

TRIM46 deficiency-induced DNA damage enhances the sensitivity of cisplatin in non-small cell lung cancer by regulating the Akt signaling pathway

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Abstract. Lung cancer is one of the most aggressive malignancies worldwide. Non-small cell lung cancer (NSCLC), in particular, is characterized by a poor 5-year survival rate, which is largely attributable to cisplatin (DDP) resistance. However, the molecular mechanisms underlying DDP resistance are still not fully understood. Tripartite motif 46 (TRIM46) is implicated in promoting the progression of lung adenocarcinoma and enhancing chemoresistance. Nevertheless, its specific role in DDP resistance remains elusive. The present study aimed to investigate the role of TRIM46 in DDP resistance. Immunohistochemistry and TUNEL staining were employed to detect the expression of TRIM46 and apoptotic cells in tumor tissues. Lentiviruses were used to construct TRIM46 overexpression and knockdown vectors in A549 and A549/DDP cells. Cell proliferation, apoptosis and DNA damage were measured by Cell Counting Kit-8, flow cytometry and comet assay, respectively. Subcutaneous implantation model through injection of A549/DDP cells with TRIM46 knockdown was performed in BALB/c nude female mice, followed by DDP treatment. The results revealed that TRIM46 was highly expressed in DDP-resistant NSCLC tumor tissues and positively associated with DDP resistance. TRIM46 overexpression attenuated the DDP-induced apoptosis and DNA damage of A549 cells. Meanwhile, the knockdown of TRIM46

enhanced the DDP-induced apoptosis and DNA damage in A549/DDP cells. Mechanistically, TRIM46 activated the Akt signaling, thus inhibiting the expression of caspase 3 and cleaved-caspase 3 as well as increasing the expression level of DNA repair protein RAD51. Furthermore, TRIM46 deficiency inhibited tumor growth and increased DDP sensitivity *in vivo*. In conclusion, the results of the present study demonstrated that TRIM46 contributed to DDP resistance by regulating the Akt signaling pathway and DNA damage, thereby offering new strategies for lung cancer therapy.

Introduction

Lung cancer is the most malignant cancer worldwide, with ~1.76 million deaths annually (1). The two major subtypes of lung cancer are non-small cell lung cancer (NSCLC), accounting for ~80% of all lung cancer cases, and small cell lung cancer (2). At present, the common first-line therapeutic regimens for lung cancer are chemotherapy, immunotherapy and radiation therapies (3-5). Despite continuous development of novel therapies, cisplatin (DDP) remains an essential and widely used agent in the multidisciplinary management of NSCLC. However, the 5-year-survival rate is only 17% for patients with NSCLC (6). One of the primary causes for this is DDP resistance, which attenuates the effect of clinical treatment (7). The underlying mechanisms of DDP resistance are still unclear. Therefore, an improved understanding of the associated molecular mechanisms involved in DDP resistance is essential for NSCLC treatment. Aberrant repair of damaged DNA represents a key mechanism contributing to DDP resistance (8). Genomic instability leads to continuous cycles of DNA damage and repair in NSCLC cells. The DNA damage response (DDR) is activated upon DNA injury to restore genomic integrity (9). However, the dysregulation of DDR pathways, such as through aberrant repair, can promote malignant progression and exacerbate NSCLC development. DDR has been associated with the resistance of cancer cells to UV radiation and chemotherapy (10,11). For

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instance, the upregulation of several key molecules of DDR, such as BRCA1/2 and RAD51, can reduce the sensitivity of chemotherapy and radiotherapy (12,13). Therefore, a number of anticancer drugs targeting DDR-related proteins have been developed to improve the sensitivity of cancer cells to chemotherapeutic drugs (14). However, the genome of NSCLC is highly unstable, and hence further investigation of the associated mechanisms is necessary.

After DNA damage, the cell fate depends on the recognition of DNA damage repair and tolerance factors, as well as the activation of apoptosis, necrosis, autophagy and senescence pathways (15). Specifically, the phosphatidylinositol 3-kinase (PI3K)/Akt pathway plays a crucial role in regulating cell behaviors such as proliferation and apoptosis and hence is involved in determining cell fate after DNA damage (16,17). Tripartite motif (TRIM)-containing proteins, carrying an N-terminal RING finger, one or two B-boxes and a coiled-coil domain, have been reported as regulators of the PI3K/Akt signaling pathway (18). TRIM13 and TRIM21 are reported to inhibit Akt signaling activation, whereas TRIM11, TRIM14, TRIM26, TRIM27, TRIM59 and TRIM44 serve as Akt pathway activators (18). Moreover, TRIM family members have been found to be associated with tumor progression. For instance, TRIM15 and TRIM24 contribute to the progression of NSCLC and prostate cancer, respectively (19,20). The knockdown of TRIM46 inhibits the proliferation of breast cancer cells (21). TRIM46 plays an oncogenic role in osteosarcoma by activating the nuclear factor κ B (NF- κ B) signaling pathway (22). Recently, TRIM46 has been found to promote lung adenocarcinoma growth and contribute to chemoresistance (23). However, the function and underlying mechanism of TRIM46 in NSCLC still need exploration.

The present study was conducted to investigate the role of TRIM46 in NSCLC. The difference in the expression of TRIM46 in NSCLC DDP-sensitive and DDP-resistant patients was evaluated. DDP-induced apoptosis and the DNA damage degree were examined by modulating the TRIM46 protein level in A549 wild-type and DDP-resistant cells. Moreover, Akt signaling pathway activation and the DNA damage-related markers were explored at different TRIM46 levels. The impact of TRIM46 on tumor growth was also assessed *in vivo*.

Materials and methods

Reagents. The anti-TRIM46 (cat. no. Ab169044; 1:1,000 for western blotting and 1:200 for immunohistochemical staining), anti-caspase 3 (cat. no. Ab32351; 1:5,000 for western blotting), anti-cleaved-caspase 3 (cat. no. Ab32042; 1:800 for western blotting) and anti-RAD51 (cat. no. Ab133534; 1:1,000 for western blotting) antibodies were purchased from Abcam. The anti-Akt (cat. no. 9272; 1:1,000 for western blotting), anti-phosphorylated (p-)Akt (cat. no. 4060; 1:1,000 for western blotting) and anti-glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibodies (cat. no. 5174; 1:3,000 for western blotting) were purchased from Cell Signaling Technology, Inc. 3,3'-Diaminobenzidine (DAB) detection kit (cat. no. 34002), Roswell Park Memorial Institute 1640 medium (RPMI-1640; cat. no. 11875101) and fetal bovine serum (FBS; cat. no. 10099141C) were purchased from Gibco (Thermo Fisher Scientific, Inc.). DDP (cat. no. S1166) was purchased

from Selleck Chemicals. LY294002 (cat. no. 440202) was purchased from Merck KGaA. Horseradish peroxidase (HRP)-conjugated secondary antibodies (cat. no. A0208 and A0216; 1:1,000 for western blotting), RIPA lysis buffer (cat. no. P0013) and BCA Protein Assay Kit (cat. no. P0011) were purchased from Beyotime Biotechnology. Immobilon Western HRP Substrate (cat. no. WBKLS0100) was purchased from MilliporeSigma.

