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Amplified TPM1 suppresses non-small cell lung cancer cells proliferation and metastasis

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Abstract

Background TPM1 a member of TPM family and acts as a crucial role in a variety of tumors progression. However, the effect and mechanism of TPM1 on NSCLC need to be further explored. Here, effect and mechanism of TPM1 on NSCLC were revealed to provide new target for clinical therapy.

Methods TPM1 expression in NSCLC tissues and normal tissues was analyzed using GEPIA online database. NSCLC cells were transfected with TPM1 overexpression plasmid. TPM1 mRNA expression of NSCLC cells was assessed by RT-qPCR. NSCLC cells proliferation and apoptosis were detected by CCK-8 and flow cytometry. Scratch healing and Transwell experiments were introduced to measure NSCLC cells migration and invasion. The effects of TPM1 overexpression on TPM1, YAP1 and EMT related proteins expression in NSCLC cells were detected by Western blot experiments. The interaction between TPM1 and YAP1 was analyzed by the HitPredict database and Co-IP assay.

Results TPM1 expression in NSCLC was decreased. High expression of TPM1 could inhibit NSCLC cells proliferation, migration and invasion and promote apoptosis. EMT marker E-Cadherin increased in TPM1 overexpression group, while Vimentin and N-Cadherin decreased. EMT process was inhibited by TPM1 overexpression. There is a mutual binding between TPM1 and YAP1, and TPM1 could down-regulate YAP1 expression. Overexpressed YAP1 could partly counteract the inhibition of NSCLC cells proliferation and metastasis induced by TPM1 overexpression.

Conclusion TPM1 was down-regulated in NSCLC, and its overexpression inhibited NSCLC cells proliferation and metastasis, and this was achieved by regulating YAP1. TPM1 may become a new therapeutic target for NSCLC.

Keywords Non-small cell lung cancer, TPM1, Cells proliferation, Metastasis, YAP1

1 Background

Lung cancer (LC) often occurs on glands or bronchial mucosa, with strong familial clustering and genetic susceptibility [1, 2]. LC has been reported to have high incidence rate and mortality, but non-small cell lung cancer (NSCLC) accounting for about 80%~85% of all cases [3, 4]. The high mortality associated with LC is largely due to the fact that the majority of patients are diagnosed at advanced stages [5], when the cancer has already

metastasized [6]. Hence, further clarifying pathogenesis and finding new therapeutic methods of NSCLC hold great significance.

Tropomyosin (TPM) is distributed in various eukaryotic cells and plays an important role in regulating muscle contraction, cell movement and promoting apoptosis [7]. TPMs relates to tumor cells proliferation, migration and invasion [7, 8]. TPM1 is a member TPM family, located on the cell membrane and affecting cell adhesion and cell signaling pathway transduction [9]. TPM1 has been identified as a key cell regulator morphology and apoptosis in normal cells and plays an essential role in maintaining cell stability and insisting malignant transformation [10]. Multiple studies have shown that TPM1 has the cancer-suppressing function, and its expression is significantly downregulated in a variety of malignant tumors [11–14]. However, its specific mechanisms in NSCLC remains unclear. This study aims to clarify the functional role of TPM1 overexpression in regulating NSCLC progression.

Yes-associated protein 1 (YAP1) is a crucial regulator of the Hippo signaling pathway and is often dysregulated in many cancers, including NSCLC [15]. Normally, YAP1 functions in tissue repair, but in the context of cancer, its hyperactivity leads to unchecked cell proliferation, invasion, and metastasis [16]. YAP1's role in epithelial-to-mesenchymal transition (EMT) further complicates tumor progression by enhancing cancer cell invasiveness [15–17]. This study investigations the potential regulation relationship between TPM1 and YAP1 in the progression of NSCLC.

This study aims to explore whether TPM1 overexpression can affect the expression of YAP1 and subsequently modulate NSCLC cells proliferation and metastasis. Based on prior evidence suggestion that TPM1 has tumor-suppressive properties [11–14] and YAP1 promotes tumor progression [15], we hypothesize that TPM1 may inhibit NSCLC progression by downregulating YAP1 expression and its associated oncogenic activities. Previous studies have demonstrated a decrease in TPM1 expression in various cancers [11–14], including NSCLC [18, 19], suggesting its potential role as a tumor suppressor. However, the molecular brands linking TPM1 to key oncogenic pathways such as YAP1 remain poorly understood. This study fills this gap by investigating how TPM1 modulates YAP1 expression and its impact on NSCLC cells behavior. Understanding the interplay between TPM1 and YAP1 in NSCLC could provide new insights into the molecular mechanisms of cancer progression and metastasis. This study contributed to the growing body of evidence supporting the potential of TPM1 as a therapeutic target in NSCLC treatment.

