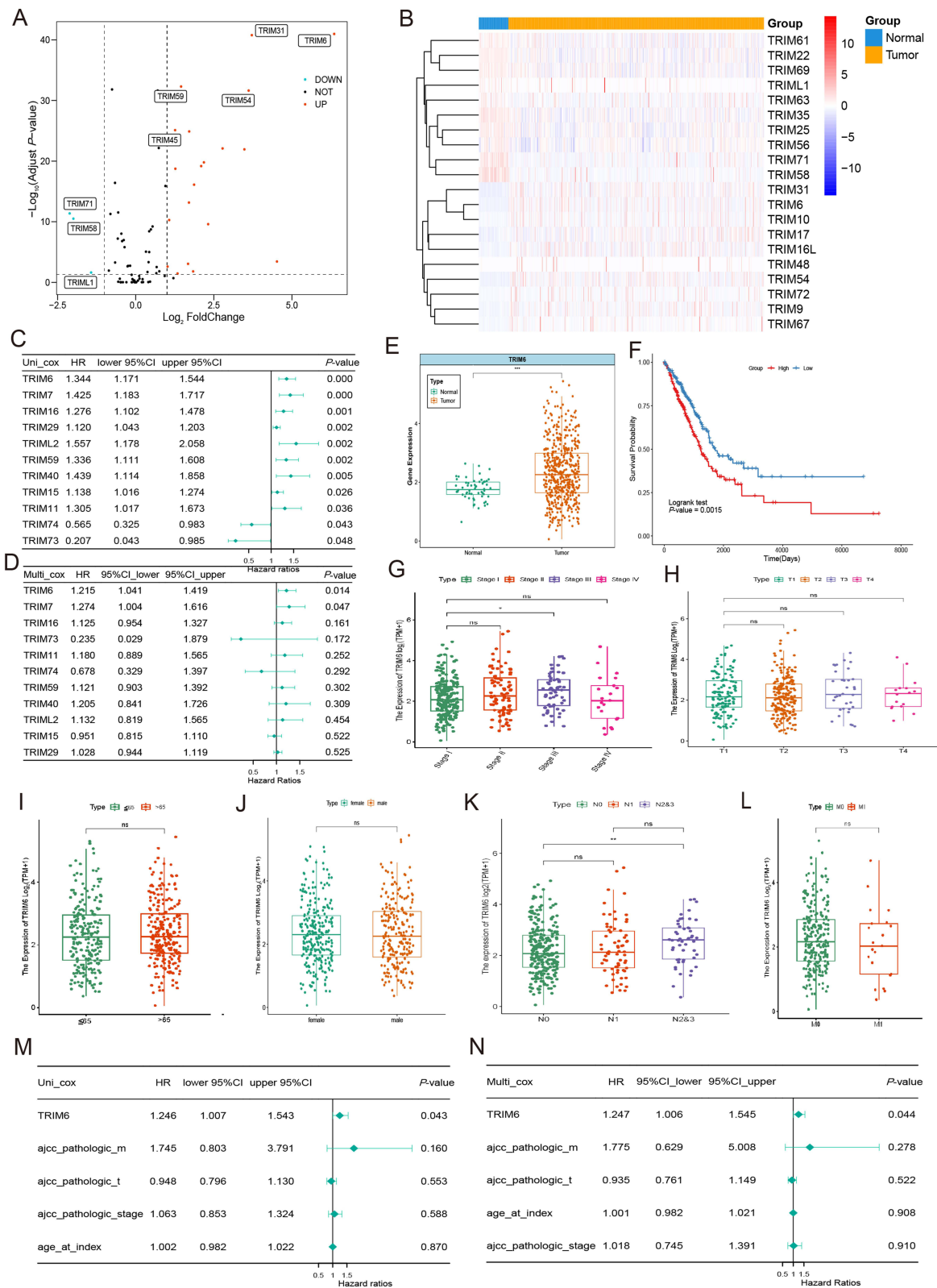
GraphPad software (v9.0) and R v4.0.3 software were applied for statistical analyses. All data were shown as the mean  $\pm$  standard deviation. The Student's unpaired *t*-test was used to compare two groups. In experiments with multiple groups, ANOVA was conducted and a *p* value of  $<0.05$  was considered statistically significant.