Immunohistochemical staining. Tissue microarray (TMA) was purchased from Shanghai Outdo Biotech Co., Ltd. (cat. no. HLugA180Su09). Tissues were fixed with 4% paraformaldehyde and then embedded in paraffin. The tissue sections (4- μ m) were deparaffinized and rehydrated in xylene and a descending series of ethanol concentrations. Antigen retrieval was performed using sodium citrate acid buffer (pH 6.0) followed by washing three times with PBS for 3 min. Then, 3% hydrogen peroxide (100°C, 20 min) was used to inhibit endogenous peroxidase. The sections were incubated with anti-TRIM46 antibody at 4°C overnight. The sections were incubated with EliVision plus Polymer HRP immunohistochemistry kit (Maxim Biotech, Inc.; cat. no. KIT-9903; 1:1,000) for 30 min at 25°C, then with DAB solution for coloration. The sections were then counterstained with hematoxylin (Sigma-Aldrich; Merck KGaA; cat. no. H9627) at 25°C for 3 min. A NanoZoomer system (Hamamatsu Photonics K.K.) was used to collect the images of the TMA. In total, two researchers evaluated the immunoreactivity based on the H-score system, considering both the percentage of positively stained cells (rated 0-4: 0, <5%; 1, $\geq$ 5% and <25%; 2, $\geq$ 25% and <50%; 3, $\geq$ 50% and <75%; 4, $\geq$ 75%) and the intensity of staining (rated 0-3: 0, negative; 1, weak; 2, moderate; 3, strong). This resulted in a total score ranging from 0 to 12. Patients were then classified into high or low expression groups based on an H-score cut-off point of 6.

Tumor formation assay in a nude mouse model. A total of 24 female BALB/c nude mice (4 to 6 weeks old, weighing 20-22 g) were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. The animals were maintained at a constant temperature of 25°C with ~50% humidity under a regular 12:12-h light/dark cycle with food and water available *ad libitum*. After 1 week of adaptive feeding, the mice were randomly divided into four groups (n=6 per group): A549/DDP cell-transplanted group [short hairpin RNA negative control (shNC)], TRIM46 knockdown A549/DDP cell-transplanted group (shTRIM46), A549/DDP cell-transplanted and DDP-treated group (shNC + DDP) and TRIM46 knockdown A549/DDP cell-transplanted and DDP-treated group (shTRIM46 + DDP). The tumor model was established by subcutaneously injecting 100 μ l 5×10^6 A549/DDP cells previously transduced with shTRIM46 or shNC lentivirus into the right side of the mice. After 12 days, the mice in the shNC + DDP and shTRIM46 + DDP groups were treated with 5 mg/kg DDP once a week as previously described (24). Tumor volume was calculated every 3 days using the following formula: Volume = $1/2 \times (\text{Length} \times \text{width}^2)$. The maximum tumor volume and diameter were 840 mm³ and 14.78 mm, respectively. After 3 weeks of DDP injection, all mice were euthanized by cervical dislocation under 5% isoflurane, and the tumors were harvested for the terminal

deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) and western blot assays. Confirmation of death was established by the absence of a pedal/toe pinch reflex and the cessation of breathing for ≥ 1 min. Animal experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the Animal Care and Use Committee of Wenzhou Traditional Chinese Medicine Hospital of Zhejiang Chinese Medical University (Wenzhou, China; approval no.WTCM-KT-2020002).

Cell lines and cell culture. Human NSCLC cell lines A549 and A549/DDP and the human bronchial epithelial cell line 16HBE were purchased from BioLeaf Biotech (Shanghai Baili Biotechnology Co., Ltd.) and cultured in RPMI-1640 medium supplemented with 10% FBS. A549 cells were treated with various concentrations of DDP (0, 5 or 10 μ M) or 20 μ M LY294002, an inhibitor of Akt or vehicle (80 mg/ml DMSO). A549/DDP cells were treated with 0, 50 or 100 μ M DDP. All cells were maintained at 37°C in a humidified incubator with 5% CO₂.

Western blot analysis. Total protein was extracted from the tumor tissue homogenate or cell lines using RIPA lysis buffer containing an inhibitor cocktail (Bio-Rad Laboratories, Inc.) on ice for 10 min. Total protein concentration was measured using a BCA Protein Assay kit. Subsequently, the proteins (20 μ g per lane) were separated by 10 or 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membranes (MilliporeSigma). After blocking with 5% non-fat milk at 25°C for 1 h, the membranes were incubated with primary antibodies at 4°C overnight, then with the corresponding HRP-conjugated secondary antibodies for 1 h at 25°C. Finally, the membranes were visualized using Immobilon Western HRP Substrate and the protein levels were semi-quantified by band densitometry (Quantity One software, version 4.62; Bio-Rad Laboratories, Inc.).

RNA isolation and reverse transcription-quantitative polymerase chain reaction (PCR) analyses. Following treatment, the cells were harvested using TRIzol (Invitrogen; Thermo Fisher Scientific, Inc.) reagent to extract total RNA. After transcribing RNA to cDNA using the RevertAid First Strand cDNA Synthesis Kit (cat. no. K1622; Thermo Fisher Scientific Inc.) according to the manufacturer's instructions, a SYBR Green Kit (cat. no. 4309155; Thermo Fisher Scientific Inc.) was used to quantify the mRNA level on an ABI7500 system. The PCR cycling conditions were 95°C for 10 min, followed by 40 cycles at 95°C for 15 sec and 60°C for 45 sec, followed by a final extension step of 95°C for 15 sec, 60°C for 1 min, 95°C for 15 sec and 60°C for 15 sec. The relative expression of TRIM46 (forward: 5'-GTCCGCATCAGTGCTTTGGG-3' and reverse: 5'-TCAGGTTCCGGAAAAGCCC-3') was analyzed using the 2^{- $\Delta\Delta$ C_q} method (25), using GAPDH (forward: 5'-TCAGACACC ATGGGGAAGGT-3' and reverse: 5'-TCCCGTTCTCAGCCA TGTAG-3') as an internal control.

Construction and packaging of lentivirus carrying TRIM46 and shTRIM46. The coding sequence of TRIM46 (NM_001282378.2) was amplified using the following primers: Forward 5'-CGGAATTCATGGCAGAGGGTGA

GGATATG-3' and reverse: 5'-CGGGATCCTCTGCATATC CTCACCCTCTG-3' and engineered into the pLVX-Puro lentiviral vector (Shanghai Lianmai Biotechnology Co., Ltd.). The shRNA sequences targeting TRIM46 (shTRIM46-1, 5'-GGTGAGGATATGCAGACCT-3'; shTRIM46-2, 5'-GATATGCAGACCTTCACTT-3'; and shTRIM46-3, 5'-AGACCTTCACTTCCATCAT-3'), as well as the shNC (5'-GATACATACTAGATCGACT-3') vector, were purchased from Shanghai GeneChem Co., Ltd and engineered into the pLKO.1 puro lentiviral vector (Addgene, Inc.). The recombinant plasmid pLVX-Puro-TRIM46 (1,000 ng) or pLKO.1 puro-shTRIM46 (1,000 ng), together with psPAX2 (100 ng; Addgene, Inc.) and pMD2G (900 ng; Addgene, Inc.), were co-transfected into 293T cells (ATCC) seeded in a 9-well plate (1x10⁵ cells/well) for 6 h at 37°C. The transfection procedures used Lipofectamine 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol. Subsequently, 48 h after transfection, the recombinant lentivirus in the cell supernatant was collected by centrifugation at 5,000 x g for 5 min and the purification and titration of recombinant lentivirus was performed as previously described (24). A549 or A549/DDP cells were plated in a 6-well plate (5x10⁵ cells/well) and infected with the recombinant lentivirus-transducing units at an MOI of 20 in the presence of 8 μ g/ml polybrene (Sigma-Aldrich; Merck KGaA) for 24 h at 37°C. Stable cells were selected by puromycin (3 μ g/ml; Thermo Fisher Scientific) for 4 more days. pLKO.1-scrambled shRNA (shNC) and blank pLVX-Puro (vector) were used as the negative controls.