2 Materials and methods

2.1 TPM1 expression in NSCLC was analyzed by GEPIA database

The GEPIA database (http://gepia.cancer-pku.cn/) was utilized to analyze TPM1 expres sion in NSCLC tissues. The following criteria were applied for screening: (1) Expression DIY: Boxplot for visualizing the data, (2) Datasets Selection: LUAD (lung adenocarcinoma) and LUSC (lung squamous cell carcinoma), (3) Match TCGA normal and GTEx data, and (4) Default settings of the online tool were used for further analysis. Expression data for 483 LUAD tissues, 347 normal tissues, 486 LUSC tissues, and 338 normal tissues were retrieved.

2.2 Cell culture and transfection

BEAS-2B and human NSCLC cells (HCC827, A549, H1299) were obtained from Pricella (Pricella, China). Cells were cultured in RPMI-1640 medium (Gibco, USA) supplemented with 10% FBS (Gibco, USA) and 1% penicillin/streptomycin (Solarbio, China) under standard culture conditions (37℃, 5% CO_2, and constant humidity). Medium was changed every 2 to 3 days. When the cell density grew to 90%, the ratio of 1 to 1 was passed, and cells in logarithmic growth phase were taken for subsequent experiments.

For gene overexpression, TPM1 or YAP1's full-length sequences were cloned into pcDNA3.1 (+) vector (Youbia, China), which was used for transfection. Cells were inoculated into 6-well plates (4×10^6 cells/well). Cells were divided into negative control (pc-NC, empty plasmids), TPM1 overexpression (oe-TPM1), YAP1 overexpression (oe-YAP1) and TPM1 and YAP1 overexpression (oe-TPM1 + oe-YAP1) groups. Transfections were performed by Lipofectamine 2000 (Invitrogen, USA). Transfection efficiency was evaluated 48 h post-transfection.

2.3 CCK-8

Cell proliferation was assessed using the CCK-8 assay (Dojindo, Japan). A total of 3×10^3 cells were seeded in 96-well plates with 100 μL of cells suspension per well. After 12 h, 10 μL CCK-8 solution was added to each well. Absorbance was measured at 450 nm at 24, 48, and 72 h using a microplate reader (BIOTEK, USA).

2.4 Cell apoptosis

Cell apoptosis was analyzed by flow cytometry using an Annexin V-FITC apoptosis detection kit (Beyotime, China). After centrifugation, the cell pellets were re-suspended in pre-cooled phosphate-buffered saline (PBS), and 300 μL of buffer was mixed with 5 μL of Annexin V-FITC and 5 μL of PI solution. The samples were incubated in the dark for 15 min in room temperature. Apoptotic cells were identified and quantified using a flow cytometry (Bio-Red, USA).

2.5 Scratch healing

For the scratch healing assay, cells were seeded in 12-well plate until 100% confluence was reached. A straight line was drawn across the center of the well using the tip of a 10 μL pipette. After removing the detached cells by PBS washings, the cells were incubated at 37℃. Images were taken at 0 and 24 h after the scratch, and the migration distance (D0h - D24h) was quantified. The cell mobility was calculated as (D0h - D24h)/D0h.

2.6 Co-immunoprecipitation (Co-IP)

Co-IP was to investigate the interaction between TPM1 and YAP1. Briefly, after protein extraction using radioimmunoprecipitation assay (RIPA) lysis (Solarbio, China), 1 μg TPM1, YAP1 and IgG antibodies (Abcam, USA) were added to the lysates and incubated overnight at 4℃. Immuno-precipitates were captured using 10 μL of protein A/G plus agarose beads (Santa Cruz Biotechnology, USA) and analyzed by Western blot to identify protein-protein interactions.

2.7 Cell invasion

Cells of each group were collected, and 100 μL Matrigel glue (BD, USA) was applied to the upper Transwell chamber (Corning, USA). 1×10^5 cells was added to each pore in the upper chamber, and 500 μL complete medium containing 10% FBS was added to the lower chamber. After incubation at 37℃ for 24 h, cells were removed and washed twice with PBS. Cells on the upper compartment were removed with cotton swabs. Cells on the lower compartment were fixed with 4% paraformaldehyde (Beyotime, China) and stained with 0.1% crystal violet (Beyotime, China) for 20 min. Cells were observed and counted.

2.8 RT-qPCR

Total RNA was extracted from each group by Trizol reagent (Invitrogen, USA). The purity and abundance of RNA samples were measured by spectrophotometer. RNA was reverse-transcribed into cDNA using reverse transcription kit (Thermo scientific, USA). RT-qPCR was performed using SYBR Green PCR Master Mix detection kit (TaKaRa, China) on the fluorescent quantitative PCR instrument (LightCycler480, Roche, Switzerland). After the reaction, the cycle threshold (Ct) values of target gene and internal reference gene were obtained, and the gene expression levels in cells were analyzed by $2^{-\Delta\Delta Ct}$ method with GAPDH as reference.