## Results

### TRIM6 Was Identified to be an Independent Prognostic Factor for LUAD

To evaluate the role of TRIM family proteins in LUAD, we screened DEGs using the LUAD dataset. Twenty genes of the TRIM family were up-regulated in LUAD specimens (Figures 1A and B). Eleven genes related to LUAD prognosis were identified based on univariate Cox regression analysis (Figure 1C). The multivariate Cox analysis revealed that TRIM6 and TRIM7 might be independent prognostic factors for LUAD (Figure 1D). Therefore, we selected TRIM6 as the primary prognostic gene.

Compared with normal tissues, TRIM6 expression was overexpressed in LUAD tissues based on TCGA datasets (Figure 1E). The Kaplan–Meier curves confirmed that the overexpression of TRIM6 contributed to the poor prognosis for



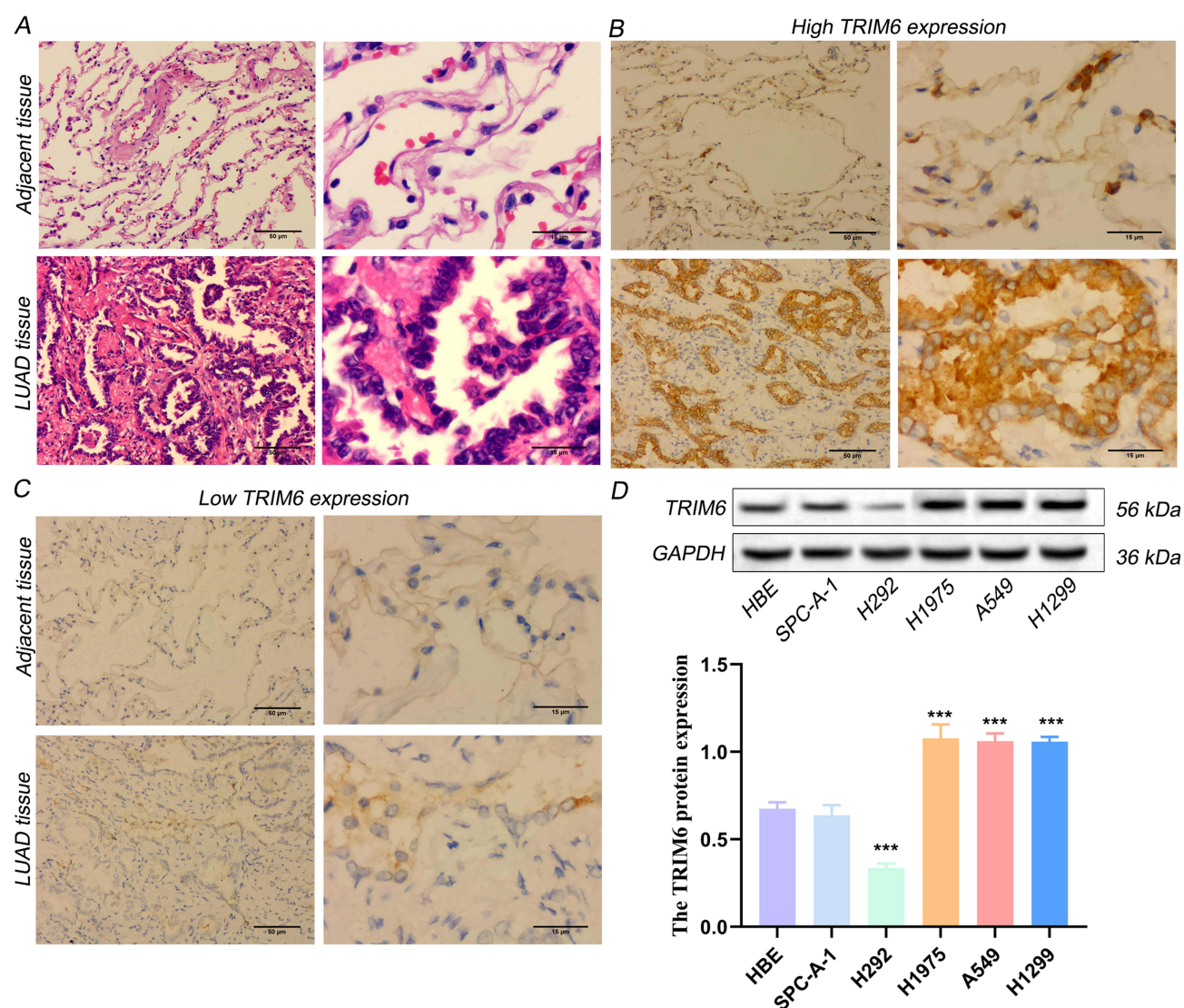
**Figure 1** Identification of independent prognostic factors based on the expression of TRIM family members in LUAD. **(A)** The volcano plots of DEG and **(B)** heatmap. **(C)** Univariate Cox and **(D)** Multivariate Cox regression analysis of TRIM family. **(E)** mRNA expression of TRIM6. **(F)** The Kaplan-Meier survival analysis associated with TRIM6 expression. Correlation analysis between TRIM6 expression and clinical stage **(G)**, T stage **(H)**, age **(I)**, gender **(J)**, N stage **(K)**, M stage **(L)**. **(M)** and **(N)** Univariate and multivariate Cox analysis of TRIM6. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .



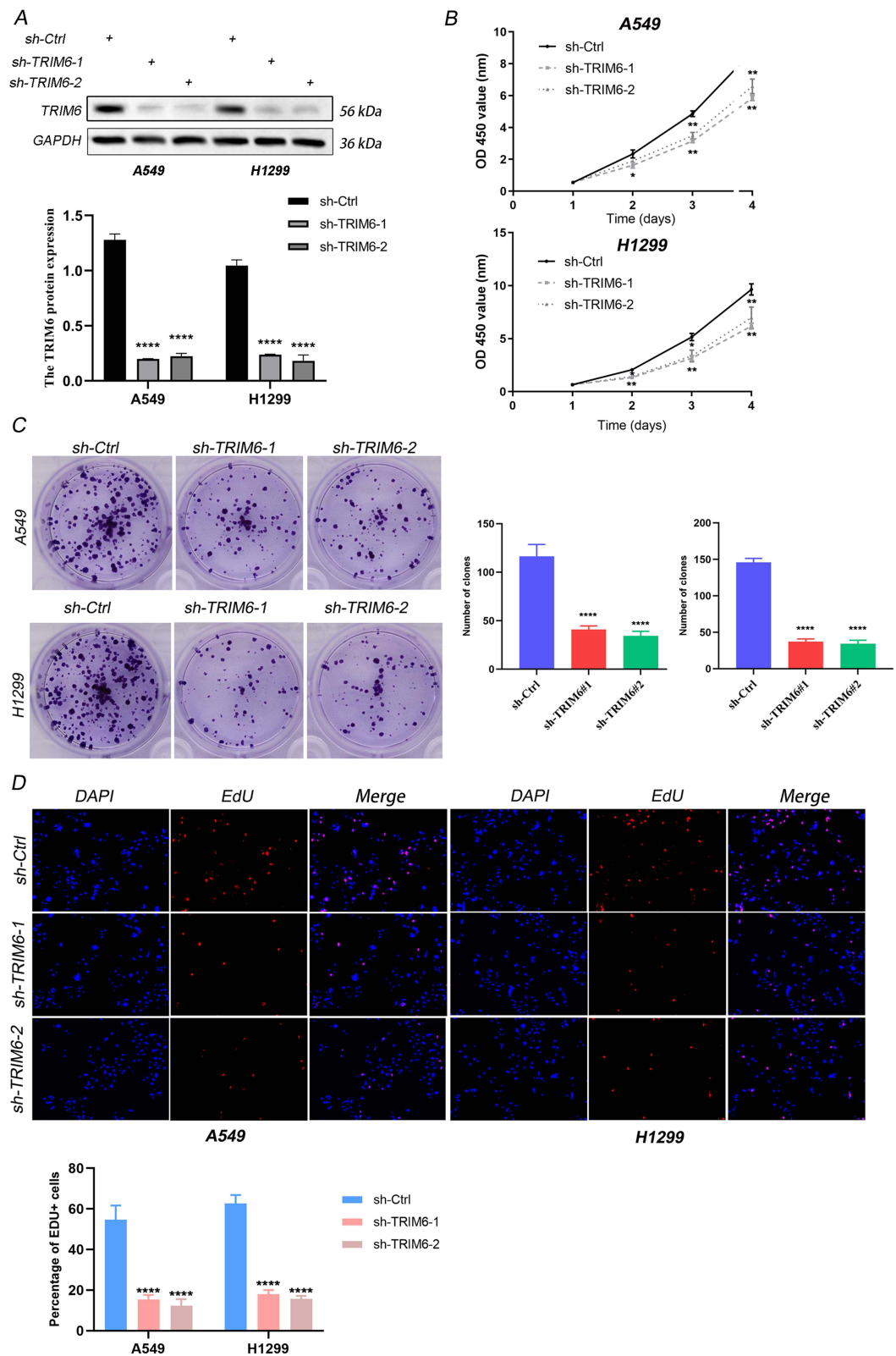
LUAD patients (Figure 1F). Consistently, the correlation analysis demonstrated that overexpression of TRIM6 was significantly associated with high tumor stage (Figure 1G–L). The LUAD TCGA dataset was used to verify the survival effect of TRIM6 on LUAD. Cox regression analysis demonstrated that TRIM6 was an independent factor associated with survival in LUAD (Figure 1M and N). The above findings indicated that TRIM6 might be a prognostic biomarker for patients with LUAD.