Cell apoptosis. Following treatment, the cells were harvested and co-stained with Annexin V-fluorescein isothiocyanate and propidium iodide following the instructions on the Annexin V apoptosis detection kit (BD Biosciences). The apoptotic cells were then quantitatively analyzed by flow cytometry (Accuri™ C6; BD Biosciences) using CellQuest Pro software, version 3.3 (Becton, Dickinson and Company).

Comet assay. The degree of DDP-induced DNA damage was examined by the comet assay, as previously described (26). Briefly, A549 cells were transfected with TRIM46-overexpressing/knockdown lentivirus or the corresponding control lentivirus and treated with DDP. Then, the cells were collected, washed with cold phosphate-buffered saline, mixed with 140 μ l of 0.5% agarose at 43°C and then seeded onto slides previously coated with 1.0% agarose. After solidification at 4°C, the slides were immersed in a cold lysis buffer (2.5 M NaCl, 100 mM EDTA and 10 mM Tris, with 1 ml of Triton X-100 per 100 ml) in the dark for 1 h at 4°C. Next, the slides were transferred to an alkaline electrophoresis solution (0.3 M sodium hydroxide and 1 mM EDTA) for a 40-min incubation at 4°C. Electrophoresis was conducted at 4°C under alkaline conditions for 20 min at 25 V/cm. The slides were washed thrice with neutralizing buffer (0.4 M Tris-HCl, pH 7.5) and stained with DAPI. A fluorescence microscope (Nikon Corporation) was used to obtain the images and the percentage of tail DNA was determined using CometScore 1.5 software (TriTek Corp).

Cell proliferation. A total of 5x10³ cells were seeded into 96-well culture plates and cultured overnight. Cell proliferation was measured using a Cell Counting Kit 8 (CKK-8) kit

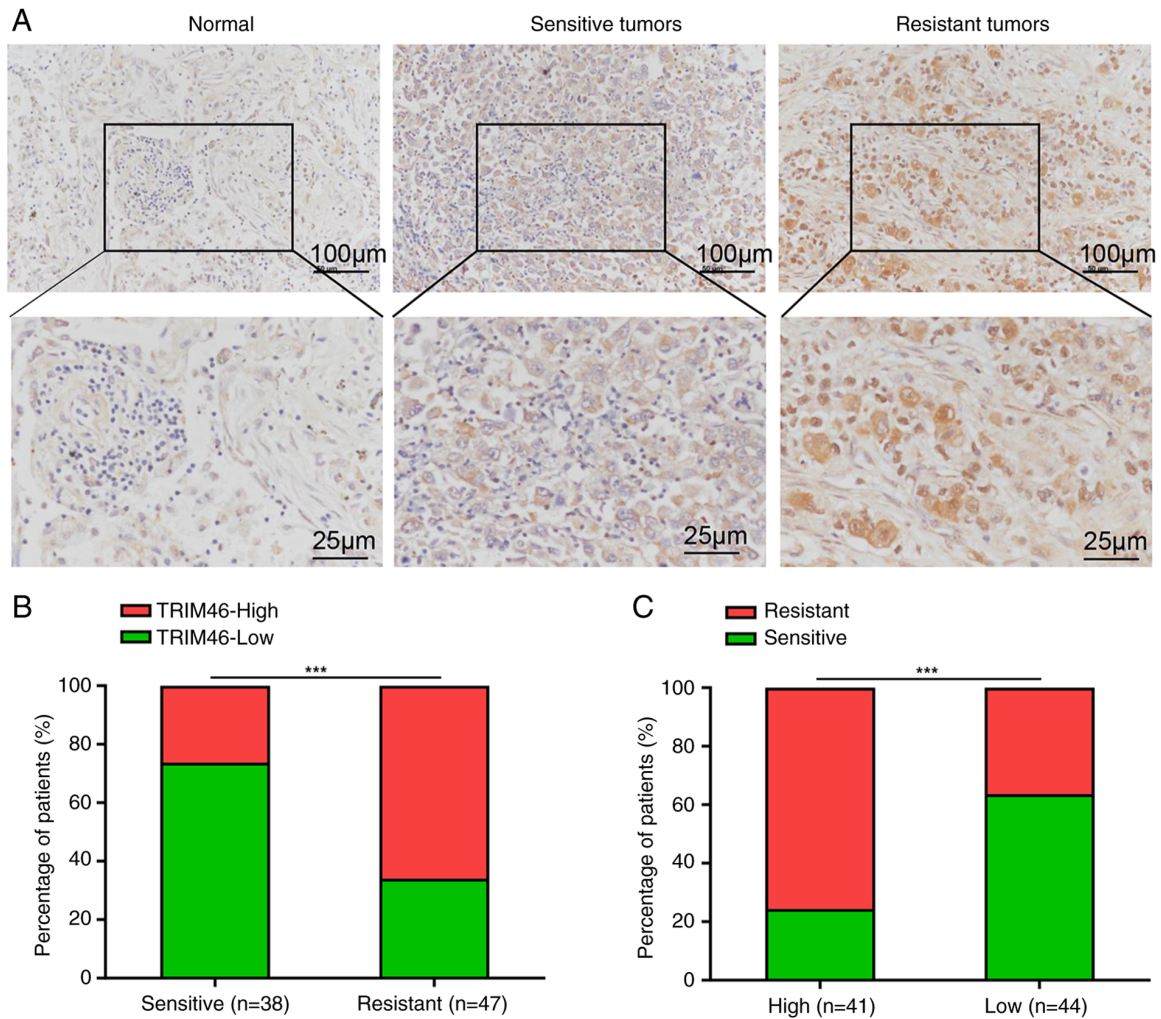


Figure 1. TRIM46 expression is associated with DDP resistance in non-small cell lung cancer tissues. (A) Immunohistochemistry staining was performed using a TRIM46 antibody and normal, DDP-sensitive and DDP-resistant tissues. (B) Percentages of tissues with low or high TRIM46 expression in DDP-sensitive (n=38) or DDP-resistant (n=47) patients. (C) Percentages of patients with DDP-resistant or DDP-sensitive tissues and low (n=44) or high (n=41) TRIM46 expression. ***P<0.001. TRIM46, tripartite motif 46; DDP, cisplatin.

(Bio-Rad Laboratories, Inc.). Briefly, at the end of the pre-set treatment, the culture medium was replaced with a mixture of 10 μ l CCK-8 solution and 90 μ l RPMI-1640. After incubation for 1 h, the optical density at 450 nm was determined using a microplate reader (Bio-Rad Laboratories, Inc.).

TUNEL. The tumor samples obtained from each group of mice were fixed with 4% paraformaldehyde at 25°C for 48 h. Subsequently, the samples were embedded in paraffin and cut into slices with a thickness of 4 μ m. The TUNEL assay was performed following the protocols of a TUNEL staining kit (cat. no. 11684817910; Roche Diagnostics). In brief, the TUNEL reaction was carried out at 37°C for 1 h. After the reaction, the sections were washed three times with PBS, incubated with anti-fluorescein antibody-peroxidase for 30 min, stained with DAB for 10 min, washed three times with PBS and then re-stained with hematoxylin. The tissue sections were then examined by light microscopy (Olympus Corporation) and the number of TUNEL-positive cells was counted using ImageJ software version 1.61 (National Institutes of Health). According to the distribution of apoptotic cells, five positive visual fields from each treatment group were imaged.