2.9 Western blot

Total protein in transfected cells was extracted using RIPA cell lysate (Solarbio, China) and protein concentration was detected by bicinchoninic acid (BCA) kit (Beyotime, China). Protein samples of 30–40 μg were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membrane (Millipore, USA) and enclosed in 5% skim milk powder overnight. Subsequently, PVDF membrane then incubated in primary antibodies at 4 °C overnight. Next, HBR-labeled secondary antibodies (Abcam, USA) was incubated for 2 h. Protein bands were colored by ECL kit (Pierce, USA) and the gray scale of the bands was analyzed by Image J software (National Institutes of Health, USA).

2.10 Statistical analysis

Statistical analysis were using GraphPad Prism 8 software (GraphPad Software Inc., USA). Data are expressed as mean ± standard deviation (SD). One-way ANOVA was used for comparison among multiple groups, and the Student's t test applied for comparisons between two groups. A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Expression of TPM1 in NSCLC

Whether it's LUAD or LUSC, the relative expression level of TPM1 mRNA is notably lower than its corresponding expression level in normal tissues (Fig. 1A). To further determine whether there is a similar difference in TPM1 expression in NSCLC cells, TPM1 expression of BEAS-2B and three NSCLC cells (HCC827, A549, H1299) was detected. TPM1 mRNA and protein levels were decreased in all three NSCLC cell lines (Fig. 1B-D).

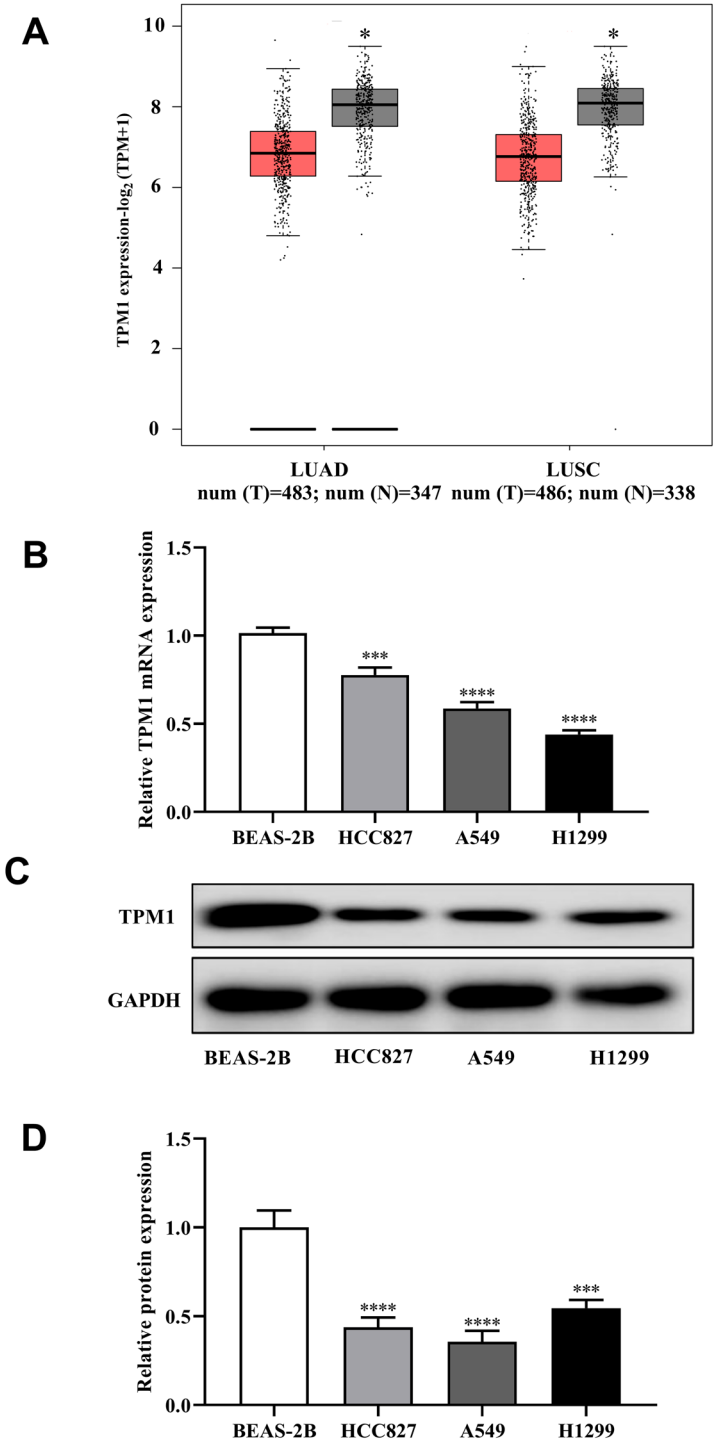

Fig. 1 Expression level of TPM1 in NSCLC. (A) Expression of TPM1 mRNA in NSCLC tumor tissues and normal tissues in TCGA database. (B, C, D) TPM1 mRNA and protein expression levels in NSCLC cells. *$P < 0.05$, ***$P < 0.001$, ****$P < 0.0001$, compared with normal or BEAS-2B group

3.2 TPM1 overexpression inhibited NSCLC cells proliferation

To gain a deeper understanding of TPM1's role in occurrence and development of NSCLC, H1299 and A549 were selected for TPM1 overexpression. TPM1 expression in H1299 and A549 cells were increased by TPM1 overexpression plasmid (Fig. 2A-F).