## TRIM6 Was Elevated in LUAD and Enhanced Proliferation Ability of LUAD Cells

To verify TRIM6 expression in LUAD specimens, we performed immunohistochemistry and HE staining. The results were consistent with those observed using TCGA dataset (Figure 2A–C), and showed strong expression of TRIM6 in LUAD tissues. Next, we examined the baseline level of TRIM6 expression in LUAD cells. As presented in Figure 2D, H1975, A549, and H1299 had a higher abundance of TRIM6 compared with other cell lines; thus, A549 and H1299 cells were selected for lentivirus infection for further analysis. We verified exposure to TRIM6-shRNAs in A549 and H1299 cells inhibited TRIM6 protein expression (Figure 3A). The biological functional assays demonstrated that TRIM6 knockdown inhibited the capacity of proliferation in LUAD cells based on the CCK-8 assay (Figure 3B). Similarly,



**Figure 2** TRIM6 expression in LUAD tissues and cells. (A) HE staining of LUAD tissues. (B and C) Immunohistochemistry analysis of TRIM6 protein expression in LUAD and adjacent tissues. (D) Western blot analysis of the expression of TRIM6 in LUAD cell lines. Data are presented as mean±SD; \*\*\* $p < 0.001$ .

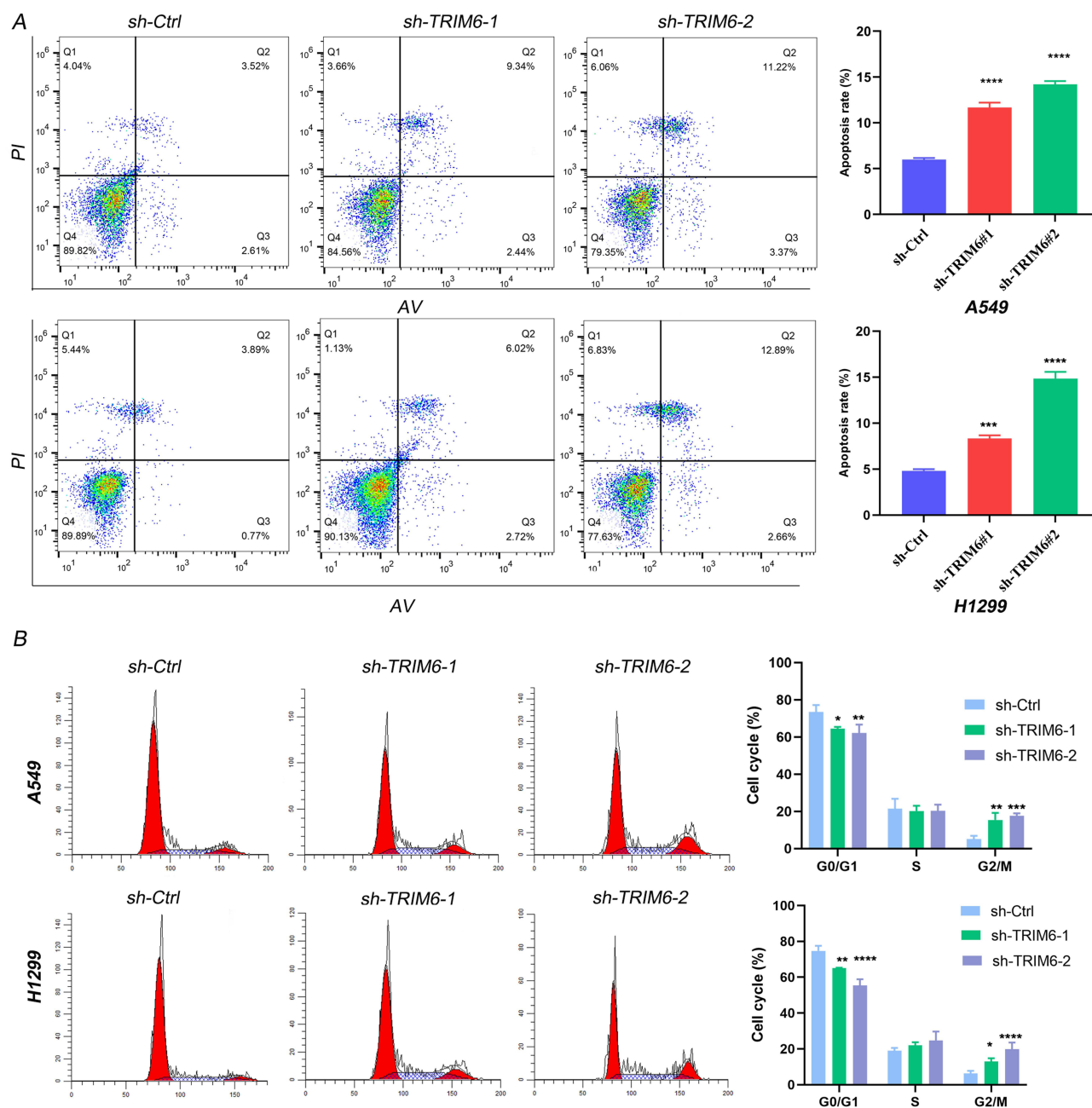


**Figure 3** TRIM6 enhanced proliferation capacity of LUAD cells. **(A)** The transfection efficacy of shRNA vectors targeting TRIM6 in A549 and H1299 cells. **(B)** CCK-8 assay. **(C)** Colony formation experiment. **(D)** The EdU assay. \*\* $p < 0.01$ , \*\*\* $p < 0.0001$ .

TRIM6 knockdown led to a lower incidence of colony formation (Figure 3C). EdU assay indicated that inhibition of TRIM6 expression decreased the proportion of EdU-positive cells (Figure 3D).