Statistical analysis. The data are presented as mean $\pm$ standard deviation. Statistical analysis was performed using GraphPad Prism 5.0 software (Dotmatics). Significant differences between groups were evaluated using one-way analysis of variance followed by Tukey's multiple comparisons test or using unpaired Student's t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

TRIM46 expression is associated with DDP resistance in NSCLC tissues. The function of TRIM46 was investigated by first determining whether TRIM46 expression was associated with DDP resistance in human samples. The immunohistochemical staining results of the TMA showed that the TRIM46 level was elevated in NSCLC tissues compared with normal tissues. Moreover, TRIM46 expression further increased in DDP-resistant tissues compared with DDP-sensitive tissues (Fig. 1A and B). The association between TRIM46 and DDP resistance was explored by dividing the patients into two groups based on low or high TRIM46 expression. It was found that the number of resistant tissues significantly increased

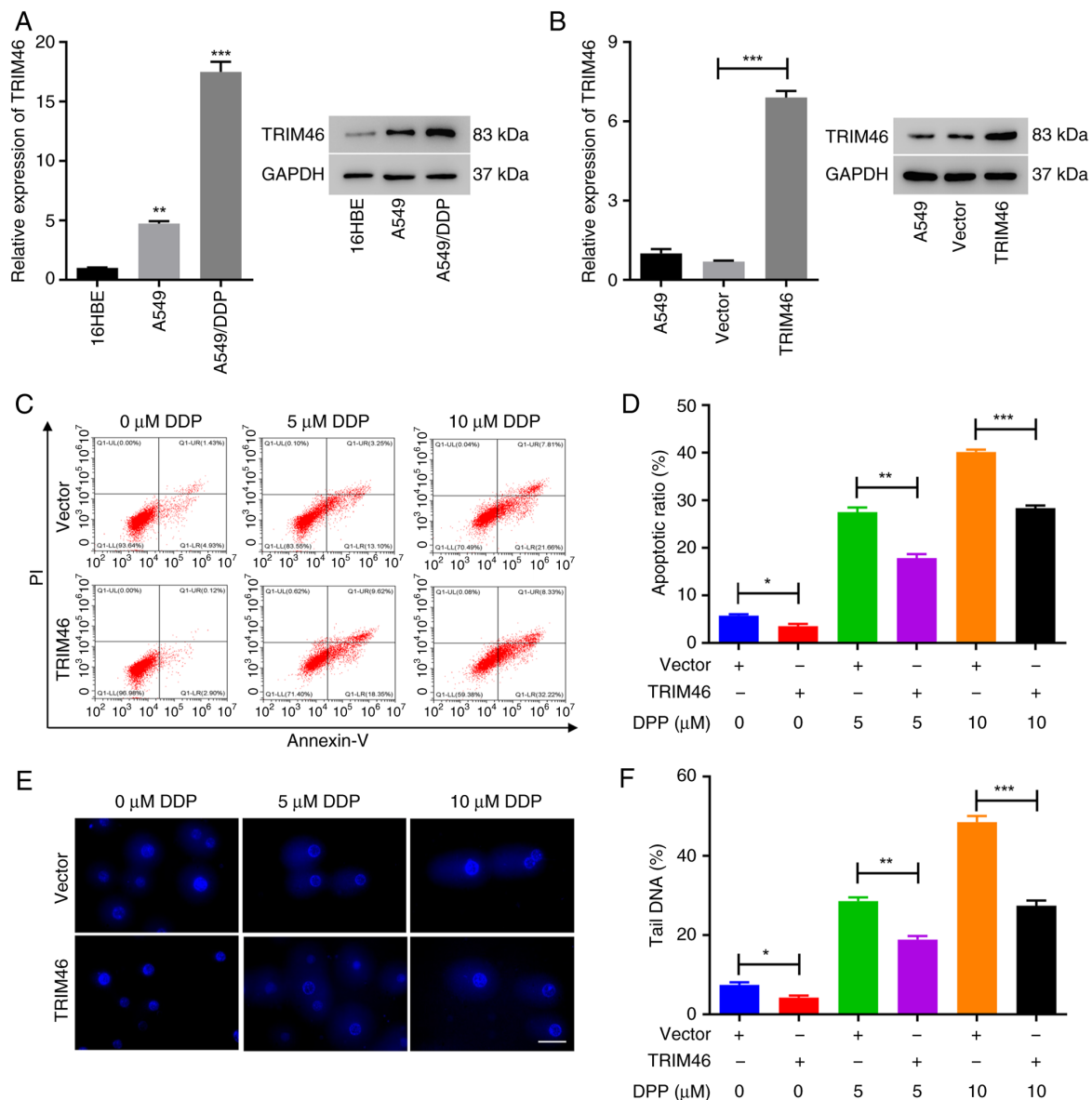


Figure 2. TRIM46 upregulation contributes to DDP resistance in non-small cell lung cancer cells. (A) RT-qPCR (left) and western blot (right) analysis of TRIM46 expression in 16HBE, A549 and A549/DDP cells. (B) RT-qPCR (left) and western blot (right) analysis of TRIM46 expression in A549 cells infected with TRIM46 overexpression lentivirus. (C) Cell apoptosis was measured after transduction with TRIM46-overexpression lentivirus and/or DDP treatment (0, 5 and 10 μ M) in A549 cells. (D) Quantitative analysis of cell apoptosis. (E) Representative images of the comet assay showing DNA fragmentation after transduction with TRIM46-overexpression lentivirus and/or DDP treatment (0, 5 and 10 μ M) in A549 cells (scale bar, 50 μ m; magnification, x400). (F) Quantification of tail DNA (%) revealing DNA damage after transduction with TRIM46-overexpression lentivirus and/or DDP treatment (0, 5 and 10 μ M) in A549 cells. * P <0.05, ** P <0.01, *** P <0.001. TRIM46, tripartite motif 46; DDP, cisplatin; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; PI, propidium iodide.

in the high-TRIM46-expression group compared with the low-TRIM46-expression group (Fig. 1C). These results indicated that TRIM46 expression may be associated with DDP resistance in NSCLC tissues.