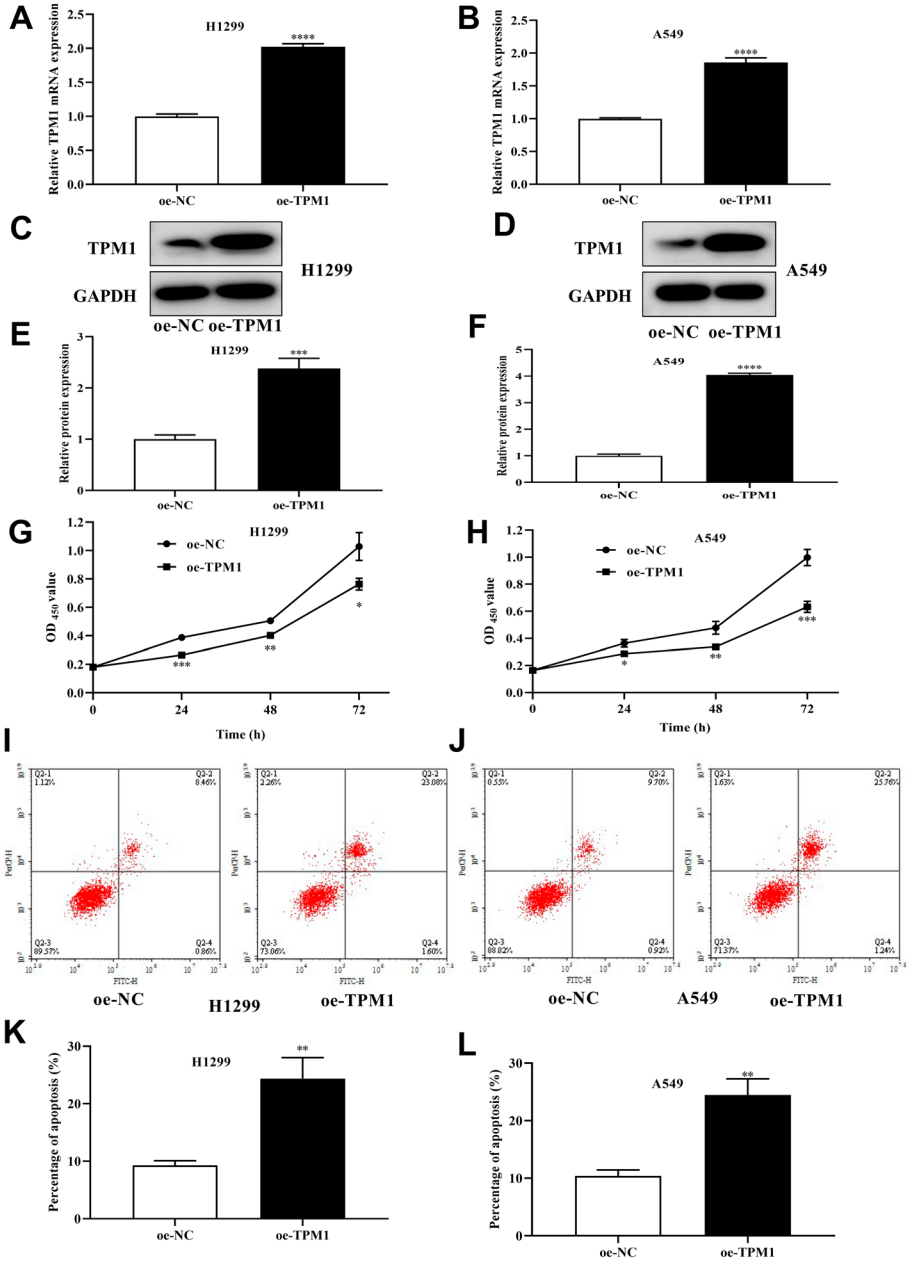

Fig. 2 TPM1 overexpression inhibited the proliferation and promoted apoptosis of NSCLC cells. (A, B, C, D, E, F) Detection of TPM1 overexpression in NSCLC cells. (G, H) CCK-8 was used to detect the effect of TPM1 overexpression on the proliferation of NSCLC cells. (I, J, K, L) Apoptosis rate of NSCLC cells after TPM1 overexpression was measured by flow cytometry. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$, compared with oe-NC group

To determine whether TPM1 affects cell proliferation, cell proliferation after TPM1 overexpression was detected by CCK8 method. TPM1 overexpression could inhibit the proliferative activity of H1299 and A549 cells (Fig. 2G, H). Meanwhile, up-regulation of TPM1 could promote apoptosis of two cell lines (Fig. 2I-L).