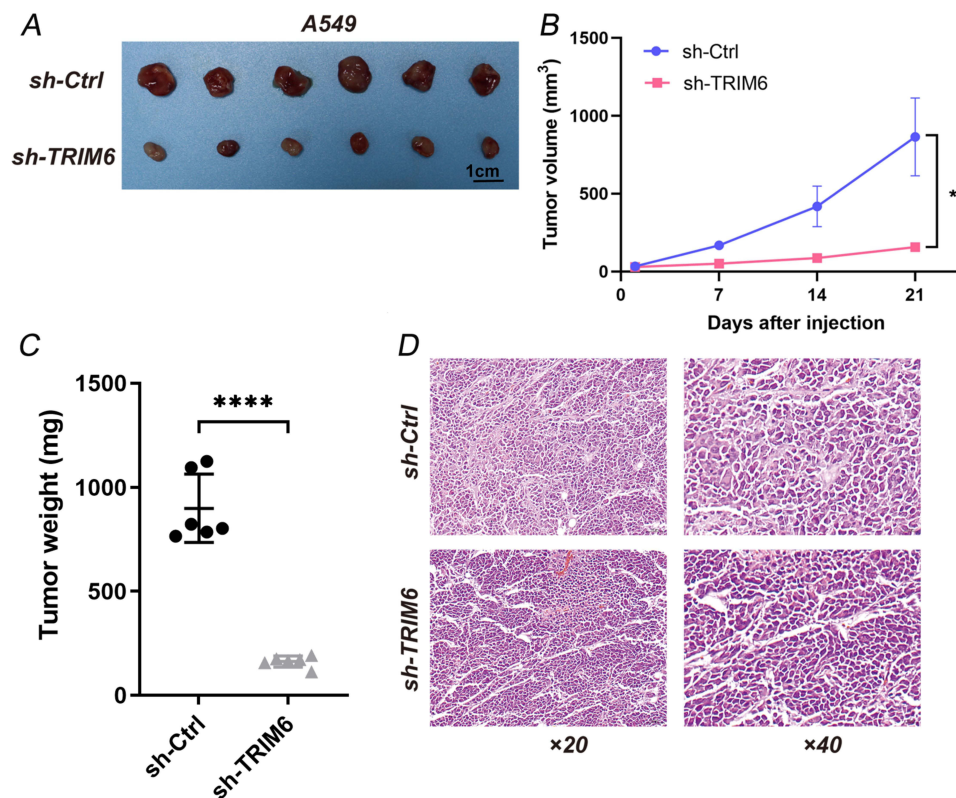
## TRIM6 Knockdown Facilitated Cell Apoptosis and Induced Cell Cycle Arrest

To further explore how TRIM6 affected LUAD cells, we conducted apoptosis detection and cell cycle assays. The downregulation of TRIM6 promoted apoptosis in LUAD cells, as shown in Figure 4A. Furthermore, low expression of TRIM6 led to G2/M cell cycle arrest (Figure 4B). The above findings suggested that TRIM6 might be an oncogene by facilitating the malignant biological behavior of LUAD.



**Figure 4** TRIM6 knockdown induced cell apoptosis and cell cycle arrest in LUAD cells. (A) Cell apoptosis. (B) Cell cycle assay. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ .





**Figure 5** The role of TRIM6 in vivo. (A) Xenograft tumors from the sh-TRIM6 and sh-CTRL groups. (B) Tumor volumes from the sh-TRIM6 and sh-CTRL groups. (C) Tumor weights in sh-TRIM6 and sh-CTRL xenograft mice. (D) HE staining of xenograft tumors. \* $p < 0.05$ , \*\*\*\* $p < 0.0001$ .