TRIM46 upregulation contributes to DDP resistance in NSCLC cells. TRIM46 expression in bronchial epithelial cells (16HBE) and DDP-sensitive (A549) and DDP-resistant (A549/DDP) NSCLC cells was measured to explore the involvement of TRIM46 in DDP resistance. As shown in Fig. 2A, the TRIM46 level was significantly elevated in NSCLC cells compared with 16HBE cells. Furthermore, TRIM46 expression was significantly upregulated in A549/DDP cells

compared with A549 cells, indicating the possible involvement of TRIM46 in DDP resistance. A549 cells were infected with blank lentivirus or TRIM46-overexpressing lentivirus to directly determine the effect of TRIM46 on DDP resistance. The results revealed that TRIM46 expression was significantly upregulated at both the mRNA and protein levels upon infection with TRIM46-overexpressing lentivirus (Fig. 2B). As shown in Fig. 2C and D, DDP induced the apoptosis of A549 cells in a concentration-dependent manner. However, TRIM46 overexpression significantly suppressed the apoptosis induced by DDP in A549 cells. Furthermore, the comet assay was employed to investigate whether TRIM46 was related to DNA damage. The formation of a 'comet' in the DNA of cells can be

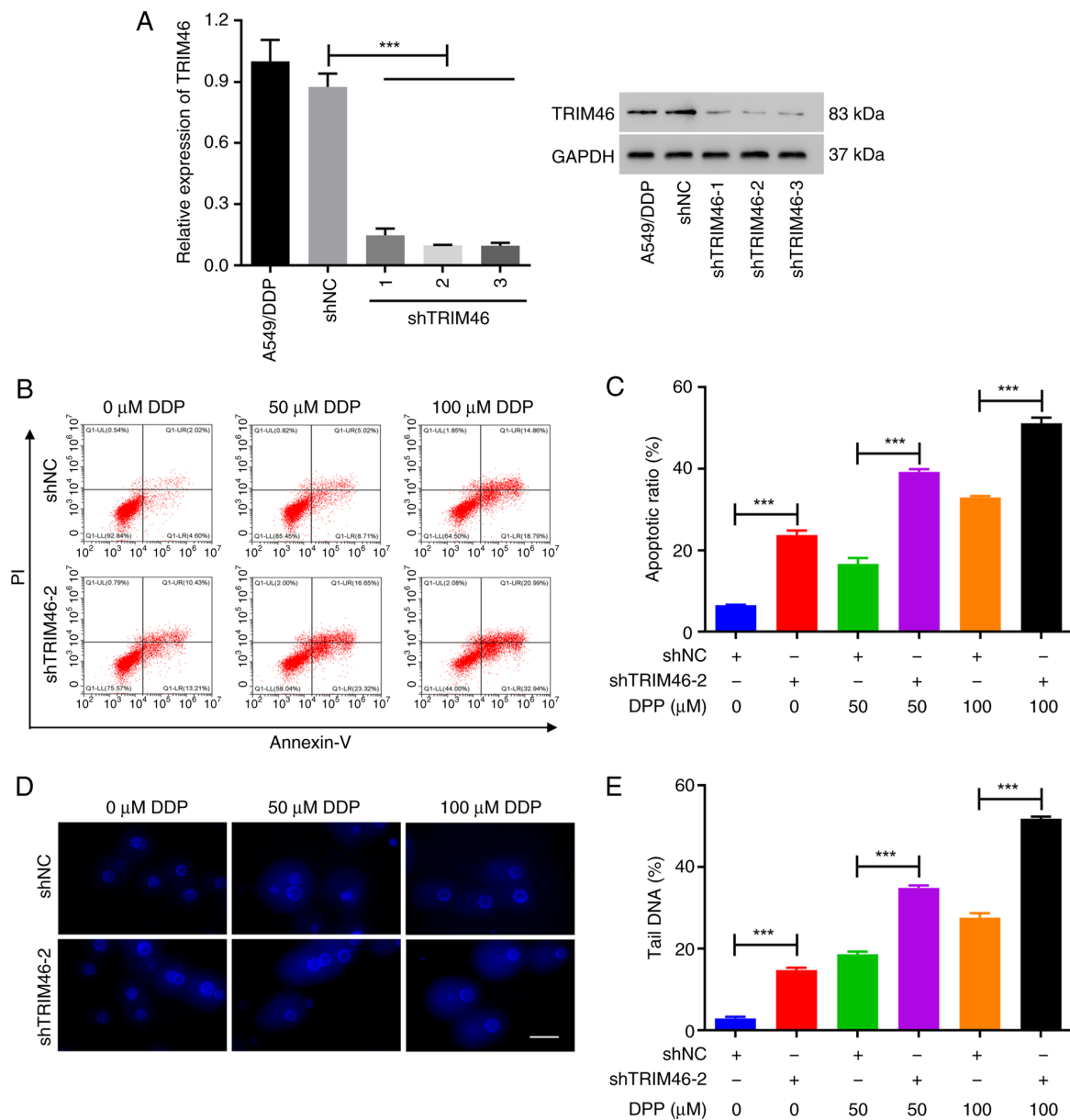


Figure 3. TRIM46 knockdown alleviates DDP resistance in non-small cell lung cancer cells. (A) Reverse transcription-quantitative polymerase chain reaction (left) and western blot (right) analysis of TRIM46 expression in A549/DDP cells infected with TRIM46 knockdown lentiviruses. (B) Cell apoptosis was measured after transduction with TRIM46 knockdown lentivirus and/or DDP treatment (0, 50 and 100 μ M) in A549/DDP cells. (C) Quantitative analysis of cell apoptosis. (D) Representative images of the comet assay showing DNA fragmentation after transduction with TRIM46 knockdown lentivirus and/or DDP treatment (0, 50 and 100 μ M) in A549/DDP cells (scale bar, 50 μ m; magnification, x400). (E) Quantification of tail DNA (%) revealing DNA damage after transduction with TRIM46 knockdown lentivirus and/or DDP treatment (0, 50 and 100 μ M) in A549/DDP cells. *** P <0.001. TRIM46, tripartite motif 46; DDP, cisplatin; sh, short hairpin; NC, negative control; PI, propidium iodide.

visualized using single-cell gel electrophoresis and indicates DNA strand breaks as the damaged DNA migrates at a different rate than the non-damaged DNA. The results demonstrated an increase in the percentage of tail DNA in DDP-treated A549 cells compared with the control group. However, TRIM46 overexpression showed a decrease in the percentage of tail DNA in A549 cells treated with DDP (Fig. 2E and F). These results indicated that TRIM46 alleviated DNA damage and the cell apoptosis of A549 cells treated with DDP.

TRIM46 knockdown alleviates DDP resistance in NSCLC cells. The function of TRIM46 was further explored using lentiviruses to knock down its expression in A549/DDP cells.

As expected, all three lentiviruses significantly decreased TRIM46 expression, and the knockdown efficiency of shTRIM46-2 was the most significant (Fig. 3A). Knockdown of TRIM46 using shTRIM46-2 lentivirus promoted the apoptosis of A549/DDP cells treated with or without DDP (Fig. 3B and C). Meanwhile, the comet assay results also showed that TRIM46 knockdown significantly enhanced DNA damage in A549/DDP cells treated with DDP (Fig. 3D and E).