3.3 TPM1 overexpression inhibited NSCLC cells metastasis

The effect of TPM1 on NSCLC cells migration and invasion was further detected by scratch healing and Transwell assays. Cells invasion and migration were inhibited after

TPM1 overexpression (Fig. 3A-H). In order to verify whether TPM1 effects EMT, EMT-related proteins expression were measured by western blot. It was found overexpression of TPM1 decreased the expression of N-cadherin and Vimentin, and increased the expression of E-cadherin, suggesting that TPM1 overexpression inhibited EMT in NSCLC cells (Fig. 3I-L).

3.4 Effect of TPM1 overexpression on YAP1 expression

The protein-protein interaction database HitPredict (http://www.hitpredict.org/) shows that TPM1 protein may interact with YAP1. The results of Co-IP showed that YAP1 protein could be detected in TPM1 immunoprecipitation products and TPM1 protein could be detected in YAP1 immunoprecipitation products in NSCLC cells, while neither TPM1 nor YAP1 could be detected in IgG immunoprecipitation products (Fig. 4A, B). In addition, transient of TPM1 overexpression in NSCLC cells could reduce the protein expression level of YAP1 (Fig. 4C-F). This indicated that TPM1 could interact with YAP1 in NSCLC cells.

3.5 YAP1 reversed the Inhibition of TPM1 on NSCLC cells proliferation and metastasis

To confirm that YAP1 can reverse the inhibitory effect of TPM1 on NSCLC cells, rescue experiments were conducted by overexpressing TPM1 and YAP1 in A549 cells. CCK-8 and flow cytometry results indicated that YAP1 overexpression could partly offset decreased proliferation and increased apoptosis induced by TPM1 overexpression (Fig. 5). Similarly, cell invasion, migration and EMT showed the same trends in rescue experiments (Fig. 6). It was confirmed that the co-overexpression group could partly reverse the malignant behavior progression caused by TPM1 overexpression.

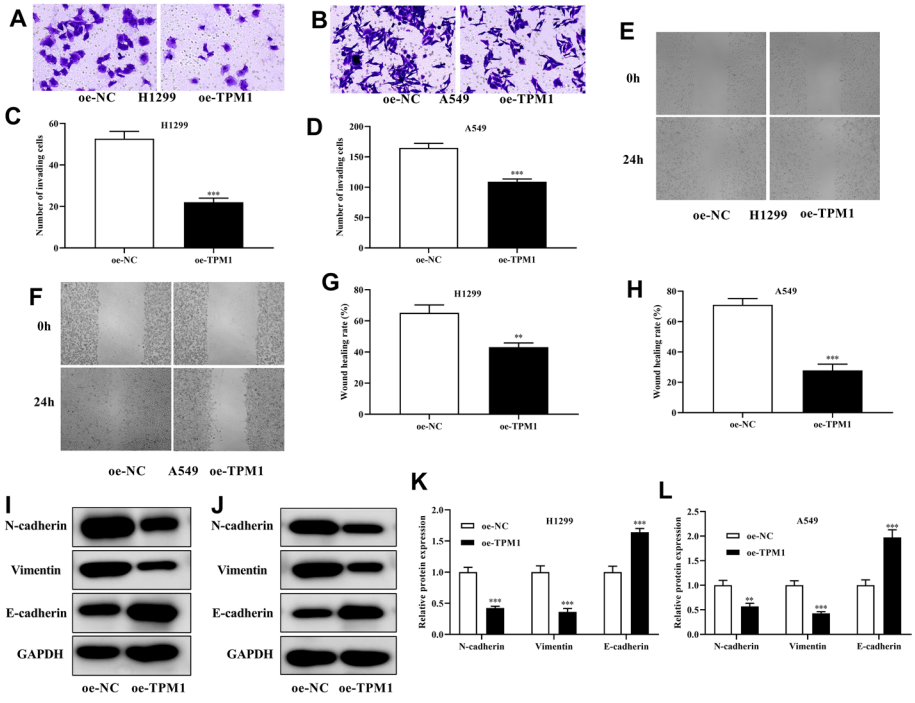

Fig. 3 TPM1 overexpression hampered invasion, migration and EMT of NSCLC cells. (A, B, C, D, E, F, G, H) The invasion and migration of NSCLC cells were inhibited by oe-TPM1. (I, J, K, L) The protein expression of E-cadherin, N-cadherin and Vimentin. $^{**}P < 0.01$, $^{***}P < 0.001$, compared with oe-NC group