## TRIM6 Knockdown Suppressed Tumor Progression in vivo

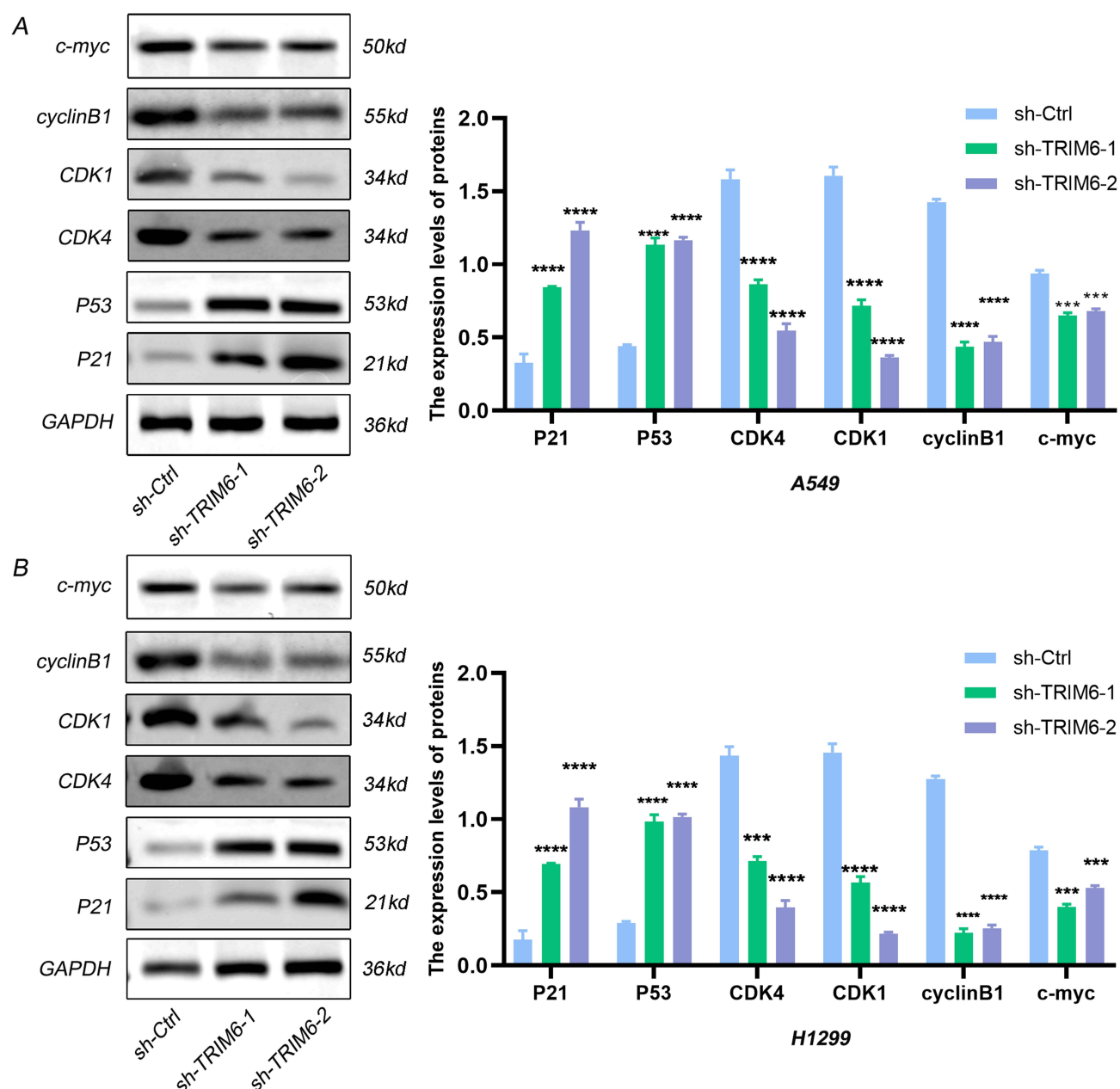
To explore the role of TRIM6 in oncogenesis in vivo, we used nude mice to establish LUAD xenograft models. The results revealed that tumors xenografts harboring TRIM6 knockdown grew more slowly than those in the control group (Figure 5A). We found a decrease in tumor weight and tumor volume, compared to sh-CTRL group (Figures 5B and C). Additionally, HE staining revealed that tumor cells with TRIM6 knockdown led to less structured cellular morphology than those from control tumors (Figure 5D). Therefore, the findings suggested that TRIM6 promotes tumor progression in vivo.

## TRIM6 Participated in Regulating the p53 Signaling Pathway

p53 signaling is involved in regulating the G2/M cell cycle.<sup>16</sup> Thus, we examined the effects of TRIM6 on the p53 signaling pathway. As regulatory proteins for G2/M phase, CDK1, CDK4, cyclin B1, and c-myc were downregulated in TRIM6 knockdown cells (Figure 6). Furthermore, TRIM6 knockdown enhanced the activity of p53 and upregulated p21 expression, which indicated that TRIM6 knockdown induced cell cycle arrest via the activation of the p53 signaling pathway.