TRIM46 depletion reduces cell proliferation by regulating the Akt signaling pathway. Cell proliferation was detected in the A549/DDP cells transduced with shTRIM46-2 and shTRIM46-3. The results showed that TRIM46

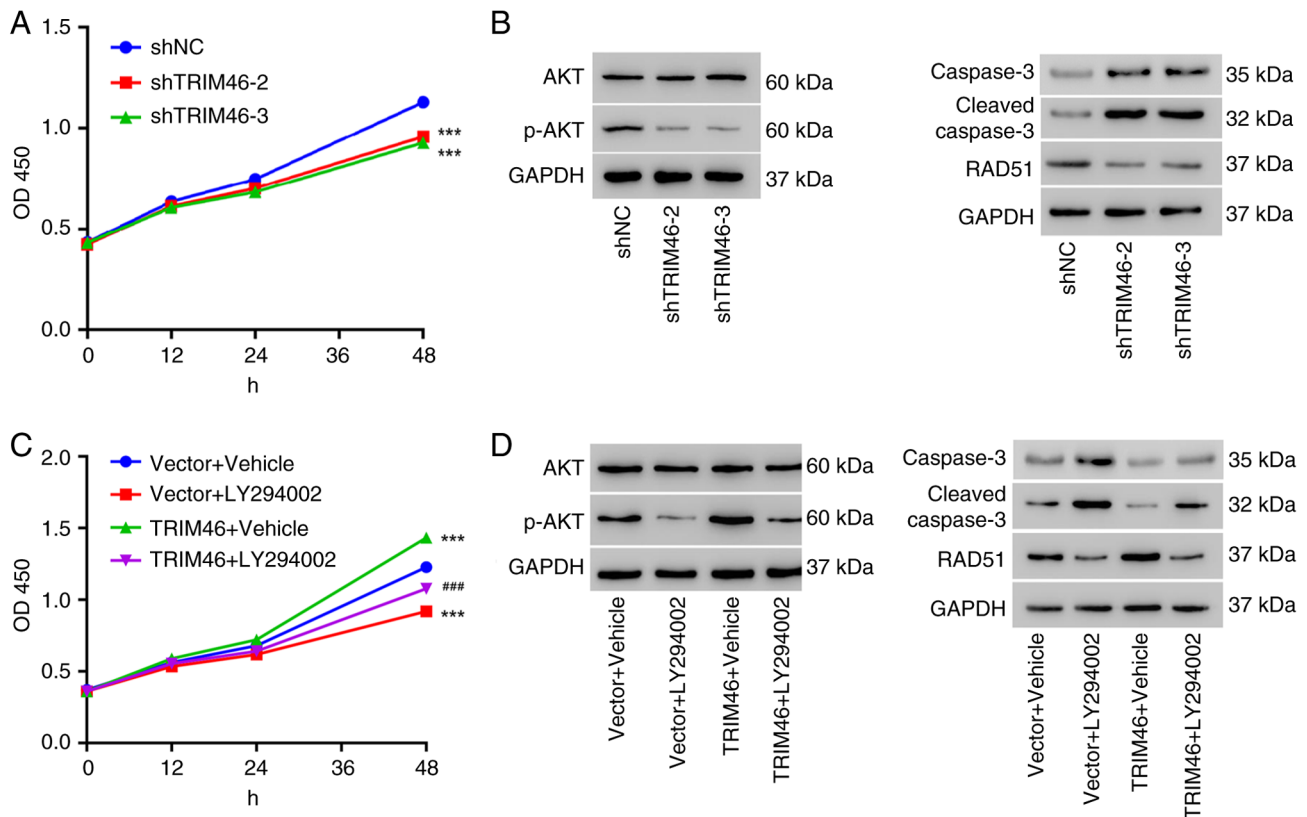


Figure 4. TRIM46 depletion inhibits cell proliferation by regulating the Akt signaling pathway. (A) Cell proliferation of A549/DDP cells transduced with TRIM46-knockdown lentiviruses. (B) Western blot analysis of p-Akt, Akt, caspase 3, cleaved-caspase 3 and RAD51 expression in A549/DDP cells transduced with TRIM46-knockdown lentiviruses. (C) Cell proliferation of A549 cells transduced with TRIM46-overexpression lentivirus and/or treated with LY294002 (20 μ M) or vehicle. (D) Western blot analysis of p-Akt, Akt, caspase 3, cleaved-caspase 3 and RAD51 in A549 cells transduced with TRIM46-overexpression lentivirus and/or treated with LY294002 (20 μ M) or vehicle. *** P <0.001 vs. shNC or Vector + Vehicle; ### P <0.001 vs. TRIM46 + Vehicle. TRIM46, tripartite motif 46; DDP, cisplatin; sh, short hairpin; NC, negative control; OD, optical density; p-, phosphorylated.

depletion effectively reduced the proliferation of A549/DDP cells (Fig. 4A). The protein levels of p-Akt (Ser 473) were measured to elucidate the role of TRIM46. It was found that TRIM46 knockdown resulted in a significant decrease in the level of p-Akt (Fig. 4B). Based on the aforementioned result depicted in Fig. 3, where TRIM46 depletion induced DNA damage, the expression of RAD51, a key protein involved in DNA repair, was further detected. As shown in Fig. 4B, TRIM46 knockdown not only decreased the protein level of RAD51 but also increased the protein levels of caspase 3 and cleaved-caspase 3 in A549/DDP cells. These findings collectively indicated that TRIM46 knockdown induced DNA damage, thereby suppressing cell proliferation. The Akt pathway is involved in regulating cell behaviors such as proliferation and apoptosis; it also plays an important role in DNA damage repair (16,17). To examine the role of the Akt pathway in regulating TRIM46-mediated DDP resistance, LY294002, an inhibitor of Akt, was applied to A549 cells infected with TRIM46-overexpression lentivirus. The CCK-8 assay results showed that TRIM46 overexpression significantly enhanced the proliferation of A549 cells compared with the vector-transfected group. Moreover, the promotive effect of cell proliferation induced by TRIM46 overexpression was alleviated by LY294002 (Fig. 4C). As shown in Fig. 4D, LY294002 treatment decreased the p-Akt level and also partially blocked the increase in p-Akt level caused by

TRIM46 overexpression. Moreover, LY294002 treatment effectively alleviated the increase in RAD51 level and the decrease in the levels of caspase 3 and cleaved-caspase3 induced by TRIM46 overexpression in A549 cells. Taken together, these findings emphasized that TRIM46 knockdown may induce DNA damage by regulating the Akt signaling pathway, thereby inhibiting the proliferation of NSCLC cells.

TRIM46 knockdown increases the sensitivity of xenograft tumors to DDP treatment. A549/DDP cells transduced with shTRIM46 or shNC lentiviruses were subcutaneously injected into nude mice to validate the function of TRIM46 *in vivo*. The mice were treated with DDP after 12 days of injection. As illustrated in Fig. 5A and B, mice receiving shTRIM46 cell injections, as well as those injected with shNC cells and treated with DDP, exhibited smaller tumor volumes compared with the shNC group. The lowest tumor volumes were observed in the mice co-treated with shTRIM46 and DDP. The TUNEL assay revealed a higher number of apoptotic cells in the shTRIM46 group compared with the shNC group. Furthermore, the group co-treated with shTRIM46 and DDP exhibited more apoptotic cells than the group co-treated with shNC and DDP (Fig. 5C and D), suggesting that TRIM46 depletion enhanced DDP-induced apoptosis. Additionally, the group co-treated with shTRIM46 and DDP displayed the lowest levels of RAD51 (Fig. 5E). These findings collectively