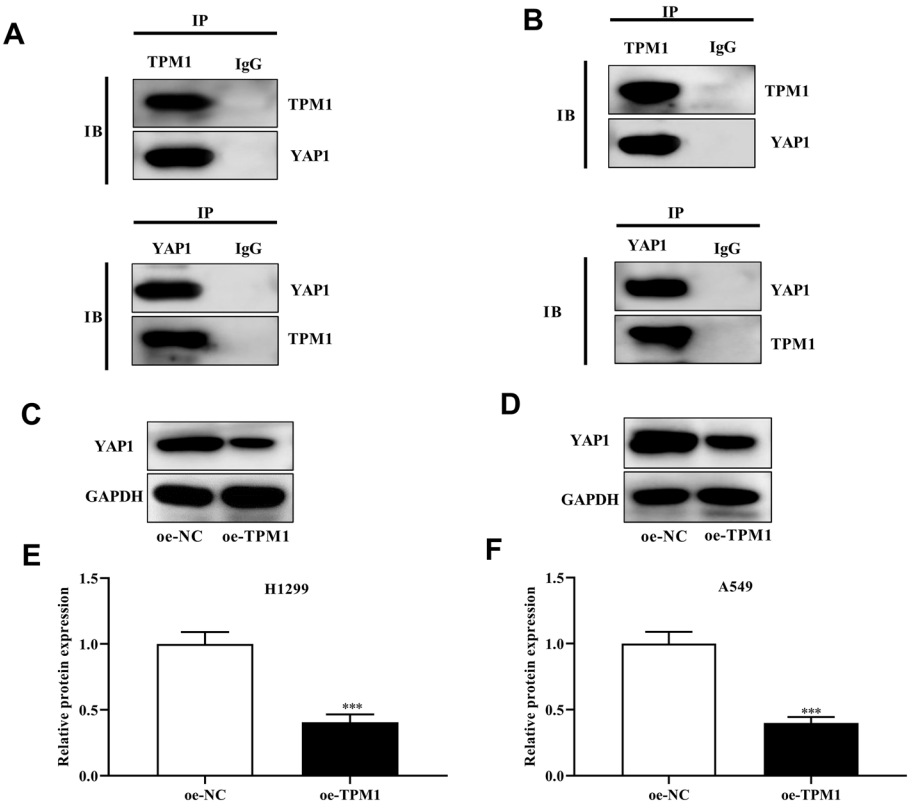

Fig. 4 TPM1 interacts with YAP1. (A, B) Co-IP was used to verify whether TPM1 binds to YAP1. (C, D, E, F) Effect of TPM1 overexpression on YAP1 protein expression levels. ***$P < 0.001$, compared with oe-NC group

4 Discussion

Despite significant advances in the treatment of NSCLC, including targeted therapies and immunotherapy, the underlying molecular the mechanisms remain incompletely understood, and the therapeutic options are still limited [20]. As a result, the prognosis for many patients with NSCLC remains poor, and recurrence rates remain high, particularly in patients who experience distant metastasis [20]. Furthermore, the metastatic behavior of NSCLC cells, including their ability to invade vital organs such as the liver, bones, and brain, continues to present a significant clinical challenge [20, 21]. Thus, a deeper understanding of the molecular mechanism driving proliferation and metastasis in NSCLC is essential for improving treatment results.

As a tumor suppressor gene, TPM1 has been implicated in regulating cell proliferation, migration, and apoptosis across various cancer types [22]. Previous studies have demonstrated that TPM1 expression is often downregulated in several cancers, including gastric cancer (GC) and colorectal cancer (CRC), where its loss is associated with poor prognosis and disease [13, 23, 24]. In the context of NSCLC, the current study confirms that overexpression of TPM1 suppresses cell proliferation, migration, and invasion, while promoting apoptosis, aligning with its previously established tumor-suppressive functions [18, 22, 24, 25]. Our findings suggest that TPM1 may serve as a critical regulator in NSCLC tumorigenesis, potentially offering a novel target for therapeutic intervention.

EMT is a crucial process of cancer metastasis, where cells undergo phenotypic changes that enhance their migratory and invasive capabilities [26]. Markers of EMT,