## Discussion

Until recently, few studies have focused on the role of TRIM6 in cancers. Studies have demonstrated that TRIM6 expression is enhanced in breast cancer and promotes proliferation through the ubiquitination-mediated degradation of STUB1.<sup>15</sup> The present study found that TRIM6 expression was elevated in LUAD compared with that in normal tissues, and further Cox analysis indicated that TRIM6 could be an independent risk factor for predicting survival of LUAD patients based on TCGA datasets. We further confirmed TRIM6 expression in LUAD tissues and cells, which confirmed the results of the TCGA dataset.



**Figure 6** TRIM6 involvement in the regulation of the p53 signaling pathway in LUAD cells. (A) Expression of the p53 signaling pathway components in A549 cells and (B) in H1299 cells by Western blotting. \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ .

The biological function of TRIM6 in LUAD was investigated using in vitro and in vivo models. TRIM6 knockdown in LUAD cells inhibited cell growth, cell cycle progression, and induced apoptosis. The same results were confirmed using an in vivo animal LUAD xenograft model. Thus, TRIM6 could exert an oncogenic role via regulation of the cell cycle and cell growth in LUAD. Aberrant cell cycle activity often leads to uncontrollable cell growth, which is shown to be a main characteristic of cancer cells.<sup>16,17</sup> TRIM6 was elevated in colorectal cancer tissue and induced cell cycle arrested at the G2/M phase, which may due to the regulation of TIS21/FoxM1 pathway.<sup>18</sup> The current study also showed that TRIM6 knockdown caused cell cycle arrest and eventually led to cell apoptosis. The Western blotting assays confirmed the results of cell cycle assay, which were consistent with findings of a previous study. Altogether, these results demonstrated that TRIM6 may act as a molecular marker for the occurrence and development of LUAD, and could be considered a promising therapeutic target for patients with LUAD.



Further studies confirmed that the expression of p53 and p21 were elevated in TRIM6 knockdown LUAD cells. P53 is known as a tumor suppressor and functions as a transcription factor by activating cyclin-dependent kinase (CDK) inhibitor p21, which leads to the arrest of the cell cycle.<sup>16</sup> Increasing evidence has indicated that TRIM family proteins participate in the regulation of the p53 signaling pathway via ubiquitination of downstream targets. TRIM21 ubiquitinates GMPS or HuR to destabilize p53 protein.<sup>19,20</sup> In gliomas, TRIM21 expression induced cellular senescence via the p53/p21 pathway.<sup>21</sup> Further, TRIM25 cooperates with G3BP2 to suppress p53 activity by promoting sumoylation of p53 in prostate cancer cells.<sup>22</sup> Therefore, it is reasonable to speculate that TRIM6 promotes cell growth and cell cycle progression via the regulation of ubiquitinating p53/p21 signaling targets. Nonetheless, further experimental work is required for validation. However, the current study also has some limitations: (1) The relationship between the mutation status of different driver genes in LUAD and TRIM6 is not clear; (2) The molecular mechanism that plays a role in the LUAD process of TRIM6 cancer needs to be clarified; (3) The relationship between high TRIM6 expression and LUAD resistance remains unclear.

## Conclusion

The present study provides evidence suggesting that TRIM6 may contribute to the acquisition of malignant behavior through the regulation of the p53 signaling pathway in LUAD. Targeting TRIM6 may represent a promising therapeutic strategy for the precise treatment and prevention of LUAD.

## Data Sharing Statement

All data can be obtained in TCGA and conclusions of this article will be made available by the corresponding author.

## Ethical Approval and Consent to Participate

This research was approved by the Ethics Committee of The Affiliated Tumour Hospital Xinjiang Medical University (Approval number: K-2022016). Written informed consent was obtained from the patients for the usage and publication of their clinical data. All research complied with the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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