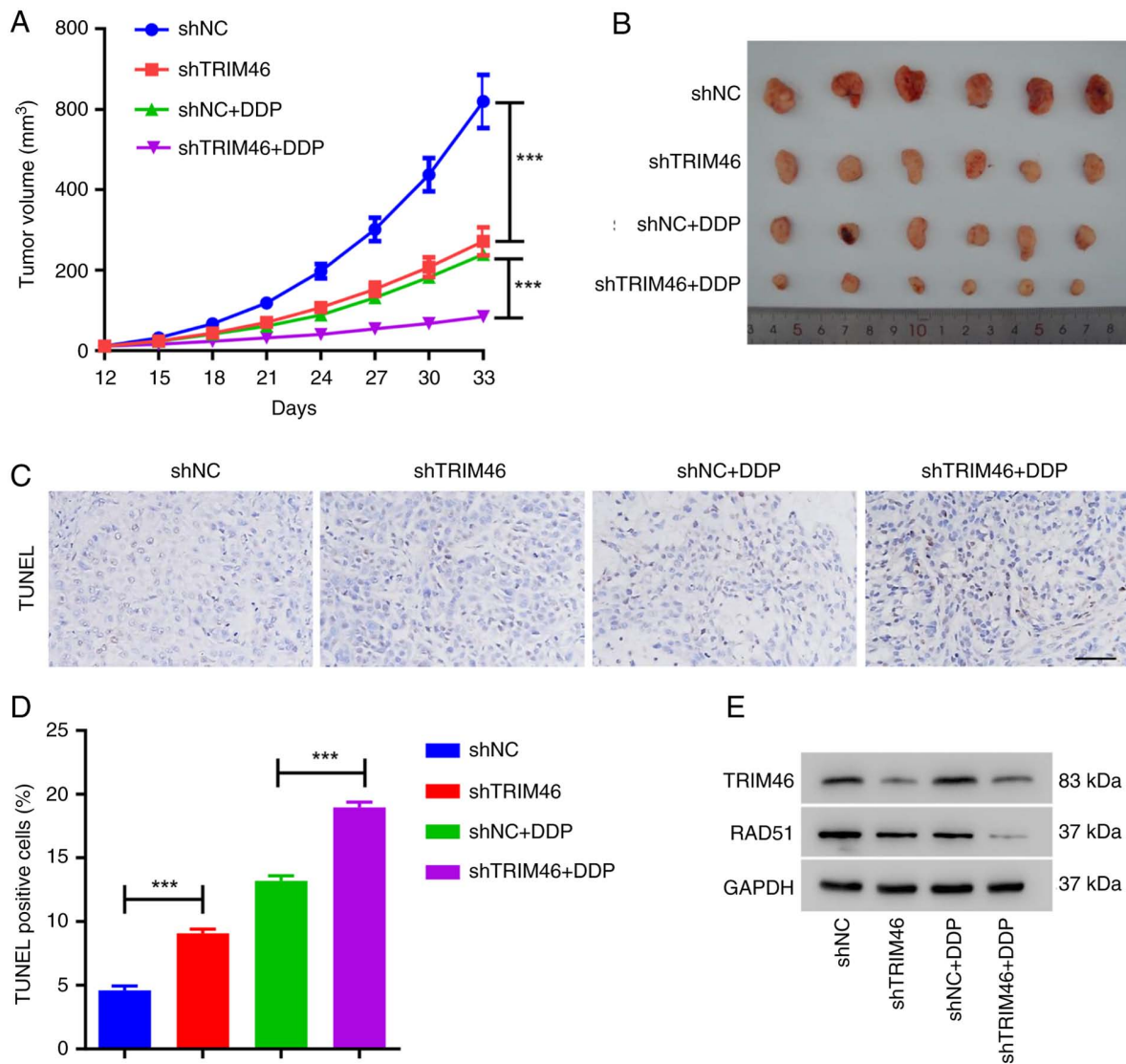


Figure 5. TRIM46 knockdown increases the sensitivity of xenograft tumors to DDP treatment. (A) Tumor volumes and (B) images of xenograft tumors in the designated groups (scale bar, 1 cm; n=6 per group). (C) TUNEL assay of xenograft tumor samples (scale bar, 100 μm; magnification, x200). (D) Statistical analysis of the TUNEL assay (n=6 per group). (E) Western blot analysis of TRIM46 and RAD51 expression in xenograft tumors. ***P<0.001. TRIM46, tripartite motif 46; DDP, cisplatin; sh, short hairpin; NC, negative control.

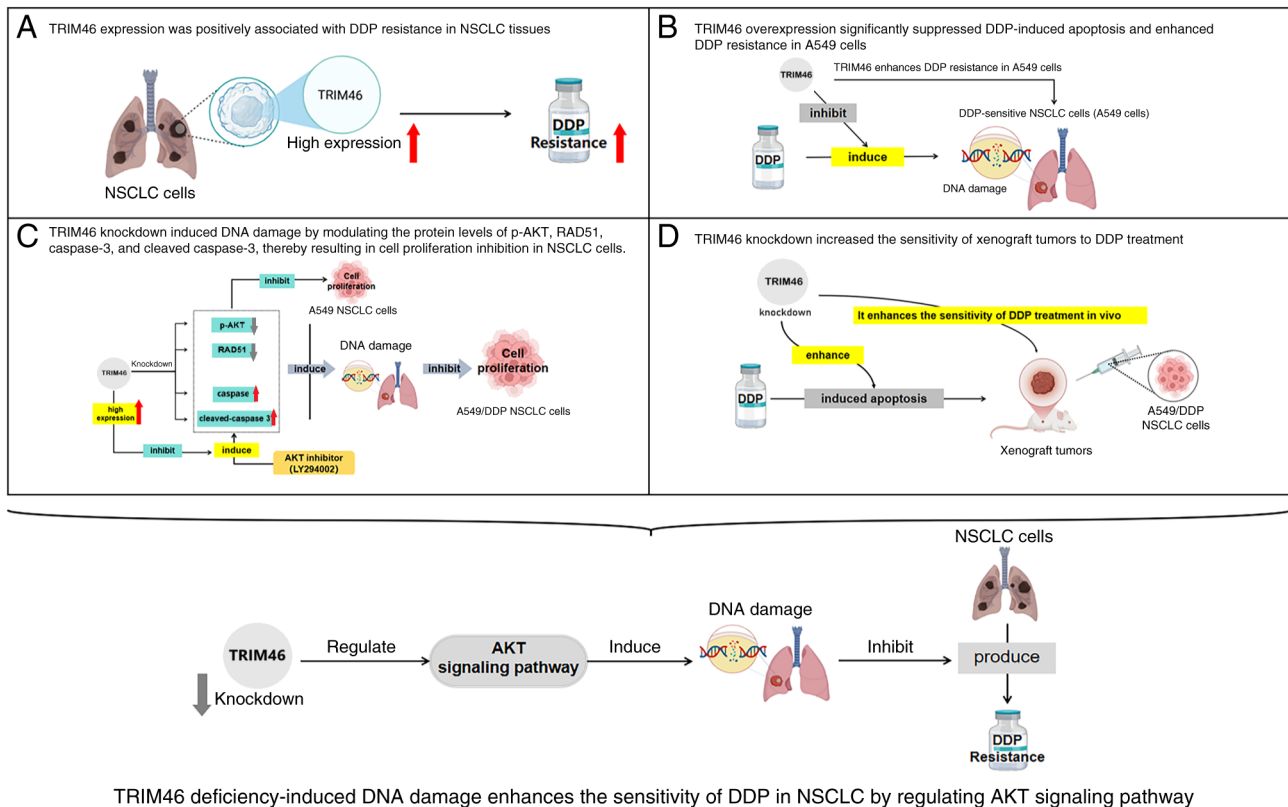
indicated that TRIM46 knockdown enhanced the sensitivity of xenograft tumors to DDP treatment *in vivo*.

Discussion

DDP was the first-in-class drug for NSCLC therapy; it activates various cytoplasmic substrates and nuclear DNA and leads to DNA damage, thus inducing tumor cell death by activating the apoptotic signaling pathway (27-29). Despite the efficacy of initial treatment, patients inevitably become resistant to DDP. DDP is one of the primary mechanisms underlying DDP resistance against NSCLC, although it is not fully understood (27). The present study showed that TRIM46 contributed to DDP resistance in NSCLC via activating Akt signaling and reducing DNA damage. Additionally, TRIM46 deficiency restored the function of DDP against NSCLC tumors (Fig. 6).