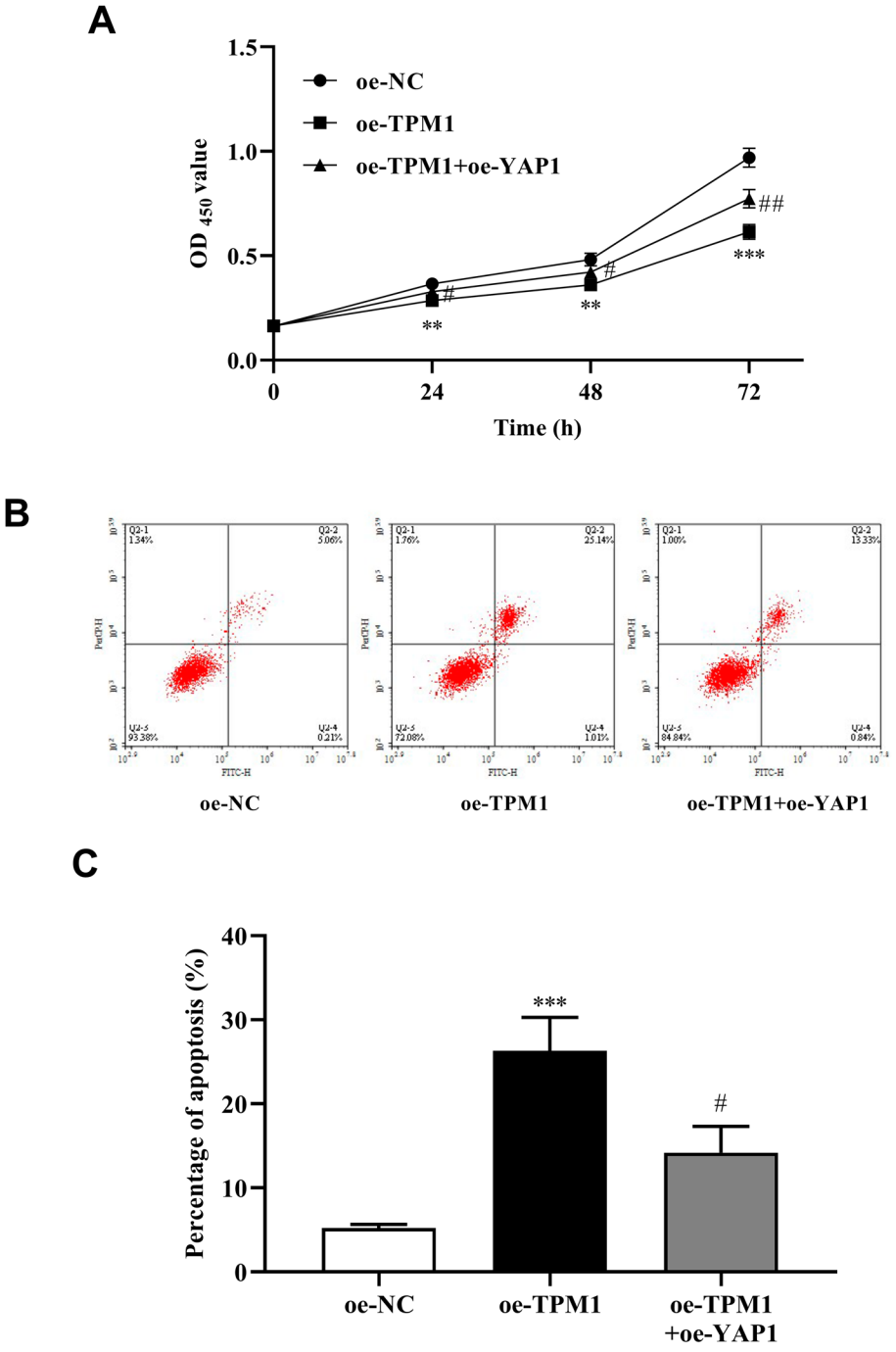

Fig. 5 Effect of TPM1 on the growth and apoptosis of NSCLC cells in vitro by regulating YAP1. (A) After TPM1 and YAP1 upregulation, CCK-8 assay was used to detect the proliferation of NSCLC cells. (B, C) After TPM1 and YAP1 overexpression, detection of NSCLC cells apoptosis. $^{**}P < 0.01$, $^{***}P < 0.001$, compared with oe-NC group. $\#P < 0.05$, $\#\#P < 0.01$, compared with oe-TPM1 group

such as N-cadherin, E-cadherin, and Vimentin, are used to predict tumor of progression and metastasis [27]. Our study found that TPM1 overexpression led to a decrease in N-cadherin and Vimentin expression while increasing E-cadherin expression, suggesting that TPM1 inhibits NSCLC metastasis by counteracting EMT processes. This finding provides insight into the potential mechanism through which TPM1 may suppress cancer cell invasiveness and migration.

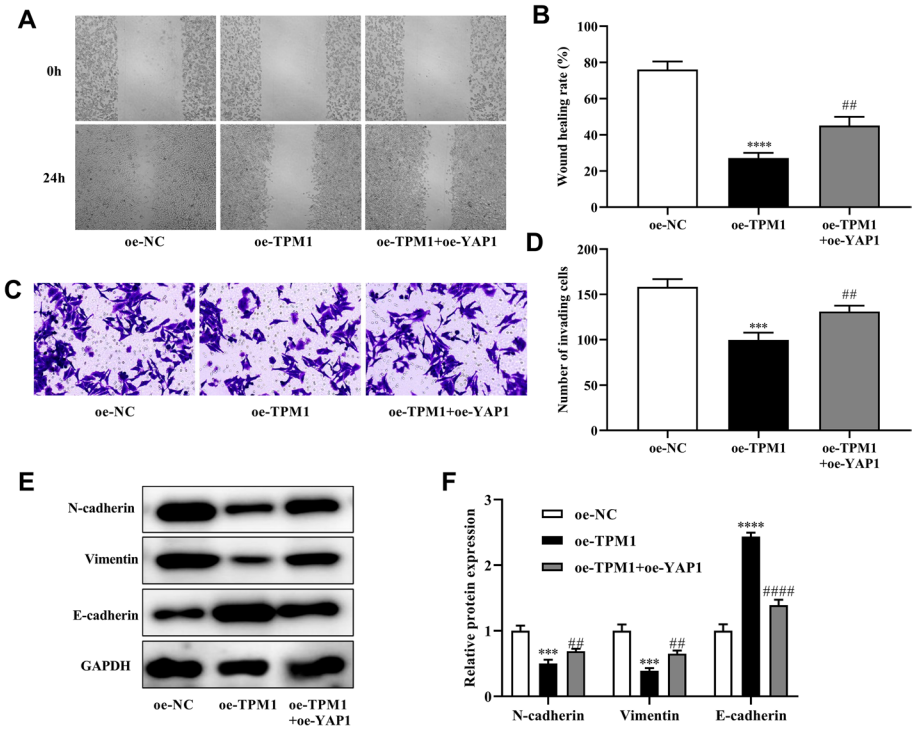

Fig. 6 Overexpression of YAP1 attenuated the ability of TPM1 overexpression on the migration, invasion and metastasis of NSCLC cells. (A, B, C, D) YAP1 overexpression reversed the inhibition of NSCLC cell invasion and migration induced by TPM1 overexpression. (E, F) YAP1 overexpression reversed the effects of TPM1 overexpression on EMT markers in NSCLC cells. ***$P < 0.001$, ****$P < 0.0001$, compared with oe-NC group. ##$P < 0.01$, ####$P < 0.0001$, compared with oe-TPM1 group

YAP1, a key effector of the Hippo signaling pathway is often dysregulated in various cancers, including NSCLC [15]. As a transcriptional cofactor, YAP1 promotes tumor of progression by enhancing cell proliferation, invasion and migration and various signaling pathways activation [28–30]. YAP1 promotes NSCLC cells proliferation, invasion and metastasis and reduces sensitivity of NSCLC to chemotherapy, radiotherapy and EGFR-TKIs [31]. In this study, we explored the interaction between TPM1 and YAP1 using protein interaction databases, confirming that TPM1 can interact with YAP1, which may contributed to its tumor suppressor activity. Importantly, we observed a significant reduction in YAP1 expression upon TPM1 overexpression, indicating that TPM1 may exert its effects on NSCLC cells proliferation and metastasis by regulating YAP1. The co-transfection experiments further demonstrated that the overexpression of both TPM1 and YAP1 partly reversed the anti-proliferative and anti-metastatic effects of TPM1, supporting the hypothesis that TPM1 may suppress NSCLC progression by downregulating YAP1 activity.

While this study provides compelling evidence that TPM1 regulates NSCLC progression through the downregulation of YAP1, it is important to recognize that TPM1 may not be solely influence NSCLC via a single gene or pathway. For example, YAP1 has been reported to result in EMT by interaction with TEAD in NSCLC [32], and the YAP1/TEAD pathway has been reported to be inhibited by inhibition of HSP90 in gastric cancer [33]. Then, whether the role of TPM1 in NSCLC is related to HSP90 and TEAD, and what is the relationship? Moreover, co-occurrence of YAP1 overexpression does not appear to fully recover the suppression of tumor cell growth and apoptotic activity, and

metastasis activity induced by TPM1 overexpression. This may indicate that TPM1 may also suppress tumors by other mechanisms. Thus, future research should aim to explore the broader molecular network involving TPM1 and other potential signaling pathways that contributed to NSCLC proliferation and metastasis. Additionally, in vivo models and clinical studies are needed to validate the therapeutic potential of targeting TPM1 in combination with YAP1 for NSCLC treatment.

5 Conclusion

In summary, TPM1 expression was decreased in NSCLC. TPM1 overexpression inhibited proliferation, metastasis and promote apoptosis by inhibiting YAP1 expression in NSCLC cells, and TPM1 may become a potential prognostic indicator and therapeutic target for NSCLC. This study helps to reveal molecular pathogenesis of NSCLC and further develop new therapies for NSCLC patients.

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Author contributions
FX and YR conceived and designed the study, and drafted the manuscript. FX, JL, SQ and LL collected, analyzed and interpreted the data. JL and YR revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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