The results of the present study revealed that TRIM46 was highly expressed in the tissues of DDP-resistant NSCLC tumors. Additionally, the level of TRIM46 was associated

with DDP resistance. A number of TRIM family members are involved in the development of lung cancer. Accumulating evidence suggests that TRIM proteins, including TRIM8, TRIM13, TRIM67, TRIM28, TRIM19 and TRIM45, regulate the abundance and activity of p53, which is a critical cancer suppressor (30). Moreover, a study has suggested that TRIM proteins activate the NF-κB pathway in all types of lung cancer (18). Over the years, TRIM proteins have been found to control the PI3K/Akt signaling pathway. TRIM10, TRIM11, TRIM26 and TRIM37 inhibit Akt signaling activation (31). By contrast, TRIM22, TRIM24, TRIM25, TRIM27, TRIM59 and TRIM44 promote Akt pathway activation (31). These results collectively suggested the complicated roles of TRIM proteins in lung cancer. Exploring the role of other TRIM members can help understand the development of lung cancer. The present study found that patients with a lower level of TRIM46 were sensitive to DDP. Vice versa, patients with a higher level of TRIM46 were resistant to DDP treatment. In line with these findings, previous studies have reported that



TRIM46 deficiency-induced DNA damage enhances the sensitivity of DDP in NSCLC by regulating AKT signaling pathway

Figure 6. Mechanism of TRIM46 deficiency-induced DNA damage, enhancing the sensitivity of DDP in NSCLC by regulating Akt signaling pathway. (A) TRIM46 expression was positively associated with DDP resistance in NSCLC tissues. (B) TRIM46 overexpression significantly suppressed DDP-induced apoptosis and enhanced DDP resistance in A549 cells. (C) TRIM46 knockdown induced DNA damage by modulating the protein levels of p-AKT, RAD51, caspase 3, and cleaved caspase 3, thereby resulting in cell proliferation inhibition in NSCLC cells. (D) TRIM46 knockdown increased the sensitivity of xenograft tumors to DDP treatment. NSCLC, non-small cell lung cancer; TRIM46, tripartite motif 46; DDP, cisplatin; p-, phosphorylated.

TRIM46 expression is increased in NSCLC tissues compared with normal lung tissues and its upregulation is associated with NSCLC cancer progression and chemoresistance by regulating the Akt or NF- κ B signaling pathways (23,32,33). Moreover, TRIM46 expression was also shown to be increased in the tissues and cell lines of pancreatic cancer, ovarian cancer and osteosarcoma as well as found to promote cancer progression by regulating the Wnt or NF- κ B signaling pathways (15,34,35). However, a previous study showed downregulation of TRIM46 in NSCLC tumor cells compared with normal tissues (36). This apparent paradox suggests a context-dependent role of TRIM46 in NSCLC pathogenesis; its expression and function may be differentially regulated during tumorigenesis vs. acquired therapy resistance. Cancer cells could selectively upregulate TRIM46 as an adaptive survival mechanism under chemotherapeutic stress such as DDP treatment, leveraging its ability to activate pro-survival Akt signaling and enhance DNA repair, even if its basal expression differs. These results imply distinct roles of TRIM46 in different conditions such as therapy response status.

The present study found that DDP resistance in NSCLC may be associated with TRIM46-mediated Akt signaling regulation. At present, the PI3K/Akt pathway has been found to phosphorylate multiple proteins, thereby stimulating tumor cell growth, suppressing apoptosis and facilitating DNA damage repair after chemotherapy (37). The PI3K/Akt/NF- κ B (17) and PI3K/Akt/mTOR (16) pathways have been found to be related to DDP treatment failure. Moreover, PI3K/Akt participates in

the induction of the ATP-binding cassette transporter, as well as the regulation of aerobic glycolysis to increase the energy supply (38,39). Among the varied reported Akt-related TRIM proteins, TRIM18 has been reported to negatively regulate protein phosphatase 2 phosphatase activator, resulting in Akt activation (40). Accordingly, another C-1 subfamily member, TRIM46, also resulted in Akt activation in lung cancer (23) and ovarian cancer cells (41). In agreement with these findings, the present study observed that the knockdown of TRIM46 reduced p-Akt levels and that TRIM46 overexpression activated Akt signaling. These results at least partially indicated that TRIM46 may contribute to DDP resistance by activating Akt signaling. These results also rendered a rationale to combine TRIM46 knockdown and an Akt pathway inhibitor to treat DDP-resistant NSCLC.

A previous study has shown that circular RNA VMP1 depletion counteracts DDP resistance, thus attenuating NSCLC tumor growth *in vivo* (42). Additionally, TRIM59, a family member of TRIM46, has been reported to enhance DDP resistance in NSCLC tumor cell lines. Blocking the expression of TRIM59 also significantly suppressed tumor growth (43). Furthermore, targeting DDP resistance by TRIM65 deficiency in A549/DDP cells was shown to effectively decrease tumor volume (44). These studies demonstrated that targeting DDP resistance is an important therapeutic strategy against NSCLC. In the present study, it was found that TRIM46 expression was positively associated with DDP-resistance in NSCLC tumor cells. Additionally, TRIM46 knockdown in A549/DDP cells

significantly attenuated tumor growth *in vivo*, indicating TRIM46 as a candidate therapeutic target of DDP-resistant NSCLC. However, more cell lines are needed to validate the function of TRIM46. Moreover, further investigations are necessary to explore the functions and mechanisms of TRIM46 in DDP resistance *in vitro* and *in vivo*.

The present study revealed that TRIM46 could act as a positive regulator of DDP resistance in NSCLC via activating Akt and reducing DNA damage. Targeting TRIM46, potentially through small-molecule inhibitors or RNA interference-based strategies (such as small interfering RNA or shRNA delivery via nanocarriers), could sensitize resistant tumors to conventional DDP chemotherapy. Combining TRIM46 inhibition with Akt pathway inhibitors might represent a particularly effective synergistic strategy, as suggested by the results using LY294002. However, this warrants further investigation.

The present study had several limitations. First, the investigation was primarily conducted using the A549 cell line model. Validating the role of TRIM46 in additional NSCLC cell lines with inherent or acquired DDP resistance can strengthen the generalizability of the conclusions. Second, it was established that TRIM46 activated Akt signaling. However, the precise molecular mechanism by which TRIM46 (potentially through its E3 ubiquitin ligase activity) regulates Akt activation warrants further elucidation. Future studies should focus on identifying the specific substrates of TRIM46 involved in this pathway.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SJ and DZ performed the experiments, collected data and drafted the manuscript. ZL, LY and JZ performed the statistical analysis and participated in the study design. YW, PJ, MP and YL participated in the analysis or interpretation of data and drafted the manuscript. All authors read and approved the final version of the manuscript. SJ, DZ and JZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Animal experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals

and approved by the Animal Care and Use Committee of Wenzhou Traditional Chinese Medicine Hospital of Zhejiang Chinese Medical University (Wenzhou, China; approval no. WTCM-KT-2020002). This study used commercially available tissue microarrays with samples obtained from fully anonymized and consented donors and involved only retrospective analysis. The institutional ethics committee reviewed the protocol and granted an exemption from ethics approval.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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